



The
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**Modifiable lifestyle factors as modulators of brain parameters and
cognitive decline in ageing and Alzheimer's disease**

By

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Corpus

A painting by Kate Sully inspired by research on obesity and Alzheimer's disease from this thesis, showcased in the Festival of the Mind 2020. Permissions to use the image can be found in Appendix A.

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative condition associated with pathological accumulations of misfolded proteins, amyloid plaques and neurofibrillary tangles. AD manifests clinically with prominent memory complaints, deficits in other cognitive domains in addition to brain structural and functional deficits. Research in the recent decades has shifted its focus on the marked vascular dysfunction observed in AD and how the interaction between vascular senescence and vascular burden arising from modifiable lifestyle factors can change the course of the disease. It is unclear whether the presence of vascular comorbidities stemming from modifiable lifestyle factors can have an additive effect in AD or whether there is an interaction between ageing, AD and cardiovascular comorbidity-related mechanisms that can result in a worse AD phenotype. The current thesis thus aims to investigate how the additional vascular contributions from modifiable lifestyle factors can alter cerebral constituents and cognitive function in normal ageing and AD, using multi-modal neuroimaging. This was done by exploring the effects of three common cardiovascular risk factors on the brain, that are modifiable through interventions facilitating lifestyle changes, namely obesity, hypertension and type 2 diabetes, in cognitively normal individuals and patients across the AD spectrum.

With reference to obesity, it appears that having parameters within the healthy weight range could make the brain more resilient to age and AD-related effects in later stages of the disease. However, in the transitional mild cognitive impairment stage, being in the overweight category could contribute towards a worse prognostic profile of AD, while being in the obese weight range in cognitively healthy controls could be detrimental to a wide range of cerebral constituents and cognitive functions. The baseline differences in the weight categories of the different diagnostic groups could have been among the main drivers for the associations found, and these differences are also consistent with what is observed in the general population, due to age and disease related effects. When comparing AD patients medicated for hypertension (who had a medical history of hypertension) with AD patients unmedicated for hypertension, no differences were found with respect to neuroimaging parameters or cognitive function. However, in the medicated group, dividing the patients according to the class of antihypertensive drug treatment revealed a preservative effect of the use of beta-blockers only, on brain structure and cerebral blood flow. Moreover, on correlating values of pulse pressure

(the difference between systolic and diastolic blood pressure) with neuroimaging parameters in the unmedicated AD patient group, a negative correlation was found between cerebral blood flow and pulse pressure in subcortical brain regions. On the other hand, when comparing AD patients with type 2 diabetes with AD patients without type 2 diabetes, AD patients with type 2 diabetes presented with a worse AD phenotype than their counterparts. On comparing AD patients with type 2 diabetes with age and sex-matched healthy controls, widespread differences were found in brain structure, cerebral blood flow and cognition between the two groups.

The work from the current thesis highlights that the additional burden from modifiable lifestyle factors is additive to the detrimental effects of AD and that these effects are exaggerated through the interaction of pathological mechanisms downstream of cardiovascular comorbidities, vascular senescence and AD. The irreversible nature of these downstream mechanisms is a crucial point for the consideration of implementing primary prevention strategies to reduce the prevalence of cardiovascular risk factors as their presence can increase the severity of AD in patients and can also lower the threshold for AD onset in healthy individuals. Considering the fact that there are several non-modifiable risk factors for AD, that there is a paucity in effective treatments and early diagnostic criteria for AD, the modifiable nature of cardiovascular risk factors makes them the crux for preventing the clinical manifestations of AD and mitigating its severity. The findings from this thesis therefore highlight the need for early interventions recommending primary prevention to reduce the burden of cardiovascular risk factors to reduce the risk of AD onset in healthy individuals and to reduce the severity of the AD phenotype in patients through pharmacological interventions and lifestyle modifications.

Abbreviations

A β : Amyloid beta; **AD**: Alzheimer's Disease; **ADD**: Alzheimer's disease dementia; **ADNI**: Alzheimer's Disease Neuroimaging Initiative; **APoE ϵ 4**: Apolipoprotein E epsilon 4; **APP**: Amyloid precursor protein; **ASL**: Arterial spin labelling; **ATN**: Amyloid, tau, neurodegeneration; **BBB**: Blood brain barrier; **BMI**: Body mass index; **CASL**: Continuous arterial spin labelling; **CBF**: Cerebral blood flow; **CN**: Cognitively normal individuals; **CRF**: Cardiovascular risk factor; **CSF**: Cerebrospinal fluid; **CT**: Computed tomography; **T2DM**: Type 2 Diabetes Mellitus; **DMN**: Default mode network; **DNA**: Deoxyribonucleic acid; **DTI**: Diffusion tensor imaging; **EOAD**: Early-onset Alzheimer's Disease; **FA**: Fractional anisotropy; **FDG**: Fluorodeoxyglucose; **FLAIR**: Fluid-attenuated inversion recovery; **fmRI**: Functional magnetic resonance imaging; **GMV**: Grey matter volume; **HAROLD**: Hemispheric asymmetry in older adults; **HDL**: High density lipoprotein; **IR**: Insulin resistance; **IWG**: International Working Group; **LDL**: Low density lipoprotein; **LOAD**: Late-onset Alzheimer's Disease; **MCI**: Mild cognitive impairment; **MD**: Mean diffusivity; **MMSE**: Mini-mental State Examination; **MNI**: Montreal Neurological Institute; **MRI**: Magnetic resonance imaging; **MTL**: Medial temporal lobe; **NIA-AA**: National Institute on Aging and Alzheimer's Association; **NFT**: Neurofibrillary tangles; **PASL**: Pulsed arterial spin labelling; **pCASL**: Pseudo-continuous arterial spin labelling; **PET**: Positron emission tomography; **PFC**: Prefrontal cortex; **PiB**: ¹¹C Pittsburgh Compound B; **rCBF**: Regional cerebral blood flow; **RD**: Radial diffusivity; **rs-fMRI**: Resting-state functional magnetic resonance imaging; **SPECT**: Single photon emission tomography; **TBSS**: Tract Based Spatial Statistics; **TDP-43**: Transactive response DNA binding protein 43; **TIV**: Total intracranial volume; **VBM**: Voxel based morphometry; **VLDL**: Very low density lipoprotein; **WC**: Waist circumference; **WMH**: White matter hyperintensities; **WMI**: White Matter Integrity

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Chapter 1: An introduction to the disease

Alzheimer's Disease (AD) is currently one of the leading causes of dementia that has led to a significant increase in the burden on the healthcare budgets, especially in the Western world (Patterson, 2018; Prince et al., 2016). As of the 'World Alzheimer Report' published in 2018, there are fifty million people living with dementia worldwide, with an annual increase of roughly ten million new cases every year. Over the next twelve years, this number is expected to rise to eighty-two million. Moreover, AD accounts for 60-70% of all dementia cases (Patterson, 2018). This disease predominantly affects the older population and the global proportions of the ageing population have been rising in tandem with rates of AD incidence (Akushevich et al., 2013; Prince, 2015).

AD is a progressive neurodegenerative disorder that is characterised pathologically by a build-up of misfolded proteins namely, extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT) (Selkoe, 2015; Shoghi-Jadid et al., 2002). It manifests clinically with a significant decline in cognitive functions, with the most prominent deficits exhibited in the memory domain that worsen with disease progression (Buckner, 2004). It is characterised by progressive global and regional brain atrophy that is most pronounced in the medial temporal lobes (MTL) across various stages of the disease (Rusinek et al., 2004; Selkoe, 2015). This atrophy has largely been attributed to the neuropathological deposits observed in AD and also to vascular pathology seen in AD brains in the medial temporal lobe regions (Braak & Braak, 1997; Matsumoto et al., 2007). In addition to the consequences of neurodegeneration, AD patients also have brain vascular pathology such as white matter abnormalities and microinfarcts, that can reduce cerebral blood flow (CBF) (Strickland, 2018). Although AD patients often experience the accumulation of vascular pathology, it is unclear whether this accumulation is the result of pathological processes seen in AD, senescence of the vascular system or the presence of comorbidities (Rius-Pérez et al., 2018). The detriments resulting from this combination of pathologies can not only cause significant reductions in the quality of life of patients diagnosed with AD, but the disease can also affect the wellbeing of carers of such patients (Cho et al., 2016). Moreover, the presence of comorbidities that can increase vascular burden can increase the severity of the AD phenotype or even accelerate the rate of disease progression (Chuang et al., 2016; Hayden et al., 2006; Solomon et al., 2011).

The current literature reflects no definitive diagnostic criteria and effective treatments for early stages of AD. The available criteria cannot be used to diagnose definitive AD and the evidence base for available treatments is weak, except for established pathobiological criteria (Knopman, Petersen, & Jack, 2019). With the numbers of individuals diagnosed with AD and the increasing prevalence of the disease there is a need to explore research focussed on biomarker identification in order to facilitate the early detection of the disease and in the development of targeted treatments. Introducing primary prevention measures to alleviate the harmful effects of cardiovascular risk factors could aid in delaying the onset of AD dementia, helping reduce the additional burden from cardiovascular diseases in AD and improving AD prognosis (Kivipelto et al., 2013; Ngandu et al., 2015).

1.1 History

AD was discovered in April 1906 by Aloysius Alzheimer after observing a patient who was undergoing treatment at a mental asylum in Frankfurt. The 51-year old patient presented with peculiar behavioural symptoms, some of which included loss of memory of newly learnt information. Alzheimer studied the patient across their lifespan and then with the help of two Italian scientists, Alzheimer performed a *post mortem* examination of the patient's brain. He identified two types of pathological features, i.e. amyloid plaques and NFT, that are now recognised as the hallmarks of AD pathology (Alzheimer, Förstl, & Levy, 1991; Alzheimer, 1907). Seventy years later, the development of novel cognitive measures such as the Mini-Mental State Examination (MMSE) facilitated the testing of the degree of cognitive decline that serves as a proxy for measuring clinical disease severity even today (Andrews et al., 2019; Black et al., 2017; Folstein, Folstein, & McHugh, 1975). In later years, there was subsequent development of therapeutic drugs and diagnostic criteria that facilitated the detection of the disease in relatively early stages (Jack et al., 2016b; Kumar, Singh, & Ekavali, 2015; McKhann et al., 1984; McKhann et al., 2011).

One of the long-standing challenges in AD diagnosis has been screening patients in early disease stages as clinical presentation occurs several years after disease onset (Dubois et al., 2016a; Dubois et al., 2016b). Therefore, irreversible progression of structural, functional and neuropathological disease-related changes that that accumulate insidiously before the disease can be detected make AD a difficult disease to treat (Chen et al., 2001; Preische et al., 2019;

Rami et al., 2012; Tondelli et al., 2012). To add to this conundrum, by far, there is no known cure for AD and most of the approved treatments are largely symptomatic (Tan et al., 2018). Experts in the field also recommend the introduction of early lifestyle interventions and primary prevention measures whereby modifying lifestyle can significantly contribute toward improving quality of life and reducing the risk for all-cause dementia and AD (Kivipelto, Mangialasche, & Ngandu, 2018; Ngandu et al., 2015). Since the disease has gained popularity with increasing awareness and increasing incidence, there have been several changes to how AD has been categorised and numerous alterations to the diagnostic criteria through the years. However, to date, there is no known cure for AD and no definitive diagnostic criteria that can accurately predict AD diagnosis, apart from histopathological ones.

1.2 Risk factors

1.2.1 Non-modifiable risk factors

1.2.1.1 Age

Increasing age is the biggest non-modifiable risk factor for AD with age-related build up of cardiovascular burden and reducing efficiency of biological mechanisms (Herrup, 2010). To name a few, increasing age is associated with reduced synaptic plasticity, mitochondrial dysfunction, increased production of reactive oxidative species and inflammation, all of which increase AD risk and facilitate neurodegeneration (Currais, 2015; Hou et al., 2019; Jurk et al., 2014; Richter, 1995; Trifunovic & Larsson, 2008). Age-associated reductions in efficiency of neural networks and cognition have been highlighted through models such as the scaffolding theory of ageing and cognition and the HAROLD (Hemispheric asymmetry reduction in older adults) model (Cabeza, 2002; Park & Reuter-Lorenz, 2009). Ageing is also accompanied with the build of amyloid beta (A β) plaques and NFT, pathological depositions that are also found in AD and can increase AD risk (Lowe et al., 2018). Moreover, ageing is linked with blood brain barrier (BBB) dysfunction that can further aggravate the accumulation of AD pathology and neurodegenerative processes in addition to increasing AD risk (Farrall & Wardlaw, 2009; Zlokovic, 2011)

The clustering and accumulation of different cardiovascular risk factors over an individual's lifetime plays a role in modifying AD risk. The current trends in the world population leading

a primarily sedentary lifestyle, has boosted the prevalence of conditions such as type 2 diabetes (T2DM) and obesity, especially among the younger population (Cho et al., 2018b; Perichart-Perera et al., 2007; Raj, Sundaram, Paul, Deepa, & Kumar, 2007). Considering that the duration of risk factors would be higher for a younger age of onset of T2DM, obesity and hypertension, individuals diagnosed at a younger age tend to have worse risk profiles and clinical outcome trajectories compared to those individuals diagnosed later in life (Armstrong et al., 2005; Donnelly et al., 2018; Raškeliene et al., 2009; Steinarsson et al., 2018). Individuals with a longer duration of such conditions are also at a higher risk of microvascular and macrovascular complications that can contribute towards AD risk (Clark et al., 2017; De Jongh et al., 2004; Glowinska et al., 2003; Zoungas et al., 2014). Prevalence of cardiovascular risk factors at midlife rather than at late-life, particularly enhance dementia and AD risk in late life (Fitzpatrick et al., 2009; Kivipelto et al., 2005; Livingston et al., 2017; Whitmer et al., 2005).

Increasing age is also linked with changes in body fat composition that can modulate cardiovascular risk and therefore AD risk. Higher abdominal and visceral fat that is seen in ageing can be the root cause of systemic insulin resistance, metabolic dysfunction and glucose intolerance, which can significantly increase the risk for T2DM, hypertension and AD (Chuang et al., 2006; Pararasa, Bailey, & Griffiths, 2015; Silva et al., 2009; Wong, Janssen, & Ross, 2003). Higher body mass index (BMI) and waist circumference (WC) in midlife have previously been identified as risk factors for AD (Fitzpatrick et al., 2009; Pedditizi, Peters, Beckett, & ageing, 2016). On the other hand, older individuals tend to experience a reduction in lean body mass and an increase in body fat, especially in the abdominal area (Kuk et al., 2009; Kyle et al., 2001). Sarcopenia or muscle loss resulting from these changes in body composition can impair physical and cognitive function and increase AD risk (Brady, Straight, & Evans, 2014; Janssen, Heymsfield, & Ross, 2002; Ogawa et al., 2018; Sugimoto et al., 2016). Sarcopenia is highly prevalent in patients across different stages of AD and the prevalence is higher than in control participants indicating that there may be a reverse causal effect of loss of lean mass in AD pathogenesis (Burns et al., 2010; Ogawa et al., 2018). In this respect, weight loss has even been identified as a preclinical, non-cognitive marker of AD (Jimenez et al., 2017). Therefore, increasing age and changes in body fat composition across the lifetime can increase cardiovascular risk, in turn increasing AD risk.

Research has consistently shown that age has a detrimental effect on brain structure and function while simultaneously being one of the biggest risk factors for AD dementia (Park &

Reuter-Lorenz, 2009). AD, being a neurodegenerative disease, also makes significant alterations to brain structure and function (Kumar & Singh, 2015). Phylogenetically and ontogenetically grey matter structures that are the first to develop are more resistant to the effects of ageing than those brain regions that develop in the later stages of life. Starting from first to last, the hippocampus, the thalamus and the prefrontal cortex correspond to the three different levels of development, respectively (Kalpouzos et al., 2009). Since the prefrontal cortex was evolutionarily one of the more recent brain regions to develop, it is one of the first to degenerate in normal ageing (Pini et al., 2016). Another brain region susceptible to ageing effects is the hippocampus. While the hippocampus and thalamus were phylogenetically later in developing, ontogenetically they show early maturations in foetal brain development, which could also make them initial targets of neural damage in an individual's lifetime (Kalpouzos et al., 2009; Toga, Thompson, & Sowell, 2006). The development of the memory system that is heavily dependent on the hippocampus and its connections, follows the hierarchical maturation gradient of these neurons (Bachevalier & Vargha-Khadem, 2005). Therefore, the susceptibility of neurons in the hippocampus to ageing and AD and their consequent neurodegeneration could manifest as characteristic memory impairments seen in AD and ageing (Bachevalier & Vargha-Khadem, 2005). However, one distinguishing factor between ageing and AD is the neurodegeneration of the entorhinal cortex, which is more vulnerable to AD, with relative sparing seen in normal ageing (Small et al., 2011).

Of the brain regions that are affected in normal ageing, the hippocampus and the prefrontal brain regions also show impairments in AD across various disease stages. Brain regions other than the hippocampus and prefrontal cortex that undergo the highest amount of atrophy across the lifespan include the cerebellum and the caudate nucleus (Raz et al., 2005). The fact that both ageing and AD have some overlap in the areas that they affect and can also independently damage other brain regions could imply that the convergence of AD and ageing processes can have extensive detrimental effects on brain structure and function. In normal ageing, there usually is an anterior to posterior gradient of degeneration in grey matter and white matter, where white matter shows greater decline than grey matter (Giorgio et al., 2010; O'Sullivan et al., 2001; Pardo et al., 2007; Salat, Kaye, & Janowsky, 1999). However, there are studies that contest this anterior-to posterior pattern of decline in ageing (Bettcher, 2017). In contrast, a posterior to anterior pattern of decline is seen in AD. This observation highlights that ageing and AD might inflict damage in opposing directions that could potentially converge or overlap at a later stage (Park & Reuter-Lorenz, 2009; Wang et al., 2015a). This can reduce the total

amount of available brain reserve, which can potentially contribute toward increasing the risk for AD or even towards exacerbating disease symptoms. Similar to the rostro-caudal decline seen in grey matter structures in normal ageing, there also seems to be an anterior-to-posterior deterioration in the structural integrity of white matter, possibly due to the higher vulnerability of the frontal lobe to vascular damage (Head et al., 2004). This could be attributed to a variety of mechanisms associated with ageing, some of which include the accumulation of multiple vascular and neural insults over an individual's lifetime (especially in the frontal lobe) and increasing number of AD-related pathological depositions and alterations in brain connectivity (Jagust, 2013). This combination of pathological mechanisms can contribute toward the development of AD, making age one of the major risk factors for AD dementia.

Detrimental ageing effects could be explained as an ensuing response to varied mechanisms. Neural structures and function undergo age-related decline that can worsen cognitive function across a range of domains. However, individuals seem to cope well with these cognitive deficits despite accumulating substantial amounts of cerebral pathology as discovered *post mortem* (Mitchell et al., 2002). Park and Reuter-Lorenz propose that there is relative preservation of cognitive function due to compensatory neural reorganisation, termed as 'scaffolding' (Park & Reuter-Lorenz, 2009). Scaffolding refers to the recruitment of additional or substitute resources in the face of challenge such as age-related neural insults or whilst engaging in a complex task. It is the neuroplastic ability of the brain that helps individuals adapt to demanding circumstances (Goh & Park, 2009). During learning and practice, individuals tend to strengthen specific networks that become highly interconnected and specialised while performing specific tasks (Kelly & Garavan, 2005; Poldrack, 2000). Damage to these highly specialised networks or performing the same task under challenge requires the recruitment of these scaffolding networks to maintain a certain level of cognitive functioning (Park & Reuter-Lorenz, 2009). This property of the brain to adapt efficiently to performing tasks under a challenge is impaired in older adults.

In young adults, there is minimal usage of scaffolding networks unless performing a task in the face of challenge. Older adults recruit scaffolding networks even during simple tasks as there is a global decline in cognitive function and performing simple tasks becomes significantly harder with the available neural resources (Park & Reuter-Lorenz, 2009). One of the reasons for this observation of recruitment of additional resources could be due to increasing neural dedifferentiation with age. Dedifferentiation refers to the age-related reduction in efficiency of

specialised networks that are strengthened with practice (Chee et al., 2006). This dedifferentiation could partly be attributed to age-related reductions in neuroplastic mechanisms (Bondareff & Geinisman, 1976; Burke & Barnes, 2006). Dedifferentiation adheres to the HAROLD (hemispheric asymmetry reduction in older adults) model which posits that there is greater bilateral frontal activation among the elderly (Cabeza, 2002). This pattern of activation represents the utilisation of additional resources or ‘scaffolding’ in order to maintain a normal level of cognitive functioning. Therefore, there is a heavy reliance on neural scaffolding with increasing age, in order to maintain cognitive function. In the presence of AD pathology, there is a global loss in cognitive functions with severe deficits in particular domains such as memory (Selkoe, 2015). Pathological changes have a putative role in disrupting essential networks (such as the default mode network or DMN) underlying cognitive function (Badhwar et al., 2017; Mevel et al., 2011). Pathological depositions can also interrupt neuroplastic mechanisms that facilitate this ‘scaffolding’ (Knafo et al., 2009; Lanz, Carter, & Merchant, 2003). Thus, with heavy reliance on scaffolding and age-related decline in network efficiency, there can be profound detrimental effects on cognitive function in AD.

1.2.1.2 Sex

Sex can play a pivotal role in modifying AD risk due to differences between men and women in various aspects such as longevity, physiology, metabolism and hormones (Mauvais-Jarvis, 2018; Young et al., 1991). Females tend to live longer than men, which confers a higher AD risk to females as a factor of higher age (Brookmeyer, Gray, & Kawas, 1998; United Nations Department of Economic Affairs, 2015; section 1.2.1.1). This difference in longevity could be attributed to higher cardiovascular risk in men compared to women that may result in higher risk of mortality before progressing to AD in men (Janghorbani et al., 1993; Jousilahti et al., 1999). This risk of mortality is even higher in men carrying the APOE ϵ 4 allele (a risk factor for AD), which could be another explanation for the observed lower AD incidence in men (Rosvall et al., 2009). On the other hand, the sex difference in the risk for cardiovascular risk factors could be due to the beneficial effect of oestrogen on cardiovascular function via the modulation of endothelial cell mediated nitric oxide production in women (Caulin-Glaser et al., 1997; Hashimoto et al., 1995; Viridis et al., 2000). The difference in risk for cardiovascular disease could also, in part, be attributed to sex difference in body fat composition. In terms of body composition, women tend to have a lower skeletal muscle mass and higher fat mass compared to men of the same age, which can promote metabolic dysfunction, glucose

intolerance and insulin resistance in women in earlier decades of life (Lemieux et al., 1994). However, abdominal visceral fat tends to be higher in men than women, which can increase cardiovascular risk in men (Lemieux et al., 1994). Therefore, women may have a higher risk for AD than men due to higher average lifespans and longer durations of comorbidities that can increase AD risk.

Baseline sex differences in brain structure and function can also increase AD risk in women. Men tend to have higher brain reserve than women, which increases the age of onset for AD by increasing the capacity to sustain more pathology before clinical presentation becomes overt (Katzman et al., 1988; Perneczky et al., 2010; Wolf et al., 2004). Additionally, women are more prone to the detrimental effects of psychosocial factors than men due their high affinity for the cardiometabolic manifestations of psychosocial and occupational stress that also supplements the risk for T2DM (Heraclides et al., 2012; Norberg et al., 2007). The interaction and clustering between these factors at various stages of life can thus increase AD risk in women. A recent review suggested that another factor that could increase women's risk for AD might be related to their more limited reliance on hippocampal dependent strategies for memory due to the effects of sex hormones that make hippocampal structures more vulnerable to ageing processes, a hypothesis termed 'network fragility hypothesis' (Torromino, Maggi, & De Leonibus, 2020). More specifically, the authors propose that women are less reliant on the hippocampus-dependent memory network because this network is less stable due to oestrogens interfering with the synaptic and structural plasticity of the hippocampus (Torromino et al., 2020). Therefore, women are more susceptible to AD than man due to several physiological factors.

1.2.1.3 Genetics

Although most individuals are diagnosed with AD much later in life, a small proportion of this population can have early-onset AD (EOAD) as a result of inheriting the autosomal dominant gene mutation, which is also known as familial AD (Lanoiselee et al., 2017). Around 13% of the EOAD cases are familial due to genetic predisposition to the disease (Campion et al., 1999). Individuals having mutations in the genes that encode the beta amyloid precursor protein (APP) on chromosome 21, Presenilin-1 on chromosome 14 and Presenilin-2 on chromosome 1 are at a risk of familial AD (Lanoiselee et al., 2017). The Apolipoprotein (APOE) gene has also been identified as a major risk factor for sporadic AD or late-onset AD (LOAD). The APOE gene has three variants namely the $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ alleles. The APOE $\epsilon 2$ isoform appears to be

protective against AD (Escott-Price et al., 2019; Levy-Lahad & Bird, 1996). On the other hand, research has shown a strong association between possessing the APOE ϵ 4 isoform and sporadic or LOAD, which can also reduce the age of onset by seven to nine years in LOAD (Jack, 2016a; Levy-Lahad & Bird, 1996). Downstream mechanisms of APOE ϵ 4 can also facilitate the deposition of amyloid plaques and NFTs (Lin et al., 2018). This pathological accumulation that is evident in the MTL structures which could likely contribute toward poor performance on tasks of memory and its accelerated decline in carriers compared to non-carriers (Caselli et al., 2009; Wolk, Dickerson & ADNI, 2010).

The APOE protein is involved in several biochemical processes that could modulate AD risk. It facilitates lipid metabolism that is essential to the integrity, growth and maintenance of neurons (Huang & Mahley, 2014). One of these lipids is cholesterol and different isoforms of APOE have different binding affinities for low density lipoprotein (LDL) cholesterol. The ϵ 4 isoform has the highest binding affinity with decreasing binding affinity seen in the ϵ 3 and ϵ 2 isoforms, in that order (Malloy et al., 2004). This could provide evidence for the ‘protective’ factor of the ϵ 2 isoform against AD. APOE ϵ 4 carriers have inherently high circulating cholesterol levels (Eichner et al., 1993; Notkola et al., 1998). Although it is logical to assume that elevated serum cholesterol would elevate cerebral cholesterol levels, evidence indicates that cerebral cholesterol levels are not affected by serum cholesterol (Dietschy & Turley, 2001; Hooijmans et al., 2007a). Instead, elevated serum cholesterol could promote processes such as atherosclerosis, which can in turn reduce CBF and increase AD risk (Beeri, et al., 2006a). In the past, presence of the APOE ϵ 4 allele has also been associated with unexplained weight loss in AD patients who are carriers, with a more pronounced effect in women (Vanhanen et al., 2001). In contrast, obese APOE ϵ 4 carriers showed lower progression of cognitive decline, improved cognitive performance and lower amyloid load compared to non-carriers (Blautzik et al., 2018). Therefore, the APOE gene can significantly alter cardiovascular and AD risk, suggesting ways in which the presence of cardiovascular comorbidities could potentially contribute towards AD.

1.2.2 Modifiable risk factors

1.2.2.1 Cardiovascular risk factors

A large number of modifiable cardiovascular risk factors have been identified as risk factors for AD which include obesity, T2DM, hypertension and metabolic syndrome (Profenno, Porsteinsson & Faraone, 2010; Vanhanen et al., 2006; Whitmer et al., 2005). According to the vascular dysfunction hypothesis for AD, vascular dysfunction can be a contributor towards neurodegeneration and the build-up of AD pathology (Zlokovic, 2011). Vascular dysfunction is an observed downstream pathophysiological mechanism that is manifested in such cardiovascular risk factors (Di Marco et al., 2015; Lang et al., 2019; Zlokovic, 2011). Given the modifiable nature of cardiovascular risk factors such as obesity, hypertension and T2DM it is important that measures are taken to mitigate the prevalence of such risk factors to reduce AD risk in healthy individuals and to improve AD prognosis in diseased individuals (Ngandu et al., 2015). These measures are crucial on account of the irreversible nature of the pathological cascade initiated by these factors and the prolonged asymptomatic period during which these irreversible changes can increase AD risk (Ammirati et al., 2017; Friedman et al., 2014). A more detailed explanation of how these modifiable cardiovascular risk factors can increase AD risk will be provided later in Chapter 2, section 2.2.2 of this thesis.

1.2.2.2 Psychosocial factors

Social activities and associated mental stimulation can reduce the risk for cognitive decline and are also associated with reduced risk of AD (Kuiper et al., 2015; Wang et al., 2002b). Work in animals has highlighted the importance of social activity in reducing the risk for cognitive decline and amyloid accumulation (Cracchiolo et al., 2007). These findings were supported by a study in which lonely individuals were twice as likely to develop AD and experienced a more rapid cognitive decline than individuals who were not lonely, although loneliness was not associated with increased AD pathology (Wilson et al., 2007). A different study showed that feelings of loneliness rather than physical isolation could be a risk factor for dementia and could indicate the beginnings of prodromal stages (Holwerda et al., 2014). Therefore, perceptions of loneliness seem to increase dementia risk rather than physical social isolation. This theory is lent support from a study on social cognition, which is defined as the processes used by an individual to perceive themselves and others (Beer & Ochsner, 2006). In this study by Verdon and colleagues, early impairment in social cognition is seen in the prodromal stages

of AD (Verdon et al., 2007). Impairment in social cognition could also have a reverse causal effect where social cognition could impair abilities to maintain social relationships, which could in turn result in increased perceived loneliness and reduced social interaction and therefore increase AD risk (Meltzer et al., 2013).

1.2.2.3 Education

Number of years in education can greatly modulate the risk for cognitive decline in AD, especially through its beneficial effect on cognitive function (Farmer et al., Regier, 1995; Stern et al., 1994). Educational attainment can contribute toward building a higher cognitive reserve, which refers to the brain's ability to adapt to pathology and insults (Stern et al., 2018). Although higher educational attainment does not attenuate the degree of pathological accumulations or neural insults, the clinical severity of dementia is reduced, possibly due to higher cognitive reserve (Brayne et al., 2010). Several studies and theoretical models such as the scaffolding theory of ageing and cognition, support the notion that higher educational attainment can reduce the risk for AD (Ott et al., 1995; Park & Reuter-Lorenz, 2009, section 1.2.1.1, Para 6 & 7). However, evidence also indicates faster rates of cognitive decline in individuals diagnosed with AD with higher educational attainment, specifically in domains of executive function and memory (Scarmeas et al., 2006). This could possibly be explained by the loss of the protective effect of higher educational attainment in later disease stages where AD neuropathological accumulations overpower this effect (Koepsell et al., 2008). It is also possible that this rapid decline could be attributed to the reduced mental stimulation following retirement or similar gaps in occupations that are cognitively demanding (Clouston & Denier 2017). On the other hand, lower education levels are associated with a higher occurrence of cardiovascular risk factors that can increase the risk for AD through unhealthy lifestyles and habits that are linked with lower educational attainment (Hoeymans et al., 1996; Panagiotakos et al., 2004). Therefore, education can significantly modulate the risk for AD.

1.2.2.4 Socioeconomic status

Higher prevalence of cardiovascular risk factors is also seen among individuals that have a lower socioeconomic status who also tend to have lower years of education, all of which contribute toward increased AD risk (Cerin & Leslie, 2008; Kestilä et al., 2012; Sattler et al., 2012). Individuals belonging to lower socioeconomic classes tend to lead unhealthier lifestyles

due to attitudes and beliefs that could contribute towards poorer behavioural choices (Wardle & Steptoe, 2003). Other factors such as hardship to support themselves and family and the lower availability of opportunities to lead a healthier lifestyle compared to individuals belonging to higher socioeconomic classes, could also contribute toward poor lifestyle choices in such individuals that can in turn increase the risk for cardiovascular risk factors (Wardle & Steptoe, 2003). Higher prevalence of cardiovascular risk factors inadvertently increases the risk for AD and thus lower socioeconomic class could be a factor in increasing AD risk (Luchsinger et al., 2005, section 2.2.2). Additionally, indulgence in leisure time physical activity is higher in individuals belonging to a higher socioeconomic class as such activities are more accessible and affordable to such individuals, which reduces AD risk (Beenackers et al., 2012; Cerin et al., 2008; Lindström, Hanson & Östergren, 2001; Sattler et al., 2012). This could in part be attributed to the contribution of leisure time physical activity toward cognitive reserve (Stern et al., 2018). As indicated previously, higher levels of physical activity, including leisure time activity can significantly reduce cardiovascular risk and risk for AD (Giada et al., 2008; Rovio et al., 2005; Scarmeas et al., 2009). Therefore, the disparity in socioeconomic status could contribute toward cardiovascular risk and therefore AD risk (Hoeymans et al., 1996).

1.2.2.5 Depression

There is a reverse causality between AD risk and depression where depression can increase risk for AD and the development of depressive symptoms is seen in the course of the disease (Barnes et al., 2006; Brendel et al., 2015; Chilovi et al., 2009; Ryu et al., 2017). Depression in early disease stages could accelerate disease progression as shown by studies where depressed MCI patients developed dementia earlier than MCI patients who did not have depression (Brendel et al., 2015; Chilovi et al., 2009). Depression shares several pathophysiological mechanisms with AD, some of which include the accumulation of AD pathology. Studies have shown that worsening anxiety and depressive symptoms are associated with increasing deposition of Amyloid Beta ($A\beta$), the main component of amyloid plaques that are observed in AD (Donovan et al., 2018; Wu et al., 2014). This increasing accumulation could be attributed to impaired metabolism of $A\beta$ observed in depressed individuals indicating how the onset of depression could increase AD risk from a very early stage (Baba et al., 2012). The inverse is also true where higher levels of plasma $A\beta$ predicted the onset of late life depression and conversion to AD in older adults (Blasko et al., 2010; Direk et al., 2013). Both these studies

also proposed that high levels of A β at baseline in addition to depressive symptoms observed in older individuals is indicative of prodromal AD (Blasko et al., 2010; Direk et al., 2013). Comorbid depression in AD is also associated with a higher load of tau pathology (Rapp et al., 2008). Therefore, neuropsychiatric symptoms such as depression could be indicative of AD in its preclinical stages and increased AD risk could be associated with long durations of depression.

According to the ‘vascular depression’ hypothesis, ischaemic lesions seen in prefrontal brain areas that manifest as deficits in attention and executive function can predispose individuals to depressive symptoms (Alexopoulos et al., 1997). Additionally, depression itself is associated with the increased risk of developing cardiovascular diseases (Penninx et al., 2001; Van der Kooy et al., 2007). Patients with depression show higher loads of vascular pathology than patients without depression that can contribute toward cognitive decline and heightened AD risk (Diniz et al., 2013; Salo et al., 2019; Yatawara et al., 2019). This association might vary with the type of depression where late-onset depression increases AD risk whereas recurrent depression could be attributed to increased risk for vascular dementia (Barnes et al., 2012). It is possible that depressive symptoms could be aggravated in AD via its modulation of the cholinergic and serotonergic systems that can further increase AD risk (Cummings & Kaufer, 1996; Wisniewski, 2019).

1.3 AD: Clinical presentation

AD is a neurodegenerative condition that is accompanied with a range of cognitive deficits, with the most severe impairment observed in the memory domain (Albert et al., 2011; Grober et al., 2008). Other cognitive deficits may include deficits in visuospatial attention, executive function and language (Albert et al., 2011; Grober et al., 2008). Most cases of AD (95%) are sporadic in nature, that is, the disease develops without a family history of AD, while only 5% of all AD cases can be considered ‘familial AD with an autosomal dominant inheritance’ (Piaceri, Nacmias, & Sorbi, 2013). AD can be divided into two types, namely early onset AD (EOAD) and late onset AD (LOAD), where in the former, presentation of symptoms occurs below the age of 60 years and in the latter, the presentation of symptoms occurs after the age of 60 years (Bateman et al., 2011; Joubert et al., 2016). Both types of AD share identical neuropathological features and diagnostic criteria (McKhann et al., 1984; McKhann et al., 2011). In the sporadic form of the disease, both EOAD and LOAD patients show a gradual and

severe decline in episodic memory along with grey matter atrophy beginning in the MTL regions before spreading to the rest of the cortex (Bateman et al., 2011; Kinnunen et al., 2018). Although both types of sporadic AD predominantly display an amnesic pattern (deficits in the memory domain), EOAD patients tend to exhibit more atypical symptoms and tend to have a more rapidly declining clinical presentation (Panegyres & Chen, 2013). More specific to the memory domain, LOAD patients show more severe impairment of semantic memory compared to EOAD patients (Joubert et al., 2016). For the purpose of the current thesis, the focus will be on patient populations with sporadic AD.

1.3.1 Mild Cognitive Impairment (MCI)

Mild cognitive impairment (MCI) or minor neurocognitive disorder refers to the transitional stage between a definitive disease diagnosis and normal cognitive functioning (American Psychiatric Association, 2013). ‘Mild cognitive impairment or MCI’ is used as an umbrella term to refer to the transitional stage that precedes a variety of neurodegenerative disorders. In this stage, patients with MCI due to AD present with mild memory impairments in isolation or along with mild deficits in other cognitive domains (Albert et al., 2011; Petersen et al., 1999). Individuals are generally able to manage activities of daily living in this stage. The diagnostic criteria for classifying patients as MCI include memory complaints with a gradual onset, excluding other disorders that could lead to an MCI diagnosis with adequate tests and volumetric magnetic resonance imaging (MRI) measurements of the hippocampus (Petersen et al., 1999). The clinical subcategories of MCI are as follows, amnesic single domain, amnesic multiple domain, non-amnesic multiple domain and non-amnesic single domain MCI. All four subtypes of MCI are likely to progress to AD dementia. However, amnesic MCI is most likely to have an AD aetiology (Beal, Lang, & Ludolph, 2005).

1.3.2 AD Dementia (ADD)

With disease progressions, MCI patients with an AD aetiology can progress to AD dementia (Albert et al., 2011). According to the diagnostic and statistical manual 5 (DSM-V) criteria, ‘‘dementia is classed as a major neurocognitive disorder, which is defined as having significant deficits in one or more cognitive domains that interfere with an individual’s ability to perform tasks of daily living,’’ (American Psychiatric Association, 2013). In addition to exhibiting progressive impairments in episodic and semantic memory, AD patients who

progress to dementia also exhibit more severe detriments in cognition in other domains such as executive function (Albert et al., 2011).

1.3.3 Atypical presentations/ Clinical AD variants

AD can also present in atypical forms where the focal effect of the disease could be on brain regions and cognitive functions that are not typically affected by AD (Murray et al., 2011).

1.3.3.1 Posterior variant: Posterior cortical atrophy

The posterior variant of AD presents as posterior cortical atrophy and is typically characterised by a progressive decline in visual processing with an insidious onset (Mendez et al., 2002). This is accompanied with marked progressive atrophy of the parieto-occipital areas that progresses to temporal areas with disease progression (Benson, Davis, & Snyder, 1988; Firth et al., 2019; Tang-Wai et al., 2004). Additionally, AD pathology has been identified as one of the major causes of posterior cortical atrophy (Tang-Wai et al., 2004). This was highlighted in a neuropathological study of 40 cases of posterior cortical atrophy, where AD was identified as the primary cause of the disease with prominent pathological depositions found in the occipital and parietal regions (Tang-Wai et al., 2004). These patients present with an insidious onset of visual deficits in the absence of ocular disease, with relative preservation of episodic memory in early stages that declines in later stages (Whitwell et al., 2007). Other deficits observed in posterior cortical atrophy include Balint's syndrome and Gerstmann's syndrome (McMonagle et al., 2006; Mendez et al., 2002; Tang-Wai et al., 2004). Posterior cortical atrophy can affect both dorsal and ventral visual streams, with the dorsal stream being more commonly affected (McMonagle et al., 2006; Tsai et al., 2011).

1.3.3.2 Logopenic variant: Primary Progressive Aphasia

Another clinical variant of AD is the logopenic variant of primary progressive aphasia, which is one of the three variants of primary progressive aphasia (non-fluent/agrammatic variant, semantic variant and logopenic variant) (Ahmed et al., 2012). Similar to the posterior variant, AD pathology is the most common cause of the logopenic variant of primary progressive aphasia and deficits are observed in the phonological loop that could be attributed to temporoparietal neurodegeneration and AD pathological depositions (Giannini et al., 2016; Josephs et al., 2013; Mesulam et al., 2008; Rabinovici et al., 2008). This syndrome is typically

characterised by a prominent language deficit that has an insidious onset with a progressive impairment in language functions (Gorno-Tempini et al., 2011; Mesulam, 2001). The deficit in language functions could influence other cognitive domains such as memory. In a study by Win and colleagues, although MTL subfields were relatively preserved in patients with the logopenic variant of primary progressive aphasia, these patients presented with an episodic memory deficit, which is generally seen in typical AD (Win et al., 2017). However, these deficits were attributed to impaired lexical abilities rather than hippocampus-mediated episodic memory deficits (Win et al., 2017).

1.3.3.3 Frontal Variant

The frontal variant of AD shows focal neuropathological deposition and cognitive dysfunction associated with the frontal lobe (Johnson et al., 1999). As a result, these patients tend to exhibit predominant frontal symptoms such as deficits in attention and executive function (Blennerhassett et al., 2014; Johnson et al., 1999; Woodward, et al., 2010b). Patients with frontal variant AD also show deficits in memory that are similar to those seen in typical AD (Johnson et al., 1999). Therefore, AD patients with the frontal variant tend to present with cognitive profiles similar to patients with frontotemporal dementia, at disease onset (Woodward, et al., 2010b). A different study by the same authors showed that the presence of behavioural symptoms could be used to distinguish between the frontal variants of AD and frontotemporal dementia, where behavioural symptoms are seen in the latter (Woodward et al., 2010a). Compared to the other two variants, the frontal variant is a less common atypical presentation of AD (Lam et al., 2013).

1.3.4 Cognitive deficits

AD is accompanied by a variety of cognitive deficits. One of the initial symptoms seen in AD is impairments of episodic memory with anterograde amnesia (Weintraub, Wicklund, & Salmon, 2012). These changes may start with simple tasks like the individual forgetting their keys and then progress to them failing to recall their home address. Deficits in visuospatial attention may also be presented in early stages of the disease, and these could ultimately lead to visual agnosia with worsening of the symptoms (Quental, Brucki, & Bueno, 2013). Patients also present with prominent semantic memory deficits and may present with language problems in which the patient finds it difficult to link the knowledge between different objects

(Weintraub et al., 2012). Patients also tend to show deficits in executive function, probably as a factor of age-related neural loss in the prefrontal brain regions (Perry & Hodges, 1999). AD patients may also show behavioural impairments, personality changes or neuropsychiatric symptoms such as apathy in prodromal stages (Ismail et al., 2016). The following sections will address typical cognitive and neuropsychiatric symptoms seen in AD.

1.3.4.1 Memory

Memory is a cognitive process that encodes an individual's experiences that can be retrieved at a different point in time. It is this construct that undergoes temporal decline with both, normal and pathological ageing although the degree and order of decline vary in the two processes (Budson & Price, 2005). Several memory systems seem to be relatively preserved in ageing, as opposed to episodic memory, which declines significantly with age (Nyberg & Pudas, 2018; Tromp, Dufour, Lithfous, Pebayle, & Despres, 2015). These deficits in episodic memory could be attributed to age-related volumetric reductions and functional deficits in neural tissue in areas such as the cingulate gyrus, prefrontal cortex and MTL structures that help in the integration of episodic memory (Tromp et al., 2015). Similarly, working memory is also associated with age-related decline due to volumetric reductions in these cerebral structures, especially the prefrontal cortex (Gazzaley et al., 2005; Prakash et al., 2009). As it has been established, memory systems are also vulnerable to AD pathology and different domains of memory are affected differently in the course of the disease. Initially presenting with a significant decline in episodic memory and deficits in working memory, there is also a notable decline in semantic memory in the early stages among AD patients (Gardini et al., 2013; Hodges & Patterson, 1995; Huntley & Howard, 2010; Mardh, Nagga, & Samuelsson, 2013; Venneri et al., 2018). Deficits in working memory have been associated with concomitant executive and attentional deficits seen in the disease (Belleville, Chertkow, & Gauthier, 2007).

In early AD, the greatest decline is seen in episodic memory and semantic memory (Mickes et al., 2007). Semantic memory decline can also be seen years before AD diagnosis (Blackwell et al., 2004; Papp et al., 2016; Wilson et al., 2011). Among these, the longitudinal study by Wilson and colleagues showed that in addition to an accelerated cognitive decline occurring 5-6 years before dementia diagnosis, a decline in semantic memory was the most prominent followed by working memory, compared to other cognitive domains (Wilson et al., 2011). This view was further supported by a review that highlighted the potential prognostic applications

of semantic memory tests in AD diagnosis (Venneri et al., 2018). Semantic memory and episodic memory tests could also be important in distinguishing between AD and frontotemporal dementia (Xie et al., 2010). Additionally, the semantic memory network is more left lateralised with overlapping areas with the language network (Binder et al., 2009). A similar preference for episodic memory is seen in left temporal lobe regions (Molinuevo et al., 2011). This lateralisation of memory functions and the stark memory deficit seen in AD makes the left cerebral hemisphere more vulnerable to the disease. Although episodic memory is one of the prominent and early presentations in AD, a large body of evidence suggests that it is not specific to the disease (Brooks, Iverson, & White, 2007; Schmid et al., 2013). Episodic memory decline in the disease is characterised by an insidious and progressive onset and has roots in MTL structures that degenerate in AD (Gallagher & Koh, 2011; McKhann et al., 2011). In the past, studies have shown that episodic memory impairments appear long before semantic memory impairments in AD (Giannakopoulos et al., 2009). However, findings from other studies contest this view and show that semantic memory decline is observed before a decline in episodic memory (Amieva et al., 2008; Wilson et al., 2011).

1.3.4.2 Executive function and attention

Higher order cognitive functions that enable an individual to plan and choose appropriate sequences of performing goal-directed tasks are coined as ‘executive functions’ (Jurado & Rosselli, 2007; Lezak et al., 2004). Executive function and attention have been closely linked and disorders pertaining to these cognitive domains have been associated with frontal lobe dysfunction (Alvarez & Emory, 2006). There is a gradual age-related decline in executive function, possibly due to the changing patterns of frontal lobe activation and structural integrity as proposed by the Hemispheric asymmetry reduction in older adults or ‘HAROLD’ model of ageing (Cabeza, 2002, section 1.2.1.1, Para 7). Executive function decline is seen in AD and is worse than that of cognitively normal age-matched adults (Kirova, Bays, & Lagalwar, 2015). A possible reason for this stark difference might be due to the additional age-related detriments in executive function and frontal lobe structure (section 1.2.1.1, Para 4).

It has been posited that executive function decline could be the by-product of impairments in working memory, as the latter is a predominant function of the prefrontal cortex (Perry & Hodges, 1999). Alternatively, impairments in working memory that are associated with lateral parietal lobe dysfunction, also seen in AD, could contribute toward deficits in executive

function (Bunge et al., 2000; Salmon et al., 1996). Working memory deficits are some of the prominent features seen in AD and could therefore contribute towards deficits observed in executive function (Stopford et al., 2012). The study by Stopford and colleagues showed that the deficits in attention and executive function seen in AD patients could be attributed to working memory functions drawing roots from the temporoparietal brain regions (Stopford et al., 2012). Although executive function deficits can appear early in the disease course, these are less pronounced than memory deficits in the initial stages and become more pronounced later in the disease course with progression of pathology and neurodegeneration in the frontal lobe (Baudic et al., 2006; Duarte et al., 2006; Harrison et al., 2019; Waltz et al., 2004). Degeneration of the prefrontal cortex in early disease stages could also manifest as executive deficits, which could be indicative of the frontal variant of AD (Guarino et al., 2018; Stopford et al., 2012, section 1.3.3.3).

1.3.4.3 Visuospatial processing

The ability to perceive a stimulus in space, to identify its location, to mentally manipulate spatial constructs and to integrate logical spatial frameworks is classed under visuospatial processing (Geldmacher, 2003; Rubenstein & Rakic, 2013). Although visuospatial information is integrated across the frontal, temporal, parietal and occipital lobes, this cognitive function draws the majority of its inputs from the parietal lobe (Zink et al., 2018). Due to an early impairment occurring in the structure and function of the parietal lobes in AD, almost a third of AD patients present with visuospatial deficits that worsen with time (Qi et al., 2010; Salimi et al., 2017; Tervo et al., 2007; Wang et al., 2009). The posterior variant of AD also involves presentation of visual processing deficits early in the disease course, which can be distinguished from typical AD with disease progression by monitoring change in cognitive profiles (section 1.3.3.1).

1.3.4.4 Language

Language functions apart from language production are relatively preserved in ageing, as semantic knowledge increases with age (Shafto & Tyler, 2014). Language deficits have been identified previously in AD and MCI patients as measured using tests of semantic processing (section 1.3.4.1, Para 2). Although language deficits can be seen early in the course of the disease, it is not certain that an individual with AD will present with problems in language

(Taler & Phillips, 2008). Language decline is not a common presentation in typical AD and this could be indicative of the presence of atypical forms of the disease such as the logopenic form or primary progressive aphasia (Foxe et al., 2016; Giannini et al., 2017, section 1.3.3.2). Problems in language could also interfere in the diagnostic process as a substantial number of cognitive tests are language based, and one should treat this with caution as the impairment may lie in the language domain as opposed to what the test actually measures.

1.3.4.5 Neuropsychiatric symptoms

Neuropsychiatric symptoms cause a significant reduction in the quality of life of AD patients and their caregivers. Their early presentation in the disease and its association with worsening cognitive symptoms has recently drawn some attention from the scientific community (Rosenberg et al., 2013; Vogel, Waldorff & Waldemar, 2010). Apathy is one of the predominant neuropsychiatric symptoms seen in AD (Craig et al., 2005). It has even been proclaimed as a predictor for conversion from cognitively normal to MCI and then transitioning from MCI to dementia (Guercio et al., 2015). The frequency of presentation of this symptom increases with disease severity, as is the case with agitation, another neuropsychiatric symptom commonly seen in AD (Lanctôt et al., 2017). Agitation in AD has been correlated with alterations within the structure and function of the salience and emotion regulation networks (Rosenberg, Nowrangi, & Lyketsos, 2015). Moreover, depressive symptoms are found in a substantial number of AD patients (Lanctôt et al., 2017). They might also be indicative of a more severe extent of damage exerted by underlying AD pathology (Holmes et al., 2003). Less common neuropsychiatric symptoms presented in AD include psychotic symptoms of delusions and hallucinations, where hallucinations are less frequent than delusions. Psychotic symptoms presented in AD are also starkly different from those presented in other diseases such as schizophrenia (Leroi et al., 2003). Other neuropsychiatric symptoms seen in AD include sleep disturbances (Lanctôt et al., 2017).

1.4 Pathophysiology

There has been considerable debate in the literature about the progression and initial presentation of pathological mechanisms seen in AD and there are several theories that try to highlight the underpinnings of the neurodegenerative processes that are observed in the disease.

1.4.1 The amyloid cascade hypothesis

According to ‘the amyloid cascade hypothesis’, A β is the main underlying cause of neurodegeneration and cognitive decline seen in AD (Hardy & Higgins, 1992). Amyloid plaque formation in AD results from an imbalance in the production and clearance of amyloid (Hardy & Higgins, 1992). The amyloid precursor protein (APP) is an important membrane protein that is modified by the actions of three proteases namely α -, β - and γ - secretases (Suh & Checler, 2002). APP is cleaved by β -secretase (BACE1) to generate a soluble version of APP (β -APPs) and a 99-residue COOH-terminal fragment (CT₉₉) which stays within the membrane. Subsequent aberrant proteolysis of the CT₉₉ by the γ -secretase results in the synthesis of the A β ₄₀ and A β ₄₂ peptides. Of these two, A β ₄₂ has a longer peptidic chain, is more hydrophobic compared to A β ₄₀ and is heavily implicated in amyloid plaque formation (Iwatsubo et al., 1994; Jarrett, Berger, & Lansbury, 1993). The mutations responsible for AD in APP that are located near the β -secretase cleavage site accelerate β -site proteolysis, in turn increasing production of the A β ₄₀ and A β ₄₂ peptides (Cai, Golde, & Younkin, 1993; Citron et al., 1992). Additionally, the mutations in APP located near the γ -site specifically increase A β ₄₂ secretion (Suzuki et al., 1994). Since A β ₄₂ is more hydrophobic of the two peptides, it is more amyloidogenic and thus more likely to form plaques. With increasing accumulation of this peptide and impaired clearance, the incremental effects of these reactions lead to the accumulation of A β plaques in the brain (Hamley, 2012). However, the assumption that there is a linear causality between AD and amyloid accumulation needs to be reviewed due to the multivariate nature of AD pathogenesis.

A β accumulation begins decades prior to the presentation of clinical symptoms. Initially, amyloid deposits begin to appear in adulthood in small patches in the basal neocortex and in poorly myelinated areas of the temporal lobe (Fig 1.1). These depositions then multiply and spread to neighbouring areas of the neocortex and the hippocampal formation. With disease progression, these deposits are eventually found throughout the cortex (Braak & Braak, 1997). Nonetheless, these do not correlate with clinical symptoms (Furst et al., 2012; Giacobini & Gold, 2013; Jung et al., 2016). These plaques are also found in brains of the elderly (especially above the age of 80 years), as there are age-related accumulations of amyloid plaques in the brain. However, these are present far less in number in the brain of a healthy individual compared to the brain of an AD patient (Rowe et al., 2007). The amyloid hypothesis has been heavily debated and its exact contribution toward AD pathophysiology remains obscure.

Albeit, quite a few contemporary treatments, therapies and diagnostic criteria are centred around amyloid clearance (section 1.7).

1.4.1.1 Cerebral amyloid angiopathy

Cerebral amyloid angiopathy refers to the accumulation of amyloid fibrils within the walls of cerebral blood vessels. This kind of pathology has been found in 55-59% of patients with all-cause dementia and can significantly contribute toward increasing the risk for thrombolysis-related intracranial haemorrhage, microbleeds and a consequent reduction in CBF, while simultaneously contributing toward cognitive decline (Biffi & Greenberg, 2011; Fotiadis et al., 2016; Keage et al., 2009; McCarron & Nicoll, 2004). Considering that both cerebral amyloid angiopathy and parenchymal amyloid depositions involve abnormal aggregation of A β , a possible common link between these two processes could be amyloid clearance. Amyloid clearance pathways include transport across the BBB, enzymatic degradation, phagocytosis and drainage from the perivascular interstitial fluid (Tarasoff-Conway et al., 2015). Of these clearance processes, ineffective drainage of A β via the perivascular route seems to create the most favourable conditions for cerebral amyloid angiopathy accumulation (Greenberg et al., 2020). Cerebral amyloid angiopathy predominantly occurs in small arteries and capillaries, sparing the larger intracranial arteries and is rarely found in the extracranial arteries (Vinters, Wang, & Secor, 1996). Topographically, cerebral amyloid angiopathy affects the occipital lobe most frequently and severely, followed by the rest of the lobes (Biffi & Greenberg, 2011). In contrast, deep brain grey matter, white matter and the brainstem are relatively devoid of cerebral amyloid angiopathy (Thal et al., 2003). However, this pathology seems to be widespread across the neocortex and the hippocampus and is also highly correlated with severe AD pathology (Greenberg et al., 2020). Moreover, the obstruction of blood flow created by cerebral amyloid angiopathy, resulting in hypoperfusion, could significantly contribute toward increasing AD severity (Daulatzai, 2017).

1.4.2 The neuronal cytoskeletal degradation hypothesis

Another neuropathological mechanism that is characteristic of AD occurs alongside the formation of amyloid plaques. This involves the formation of NFT, which are composed of paired helical filaments of hyperphosphorylated tau (Lee, Goedert, & Trojanowski, 2001). Tau is a microtubule associated protein and has been associated with various functions such as

transportation along neuronal axons and stabilizing microtubules that compose neuronal cytoskeletons (Lee et al., 2001). It has six main isoforms, out of which varying ratios of the 3R and 4R isoforms are responsible for tau-related neurodegeneration (Goedert, 1989). Hyperphosphorylation of tau can occur via the modulatory actions of kinases such as cyclin-dependent kinase 5, glycogen synthase kinase 3, the microtubule-affinity-regulating kinase and extracellular signal-regulated kinase 2 and the downregulation of certain phosphatases (Duan et al., 2012). This can consequently cause microtubules to depolymerize and therefore damage the neuronal cytoskeleton and trigger cell apoptosis (Duan et al., 2012).

In the initial stages, NFT start forming in the transentorhinal region in the temporal lobe (Fig 1.1.). These tangles then gradually spread to other limbic and association areas, possibly via transgene expression in neurons located downstream of the pathology (Braak & Braak, 1997; Duan et al., 2012). The pathology then gradually spreads to other areas of the neocortex (Braak & Braak, 1997). In the past, NFT pathology has been found in the normal ageing brain, but again far less in number compared to an AD patient (Guillozet et al., 2003). More recent studies have shown that tau pathology can spread along highly functionally and structurally connected networks that coincide with the impaired networks in AD, such as the default mode network (DMN) (Cope et al., 2018; Hoenig et al., 2018). The progression of tau pathology (as observed using Braak staging) from the entorhinal cortex and MTL to other limbic regions appears to spread along the anatomical connections between these brain areas. Additionally, this pattern of tau progression is also highly correlated with clinical manifestations of cognitive symptoms compared to the progression of amyloid deposition (Giacobini & Gold, 2013). Although amyloid plaques and NFT are both the hallmarks of AD, the contributions of these pathological processes toward cognitive impairment are still disputed.

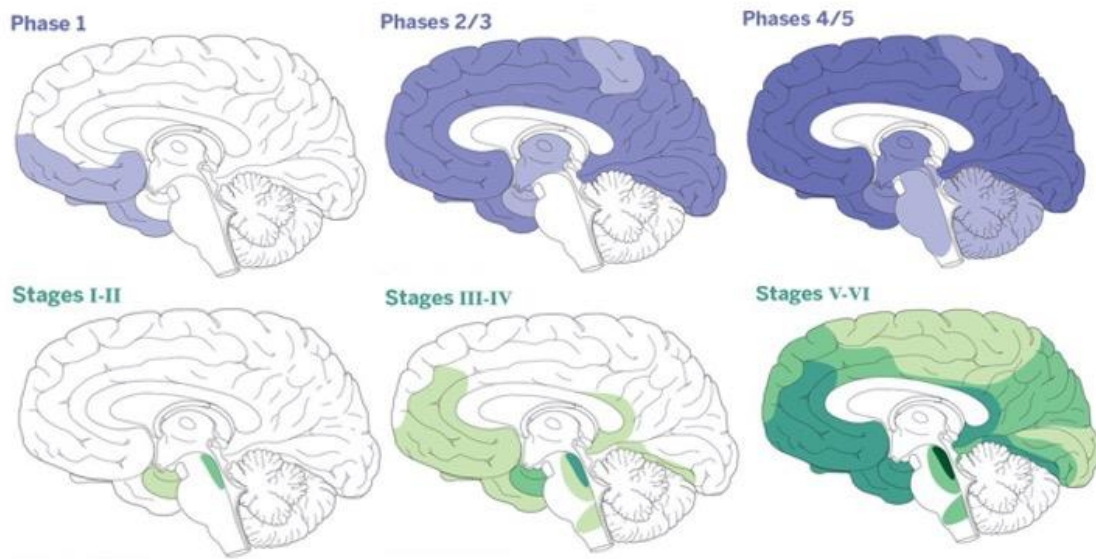


Figure 1.1 *Stages of the progression of AD pathology*

Top row: Pathological progression of A β plaques is highlighted in blue where the accumulation begins in the basal forebrain, temporal and orbitofrontal areas before spreading to other brain regions. Bottom row: Braak staging of the progression of tau pathology (NFT) is depicted in green. Tau pathology begins in the medial temporal areas before progressing to anatomically connected brain regions and then further progressing to accumulate in the neocortex, with disease progression. Adapted with permission from (Goedert, 2015). Please refer to Appendix A for more details about image permissions.

1.4.3 Cholinergic hypothesis

AD is also characterised by a significant reduction in the production and circulation of acetylcholine (that is synthesised by the enzyme choline acetyltransferase) (Davies & Maloney, 1976; Perry et al., 1977; White et al., 1977; Wilcock et al., 1982). There is a marked reduction of cholinergic neurons observed in the basal forebrain (specifically the nucleus basalis of Meynert) in AD (Shinotoh et al., 2000; Teipel et al., 2005). Research suggests that this deficit becomes more apparent in the dementia stage and that there could be differential effects on cholinergic action depending on diagnostic status or severity of the disease (Davis et al., 1999; Ikonovic et al., 2003; Iyo et al., 1997). There may also be an upregulation of cholinergic activity as a compensatory mechanism in response to a loss of connections between the hippocampus and the entorhinal cortex in early disease stages (DeKosky et al., 2002; Ikonovic et al., 2003).

In the past, the depletion of cholinergic neurons in AD has been associated with cognitive decline (Bohnen et al., 2005; Perry et al., 1978; Shinotoh et al., 2000). The basal forebrain cholinergic neurons send projections to brain regions involved in memory function (such as the hippocampus), which are also vulnerable to AD pathology (Braak & Braak, 1991; Hedreen et al., 1984; Mesulam et al., 1983; Perry et al., 1984). This could potentially explain the progressive memory decline seen in AD. However, a PET study on mild to moderate AD patients showed that acetylcholinesterase activity was associated with performance on tests of attention and working memory rather than primary tests of memory (Bohnen et al., 2005). Therefore, disruptions in cholinergic transmission could result in varied changes in cognition and might not be the root cause of memory deficits seen in early AD. This was supported by findings from a different study that showed that short term memory deficits in MCI patients are not explained by cholinergic dysfunction (Ikonovic et al., 2003). Disruptions in cholinergic action and transmission have also been associated with the formation of A β pathology via the modulation of APP (Mesulam, 1986; Moran, Mufson, & Gomez-Ramos, 1993; Racchi et al., 2001). The fact that A β accumulation begins near the basal forebrain, (one of the primary regions involved in cholinergic transmission), appears to suggest that the depletion of cholinergic neurons and A β pathological formation in AD could be interlinked (Baker-Nigh et al., 2015; Teipel et al., 2014).

1.4.4 Failure of plasticity hypothesis

A number of dysfunctional processes in AD can alter synaptic plasticity and therefore cause a reduction in the brain's neuroplastic abilities to cope with damage dealt by age and disease-related effects. According to the synaptic A β hypothesis, non-fibrillar A β can have adverse effects at the synapse and influence synaptic plasticity (Ondrejcek et al., 2010; Walsh et al., 2002; Wang et al., 2002a). This hypothesis has gained momentum after the much-debated amyloid hypothesis which claims amyloid as one of the main underlying causes of neurodegeneration and cognitive decline seen in AD (Ellis et al., 2013; Hardy & Higgins, 1992; Resnick et al., 2010; Selkoe, 1991). Although the role of amyloid pathology in neurodegeneration has been consistent, its role in cognitive decline has been disputed (Furst et al., 2012; Jung et al., 2016). Past work has shown that A β can disrupt actions of long-term potentiation, a process heavily implicated in learning and memory (Rowan et al., 2005; Wang et al., 2002a). Research also suggests that long term potentiation may be impaired even before the formation of AD pathology and the appearance of memory deficits (Jacobsen et al., 2006; Ma et al., 2010). This impairment could be due to the disruptions in synaptic functions that are caused by non-fibrillar amyloid or soluble A β oligomers (Lambert et al., 1998; Walsh et al., 2002). This notion is supported from findings from a previous study that showed that the accumulation of amyloid pathology did not correspond with deficits in neuropsychological measures while a loss in synaptic density did correlate with these measures (Terry et al., 1991). Therefore, non-fibrillar A β can produce neurotoxicity, inducing synaptic loss that can be detrimental to cognition while the accumulation of fibrillar amyloid could contribute toward neurodegeneration (section 1.4.4, Para 1). Moreover, the characteristic degeneration of the basal forebrain cholinergic system can also hamper neural plasticity (Conner, Chiba, & Tuszynski, 2005). Therefore, a reduction in inherent neuroplastic mechanisms resulting from dysfunctional processes seen in AD could be the initial signs of developing pathophysiology.

1.4.5 Retrogenesis: “Last in, first out” hypothesis

The retrogenesis hypothesis proposes that white matter degeneration seen in AD is the antithesis of myelogenesis (Reisberg et al., 1999). According to this ‘last in, first out’ model, neurons with large axonal diameters that were first myelinated in the neural developmental process (eg. motor neurons) are the last neurons to be affected in the neurodegenerative process (Stricker et al., 2009, section 1.1, Para 4). Conversely, neuronal pathways with smaller axonal

diameters that are myelinated later in life are severely affected in AD (Bartzokis, 2004). This could, in part, be attributed to the eccentric myelinating properties of oligodendrocytes in early neural development. Axons that were myelinated early in the neurodevelopmental process are generally myelinated by fewer oligodendrocytes, with some fibres being myelinated by as few as a single oligodendrocyte. On the other hand, a single oligodendrocyte that differentiates later in life is more likely to myelinate more than one axonal segment per cell (Amlien & Fjell, 2014). The natural age-related build-up of cardiovascular burden over one's lifetime and the accumulation of AD pathology is detrimental to oligodendrocytes (Cai & Xiao, 2016). Therefore, multiple neurons that are myelinated later in life by single oligodendrocytes are more susceptible to damage in the presence of these factors, where the 'last' neurons to be myelinated are the 'first out.'

The Wallerian degeneration hypothesis states that nerve fibres that suffer damage to their axonal segments are susceptible to neurodegeneration (Coleman, 2005; Stricker et al., 2009; Waller, 1850). It is possible that the susceptibility of oligodendrocytes to vascular burden and AD pathology could play a role in the retrogenesis hypothesis in the light of Wallerian degeneration (Coleman, 2005; Waller, 1850). Allocortical and mesocortical brain regions (that include structures such as the hippocampus and basal limbic regions) are some of the last areas to be myelinated and are therefore poorly myelinated, making them more susceptible to damage (Braak et al., 2000; Bartzokis, 2004). In AD, we see significant damage inflicted on structures housed in the allocortical and mesocortical regions (Braak et al., 2000). Damage to oligodendrocytes in these regions and consequent damage to the axons myelinated by them could indicate that the myelinating properties of oligodendrocytes could play a role in AD pathogenesis. Additionally, grey matter atrophy as a downstream effect of AD pathology and subsequent degeneration of the axons arising from damaged neurons could also be explained by Wallerian degeneration.

1.4.6 The vascular dysfunction hypothesis

It is possible that the neurodegenerative process in AD is initiated through the downstream effects of chronic hypoperfusion resulting from the effects of ageing and the build-up of cardiovascular burden over one's lifetime (Di Marco et al., 2015). A myriad of microvascular changes that are observed in chronic cerebral hypoperfusion can increase levels of neurotoxicity (Cai, Zhao, & Ratka, 2011; Kelleher & Soiza, 2013; Sanchez et al., 2013). A

simultaneous decrease in nutrient supply and higher exposure to toxicity, seen in hypoperfusion can damage neural structure (Menzies et al., 2017). Moreover, damage to the BBB has shown to reduce cerebral perfusion while simultaneously augmenting neurodegenerative processes. Research also claims that A β plaque and NFT accumulations could be the result of the downstream mechanisms of chronic cerebral hypoperfusion (Di Marco et al., 2015; Sun & Alkon, 2004).

The two-hit vascular hypothesis proposed by Zlokovic suggests that an initial insult or ‘first hit’ is inflicted due to damage to the cerebral microvasculature and BBB (Zlokovic, 2011). This ‘first hit’ can initiate a cascade of pathological mechanisms that can promote the accumulation AD pathology via the non-amyloidogenic pathway (Zlokovic, 2011). The ‘second hit’ consists of the accumulation of A β peptides (as a result of increased generation and impaired clearance of A β), which results in the release of vasotoxic and neurotoxic substrates that further add to the neurodegenerative process (Sweeney, Sagare, & Zlokovic, 2018). Hence, vascular dysfunction might be one of the underlying mechanisms of AD that can contribute to the neurodegenerative process.

1.4.6.1 Mechanisms Influencing Blood Perfusion in AD

Considering that some of the detrimental effects of AD seem to stem from increased vascular dysfunction, it is important to investigate the mechanisms underlying them. It is already known that AD patients present with vascular pathology and that AD has been known to have a vascular aetiology (Toledo et al., 2013). Nevertheless, it is unclear whether the formation of vascular pathology is directly associated with AD, whether the AD pathological cascade is initiated due to age-related and cardiovascular comorbidity-related mechanisms or whether AD and vascular pathology are concurrent processes that are merely additive that increase the likelihood of AD (Graham et al., 1996; Hofman et al., 1997a; Launer et al., 2008; Toledo et al., 2013). The following sections will discuss how vascular dysfunction could contribute toward neural injury at the microstructural level.

1.4.6.1.1 Microvascular: Blood Brain Barrier

The BBB is a cellular barrier that promotes the exchange of essential nutrients while blocking the transmission of pathogens in the human brain. Specialised mechanisms which are highly

expressed in the neural endothelium allow the BBB to mediate the transportation of large molecules such as proteins from the blood to the neural tissue. On account of the vascular dysfunction seen in AD, there is a disruption in the homeostatic balance of exchange across the BBB (Sweeney et al., 2018). The neurovascular unit is made up of pericytes, tight junction proteins, their molecules, adherent junctions and basement membrane proteins in the endothelium, that experience decreased tone as a consequence of vascular dysfunction mediated injury in AD (Nelson et al., 2016). Additionally, with increasing age and existing AD pathology, the number of pericytes gradually decreases over time (Erdő, Denes, & de Lange, 2017; Halliday et al., 2016). Pericytes are integral components in the formation and maintenance of the BBB. Lower pericyte numbers can reduce available tight junction proteins resulting in BBB breakdown (Ahmad et al., 2011). These alterations permit the leakage of numerous macromolecules into the brain parenchyma (Sweeney et al., 2018). The extravasation of these molecules results in the accumulation of superfluous proteins leading to detrimental downstream processes, namely cerebral oedema and blocking capillary blood flow (albumin and immunoglobulins), neurotoxicity and memory impairment (thrombin), neuronal injury (plasmin) and neurovascular damage (fibrin) (Zlokovic, 2011). With disease progression, there is extravasation of larger substrates across the BBB. The blood from the vessels can also result in the leakage of red blood corpuscles which increases the deposition of neurotoxic products that are generated as a by-product of haemoglobin breakdown (such as iron). These neurotoxic deposits produce reactive oxygen species that are again, detrimental to neural tissue (Sweeney et al., 2018). Prolonged extravasation as a consequence of BBB breakdown can thus initiate a cascade of events that can eventually result in neuronal death.

In AD, downstream mechanisms pertaining to BBB breakdown can also contribute toward neurodegeneration through vascular injury mediated mechanisms. One of these mechanisms is inefficient transportation of glucose across the BBB (Marco et al., 2015; Erickson & Banks, 2013). In the past, post-mortem studies on AD brains have shown a diminished proportion of GLUT1 transporters (Horwood & Davies, 1994; Kalaria & Harik, 1989). A reduction of GLUT1 transporters is also observed with the breakdown of the BBB, which can result in a loss in glucose supply to the brain tissue (Di Marco et al., 2015). There is conflicting research that highlights that the glucose transport impairment does not alter the intracerebral glucose metabolism rate (Friedland et al., 1989; Jagust et al., 1991). It is possible that mitochondrial dysfunction within the BBB endothelium could contribute to this impairment in glucose transport (Di Marco et al., 2015). Additionally, there are other mechanisms that could also

contribute toward the neurodegeneration seen in AD. Nitrous oxide is a regulatory molecule that mediates neurovascular homeostasis. There is a marked reduction in nitrous oxide concentrations in the human body with advancing age that can promote the build-up of oxidative stress, a reduction in CBF and impaired vasodilation, also observed in AD (Aliev et al., 2009). Both, oxidative stress and nitrous oxide reduction, are salient features of ageing and AD (Cahill-Smith & Li, 2014; Finkel & Holbrook, 2000). Increasing accumulations of cerebral amyloid pathology (as seen in ageing and AD) around cerebral microvasculature can increase the susceptibility of the BBB endothelium to oxidative damage (section 1.4.1.1). These mechanisms can also contribute toward chronic inflammation that can eventually lead to cell death (Di Marco et al., 2015). A lot of these mechanisms are inter-dependent, and the initiation of the pathological cascade can lead to the manifestation of all of the above mechanisms that eventually contribute toward AD pathogenesis (Di Marco et al., 2015).

1.4.6.1.2 Macrovascular: Hypoperfusion/Hypoxia

BBB dysfunction can have profound effects on rCBF and perfusion. Neurovascular coupling is a phenomenon that occurs when increased blood flow or metabolism is observed in regions displaying neuronal activity (Huneau, Benali, & Chabriat, 2015). Secondary arteries namely the pial and intracerebral arteries modulate regional changes in CBF as an effect of neurovascular coupling. Effective neurovascular coupling demands intact pial circulation, and adequate responses from the arterial walls (controlled by vascular smooth muscle cells) and pericytes to vasoactive stimuli (Bell et al., 2010; Iadecola, 2004; Peppiatt et al., 2006). Pericytes also regulate the diameter of brain capillaries which can block capillary flow during ischaemia (Peppiatt et al., 2006). Therefore, a lower number of pericytes (as seen in AD) could increase the chance of exposure to hypoxic conditions. Chronic hypoperfusion can have devastating effects on neural tissue. Transient hypoperfusion influences protein synthesis required for synaptic plasticity that mediates learning and memory functions (Iadecola, 2004). A further, more chronic reduction in rCBF can cause microvascular changes such as mitochondrial dysfunction, cerebral oedema, the accumulation of toxins and AD pathology and macrovascular changes such as white matter lesions and atherosclerosis (Zlokovic, 2011). In the past, animal studies have shown that CBF changes can aggravate the development of AD pathology, eliciting the fact that vascular dysfunction resulting in hypoperfusion can not only facilitate neurodegenerative mechanisms in AD but can also initiate a cascade of mechanisms that accelerates the AD pathological process (Di Marco et al., 2015).

In a nutshell, AD is a complex disease that results from a cascade of pathological mechanisms involving vascular dysfunction, build-up of AD pathology, the properties of the phylogenetic roots of neurons and neurodegeneration. These mechanisms can result in profound detriments to brain structure and function. It is important to understand how these mechanisms can alter the ageing brain and manifest as a clinical disease. The following sections (section 1.5; section 1.6), therefore, will explore the diagnostic criteria used to identify clinical AD and the typical macrostructural and functional changes associated with it.

1.5 Diagnostic criteria

There are several different diagnostic criteria that have been used in the past to classify individuals as having probable AD (Dubois et al., 2016). The use of the word ‘probable’ is on account of the dilemma of making a definitive AD diagnosis based on current criteria, as the diagnosis cannot be confirmed until after a histopathological examination post-mortem (Jonkman et al., 2019; Perl, 2010). However, evidence of cerebral AD pathology can be detected using molecular imaging (eg. Positron emission tomography or PET) and analysis of cerebrospinal fluid (CSF) (Blennow et al., 2015; Meredith Jr et al., 2013; Okamura et al., 2014). The current thesis uses The National Institute on Aging and Alzheimer’s Association (NIA-AA) criteria for AD dementia diagnosis, which states that “the patient must present with cognitive deficits in two or more domains along with an inability to perform tasks of daily living” (McKhann et al., 2011). This set of criteria proposes three classifications where biomarkers are available, namely preclinical AD, MCI due to AD and AD dementia (due to AD). In cases where biomarkers are unavailable, the criteria recommend a diagnosis based on the core clinical criteria. In addition to fulfilling the criteria for dementia diagnosis, the patient must fulfil the other clinical criteria for a diagnosis of probable AD. These criteria state that the disease must have a sudden onset with a progressive worsening of cognitive function. Initially, cognitive symptoms exhibited might have an amnesic presentation (failure to learn or recall newly acquired information) or a non-amnesic presentation that could include deficits in visuospatial processing, language or executive function. “Exclusion criteria for AD include the presence of cerebrovascular disease, prominent features of primary progressive aphasia (semantic variant), Lewy Body Dementia or Frontotemporal Dementia, neurological disease, use of cognition-altering medication and a non-neurological medical comorbidity,” (McKhann et al., 2011). With respect to biomarkers, individuals are classified into three stages of

preclinical AD as follows: Stage 1: Amyloid positive markers ('low CSF A β ₄₂ and positive PET amyloid'); Stage 2: Amyloid and neuronal injury positive markers ('increased CSF total and phosphorylated tau, lower ¹⁸fluorodeoxyglucose or FDG uptake on PET in temporoparietal cortices and significant structural atrophy on magnetic resonance imaging (MRI) in medial and lateral temporal and medial parietal cortices'); Stage 3: Amyloid and neuronal injury positive markers and cognitive impairments. For classification of AD dementia and MCI due to AD, abnormal amyloid and neuronal injury markers indicate a high probability of AD. If either of these two markers are abnormal in combination with one of the markers being normal, the biomarkers are considered as uninformative (McKhann et al., 2011).

According to The International Working Group (IWG)-2 criteria (Dubois & Albert, 2004; Dubois et al., 2014) for AD diagnosis, typical AD is classified as individuals exhibiting a gradual worsening of episodic memory as measured using neuropsychological tests specific for AD, while the NIA-AA criteria did not recommend a specific memory impairment (McKhann et al., 2011). Additionally, according to the IWG-2 criteria, the presence of MTL atrophy and abnormal cerebrospinal fluid (CSF) markers of amyloid and or tau are supportive features contributing toward AD diagnosis (Dubois et al., 2007). Exclusion criteria for the diagnosis include those stated as part of the NIA-AA criteria in addition to a sudden onset of symptoms, early presentation of symptoms such as hallucinations, extrapyramidal signs, gait disturbances, seizures and behavioural changes (Dubois et al., 2014). In terms of biomarkers, individuals are classed as having typical AD in the event of positive amyloid markers in combination with positive tau markers or evidence of tracer retention as seen in amyloid PET imaging or the presence of a genetic mutation for AD (in PSEN1, PSEN2, APP) (Dubois et al., 2014). Although both IWG-2 criteria and NIA-AA criteria depend on the same biomarkers for AD diagnosis, the classification in the two cases differs in terms of how the combination of biomarkers is used to determine AD diagnosis (Visser et al., 2012).

The most recent diagnostic criteria known as the 'A-T-N' criteria are proposed based on AD biomarkers (Jack et al., 2016b). The acronym has been created based on the presence of three biomarkers namely, amyloid, tau and neurodegeneration. Indication of A β accumulation is measured using CSF A β ₄₂ or retention of amyloid PET tracers, tau pathology is determined using measurements of phosphorylated tau (p-tau) in the CSF or tau PET while markers of AD-type neurodegeneration or neuronal injury are measured using total tau (t-tau) in the CSF, FDG-

PET hypometabolism and MTL atrophy on structural MRI (Jack Jr et al., 2018a). Although these biomarkers are highly correlated with deficits in several cognitive domains (except for amyloid markers), the current A-T-N criteria are heavily reliant on biomarkers without accounting for cognitive deficits. The criteria overlook the fundamental principles of cognitive reserve where an individual is able to perform relatively well on tests of cognition in the presence of extensive damage and pathological burden (Groot et al., 2017; Perneczky et al., 2019). Using the cognitive component as a screening tool for AD is also a cheaper, less invasive and a more convenient medium compared to the other elements under the ATN framework. The cognitive component could instead be used to facilitate cognitive staging to assess the level of cognitive impairment in individuals with AD in order to determine treatment and disease management strategies (Jack Jr et al., 2018a). However, clinically, the A-T-N criteria could be beneficial in terms of detecting the disease in its presymptomatic or early stages through frequent screening. Nevertheless, a criticism of the A-T-N framework is the arbitrary nature of the cut-off points for determining positivity for the biomarkers, which need to be defined in order to improve the accuracy of AD diagnosis (Jack Jr. et al., 2016b; Knopman et al., 2018).

Considering the diagnostic challenges posed by a disease that is substantially complex (AD) and the dynamic nature of the natural course of any disease, it is important that diagnostic criteria are constantly reviewed. However, one of the major drawbacks of changing diagnostic criteria across the years confounds evidence-based research whereby changing classifications over time can alter implications and comparability of current research to previous findings (Prince et al., 2016, Bertens et al., 2017). Future research converging on a mutual agreement on the use of diagnostic criteria for AD can thus help increase the reliability and validity of AD research.

1.6 Neural correlates of AD

1.6.1 Structural neuroimaging in AD

AD pathology is accompanied with a myriad of dysfunctional processes. The following section examines the pattern in which these dysfunctional processes can affect brain structure and function in normal ageing and AD.

1.6.1.1 Grey Matter Volume

In AD, there is a global reduction in gross brain matter although there are some typical atrophic patterns that are specifically seen in AD that are typically seen along brain regions that undergo depositions of AD pathology. The MTL areas are the most severely affected by the harmful effects of AD as they are targeted right from the early stages of the disease (Mattsson et al., 2016). Grey matter loss is initially observed in the hippocampus and entorhinal cortices that can be detected on MRI, that can precede the presentation of cognitive symptoms (Killiany et al., 2002). This grey matter loss can be attributed to the build-up of NFT, cerebral amyloid angiopathy, TDP-43 (Transactive response deoxyribonucleic acid (DNA) binding protein 43) pathology and cerebrovascular burden in subfields of the hippocampus and MTL regions (Dallaire-Theroux et al., 2017). Another explanation for the hippocampal atrophy could be due to its ontogenetic development and its consequent susceptibility to neurodegeneration (section 1.1, Para 4). With advancing disease stages, substantial atrophic changes are seen in the posterior cingulate cortex, cuneus and the basal ganglia with even further atrophy observed in the MTL regions (Chételat et al., 2007; Thompson et al., 2003; Wang et al., 2015b). Aside from the basal ganglia, these atrophic grey matter regions are part of the DMN (section 1.6.2.1, Para 1), a network which shows aberrant functional connectivity in very early disease stages and subsequent atrophy in its components with disease progression (Goto et al., 2015; Wang et al., 2015a).

On the other hand, anterior structures involved in the DMN, are relatively less affected until later stages of the disease although these areas are functionally and anatomically connected to the posterior cingulate gyrus and hippocampus, via the limbic system (Frisoni et al., 2007). Researchers have also posited that the grey matter structures that comprise the limbic system in the more posterior and basal regions might be more susceptible to the detrimental effects of AD compared to those in the frontal brain regions (Thompson et al., 2003; Whitwell et al., 2012). Frontal grey matter tends to be susceptible to age-related effects (Ge et al., 2002; Park & Reuter-Lorenz, 2009). However, the rate of atrophy that is seen in AD is far more aggressive than that which is seen in ageing (Frisoni et al., 2007). With age being a risk factor for AD, and with it affecting brain regions that are spared in the early stages of AD, the resultant convergence of disease and age-related effects could accelerate the degeneration of grey matter.

The pattern of structural atrophy seen in AD is mildly asymmetrical, where the left hemisphere experiences more grey matter detriments than the right hemisphere (Thompson et al., 2003). One of the reasons for this asymmetry might be due to the dominant nature of the left hemisphere in humans. Generally, increased activation of the left hemisphere is observed during tasks of language, speech and auditory processing in healthy individuals (Rathi et al., 2014). This increased activation can be attributed to the higher metabolic requirements of the brain regions involved in these processes (Tyler et al., 2010). With increasing age, there is a reduction in this heterogeneity between the hemispheres, and instead, a bilateral compensatory activation of both hemispheres is observed (Tyler et al., 2010). However, due to lifelong higher metabolic demands of the left hemisphere compared to the right, there might be insufficient resources available to the left hemisphere (as shown by hypometabolism in PET studies), which is detrimental to neuronal structure and function. Especially in AD, the repercussions of global reductions in metabolism and available neural resources can have severe consequences (Bozzali et al., 2011). This deficit in resources could potentially lead to a loss in grey matter volume (GMV). With the added effect of AD pathology, there might be further volumetric reductions, which are reflected in the asymmetric hemispheric atrophy seen in AD.

1.6.1.2 White Matter Integrity

While grey matter loss has an early onset and slow progression across ageing, white matter loss comparatively starts in later stages of life and has a steeper trajectory of decline (Raz et al., 2005). Therefore, it is possible that white matter loss is an indicator of advanced age (Salat, Kaye, & Janowsky, 1999). Similar to the pattern seen in grey matter atrophy, white matter integrity (WMI) has an anterior to posterior gradient of decline in normal ageing, while there is a posterior to anterior gradient of decline of WMI seen in AD (Head et al., 2004). This posterior to anterior gradient of decline of WMI maps well with the grey matter atrophic presentations in the disease as, it is the connections arising from atrophic grey matter regions (such as the MTL regions) that show the highest reductions in WMI (Bartzokis, 2004; Braak et al., 2000; Yin et al., 2015). Areas presenting with lower WMI in AD also undergo retrogenesis (section 1.4.5, Para 1), which points towards how age as a cumulative factor could contribute toward AD pathogenesis.

There are different mechanisms that could explain the patterns of white matter degeneration seen in AD. One of the theories behind white matter damage is the ‘Wallerian degeneration’

hypothesis, that can significantly contribute toward cell death in AD (Coleman & Freeman, 2010, section 1.4.5, Para 2). White matter contains axons that integrate numerous grey matter structures; therefore, a decline in WMI could be a consequence of grey matter atrophy in the brain region where the white matter tracts originate or resultant axonal injury (Agosta et al., 2011). Lower WMI was seen in the tracts connecting the hippocampus and the posterior cingulate gyrus among AD patients compared to healthy controls (Zhang et al., 2007b). This finding shows patterns similar to what is observed in AD, which is also reflected in a meta-analysis that showed white matter abnormalities initially presenting in the entorhinal cortex and hippocampus before a progressive decline is observed in the temporal and parietal association cortices (Sexton et al., 2011). This pattern of neuronal degeneration highlights the vulnerability of limbic structures (specifically, posterior and inferior limbic regions, also part of the DMN) to AD. It is also possible that decline in WMI follows the pattern of tau progression from the hippocampus to the limbic structures in AD (see section 1.4.2, Para 2).

The temporal trajectory of reduction of WMI and its relation to grey matter atrophy is still under dispute. Evidence suggests that deficits in WMI are less prominent in the early stages of and that these deficits are independent of the volumetric reductions in grey matter seen in the disease (Amlie & Fjell, 2014). Additionally, white matter is largely influenced by vascular insults that could be inflicted by age and AD-related effects (Jang et al., 2017). Therefore, decline in WMI in AD could be explained by different mechanisms. The independence of the structural decline in grey matter and white matter was seen in a study where higher white matter damage to the fornix was linked with hippocampal atrophy in late-stage MCI patients whereas damage to the fornix and hippocampal damage showed no correlation in early-stage MCI patients (Zhuang et al., 2013). It is possible that the association between grey matter and white matter damage could be interrelated in later stages of the disease (Zhuang et al., 2013). However, the determination of the temporal order of the manifestation of the mechanisms and the mechanisms that propagate grey matter and white matter damage in AD still remain unclear.

In addition to the limbic structures, lower WMI in AD has also been found in the genu and splenium of the corpus callosum, uncinate fasciculus and superior longitudinal fasciculus (Sexton et al., 2011; Yin et al., 2015). These white matter tracts are responsible for connecting brain regions that are vital to execute a number of cognitive processes effectively (Zhang et al., 2019). It also appears that different diffusion metrics seem to vary significantly across the AD, MCI and control groups suggesting that research should examine these more closely and

interpret these data with caution (Amlien & Fjell, 2014). In light of this argument, Amlien and colleagues observed that there is a gradual reduction of fractional anisotropy (FA: defines the degree of anisotropy of the diffusivity of water molecules), increase in radial diffusivity and stable axial diffusivity in AD. In the initial stages of AD however, higher levels of axial diffusivity and mean diffusivity were observed (Amlien & Fjell, 2014). Nevertheless, the pattern of white matter degeneration displayed in AD seems to be consistent and the product of the combined effects of ageing, build-up of cardiovascular burden and AD-related pathological changes.

1.6.2 Functional Neuroimaging in AD

1.6.2.1 Resting-state functional magnetic resonance imaging (rs-fMRI): The default mode network (DMN)

In light of the structural decline seen in components of the DMN, functional changes in this network would be expected. The DMN is a set of interlinked brain areas that exhibit neural activity when the brain is at rest and when a person is engaged in self-referential thought, while simultaneously not engaging in a goal-directed task. (Broyd et al., 2009). The DMN consists of the lateral and inferior parietal cortices, posterior cingulate gyrus, precuneus, regions of the prefrontal cortex and the hippocampus (Raichle, 2015; Raichle et al., 2001, Fig 1.2). Past evidence has indicated the involvement of the hippocampus in modulating the functional connectivity of the DMN (Bellana et al., Moscovitch, 2017; Greicius et al., 2004). Past work suggests that different areas of this network are structurally connected by certain white matter tracts (De Luca et al., 2006; Greicius et al., 2009). This could possibly be the link that could explain how the spread of tau pathology within functionally connected areas could propagate neurodegeneration and associated cognitive decline. Moreover, changes in the functional connectivity of the DMN, detectable on MRI, can precede cognitive or structural deficits in the disease (Jacobs et al., 2013; Nordberg, 2004). This is why it has also been proposed as an early marker for AD in the past (Koch et al., 2012; Zhang et al., 2010). Therefore, the underpinnings of aberrant functional connectivity seen in the DMN could help optimise diagnostic markers and strategies to target treatments and interventions.

Altered functional connectivity or hypometabolism in the posterior cingulate gyrus has been a consistent finding across various disease stages in AD (Teipel, Grothe, & ADNI, 2016). The DMN exhibits aberrant functional connectivity in AD, probably due to the heavy involvement of the posterior cingulate gyrus that has connections with the hippocampal formation. A likely cause for this aberrant functional connectivity might be the putative disconnection seen between the posterior cingulate gyrus and other components of the DMN in AD (Badhwar et al., 2017; Mevel et al., 2011). There are two different kinds of disconnections seen in AD, where the initial disconnection observed, is between the posterior cingulate gyrus and hippocampus (Damoiseaux & Greicius, 2009; Yin et al., 2015). Two of the major contributors toward this disconnection could be lower WMI seen between the hippocampus and posterior cingulate gyrus in addition to grey matter atrophy seen in the hippocampal formation in the early stages of the disease (Radanovic et al., 2013; Wang et al., 2015b). There is evidence that shows that both of these phenomena can modulate functional connectivity, albeit this relationship is not necessarily reciprocal (Damoiseaux & Greicius, 2009). However, there are studies to suggest that grey matter atrophy observed in the hippocampus could lead to a loss of connections to the posterior cingulate gyrus as a diaschisis effect, which could be a factor in promoting aberrant functional connectivity in the posterior cingulate gyrus (Teipel et al., 2016; Yakushev et al., 2011). The contribution of structural decline toward aberrant functional connectivity would increase temporally (more so in later stages), as changes in functional connectivity can be observed years before structural changes (Jacobs et al., 2013; Nordberg, 2004). The second kind of disconnection is seen in the later stages of the disease between the anterior and posterior components of the DMN, with the spread of age-related insults, pathology and neural damage inflicted. There also seems to be a progressive increase in this disconnection with disease progression, which could be explained by the opposing trajectories of neural decline seen in ageing and AD (Zhang et al., 2010, section 1.1, Para 5). Thus, the posterior DMN disconnection and posterior cingulate hypometabolism is a distinctive feature seen in the disease and can be used as a biomarker to predict conversion to AD (Jones et al., 2011). The pattern of altered functional connectivity in the DMN also appears to coincide with the structural decline observed in AD (section 1.6.1.1, Para 2; section 1.6.1.2, Para 2). However, the specificity of aberrant functional connectivity in the DMN needs to be examined closely, as disrupted functional connectivity in the posterior cingulate could also be a marker of ‘neural vulnerability to degeneration’ rather than AD-specific neurodegeneration (De Marco, Ourselin, & Venneri, 2019).

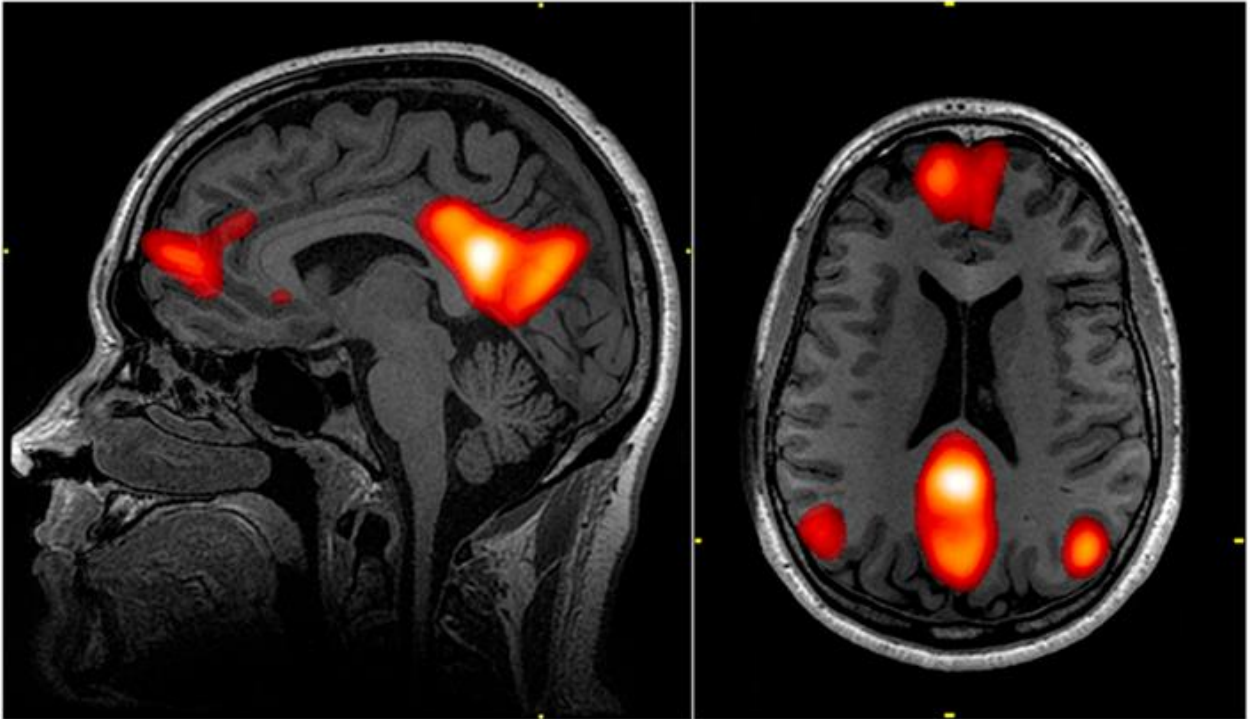


Figure 1.2 *The default mode network (DMN)*

This image shows the brain regions that are activated in the default mode network. The image on the left shows activation of the posterior cingulate gyrus and medial parietal areas and the anterior cingulate gyrus and frontal brain regions in a sagittal section whereas the image in the right represents these activations in the axial section in addition to showing activations in lateral parietal brain regions. Reused from Graner et al., 2013, under the Creative Commons License agreement included in Appendix A (Graner, Oakes, French, & Riedy, 2013).

Other resting state networks

Although the DMN is one of the most profoundly affected networks in AD, there are other networks that are influenced by AD pathology. While there is a reduction in functional connectivity in the DMN, there seems to be increased activity in the frontal networks in AD (Agosta et al., 2012). Although this study found no change in general functional connectivity in the frontal region, previous studies have reported higher functional connectivity in the frontal lobe in amnesic MCI patients (Agosta et al., 2012; Bai et al., 2009; Qi et al., 2010). Higher functional connectivity is particularly observed in the salience network among AD patients, which is comprised of the frontoinsula circuit and the anterior cingulate gyrus (Brier et al., 2012; Seeley et al., 2007; Zhou et al., 2010b). This higher functional connectivity could be the result of maladaptive compensatory mechanisms whereby the brain tries to recruit additional areas in order to cope with damage to existing regions in the network (Reuter-Lorenz & Park, 2014). Two studies also showed that frontal resting state networks that exhibit enhanced functional connectivity in AD might be involved in executive function and salience appraisal, which are impaired in AD (Agosta et al., 2012; Zhou et al., 2010b). This trade-off between posterior DMN deactivation and increased frontal resting state network activation could be the denouement of compensatory neural reorganisation that form the foundations of cognitive reserve, adhering to some principles propounded by the scaffolding theory of ageing and cognition (Agosta et al., 2012; Park & Reuter-Lorenz, 2009). Cognitive reserve is a concept that refers to the discrepancy between neuronal damage and its clinical manifestations. Having high levels of cognitive reserve can help delay the manifestations of clinical symptoms and can also help in the effective recruitment of compensatory neural resources to cope with AD pathology and neurodegeneration (Stern, 2009). Moreover, frontal lobe damage resulting from ageing could hamper the ability to compensate for neural damage, further contributing toward the cognitive decline seen in AD. Aberrant functional connectivity as seen in resting-state networks could help identify patient populations.

1.6.2.2 Positron Emission Tomography (PET)

PET is an invasive neuroimaging technique that utilises radioactive ligands that are injected into the patient in order to infer metabolic processes in the body *in vivo*, that can aid in disease diagnosis (Nordberg, 2004). Owing to its affinity for amyloid, one of the first PET tracers to be used was the PiB or ¹¹C Pittsburgh Compound B, that was used to detect cerebral amyloid (Klunk et al., 2007). In AD patients, retention of PiB is seen in the frontal and temporoparietal

areas and the magnitude of retention of PiB in AD patients is significantly higher compared to controls, specifically in the frontal lobe (Klunk et al., 2004). Some other PET tracers that bind to amyloid include florbetapir, florbetaben and flutemetamol. Cortical retention for these tracers is slightly different to PiB where flutemetol and florbetaben display higher retention in white matter while florbetapir displays lower cortical retention compared to PiB (Landau et al., 2014; Auvity et al., 2020). The higher binding affinity and lower half lives of florbetapir and florbetaben also make them effective imaging tracers to detect aspects of neurodegeneration (Auvity et al., 2020). When comparing the use of PiB and florbetaben in examining cortical amyloid distribution, results were comparable between the two tracers and a clear distinction between healthy controls and patients with AD can be facilitated (Villemagne et al., 2012). However, the diffused distribution of amyloid depositions across the neocortex and the unspecific nature of the relationship with hypometabolism, atrophy and clinical symptoms makes PET amyloid imaging a relatively ineffective tool in definitive AD diagnosis, but an effective tool in assessing amyloid load (Ossenkoppele et al., 2016).

In the past decade, the more recent practice of using tau-binding tracers has shed new light on the diagnostic applications of this form of molecular imaging. This ligand binds to paired helical filament tau pathology. This binding ability has not only shown adherence to the Braak staging of tau but is also in accordance with the neuroanatomical progression of tau pathology in AD (Cho et al., 2016; Jack Jr, et al., 2018b; Ossenkoppele et al., 2016). Uptake of this type of ligand has also been associated with worse cognitive performance (Ossenkoppele et al., 2016). Therefore, tau tracers could be a useful tool in studying the spread of pathology and disease progression and AD diagnosis. However, tau tracers have not been around long enough to determine their utility in diagnosis and research (Xia et al., 2013a). Nevertheless, tau-binding PET tracers are more specific markers of AD in comparison with amyloid and fluorodeoxyglucose PET (FDG-PET). FDG-PET is a consolidated technique to examine glucose metabolism in the brain. As measured using FDG-PET, hypometabolism in the posterior cingulate gyrus and precuneus is an early marker of AD. This hypometabolism subsequently progresses to the posterior temporoparietal regions followed by the frontal cortices, which are relatively spared until advanced disease stages (Valotassiou et al., 2018). This pattern of hypometabolism can be attributed to the putative disconnection seen in AD between the posterior cingulate gyrus and downstream subcortical and cortical brain regions, in some measure (Teipel et al., 2016). In terms of its correlation with clinical manifestations,

the temporal link between hypometabolism in the posterior cingulate gyrus as measured using FDG-PET and clinical symptoms is inconsistent (Iaccarino et al., 2017).

1.6.2.3 Cerebral Blood Flow Neuroimaging in AD

1.6.2.3.1 Arterial spin labelling

Arterial spin labelling or ‘ASL’ refers to a non-invasive neuroimaging technique used to measure CBF. Additionally, ASL, like fMRI can be used to measure brain function, which is why some convergence of findings is expected between both these techniques (Detre, Rao, Wang, Chen, & Wang, 2012). Results from previous ASL studies show comparable findings to those from PET and fMRI studies (section 1.6.2.1; section 1.6.2.2; Alsop et al., 2010; Ma et al., 2017; Teipel et al., 2016). A reduction in CBF is observed in previous ASL studies in AD patients, particularly to the precuneus, posterior cingulate gyrus, parietal association cortices and inferior frontal regions, which sufficiently mirrors findings from past fMRI studies (section 1.6.2.1; Alsop et al., 2010; Dai et al., 2009; Ma et al., 2017; Vercllytte et al., 2016). Changes resembling these patterns of reductions in CBF have also been observed in the precuneus, inferior parietal lobe and posterior cingulate gyrus in studies including only MCI patients (Alexopoulos et al., 2012; Johnson et al., 2005; Xu et al., 2007).

Even though there is a degree of similarity in the patterns of reductions in CBF between MCI patients and patients in later stages of AD, the extent of these rCBF reductions is more profound in the latter. However, given the consistently similar pattern of reductions in rCBF across various AD stages, ASL has even been investigated as a candidate for predicting conversion to AD and MCI from cognitively normal and MCI stages, respectively (Alsop et al., 2010; Chao et al., 2010; Zhang, Gordon, & Goldberg, 2017b). As AD pathology typically initiates from the MTL regions, regional changes in CBF would be expected in these areas. In contrast to the posterior cingulate gyrus, increased CBF is observed in the MTL regions the early stages of AD (Alsop et al., 2008; Dai et al., 2009; Fleisher et al., 2009). These changes in CBF in the MTL regions could be explained by maladaptive compensatory mechanisms, where a higher blood flow to that brain region results from excessive demands from that brain region in order to maintain its normal level of cognitive functioning, in the presence of damage (Gardini et al., 2015). There is a similarity between aberrant functional connectivity seen in the DMN and

hypoperfusion seen in AD patients indicating the presence of a strong vascular component in the pathophysiology of AD.

1.6.2.3.2 Single photon emission tomography (SPECT)

SPECT or ‘Single Photon Emission Tomography’ is a neuroimaging technique that can help detect the retention of specific ligands in certain parts of the body. It can help look at various measures such as amyloid burden, cerebral perfusion, metabolism and more (Declercq et al., 2016). Similar to ASL and FDG-PET studies, perfusion SPECT studies have shown hypoperfusion in the precuneus and posterior cingulate gyrus in early stages of the disease, with subsequent hypometabolism in the posterior temporoparietal cortices before expanding over to the frontal lobes in relatively later stages of AD (Valotassiou et al., 2018). However, FDG-PET has more sensitivity and specificity compared to SPECT in distinguishing between healthy controls and AD patients and also conversion to AD dementia from MCI (Valotassiou et al., 2018). While perfusion SPECT and ASL have equal utility in AD, SPECT is a more invasive technique that involves the individual having an injection or inhalation of a radioactive agent in order to facilitate perfusion imaging (Takahashi et al., 2014).

In summary, AD seems to have a more posterior effect on cerebral perfusion and functional connectivity, specifically in the posterior cingulate gyrus. The disease can propagate maladaptive compensatory mechanisms that can manifest as hyperperfusion in the MTL structures such as the hippocampus in early disease stages. Taking into account age-related reductions in frontal lobe perfusion, expansion of AD-related hypoperfusion to these regions in later disease stages can be extremely detrimental to neuronal and cognitive health. This could partly explain the late manifestations of executive dysfunction or even early manifestations with prefrontal cortex deficits (Guarino et al., 2018). Therefore, vascular dysfunction in AD facilitate conditions conducive to the detrimental effects of ageing and the neurodegenerative conditions manifested in AD or the hypoperfusion observed could be a reverse-causal effect.

1.7 Treatments

To date, AD remains a disease without a cure and with limited methods available to slow down the rate of disease progression (de la Torre, 2010). This scenario is made worse by the lack of specificity and effectiveness of available diagnostic criteria in order to detect AD in early stages

(section 1.5, Para 2). Some advances have been made which have facilitated certain pharmacological treatments that could potentially help slow down the rate of disease progression and some others in the form of health interventions that have gone a long way in delaying the onset of AD and reducing its incidence.

Pharmacological treatments can be classified depending on their action into ‘disease modifying’ and ‘symptomatic’ drugs. Treatments that can retard the progression of structural damage are coined as ‘disease-modifying drugs,’ whereby discontinuation of the treatment can result in disease progression (Salomone et al., 2012). There are several clinical trials that focus on administering drugs that would help in reducing A β production, clearance and aggregation. One of the most recent drugs that passed Phase III of the clinical trials is ‘aducanumab,’ which is a monoclonal anti-body designed to reduce the aggregation of A β , using an immunotherapeutic approach (Sevigny et al., 2016). However, the use of this drug for AD treatment has been heavily criticised as it is solely based on the amyloid hypothesis, and some claim that amyloid accumulation has no impact on cognitive function (Giannakopoulos et al., 2003; Serrano-Pozo et al., 2016). On the other hand, as the name suggests, ‘symptomatic drugs’ are those drugs that only help alleviate the symptoms of a disease without tackling the underlying causes (Salomone et al., 2011). By far, there are only five approved treatments to treat the cognitive symptoms of AD which include cholinesterase inhibitors namely rivastigmine, galantamine and donepezil and one N-methyl-D-aspartate receptor antagonist, memantine. A fifth treatment option has been approved in the USA, which is a combination of memantine and donepezil (Cummings et al., 2019; Deardorff & Grossberg 2016). The limited availability of effective treatments for AD has resulted in the foundation and implementation of preventive interventions instead (section 1.8).

1.8 Prevention

As the global population multiplies, there has been a concomitant increase in longevity as a result of improved healthcare services. The incidence of AD dementia has seen a simultaneous increase as age is a predominant risk factor for this disease. As a result of the growing ageing population in the world, the G8 nations have raised concerns about the growing rates of AD dementia in the Dementia Summit Declaration (Global Action Against Dementia, 2014). This has encouraged governments across the globe to formulate policies dedicated toward the implementation of prevention strategies, in order to reduce the incidence of AD dementia and

in order to improve quality of life in ageing, on a large scale (Norton et al., 2014). Prevention strategies can be broadly categorised into primary, secondary and tertiary based on the measures taken to implement the strategy. Primary prevention refers to the act of trying to reduce the development of risk factors for the disease. Secondary prevention, on the other hand, deals with detecting diseases in their prodromal stages based on established biomarkers. Diagnosis in the early stages can facilitate the benefits received from interventions to reduce the severity of the diseases in progressive stages. Tertiary prevention refers to disease management, which entails providing optimal care for those already diagnosed with the disease (Matthews et al., 2013). The reason for the establishment of prevention strategies is largely due to the modifiable nature of cardiovascular risk factors. Preventing the onset of the cardiovascular risk factors can not only help delay or even prevent the onset of AD but can also help to reduce the burden on the healthcare economy by helping prevent the development of a multitude of diseases (Freisling et al., 2020; Ngandu et al., 2015; Thavendiranathan et al., 2006).

A review of several different meta-analytical reviews revealed that AD is associated with the presence of seven different cardiovascular risk factors namely diabetes, midlife hypertension, midlife obesity, depression, smoking, low education levels and physical inactivity. The review also assessed the potency of reducing the incidence of the individual risk factors and proposed almost a 51% reduction of the risk factors (Barnes & Yaffe, 2011). However, the majority of these factors are interdependent and they share some common downstream mechanisms that have a detrimental effect on an individual's health. A caveat in Barnes and Yaffe's work is the lack of consideration of the overlapping nature of these comorbidities. Norton and colleagues (2014), on the other hand, attempted to account for these interdependencies to calculate the prospective effects of reducing the prevalence of cardiovascular risk factors. Out of the seven risk factors mentioned in Barnes and Yaffe's work, Norton and colleagues presented physical inactivity to be the biggest risk factor contributing toward AD incidence (Norton et al., 2014). Since most of the literature search consisted of cross-sectional studies, a limitation of this research was the variability and ambiguity in the effects of cardiovascular risk factors over one's lifetime. Norton and colleagues posited that taking steps toward primary prevention could lower the risk of dementia at the current age that it is contracted at, which could in turn reduce the global prevalence of AD (Norton et al., 2014). A consideration of the improvement in quality of life as a result of reducing the prevalence of cardiovascular risk factors could possibly benefit the global population in the longer run. Thus, preventing the onset of cardiovascular

risk factors could be a step toward lowering the incidence of AD, prolonging the age of onset and providing a better life for those afflicted with the disease and their caregivers.

The changing approach to primary care with a focus on reducing cardiovascular risk, has shown that the increase in dementia incidence and prevalence is not as large as it was predicted to be (Matthews et al., 2016; Schrijvers et al., 2012). The cognitive function and ageing study was designed to record and examine factors that could contribute towards cognitive decline and dementia in individuals aged 65 years and above in the UK (<http://www.cfas.ac.uk>). Examination of the study cohorts showed that individuals that have been born later in the past century show a lower prevalence of dementia compared to individuals born earlier in the century, while incidence remains relatively stable (Matthews et al., 2013; Matthews et al., 2016). This could, in part, be due to the increased use of drugs to treat cardiovascular conditions in these cohorts (Gao et al., 2018). It appears that adopting recommendations from such studies could contribute towards reducing dementia prevalence and incidence (Jagger et al., 2009; Valenzuela et al., 2011). Similarly, findings from another cohort study (The Rotterdam Study) has shown that cardiovascular risk factors such as smoking and diabetes that increase the risk for cognitive decline are also risk factors for AD (Hofman et al., 1997; Ott et al., 1998; Ott et al., 1999). There is strong evidence from this initiative that confirms the effectiveness of prevention strategies in reducing the risk of developing cardiovascular risk factors that could aid in delaying the onset of neurodegenerative diseases such as AD (Bos et al., 2014; de Bruijn et al., 2015; Hofman et al., 2006). Similar findings have been reported from some Swedish cohort studies that highlight the importance of primary prevention and multi-domain interventions to reduce dementia risk (Gatz et al., 2006; Qiu, Winblad, & Fratiglioni, 2005; Qiu, Xu, & Fratiglioni, 2010).

1.9 Interventions

Due to the lack of definitive diagnostic criteria and the unavailability of a cure for AD, intervention strategies have inclined towards taking a preventive approach. This has led to the development of several interventions to reduce the incidence of AD using interventions of primary and secondary prevention for AD. One of the biggest initiatives to reduce the prevalence of modifiable lifestyle risk factors is the World Wide (WW) – FINGERS initiative (<https://www.alz.org/wwfingers/overview.asp>), which is an arborisation of the The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

(Rosenberg et al., 2019). The FINGER Study consisted of a two year long multi-domain intervention that entailed tailored nutrition advice, fixed physical activity regimens, cognitive stimulation and increased social interactions along with help in regulating metabolic and vascular risk factors (Kivipelto et al., 2013). The outcomes of the study as measured using neuropsychological test batteries showed that monitoring and regulating modifiable lifestyle risk factors were associated with a significant preservation of cognitive function, specifically in the older population that is at risk of getting AD (Ngandu et al., 2015). As a result of the successful outcomes from the study, it is noteworthy that the FINGER study has been extended to Australia, China, Singapore, France, Germany, Sweden and The United States of America, to create the WW-FINGERS (Ngandu et al., 2015).

There are other similar interventions that have been implemented that did not witness as much success as the FINGER. The Prevention of Vascular Dementia by Intensive Care (PreDIVA) trial recruited 3700 elderly participants and provided them with intensive vascular care in order to examine whether this type of intervention could have any impact on reducing the incidence of dementia, cognitive function and mortality (Richard et al., 2009). However, the study did not show that the modulation of vascular factors in a population aged between 70-78 years had any effect on dementia incidence, mortality, cardiovascular disease or disability (Richard et al., 2009). A plausible explanation for this trend of results might be that the implementation of interventions in early stages (as opposed to implementing in patients with dementia and elderly population) and cognitively normal individuals can go a long way in slowing the rate of cognitive decline and reducing the incidence of dementia, respectively. On account of their old age and being in the later stages of the disease, the beneficial effects of the intervention by Richard and colleagues may have been negligible (Richard et al., 2009). Moreover, the study only focused on a single aspect of prevention, namely vascular risk (Richard et al., 2009). Nevertheless, in a different study, administration of hypertensive medication has been shown to prevent cognitive decline and reduce the risk for dementia in 1,346,176 participants with an average age of 74 years (Rouch et al., 2015). The differences in the components of the study designs could possibly explain the differences in the outcomes. Additionally, some other studies exploring the effects of a single-domain intervention did not show promising results (Brasure et al., 2018; Rosenberg et al., 2019). Therefore, it is vital that the design and components of intervention strategies are carefully considered and catered to the requirements of different populations and age groups. Specifically, multi-domain interventions should target individuals in midlife as the presence of cardiovascular risk factors in this time period poses

the highest risk for AD via the build-up of cardiovascular burden that can cause irreversible neuronal damage (Conner et al., 2019). However, it is of note that these intervention studies are targeted to reduce dementia risk and although they might have an effect on the course of AD in individuals, these studies are not specific to AD.

1.10 Conclusion

AD is a complex disease that entails a variety of pathological mechanisms that contribute toward its development. These mechanisms include vascular dysfunction, age-related effects (such as build of cerebrovascular burden) and the build-up of AD pathology. It is a progressive neurodegenerative disease that presents with progressively worsening cognitive symptoms especially in the memory domain with the most prominent deficits seen in semantic and episodic memory. Prior to presenting with signs of structural decline, AD presents with functional and metabolic reductions in the posterior cingulate gyrus in the early disease stages as the possible outcome of a diaschisis effect resulting from a loss of connections from the hippocampus. Subsequently, progressive disconnection is seen between components of the DMN. This presentation could be due to the initial predominance of a tau-related neurodegenerative profile of AD that spreads along functionally and structurally connected brain areas. The pathology originates in the MTL regions (such as the hippocampus), and subsequently spreads to other brain regions with an affinity for structures housed in the limbic system. This progression of pathology can largely be linked with progression of clinical symptoms. Amyloid depositions on the other hand originate in frontal and basal brain regions before progressing to the rest of the cortex and have a poor temporal link with clinical symptoms. Other dysfunctional processes such as failure of neural plasticity and the degeneration of the cortico-basal cholinergic system are also involved in the AD pathogenesis. These dysfunctional processes are largely irreversible and tend to initiate in the preclinical stages. AD patients also present with vascular pathology. The vascular aetiology of AD can also contribute towards disease development and progression. However, it is unclear whether vascular pathology is a causal effect of AD, whether AD pathology stems from age and cardiovascular risk factor-related mechanisms or whether vascular dysfunction and AD are independent processes that are additive to each other. Nevertheless, a significant proportion of cardiovascular risk factors can be mitigated through lifestyle modification and treatment. Due to the lack of available treatments for AD and the irreversible nature of the damage inflicted in asymptomatic stages of the disease, more attention has been drawn toward preventive strategies

that could potentially help reduce the incidence and prevalence of AD. The current thesis therefore explores the vascular mechanisms that contribute toward AD pathogenesis with a focus on three different modifiable cardiovascular risk factors, namely type 2 diabetes (T2DM), obesity and hypertension.

Chapter 2: Vascular Contributions to Neurodegeneration in AD

Recently, the vascular hypothesis of AD has received increased scrutiny. Accumulating evidence suggests that vascular dysfunction plays a strong role in increasing AD risk and that prevention of cardiovascular risk factors can significantly lower AD risk and reduce incidence (Luchsinger et al., 2005; Mayer et al., 2018). There has also been a recent rise in the prevalence of cardiovascular risk factors such as obesity, hypertension and T2DM (Chowdhury et al., 2020b; Leiva et al., 2017; Norton et al., 2014). These cardiovascular risk factors are chronic conditions that degrade quality of life and have negative health consequences (De Smedt et al., 2013; Martinelli et al., 2008). The chronic nature of these conditions and need for medical attention can be a huge burden on a nation's economy (Eckel et al., 2014). However, a significant proportion of these risk factors are modifiable through early intervention and primary prevention (Norton et al., 2014). Additionally, cardiovascular risk factors such as diabetes and obesity have been identified as risk factors for AD (Kivipelto et al., 2005; Piepoli et al., 2016; Vagelatos & Eslick, 2013). Considering the paucity in AD treatments and appropriate markers for a timely AD diagnosis, risk factors that are modifiable and pose a risk for AD and cognitive decline need to be targeted to facilitate their prevention (Baumgart et al., 2015, section 1.5, 1.8, 1.9). Given the asymptomatic phase of AD where structural and functional changes in the brain manifest long before the presentation of symptoms, prevention of risk factors for AD can substantially help reduce its incidence (Brier et al., 2014; Tondelli et al., 2012). Prevention of such risk factors can also go a long way in reducing the burden on the healthcare economy, improving the quality of life of individuals and even reducing the risk for progressing to AD dementia in patients (de Bruijn & Ikram, 2014). More importantly, prevention measures can help delay the onset of dementia in addition to reducing the severity of disease symptoms in individuals diagnosed with AD (section 1.8, 1.9). The current thesis attempts to focus on these aspects to explore the effects of three cardiovascular risk factors namely obesity, hypertension and T2DM in patients across the AD spectrum and cognitively normal individuals.

2.1 Mechanisms of modifiable risk factors contributing toward neurodegeneration in AD

2.1.1 Vascular dysfunction

According to the vascular hypothesis of neurodegeneration, vascular damage can result from lower cerebral perfusion/hypoxia or BBB disintegration. Reduction of BBB permeability causing the extravasation of vessel contents can facilitate toxic accumulations harmful to neural tissue. Lower cerebral perfusion and reduced integrity of the BBB could contribute toward neurodegeneration (Zlokovic, 2010). Vascular dysfunction seen in cardiovascular risk factors could thus contribute toward neurodegenerative processes and increase the risk of AD or increase AD severity.

2.1.1.1 Microvascular

The BBB is a selectively permeable membrane that lines vascular endothelial cells facilitating the exchange of compounds between the blood and the brain parenchyma (Ballabh, Braun, & Nedergaard, 2004). The layer of endothelial cells is surrounded by pericytes, neurons and astrocytes (Sweeney, Ayyadurai, & Zlokovic, 2016). Endothelial cells form the inner lining of blood vessels that extends into the capillaries where this lining acts as an interface between blood and brain tissue (Rafii, Butler, & Ding, 2016; Zhao, Nelson, Betsholtz & Zlokovic, 2015). A corollary of the pathological mechanisms of cardiovascular risk factors and AD is increased BBB permeability, which can lead to changes in cerebral blood supply (Janelidze et al., 2017; Starr et al., 2009). Reduced integrity or increased permeability of the BBB causes the extravasation of the vessel contents including neurotoxic proteins such as A β that is observed in AD and cardiovascular diseases (Zlokovic, 2011). This can lead to the accumulation of these toxic proteins in extracellular spaces, causing neuronal damage (Sweeney, Sagare & Zlokovic, 2018; Lopez et al., 2014; Pluta, Ułamek, & Januszewski, 2006). Accumulation of amyloid plaques has also previously been associated with increased oxidative stress, neuroinflammation and reduced BBB integrity in AD (section 1.4.6.1.1, Para 2). There is also additional evidence, however, that suggests that AD patients in the prodromal and preclinical disease stages do not show any changes in BBB (Janelidze et al., 2017).

Insulin can have a profound effect on cerebral perfusion and can modulate the amount of blood delivered to tissues, without altering total blood flow (Clark et al., 2003; Richards, Raines, & Attie, 2010). Specifically, it can redirect blood flow from non-nutritive to nutritive pathways, to maximise the exchange of nutrients (Meijer et al., 2012; Serné et al., 2002). In short, it aids in making perfusion more efficient by decreasing blood flow to vessels supplying tissues that have little or no exchange with the surrounding interstitial fluid (Clark et al., 2000). Simultaneously, it increases blood flow to the underperfused vessels that allows for the exchange of nutrients with the interstitial fluid (Clark, 2008; Richards et al., 2010). This shift in blood perfusion is facilitated by insulin action on the vasomotion of capillaries and arterioles (de Boer et al., 2014). Insulin facilitates the production of vascular endothelial cell-mediated secretions of nitric oxide, which possesses vasodilatory properties in addition to being responsible for the release of Endothelin ET-1, which has vasoconstrictive properties (de Boer et al., 2014; Mather, Anderson, & Verma, 2001; Muniyappa & Quon, 2007; Randriamboavonjy et al., 2004). Insulin resistance (IR), a condition in which the body is not able to process the effects of normally regulated insulin, is seen in AD and in the presence of comorbidities such as T2DM and obesity (Castro et al., 2013; Kahn, Hull, & Utzschneider, 2006; Talbot et al., 2012). Therefore, cerebral IR seen in AD, obesity and T2DM could hamper these functions, resulting in impaired vasomotion and consequent hypoperfusion of neural tissue that could contribute towards neurodegeneration in AD.

Considering the synergistic relationship between insulin and glucose, IR mediated glucose dysregulation can also influence BBB integrity. One of the pathological mechanisms contributing toward BBB dysfunction is hyperglycaemia (Shao & Bayraktutan, 2014). However, the extent of the detrimental effects of hyperglycaemia on the BBB is dependent on the duration of the hyperglycaemic episode. Acute hyperglycaemia does not seem to have any major effects on the BBB. A magnetic resonance spectroscopy study revealed that acute hyperglycaemia did not affect CBF or regional glucose metabolism (Nielsen et al., 2005). These results were supported by findings from a different PET study (Hasselbalch et al., 2001). Yet another study claims that there are no major CBF or BBB changes mediated by acute hyperglycaemia (Seaquist et al., 2005). Chronic hyperglycaemia on the other hand is associated with thickening of the capillary beds and vascular basement membranes and the degeneration of endothelial cells and pericytes, which can reduce BBB integrity and alter CBF (Duckrow, Beard, & Brennan, 1985; Harik & LaManna, 1988; Roy et al., 2010). Endothelial cell dysfunction is not only restricted to the downstream actions of IR but can also be the product

of hyperglycemia seen in T2DM (Eelen et al., 2015). Therefore, in conditions that promote IR, the cross-talk between glucose regulating mechanisms and insulin mediated mechanisms could promote BBB dysfunction that could contribute towards neurodegenerative processes.

Increased blood glucose levels commonly observed in diabetes and obesity change the metabolic properties of endothelial cells causing increased production of reactive oxygen species that promote oxidative stress (Ceriello et al., 2008; Monnier et al., 2006). This leads to the generation of advanced glycation end products that are toxic to endothelial cells, macromolecular complexes in the extracellular matrix and other cells (Basta et al., 2002; Eelen et al., 2015; Miyata et al., 1997; Vlassara & Uribarri, 2014). Therefore, increased production of advanced glycation end products is observed under hyperglycaemic conditions, which could, in turn, increase the generation of reactive oxygen species and raise oxidative stress (Nowotny et al., 2015; Uribarri et al., 2007). Although the nature of the interaction between advanced glycation end products and reactive oxidative species is unclear, their production is evident in metabolic conditions such as T2DM and obesity and also in normal ageing (Negrean et al., 2007; Patel et al., 2007; Uribarri et al., 2007). Additionally, production of these species is also seen in AD (Sasaki et al., 1998).

Advanced glycation end products facilitate the cross linkage between the molecules that compose vessel walls, consequently leading to the thickening of the extracellular basement membrane that causes stiffening of the arterial walls (Gardiner et al., 2003; Goldin et al., 2006). This could contribute toward arteriosclerosis (section 2.1.1.2, Para 1) that can inadvertently influence blood flow (Goldin et al., 2006; Kiuchi et al., 2001). Advanced glycation end products can also promote atherosclerosis (Basta et al., 2004; Soro-Paavonen et al., 2008) via mechanisms such as the ligation of the advanced glycation end products receptor (RAGE) (expressed in monocytes, smooth muscle cells and endothelial cells), which aids the intracellular circulation of these substrates and heightens clotting effects exerted by endothelial cells (de Vos, et al., 2016; Eelen et al., 2015). RAGE ligation in monocytes increases the generation of macrophages, with a resultant increase in the influx of cholesterol (Basta, 2008). Increased coagulant action and high cholesterol concentrations (as seen in AD, T2DM and obesity) ultimately pave the way for atherogenesis (section 2.1.4, Para 2). Moreover, advanced glycation end products contribute toward the development of amyloid plaques and NFTs (Carnevale et al., 2012; Pugazhenthii, Qin, & Reddy, 2017; Srikanth et al., 2011). Therefore, microvascular changes seen in T2DM, obesity and ageing could contribute toward AD by

promoting mechanisms that facilitate neurodegeneration, vascular dysfunction and pathological accumulations typical of AD.

2.1.1.2 Macrovascular

There are considerable changes to the haemodynamics of the blood vessels in T2DM, obesity, hypertension and AD. Two common age-related arteriopathies presented in these conditions are arteriosclerosis and atherosclerosis (Kawamori et al., 1992; Lakka et al., 2001; Matsumoto et al., 2002; Schäfer et al., 2016). Arteriosclerosis refers to the age-related stiffening and calcification in the media of the arterial walls (Tölle et al., 2015). When blood travels through the arteries before it is delivered to the tissue, it is propelled at substantial pressure from the heart before it reaches the vascular bed. Efficient transport of the blood through the arteries is dependent on the ability of the arterial walls to expand effectively or to contract in response to the influx of blood and the diameter of the vessel walls (Aalkjær, Boedtkjer, & Matchkov, 2011). Therefore, reduction in the elasticity of arterial walls and calcifications lining the media of the blood vessel that can develop with age and in cardiovascular diseases results in inefficient vascular compliance (Safar, O'Rourke, & Frohlich, 2014; Shirwany & Zou, 2010). Stiffening of arterial walls can further contribute toward development of atherosclerotic pathology causing alterations in blood flow and vascular compliance (Ohayon et al., 2011). Failure to regulate arterial pulse pressure resulting from inefficient vascular compliance in large vessels can consequently lead to fluctuations in blood pressure resulting in inconsistencies in the volume of blood propelled through the blood vessel during one single pulse (Maroules et al., 2014; Schiffrin, 2004; Webb et al., 2012). These inconsistencies damage perforator arteries and arteries with a delicate structure, as these arteries do not possess the tensile strength to endure erratic 'bursts' or pulses of blood (Veglio et al., 2009). This damage in addition to increased BBB permeability results in the extravasation of vessel contents from small arteries or 'perforators' such as the lenticulostriate arteries, causing a reduction in blood flow to the target organs, ultimately paving the way for neurodegeneration (Chamorro et al., 1996; Hu & Feng, 2017; Veglio et al., 2009).

Atherosclerosis is a condition that is characterised by the build-up of plaques in the media of blood vessels that narrows the lumen diameter that can lead to reductions in blood flow and alterations in blood pressure (Weber & Noels, 2011). As it has been established before, obese and hypertensive patients, patients with T2DM and AD have an increased risk of developing

atherosclerotic pathology (Hofman et al., 1997; Lakka et al., 2001; Sipahi et al., 2006; Weiss, Kools, & Taylor, 2001). A plethora of downstream pathological mechanisms of obesity, T2DM, hypertension and AD such as endothelial dysfunction, impaired nitric oxide production, high circulating cholesterol levels, release of pro-inflammatory cytokines and proliferation of vascular endothelial smooth muscle cells facilitate atherosclerotic plaque formation (Casscells et al., 1996; Miyazaki et al., 1999; Mudau et al., 2012; Tsai et al., 1994, section 2.1.4). Atherosclerotic lesions have a tendency to accumulate at bifurcations of branching arteries and areas of high blood pressure and multi-directional flow (Johansson et al., 2006; Morbiducci et al., 2016; Salzar, Thubrikar, & Eppink, 1995; Zarins et al., 1983). Accumulations of such plaques also increases the risk for pro-thrombotic events and embolisms, where a small portion of the plaque breaks off and travels to distal arteries, lodging itself in arteries with smaller lumen diameters to block blood flow (Davies et al., 1993; Gutierrez et al., 2015; Prandoni et al., 2017; Rauch et al., 2001). The increased risk of developing atherosclerotic plaques also tends to increase A β plaque deposits by altering its production and clearance from the cerebrovascular system, a phenomenon observed in AD and T2DM (Iadecola, 2010; Li et al., 2003). However, there is contradictory evidence that shows that intracranial atherosclerosis does not correlate with A β depositions in the brain (Gottesman et al., 2020). However, there is evidence pointing toward the role of A β in promoting atherogenesis indicating that AD and atherosclerosis might coexist in a synergistic relationship in the pathogenesis of blood vessel damage (Gupta & Iadecola, 2015; Song et al., 2010).

Initially, patients with systemic atherosclerosis tend to develop the pathology in large blood vessels such as the subclavian, innominate and common carotid arteries, leading to growing build-up of plaques in the arterial walls (VanderLaan et al., 2004). Increase in the size of plaques in the bigger arteries increases the risk for embolisms and pro-thrombotic events that can occlude blood flow in more distal arteries with smaller diameters (Derdeyn, 2007; Nah et al., 2010; Pu et al., 2017). Similarly, following plaque build-up in bigger arteries, the development of intracranial atherosclerosis can reduce blood flow and cause fluctuations in blood pressure that can result in reduced blood flow and vascular damage. Moreover, cerebral lesions resulting from microvascular damage tend to be relatively mild or ‘silent,’ which can also be the result of end-organ damage as a consequence of fluctuations in blood pressure (Blanco-Rojas et al., 2013; Saji et al., 2012; Veglio et al., 2009). A build-up of substantial neural insults over time results in the clinical manifestations of these vascular events that cause substantial cognitive decline (Arenillas, 2011; Ghanem et al., 2017; Huijts et al., 2013).

2.1.1.3 Brain blood supply

The brain is supplied by the internal carotid arteries and the vertebral arteries that are branches of the common carotid and subclavian arteries respectively (Konan & Mesfin, 2019; Manninen et al., 2008; Sato et al., 2011). The internal carotid arteries that supply blood to the anterior cerebral circulation, enter the brain to form the anterior portion of the Circle of Willis and supply a majority of the blood to the anterior cerebral circulation (Alastruey et al., 2007; Hendrikse et al., 2001; Kablak-Ziembicka et al., 2006). The Circle of Willis further branches out via collaterals giving rise to the anterior and middle cerebral arteries and posterior communicating arteries (which branch out to connect the posterior cerebral arteries) (Alastruey et al., 2007; Kablak-Ziembicka et al., 2006; Saeki & Rhoton, 1977). The middle cerebral artery, being the biggest cerebral artery supplies a vast proportion of the lateral surfaces of the cerebrum and is at a high risk of vascular damage (Bustamante et al., 2016; Caplan, 2015; Momjian-Mayor & Baron, 2005). The regions supplied by the middle cerebral artery include the lateral portions of the frontal lobe (inferior and middle frontal gyri), middle and inferior portions of the precentral, central and postcentral gyri, the insula, the temporoparietal junction, superior and middle temporal gyri and the striatum (Cilliers & Page, 2017; Goyal et al., 2016; Phan et al., 2005). Occlusions or ischaemic injury to this artery can result in profound neurological deficits as it supplies blood to an extensive cerebral territory (Goyal et al., 2016; Phan et al., 2005).

Similarly, the anterior cerebral artery which supplies the corpus callosum, anterior portions of the caudate and putamen, anterior two-thirds of the cingulate gyrus and medial portions of the frontal, paracentral and parietal lobes can also be affected by underlying conditions such as obesity, hypertension, T2DM and AD (Tahir et al., 2019). The posterior cerebral artery on the other hand supplies the MTL regions (including the hippocampus), the lateral and inferior temporal areas, the occipital areas and the midbrain (Brandt et al., 2000; Spallazzi et al., 2019). The infero-posterior portions of the brain are mostly irrigated by the posterior circulation system that receives its blood supply from the vertebrobasilar system (Tatu et al., 1996). The vertebral arteries merge to form the basilar artery at the medulla, which ascends superiorly toward the circle of Willis and gives off collaterals namely the posterior cerebral artery, the superior cerebellar artery and the anterior inferior cerebellar artery (Tatu et al., 1996). The vertebral arteries are also parent arteries to the posterior inferior cerebellar artery. The cerebellar arteries supply various portions of the brainstem and cerebellum (Savoiaro et al.,

1987; Tatu et al., 1996). Compared to the posterior circulation system, the anterior circulation system is more susceptible to adverse vascular events and therefore more prone to damage in the presence of cardiovascular risk factors (Bamford et al., 1991; Hollander et al., 2002; Sato et al., 2008). Considering the systemic effect of the arteriopathies seen in cardiovascular diseases, ageing and AD (such as atherosclerosis and arteriosclerosis), a general reduction in blood flow would be expected in cerebral arteries. Reduced blood flow, alterations in blood pressure and consequent vascular damage fosters neurodegeneration and accumulation of AD pathology (section 2.1.1.1, Para 1; section 2.1.1.2, Para 2). The vascular territories of major cerebral arteries and the trajectory of cerebral arteries and the Circle of Willis are shown in Figure 2.1.

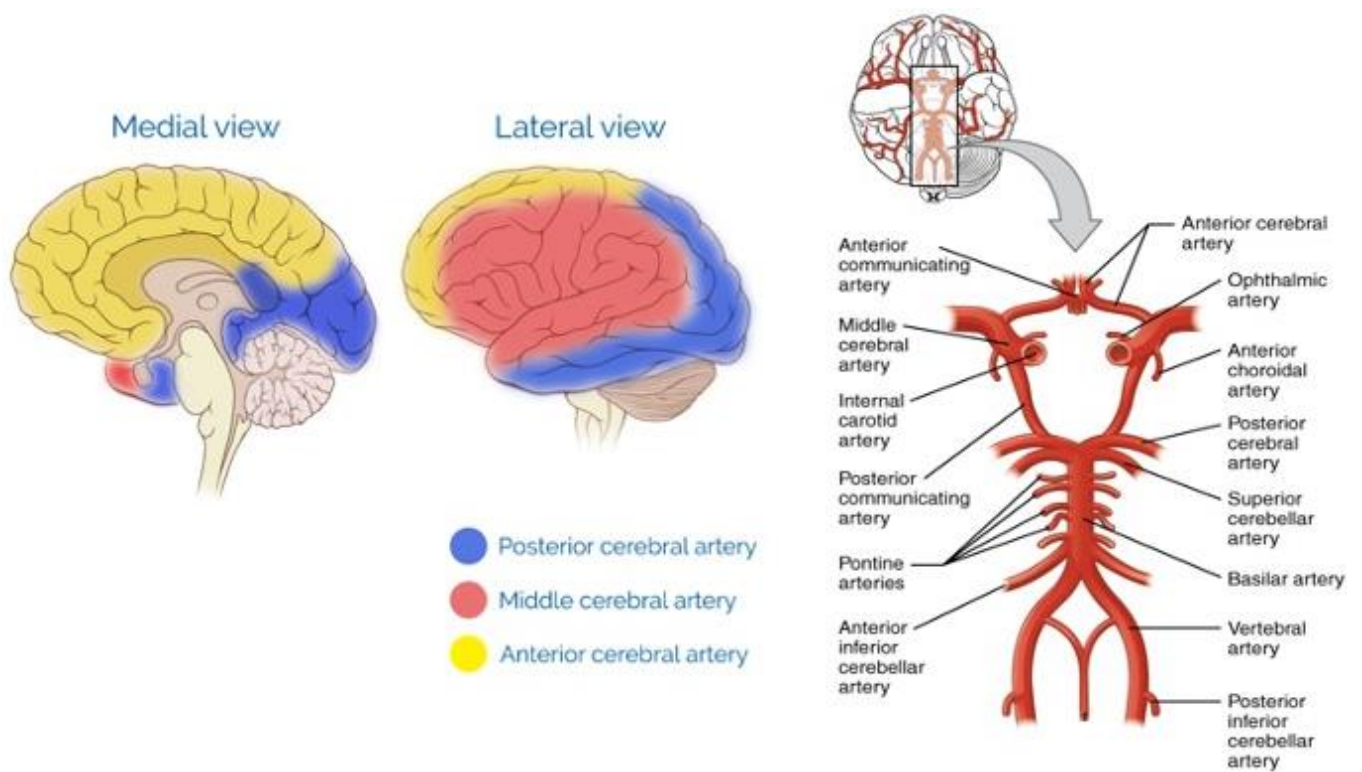


Figure 2.1 *Cerebral blood supply*

To the left are two images representing the vascular territories supplied by major cerebral arteries in the sagittal section in the medial and lateral views respectively (Adapted from the adaptation of Frank Gaillard and Patrick J. Lynch's work by Geeky Meds. Creative Commons license in Appendix A). To the right is an image of the trajectory of the cerebral arteries and the Circle of Willis (Adapted from the work by Open Stax. Creative Commons license in Appendix A).

2.1.2 Glucose regulation

Cerebral glucose is the primary source of energy for the human brain which is why maintaining glucose homeostasis is crucial for brain structure and function (Mergenthaler et al., 2013). It is vital to brain functions such as neurotransmitter release, adenosinetriphosphate (ATP) production, the management of oxidative stress and the regulation of cell apoptosis (Amoroso et al., 1990; Baumgartner-Parzer et al., 1995; Dienel, 2019; Gibson & Zhang, 2000). It also plays a role in neurovascular coupling, regulation of appetite and memory consolidation (Hossain et al., 2020; Ko et al., 1990; Mergenthaler et al., 2013). Glucose regulation in the human body relies on the cross-talk between pancreatic insulin and glucagon secretion (Kahn, Cooper, & Del Prato, 2014). Impairments in glucose metabolism can alter these functions and contribute toward AD risk.

Glucose supply to the brain is mediated via special glucose transporters that facilitate glucose supply via the BBB (Barbagallo & Dominguez, 2014; Cornford et al., 1994). Impaired glucose metabolism is seen in temporoparietal areas on FDG-PET in patients with early AD (section 1.6.2.2). This could be attributed to the down regulation of the glucose transporters that is commonly observed in AD (Gu et al., 2018; Liu et al., 2008). A downregulation of glucose transporters is also seen in normal ageing, which can contribute toward the glucose deficit in AD (Hooijmans et al., 2007b; Rahmoune et al., 2005). This phenomenon can not only increase tau phosphorylation, but can also impair glucose transport across the BBB and result in lower energy supply to the brain parenchyma (Cornford et al., 1994; Patching, 2017). This suggestion was supported by a study that showed decreased glucose transporters in known predilection sites for tau phosphorylation in AD that could contribute toward neurodegeneration (Liu et al., 2008). Additionally, higher amyloid load seen in ageing and conditions such as T2DM, obesity and hypertension can further impair glucose transport creating an additional energy deficit to the brain parenchyma (Bischof et al., 2016; Copani, Koh, & Cotman, 1991; Sweeney et al., 2018). Glucose dysregulation can significantly influence memory consolidation and structural atrophy in the hippocampus (a clinical hallmark of AD), which highlights other potential mechanisms through which glucose dysregulation could increase AD severity (Convit et al., 2003).

Different levels of circulating glucose can also alter the risk for AD. Hyperglycaemia, characterised by the chronic circulation of elevated glucose levels, is associated with the

generation of advanced glycation end products that have a detrimental effect on cerebral microvasculature (Goldin et al., 2006). Hyperglycaemia or chronically high circulating blood glucose levels are frequently comorbid in obesity and T2DM (He et al., 2009; Swislocki, Hoffman, & Reaven, 1989). Hypertension is often comorbid in obesity and T2DM, and hyperglycaemia in the presence of hypertension is even more deleterious to the cerebral constituents (Swislocki et al., 1989; Tarr et al., 2013; Tropeano et al., 2004). Hyperglycaemia is treatable, but a common problem with its treatment is achieving optimal glycaemic control and a strict medical regimen without frequent monitoring can result in intermittent episodes of hypoglycaemia (Miller et al., 2001; Turnbull et al., 2009). Both hyperglycaemia and acute and severe hypoglycaemic events have been associated with structural brain damage, cognitive decline and risk of dementia (Cox et al., 2005; Meneilly & Tessier, 2016; Puente et al., 2010; Wang et al., 2017; Whitmer et al., 2009). However, evidence for the association between recurrent moderate hypoglycaemic events and cognitive decline and dementia risk is currently lacking (Sheen & Sheu, 2016). Therefore, impairments in glucose regulation seen in AD and the presence of cardiovascular comorbidities could contribute towards neurodegenerative processes that increase AD severity.

2.1.3 Insulin resistance

Insulin contributes towards several key processes in the brain such as synaptic function and plasticity, nutrient homeostasis, neuroprotection and modulating cognition (especially memory) and mood (Blázquez et al., 2014; Cheng et al., 2000; Spinelli et al., 2017). The hormone enters the brain either as a function of endemic production or via the transport of peripheral insulin across the blood brain barrier, although the former has a limited evidence base (Arnold et al., 2018; Banks et al., 1997; Blázquez et al., 2014; Devaskar et al., 1994; Kullmann et al., 2015; Lacroix et al., 2008). Past work has shown *de novo* insulin production in brain areas that are implicated in memory which include the hippocampus, prefrontal cortex, olfactory bulb and the entorhinal cortex (Devaskar et al., 1994; Mehran et al., 2012). These areas are also known predilection sites vulnerable to neurodegeneration due to AD pathology, except for the olfactory bulb, which has variable vulnerability to the disease (Murphy, 2019; Servello et al., 2015; Thomann et al., 2009). Studies suggest that most of the brain's insulin is derived from pancreatic secretions via transport across the cerebrospinal fluid (CSF) and the BBB, where a majority of the insulin is delivered across the BBB (Banks, 2004; Gray, Meijer, & Barrett, 2014; Heni et al., 2015). Therefore, in conditions that induce systemic IR, a

condition in which the body is unable to process the effects of normally regulated insulin, there is a high probability that this pathological process could have detrimental effects on the brain and initiate neurodegenerative processes (Arnold et al., 2018; Moroz et al., 2008).

A current conundrum in the literature is that IR is seen in the brains of patients with AD in the absence of an underlying metabolic condition (Arnold et al., 2018; Talbot et al., 2012). IR has also previously been associated with memory deficits and structural hippocampal deficits, which are both seen in AD (Fadel & Reagan, 2016; Spinelli et al., 2017). IR initiates a pathological cascade promoting the build-up of AD pathology, neurodegeneration, and increasing neural vulnerability (Baranowska-Bik & Bik, 2019; Ma, Wang, & Li, 2015). Several studies have shown increased accumulation of A β plaques and NFT in the brain associated with IR, which is even higher in individuals carrying the APOE ϵ 4 allele (Craft et al., 2000; Ekblad et al., 2018; Matsuzaki et al., 2010; Špolcová et al., 2014; Starks et al., 2015; Willette et al., 2015). Moreover, insulin has vasodilatory properties that modulate the coupling of metabolic and haemodynamic homeostasis under normal conditions (Anderson & Mark, 1993; Miller et al., 2002; Xiang et al., 2008). Therefore, IR and resultant compromises in vasodilation can lead to irregularities in blood pressure, a factor that is additive to vascular dysfunction mediated cerebral insults (Hamburg et al., 2008; Han et al., 2011). IR, therefore, seems to foster neurodegenerative processes, the accumulation of AD pathology and the promotion of vascular dysfunction, all of which can increase AD severity.

2.1.4 Cholesterol regulation

Cholesterol is a lipoprotein that is essential for the maintenance of cellular membranes, while in the brain it largely contributes towards myelin sheath maintenance and composition (Cooper, 1978; Saher et al., 2005). Cholesterol has an age-dependent effect on AD risk, where high cholesterol in midlife is associated with increased AD risk, whereas high cholesterol in late-life is associated with reduced AD risk (Anstey, Ashby-Mitchell, & Peters, 2017; Kivipelto et al., 2001; Kivipelto et al., 2005; Mielke et al., 2005; Solomon et al., 2007). Like all lipoproteins, cholesterol can be categorised into low density lipoprotein (LDL), very low density (VLDL) and high density (HDL) cholesterol, respectively (Wang & Eckel, 2014). HDL cholesterol ('good' cholesterol) has antiatherogenic properties that promote reverse cholesterol transport and clearance of cholesterol from the rest of the body back to the liver (Rader et al., 2009).

LDL and VLDL cholesterol, on the other hand, promote atherosclerosis as these substrates facilitate the delivery of fat to cells, which can be deposited within arterial walls (Fernández-Friera et al., 2017; Knouff et al., 2004; Nakajima & Tanaka, 2018). Varying concentrations of different cholesterol density can also alter formations of AD-type pathological depositions (Reed et al., 2014). This was highlighted in a study which showed that AD patients had lower HDL cholesterol and higher LDL cholesterol levels compared to controls (Warren, Hynan, & Weiner, 2012).

The APOE protein is closely linked with modulating cholesterol action to facilitate neuronal growth, repair and maintenance (Boyles, Notterpek, & Anderson, 1990; Poirier et al., 1991). Among the different alleles of APOE, the $\epsilon 4$ allele has the highest binding affinity to VLDL cholesterol (Mamotte et al., 1999). This binding affinity to VLDLs confers a risk of developing atherosclerotic pathology in APOE $\epsilon 4$ carriers, a pathological process that can increase AD risk (Cheng et al., 2005; Li et al., 2013). Considering this relationship and the fact that APOE $\epsilon 4$ is one of the most significant modulators of AD risk, cholesterol could be the link between APOE and AD that contributes towards AD pathogenesis (Borroni et al., 2006; Hoshino, Kamino, & Matsumoto, 2002). Increased AD risk and risk of AD progression as a consequence of cholesterol and APOE $\epsilon 4$ interaction has been observed in several studies (Borroni et al., 2006; Evans et al., 2000; Hall et al., 2006). However, some work suggests that cholesterol can alter AD risk independent of APOE (Toro et al., 2014). This discrepancy could be explained via APOE independent tau phosphorylation discussed later in this section.

Cholesterol is associated with the increased accumulation of AD pathology. Higher brain cholesterol can increase accumulation of amyloid plaques by promoting the β -secretase cleavage of APP followed by γ -secretase, in the amyloidogenic pathway (Burns et al., 2003; Frears et al., 1999; Hughes et al., 2014; Reed et al., 2014). This increase in amyloid deposition could in turn increase tau hyperphosphorylation, thus increasing accumulation of AD pathology (Ghribi et al., 2006; Nicholson & Ferreira, 2009). On the contrary, there is evidence for increased tau phosphorylation in animals deficient in APOE activity indicating how cholesterol increases AD risk independent of APOE (Glöckner et al., 2011; Rahman et al., 2005). In addition to pathological depositions typical of AD, high circulating cholesterol also increases the risk for atherosclerotic plaque formation, resulting in reduced CBF that can contribute toward neurodegeneration (Gao et al., 2017; Seijkens et al., 2014).

Apart from modulating formation of pathological depositions, cholesterol can alter neuronal and cerebrovascular structure and function. High circulating cholesterol can increase BBB permeability, induce neuroinflammation, cause a loss of cholinergic function and reduce nitric oxide levels, altering vasodilation (Chen et al., 2008; Creager et al., 1990; Ehrlich & Humpel, 2012; Ullrich, Pirchl, & Humpel, 2010). Some of these pathological mechanisms can also lead to cognitive deficits in memory (Ullrich et al., 2010). Additionally, higher serum cholesterol levels can result in hypometabolism in known predilection sites for AD that is more pronounced in APOE ϵ 4 carriers (Reiman et al., 2010). Therefore, cholesterol can increase the risk of AD via interaction with APOE, vascular dysfunction and facilitating the accumulation of AD pathology.

2.1.5 Adipokine regulation

Adipokines or adipocytokines are secretions derived from adipose tissue that have several metabolic, endocrine and anti-inflammatory properties that can protect the brain against neurodegeneration and alter AD risk (Chen et al., 2009; Lee et al., 1999; Ng & Chan, 2017; Nicolas et al., 2017). Levels of circulating adipokines change in the presence of metabolic conditions such as T2DM and obesity that can independently alter AD risk (Misra et al., 2001; Silha et al., 2003). Unstable glucose metabolism can alter the expression and secretion of adipokines, which can in turn alter AD risk (Padilha et al., 2011; Wellhoener et al., 2000). This relationship can also be reciprocal, where altered serum adipokine levels can alter glucose metabolism and insulin action, although this effect is indirect and is executed via secretions from the hypothalamus following signalling from adipokines (Bates et al., 2004; Frühbeck & Salvador, 2000; Koch et al., 2010; Minokoshi, Haque, & Shimazu, 1999).

2.1.5.1 *Leptin*

Leptin (also known as the ‘satiety hormone’) is a hormone derived from adipose tissue that helps regulate appetite through communication with the hypothalamus in addition to altering glucose metabolism and insulin sensitivity (Koch et al., 2010; Morton et al., 2005; Van De Wall et al., 2008; Zimmet et al., 1998). Leptin has a number of beneficial effects on the brain that can help preserve brain structure in the presence of conditions inflicting cerebrovascular insults (Dicou, Attoub, & Gressens, 2001; Zhang et al., 2007a). Higher circulating leptin levels

in late-life reduce AD risk (but not in obese individuals), whereas midlife leptin levels are not associated with AD risk (Gustafson et al., 2012; Lieb et al., 2009; Zeki Al Hazzouri et al., 2013). Therefore, higher circulating leptin as a function of higher body mass could be protective against neurodegeneration in late-life in the presence of age-related weight loss (Lieb et al., 2009; Power et al., 2011). Higher circulating leptin levels are associated with increasing body mass, but this relationship is reversed when correlating circulating leptin levels with abdominal fat mass (Lönngqvist, Wennlund, & Arner, 1997; Perego et al., 2005). On the contrary, intra-abdominal fat mass is associated with IR, while subcutaneous fat mass is associated with elevated levels of leptin (Cnop et al., 2002). Age-related changes in body fat distribution (specially increasing abdominal mass) could thus play a role modulating circulating leptin levels, which alter AD risk. Lower leptin levels have previously been found in AD patients (Baranowska-Bik et al., 2015; Warren et al., 2012). Additionally, gender could also play a role in leptin action and AD risk, where age-related reductions in leptin are seen in women, an association that is absent in men (Schautz et al., 2012). This could confer a higher risk of AD in women due to comparatively reduced protective actions of leptin against neurodegeneration in AD (Schautz et al., 2012).

Leptin has several properties that protect the brain against neurodegeneration. One of these properties is the role of leptin in preventing amyloid accumulation (Greco et al., 2009; Niedowicz et al., 2013; Perez-Gonzalez et al., 2014). Amyloid accumulation on the other hand could be a driver of weight loss, which can in turn lower leptin secretion, thereby reducing its protective effects (Ishii et al., 2014; James, Kang & Park, 2014). In addition to amyloid accumulation leptin action can also attenuate tau phosphorylation and reduce AD risk (Greco et al., 2008; Marwarha et al., 2010). Moreover, leptin plays a significant role in synaptic plasticity and therefore has important implications in promoting memory function (Greco et al., 2010; Oomura et al., 2006). It is already known that hampered synaptic plasticity and memory deficits are early features of AD, therefore altered leptin function could reduce its beneficial effects on memory and plasticity, increasing AD risk (section 1.3.4.1, Para 1; section 1.4.4).

Similar to its effect on neuronal function, leptin can also have a protective effect on cerebrovascular function. Leptin treatment in rats with cerebrovascular damage showed improved vascular tone over a course of twenty-four hours, pointing towards beneficial effects of leptin on vascular function (Busch et al., 2011). Leptin delivery to the brain is mediated by

transporters located in the BBB; increased BBB permeability in AD and cardiovascular diseases reduces leptin delivery to the brain parenchyma and this reduction can lead to neurodegeneration (Banks, Kastin, Huang, Jaspán, & Maness, 1996; Stranahan et al., 2016). Recent evidence also suggests that a deficiency in leptin receptors could be implicated in BBB disintegration, which increases AD risk (Corem et al., 2019). Leptin can also modify sensitivity to insulin and therefore regulate insulin-mediated mechanisms such as vascular compliance that could alter CBF (Haffner et al., 1997; Segal, Landt, & Klein, 1996). Therefore, reduced sensitivity to leptin can increase AD risk, which is seen in obesity, T2DM and normal ageing (Gabriely et al., 2002; Platt et al., 2016).

2.1.5.2 Adiponectin

Adiponectin is another adipokine that has distinct effects to leptin and it acts by increasing energy expenditure to create a negative energy balance. Unlike leptin, higher body mass is associated with lower levels of adiponectin (Arita et al., 1999; Coimbra et al., 2014). This is because changes in levels of adiponectin and leptin as a factor of ageing are inversely related, which can be independent of age-related changes in body fat distribution (Schautz et al., 2012, section 1.2.1.1, Para 3). However, adiponectin levels tend to reach higher thresholds with increasing age, which are even higher in women compared to men (Cnop et al., 2003; Schautz et al., 2012). Higher plasma adiponectin levels can be found in AD patients, are associated with increased cardiovascular risk and can also be a strong predictor of clinical outcomes following ischaemic cerebral injury (Shen et al., 2014; Une et al., 2011). This claim has been supported by studies that have found higher adiponectin levels in AD patients compared to controls (Khemka et al., 2014; Letra et al., 2019). Similar to leptin, effects of adiponectin on the brain seem to be modified by gender, where women show cognitive deficits associated with higher adiponectin levels (van Andel et al., 2020). It is possible that these gender differences in adiponectin action could confer a higher AD risk in women. This notion is supported by a study which showed that adiponectin levels were associated with a heightened AD risk in women (Van Himbergen et al., 2012).

Adiponectin can significantly alter AD risk by influencing the formations of AD pathological accumulations primarily by altering insulin sensitivity. A study showed that decreased insulin sensitivity as a consequence of chronic deficiency of adiponectin led to the increased accumulations of A β and hyperphosphorylated tau in addition to the presentation of memory

and spatial deficits in mice (Ng et al., 2016). These mice also exhibited neuronal and synaptic loss (Ng et al., 2016). Most importantly, mechanisms of adiponectin can protect the brain and the BBB against A β induced neurotoxicity and inflammation (Chan et al., 2012; Jian et al., 2019; Song et al., 2017). Additionally, adiponectin has myriad beneficial effects on vascular function that can reduce risk for cardiovascular diseases and therefore could have implications for neurodegeneration in AD (Kojima et al., 2003; Pischon et al., 2004). An example of such an effect is reductions in atherosclerotic accumulations attributed to the mechanisms of adiponectin (Bang et al., 2007; Yamauchi et al., 2003). Studies have also shown adiponectin involvement in the generation of endothelial cell mediated nitric oxide production that helps in the regulation of blood pressure, which could affect vascular function and therefore neurodegeneration (Cheng et al., 2007; Osuka et al., 2012). Therefore, adiponectin can alter AD risk by reducing the risk for cardiovascular diseases and altering AD pathological accumulations by modulating insulin sensitivity and vascular function, which is more pronounced in women.

2.1.6 Neurodegeneration

There are multiple downstream mechanisms of cardiovascular risk factors that can contribute toward neurodegenerative processes. One of these mechanisms is mitochondrial dysfunction, a phenomenon seen in ageing, AD and metabolic conditions such as T2DM and obesity (Bach et al., 2005; Hirai et al., 2001; Pugazhenti, Qin & Reddy, 2017; Zorzano et al., 2009). The mitochondria produce energy in the form of ATP which is derived from glucose, the primary energy source for the brain (Drew & Leeuwenburgh, 2003). The formation of ATP involves closure of ATP-sensitive potassium channels and high influx of intracellular calcium that facilitates insulin secretion (Fuhrer, Kobayashi & Jiang, 2001). Glucose is transported across the BBB via specialised glucose transporters (section 2.1.2, Para 2). Impairment in glucose transport and increased BBB permeability that can induce hypoxia is seen in metabolic conditions such as T2DM and obesity and could therefore result in reduced ATP delivery to the brain parenchyma (Minet & Gaster, 2010; Tran et al., 2019).

Mitochondria within the endothelial cells power sodium-potassium and calcium pumps using ATP that control the levels of substrates within the interstitial fluids (Lee et al., 2003; Rottenberg, 1973). Levels of these substrates control action potentials that regulate neuronal activity and can also modulate vasodilation (Erecińska & Dagani, 1990; Filosa et al., 2006).

Therefore, mitochondrial dysfunction observed in the presence of cardiovascular risk factors, ageing and AD impairs synaptic plasticity and vascular function. Mitochondrial dysfunction additionally contributes toward accumulation of oxidative stress that eventually leads to cell death (Ott et al., 2007). Elevated oxidative stress, primarily a consequence of mitochondrial dysfunction, is a central feature seen in ageing, AD, obesity, T2DM and hypertension (Finkel & Holbrook, 2000; Furukawa et al., 2017; Minuz et al., 2002; Monnier et al., 2006; Zafrilla et al., 2006). It also has a reverse causal effect where elevated oxidative stress can damage mitochondria (Belhadj Slimen et al., 2014; Liu et al., 2012).

Vascular dysfunction seen in conditions such obesity, T2DM and hypertension can reduce blood supply to neurons and create hypoxic conditions that can initiate a pathological cascade of mechanisms that leads to neurodegeneration. In turn, hypoxia can induce inflammation via the activation of microglia and inflammatory mediators, increase oxidative stress and BBB permeability (Brooks et al., 2005; Stolp et al., 2005). Low-grade inflammation resulting from the release of inflammatory mediators is also commonly observed in ageing and in the presence of cardiovascular risk factors (Zhang et al., 2017a; Zhao et al., 2004). Additionally, modulators of neuroinflammation are found in AD patients that add further detriments to neurons in the presence of vascular hypoxia mediated insults (Zhang et al., 2017a). Hypoxic conditions also facilitate the accumulation of neurotoxic products such as A β and hyperphosphorylated tau that can result in neuronal death (Gao et al., 2013; Raz et al., 2019). Hypoxia facilitates the splicing of APP via the amyloidogenic pathway in addition to promoting tau phosphorylation that can increase AD neuropathological accumulation (Li et al., 2009). The corollary of effects resulting from cardiovascular risk factor-induced hypoxia thus contributes towards promoting neurodegenerative processes that increase AD risk or could increase the severity of the disease.

2.1.7 Neuropathology in vascular comorbidities

2.1.7.1 AD pathology in vascular comorbidities

2.1.7.1.1 Obesity

Obesity has previously been associated with higher accumulations of AD pathology. Neuropathological examination and amyloid imaging in demented and non-demented individuals revealed that higher midlife body mass index was associated with a higher burden

of AD pathology (Chuang et al., 2016). The same study showed that each unit increase in body mass index predicted an earlier onset of AD (Chuang et al., 2016). A different study showed similar neuropathological findings of AD pathology in the brains of a small sample of elderly morbidly obese individuals (Mrak, 2009). However, some studies using animal models show no evidence of obesity-mediated formations of AD pathology (Moroz et al., 2008; Niedowicz et al., 2014), while other studies show contradictory evidence (Ho et al., 2004; Walker et al., 2017). Niedowicz and colleagues also proposed that obesity/T2DM in mice could induce vascular dysfunction that can alter cognition and that this could be independent of A β deposition (Niedowicz et al., 2014). Similar to what is seen in T2DM, accumulation of AD pathology in obesity can be higher in the presence of the APOE ϵ 4 allele (Moser & Pike, 2017). However, lower AD pathological accumulation is also observed in obese carriers of APOE ϵ 4 who also show slower progressive cognitive decline and higher metabolism in the posterior cingulate regions (Blautzik et al., 2018). It is possible that higher leptin circulation seen in individuals with higher BMI could provide protection against age and disease related insults (leptin) in late-life (section 2.1.5.1). Therefore, the relationship between obesity and AD risk needs to be examined more closely.

2.1.7.1.2 Hypertension

Similarly, hypertension is also associated with the increased accumulation of AD pathology. A study showed higher depositions of senile plaques and NFT in hypertensive individuals than patients with coronary artery disease and controls (Sparks et al., 1995). This was supported by a study in rats, which showed increased A β depositions in hypertensive animals (Diaz-Ruiz et al., 2009). As is seen in T2DM, medication seems to attenuate the formation of AD neuropathology in hypertensive individuals (Hoffman et al., 2009). Analogous to the effects seen in obesity and T2DM studies, APOE ϵ 4 significantly modulates cerebral AD neuropathological accumulation. A study by Jeon and colleagues showed increased A β depositions in hypertensive APOE ϵ 4 carriers while non-carriers exhibited reductions in cortical thickness similar to those observed in AD (Jeon et al., 2019). An unusual finding in the same study was lower A β depositions in hypertensive AD patients compared to normotensive AD patients that was independent of APOE status (Jeon et al., 2019). It is possible that this discrepancy could be explained by the effect of medication on the attenuation of AD neuropathological accumulation in hypertensive AD patients (Hoffman et al., 2009).

2.1.7.1.3 Type 2 Diabetes

There is some degree of variability in the neuropathological accumulations observed in T2DM and hypertension. Although AD and T2DM share several pathophysiological mechanisms, evidence shows that T2DM is not commonly associated with the deposition of A β plaques and NFTs (Abner et al., 2016; dos Santos Matioli et al., 2017; Malek-Ahmadi et al., 2013). In fact, patients with diabetes present with lower pathological depositions typical of AD, than those without diabetes (Ahtiluoto et al., 2010; Beeri et al., 2005). It is possible that the medical regimen among these patients could have alleviated the pathological processes facilitated in T2DM that could explain the lack of AD-like pathological depositions (Ahtiluoto et al., 2010a; Beeri et al., 2005). This was supported by an animal study which showed that in obese, leptin-resistant mice, administration of metformin (a medication used for glycaemic control in T2DM) limits the accumulation of AD pathology (Li et al., 2012). However, accumulations of A β plaques do seem to increase with longer duration of T2DM (Janson et al., 2004; Zhang et al., 2017c). A subset of studies that looked at APOE status also showed that individuals with T2DM carrying the APOE ϵ 4 allele did show the presence of typical AD pathology (dos Santos Matioli et al., 2017; Malek-Ahmadi et al., 2013; Peila, Rodriguez, & Launer, 2002). Therefore, interactions between APOE ϵ 4 and diabetes duration could pose a higher risk for AD as opposed to a diabetes diagnosis by itself.

2.1.7.2 Vascular pathology in comorbidities

2.1.7.2.1 Obesity

In obesity, there is evidence to show cerebrovascular pathological depositions that can increase AD risk. Increasing waist to hip ratio is associated with a higher burden of white matter hyperintensities (WMH) that is independent of the effects of blood pressure and glucose levels (Marini et al., 2020). Animal studies support these associations and have shown vascular dysfunction and cognitive impairment associated with diabetes and obesity (Niedowicz et al., 2014). Particularly, high visceral fat is linked with the development of WMH in obese individuals and this relationship is mediated by the release of proinflammatory markers seen in such patients (Lampe et al., 2019). The WMH exhibit a preference to form in the prefrontal cortex in obesity that can alter functional and structural connectivity (Cohen, Cazettes, & Convit, 2011; Park et al., 2020). The prefrontal cortex is not affected by AD until later stages,

therefore vascular pathology in this brain region resulting from obesity could increase the severity of AD (section 1.6.1).

2.1.7.2.2 Hypertension

Hypertension on the other hand, has largely been associated with the formation of cerebral microbleeds, especially in subcortical structures and cerebral white matter (De Leeuw et al., 2002; van Dijk et al., 2004). A study by Hajjar and colleagues showed a high frequency of WMH in hypertensive individuals. These WMH were also associated with impairments in cognition and mood alterations (Hajjar et al., 2011). The co-occurrence of cerebral amyloid angiopathy observed in AD and hypertension-induced small vessel disease can result in more profound effects on brain structure and function, by increasing the risk for intracranial haemorrhage (Ritter et al., 2005). Cerebral amyloid angiopathy not only obstructs blood flow, but it is also a cause for increased BBB permeability and increased accumulation of AD pathology (section 1.4.1.1). However, cerebral amyloid angiopathy and hypertension induced small vessel disease tends to affect varied brain regions that are not typically affected in AD (Pasi et al., 2017). Therefore, comorbid hypertension could increase disease severity in AD patients.

2.1.7.2.3 Type 2 Diabetes

It has already been established that T2DM contributes towards the development of vascular pathology (Paneni, Costantino, & Cosentino, 2014). Studies have shown more frequent occurrences of cerebrovascular pathology as opposed to depositions of typical AD pathology in T2DM, and these have been associated with deficits in cognition (Abner et al., 2016; Ahtiluoto et al., 2010; Nelson et al., 2009). This finding was supported by a meta-analysis which showed that T2DM patients had a higher frequency of cerebral infarcts than AD pathology and that this higher frequency lowered the threshold of AD pathology required for a clinical dementia diagnosis (Vagelatos & Eslick, 2013). The same study showed that dementia is associated with both AD pathology and cerebrovascular lesions (Vagelatos & Eslick, 2013). Therefore, it is possible that cognitive deficits and neurodegeneration seen in T2DM might stem from the cumulative effects of cerebrovascular and AD pathology. Additionally, vascular dysfunction mediated by T2DM can also facilitate neurodegenerative mechanisms, thereby increasing the risk of AD (Di Marco et al., 2015).

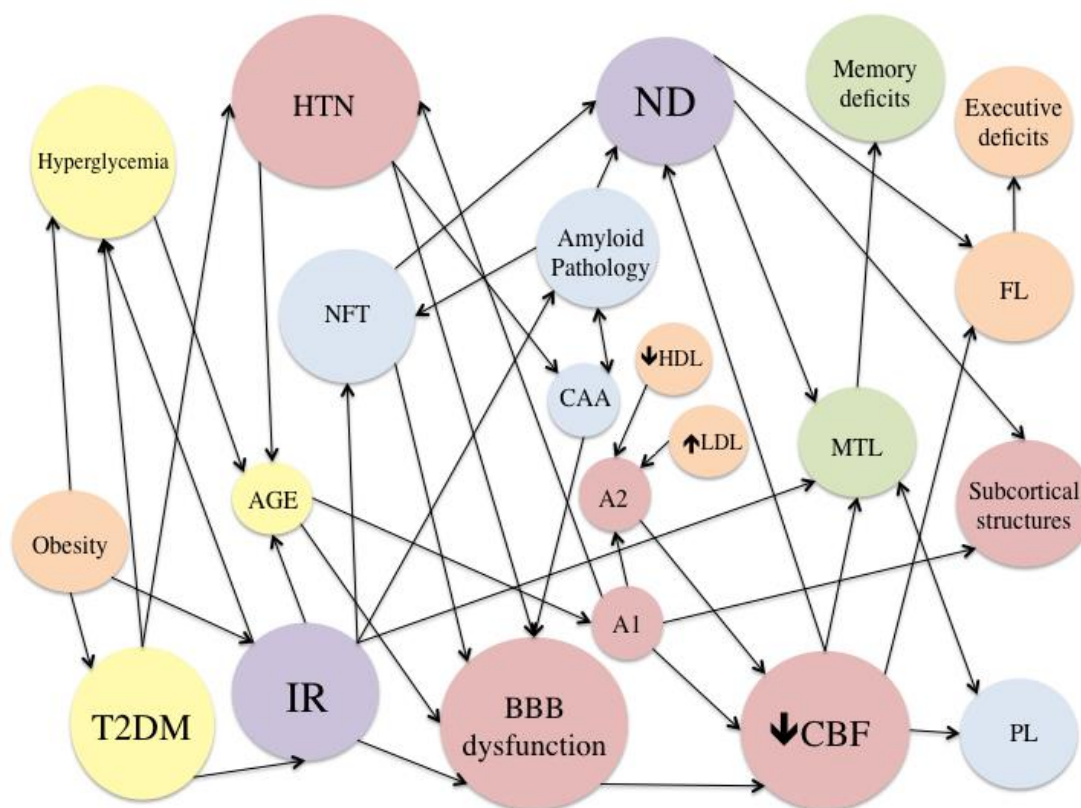


Figure 2.2 Shared mechanisms between obesity, T2DM and hypertension that contribute toward AD risk or AD progression

Key: The following colours represent the specific effects exerted by the respective conditions (It is important to note that although the image indicates a detrimental effect of specific conditions on cognitive domains and specific brain regions, it represents a predominant effect of that condition and that the cognitive domains and brain regions can be affected by other factors in addition to those represented in the image by the respective colours)

Yellow: T2DM; Orange: Obesity; Blue: AD; Purple: T2DM + Obesity + T2DM; Green: AD + T2DM; Red: Vascular dysfunction.

Abbreviations: AGE: Advanced glycation end products; A1: Arteriosclerosis; A2: Atherosclerosis; BBB: Blood brain barrier; CAA: Cerebral amyloid angiopathy; CBF: Cerebral blood flow; FL: Frontal lobe; HDL: High density lipoprotein; HTN: Hypertension; IR: Insulin resistance; LDL: Low density lipoprotein; MTL: Medial temporal lobe; ND: Neurodegeneration; NFT: Neurofibrillary Tangles; PL: Parietal lobe

This image has been altered and reused from the work by Osman et al., 2020 (Shabir et al., 2020). Permissions to alter and reuse image obtained from the authors (Appendix A). Link to manuscript included in Appendix D, D.2.

2.2 Risk factors for AD and Cardiovascular Disease

2.2.1 Lifestyle factors

2.2.1.1 Diet

Diet plays a vital role in regulating blood pressure, glucose homeostasis, fat percentage and hormones (Blumenthal et al., 2010; Miyashita et al., 2004; Norat, 2019; Sacks et al., 2001). With the advancements in technology, there has been a rapid growth in the food distribution industry, making access to a broad variety of food, especially fast food, a widely available commodity (Ludwig, 2011; Popkin, 2015). Consumption of fast food has increased significantly in developing countries due to aggressive campaigning from multinational food corporations to increase their consumer market (Kearney, 2010). This trend has contributed toward the obesity pandemic and towards the simultaneous increase in the incidence of T2DM, obesity and hypertension (Commodore-Mensah et al., 2018; Kotsis et al., 2018; Price et al., 2018; Zobel et al., 2016). This increasing prevalence of CRF has led to an increased risk of AD (Hazar et al., 2016; Luchsinger et al., 2005).

On the other hand, diet composition can significantly contribute toward modulating cardiovascular risk. A meta-analysis investigating ‘how diet can modify the risk of developing T2DM,’ showed that whole grain, cereal fibre and moderate levels of alcohol intake reduced the risk of developing cardiovascular risk factors (Norat, 2019). Conversely, it also showed that the consumption of processed meat, sweetened drinks and red meat was associated with increased risk of developing cardiovascular risk factors (Norat, 2019). Nevertheless, the independent effect of diet on the risk of cardiovascular risk factors cannot be isolated and needs to be adjusted depending on other lifestyle tendencies. The dietary approach to stop hypertension that advocates increased consumption of fruits and vegetables and decreased consumption of high-fat dairy products has also proven effective in reducing overall cardiovascular risk (Blumenthal et al., 2010; Moore et al., 2001). Although diet by itself can help reduce cardiovascular risk, when adhered to in combination with aerobic activity and caloric restriction, it has a broad range of benefits that include weight loss, improved glucose regulation and insulin sensitivity in addition to lowering the levels of circulating total cholesterol and triglycerides (Blumenthal et al., 2010). A meta-analysis on this dietary approach showed a significant reduction in cardiovascular risk and blood pressure while

simultaneously indicating a potential attenuation of the Framingham risk score for cardiovascular disease (Siervo et al., 2015). Following the Mediterranean diet has also shown relatively reduced risk of cardiovascular disease and AD (Sofi et al., 2008). The dietary approach to stop hypertension, the Mediterranean diet and a hybrid of the two have all shown promise of reducing AD risk (Morris et al., 2015; Sofi et al., 2008). Therefore, diet that is rich in fresh food, whole grains and legumes, low in saturated and trans fats is recommended to help reduce cardiovascular risk and therefore AD risk (Barnard et al., 2014).

2.2.1.2 Alcohol consumption

There is conflicting evidence regarding alcohol consumption and dementia risk (Verplaetse et al., 2020; Wiegmann et al., 2020). This conflicting evidence may arise from the quantity and frequency of alcohol consumption. High consumption of alcohol is associated with elevated cardiovascular risk, especially high blood pressure (Foerster et al., 2009; Nanchahal, Ashton, & Wood, 2000). Research indicates that heavy alcohol use increases the risk of AD, reduces the age of onset, in addition to accelerating disease progression (Harwood et al., 2010; Heymann et al., 2016; Rehm et al., 2019; Xu et al., 2017). However, there is conflicting meta-analytical evidence indicating that there is no difference in dementia risk between heavy drinkers and individuals who do not drink (Anstey, Mack, & Cherbuin, 2009). On the other hand, light to moderate consumption of alcohol has largely been associated with reduced risk of cardiovascular disease, thus reducing AD risk (Albert et al., 1999; Foerster et al., 2009; Naimi et al., 2005; Xu et al., 2017). This association may also be age-dependent where moderate alcohol consumption in late-life may reduce dementia risk (Anstey et al., 2009; Huang et al., 2002). There is some evidence for the type of alcohol consumption and AD risk where consumption of beer and wine is considered less harmful than hard liquor in modulating dementia risk (Heymann et al., 2016; Luchsinger et al., 2004). This is conflicted by findings from the Rotterdam study that found no difference in the type of alcohol and dementia risk (Ruitenberg et al., 2002). A different study showed that a higher frequency of alcohol consumption is associated with higher AD risk (Langballe et al., 2015). Therefore, it appears that heavy alcohol consumption with high frequency can increase AD risk, whereas low to moderate alcohol consumption, especially in late-life is associated with reduced AD risk.

2.2.1.3 Exercise/ Physical Activity

Exercise plays a pivotal role in reducing cardiometabolic risk. High levels of physical inactivity can promote the development of visceral adiposity, cardiovascular irregularities, hypertension, insulin resistance and atherosclerosis, consequently increasing the risk of the development of cardiovascular disease and AD (Fogelholm et al., 2007; Hamburg et al., 2007; Sobngwi et al., 2002). Moreover, physical activity can facilitate improvements in cognitive performance in addition to protection from myriad other conditions such as cancer, that significantly reduce quality of life and increase rates of disability and mortality (Neufer et al., 2015; Weuve et al., 2004). Physical activity can also reduce AD risk by modulating levels of AD pathology, stimulating the production of neurotransmitters and growth factors and reducing inflammation (Coelho et al., 2014; Law et al., 2018; Ryan & Kelly, 2016; Sutoo & Akiyama, 2003). A study also showed that cardiorespiratory fitness can reduce AD risk in at-risk individuals (Boots et al., 2015). In the study, higher cardiovascular fitness was associated with higher grey matter volume (GMV) in areas that are known predilection sites for AD, lower burden of WMH and also better cognitive performance (Boots et al., 2015). A different study showed that while aerobic and mind-body exercises helped reduce dementia risk, stretching and toning exercises were not associated with reduced dementia risk (Lee et al., 2015). Even leisurely physical activity such as walking can help reduce dementia risk (Abbott et al., 2004; Ogino et al., 2019; Rovio et al., 2005). It is evident that following regular exercise regimes can significantly reduce AD risk (Cox et al., 2019a; Dougherty et al., 2016; Ogino et al., 2019).

2.2.1.4 Smoking

Smoking can significantly increase AD risk by influencing the cardiovascular system, inducing neuroinflammation and facilitating the accumulation of AD pathology. One of the key pathological effects of smoking is elevated production of reactive oxidative species that can increase oxidative stress and neuroinflammation, both of which are seen in AD (Al Rifai et al., 2017; Khanna et al., 2013). In addition to these factors, smoking can also facilitate vascular dysfunction that contributes toward AD risk. Tobacco smoke can result in reduced integrity of the BBB in addition to promoting atherogenic processes, both of which can reduce CBF (Kianoush et al., 2017; Lee et al., 2017). Other ways smoking can alter blood flow are by restricting nitric oxide synthesis, which can hamper vasomotion and vascular tone, therefore affecting CBF (Kugiyama et al., 1996; Morita-Tsuzuki, Bouskela, & Hardebo, 1993).

Additionally, smoking can accelerate the accumulation of AD pathology. Animal studies have shown increased amyloid accumulation, and tau phosphorylation associated with cigarette smoke (Ho et al., 2012; Moreno-Gonzalez et al., 2013). The downstream pathological effects of smoking that increase AD risk can also result in deficits in cognition and cerebral glucose metabolism that are most pronounced in APOE ϵ 4 carriers (Durazzo et al., 2015).

Smoking can interact with the APOE ϵ 4 allele to modify AD risk significantly. Studies have shown that midlife smoking was associated with a higher AD risk in APOE ϵ 4 carriers in comparison to non-carriers (Kivipelto et al., 2008; Rusanen et al., 2010). However, there is contradictory evidence that indicates the opposite where increased dementia risk is more prominent in smokers who are non-carriers of APOE ϵ 4 compared to smokers who are carriers (Ott et al., 1998; Reitz et al., 2007a). It is possible that elevated cardiovascular risk in APOE ϵ 4 smokers could have increased risk for mortality before individuals could develop AD (Grammer et al., 2013; Jacobsen et al., 2010). Additionally, both studies were derived from cohorts from the Rotterdam study that could explain the discrepancy in the findings from these studies and other studies (Ott et al., 1998; Reitz et al., 2007a).

2.2.2 Modifiable risk factors

2.2.2.1 Obesity

Obesity, which is a condition characterised by excess body fat can significantly increase the risk for cardiovascular disease and AD (Pérez et al., 2007; Xu et al., 2011). Higher body fat can negatively influence the vascular system and cause alterations in CBF that is detrimental to neural health (Selim et al., 2008; Willeumier, Taylor, & Amen, 2011). However, this relationship can change across the lifespan as there are age-related changes in body fat metabolism and distribution (Arner et al., 2019; Unger, 2005). Studies examining dementia risk and indices of body mass have found a paradoxical relationship between these two variables which show that higher body mass in midlife can increase dementia risk whereas higher body mass in late-life is associated with reduced dementia risk (Fitzpatrick et al., 2009; Hughes et al., 2009; Kivimäki et al., 2018; Whitmer et al., 2007; Xu et al., 2011). Findings from the study by Kivimaki and colleagues highlighted this, where BMI measured more than twenty years before dementia onset was associated with increased dementia risk while BMI measured less than ten years before dementia onset was associated with reduced dementia risk

(Kivimäki et al., 2018). Considering that the age of onset for dementia is in the later decades of life, BMI measured twenty years before the age of dementia onset could be closer to midlife. Higher midlife BMI has the most negative effects on the brain compared to other stages of life (Anstey et al., 2011; Fitzpatrick et al., 2009; Pedditizi et al., 2016). The obesity paradox is further supported by a study that showed that in late-life, there was a reduction in dementia risk with higher baseline BMI and slower rate of decline in BMI (Hughes et al., 2009). The same study also showed that a rapid decline in BMI could be indicative of preclinical AD, which could be more pronounced for individuals who have a history of obesity or overweight (Hughes et al., 2009). The obesity paradox could be due to observed age and disease-related weight loss, where higher BMI in late-life could help preserve neural constituents and help the brain cope with damage via the availability of additional resources and better nutrition (Buchman et al., 2005; Hsu et al., 2015; Lieb et al., 2009; Pancani et al., 2013). Therefore, it is evident that higher BMI in midlife increases the risk for AD while late-life high BMI could have some protective effects against neurodegeneration in the disease. Nevertheless, a majority of the studies on obesity do not consider the effect of sex.

Detrimental effects of obesity in midlife that increase the risk for cognitive decline and AD could be attributed to inflammatory pathways activated by obesity (de Kloet et al., 2014; Jayaraman, Lent-Schochet, & Pike, 2014a; Pugazhenthii et al., 2017). In obesity, a release of pro-inflammatory cytokines is observed due to the initiation of an immune response via toll-like receptors (TLR) (DeFuria et al., 2013; Mohamed-Ali et al., 1997). Low grade systemic inflammation as a result of higher circulating pro-inflammatory cytokines can in turn lead to IR and facilitate neurodegeneration, increasing AD risk (Hildreth, Van Pelt, & Schwartz, 2012; Ho et al., 2004; Hunter et al., 2007; Matsuzaki et al., 2010; Yudkin et al., 1999). Defective insulin action and neuroinflammation can not only contribute toward accumulation of AD pathology, but it can also alter BBB permeability resulting in a reverse causal effect which can increase pathological depositions typical of AD (Clifford et al., 2007; Huber, VanGilder & Houser, 2006; Iadecola, 2015; Matsuzaki et al., 2010; Pluta et al., 2006; Takechi et al., 2017). Systemic inflammation can also induce mitochondrial dysfunction (a phenomenon often seen in metabolic conditions like obesity), facilitating neurodegenerative processes by elevating levels of oxidative stress (Arruda et al., 2014; Hunter et al., 2007). Obesity is also associated with high total cholesterol, which can facilitate atherogenesis that furthers the contributions towards neurodegeneration in AD via the vascular dysfunction route (Casserly & Topol, 2004; Garrison et al., 1980; Kivipelto et al., 2005; Kusters et al., 2017). The metabolic dysfunction

seen in obesity can also increase the risk for other cardiovascular risk factors such as T2DM and hypertension, which are independent risk factors for AD (Lavie, Milani, & Ventura, 2009). Therefore, systemic inflammation, mitochondrial dysfunction, increased oxidative stress and vascular dysfunction can contribute toward obesity-mediated neurodegeneration and increase AD risk. Moreover, a longer duration of such an obesogenic profile could explain why mid-life obesity poses a higher risk for AD than in late-life (Fitzpatrick et al., 2009).

2.2.2.2 Hypertension

Hypertension is defined as the ‘chronic elevation of systemic arterial pressure above a thresholded value’ that can significantly alter haemodynamics and vascular architecture (Giles et al., 2005; Giles et al., 2009; Williams et al., 2018). Similar to obesity and several other cardiovascular risk factors, hypertension at midlife is a risk factor for AD, especially uncontrolled hypertension (Launer et al., 2000; Lennon et al., 2019; Livingston et al., 2017). A majority of the AD risk conferred from possessing chronically high blood pressure is the resultant irreversible vascular damage that can contribute toward neurodegeneration (de la Torre, 2012). At the microvascular level, hypertension can increase BBB permeability by damaging components of the neurovascular unit (de Montgolfier et al., 2019; Van Deurs, 1976). This can lead to the extravasation of plasma contents into the brain parenchyma, increasing AD pathological accumulations, which could be more pronounced in APOE ϵ 4 carriers (Clifford et al., 2007; Iadecola, 2015; Jeon et al., 2019; Pluta et al., 2006). Amyloid accumulation in AD can be seen around cerebral microvessels (also known as cerebral amyloid angiopathy) and this process is aggravated by hypertension (Cifuentes et al., 2015; Faraco et al., 2016; section 1.4.1.1). Hypertension, in combination with cerebral amyloid angiopathy can increase the risk for cerebral microbleeds that are more prominent in deep brain regions and can contribute toward neurodegeneration, cognitive decline and AD dementia (Akoudad et al., 2016; De Reuck et al., 2011; Gurol et al., 2012; Romero et al., 2014). These alterations are largely irreversible and therefore, pathological burden due to hypertension tends to accumulate across the lifetime. Hypertension is also accompanied with a prolonged asymptomatic or ‘silent’ phase, which can result in significant irreversible cerebral damage before treatment can be initiated (Cova et al., 2013). Therefore, strategies to improve primary prevention measures could help reduce the damaging effects of hypertension on the brain and reducing AD risk (section 1.8).

Microvascular damage inflicted by hypertension can negatively impact CBF at the macrostructural level in AD. Increased amyloid load mediated by hypertension can form depositions within capillaries and constrict them, therefore causing a reduction in rCBF (Carrano et al., 2011; Nortley et al., 2019). Evidence also shows that alterations in haemodynamics of blood vessels in hypertension can damage the delicate structure of distal cerebral microvasculature (Scuteri, 2012). Variations in blood pressure can also be attributed to age-associated arterial stiffening and consequent erratic changes in arterial blood pressure (Lam et al., 2009; Laogun & Gosling, 1982). These erratic ‘bursts’ or pulses of blood can damage the walls of arteries and further reduce rCBF (Lam et al., 2009). Moreover, arterial stiffening can increase pulse pressure (the difference between systolic and diastolic blood pressure) that increases the risk for neural damage, which is more pronounced in APOE ϵ 4 carriers (Dao et al., 2005; Mitchell et al., 2011; Nation et al., 2016; Wallace et al., 2007). Hypertension can also impair neurovascular coupling which can manifest as detriments in cognitive function (Capone et al., 2012; Elias et al., 1993; Jennings et al., 2005). Therefore, hypertension can increase AD risk through a myriad of dysfunctional vascular processes.

2.2.2.3 Type 2 diabetes

Type 2 diabetes (T2DM) is a chronic condition that is characterised by IR and insufficient insulin secretion by pancreatic beta cells (American Diabetes Association, 2016). T2DM and AD share common mechanisms that can double the risk of AD (Moreno-Gonzalez et al., 2017; Ott et al., 1999). One of these mechanisms is disruption in the cerebral glucose metabolism rate, which is commonly seen in T2DM (Baker et al., 2011; Sabri et al., 2000). In addition to increasing AD risk, these disruptions in glucose metabolism increase the risk of cognitive decline in cognitively normal individuals (Rawlings et al., 2017). Glucose dysregulation is also a feature seen in AD (Drzezga et al., 2003; Li et al., 2008b). The marked IR seen in T2DM could contribute toward impaired cerebral glucose metabolism (Baker et al., 2011). In the past, insulin has proved to be beneficial in protecting the integrity of the BBB and arterial vessel walls via mediating actions of vascular endothelial cells (Rask-Madsen et al., 2010). In the presence of IR, there is insufficient insulin delivery to cells, which can reduce integrity of the BBB and promote the extravasation of vessel contents (Ito et al., 2017; Takechi et al., 2017). This process can in turn accelerate the accumulation of misfolded proteins such as A β and tau (which form characteristic aggregations seen in AD pathology) and facilitates the acceleration of neurodegenerative processes (Acharya et al., 2013; Fujii et al., 2017). There can also be a

reverse-causal effect where pre-existing pathological accumulations of tau and A β (seen in AD) can increase BBB permeability and therefore increase these pathological accumulations (section 1.4.6.1.1, Para 2). Additionally, IR and glucose dysregulation can induce the production of advanced glycation end products that are implicated in the pathogenesis of arteriopathies (namely atherosclerosis and arteriosclerosis), which cause a reduction in cerebral blood supply that is detrimental to neural health (Brüel & Oxlund, 1996; Soro-Paavonen et al., 2008; Tahara et al., 2012; Wolffenbuttel et al., 1998). Pathological mechanisms as a consequence of increased production of advanced glycation end products can also increase BBB permeability, increasing AD risk (Niiya et al., 2012; Shimizu et al., 2013). Downstream effects of T2DM can also result in cognitive decline, specifically in the domains of memory, also seen in AD (Gold et al., 2007; Sadanand, Balachandar & Bharath, 2016; section 1.3.4.1).

Therefore, the systemic alterations induced by the T2DM pathophysiological cascade can negatively affect cerebral blood vessels, promote neurodegenerative processes and cognitive decline that can increase the risk of AD. Obesity and hypertension are often comorbid in T2DM and the pathological effects of these conditions could be additive to the detriments inflicted by T2DM on the brain (Iglay et al., 2016; Jelinek et al., 2017). Along with increasing the risk for neurodegenerative diseases, the presence of comorbidities such as T2DM that induce vascular dysfunction in diseases that already present with vascular pathology (such as AD), could increase the severity of the symptoms or accelerate the rate of disease progression (Alagiakrishnan & Sclater, 2012; Jayaraman & Pike, 2014b).

2.2.2.4 *Metabolic Syndrome*

With a surge in the proportion of the global obese population, there has been a proportionate rise in the prevalence of metabolic syndrome (Piepoli et al., 2016). It is a condition that is characterised by the presence of three main symptoms namely, visceral or abdominal obesity, IR and hypertension (Punthakee, Goldenberg, & Katz, 2018). Complementary with these symptoms, dyslipidaemia, endothelial dysfunction and chronic stress are often comorbid with metabolic syndrome (Grundy et al., 2005; O'Neill & O'Driscoll, 2015). These pathological mechanisms contribute toward increased BBB permeability, accumulation of AD pathology, neurodegeneration and cognitive decline (Barron et al., 2013; Campos-Pena et al., 2017; Lin et al., 2014; Segura et al., 2009; Van Dyken & Lacoste, 2018). In addition to increasing the risk of developing T2DM (almost 5-fold), metabolic syndrome increases the probability of

having an adverse vascular episode(s) resulting from thrombotic events such as stroke and myocardial infarction (Kaur, 2014; Li et al., 2008a). The culmination of symptoms seen in metabolic syndrome also increases the risk of AD dementia (Alberti et al., 2009; Alberti et al., 2005). The downstream pathological mechanisms of metabolic syndrome that increase AD risk are similar to those seen in obesity, T2DM and hypertension (Nguyen et al., 2008; Raffaitin et al., 2009; Suzanne, 2012; Vanhanen et al., 2006).

2.2.3 Non-modifiable risk factors

2.2.3.1 Genetics

Genetics are inherited factors and therefore cannot be modified and different genes that increase risk of cardiovascular risk factors could also therefore increase AD risk. T2DM is a known risk factor of AD and can significantly increase AD risk (Paul, Jerrett, & Ritz, 2018). A network-based analysis on differentially expressed genes showed common pathways that were disturbed by upregulated genes in T2DM and AD. Twenty-one such genes were identified, some of which include HLA-DRB4 (cell adhesion molecules), IGH (immunoglobulins) and IGHA2 (Beta cell regulation) (Chowdhury et al., 2020). In addition to disturbing pathways such as beta cell regulation, upregulated genes in T2DM also disturbed pathways mediating long term potentiation, dopaminergic synapses, beta cell receptor signalling and Ras signalling, which are common pathways disturbed in AD (Chowdhury et al., 2020). Therefore, the upregulation of genes in T2DM that can disturb pathways commonly affected in AD could increase the risk of AD.

With respect to obesity there are several genes that have been identified that increase polygenic risk for obesity, some of which include FTO, PCSK1 and MC4R (Benzinou et al., 2008; Ewens et al., 2011). Of these, possessing genetic variations on introns 1 and 2 of the FTO gene can increase AD risk (Reitz et al., 2012). Furthermore, interaction with the APOE ϵ 4 gene and the FTO gene (especially carriers of the AA variant) can substantially increase risk of AD (Keller et al., 2011). A different study using bioinformatics analysis identified thirty-one single nucleotide polymorphisms on seven genes that are shared between AD and obesity namely PSMC3, CELF1, MYBPC3, SPI1, APOE, MTCH2 and RAPSN (Zhuang et al., 2017). With respect to hypertension, the genes that can alter blood pressure often modulate the risk of hypertension (Levy et al., 2009). The study by Levy and colleagues found that only the

ATP2B1 gene was associated with hypertension (Levy et al., 2009). This finding was replicated in a different study on Korean individuals (Hong et al., 2010). However, there is limited evidence indicating a link between genetic risk of hypertension and AD. This was highlighted in a study which showed that hypertensive AD individuals instead present with a heterogeneous genotype (Nazarian et al., 2019). Therefore, it is possible that hypertension might increase AD risk predominantly through mechanisms that propagate vascular dysfunction.

2.2.3.2 Demographic factors

Demographic factors such as age, sex, educational attainment and socioeconomic status can also modulate AD risk (section 1.2).

2.3 Conclusions

Several pathological changes observed in cardiovascular risk factors such as T2DM, obesity and hypertension initiate a pathological cascade that predisposes the brain to neurodegeneration and increases the risk of AD (Figure 2.2). The presence of comorbid cardiovascular risk factors propagates neurodegenerative changes primarily through vascular mechanisms. Developing these risk factors at midlife and clustering of these risk factors significantly furthers this risk. Chronic effects of these conditions reduce blood flow to vital brain regions via BBB dysfunction and development of arteriopathies such as atherosclerosis and arteriosclerosis that can even impair cognitive function. These pathological changes also create an environment conducive to the development of AD pathology and neurodegeneration that increase AD risk. Additionally, these pathological changes occur years before the clinical onset of symptoms of cognitive decline and can lower the threshold for AD. However, it is still unclear whether the neurodegenerative process in AD is initiated as a result of the presence of comorbidities, whether the effect of cardiovascular risk factors is additive, and therefore may increase disease severity or whether AD and cardiovascular risk factor-mediated mechanisms are independent pathobiological processes that contribute toward neurodegeneration

Chapter 3: Aims and Objectives

AD has long been identified as a disease that is associated with a compromised vascular system (section 1.4.6). However, it remains unclear whether this vascular compromise has an aetiology stemming from AD, vascular senescence or the presence of a cardiovascular comorbidity. The presence of a cardiovascular comorbidity can increase the risk of AD by hastening disease progression or increasing disease severity by driving vascular dysfunction-mediated changes in neuronal structure and function, accelerating the formations of AD pathology or by facilitating other downstream mechanisms of cardiovascular comorbidities in propagating these effects (Zlokovic, 2011; section 2.1.7). This gives rise to the possibility that the vascular compromise in AD could partly be a reflection of the distinct reductions in brain tissue and decline in cognitive function observed as an effect of ageing and the presence of vascular comorbidities. Nevertheless, it is uncertain whether the effects exerted by the presence of a cardiovascular comorbidity stemming from modifiable lifestyle factors are additive to the effects mediated by ageing and AD or whether there is an interactive effect between ageing, AD and the cardiovascular comorbidity that increase AD severity. Thus, the gap in the literature currently lies in understanding the precise nature of cardiovascular comorbidities in driving the evident vascular compromise in AD. Considering the paucity in available therapeutic options to treat AD, a focus on understanding how preventable and treatable cardiovascular risk factors can affect the brain in AD is imperative. Therefore, this thesis primarily aims to explore whether different cerebral properties quantified using multi-modal neuroimaging are vulnerable to the mechanistic interplay between cardiovascular comorbidities, normal ageing and AD or whether this vulnerability is grounded in the additive effect of the presence of a cardiovascular comorbidity. Three highly prevalent cardiovascular risk factors that have also been recognised as risk factors for AD include obesity, hypertension and type 2 diabetes (section 2.2.2). Each of the experimental chapters investigates how each of these specific comorbid conditions can affect the brain in AD and normal ageing. The secondary aim of this thesis is to examine whether the additional burden of cardiovascular comorbidities is associated with a comparable deficit in cognitive function.

The use of multi-modal MRI provides a holistic approach to visualise the pattern of insults inflicted by vascular comorbidities and AD at the whole brain and regional levels. Although

past work has shown that vascular dysfunction tends to co-localise with brain regions that show detriments in brain structure and function, this has not been done in AD patients before (as has been elucidated in the review of neuroimaging studies in the respective experimental chapters). In this thesis, arterial spin labelling (ASL) has been used to approximate CBF, diffusion tensor imaging (DTI) to estimate white matter integrity (WMI) and voxel based morphometry (VBM) to quantify grey matter volume (GMV) among the participants. These brain parameters will then be used in statistical models to draw inferences about the effects of comorbidities, ageing and AD.

At present, primary prevention strategies and interventions to modify cardiovascular risk have proven to be the most effective in reducing dementia incidence and slowing down disease progression, although the majority of these studies is not specific to AD (section 1.8 and 1.9). It is imperative that research examines how modifiable comorbid conditions can alter brain properties and whether modifiable comorbidities could contribute towards increasing the risk of neurodegeneration in AD. Such an investigation could help identify downstream mechanisms of modifiable comorbidities that could be prevented through interventions in early stages in order to improve AD prognosis or to reduce AD risk. Therefore, the current thesis also aims to examine the manner in which the additional burden from modifiable cardiovascular risk factors could increase the vulnerability of the brain to neurodegeneration in healthy ageing and in patients with AD. A specific focus has been given to the manner in which macrovascular changes and the trajectory of cerebral arteries can increase the susceptibility of brain macrostructure to the insults inflicted by AD, cardiovascular comorbidities and ageing, in the interpretation of the results. More specifically, the current thesis attempts to use multi-modal neuroimaging to address the following aims:

1. *To investigate the association between anthropometric measures of obesity, cerebral blood flow and brain structure in normal ageing, MCI and AD dementia:* In order to clarify the relationship between obesity measures and the brain, in this study, the participants were stratified according to their cognitive status into cognitively normal individuals (CN), patients with MCI and patients with AD dementia (ADD). The relationships between obesity measures and measures of brain parameters were investigated for each of the groups stratified by cognitive status. The findings related to the associations between cerebral parameters and obesity measures are presented in chapter 4. A detrimental effect of higher anthropometric measures of obesity in CN was

expected primarily in the frontal lobe and MTL regions, which would be less severe in MCI and ADD patients, in that order. This is the first study to explore the association between obesity measures and the brain using multi-modal neuroimaging measures with CBF imaging in AD dementia patients.

2. *To investigate the differences in GMV, WMI and CBF between AD patients medicated and unmedicated for hypertension:* Patients with mild to moderate AD were stratified into groups of medicated and unmedicated patients and compared to examine differences between the two groups in terms of cerebral properties namely GMV, WMI and CBF and cognitive function in chapter 5. It was predicted that AD patients on antihypertensive treatment would show less detriments in cognitive function and cerebral properties in subcortical and frontal regions compared to unmedicated AD patients. Limited studies have explored the association between antihypertensive drug use and cerebral parameters in AD patients while this is the first study to use multi-modal neuroimaging to address this issue.

3. *To investigate whether the vascular contributions of T2DM in AD can alter brain structure:* This investigation was carried out by comparing three groups, namely, patients across the AD spectrum diagnosed with T2DM, AD patients without T2DM and cognitively normal individuals. The main aim of this study was to show that there are AD- and T2DM-mediated mechanisms that can be detrimental to CBF, brain structure and function in MTL and subcortical regions. This relationship was investigated across neuroimaging experiments that are presented in chapter 6. It was expected that the comparison between the three groups would help highlight that there is a gradual increase in the deficits accrued from CN to AD patients without T2DM to AD patients with T2DM and that the additional burden of T2DM can exacerbate the detriments observed in AD. This is the first study to investigate the relationship between AD and T2DM using multi-modal neuroimaging that assesses CBF and brain structure.

Chapter 4: Effects of Obesity on the brain and cognition in ageing and Alzheimer's disease

4.1 Introduction

Obesity, a condition that is widely prevalent across the world, is characterised by the accumulation of excess body fat resulting from an imbalance between energy consumption and energy expenditure (Faria, et al., 2012). According to the World Health Organisation, obesity prevalence has tripled since 1975 accumulating to about 1.9 billion adults who were overweight in 2016 and 34% of these individuals were obese (<https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight>). If current trends continue, rates of obesity and overweight will see a substantial rise by 2025 (Abarca-Gómez et al., 2017). Accumulating evidence shows that obesity and its downstream pathological mechanisms can induce systemic inflammation, promote neurodegeneration, induce cerebrovascular dysfunction and facilitate the build-up of AD pathology in the brain (section 2.1.7.1.1 and 2.1.7.2.1). All of these factors contribute toward increasing the risk of AD. With the disproportionate rise in obesity numbers, there is an urgent need to investigate the precise impact of obesity on the brain that can increase this risk. Examining the vulnerability of cerebral constituents to the downstream effects of obesity in patients with mild to moderate AD and cognitively normal individuals, could help develop interventions to target individuals at risk of AD or to prevent a more severe neurodegenerative phenotype in individuals diagnosed with AD. Therefore, the current chapter uses multi-modal neuroimaging to explore the effects of anthropometric obesity measures on brain structure, CBF and cognitive function in patients with ADD, MCI and CN.

Obesity classification

The National Institute for Health and Care Excellence (NICE) has proposed guidelines that outline different weight categories based on body mass index (BMI). According to these guidelines, individuals with a BMI below 18.5 fall in the underweight category and those ranging between 18.5 and 24.9 are within the healthy weight category (Stegenga et al., 2014). An individual is classed as overweight if their BMI ranges between 25 and 29.9 and they are classed as obese if their BMI exceeds 30 (Schutz et al., 2019; Stegenga et al., 2014). Obesity

can further be graded into three obesity classes with an incremental increase of 5 units for each subsequent class (Schutz et al., 2019) (Table 4.1). While BMI provides a more general measure of obesity, abdominal obesity is a better indicator of visceral fat that increases cardiometabolic risk (Liao et al., 2018; Lofgren et al., 2004; Lukács et al., 2019; Seo, Choe, & Torabi, 2017). Abdominal obesity, as measured using waist circumference, increases cardiometabolic risk if it exceeds 88cm in women and 94 cm in men (Schutz et al., 2019) (Table 4.1).

Table 4.1 *Weight categories with limits for anthropometric measures of central and global obesity (National Institute for Health and Care Excellence, 2016; Conolly, Saunders & Neave, 2017; Schutz et al., 2019)*

Weight category	BMI (in kg/m ²)	WC* (in cm)	
		Men	Women
Underweight	<18.5		
Normal weight	18.5-24.9	<94	<80
Overweight	25.0-29.9	94-102	80-88
Obese	≥30	>102	>88
Class I	30.0-34.9		
Class II	34.9-39.9		
Class III	≥40		

*WC is normally used to assess cardiometabolic risk and is not used to assess clinical obesity

4.1.1 Neuroimaging

The brain has variable vulnerability to obesity related effects and this vulnerability can be exaggerated in the presence of AD. The following sections will review the effects of obesity on brain structure and function across different imaging modalities in normal ageing and in patients across the AD spectrum.

4.1.1.1 Structural neuroimaging in obesity and AD

4.1.1.1.1 Grey Matter Volume

Structures housed in the frontal, temporal and cerebellar brain regions are predominantly vulnerable to the detrimental effects of obesity as shown by meta-analytical evidence (García-

García et al., 2019; Herrmann et al., 2019). This was highlighted by a study in women that showed that higher BMI was associated with lower GMV in the bilateral prefrontal areas, the right precentral gyrus, the right inferior and MTL regions and the right cerebellum (Walther, et al., 2010). Obese women also showed poorer performance on tasks of executive function, and this poorer performance was associated with lower GMV in the right orbitofrontal region (Walther et al., 2010). This study showed a predominant effect of obesity in the right hemisphere (Walther et al., 2010). Results from this study were fairly consistent with those of another study that showed atrophy in frontal brain regions (including the anterior cingulate gyrus), the hippocampus and the thalamus associated with higher BMI (Raji et al., 2010). Both of these studies were conducted on cognitively normal individuals (>50 years), indicating a negative effect of higher BMI on GMV. These findings are contradictory to some of the research that shows that higher BMI in late-life can be protective for the brain (section 2.2.2.1, Para 1). High midlife BMI on the other hand, is associated with AD, neurodegeneration and cognitive decline (Dahl et al., 2013; Shaw et al., 2017). Therefore, the wide age range and the fact that only female participants are included in the study by Walther and colleagues could be a factor in this inconsistency (Walther et al., 2010). However, the study by Raji and colleagues included elderly individuals (> 70 years) and could imply that overweight and obesity might have a negative effect on the brain even in late-life (Raji et al., 2010).

Often, waist circumference (WC) and waist to hip ratio are used as measures of abdominal obesity, whereas BMI is used as a measure of general obesity (Goh et al., 2014). Abdominal obesity is associated with a higher cardiometabolic risk than general obesity and can therefore exert more detrimental effects on the brain (Lukács et al., 2019). This was highlighted in a study that showed lower hippocampal volume associated with higher waist to hip ratio, another measure of abdominal obesity (Jagust et al., 2005). This decrease in hippocampal volume was attributed to an increase in vascular burden as measured by WMH volume (Jagust et al., 2005). The comparatively higher detrimental effect of abdominal obesity was also highlighted in different studies that showed that WC was a more reliable indicator of the detrimental effects of obesity than BMI, especially among women (Hayakawa et al., 2018; Kurth et al., 2013). The study by Kurth and colleagues revealed negative associations between GMV and obesity measures in the anterior prefrontal cortex, orbitofrontal cortex the middle and superior temporal gyri and hippocampi, which were more widespread with WC than BMI (Kurth et al., 2013). Additional negative associations between GMV and WC were also found in the insula, globus pallidus and inferior parietal lobe, which were not found with BMI (Kurth et al., 2013). In the

study by Hayakawa and colleagues, obesity measures were negatively correlated with GMV in the precuneus, inferior parietal lobe, cingulate gyrus, insula, superior temporal gyrus, lingual gyrus, thalamus, precentral gyrus and frontal gyrus (Hayakawa et al., 2018). Therefore, abdominal obesity can have a widespread detrimental effect on GMV, which can be more extensive than that exerted by general obesity as measured using BMI.

Longitudinal decline in GMV in relation to various obesity indices is observed in the precuneus, cingulate gyrus (anterior and posterior), the occipital lobe, hippocampus and orbitofrontal gyri (Bobb et al., 2014; Driscoll et al., 2012; Shaw et al., 2017). Nevertheless, this decline can be influenced by weight loss in the elderly (Pegueroles et al., 2018). A study that performed a stratified analysis on individuals ranging from normal weight to obese categories showed that stable weight was associated with atrophy in the hippocampus, occipital, parietal (precuneus) and the frontal brain regions, whereas weight loss was associated with increased cortical thickness (Pegueroles et al., 2018). These findings indicate that obesity and overweight can exert negative effects on cerebral constituency over time and that weight loss could be protective by changing body composition and alleviating the negative effects exerted by obesity and overweight (Pegueroles et al., 2018). Although varied, findings from studies examining the association between obesity measures and the brain implicate structures involved in the DMN. This is particularly evident in the work by Hayakawa and colleagues that shows negative correlations between GMV and WC and BMI across the cingulate gyrus, parahippocampal gyrus and lateral parietal areas in addition to other brain regions (Hayakawa et al., 2018). Structural alterations in the DMN are found in patients with AD, thus pointing toward shared vulnerability of brain regions to obesity and AD and how obesity could increase the radiological severity of the AD phenotype (section 1.6.1.1, Para 2; section 1.6.1.2, Para 2). In addition to regions involved in the DMN, there is also evidence for subcortical involvement in obesity-related detriments to GMV (Dekkers, Jansen, & Lamb, 2019; Hamer & Batty, 2019). Another potential link between AD and obesity is the deficits in cognitive function associated with obesity-related detriments. Studies have shown obesity-related deficits in domains of memory, attention and executive function, that are also seen in AD (Isaac et al., 2011; Walther et al., 2010). Obesity is predominantly associated with a decline in executive function, a cognitive domain which is substantially affected in much later stages of AD (Isaac et al., 2011; Walther et al., 2010; section 1.3.4.2, Para 2). This again illustrates how the presence of comorbid obesity could increase the clinical severity of the AD phenotype or even lower the age of onset for clinical AD in cognitively normal individuals.

There are limited studies that have explored the association between obesity and GMV in AD patients. One of these studies examined 700 AD and MCI patients using tensor-based morphometry (Ho et al., 2010a). The study found lower regional volumes associated with higher BMI across widespread brain regions including the brainstem and cerebellum (Ho et al., 2010a). A different study showed negative effects of obesity on the frontal lobe in AD patients (Boyle et al., 2015). In this study on patients with AD dementia and MCI, a conjunction analysis between diagnosis and BMI showed lower brain volumes that were widespread, with the most prominent deficits found in frontal brain regions (Boyle et al., 2015). In a different study, a region-specific analysis on the hippocampus showed that the anterior hippocampus was most vulnerable to the effects of obesity in AD patients (Ho et al., 2011). The anterior hippocampus is also affected in initial stages of AD (Braak & Braak, 1991). Therefore, findings from the above studies highlight how the cumulative effects of AD and higher BMI could increase the radiological severity of the AD phenotype. This is in contrast to a wealth of evidence indicating a protective effect of higher BMI in individuals with AD (section 2.2.2.1). This discrepancy could be explained by the baseline measures of BMI in the patient cohorts used in the above studies that are slightly above the cut-off for the normal weight category for BMI (>25) (Boyle et al., 2015; Ho et al., 2010a; Ho et al., 2011). In support of this, a recent study showed that higher late-life BMI was linked with lower levels of AD neuropathological and neurodegenerative markers, in addition to larger volumes observed in the hippocampus, entorhinal cortex and MTL regions in individuals with prodromal AD (Sun et al., 2020). Therefore, obesity and overweight in AD seem to be detrimental to widespread brain regions, with a higher affinity for frontal lobe structures and structures within the DMN. Although there is evidence indicating that higher BMI could be beneficial for GMV in prodromal AD, no neuroimaging studies have established this effect in individuals with ADD.

4.1.1.1.2 White Matter Integrity

Several studies have explored the relationship between measures of obesity and WMI. These studies indicate that obesity has a variable but profound effect on a variety of white matter tracts, with a predominant negative effect seen in the frontal white matter. In a study by Kullman and colleagues, alterations in mean and axial diffusivity were found in the white matter tracts connecting structures housed in the limbic system to prefrontal brain regions in obese individuals, compared to lean and overweight counterparts (Kullmann et al., 2016).

Other studies also indicate a negative effect of obesity on white matter tracts in learning and reward-based circuits. In one such study that included obese individuals, higher BMI was linked with lower FA in the cingulum (including the hippocampal white matter), anterior and posterior thalamic radiations, inferior fronto-occipital fasciculus, superior and inferior longitudinal fasciculus, uncinate fasciculus, corticospinal tracts, internal capsule and corpus callosum (Papageorgiou et al., 2017). These findings were supported by another study that reported similar decrements in WMI associated with higher BMI in obese women (Shott et al., 2015). This study also showed disruptions in connectivity in tracts linking the limbic system with prefrontal brain regions, similar to the findings from the study by Kullman and colleagues (Kullmann et al., 2016; Shott et al., 2015). WMI disruptions associated with higher BMI have also been reported in the fornix and corpus callosum (Stanek et al., 2011). Furthermore, alterations in the white matter tracts comprising the taste-reward circuitry with a predominant negative effect seen in frontal white matter were found in other studies on obese individuals (Marqués-Iturria et al., 2015; Riederer et al., 2016). A couple of studies also show lower WMI in the cerebellar white matter tracts associated with obesity (Kullmann et al., 2016; Zhang et al., 2018). Therefore, obesity-associated detriments to white matter tracts are predominantly found in the frontal lobe and those connecting limbic and reward-based circuits.

Sex differences in body fat distribution can alter the relationship between obesity measures and WMI (section 1.2.1.2, Para 1). On correlating BMI with diffusivity measures among males and females matched for age and BMI, abnormal axial diffusivity was found in the corpus callosum in women only (Mueller et al., 2011). However, only women exhibited a positive association between radial diffusivity (indicating lower WMI), BMI and leptin levels in the genu of the corpus callosum (Mueller et al., 2011). Yet another study on men and women showed a negative correlation between total body fat and mean diffusivity in women (Dekkers et al., 2019). Therefore, sex differences in body fat patterning could increase the propensity of women to white matter damage. This effect in women could largely be due to their higher affinity to accumulate fat around the abdominal region, as abdominal fat tends to be more detrimental to brain health than subcutaneous fat (Kurth et al., 2013; section 1.2.1.2, Para 1). Similar to the effects seen in grey matter, although both global and abdominal obesity are associated with detriments to white matter, abdominal obesity exerts more profound and widespread negative effects on white matter than global obesity (Debette et al., 2014; Marks et al., 2011; Spieker et al., 2015).

Compromised WMI could also manifest as deficits in cognitive function. Higher BMI and waist to hip ratio were associated with lower FA in white matter tracts connecting visual and associative areas (Zhang et al., 2018). This negative association was linked with poor performance on tasks of executive function and processing speed (Zhang et al., 2018). However, a different study showed no associations between compromised WMI and cognitive performance although obese patients did show impairments in long term memory compared to controls (Samara et al., 2020). The average age of participants in the latter study was twenty years less than the average age of the participants in the former study, a difference that could account for the discrepancy in the findings as a longer duration of an obesogenic profile in older participants would have exerted more detrimental effects on the brain (section 1.2.1.1, Para 2). The evidence elucidating the relationship between obesity measures and WMI in AD patients is sparse. One study that examined individuals with a family history of dementia and carriers of the APOE ϵ 4 allele found that obesity was linked with damage to the right parahippocampal cingulum bundle (Mole et al., 2020). However, to our knowledge, no studies have explored the relationship between WMI and obesity measures in patients with AD so far.

4.1.1.1.3 White Matter Hyperintensities

Accounting for the vascular dysfunction facilitated by the downstream pathological processes in obesity, the occurrence of WMH in obese individuals is widely prevalent (Kim et al., 2017; Park et al., 2020). The majority of the studies indicates a strong link between abdominal obesity and the occurrence of WMH (Kim et al., 2017; Lampe et al., 2019; Marini et al., 2020; Nam et al., 2019; Pasha et al., 2017). In fact, one of these studies showed that a genetic predisposition to higher waist to hip ratio was associated with an increased risk of elevated WMH volume that was not seen in associations with a genetic predisposition to higher BMI (Marini et al., 2020). The dominant role of abdominal obesity in increasing WMH burden could be attributed to inflammatory pathways activated in obesity (Lampe et al., 2019). It is also due to the higher cardiometabolic risk posed by abdominal obesity compared to general obesity (Lukács et al., 2019). This effect of obesity is stipulated to be independent of comorbidities such as hypertension, which frequently co-occur in obesity (Jagust et al., 2005; Lampe et al., 2019). Moreover, WMH could contribute toward altering brain function as evidenced in a study that showed that WMH in the prefrontal cortex modulate functional connectivity in obese individuals (Park et al., 2020). It has already been established that midlife vascular risk factors can increase the risk of dementia in late-life (Livingston et al., 2017). Mid-life obesity is linked

with a higher burden of WMH in late-life and higher WMH burden has previously been associated with heightened AD risk (Brickman et al., 2015; Vuorinen et al., 2011). This could again be attributed to longer durations of an obesogenic profile with increasing age (section 1.2.1.1, Para 2). However, there is contradictory evidence that shows that midlife overweight and obesity are not associated with increased WMH burden (Albanese et al., 2015). Therefore, the relationship by which midlife obesity and WMH burden can elevate AD risk is still unclear.

Often, WMH tend to be clinically silent and begin to accumulate long before the emergence of any related cognitive symptoms (Pasha et al., 2017). However, the accumulation of a significant volume of WMH can manifest as overt deficits in cognitive function (Au et al., 2006). This property of WMH to increase risk of cognitive decline tends to increase the risk of AD (Brickman et al., 2015). This was highlighted in a study that showed that the presence of WMH in the parietal lobes was associated with incident AD (Brickman et al., 2015). Accelerated cognitive decline as a result of increased WMH burden and cerebral atrophy in patients with mild AD supports the notion that the presence of WMH burden in AD facilitates cognitive impairment (Brickman et al., 2008; Carmichael et al., 2010). This was supported by findings from another study that showed that higher WMH burden was associated with lifestyle related vascular risk factors (obesity as measured using BMI being one of these factors) and cognitive impairment (Arai et al., 2012).

4.1.1.2 Functional neuroimaging in obesity and AD

4.1.1.2.1 Resting-state functional magnetic resonance imaging (rs-fMRI): The default mode network (DMN)

Obesity and AD both have been associated with aberrant functional connectivity in the DMN. This association with obesity was evidenced in a study that found higher functional connectivity in the bilateral precuneus and decreased functional connectivity in the right anterior cingulate gyrus in the DMN in cognitively normal obese individuals (Kullmann et al., 2012). The intensity of the blood oxygenation level dependent signal in these regions was modulated by BMI (Kullmann et al., 2012). A different study showed that obese individuals had lower functional connectivity in the medial prefrontal cortex, posterior cingulate cortex and the precuneus within the DMN compared to individuals within the normal weight range (Ding et al., 2020). Another study showed that higher BMI was associated with lower functional connectivity in the posterior cingulate cortex and the precuneus in older adults

(Beyer et al., 2017). Altered functional connectivity in the posterior cingulate and precuneus are proposed biomarkers that mark very early stages of AD even before the manifestations of structural or cognitive decline (section 1.6.2.1, Para 2). Therefore, the convergence of the DMN regions affected by AD and obesity highlights pathways through which obesity could potentially increase AD risk.

Obesity can also have an effect on other resting-state networks. The salience network and naturally the central executive network (on account of the predominant effect of obesity on executive function) are significantly impaired in obese and overweight individuals (Doucet et al., 2018; García-García et al., 2013; Lips et al., 2014). However, this relationship changes with fasting states in obese individuals where stronger functional connectivity is observed between brain regions involved in reward, motivation and cognitive control during fasting (Lips et al., 2014). However, following food intake, the increased functional connectivity was diminished (Lips et al., 2014). The reward and learning circuits are heavily impaired in obesity pathogenesis (Horstmann, 2017; Stice et al., 2013). Several studies show disruptions in the functional connectivity of the putamen to resting-state networks, including the salience network and other networks involved in the reward-based circuits (Baek, et al., 2017; García-García et al., 2013; Hogenkamp et al., 2016; Kullmann et al., 2012). These findings complement the findings from studies that show altered structural connectivity in white matter tracts connecting limbic and reward-based circuitry, some of which are also impaired in AD (section 1.6.1.2, Para 2; section 4.1.1.1.2, Para 1).

Most of these studies, however, show that obesity is associated with aberrant functional connectivity in the frontal lobe (Kullmann et al., 2012; Zhang et al., 2015). This disruption in frontal cortex connectivity can hamper its ability to suppress the striatum resulting in an impaired reward-based circuitry (Zhang et al., 2015). This impairment in reward-based circuitry could potentially lead to a reverse causal effect where a failure to suppress the striatum could lead to overeating and obesity (Zhang et al., 2015). There is a substantial gap in the literature in terms of understanding the relationship between obesity and functional connectivity in individuals with AD. From the existing data, it can be inferred that obesity tends to affect functional connectivity in widespread brain regions. It can increase the risk for AD by altering functional connectivity in known predilection sites for AD (such as the posterior cingulate cortex) (Jacobs et al., 2013). Comorbid obesity could thus increase disease severity by affecting functional connectivity in brain regions that are affected in AD in later stages such

as the frontal lobe or by augmenting the damage inflicted by AD in addition to increasing the risk of it.

4.1.1.2.2 Perfusion studies

Obesity being a cardiovascular risk factor is detrimental to CBF and alterations in CBF can significantly contribute toward increased AD risk (section 1.4.6.1.2). This is exemplified in the work done by Selim and colleagues who showed that higher BMI was associated with lower CBF velocities and increased cardiovascular risk (Selim et al., 2008). Moreover, the predominant detrimental effect of obesity on the frontal lobe is seen in parameters of blood flow as well. A study using single photon emission tomography (SPECT) found that rCBF was associated with higher BMI in prefrontal brain regions that are involved in modulating attention, executive function and reasoning (Willeumier et al., 2011). Another SPECT study found that compared to their lean counterparts, obese women displayed higher CBF in the left hemisphere predominantly in the frontal and prefrontal brain regions (Karhunen et al., 2000). The findings from these studies illustrate the preferential effect that obesity has on CBF in frontal and prefrontal brain regions. However, a more recent SPECT study on 35,442 participants with ages ranging from 18 to 94 years, showed more widespread deficits in perfusion associated with BMI during adulthood (Amen et al., 2020). This study shows a more global pattern of obesity-related detriments on CBF, including known predilection sites for AD, such as the hippocampus (Amen et al., 2020). It is possible that this finding reflects variable effects of higher BMI across different age groups, therefore confounding the predominant effect of obesity found in the frontal lobe in the later decades of life.

Functional connectivity studies on obese individuals have previously found a strong effect of obesity on structures in the DMN, a finding that could imply a negative effect on CBF in these regions. A study found lower rCBF in structures that comprise the DMN in addition to some subcortical regions associated with obesity (MacIntosh et al., 2020). In contrast, Silvah and colleagues report findings where obese women show higher rCBF in limbic and prefrontal brain regions in the DMN (Silvah et al., 2020). This was further supported by a PET study that showed lower rCBF in the posterior cingulate, temporal and the orbitofrontal cortices in obese individuals compared to their lean counterparts (DeLParigi et al., 2005). The discrepancy in findings of higher CBF associated with obesity could be attributed to maladaptive compensatory processes in obese individuals exhibiting higher CBF parameters (Mohan &

Vanneste, 2017). The study by Silvah and colleagues also showed higher CBF in the salience network and in the left frontoparietal network (Silvah et al., 2020). In conjunction with the work by Karhunen and colleagues, obese individuals tend to exhibit higher rCBF in frontoparietal regions, a finding that could be reflective of maladaptive processes that could impair the ability to detect alterations in energy homeostasis in obesity (Karhunen et al., 2000; Silvah et al., 2020). Generally, AD patients exhibit lower CBF compared to healthy controls, a difference probably reflective of an underlying vascular dysfunction (Roher et al., 2012; Yoshiura et al., 2009). In this context, the vascular dysfunction facilitated by obesity and the resultant additional cerebrovascular burden could all lower CBF in AD patients even further. Although studies have looked at modulations in CBF associated with AD and obesity independently, no study has investigated how the interaction between obesity and AD could affect CBF in AD patients.

4.2 Hypotheses and Rationale

As evidenced by the literature, obesity has a profound detrimental effect on cerebrovascular blood supply that could enhance AD severity (section 4.1.1). However, there is a paradoxical temporal relationship between body mass and AD risk where higher body mass measures in midlife are associated with increased AD risk, while in late-life, higher body mass is protective against AD (section 2.2.2.1, Para 1). There are still several points of contention surrounding this paradox and the relationship between body mass measures and AD continues to remain vague. The majority of neuroimaging studies on healthy elderly (>60 years) obese individuals indicate a stark detrimental effect of obesity on cerebral constituents (section 4.1.1). Nevertheless, there is an indication in the available evidence that the ‘protective’ effect of higher body mass in late-life could be a product of the availability of better nutrition in individuals with a higher body mass, that could help the brain cope with damage in the face of AD and ageing related detriments (Besser et al., 2014; Sun et al., 2020). Weight loss in healthy elderly has also been proposed as a non-cognitive sign of preclinical AD (Jimenez et al., 2017). Therefore, higher indices of body mass in individuals with AD could suggest that individuals with better nutrition could be better equipped to preserve brain structure and function in the presence of ageing and disease related insults. It is unclear whether this effect is a factor mediated via the beneficial effects on CBF or other obesity-related mechanisms. It is also unclear whether this phenomenon is observed as a confounding effect of sex differences in hormones that can modulate effects of obesity on the brain and AD risk (Torromino et al., 2020).

So far, no neuroimaging study has identified protective effects of higher body mass in AD patients nor used multi-modal neuroimaging (that includes CBF imaging) to clarify this relationship. Therefore, the current study uses maps of GMV, WMI and CBF to explore the associations between these neuroimaging parameters and anthropometric measures of abdominal and global obesity in normal and pathological ageing. This will be done by stratifying the study participants into groups by cognitive staging namely ADD, MCI and CN. We hypothesised that we would find the following associations:

Cognitively normal individuals (CN): Negative associations would be found between neuroimaging parameters and anthropometric measures of obesity that would be predominantly

located in the prefrontal and parietal brain regions. This was predicted due to the susceptibility of these brain regions to the detrimental effects of obesity. Associations found in these brain areas would also be linked with poor performance on tasks of executive function.

Mild cognitive impairment (MCI): Negative correlations were expected between neuroimaging parameters and anthropometric measures of obesity. It was predicted that these associations would be found in prefrontal, parietal and MTL regions. In this group, it was expected that the results would reflect a combination of both AD and obesity related effects, with a primary effect of AD expected on the MTL, and a primary effect of obesity on prefrontal and parietal brain regions. Simultaneously, assuming that there is a protective effect of higher body mass in individuals with AD, less severe associations were expected in MCI patients with increasing obesity measures than the associations found with obesity measures in CN. Additionally, it was expected that these associations would be linked with poor performance on tasks of memory and executive function.

AD dementia (ADD): There would be a negative correlation between obesity measures and brain parameters in the prefrontal brain regions. However, in light of the protective effect of higher body mass in AD, these associations would be the least severe in the ADD group compared to MCI and CN.

It was also predicted that measures of abdominal obesity would yield more severe negative associations than measures of general obesity, as the former has a higher propensity for cardiometabolic risk and therefore risk of vascular insult (Lukács et al., 2019).

4.3 Methods

4.3.1 Participants

The current study used multi-modal neuroimaging to study the main and interaction effects between diagnostic group (ADD, MCI and CN; $N = 172$) and body mass categories, where those with BMI below 25 lay in the low body mass category and those with BMI above 25 were included in the high body mass category. Additionally, the study correlates maps of GMV, WMI and CBF with measures of global and abdominal obesity across three diagnostic groups ($N = 172$) that were stratified according to their cognitive status as follows: 47 patients with mild to moderate ADD, 68 MCI patients and 57 cognitively normal individuals (CN). The study uses data collected as a part of the VPH-DARE project, a multi-centre neuroimaging initiative focusing on the effects of modifiable lifestyle factors in ageing and AD (Seventh Framework Program - FP7/2007e2013 - under grant agreement no. 601055, VPH-DARE@IT). This data has also been used in a study that is published in the Journal of Alzheimer's Disease Reports (Dake et al., 2021; Appendix D, D.1). Participants were recruited from memory clinics across Sheffield (UK) and Kuopio (Finland). All participants were required to undergo neuropsychological assessments (section 4.3.4) and physical assessments (section 4.3.2) to obtain anthropometric measurements. Patients with ADD were diagnosed by a senior neurologist using the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) criteria (McKhann et al., 2011), while the diagnosis for MCI patients was determined using the MCI criteria given by Petersen and colleagues (Petersen, 2001; Petersen et al., 1999). Patients with MCI were also in fulfilment of the criteria that was suggestive of an AD aetiology (Albert et al., 2011). The diagnosis of the patients was determined following the examination of their clinical profiles by a senior neurologist and a senior clinical neuropsychologist. All patients were followed up regularly for a minimum duration of four years at regular intervals to confirm the diagnosis.

Participants were excluded from the study if they were suffering from any major medical conditions, including the presence of transient ischaemic attacks, chronic or acute cardiovascular/cerebrovascular disease and a history of stroke. These were included as exclusion criteria to rule out any major medical conditions that could have impacted

cerebrovascular health. Participants who were ineligible to qualify for an MRI due to the presence of metallic implants such as pacemakers were also excluded from the study. The presence of neuropathy with conduction defects, sick sinus syndrome, uncontrolled seizures and peptic ulcers were also part of the exclusion criteria to assess for eligibility for the study. These were included in the exclusion criteria to eliminate any confounding factors that could interfere in studying the effects of modifiable vascular risk factors on the brain. Participants who were identified with structural defects or vascular abnormalities on the MRI scans by a senior clinician were also considered to be ineligible for enrolment. Additionally, participants with abnormal levels of thyroid stimulating hormone, vitamin B12 and folate were excluded.

Ethical approval for this study was obtained from Regional Ethics Committee of Yorkshire and Humber for patients recruited at the memory clinical in Sheffield and from the ethics committee of the Northern Savonia Hospital District for the participants recruited from the memory clinic in Kuopio. Written, informed consent was given by all participants at the time of recruitment and all patients had the mental capacity to provide consent. All the experimental procedures complied with the regulations of the declaration of Helsinki.

4.3.2 Physical assessments

All participants had to undergo physical assessments. The assessment included a health questionnaire pertaining to lifestyles habits that included diet, smoking and physical activity. Part of the assessment also included recording the participants' medications and other medical conditions. All patients also underwent physical assessments carried out by an experienced research nurse in order to obtain information about different anthropometric measures that included height, weight, waist and hip circumference, blood pressure and heart rate.

4.3.3 Obesity measures

Two different measures of body mass were used to examine the association between obesity measures and the neuroimaging parameters. Quetelet's index was used to obtain BMI (kg/m^2); this index is calculated as an individual's weight in kilograms divided by the square of their height in metres. BMI was used as a measure of global or general obesity (Goh et al., 2014). On the other hand, WC, measured in cm, was used as a measure of abdominal or

central obesity (Goh et al., 2014).

4.3.4 Neuropsychological assessment

The neuropsychological assessment was administered as a battery of tests that measured performance on several cognitive domains including tests of memory (prose memory tests, category fluency), attention (digit span-forward), executive function (stroop task, digit span-backward, phonemic fluency), and language (similarities test, confrontational naming test). The prose memory test has been designed to assess new learning, episodic memory and short term retention, where a short story paragraph is read aloud to the participant after which they are asked to iterate the short story (immediate recall condition) and then reiterate the same story after a delay period (delayed recall condition). Scores are determined based on the number of elements the participant can recall about the story (Wechsler, 1987). These prose memory tests are part of the Wechsler Memory Scale. Higher scores on the tests were indicative of better performance. The similarities test is a subset of the Wechsler Adult Intelligence Scale and measures abstract and conceptual thought where the participant is given a pair of words and is asked to identify how these words are interconnected or ‘similar’ to each other. The test is scored using a predetermined key that assigns points (ranging from 0 to 2) to the terms used to describe the similarities between the words (Wechsler, 1958). The higher the score, the better the performance.

The digit span test, a subset of the Wechsler Adult Intelligence Scale, measures immediate auditory recall and attention. The digit span forward is administered by reading out a predetermined string of numbers to the participant, after which the participant is asked to iterate the numbers in the same order. The numbers begin with strings of three and the strings incrementally increase by one. The strings are administered sequentially until the participant makes an error. In the digit span backward, the participant is asked to repeat the numbers read out to them in reverse order. Similar to the digit span forward, the number strings start with a length of three and increase incrementally by one until the patient makes a mistake. In both tasks, a string of two numbers is given initially to demonstrate the procedure for the test to the participant. Additionally, if the patient makes a mistake, the assessor can pick another predetermined string of numbers of the same length to allow the participant to try again. If the second attempt fails, that trial is considered as an error and the test is stopped there. The highest string recalled by the participant without any error is considered as their final score in both

conditions and higher strings are associated with better cognitive performance (Wechsler, 1981).

The semantic fluency or the category fluency test is a test of semantic memory, which refers to a type of declarative memory or knowledge that an individual accumulates over their lifetime (Lezak et al., 2004). The semantic memory test is administered by first presenting the participant with a category, and then asking them to list all the words that they can associate with that category, within one minute. The test is then scored by counting the number of correct responses while excluding intrusions (incorrect responses in that category) and perseverations (repetitions) in the final scoring. The three categories presented to the participants in the current study were cities, animals and fruits. However, the test that was administered on the participants from Finland only used the ‘animals’ category. To overcome this difference and between-centre variability only data from shared categories across centres were included in the analysis. Phonemic fluency or letter fluency is a test that measures language production and executive function (Lezak et al., 2004). It is administered in a similar manner to the semantic fluency test where the individual is given a letter (instead of a category) and is asked to produce a list of words beginning with that letter. The number of correct responses is then counted in order to score the test, while excluding intrusions and perseverations. The three letter categories used in the present study were ‘F,’ ‘P’ and ‘L’ (Lezak et al., 2004). Again, only data from shared letters across centres were used.

As part of the neuropsychological assessment, participants also underwent the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) test battery (Welsh et al., 1994). The Boston naming test, which is a subset of the CERAD, is a test of visual confrontational naming that is used to measure language function. The longer version consists of 60 items and is widely used as a test for confrontational naming. The present study uses the shorter version, which consists of 15 items. The test is administered by showing the participant a picture for a duration of 20 seconds, after which the participant is asked to identify the object in the picture. If the individual is unable to identify the picture correctly, the assessor may provide a phonemic cue (the initial sound in the word to be said) that could help the participant. The test is scored by counting the number of correct responses and better performance is associated with higher scores (Kaplan, Goodglass, & Weintraub, 1983).

The Stroop task measures inhibitory control or executive function where the participant is presented with three different conditions. In the first condition, the participant is presented with a sheet that has a list of thirty names of different colours written in black ink in three vertical columns, with ten names in each column. Starting from left to right and top to bottom, the participant is asked to read the names of the colours out loud. In the second condition, participants are presented with another sheet containing columns of coloured dots (instead of names of colours as was done in the first condition), where the participant is asked to identify the colour that they see from left to right and from top to bottom. The third task entails another sheet that contains names of colours written in coloured ink, but the colour of the ink does not correspond with the name of the colour that appears on the sheet. Again, all the words are placed in a matrix of 3 x 10, similar to the first two conditions. The participant is asked to name the colour of the ink that the word (name of the colour) is written in from left to right and from top to bottom. The discrepancy between the automatic response to read the word as opposed to identifying other features of the word (such as the colour of the ink that the word is written in), is what helps measure inhibitory control. For all three conditions, the time taken for each individual condition is recorded, along with the number of errors and correct responses (Stroop, 1935). The lower the number of errors and lesser the time taken to complete the task, the better the performance. The final score of the test was calculated as a composite error interference score by combining the error scores across the three conditions. This was done by subtracting the average of the error scores from conditions 1 and 2 from the errors in condition 3 (Caffarra et al., 2002).

4.3.5 Imaging protocol

All MRI scans for this study were acquired using a Philips Ingenia 3.0 T Scanner. The imaging protocol included the acquisition of T1-weighted, T2-weighted, Fluid Attenuated Inversion Recovery (FLAIR), diffusion tensor imaging and arterial spin labelling scans.

4.3.5.1 T1-weighted scan

Three-dimensional structural T1-weighted scans were acquired sagittally using the following acquisition parameters: Slice thickness: 1 mm; Slice gap: 0 mm; FOV (Field of view): anterior to posterior (ap): 240mm, foot to head (fh): 240mm, right to left (rl):170; Voxel dimensions:

0.94 × 0.94 × 1.0 mm; Field of view (FOV): 256 mm; Matrix size: 256 × 256 × 124; Repetition time: 8.2 ms; Echo time: 3.84 ms; Flip angle: 8°.

4.3.5.2 T2-weighted scan

The T2-weighted scans were acquired using the following acquisition parameters: Slice thickness: 1mm; Slice gap: 0 mm ; FOV (Field of view): ap: 230mm, fh : 140mm, rl :181.81; Voxel dimensions: 0.532 × 0.532 × 4 (in mm); Matrix size: 432 × 432 × 35; Repetition time: 3000 ms; Echo time: 80 ms; Flip angle: 8°.

4.3.5.3 Diffusion Tensor Imaging

Diffusion-weighted echo planar images were acquired axially using the following parameters: FOV: 240 x 240 mm²; Slice thickness: 2.5 mm; TR: 3000 ms; Echo time: 98 ms; Directions: 32; Diffusion-encoding gradients b = 0 and 1000 s/mm²; Matrix size = 96 x 94.

4.3.5.4 Arterial spin labelling

All ASL images were acquired as part of the resting state WIP pCASL SENSE protocol using the following acquisition parameters: TR: 4000 ms; Echo time: 14 ms; Slice orientation: Axial; Slice thickness: 7 mm; Slice gap: 1mm; FOV: ap: 240 mm, fh: 135 mm, rl: 240mm; Matrix size: 80 x 80 ;Number of slices /axial sections: 17; Number of label/control pairs: 73; Total scan time: 592 seconds; Flip angle: 40° ;Voxel dimensions: 3 x 3 x 8; Labelling gap: 20 mm; Labelling duration: 1.65 seconds; Post-labelling delay time: 1.525sec

The M0 estimation scan was acquired using the same parameters apart from the repetition time which was 10000 ms and the scan acquisition time which was 50 ms.

4.3.5.5 FLAIR

3D T2-weighted fluid attenuated inversion recovery (FLAIR) images were acquired using: FOV: 250 x 250 mm²; Slice thickness: 1.12 mm; TR: 4800 ms; Echo time: 289 ms; Matrix size = 224 x 224.

4.3.6 Preprocessing

4.3.6.1 Voxel-based morphometry

The T1-weighted scans were preprocessed using voxel-based morphometry, which was performed using the Statistical Parametric Mapping (SPM12) software developed by the Wellcome Centre for Human Neuroimaging, London, UK, running in a Matlab (Mathworks Inc., UK) environment. Voxel-based morphometry is a technique that enables the measurement of brain volume using a whole brain approach which facilitates statistical analysis on voxels without an *a priori* identification of a hypothesis encompassing specific brain regions (Ashburner & Friston, 2000). This is done by parcellating the brain into many different voxels that act as 3-dimensional units of measurement of brain tissue using T1-weighted MRI scans (Ashburner & Friston, 2000). All scans were initially checked to ensure that there were no image abnormalities or artefacts.

Reorientation and segmentation

First, all images were spatially reoriented to set a uniform origin located at the anterior commissure that was aligned with the anterior commissure-posterior commissure plane (AC-PC line). Next, a tissue classed probabilistic segmentation was run to separate the different types of neural tissue into grey matter, white matter and cerebrospinal fluid (CSF) in the native MNI (Montreal Neurological Institute) space. The segmentation was checked to rule out any deviations or processing abnormalities. The ‘get_totals’ script (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) in Matlab was used to extract the volumes of grey matter, white matter and CSF. The sum of these three volumes was calculated to obtain total intracranial volume (TIV).

Normalisation and smoothing

In order to normalise the segmented scans, the standard template in SPM12 for European brains was used to reconstruct the images. These images were then warped and modulated to co-register with the template in order to facilitate statistical analysis. All the images were finally smoothed using a Gaussian kernel with a full-width half-maximum value of 8 mm³ (<https://www.fil.ion.ucl.ac.uk/~john/misc/VBMclass10.pdf>). The smoothed images were subsequently used to run the statistical models.

4.3.6.2 Tract-based spatial statistics

Tract-based spatial statistics (TBSS) was used to infer the anisotropic diffusion properties of water molecules in white matter tracts in order to derive information about structural connectivity between different brain regions from diffusion tensor imaging (DTI) scans (Smith et al., 2006). In DTI, the motion of water molecules is used to derive the neuroanatomical structure of white matter tracts. This motion of water is derived by detecting the direction of travel along three principal axes that are fitted to a 3-dimensional ellipsoid (Mori & Zhang, 2006). This ellipsoid represents the direction and distance of diffusion along these axes. The parameters of these axes are obtained from the properties of the ellipsoid where the lengths of the axes are represented by eigenvalues and their orientations are represented by eigenvectors. These measurements are then converted into a 3 x 3 matrix called a tensor that is then used in the TBSS analysis (Mori & Zhang, 2006). TBSS is performed on scans acquired using diffusion tensor imaging parameters. The most commonly used diffusivity measure is FA, but TBSS also allows the extraction of information about other diffusivity measures namely axial diffusivity, radial diffusivity and mean diffusivity. The values are calculated based on the diffusion tensor that can be visualised as an ellipsoid (Alexander et al., 2007). The ellipsoid consists of three eigenvectors that represent the directions of the principal axes and eigenvalues representing the radii of the ellipsoid (Alexander et al., 2007).

While FA is the most widely used measure used to examine the structural integrity of white matter, the other diffusivity measures can give us different information pertaining to different properties of white matter (Assaf & Pasternak, 2008; Heni, Kullmann, Preissl, Fritsche, & Häring, 2015). FA measures the degree of anisotropy of diffusion thus forming a measure of the directional restriction of water molecules, although it cannot represent the shape of the tensor in its entirety (Alexander et al., 2007). It is calculated as follows (Basser & Pierpaoli, 2011):

$$FA = \sqrt{\frac{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

where ‘ λ ’ represents the eigenvalue and MD refers to mean diffusivity. Mean diffusivity is calculated as the average of the three eigenvalues and helps measure the extent of the restriction of water molecules or the extent of obstructions in diffusion of water molecules (Le Bihan et

al., 2001). Most importantly, mean diffusivity is independent of the direction of diffusion. Axial diffusivity calculated as the largest eigenvalue ' λ_1 ' (in anisotropic tissue like white matter) gives the degree of diffusion in the direction parallel to the axon, which could help reveal information about axonal integrity (Song et al., 2002). Radial diffusivity is calculated as the average of the smallest two eigenvalues ($\lambda_2 + \lambda_3$) and gives a measure of the diffusion of water molecules in the direction perpendicular to the axon. This could help derive information about the integrity of the myelin sheath encasing the axons (Alexander et al., 2007).

4.3.6.2.1 Fractional Anisotropy (FA)

The diffusion-weighted data were processed initially using the FMRIB Software Library v5.0.8 (FSL, <http://www.fmrib.ox.ac.uk/fsl>). The FSL Diffusion Toolbox was used to correct for MRI and motion artefacts. Following this, a fractional intensity threshold of 0.5 was applied to the resultant image in order to strip bone tissue from the skull and generate a binary brain mask using the Brain Extraction Tool. The binary brain mask was then used to create FA maps in the form of eigenvalues for each patient, by fitting the mask with the diffusion tensor model at each voxel. This step also generated other eigenvalues, some of which corresponded with other diffusivity measures. Tract based spatial statistics was then used to process the generated FA maps (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide>). In the first step, the FA maps were eroded in order to eliminate any outliers that were produced in the previous steps. Next, all the FA maps were examined to identify the most representative FA map or the 'target image' in the sample. The subsequent step facilitated the non-linear registration of all images to the target image, affine alignment to the standard MNI space and an output containing an average of the FA maps. The resultant 'average' FA map was then skeletonised by creating a binary mask applying a threshold of 0.2, in order to preserve only those voxels that were common to the participants used to create the 'target image' (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide>). The final step consisted of projecting the FA images onto the skeletonised FA maps. These maps were then used to assess group differences in structural connectivity.

4.3.6.2.2 Other diffusivity indices (Axial, Mean and Radial diffusivity)

The FA non-linear warps and skeleton projections and the respective diffusivity values were used for the TBSS preprocessing of the rest of the diffusivity indices (namely axial diffusivity,

mean diffusivity and radial diffusivity) (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide>). In order to do this, non-linear registrations were applied to the eigenvalues corresponding to the correct diffusivity measure and warped eigenvalue data for each participant were merged together to create an average image. This image was then projected onto the mean FA skeleton created in the preceding tract based spatial statistics steps. The output maps were then used to run statistical models using the ‘randomise’ tool.

4.3.6.3 Arterial spin labelling

ASL is a non-invasive technique used to measure blood perfusion, which refers to the amount of blood delivered to the tissue. ASL utilises a blood-borne tracer, which is generated when the patient is inside the MRI scanner via the magnetic inversion of hydrogen nuclei present in the blood (Alsop et al., 2015). This process is known as ‘labelling.’ A delay period is allowed for the labelled blood to travel to the brain, at which point a snapshot of the labelled blood is taken in order to record the extent to which the labelled blood accumulates in the tissue before the inversion signal decays. A separate control image is obtained without labelling any blood. The control image and the labelled image are then subtracted to obtain the perfusion maps. Due to the low signal to noise ratio seen in ASL, the control and labelled images are acquired multiple times and an average of the subtractions between the corresponding images is used as the perfusion map (Chappell, MacIntosh, & Okell, 2018).

There are three different labelling approaches used in ASL, continuous ASL (CASL), pulsed ASL (PASL) and pseudo-continuous ASL (pCASL). In CASL, the labelling period is relatively long and a continuous radio frequency pulse is applied to invert the blood water (Detre, Leigh, Williams, & Koretsky, 1992; Wang et al., 2005). In PASL, multiple short pulses or a single long pulse is applied to label the blood water (Wong, 2005). Owing to the relatively short exposure to the radiofrequency pulse and the limiting properties of the radio frequency coil to transmit the pulse in terms of spatial coverage, PASL renders lower signal to noise ratio to images compared to CASL images (Alsop et al., 2015). A third labelling technique, pCASL, which is the clinically recommended standard for ASL imaging, combines the benefits of both, PASL and CASL. It is a form of CASL that is acquired by applying over a 1000 radiofrequency pulses to the blood water in quick succession (Alsop et al., 2015). By virtue of its labelling efficiency and recommendations for clinical use, the current thesis uses images acquired using the pCASL labelling technique.

Perfusion maps

Perfusion maps were created using the nordicICE software (<http://www.nordicneurolab.com/products/nordicICE/>), using the pCASL and M0 estimation images. Average CBF maps obtained from the subtractions between the labelled and the control images were used as the perfusion maps.

Co-registration with structural images

Perfusion maps were co-registered with the structural images in SPM12 running in a Matlab environment. Two sets of co-registrations were run to improve the anatomical demarcation of the different types of brain tissue and to improve the spatial locations of brain regions. This was done by first co-registering the perfusion map with the T2-weighted scan and then the resultant image was co-registered with the T1-weighted scan. Co-registrations were run to improve the spatial mapping of the ASL data for accurate anatomical tessellation and to account for the low signal to noise ratio of ASL (Kim et al., 2013). Co-registration of these images is also required for the normalisation of the image to the MNI space and the partial volume correction (Abad, García-Polo, O'Daly, Hernández-Tamames, & Zelaya, 2016). After the co-registrations, the maps were corrected to minimise the contribution of CSF to the cerebral perfusion signal and in order to increase statistical power. This was done by only considering CBF values in voxels that enclosed more than 50% of the grey and white matter (i.e., grey matter + white matter > 0.5). This was done using the 'ImCalc' function in SPM12 using the following formula (Kim et al., 2013):

$$i1.*(i2 + i3 > 0.5)$$

where, $i1$ = co-registered rCBF map; $i2$ = grey matter; $i3$ = white matter

This step helped improve the signal to noise ratio and the resultant image was named ImCalc1.

Partial volume correction

The segmented maps from the voxel-based morphometry pre-processing (section 4.3.6.1) were used to generate an image to perform a partial volume correction using the 'ImCalc' function in SPM12. In functional neuroimaging techniques like Positron Emission Tomography and Arterial Spin Labelling, there is low signal to noise ratio due to low spatial resolution. In order

to account for the deficits in low resolution, it is common practice to perform a correction for partial volume effects (Borogovac & Asllani, 2012). Partial volume effects are seen due to differences in the metabolic and absorptive properties of different brain tissues which can distort the contributions to the signal from the respective tissues (Rousset, Rahmim, Alavi, & Zaidi, 2007). Therefore, a fundamental difference is expected in the perfusion properties of white matter and grey matter. Under the assumption that the perfusion of white matter accounts for only 40% of that of grey matter, the following formula was used to generate the image used for the partial volume correction (Kim et al., 2013):

$$i1 + 0.4*i2$$

where, $i1$ = grey matter; $i2$ = white matter

The resultant image was named ImCalc2. The image division was performed using `fslmaths` using the '-div' command in the shell script terminal by dividing 'ImCalc1' by 'ImCalc2.'

Normalisation and smoothing

All the scans were normalised to the standard fMRI template for European brains in order to apply diffeomorphic parameters so that the images tessellated with each other. All images were then smoothed using a 10mm x 10mm x 12mm full-width at half-maximum Gaussian kernel (Kim et al., 2013). The smoothed images were then used in statistically modelling the data.

4.3.6.4 Lesion segmentation

The 'LST' or the lesion segmentation tool was used to quantify the number of lesions and the volume of these lesions (in millilitres). The LST is an open-source toolbox and was run in SPM12 in order to segment T2 hyperintense lesions using a combination of T1-weighted and FLAIR images (Schmidt et al., 2012). Although the algorithm was originally developed to quantify lesions in multiple sclerosis, it can also help identify lesions that are the downstream effects of diseases such as AD and T2DM (Schmidt et al., 2012). The Lesion Growth Algorithm (LGA) was used in order to segment the lesions. This was done by initially using a tissue-classed probabilistic segmentation of the T1-weighted images into grey matter, white matter and CSF and then subsequently applying this information to the FLAIR intensities to quantify

a lesion probability map. A thresholded kappa value of 0.3 was applied in order to obtain a binary lesion map before applying the segmented information from T1-weighted images to the hyperintense voxels on FLAIR images to obtain a binary lesion probability map. The number of lesions and lesion volumes for each participant were then obtained from html reports generated by the toolbox.

4.3.7 Statistical analysis

4.3.7.1 Demographic variables

A one-way ANOVA was performed in SPSS to compare the ADD, MCI and CN groups on their demographic characteristics. *Post hoc* analyses were run to identify which two groups differed in their specific demographic characteristics. All the demographic variables were checked to make sure that they met the assumptions of parametric data for a one-way ANOVA. A *t*-test was performed *post hoc*, in order to determine which two specific groups differed from one another. A Kruskal-Wallis *H* test was run on the variables that did not meet the assumptions in order to determine if the three groups significantly differed from one another. The Mann-Whitney *U* test was carried out *post hoc* to identify specifically which groups were significantly different from one another. Chi-square tests were run to assess whether categorical variables were independent of one another.

4.3.7.2 Cognitive variables

In order to compare the cognitive profiles of the three groups, a one-way ANOVA was run to examine differences in neuropsychological tests followed by a *post hoc* analysis using *t*-tests, that was to determine which two groups differed from one another. On the other hand, the Kruskal-Wallis *H* tests were used to analyse groups that violated the assumptions of parametric data followed by a *post hoc* analysis using Mann-Whitney *U* tests to identify which of the groups specifically differed from one another.

4.3.7.3 Voxel-based morphometry

Initially, an analysis was run to study the main and interaction effects between the diagnostic groups and body mass categories on GMV. This model was controlled for the effects of age, TIV, centre of recruitment and sex. Age was used as a covariate to control for the age-related

effects in the current analysis, such as vascular senescence, changes in body fat distribution and accumulation of AD pathology (section 1.2.1.1). TIV was used as a covariate to account for inter-individual differences in head size and as a proxy for brain reserve (Groot et al., 2017; Stern et al., 2018). Sex was included as a covariate to control for the effects of sex due to inherent differences in body fat distribution and hormones between the sexes (section 1.2.1.2, Para 1) and for the effects of centre to account for variability in geographical location and lifestyle that could influence body fat (Katzmarzyk et al., 2015; Zhou et al., 2019). Sex and centre were converted into categorical variables, where numerical values represented the membership of a participant to a particular category. For example, females and males were categorised as values of 1 and 0 where '1' was representative of a female participant while '0' signified a male participant. A threshold of $p < .001$ and 500 voxels was used at the set-level whereas a family-wise error corrected threshold (to correct for multiple comparisons) of $p < .05$ was used at the cluster level to identify the significant clusters. A threshold of $p < .001$ was used based on previous literature (Ashburner, 2015; Lieberman & Cunningham, 2009). Blood pressure was not included as a covariate as only a single time point measurement was available, and this measurement is highly variable through the day and from visit to visit (Lim et al., 2019).

Next, a linear regression was performed between BMI and maps of GMV obtained using voxel-based morphometry in the ADD group. Identical independent analyses between BMI and GMV maps were run among the MCI and CN groups. Both, positive and negative correlation contrasts were run for each of the groups. The entire procedure was repeated to assess the relationship between WC (in place of BMI) and maps of GMV across all three groups. All the analyses were controlled for the effects of age, TIV, MMSE (except CN), sex and centre of recruitment for the reasons specified earlier in this section. The MMSE was used as a covariate to account for differences in disease severity. The MMSE measures general level of cognitive functioning and is often used as a proxy for disease severity (Andrews et al., 2019; Clark et al., 1999; Teng, Chui, Schneider, & Metzger, 1987). The MMSE was excluded as a covariate in the analyses conducted among the CN group due to lack of variance in scores. A threshold of $p < .001$ and 500 voxels was used at the set-level whereas a family-wise error corrected threshold (to correct for multiple comparisons) of $p < .05$ was used at the cluster level to identify the significant clusters.

4.3.7.4 Tract-based spatial statistics

The ‘randomise’ tool in FSL was used to perform the statistical analysis on maps of diffusivity indices namely FA, mean diffusivity, axial diffusivity and radial diffusivity, derived using TBSS. The analysis using the ‘randomise’ tool was restricted to the skeleton of the white matter tracts, a procedure that removed the need for correction for multiple comparisons. Similar to what was done in the voxel-based morphometry analysis, first an analysis was run to study the main and interaction effects between the diagnostic groups and body mass categories on WMI. The model was controlled for the effects of age, TIV, centre of recruitment and sex for the reasons specified in section 4.3.7.3, Paragraph 1. A data matrix was created that included all the participants that were divided into six groups. Each of the three diagnostic groups (i.e. groups divided by cognitive staging: ADD, MCI and CN) were further divided into groups with low BMI and high BMI. The data matrix was coded to indicate group assignment of the participants and also included the covariate values in the corresponding columns. The contrast matrix included eight contrasts that tested the main and interaction effects between cognitive staging and body mass categories.

For the subsequent regression analysis, a data matrix was created for each diagnostic group separately, that listed the main independent variable, which was BMI and the control variables. The control variables used were identical to the ones used in the VBM analysis namely age, MMSE, TIV, sex and centre of recruitment. Similar to what was done in the voxel-based morphometry analysis, sex and centre of recruitment were converted into numerical variables (section 4.3.7.3). The first column of the matrix was coded as ‘1’ to indicate that the participant was assigned to that group. The contents of the following columns consisted of values of the control variables or covariates. Subsequently, a contrast matrix was created to perform the multiple regressions. The contrast matrix consisted of two contrasts; the first contrast ‘0 1’ represented a positive correlation between BMI and the diffusivity map. The second contrast ‘0 -1’ signified a negative correlation between BMI and the diffusivity map. Using the ‘randomise’ tool, five thousand permutations were carried out in order to build the null distribution to test each contrast and a value of $p < .05$ was used as a threshold to identify significant white matter tracts. The procedure was repeated to examine the associations between maps of diffusivity indices and WC (instead of BMI).

4.3.7.5 Arterial spin labelling

Analogous to the voxel-based morphometry statistical analysis, main and interaction effects were examined between the diagnostic groups and body mass categories on CBF. The analysis was controlled for the effects of age, MMSE, TIV, sex and centre of recruitment. The analyses were conducted by using a cluster-forming threshold of $p < .01$ and 500 voxels at the set-level. The family-wise error corrected threshold of $p < .05$ was used to identify significant clusters at the cluster level. Additionally, linear regressions were performed between maps of CBF and BMI while controlling for the effects of age, MMSE, TIV, sex and centre of recruitment. Separate analyses were conducted for the independent diagnostic groups. Both, positive and negative correlation contrasts were run for each of the analyses. The procedure was repeated to examine associations between CBF and WC across the three groups. The analyses were conducted by using a cluster-forming threshold of $p < .01$ and 500 voxels at the set-level. A less conservative threshold of $p < .01$ was used to account for the lower spatial resolution in arterial spin labelling and differences in voxel size (Woo, Krishnan & Wager, 2014). This threshold has also been used in a previous experimental study (Kim et al., 2013). The family-wise error corrected threshold of $p < .05$ was used to identify significant clusters at the cluster level.

4.3.7.6 Post hoc analysis

4.3.7.6.1 Identification of brain regions

Brain regions that were significant in the statistical analyses that were run across all three modalities were identified using co-ordinates within the MNI space. The MNI co-ordinates were converted into Talairach co-ordinates using the Java application ‘GingerALE’ (<http://brainmap.org/ale>). The Talairach co-ordinates were then examined using the Talairach Daemon Client (<http://www.talairach.org/client.html>) to identify the significant brain regions of interest. The location of the co-ordinates was cross-checked by mapping the MNI co-ordinates on the following atlases using FSL view (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>): Harvard-Oxford cortical and subcortical structural atlases (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006) and the JHU white-matter tractography atlas (Hua et al., 2008; Mori, Wakana, Van Zijl, & Nagae-Poetscher, 2005; Wakana et al., 2007).

4.3.7.6.2 *Signal extraction*

Following the voxel-wise analysis, the signal from the significant clusters was extracted for the *post hoc* analysis. For the voxel-based morphometry and ASL analysis, the significant clusters were saved at their thresholded values to create a region of interest. The region of interest was then used to create a binary mask that would be used to define the regions for signal extraction using ‘fslmaths’ (<https://fsl.fmrib.ox.ac.uk/fslcourse/lectures/practicals/intro3/index.html>). For analyses that revealed widespread results across the brain, regions of interest were created using the ‘Wake Forest University (wfu) PickAtlas’ tool from the SPM12 toolbox (http://www.nitrc.org/projects/wfu_pickatlas/). This was done to ensure that signal was extracted from specific regions as the significant clusters extended over several brain regions. For regions of interest created using this method, the created region was co-registered with a structural 3D T1-weighted image before extracting the values to ensure tessellation of the region of interest with the MNI space. The voxel values within the regions of interest were treated as a collection of several samples of the same signal. Therefore, all the voxels contained within a region of interest were calculated as a summary value in order to represent a collective value for all the voxels, as an average. The ‘get_totals’ (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) script was then used in Matlab to extract the mean signal values within the regions of interest.

In order to extract the average signal values from the tract based spatial statistics analysis, a similar procedure was carried out using ‘fslmaths’. First, a region of interest was created using the JHU white-matter tractography atlas to select the tracts of interest. The region of interest was subsequently thresholded at 12 voxels to exclude voxels that lay outside the tract of interest. There are no definite rules as to the threshold to be used that allows for the creation of a binary mask of the white matter (Wasserthal, Neher & Maier-Hein, 2018). Therefore, following a visual inspection, a liberal threshold of 12 voxels was applied to preserve voxels within the tracts of interest and to eliminate those voxels that lay outside these tracts. Although 12% probability may be considered liberal, it only served to create the binary mask that was skeletonised in subsequent steps. Subsequently, the mean FA skeleton mask was binarised and the binarised mask created using the region of interest was subtracted from this to obtain the difference image between the two. This difference image was binarised again and subtracted from the mean FA skeleton mask to obtain the skeletonised region of interest. To ensure the

exclusion of unwanted voxels, this image was binarised again and was then used to extract the FA signal from the tract of interest. This procedure was repeated for the other diffusivity indices namely (axial, mean and radial diffusivity). The mean signal values were subsequently used to correlate the extracted signal with neuropsychological tests to assess whether the signal was associated with performance on the tests. For the data that violated the assumptions of parametric data, non-parametric tests were used to perform the correlations. The Bonferroni correction was applied to account for multiple comparisons and a resultant threshold of $p < .005$ was used to identify the significant correlations. All the analyses were corrected for multiple comparisons to account for the number of variables correlated. When a large number of simultaneous statistical inferences are concerned, the use of an uncorrected threshold can increase the likelihood of a type 1 error (Abdi, 2007). A correction for multiple comparisons helps minimise this error, and that is the reason why this correction was applied to these analyses.

4.4 Results

4.4.1 Demographic characteristics

The three diagnostic groups did not differ in terms of age, WC, WMV and TIV. The statistics for the demographic variables have been reported in Table 4.2. In terms of their distributions, age, WC, GMV, CSF and TIV were variables that were normally distributed whereas education, MMSE, BMI, WMV and WMH volume were variables with non-parametric distributions. Means and standard deviations for non-parametric data have been included in Appendix B, Table B4.2. The CN group had higher number of years in education than the ADD, $U = 679.00, p < .001$, and MCI, $U = 1128.50, p < .001$, groups. There was no difference between the ADD and MCI groups with respect to years in education. The CN group had higher scores on the MMSE than the ADD, $U = 216.50, p < .001$, and the MCI, $U = 974.50, p < .001$, groups. Between the two patient groups, MCI patients had higher MMSE scores than the ADD patients, $U = 633.00, p < .001$. When comparing BMI, only the CN group had higher BMI indices than the ADD group, $U = 679.00, p = .005$, while no significant differences were found in BMI indices between the MCI and CN groups and also between the MCI and ADD groups. The CN group had more GMV than the ADD, $t(102) = -4.85, p < .001$, and MCI, $t(123) = -2.36, p = .020$, patients. Among the patient groups, MCI patients had more GMV than ADD patients, $t(113) = -2.72, p = .008$. With respect to CSF, CN had less volumes of CSF than ADD patients, $t(102) = 3.30, p < 0.001$, whereas in the patient groups, ADD patients had more CSF than MCI patients, $t(113) = 3.12, p = .002$. There was no difference in CSF between the MCI and CN groups. CN had lower volumes of white matter hyperintensities than ADD, $U = 781.00, p < .001$, and MCI, $U = 1508.00, p = .05$, patients. On comparing the two patient groups, no difference was observed in WMH volume.

Table 4.2 Demographic characteristics of ADD, MCI and CN groups reported using means and standard deviations for parametric data and medians and interquartile ranges for non-parametric data.

Demographic variable (units)	ADD (n = 47)	MCI (n = 68)	CN (n = 57)	Statistic
Parametric tests^a				
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>F</i>
Age (years)	68.09 (9.88)	68.56 (9.45)	66.51 (11.11)	0.67
WC (cm)	92.11 (10.95)	96.08 (14.39)	96.40 (13.22)	1.69
GMV (ml)	567.01 (74.62)	605.37 (74.34)	636.19 (70.40)	11.52***
CSF (ml)	516.31 (136.19)	438.22 (129.32)	428.71 (133.42)	6.68**
TIV (ml)	1488.36 (155.90)	1454.14 (143.53)	1495.70 (173.28)	1.24
Non - Parametric tests^b				
	<i>Mdn (IQR)</i>	<i>Mdn (IQR)</i>	<i>Mdn (IQR)</i>	<i>H</i>
Education (years)	11 (8 – 15)	12 (8 – 14)	15 (12 – 17)	23.70***
MMSE	21 (17 – 25)	26 (25 – 28)	28 (27 – 29)	69.10***
BMI (kg/m ²)	24.82 (22.86 – 28.37)	26.76 (23.41 – 30.13)	27.70 (24.94 – 31.01)	7.87*
WMV (ml)	416.04 (369.51 – 416.04)	407.54 (370.71 – 446.86)	430.04 (381.55 – 469.56)	4.08
WMH volume (ml)	3.53 (1.83 – 7.79)	2.22 (0.64 – 7.86)	1.70 (0.22 – 3.55)	11.44**
Chi square tests^c				
	<i>n</i>	<i>n</i>	<i>n</i>	χ^2
Males/Females	29/18	31/37	26/31	3.54
APOE genotype: ε2ε2/ε2ε3/ε3ε3/ε4ε2/ε 4ε3/ε4ε4	0/6/13/0/16/11	0/3/28/5/28/4	0/7/38/2/9/1	36.96***
APOE ε4 non- carriers/ ε4 carriers	19/27	31/37	45/12	19.15***
Centre (UK/Finland)	24/23	29/39	38/19	7.27*

* Comparison is significant at 0.05 level (two tailed)

** Comparison is significant at 0.01 level (two tailed)

*** Comparison is significant at 0.001 level (two tailed)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation; *F* = *F*-statistic; *Mdn* = median; *IQR* = Interquartile range, which has been reported as Quartile 1 – Quartile 3; *H* = *H*-statistic; χ^2 = Chi-square statistic

^a A one-way ANOVA was run for data that was normally distributed

^b Non-parametric Kruskal-Wallis *H* tests were run for data that were not normally distributed.

^c Pearson Chi-square tests were run to examine the independence of categorical variables.

Means and standard deviations for non-parametric data have been reported in Appendix B, Table B4.2.

4.4.2 Cognitive variables

There were significant differences in the cognitive profiles of all three groups and all the variables had a non-parametric distribution (Table 4.3). Means and standard deviations for the data have been included in Appendix B, Table B4.3. The groups had a comparatively similar performance on the digit span forward task that measures immediate auditory recall and attention (section 4.3.4). On the prose memory-immediate recall task, CN scored higher than ADD, $U = 118.00, p < 0.001$, and MCI, $U = 488.50, p < .001$, patients. When the patient groups were compared, MCI patients performed better than the ADD patients on the prose memory-immediate recall task, $U = 700.50, p < .001$. On the prose memory-delayed recall task, CN performed better than ADD, $U = 76.00, p < .001$, and MCI, $U = 388.50, p < .001$, patients, while MCI patients performed better than the ADD patients $U = 646.00, p < 0.001$. No significant differences were found between the digit span - forward test between any of the groups. On the digit span backward test, CN performed better than ADD patients, $U = 592.00, p < 0.001$, and MCI patients, $U = 1310.00, p = .010$. The patient groups also differed on the digit span backward test, where MCI patients performed better than the ADD patients, $U = 1044.50, p = .032$.

On tests of semantic fluency, CN performed better than the ADD patients, $U = 315.50.00, p < .001$, and MCI patients, $U = 1185.00, p < .001$, and among the patient groups, the MCI patients performed better than the ADD patients, $U = 723.50, p < 0.001$. Similar to the results found with semantic fluency, CN performed better than ADD patients, $U = 374.50, p < .001$, and MCI patients, $U = 949.50, p < .001$, on the phonemic fluency test, and consistent with what has been observed for other tests, MCI patients also performed better than ADD patients on the phonemic fluency test, $U = 1001.50, p = .005$. On the similarities test, CN performed better than ADD patients, $U = 378.00, p < 0.001$ and MCI patients, $U = 853.50, p < .001$, whereas among the patient groups, MCI patients had better performance than ADD patients, $U = 991.00, p = .007$. On the test of confrontational naming, CN performed better than the ADD patients, $U = 408.00, p < .001$, and the MCI patients, $U = 841.50, p < .001$ and between the patient groups, MCI patients performed better than ADD patients, $U = 1161.00, p = .032$. Moreover, on the Stroop task, CN performed better than ADD patients, $U = 577.00, p < .001$, and MCI patients, $U = 1228.00, p = 0.003$, while in the patient groups, MCI patients had better performance than ADD patients, $U = 864.50, p = 0.039$.

Table 4.3 Cognitive profiles of CN and patients with MCI and ADD, reported using medians and interquartile ranges for non-parametric data.

Neuropsychological test	ADD (<i>n</i> = 47)	MCI (<i>n</i> = 68)	CN (<i>n</i> = 57)	Statistic
Non- Parametric tests ^a	<i>Mdn</i> (IQR)	<i>Mdn</i> (IQR)	<i>Mdn</i> (IQR)	<i>H</i>
Prose Memory-Immediate recall	6 (2.25 – 9.75)	10 (7.50 – 13.00)	17 (14.00 – 19.00)	81.04 ^{***}
Prose Memory-Delayed recall	4 (2 – 8)	11 (6 – 14)	18 (16 – 20)	90.64 ^{***}
Digit Span-Forward	6 (5 – 8)	6 (5 – 8)	7 (5 – 8)	0.76
Digit Span-Backward	4 (3 – 5)	5 (4 – 6)	5 (4 – 6)	19.75 ^{***}
Semantic Fluency	12 (9.00 – 15.25)	16.50 (14 – 21.75)	21 (17 – 25)	51.95 ^{***}
Phonemic Fluency	22 (14 – 32)	29 (20.00 – 44.25)	45 (32.50 – 55.00)	43.75 ^{***}
Similarities	13 (8.00 – 20.75)	18 (12.50 – 23.50)	25 (21.50 – 27.50)	45.90 ^{***}
Confrontational Naming Task	12 (10.75 – 14.00)	13 (12-14)	15 (14-15)	45.80 ^{***}
Stroop-Error interference	2.50 (0 – 14.25)	0.50 (0 – 2.00)	0 (0 – 0)	17.80 ^{***}

* Comparison is significant at 0.05 level (two tailed)

** Comparison is significant at 0.01 level (two tailed)

*** Comparison is significant at 0.001 level (two tailed)

Key: *n* = sample size; *Mdn* = median; *IQR* = Interquartile range which has been reported as Quartile 1 – Quartile 3; *H* = *H*-statistic

^a Non-parametric Kruskal-Wallis *H* tests were run for data that was not normally distributed.

Means and standard deviations for non-parametric data have been reported in Appendix B, Table B4.3.

4.4.3 Voxel-based morphometry

4.4.3.1 Main effects and interaction analysis

The analysis showed a main effect of body mass categories on GMV where the participants in the lower body mass category showed better preservation of GMV than those that lay in the higher body mass category in the bilateral cerebellum and the left orbitofrontal cortex (Table 4.4, Fig 4.1). The opposite contrast did not yield any significant findings. A significant interaction was observed between diagnostic group and body mass categories where the low BMI > high BMI difference in GMV between the body mass categories was higher in the ADD group than the difference in the CN and MCI groups. This interaction effect was observed in the right prefrontal cortex and the right occipital lobe (Table 4.4, Fig 4.1). Another interaction effect was observed where the low BMI > high BMI difference in GMV between the body mass categories was higher in MCI than in the ADD and CN groups in the primary and supplementary motor areas and the bilateral occipital lobes (Table 4.4, Fig 4.1). No other significant interactions were observed using the other contrasts.

Table 4.4 Brain regions showing main and interaction effects between diagnostic group and body mass categories on GMV

Voxels (Cluster extent)	Cluster level pFWE	Brain region (Brodmann area)	Side	Z-score	MNI ordinates		
					x	y	z
Low BMI > High BMI							
1081	0.003	Orbitofrontal cortex (47)	L	5.39	-50	40	-15
		Broca's area (45)	L	4.53	-57	27	8
		Orbitofrontal cortex (47)	L	4.45	-56	30	-6
1724	0.000	Cerebellum – Posterior lobe	R	5.28	32	-82	-48
586	0.044	Cerebellum – Posterior lobe	L	5.27	-33	-78	-54
587	0.044	Orbitofrontal cortex (11)	L	4.43	-10	66	-15
ADD (low BMI > high BMI) > MCI + CN (low BMI > high BMI)							
748	0.018	Anterior prefrontal cortex (10)	R	4.69	26	56	20
		Dorsolateral prefrontal cortex (9)	R	4.26	21	45	33
796	0.013	Occipital lobe (18)	R	4.17	36	-87	-3
		Occipital lobe (18)	R	3.77	33	-86	8

MCI (low BMI > high BMI) > ADD + CN (low BMI > high BMI)							
7561	0.000	Occipital lobe (18)	R	5.07	-6	-92	-10
799	0.013	Occipital lobe (19)	L	4.34	-21	-90	20
702	0.023	Premotor cortex (6)	L	4.33	-51	2	32
		Primary motor cortex (4)	L	3.83	-42	-10	20

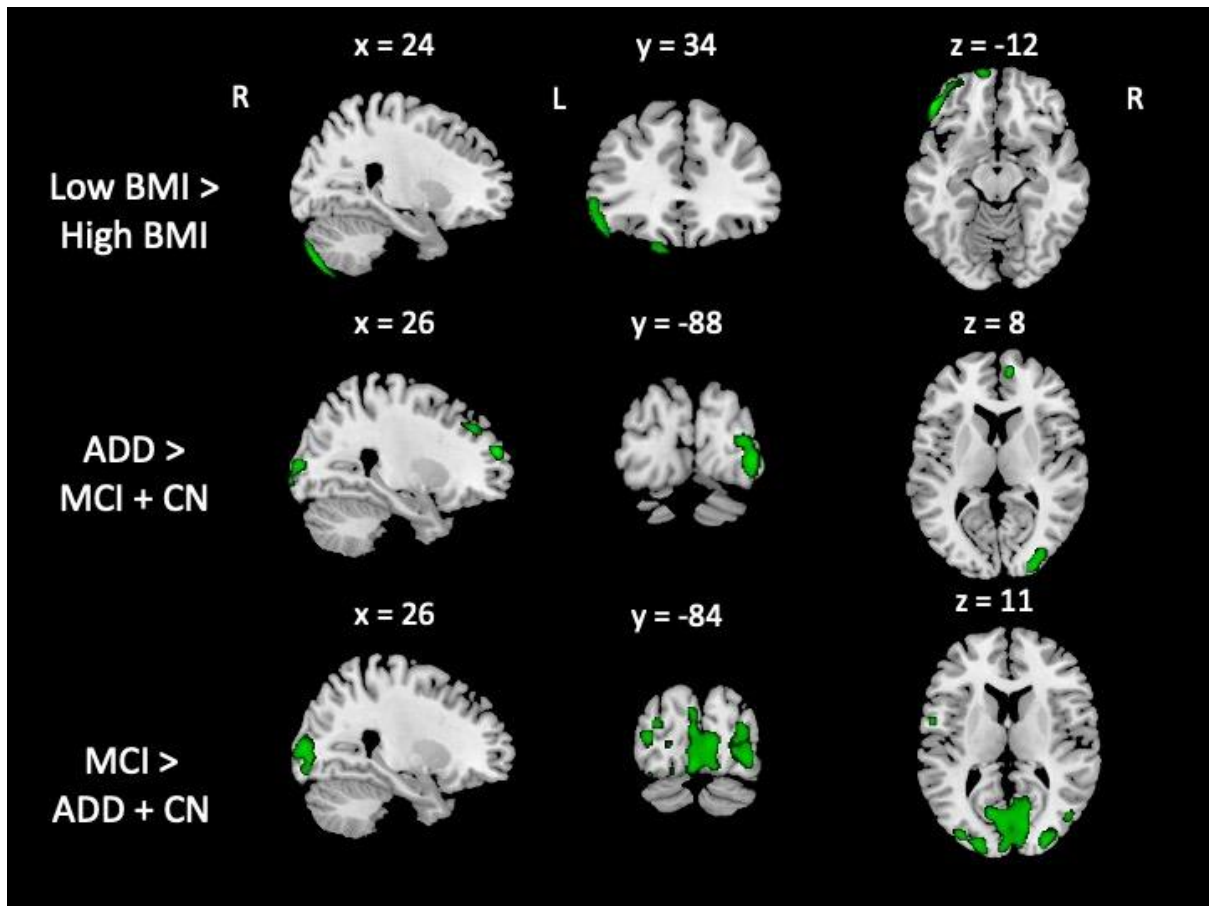


Figure 4.1 Brain regions showing main and interaction effects between diagnostic group and body mass categories on GMV

The three rows show main and interaction effects between diagnostic group and body mass measures on GMV. Each of the rows are represented in the sagittal, coronal and axial orientations from left to right. The ‘x’, ‘y’ and ‘z’ co-ordinates have been reported based on the MNI space. Top row: Main effect of body mass measures on GMV where participants in the low body mass category show better preservation of GMV than participants in the high body mass category; Middle row: The low BMI > high BMI difference in GMV between participants belonging to different body mass categories is greater in the ADD group compared to the CN and MCI groups; Bottom row: The low BMI > high BMI difference in GMV between participants belonging to different body mass categories is greater in the MCI group compared to the CN and ADD groups

4.4.3.2 Regression analysis

4.4.3.2.1 ADD

BMI

A positive correlation was found between BMI and GMV among the ADD patients in the postero-inferior brain regions in the right hemisphere (Table 4.5, Fig 4.2). The cluster spanned across regions of the temporoparietal junction extending posteriorly into the cuneus, precuneus and a major proportion of the occipital lobe. While a majority of the voxels lined the borders of the surface of the cerebrum, significant voxels were also found in the medial parietal areas and medial occipital areas. Anteriorly, the extensions of the cluster spilled into the MTL (in close proximity to the hippocampus) and superior temporal regions. When correlating the extracted signal with tests of cognition, a positive correlation was found between the extracted signal and the prose memory-delayed recall test, $r_s = .35$, $p = .021$, and the similarities test, $r_s = .40$, $p = .008$. On correlating the extracted GMV signal with WMH volume, no correlations were found. No significant negative correlations were found between BMI and the GMV maps.

WC

A considerable proportion of the positive associations found with WC were co-localised with the associations found between BMI and GMV among ADD patients (Table 4.5, Fig 4.2). Although most of the results were lateralised to the right hemisphere, some significant voxels were also found in the precuneus in the superior parietal lobe in the left hemisphere. In the occipital brain regions, voxels displaying significant associations with WC were more scattered and appeared more 'attenuated' compared to the associations found with BMI. Additionally, associations with WC also partially involved frontal brain regions in the insula and inferior frontal gyrus. A positive correlation was found between the extracted signal and scores on the prose memory - delayed recall test, $r_s = .37$, $p = .014$, and the similarities test, $r_s = .38$, $p = .012$. No correlations were found on correlating the extracted GMV signal with WMH volume. No significant negative correlations were found between WC and the GMV maps.

Results from associations with both indices of body mass and GMV were located in the territories supplied by the middle cerebral and posterior cerebral arteries (Fig 4.9).

Table 4.5 Brain regions showing a positive correlation between GMV and obesity measures in ADD patients

Voxels (Cluster extent)	Cluster level pFWE	Brain region (Broadmann area)	Side	Z-score	MNI ordinates		
					x	y	z
<i>BMI</i>							
16986	0.000	Superior parietal lobule (7)	R	5.64	40	-58	42
		Cuneus (18)	R	4.91	22	-88	18
		Middle temporal gyrus (39)	R	4.76	57	-44	6
		Superior temporal gyrus (22)	R	4.76	44	-33	10
634	0.036	Superior temporal gyrus (39)	L	3.89	-46	-61	22
		Superior temporal gyrus (39)	L	3.83	-50	-53	28
<i>WC</i>							
13284	0.000	Superior parietal lobule (7)	R	6.11	42	-58	39
		Superior parietal lobule (7)	L	4.70	-24	-62	47
		Superior occipital gyrus (19)	R	4.39	38	-73	22
		Superior temporal gyrus (22)	R	4.16	55	-48	8
905	0.009	Inferior frontal gyrus (44)	R	4.30	44	6	11
		Insula (13)	R	4.08	32	-13	17
787	0.016	Posterior lobe of the cerebellum	R				-
				4.05	28	-52	40

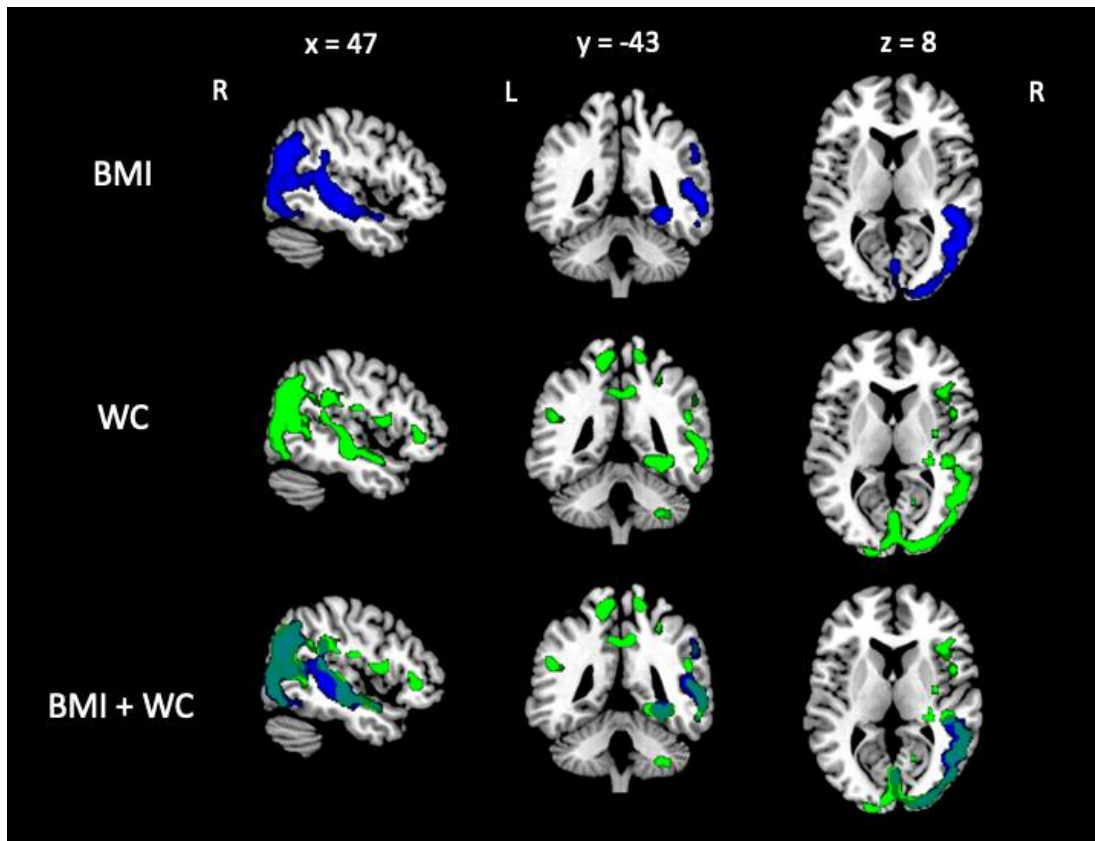


Figure 4.2 Brain regions showing a positive association between GMV and obesity indices in ADD patients.

The three rows show positive associations between GMV and obesity measures using voxel-based morphometry in ADD patients. Each of the associations is represented in the sagittal, coronal and axial orientations from left to right. The 'x', 'y' and 'z' co-ordinates have been in MNI space. Top row: Positive associations found between BMI and GMV in the right hemisphere in and around the temporoparietal junction, superior hippocampus, occipital lobe and precuneus have been depicted in blue; Middle row: Positive associations found between WC and GMV in the right hemisphere around the temporoparietal junction, superior hippocampus, occipital lobe and precuneus, insula and in the superior and lateral parietal lobe and occipital lobe in the left hemisphere are highlighted in green; Bottom row: Overlap between the associations found between GMV, BMI and WC.

4.4.3.2.2 MCI

BMI

In MCI patients, negative associations were found in various brain regions that included frontal, occipital and cerebellar brain regions (Table 4.6, Fig 4.3). The associations mostly covered the lateral surfaces of the brain. In the frontal brain regions, associations were found in bilateral orbitofrontal cortices while in the posterior brain regions, the associations enclosed most of the lateral surfaces of the occipital lobe bilaterally, with relative sparing of the majority of the postero-lateral surface. Moreover, some significant voxels were also found in the medial portions of the occipital lobe. In the cerebellum, negative associations were found only in the right cerebellar hemisphere that covered the infero-lateral surfaces. The extracted GMV signal was positively correlated with scores on the phonemic fluency test, $r_s = .29$, $p = .02$. On correlating the extracted GMV signal with WMH volume, a negative correlation was found, $r_s = -.42$, $p < .001$. No significant positive correlations were found between BMI and the GMV maps.

WC

Negative associations found with WC were almost entirely identical to the associations found with BMI (Table 4.6, Fig 4.3). Some additional associations found included a small cluster that stretched across the lateral parts of Broca's area, the insula, the premotor cortex and the supramarginal gyrus. The extent of the associations found in the medial portions of the occipital lobe were slightly wider than those found with BMI. Furthermore, negative associations with WC were found in the left cerebellum in the lateral inferior areas. The extracted GMV signal was positively correlated with performance on the phonemic fluency test, $r = .35$, $p = .004$ and the digit span – backward test, $r_s = .25$, $p = .05$. Similar to what was seen in associations with BMI, a negative correlation was found between the extracted GMV signal (from the association between GMV and WC) and WMH volume, $r_s = -.43$, $p < .001$. No significant positive correlations were found between WC and the GMV maps.

Across the two obesity measures negative associations with GMV were located across the territories of a range of cerebral arteries that included the cerebellar arteries, the anterior cerebral artery, the middle cerebral artery and the posterior cerebral artery. However, these associations were primarily restricted to the distal ends of these arteries (Fig 4.9).

Table 4.6 Brain regions showing a negative association between GMV and obesity measures in MCI patients

Voxels (Cluster extent)	Cluster level pFWE	Brain region (Brodmann area)	Side	Z- score	MNI ordinates		
					x	y	z
<i>BMI</i>							
1178	0.002	Inferior frontal gyrus (47)	L	5.29	-48	32	-16
4662	0.000	Inferior occipital gyrus (18)	R	4.77	48	-82	-3
		Cerebellum- posterior lobe	R	4.71	40	-74	-40
615	0.043	Cerebellum- posterior lobe	L	3.88	-40	-77	-33
611	0.044	Inferior frontal gyrus (47)	R	4.50	53	27	-11
1872	0.000	Inferior occipital gyrus (18)	L	4.49	-38	-91	-8
1478	0.001	Precentral gyrus (6)	L	4.24	-57	4	20
<i>WC</i>							
1178	0.002	Inferior frontal gyrus (47)	L	5.29	-48	32	-16
4662	0.000	Inferior occipital gyrus (18)	R	4.77	48	-82	-3
		Posterior lobe of the cerebellum	R	4.71	40	-74	-40
615	0.043	Insula (13)	L	3.88	-40	-77	-33
611	0.044	Inferior frontal gyrus (47)	R	4.50	53	27	-11
1872	0.000	Inferior occipital gyrus (18)	L	4.49	-38	-91	-8
1478	0.001	Precentral gyrus (6)	L	4.24	-57	4	20

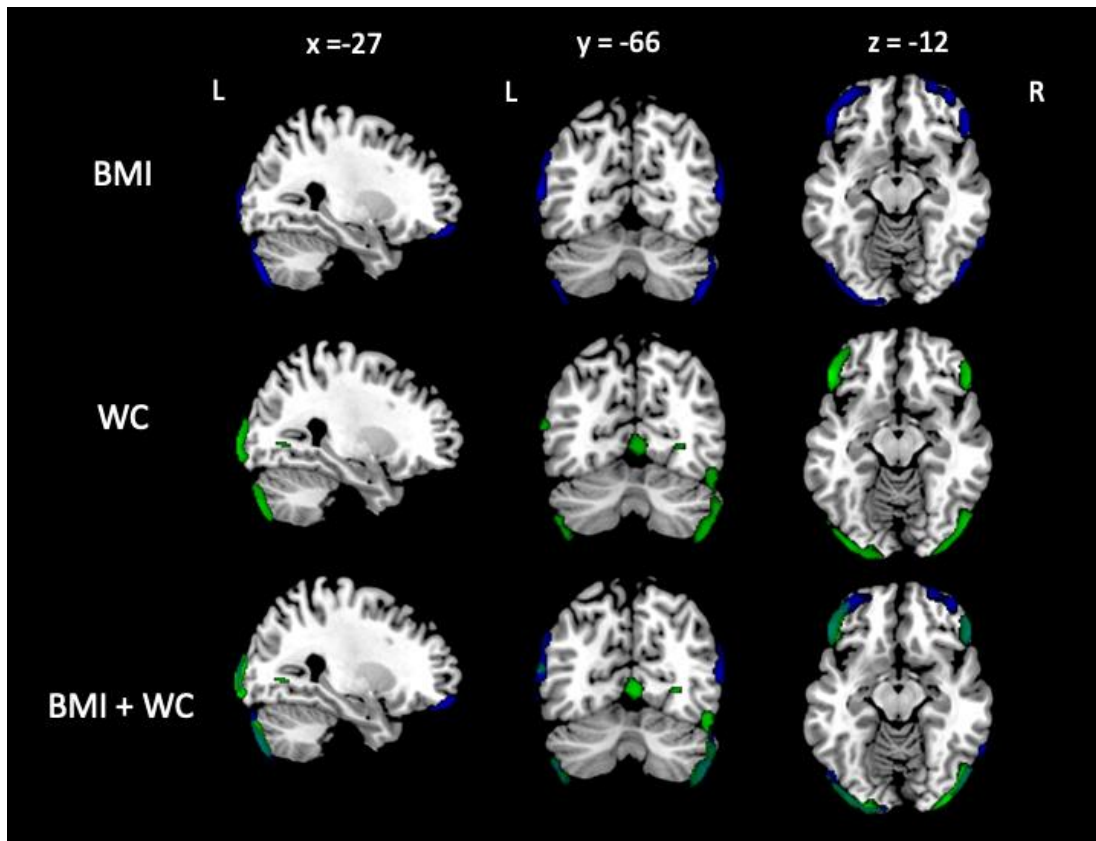


Figure 4.3 Brain regions showing a negative association between GMV and obesity indices in MCI patients

The three rows show negative associations between GMV and obesity measures using voxel-based morphometry in MCI patients. Each of the associations is represented in the sagittal, coronal and axial orientations from left to right. The ‘x’, ‘y’ and ‘z’ co-ordinates have been reported based on the MNI space. Top row: Negative associations found between BMI and GMV in the bilateral occipital lobes, cerebellum and the orbitofrontal cortices depicted in blue; Middle row: Negative associations found between WC and GMV in the bilateral occipital lobes, cerebellum and the orbitofrontal cortices highlighted in green; Bottom row: Overlap between the associations found with BMI and WC.

4.4.3.2.3 CN

BMI

Negative associations were found between BMI and GMV in CN individuals that were dispersed across various brain regions, mostly concentrated in the inferior areas (Table 4.7, Fig 4.4). In the frontal brain regions, negative associations were found in the bilateral ventrolateral prefrontal cortex and the orbitofrontal brain regions in addition to some portions of the body of the cingulate gyrus. The left insula and the right lateral anterior temporal lobe were also significant areas that displayed negative associations between BMI and GMV. Significant voxels were also found superiorly in the left posterior hippocampus. In the more posterior brain areas, negative associations were mostly located on the lateral surfaces of the bilateral occipital and cerebellar lobes. Within the deep brain regions, negative associations were also found in the bilateral thalamus lining the medial borders. The extracted GMV signal was positively correlated with performance on the semantic fluency test, $r = .41, p = .002$, the prose memory - immediate recall test, $r_s = .48, p < .001$, the prose memory - delayed recall test, $r_s = .38, p = .004$ and the similarities test, $r = .38, p = .004$. No significant correlations were found between the extracted GMV signal and WMH volume. No significant positive correlations were found between BMI and the GMV maps.

WC

Negative associations observed between WC and GMV were fairly consistent with the associations found with BMI (Table 4.7, Fig 4.4). A discrepancy between the two measures was the absence of negative associations in the right dorsolateral prefrontal cortex in the analysis with WC. Instead, a cluster showing negative associations between WC and GMV was found located in and around the insula. Another inconsistency was the absence of the association found in the posterior hippocampus with WC. The rest of the associations were identical to those found with BMI. A positive correlation was found between the extracted GMV signal and scores on the semantic fluency test, $r = .44, p = .001$, the prose memory - immediate recall test, $r_s = .43, p = .001$, the prose memory - delayed recall test, $r_s = .41, p = .002$, and the similarities test, $r = .40, p = .002$. No significant correlations were found between the extracted GMV signal and WMH volume. No significant positive correlations were found between WC and the GMV maps.

Similar to the observation in the MCI patients, the negative associations in the CN group spanned across a multitude of vascular territories of cerebral arteries that included the cerebellar arteries, middle cerebral artery, anterior cerebral artery and the posterior cerebral artery. The associations found were restricted to the distal ends of the major arteries including certain subcortical regions that showed volumetric detriments in grey matter (Fig 4.9).

Table 4.7 Brain regions showing a negative association between obesity measures and GMV in CN

Voxels (Cluster extent)	Cluster level <i>p</i> FWE	Brain region	Broadmann area	Side	Z- score	MNI ordinates		
						x	y	z
<i>BMI</i>								
1701	0.000	Thalamus		L	3.60	-12	-12	18
1029	0.001	Cerebellum-posterior lobe		R	4.43	36	-81	-35
543	0.024	Cerebellum-posterior lobe		L	4.27	-36	-81	-38
1015	0.001	Anterior cingulate gyrus	24	L	4.36	-3	16	21
631	0.013	Inferior occipital gyrus	18	L	4.34	-38	-91	-9
1218	0.000	Inferior frontal gyrus	47	R	3.94	50	40	-15
1386	0.000	Insula	44	L	4.19	-36	14	1
879	0.002	Inferior frontal gyrus	47	L	3.92	-46	44	-16
793	0.000	Inferior occipital gyrus	18	R	3.89	39	-91	-6
<i>WC</i>								
1506	0.000	Inferior occipital gyrus	19	L	4.80	-36	-92	-9
669	0.001	Middle temporal gyrus	38	R	4.77	62	6	-30
1096	0.001	Cerebellum-posterior lobe		R	4.67	38	-81	-48
1451	0.000	Thalamus		L	4.05	-12	-11	19
704	0.008	Anterior cingulate gyrus	24	L	4.48	-2	17	19
1769	0.000	Lingual gyrus	18	R	4.30	42	-92	-9
821	0.003	Insula	13	L	4.28	-42	-10	-5

661	0.003	Cerebellum-posterior lobe		L	4.26	-39	-80	-50
641	0.012	Insula	13	L	4.22	-39	9	-15
503	0.033	Middle frontal gyrus	10	R	4.04	34	58	-16

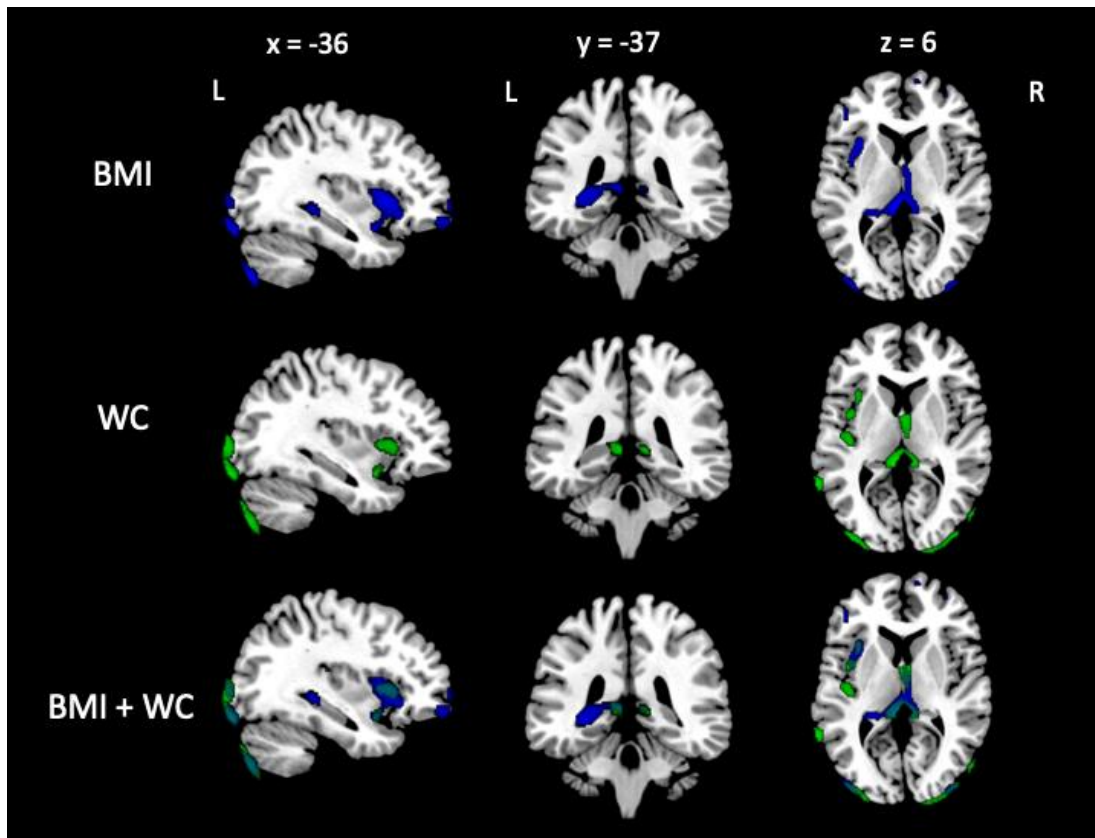


Figure 4.4 Brain regions showing a negative association between GMV and obesity indices in CN participants

The three rows show negative associations between GMV and obesity measures using VBM in CN participants. Each of the associations is represented in the sagittal, coronal and axial orientations from left to right. The ‘x’, ‘y’ and ‘z’ co-ordinates have been reported based on the MNI space. Top row: Negative associations were found between BMI and GMV in the bilateral occipital lobes, cerebellum and the prefrontal frontal cortices including the left hippocampus and the left insula depicted in blue; Middle row: Negative associations were found between WC and GMV in the bilateral occipital lobes, cerebellum and the prefrontal frontal cortices including the left insula highlighted in green; Bottom row: Overlap between the associations found between GMV, BMI and WC.

4.4.4 Tract-based spatial statistics

4.4.4.1 Main effects and interaction analysis

There were no main effects or interactions found between any of the diffusivity measures across the three groups and the body mass categories.

4.4.4.2 Correlation analysis

4.4.4.2.1 ADD

There was no significant correlation between any of the diffusivity or FA maps and both the obesity measures across both contrasts in the ADD group.

4.4.4.2.2 MCI

There was no significant correlation between any of the diffusivity or FA maps and both the obesity measures in the across both contrasts in the MCI group.

4.4.4.2.3 CN

BMI

Widespread negative correlations were found between BMI and maps of FA in the CN participants. Specifically, these were found in the corpus callosum, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, cingulum, uncinate fasciculus, optic radiations, cerebellar peduncles, forceps minor and major, cingulum, parahippocampal and hippocampal white matter and the fornix. Additionally, associations were also found in the subcortical white matter that were situated in and around the basal ganglia and thalamus (Table 4.8, Fig 4.5). No other relationships with other diffusivity indices namely mean diffusivity, radial diffusivity and axial diffusivity were found. There was a positive correlation between the extracted signal and scores on semantic fluency, $r = .52$, $p < .001$ and prose memory - immediate recall, $r_s = .52$, $p < .001$, tests. On examining the association between WMH volume and the extracted FA signal, a negative correlation was found, $r_s = -.34$, $p = .013$. No significant positive correlations were found between any of the diffusivity measures and BMI.

WC

The associations between WC and maps of FA revealed similar findings to those seen with BMI (Table 4.8, Fig 4.5). The negative associations were found in the same white matter tracts listed above. No other relationships with other diffusivity measures were found. There was a positive correlation between the extracted signal and scores on semantic fluency, $r = .52, p < .001$ and prose memory - immediate recall, $r_s = .51, p < .001$, tests. A negative correlation was found between the extracted FA signal and WMH volume, $r_s = -.33, p = .011$. No significant positive correlations were found between any of the diffusivity measures and WC.

Negative correlations between the obesity indices and FA were located across a wide range of vascular territories of major cerebral arteries (Fig 4.9).

Table 4.8 *Regions showing a negative association between obesity measures and fractional anisotropy in CN*

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z- score	MNI ordinates		
					x	y	z
<i>BMI</i>							
54045	0.001	Fornix	L	7.75	-28	-27	-4
		Fornix	L	7.13	-28	-29	-1
		Superior longitudinal fasciculus	L	6.9	-37	34	6
		Cingulum	R	6.66	9	-5	34
		Inferior fronto-occipital fasciculus	R	6.62	26	29	-10
		Superior longitudinal fasciculus	L	6.62	36	14	18
<i>WC</i>							
55438	0.001	Anterior thalamic radiation	L	7.49	-28	-30	0
		Inferior fronto-occipital fasciculus	R	7.47	26	29	-10
		Fornix	L	7.05	-29	-26	-3
		Cingulum	R	6.92	9	-5	34
		Inferior fronto-occipital fasciculus	L	6.85	-35	-55	0
		Inferior fronto-occipital fasciculus	L	6.8	-37	34	6

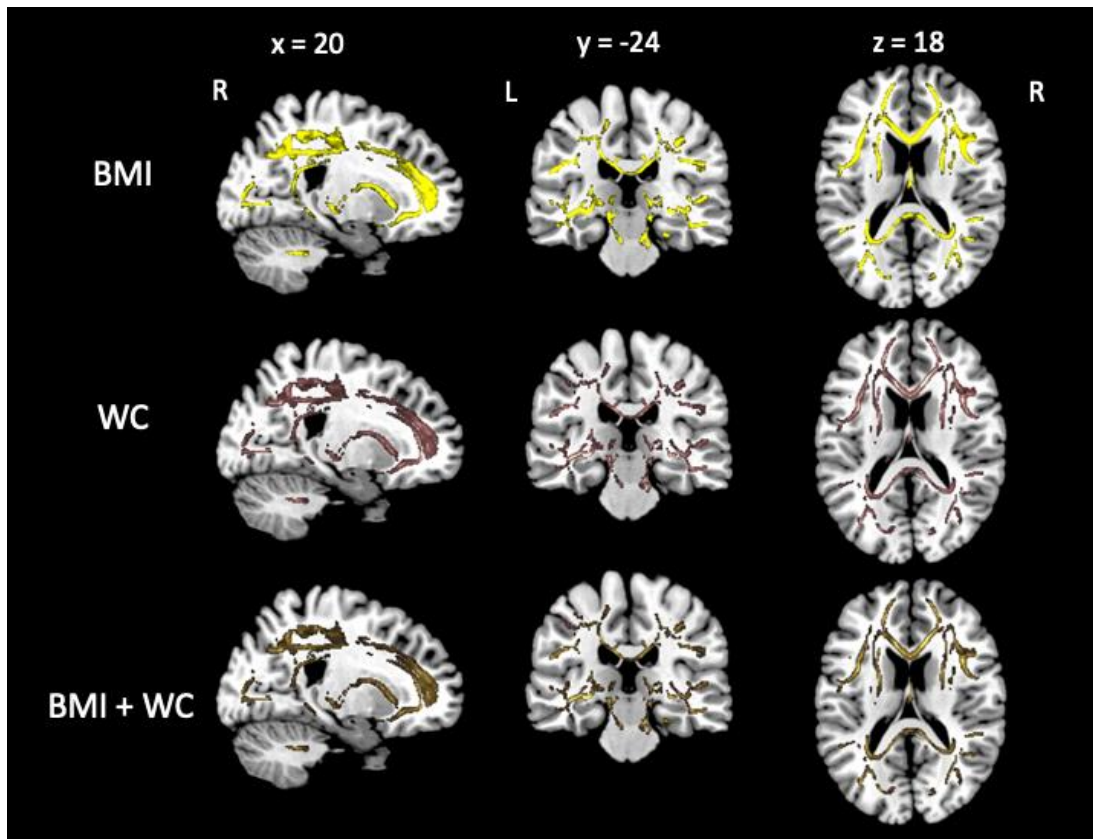


Figure 4.5 Brain regions showing a negative association between fractional anisotropy and obesity indices in CN participants

The three rows show negative associations between WMI and obesity measures using TBSS in CN participants. Each of the associations is represented in the sagittal, coronal and axial orientations from left to right. The 'x', 'y' and 'z' co-ordinates have been reported based on the MNI space. Top row: Negative associations found between BMI and fractional anisotropy in the tracts connecting limbic and subcortical brain regions to prefrontal areas are represented in yellow; Middle row: Negative associations found between BMI and fractional anisotropy in the tracts connecting limbic and subcortical brain regions to prefrontal areas are highlighted in pink; Bottom row: Overlap between the associations found with BMI and WC.

4.4.5 Arterial spin labelling

4.4.5.1 Main effects and interaction analysis

A main effect of body mass categories was observed where the participants in the low body mass category showed better preservation of CBF compared to the participants in the high body mass category. This main effect was observed primarily in the basal brain regions extending across areas of the midbrain, corticospinal tracts, inferior temporal regions and parts of the cingulum bundle (Table 4.9, Fig 4.6). The other contrast did not yield any significant results. No interaction effects were observed between diagnostic group and body mass categories on CBF.

Table 4.9 Brain regions showing main and interaction effects between diagnostic group and body mass categories on CBF

Voxels (Cluster extent)	Cluster level <i>p</i> FWE	Brain region (Brodmann area)	Side	Z-score	MNI ordinates		
					x	y	z
Low BMI > High BMI							
3108	0.002	Corticospinal tracts (WM)	L	3.72	-12	-20	-12
		Corticospinal tracts (WM)	R	3.65	16	-8	-10
		Inferior temporal gyrus (20)	L	3.61	-40	-24	-18
999	0.176	Cingulum (WM)	L	3.47	-14	-10	40
		Cingulum (WM)	L	3.09	-8	0	34
		Superior longitudinal fasciculus (WM)		2.98	-20	6	40

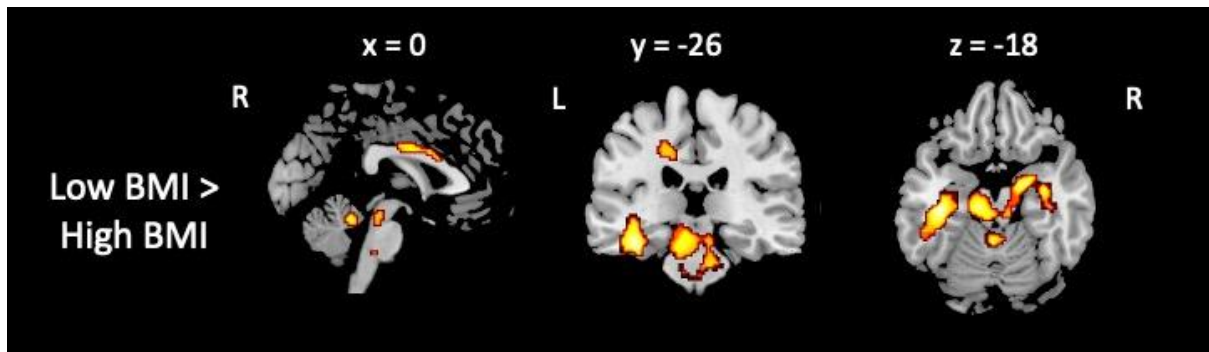


Figure 4.6 Brain regions showing a main effect of body mass categories on GMV.

The row shows a main effect of body mass categories on CBF where participants belonging to the lower body mass category showed better preservation of CBF than participants in the high body mass category. The main effect is represented in the sagittal, coronal and axial orientations from left to right. The 'x', 'y' and 'z' co-ordinates have been reported based on the MNI space.

4.4.5.2 Regression analysis

4.4.5.2.1 ADD

There were no significant associations found between obesity measures and CBF in ADD patients across both contrasts. Although the results did not survive the significance threshold, a trend of a positive correlation was found in and around the regions of the temporoparietal junction across both obesity measures. This was the same brain region that showed a positive correlation between obesity measures and GMV in ADD patients (Appendix C, Fig C.1).

4.4.5.2.2 MCI

BMI

BMI was negatively correlated with CBF in MCI patients mainly in the frontal, MTL, subcortical and brainstem regions. In the frontal lobe, one large cluster was found in the left hemisphere that began in the anterior frontal lobe and extended rostro-caudally until the posterior border of the frontal lobe (Table 4.10, Fig 4.7). A different cluster that ran parallel to this cluster (in the frontal lobe) in the right hemisphere had a smaller expanse; beginning at the primary motor cortex, it extended rostro-caudally toward the parietal lobe. This cluster was restricted to the anterior portions of the parietal lobe. Negative associations between CBF and BMI were also found in MTL regions that included the left parahippocampal parenchyma. Additionally, significant clusters were found in the posterior portions of the brainstem and cerebellum. No correlations were found with the extracted signal and performance on neuropsychological tests. However, a negative correlation was found between the extracted CBF signal and WMH volume, $r_s = -.34$, $p = .004$. No significant positive correlations were found between CBF and BMI.

WC

Negative associations found between WC and CBF in MCI patients were similar to the findings with BMI (Table 4.10, Fig 4.7). However, the extent of the results found with WC as an obesity measure was more widespread than the associations found with BMI. The clusters that ran parallel had analogous trajectories beginning in the anterior frontal lobe and extending rostro-caudally until the anterior parietal lobe. In the temporal areas, negative associations with CBF extended to the bilateral hippocampi, while associations in the brainstem remained largely the

same. No significant correlations were found with the extracted CBF signal and performance on neuropsychological tests. A negative correlation was found between the extracted CBF signal and WMH volume, $r_s = -.39$, $p = .001$. No significant positive correlations were found between CBF and WC.

The negative associations with CBF in the MCI patients visibly appeared to follow the trajectory of the anterior cerebral arteries in the anterior brain regions. Additionally, negative correlations were observed in vascular territories supplied by the posterior cerebral and cerebellar arteries (Fig 4.9).

Table 4.10 Brain regions showing a negative association between obesity measures and CBF in MCI patients

Voxels (Cluster extent)	Cluster level p FWE	Brain region (Broadmann area)	Side	Z- score	MNI ordinates		
					x	y	z
<i>BMI</i>							
4529	0.000	Inferior fronto-occipital fasciculus	L	3.77	-28	39	11
		Middle frontal gyrus (6)	L	3.39	-34	5	27
		Corticospinal tract	L	3.67	-22	-23	45
2555	0.002	Midbrain	L	3.68	-6	-28	-9
		Parahippocampal gyrus	L	3.52	-42	-32	-9
3266	0.000	Superior longitudinal fasciculus	R	3.42	22	0	42
		Precuneus (39)	R	3.32	28	-65	29
<i>WC</i>							
5626	0.001	Hippocampus (36)	R	5.23	36	-11	-16
		Thalamus	R	3.77	12	-16	-4
		Hippocampus	L	3.52	-28	-22	-11
10179	0.001	Anterior cingulate gyrus (BA 32)	L	4.64	-20	31	28
		Corticospinal tracts	L	4.44	-22	-23	47
		Middle frontal gyrus (BA 6)	R	3.75	28	-13	49
		Superior longitudinal fasciculus	R	3.53	36	-43	33

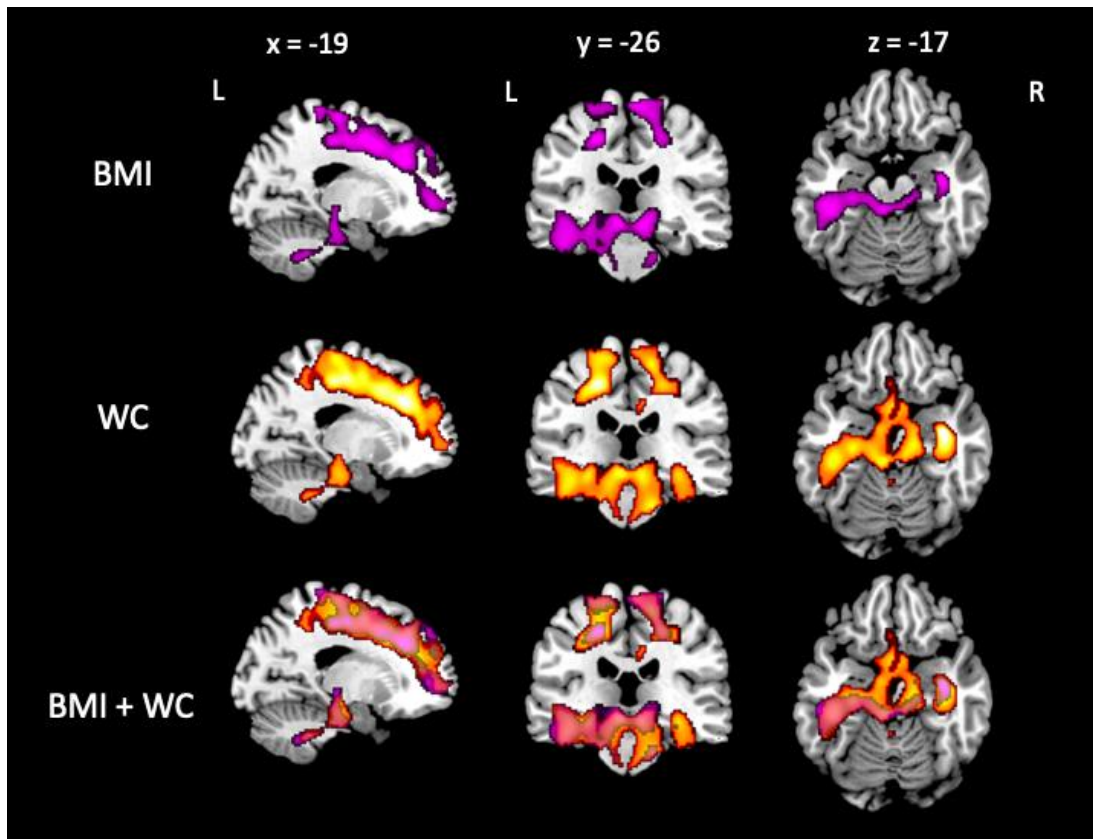


Figure 4.7 Brain regions showing a negative association between CBF and obesity indices in MCI patients

The three rows show negative associations between CBF and obesity measures in MCI patients. Each of the associations is represented in the sagittal, coronal and axial orientations from left to right. The 'x', 'y' and 'z' co-ordinates have been reported based on the MNI space. Top row: Negative associations found between BMI and CBF in the bilateral MTL, frontoparietal areas (largely periventricular), cerebellum and brainstem depicted in purple. These were slightly attenuated in the right hemisphere; Middle row: Negative associations found between BMI and CBF in the bilateral MTL, frontoparietal areas (largely periventricular), cerebellum and brainstem highlighted in red; Bottom row: Overlap between the associations found with BMI and WC.

4.4.5.2.3 CN

BMI

Negative associations between CBF and BMI were found in frontal, parietal, cerebellar and temporal brain regions (Table 4.11, Fig 4.8). In the frontal lobe, a small cluster was located on the lateral borders of the right dorsolateral prefrontal cortex. The other negative correlations found, lay deeper in the frontal lobe. Two parallel clusters toward the midline (one in the left hemisphere and the other in the right hemisphere) beginning at the posterior ends of the anterior cingulate gyrus, stretched rostro-caudally into the parietal lobe. These clusters diverged in the parietal lobe away from the midline and continued caudo-rostrally towards more inferior brain regions. In the right hemisphere, some voxels from the cluster in the right hemisphere spilled into the posterior temporal lobe. In the left hemisphere, some voxels from the cluster spilled into the occipital lobe. These two clusters appeared to follow the trajectory of the lateral ventricles. Negative associations with CBF were also found in the inferior cerebellum that were predominantly located in the left cerebellar hemisphere. No correlations were found with the extracted CBF signal, neuropsychological tests and WMH volume. No significant positive correlations were found between CBF and BMI.

WC

Negative associations between WC and CBF were far more pervasive than those found with BMI (Table 4.11, Fig 4.8). In addition to the associations found with BMI (that slightly expanded in the associations with WC), the two clusters that ran parallel to each other joined at the midline in the medial parietal areas before extending inferiorly. Posteriorly and inferiorly, these two clusters closely followed the trajectory of the lateral ventricles, with significant voxels found in the MTL (in close proximity to the hippocampus) and occipital areas. Negative associations were also found in subcortical brain regions specifically in the caudate nucleus and the thalamus. Associations found in the brainstem and cerebellum were more or less identical, but more extensive in the association with WC. On using a more conservative threshold of $p < .001$ at the set-level only the associations found in the medial parietal lobes and the cerebellum remain significant. No correlations were found between the extracted CBF signal, performance on neuropsychological tests and WMH volume. No significant positive correlations were found between CBF and WC.

Negative correlations between the obesity indices and CBF were located across a wide range of vascular territories of major cerebral arteries (Fig 4.9).

Table 4.11 Brain regions showing a negative association between obesity measures and CBF in CN

Voxels (Cluster extent)	Cluster level <i>p</i> FWE	Brain region	Side	Z- score	MNI ordinates		
					x	y	z
<i>BMI</i>							
1438	0.045	Cerebellum-posterior lobe	L	4.10	-8	-56	-48
		Medulla oblongata	R	3.89	4	-44	-54
2365	0.015	Superior longitudinal fasciculus	L	3.23	-26	-14	36
		Cingulum (posterior)	L	2.83	-24	-47	2
1432	0.045	Cingulum (anterior)	R	3.41	16	20	26
		Superior longitudinal fasciculus	R	3.39	16	46	48
2546	0.011	Superior longitudinal fasciculus	R	3.33	22	-8	39
		Inferior longitudinal fasciculus	R	2.84	42	-31	-2
<i>WC</i>							
1879	0.041	Cerebellum- posterior lobe	L	4.55	-10	-54	-39
		Cerebellum- posterior lobe	R	2.70	20	-70	-34
13608	0.000	Superior longitudinal fasciculus	R	3.73	32	-47	30
		Superior longitudinal fasciculus	L	3.72	-28	-51	30
		Superior longitudinal fasciculus (temporal)	L	3.56	-42	-33	0
		Superior longitudinal fasciculus (temporal)	R	3.43	42	-39	6

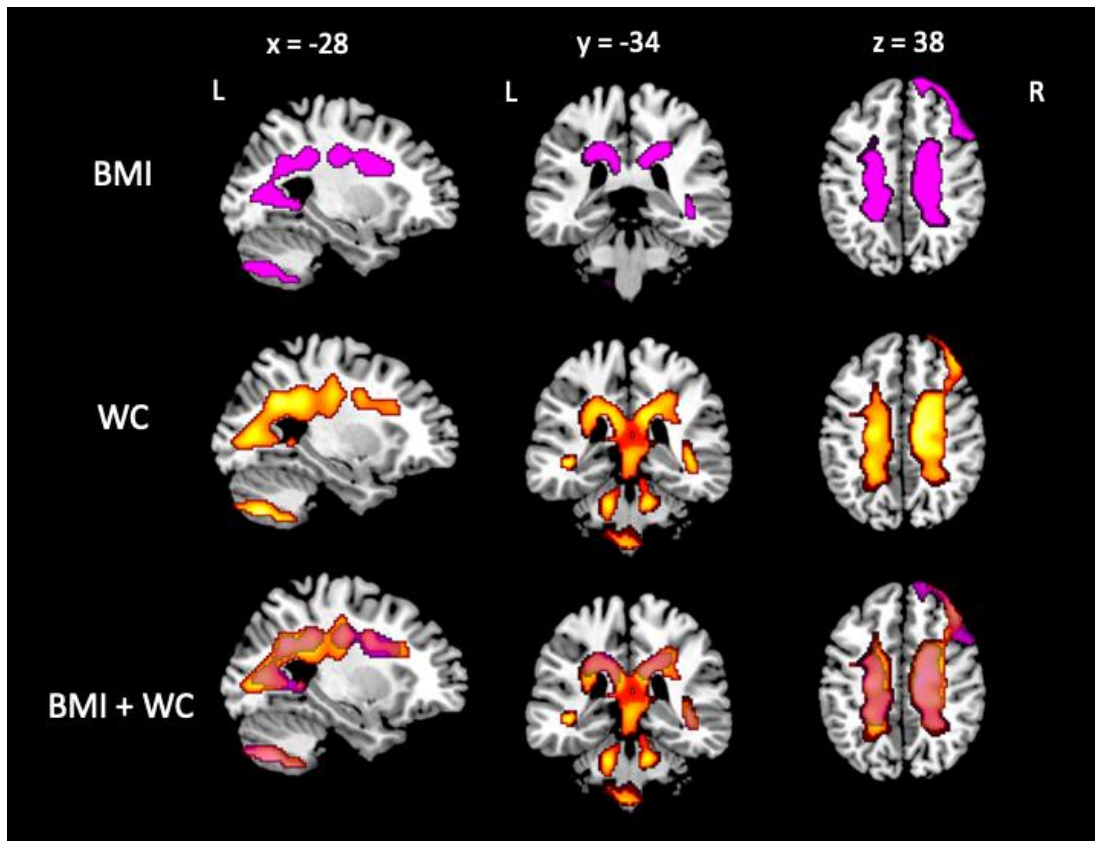


Figure 4.8 Brain regions showing a negative association between CBF and obesity indices in CN participants

The three rows show negative associations between CBF and obesity measures in CN participants. Each of the associations is represented in the sagittal, coronal and axial orientations from left to right. The 'x', 'y' and 'z' co-ordinates have been reported based on the MNI space. Top row: Negative associations found between BMI and CBF in the bilateral temporoparietal areas, posterior frontal areas, cerebellum, brainstem and MTL depicted in purple; Middle row: Negative associations found between BMI and CBF in the bilateral temporoparietal areas, posterior frontal areas, cerebellum, brainstem and MTL depicted in red. These were slightly more extensive than the associations found with BMI; Bottom row: Overlap between the associations found with BMI and WC.

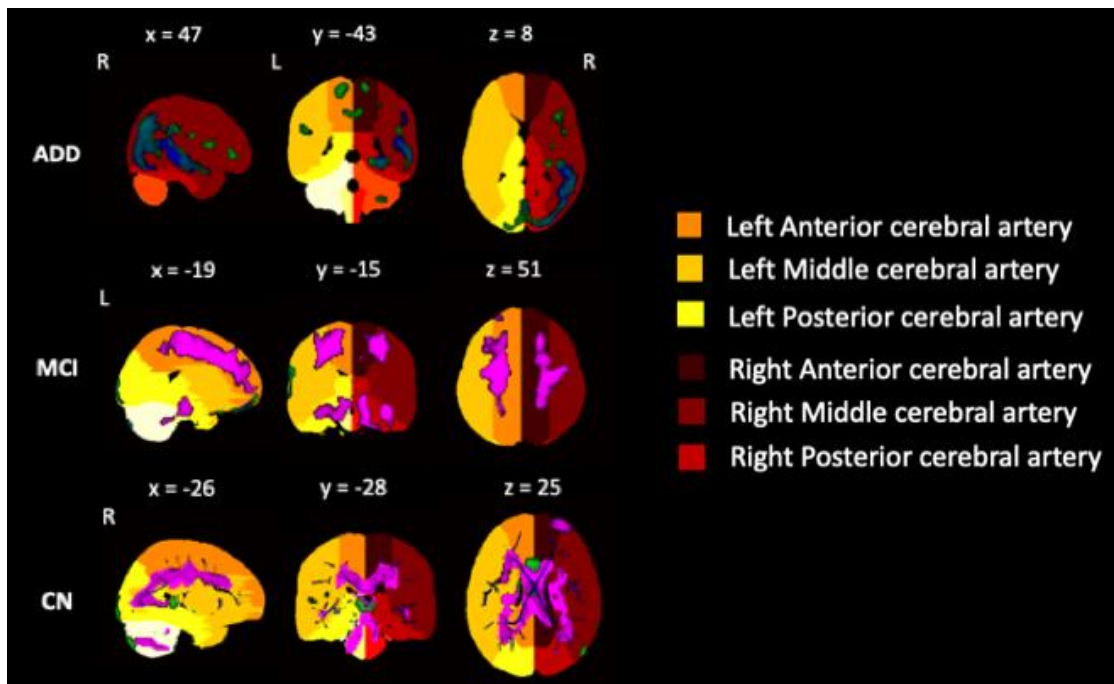


Figure 4.9 *Vascular territories of major cerebral arteries and their overlap with the associations found between obesity measures and neuroimaging parameters among ADD and MCI patients and CN participants*

The three rows show negative associations between neuroimaging parameters (namely GMV, WMI and CBF) and obesity measures in ADD and MCI patients and CN participants. The associations have been mapped onto the vascular territories of major cerebral arteries. The key on the right indicates the colour codes for the respective vascular territories irrigated by the major cerebral arteries. All the associations are represented in the sagittal, coronal and axial orientations from left to right. The 'x', 'y' and 'z' co-ordinates have been reported based on the MNI space. Top row: Positive associations found between obesity measures and GMV around the right temporoparietal junction primarily lie in the vascular territory of the middle cerebral artery; Middle row: Negative associations found between obesity measures, GMV and CBF in MCI patients lie in vascular territories primarily supplied by the anterior cerebral artery in addition to some cerebellar arteries and the posterior cerebral artery in addition to some territories of the middle cerebral artery; Bottom row: Negative associations found between obesity measures, GMV, WMI and CBF in CN participants lie in vascular territories supplied by numerous major cerebral arteries.

4.4.6 White Matter Hyperintensity Volume

On correlating the volume of WMH with neuropsychological performance, no correlations were found in ADD patients. In the MCI patients, a negative correlation was found between WMH volume and performance on the semantic fluency test, $r_s = -.33$, $p = .005$, the prose memory - immediate recall test, $r_s = -.26$, $p = .047$, and the prose memory - delayed recall test, $r_s = -.26$, $p = .047$. Among the CN group, a negative correlation was found between WMH volume and performance on the semantic fluency test, $r_s = -.31$, $p = .022$.

4.5 Discussion

Using multi-modal neuroimaging the current study shows for the first time, a positive correlation between indices of obesity in patients with ADD. The detected associations, however, vary across the three diagnostic groups assessed in the study, possibly as a factor of the evident baseline differences in the distribution of their obesity indices. These baseline differences in BMI could be among the drivers of the associations found. The distribution of BMI in the CN group fell in part within the obese range, that of the MCI group fell in the overweight range, while the distribution of the ADD group was within the normal range. These differences could be the result of observed age and disease-related weight loss, where the trends of body mass distributions seen in this study are consistent with the existing literature (Jimenez et al., 2017; Kuk et al., 2009; Kyle et al., 2001). The interaction analysis revealed that overall, participants who fell in the lower BMI category were more likely to show preservation of GMV and CBF. It is noteworthy that this main effect in terms of GMV was observed in the orbitofrontal cortex and the cerebellum, brain regions that also tend to be affected in obesity. This might indicate that as a general trend, having a lower BMI appeared to be beneficial to cerebral constituents in the presence of age and disease-related insults in the participants included in the current study.

In contrast to the associations found in the ADD group, negative associations were found between obesity indices and neuroimaging parameters in the CN and MCI groups. Nevertheless, the groups did not differ on measures of abdominal obesity, as measured using WC, although there was a trend indicating that CN had the highest parameters of WC followed by the MCI and ADD patients, respectively. Higher WC is a factor that is associated with elevated cardiometabolic risk as opposed to BMI (Liao et al., 2018; Lofgren et al., 2004; Lukács et al., 2019; Seo, Choe, & Torabi, 2017). Although there was an absence of a significant difference in WC, the trend of WC measurements in the different diagnostic groups could have accounted for the differences in associations with obesity measures found. However, the groups did not differ on age, which made the groups comparable to one another. There was also no significant difference in terms of the years in education. The differences found in the MMSE scores, neuropsychological performance and cerebral parameters namely GMV and CSF are consistent with the pattern of these parameters found across the different diagnostic groups, where CN have the highest parameters followed by the MCI and then the ADD patients, respectively.

The findings indicate that higher indices of obesity within the overweight and obese ranges are linked with lower volumetric or integrity measurements of brain structure and CBF in CN and MCI patients. In contrast, higher indices of body mass within the normal range are linked to higher retention of GMV parameters in ADD patients. This trend could be linked with downstream mechanisms resulting from circulating hormones associated with body fat such leptin, gender, age and disease related weight loss and the interaction between AD and obesity. The following discussion tries to elaborate on and identify such mechanisms that could offer an explanation for the findings, with a specific focus on the vascular contributions of obesity.

4.5.1 ADD

In the initial interaction analysis, the comparison where participants in the low BMI category showed better preservation of GMV than participants in the high BMI category showed a higher difference in the ADD group compared to the other two groups. This finding suggests that having a body mass index between the normal weight range could aid in the preservation of GMV among the ADD patients compared to the other two groups. The positive correlation between GMV and both indices of obesity in ADD patients is a novel finding that supports the findings from the interaction analysis and suggests a resilient effect of higher body-fat store within the normal weight range in progressive disease stages. This suggests that among those patients who have progressed to ADD, those with better nutrition are better able to cope with the progressive cerebral damage inflicted by age and disease, that could result in a better prognostic profile of ADD (Coin et al., 2012; Vassallo, Poynter, Sharma, & Kwan, 2016). In fact, a study shows that cognitively impaired patients with a BMI below 20 who were admitted for rehabilitation (aimed at improving nutrition and physical activity) were less likely to show improvements in functional activities following rehabilitation, compared to cognitively impaired patients with a BMI above 20 (Vassallo et al., 2016). The preclinical phase of AD is often associated with weight loss (Jimenez et al., 2017; Johnson, Wilkins & Morris, 2006). Findings from the study by Vassallo and colleagues and the weight loss observed in preclinical AD might indicate the need for early diagnosis and intervention to prevent extensive weight loss in the preclinical disease stages to improve the effectiveness of multi-domain interventions in ADD patients. Further support for this finding comes from a different longitudinal study by Cova and colleagues which shows that higher indices of BMI were linked with lower risk of AD and dementia in older individuals with MCI (~75 years) (Cova et al., 2016). The same

study indicated a higher dementia risk associated with being underweight in MCI patients (Cova et al., 2016).

There are a couple of mechanisms that could be extrapolated from the results found in the study. One of these could be grounded in vascular mechanisms. Although the results did not survive the significance threshold, a positive correlation between CBF and obesity measures was found in and around the temporoparietal junction in the ADD patients (Appendix C, Fig C.1). This trend of findings could insinuate that higher BMI in the normal weight range and its downstream secretions, could supplement vascular function and therefore aid in the preservation of brain structure. However, the cross-sectional nature of this study limits the derivation of any causal inferences. Therefore, the observation showing a spatial overlap in the positive associations found between obesity measures, GMV and CBF, is speculative. There is evidence to suggest that obesity-mediated hormones such as adiponectin and leptin interact with insulin to exert beneficial effects on the structure and haemodynamics of the cerebral vasculature (Serné et al., 2002; Zalatel, Barlovic & Prezelj, 2010). Therefore, body-fat mediated secretions of adipokines could help alleviate the detrimental effects of vascular dysfunction seen in AD. Additionally, leptin has previously indicated a direct beneficial effect on brain structure through its independent actions and its role in protecting against vascular injury (Dicou et al., 2001; Zhang et al., 2007a). This factor could be crucial in limiting progressive decrements in ADD patients with extensive cerebral damage, in the presence of age and disease related insults. Obesity-mediated secretions as a result of higher body weight within the normal weight range could thus contribute toward preservation of grey matter in ADD patients.

Moreover, a major proportion of these brain regions is supplied by the middle cerebral artery that is the biggest cerebral artery and most prone to adverse vascular events (Goyal et al., 2016; Huang et al., 2007). Research even shows that the right middle cerebral artery is more prone to adverse vascular events than the left middle cerebral artery (Stead et al., 2015). Therefore, the results from the current study suggest that brain regions most vulnerable to the damaging effects of obesity and AD on cerebral vasculature may benefit the most from the resilient effects of higher body mass in ADD. Higher BMI in the normal weight ranges could potentially promote the anti-atherogenic and vasodilatory properties of adiponectin, an adipokine which could help preserve vascular function and brain structure in ADD patients (Yamauchi et al., 2003; Bang et al., 2007; Cheng et al., 2007; Osuka et al., 2012). Therefore, higher body mass

within the normal weight range in ADD patients could help provide a resilient quality to the brain that could aid in preserving brain structure through myriad mechanisms. This notion is supported by findings from some animal studies that show improved cognition and preservation of brain structure with nutritional supplementation in AD mice (Van der Auwera et al., 2005; Wolf et al., 2012). In fact, a study among AD patients showed that the administration of a ketogenic compound was successful in improving cognition among AD patients (Henderson et al., 2009). These results provide further insight into the obesity paradox that states that there might be a beneficial effect of higher BMI in vulnerable populations. The findings from the present study also lend further support to the speculations made by Pegueroles and colleagues that weight loss observed in preclinical AD could change the relationship between the brain and BMI, where higher BMI in later stages could confer greater resilience to the brain from progressive disease-related damage (Pegueroles et al., 2018).

Furthermore, the positive association between GMV and obesity measures was linked with better performance on tests measuring long-term memory (prose memory - delayed recall test) and abstract reasoning (similarities test) (Wechsler, 1958; Wechsler, 1987). This association is particularly of note, as these cognitive sub-domains are affected early in the disease course with progressive decline observed with disease progression (Jacobs et al., 1995; Stern et al., 1999). This could indicate that in addition to preserving brain structure, a healthy weight within the normal weight range could potentially help limit progressive damage to these cognitive domains, which could improve AD prognosis in the dementia stage. This was supported by findings from a previous longitudinal study that examined changes in BMI and cognitive decline in MCI patients over intervals of six months and one year (Cronk et al., 2010). The study found that lower baseline BMI was linked with a more rapid decline in MCI patients. However, the study found no association between baseline BMI and conversion to ADD (Cronk et al., 2010). It is possible that this association was not detected due to the short one-year period of monitoring of the patients (Cronk et al., 2010). It is difficult to speculate whether the observations found in the present study are an effect of higher BMI within the healthy range, or whether life-long changes in BMI could have resulted in the observed association with preservation of brain structure and cognitive function, due to its cross-sectional design. Nevertheless, this is the first multi-modal neuroimaging study to find preservation of cognitive function and brain structure associated with higher obesity measures within a healthy weight range, in patients with ADD.

4.5.2 MCI

The initial interaction analysis showed that MCI patients in the lower weight category showed better preservation of GMV than MCI patients in the high BMI category. In this comparison, there was a higher difference compared to the ADD and CN groups. This finding appears to suggest that being in the low BMI category could be more beneficial for the preservation of GMV in the MCI patients compared to the other two groups. The fact that a negative correlation is found between GMV and obesity indices in the overweight MCI group lends further support to the notion that being in the low BMI category might lead to better preservation of GMV in this patient group.

In contrast to the associations found in the ADD patients, in MCI patients, negative correlations were observed between obesity indices and GMV and CBF. It is important to note that the MCI patients in the current study lay in the overweight range and belonging to this weight category could be one of the main drivers of the associations found in this group. Negative associations between the obesity measures and GMV were found in frontal, occipital and cerebellar brain regions. This is fairly consistent with the results found in two separate meta-analytical studies on the effects of obesity on the brain (García-García et al., 2019; Herrmann et al., 2019). However, there was a discrepancy between the findings of the studies in this thesis and those from one of the published meta-analytical studies that showed increased GMV in obese patients in the occipital lobe and the precuneus (Herrmann et al., 2019). Herrmann and colleagues attributed this increase in GMV to practice effects to tasks performed by participants in the studies or higher activation in patients with anxiety disorders, and due to the fact that a vast proportion of anxiety disorders are often linked with obesity (Herrmann et al., 2019). The negative correlations found in the current study between obesity measures and GMV in the occipital lobe are equally poorly explained. However, this observation could be related to the longitudinal obesity related detriments on the occipital lobe, a finding observed in several neuroimaging studies (section 4.1.1.1.1). However, the data used in the current study are cross-sectional in nature. This methodological shortcoming limits the examination of life-long changes in BMI and how these could have affected neural structure.

Higher neuritic plaque and neuropil thread accumulation has previously been found in temporal and occipital lobes compared to other brain regions in patients with AD, a pathological process that could also potentially contribute toward structural damage in these brain regions (Arnold

et al., 1991; Braak, Braak, & Kalus, 1989; Rafalowska et al., 1988). Nevertheless, atrophy in the occipital lobes is not found in AD patients until later disease stages and therefore the current results could be indicative of a more severe radiological AD phenotype in the sample of MCI patients (Karas et al., 2003; Zakzanis, Graham, & Campbell, 2003). Additionally, past studies have shown that a genetic risk for obesity or higher BMI can be linked with lower brain volumes in the occipital and frontal lobes (Gazdzinski et al., 2008; Ho, et al., 2010b; Pannacciulli et al., 2006; Raji et al., 2010). Therefore, an interaction between AD pathology and obesity-related structural deficits could explain the negative associations found between GMV and obesity measures in the occipital lobe in MCI patients.

The negative associations found between obesity measures and GMV in the orbitofrontal cortex could reflect a predominant effect of obesity. There is ample evidence that suggests that the frontal lobe and especially the prefrontal cortex is specifically vulnerable to the detrimental effect of obesity and that these might be linked with deficits in executive function (section 4.1.1). This is particularly of note as the extracted GMV signal was linked with poor performance on the phonemic fluency test, a task of executive function and attention. Pronounced deficits in executive function and structural damage in the frontal lobe are usually presented in much later stages of AD (section 1.3.4.2, Para 2; section 1.6.1.1, Para 2). If the observed association were assumed to be causal, an earlier executive deficit and frontal impairment could indicate that overweight in MCI patients could result in heightened clinical disease severity. Therefore, overweight in MCI patients that may be detrimental to brain structure in the orbitofrontal cortex could clinically manifest as deficits in executive function and attention.

It is of significance that executive function was not associated with vascular burden (as measured using WMH volume), as higher vascular burden is often associated with deficits in this cognitive domain (Heinzel et al., 2014; Villeneuve et al., 2009). However, the extracted GMV and CBF signal from the analyses was negatively correlated with WMH load, which could indicate that executive function could be hampered as a secondary effect on GMV from the additional vascular burden in overweight MCI patients. Nevertheless, the directionality of the causality between these associations remains in contention. On the other hand, WMH load in the MCI patients was associated with poor performance on memory domains (semantic memory and long-term memory). It is noteworthy that the association between the extracted GMV and CBF signal were not associated with memory performance, although WMH load

was negatively associated with the extracted GMV and CBF signal. Therefore, these associations could signify that the additional vascular burden from being overweight is linked with deficits in volumetric brain structure and CBF and that vascular pathology could have a secondary effect on executive function through mediation of CBF and GMV, while higher vascular burden could have a primary effect on the memory domain. It is possible that the MCI patients may have a higher baseline WMH load as a result of the amalgamation of AD and overweight-related vascular pathology (Holland et al., 2008; Lampe et al., 2019). Therefore, an effect of the interaction between AD and vascular pathology on cerebral constituents could be reflective of additive decrements in cognitive function in overweight MCI patients.

Another observation that could indicate increased radiological severity due to overweight in MCI is the negative associations found in the cerebellum. The cerebellum is relatively resistant to the effects of AD and does not present with atrophy until much later in the disease course (Braak & Braak, 1997b; Thal et al., 2002; Xu et al., 2019). The cerebellum also has extensive connections to the frontal lobe and the observed associations could be attributed to the ‘die back’ effect due to loss of input from the frontal lobe (Allen et al., 2005; Watson et al., 2014). The fact that the cerebellum is linked with lower GMV associated with overweight in MCI patients could indicate increased radiological severity in addition to the detriments found in the occipital and frontal lobes. Additionally, all the negative associations with GMV were found in brain regions that are supplied by the distal branches of major cerebral arteries (Hendrikse et al., 2008). Distal branches have smaller lumen diameters that make them prone to adverse vascular events such as embolisms, especially in the presence of conditions such as obesity (Gutierrez et al., 2015). This quality of distal arteries could offer an explanation for the negative associations found in brain structures supplied by terminating branches of major cerebral arteries.

The absence of any associations between obesity measures and WMI in the presence of GMV deficits was inconsistent as white matter is more prone to ischaemic damage compared to grey matter (Jang et al., 2017). One possible explanation for this discrepancy is the difference in the methodologies used to assess these two cerebral properties, where TBSS (the methodology used to analyse WMI) might be less sensitive in detecting these associations than those detected using voxel-based morphometry. This finding could also indicate a less profound effect of overweight in the MCI group compared to the CN group as negative associations between obesity measures and WMI were found in the latter. However, there is a possibility that the

MCI patients could have been obese in earlier decades of life and experienced disease-related weight loss that could have limited progressive detriments to the brain. Another possibility is that this subset of patients did not reach the overweight/obesity threshold for extensive damage to white matter, which could explain the absence of this effect. The cross-sectional design of the study limits the inferences that can be drawn to explain the absence of this association. As predicted in our hypothesis, less detrimental associations with obesity measures and brain parameters are seen in the MCI group, possibly as a factor of the resilient effect of higher body mass indices in diseased individuals (Pegueroles et al., 2018). However, it is also possible that the effect of obesity is less profound in this group due to the baseline differences in the range of obesity indices between the MCI and CN groups that lay in the overweight and obese ranges, respectively.

In terms of CBF, negative correlations with obesity measures were found mainly in frontoparietal, MTL, cerebellar and brainstem regions in MCI patients. The clusters in the frontal lobe extending posteriorly into the parietal lobe, traversed the trajectory of the anterior cerebral artery, running parallel to one another. There was a slight difference in the associations between obesity measures and CBF, where the associations with WC were more extensive than those observed with BMI. This could be attributed to the property of WC as a better predictor of cardiometabolic risk than BMI (Lukács et al., 2019). Pathological effects of obesity such as atherosclerosis can contribute toward reduced CBF in cerebral arteries (McGill Jr et al., 2002). Atherosclerotic plaques tend to form at bifurcations and at arterial junctions involving multidirectional flow and fast-flowing blood (Johansson et al., 2006; Morbiducci et al., 2016; Salzar et al., 1995; Singh & Tubbs, 2018; Zarins et al., 1983). The Circle of Willis is one such site and obesity has been associated with increased plaque deposition in the Circle of Willis in the past (Rodríguez-Flores, Rodríguez-Saldaña, Cantú-Brito, Aguirre-García, & Alejandro, 2013). Moreover, past studies have also shown that atherosclerosis in the Circle of Willis is associated with sporadic AD (Beach et al., 2007; Roher et al., 2003). A reduction in CBF in the Circle of Willis can thus result in a reduction in CBF to the arteries irrigated by it, which could offer an explanation for the pattern of results found.

Just as lower CBF could contribute toward damage to GMV, the inverse may also be true that structural atrophy could manifest as lower CBF in that brain region, which could explain the associations found in the MTL in MCI patients. However, the current study controlled for partial volume effects, which should have accounted for any negative associations with CBF

found due to atrophy (Matsuda et al., 2002). In support of the findings from the present study, a longitudinal study in healthy individuals that showed that lower parenchymal volume at baseline was associated with reductions in CBF in individuals below the age of 65 years (Zonneveld et al., 2015). In contrast, this relationship was inverted in individuals above the age of 65 years where lower CBF at baseline was linked with declining brain volumes (Zonneveld et al., 2015). Considering that the MCI patients in the current study had an average age of 69 years, the findings from the study by Zonneveld and colleagues could provide a possible support for the theory that the negative association found between CBF and obesity measures in the MTL regions could be an additive effect of overweight in these patients. Midlife obesity has also been associated with lower CBF in the MTL regions (Amen et al., 2020). This could indicate that the interaction between AD and obesity could have an additional negative effect on CBF in the MTL regions. This highlights that overweight-mediated lower CBF in the MTL regions that is additional to that seen in AD could add to the progressive MTL deficits seen in AD, another indication of heightened radiological disease severity. Similarly, negative associations with CBF in the brainstem, in the tracts going to and from the cerebellum, the cerebral peduncles and potentially certain brainstem nuclei could indicate that overweight in MCI patients can be detrimental to CBF in brain regions affected by AD. Thus, the pattern of results observed in the MCI group represents that of detriments that appear to exaggerate the insults already inflicted by AD as an effect of the additional vascular burden seen in overweight patients.

4.5.3 CN

Aligned with the associations seen in MCI patients, CN also presented with negative associations between indices of obesity, GMV and CBF. Additionally, negative associations with maps of WMI were also found in this group. The associations found with CBF and GMV were more extensive compared to those seen in the MCI group. The CN group also ranked highest in the range of obesity measures, falling in the obese and overweight categories, which could be contributing factors to the extensive associations found in these participants compared to the patient groups. Analogous to the associations found between the obesity measures and GMV in the MCI groups, CN showed deficits in GMV in the orbitofrontal cortex, occipital and cerebellar brain regions in addition to certain deep brain regions (thalamus), the insula, the posterior hippocampus and the cingulate gyrus. Another similar finding in the CN group compared to the MCI group was that the negative associations between GMV and obesity

measures were located in the brain regions supplied by the distal ends of cerebral arteries. This finding could be attributed to the susceptibility of the distal ends of arteries to adverse vascular events (section 4.5.2, Para 5).

The detriments found in the anterior cingulate gyrus and insula can be attributed to frontal lobe vulnerability to obesity that has been highlighted by past neuroimaging evidence (section 4.1.1). The deep brain regions on the other hand could be susceptible to obesity-related comorbidities such as high blood pressure or other downstream pathobiological processes, mainly due to the delicate nature of the vasculature supplying these structures (Cox et al., 2019b). Lower GMV values were further linked with poor performance on long-term and short-term memory (prose memory tests) in addition to abstract reasoning (similarities test). AD patients tend to have poor performance on these cognitive domains (Amieva et al., 2008; section 1.3.4). The convergence of findings of poor performance on memory and reasoning tasks associated with obesity measures in obese CN, with the cognitive deficits observed in typical AD points towards how obesity could lower the threshold for AD in CN. No significant correlations were found between the extracted GMV and WMH load that could indicate that mechanisms other than an underlying vascular pathology could have contributed to the observed associations.

Extensive negative associations with FA, an index of WMI were also seen in CN participants. The deficits were primarily located in the genu of the corpus callosum, the optic radiations and diffused across the cingulum bundle. Other notable associations were scattered across other tracts including the inferior fronto-occipital fasciculus, superior longitudinal fasciculus, subcortical white matter, corticospinal tracts and cerebellar white matter tracts. Overall, it appears that damage in structural integrity was mainly found in the tracts connecting the grey matter structures that showed obesity-related detriments in these individuals. One of the mechanisms that could explain this observation is Wallerian degeneration, where damage to one part of the nerve fibre could promote neurodegeneration in a part that is distal to the injury (Conforti, Gilley, & Coleman, 2014; Pierpaoli et al., 2001). However, this assumption is speculative as the directionality of the white matter and grey matter damage cannot be inferred due to the cross-sectional nature of the data. Nevertheless, these tracts also show detriments in obese individuals and AD patients as evidenced in the review of neuroimaging studies (section 4.1.1.1.2; section 1.6.1.2).

A large proportion of the white matter tracts showing obesity-related detriments overlapped with the negative associations found with CBF. This could indicate that reductions in CBF that could lead to reductions in WMI in the tracts connecting grey matter regions could explain the patterns of findings, if these relationships were causal. The extracted FA signal was also linked with higher WMH load in CN. This could indicate that the additional vascular burden from being obese could impact the structural integrity of white matter in CN individuals. In support of this finding, past studies have previously indicated higher WMH load in obese cognitively healthy individuals (Gustafson, Steen & Skoog, 2004; Jagust et al., 2005). Moreover, the extracted FA signal was associated with poor performance on memory tasks that could indicate that obesity-associated modulations of WMI could have an impact on cognition, especially on domains typically affected in AD.

It is of note that the CBF signal was not associated with WMH load that could indicate that these associations could be indicative of underlying damage to brain structure. However, the partial volume correction applied to the analyses in the current study helps rule out this possibility (Matsuda et al., 2002). Additionally, past work has also indicated divergent patterns of CBF and grey matter atrophy in AD patients (Wirth et al., 2017). Therefore, it is also possible that the associations found with CBF could be a manifestation of downstream obesity-related pathological mechanisms independent of related vascular pathology. However, WMH load was correlated with poor performance on tasks of semantic memory, a cognitive domain heavily affected through the course of AD (section 1.3.4.1). This could be an indication of how the presence of obesity in CN individuals with an underlying vascular pathology could lower the threshold for AD.

Combining the negative associations found across all three imaging modalities, there appears to be a considerable overlap between areas that exhibit obesity-associated vascular dysfunction and brain regions showing negative associations with brain structure (especially WMI) in CN individuals. The pattern of findings also had a similar appearance to the ‘disconnection’ typically seen in AD (section 1.6.2.1, Para 1). This indicates that the vascular damage associated with obesity could alter cerebral structure in brain regions that are typically affected by AD. Another novel finding in the current study is the poor performance on tasks of memory associated with WMH load and the extracted signal from the negative associations found in brain structure, in the absence of poor performance in executive function (that are typically seen in obesity). A similar cognitive profile is typically seen in AD patients where memory

deficits are more pronounced than less-prominent deficits in executive function (section 1.3.4.1; section 1.3.4.2). Therefore, the constellation of obesity-related detriments observed in the present study in CN participants have a strong resemblance to an AD-like phenotype.

4.5.4 Limitations

It is important to note that due to the cross-sectional nature of the data, we cannot draw inferences about the life-long effects of obesity or high body fat or how the interaction between body weight changes with the development of AD pathology. It also limits the examination of the manner in which changes in body fat could alter cerebral properties. Additionally, the inherent differences in the weight categories between the different diagnostic groups also limit the inferences that can be drawn if the participants belonged to a different range of weight categories. It is possible that a different pattern and direction of associations could be found if the participants in the MCI and CN groups fell within the normal weight range. Moreover, as a consequence of age and disease related weight loss, there is a limited population of obese ADD patients and therefore, it is difficult to measure the relationship between obesity and AD among patients in later disease stages.

4.5.5 Conclusions

In conclusion, our study found diminished CBF, structural and cognitive measures associated with obesity in CN that resemble features that are typically induced by AD. With respect to the MCI group, the associations found resemble an amalgamation of the detrimental effects exerted by obesity and AD. The associations found were also linked with higher vascular burden that could indicate that in MCI patients, the additional burden from being overweight in the presence of AD pathology increases the severity of the AD phenotype. This trend of findings could indicate that susceptible pathways that are shared between AD and obesity could contribute toward the initiation of a pathophysiological cascade that may push the brain over the threshold for potential progression from CN to MCI and from MCI to ADD. Therefore, primary prevention measures to help reduce the prevalence of cardiovascular risk factors such as obesity could contribute toward reducing the risk for AD risk and progression. Specifically, interventions to improve anterior cerebral artery and parietal lobe blood flow could help alleviate some of the obesity-related risk in AD patients. However, this relationship may change in individuals in later disease stages, where having a higher body weight remaining

within the normal weight range may confer a resilient quality to brain structure in the presence of ageing and disease related insults. This effect seems to be the most pronounced in brain regions supplied by the middle cerebral artery. Therefore, introducing measures to promote early diagnosis and timely nutritional interventions to modulate the weight of ADD patients to fit within the higher weight measures, but within the normal weight range, could help preserve brain structure and potentially limit disease progression in addition to reducing clinical disease severity. It is noteworthy that these results were consistent across the two different anthropometric indices of obesity.

Chapter 5: The Impact of Hypertension and its

Treatment on the Brain in Alzheimer's Disease

5.1 Introduction

Hypertension is a chronic condition which is characterised by persistently elevated levels of blood pressure in the arteries (Jones et al., 2020). According to the guidelines proposed by the European Society of Cardiology and the European Society of Hypertension, hypertension is defined as chronic systolic blood pressure values of 140 or higher and diastolic blood pressure values of 90 or higher (Williams et al., 2019a). It has different levels of classification as listed in Table 5.1. It is the leading cause of mortality with roughly 1.3 billion cases of hypertension worldwide and the majority of this population is still untreated for hypertension (<https://www.who.int/news-room/fact-sheets/detail/hypertension>). In addition to being one of the leading causes of mortality and increasing cardiovascular risk, it has a systemic effect and can damage several organs if not treated in a timely manner (Jones et al., 2020; Stanaway et al., 2018). This is largely due to the 'silent' nature of the disease that can allow it to go undetected before the accumulation of significant insult that can eventually manifest as symptoms (Eguchi, Kario, & Shimada, 2003; Sawicka et al., 2011).

As is the case with several other cardiovascular risk factors, hypertension can increase the risk of AD (Lennon et al., 2019). More specifically, midlife hypertension has been identified as a bigger risk factor of AD than hypertension in late-life (Lennon et al., 2019; McGrath et al., 2017; Walker et al., 2019). This could be attributed to the cumulative insults inflicted by chronically elevated blood pressure on the brain. Hypertension is frequently associated with the accumulation of brain infarcts that are clinically 'silent' or asymptomatic but can contribute toward considerable cognitive decline (Gottesman et al., 2014). The 'silent' nature of the damage caused by hypertension is particularly dangerous because if it passes undetected, especially in AD patients who already present with significant cognitive decline, it can lead to the patient developing a more severe radiological and clinical phenotype of AD in addition to increasing the risk of mortality (Bellew et al., 2004; Stanaway et al., 2018). Considering that the majority of patients are diagnosed with AD in late-life, those with longer durations of

hypertension, having accumulated significant irreversible damage across their lifetime, would have a more severe clinical AD phenotype than those individuals who develop hypertension in late-life (Bellew et al., 2004; Gottesman et al., 2014).

Table 5.1 *Blood pressure measurements (in mmHg) classified into hypertensive and normotensive ranges (Jones et al., 2020)*

Category	Systolic	Diastolic
Optimal	<120	<80
Normal	120-129	80-84
High normal	130-139	85-89
Hypertension: Grade 1	140-159	90-99
Hypertension: Grade 2	160-179	100-109
Hypertension: Grade 3	≥ 180	≥ 110

5.1.1 Neuroimaging

Life-long fluctuations in blood pressure, especially chronically high blood pressure as is seen in hypertension, is detrimental to brain structure and function (Bellew et al., 2004; Lane et al., 2019). This vulnerability of the brain to the effects of high blood pressure can not only increase the risk of AD, but also increases the severity of the AD phenotype in patients (Bellew et al., 2004; Lane et al., 2019). There is also evidence to suggest that a timely administration of antihypertensive treatment could protect the brain against damage resulting from elevated blood pressure and limit the development of AD pathology (Hoffman et al., 2009; Kivipelto et al., 2018). In order to explore the effects of chronically elevated blood pressure on different cerebral properties and how these effects could result in a more severe pathological and cognitive phenotype of AD, the following sections will review studies that explore the relationship between the brain and hypertension in AD across various imaging modalities. The review examines how the administration of antihypertensive treatment could change this relationship.

5.1.1.1 Structural neuroimaging in hypertension and AD

5.1.1.1.1 Grey Matter Volume

Fluctuations in blood pressure can result in variable damage to GMV. In healthy elderly individuals untreated for hypertension (>60 years), high systolic blood pressure was linked with lower hippocampal volume and this damage was amplified in medicated individuals with low diastolic blood pressure (den Heijer et al., 2005). These findings were replicated in a different study that looked at the effect of antihypertensive medication and blood pressure on hippocampal volume (Korf et al., 2004). Therefore, the hippocampus, a brain region most commonly affected in AD is susceptible to the damaging effects of hypertension. In addition to the hippocampus, the cerebellum also seems susceptible to the effects of hypertension and these GMV deficits have been associated with poor performance on tasks of memory and language (Alosco et al., 2014; Strassburger et al., 1997). With higher age, the detrimental effect of hypertension also affects the occipital lobe (Strassburger et al., 1997). Moreover, frontal brain regions are vulnerable to the negative effects of hypertension. This was demonstrated in a study that showed accelerated atrophy in the prefrontal cortex and the hippocampus in hypertensive individuals (Raz et al., 2007). Furthermore, the duration of hypertension can accelerate the rate of cortical thinning especially in the right superior temporal gyrus, a detrimental effect that was further accelerated by greater variability in systolic blood pressure but not diastolic blood pressure (Gonzalez et al., 2015).

Sex may modulate the effects of blood pressure on regional GMV as evidenced in a study by Taki and colleagues (Taki et al., 2004). The study showed that higher systolic blood pressure was linked with lower GMV in the left cuneus and right inferior temporal gyrus in men while in women, similar associations were found in the right cuneus and left medial frontal gyrus (Taki et al., 2004). Gender differences were also found in a different study where lower GMV was found in men in the medial frontal and right superior frontal areas and the left superior temporal lobe whereas no associations were found in women (Chen et al., 2006). Although the study controlled for the effects of other vascular risk factors, there were more hypertensive men than women, an imbalance that could have resulted in a larger effect that could reach significance in men, but not in women (Chen et al., 2006). Nevertheless, a different study found similar findings in men who had lower regional GMV in the anterior cingulate gyrus, supplementary motor area, superior frontal gyrus and the middle temporal gyrus associated

with systolic blood pressure, that were linked with deficits in executive function and working memory (Gianaros et al., 2006). No significant associations were found in women (Gianaros et al., 2006). In addition to being more vulnerable to developing hypertension, men also seem to have a higher susceptibility to grey matter detriments due to high blood pressure (Vokonas, Kannel & Cupples, 1988, Gelber et al., 2007).

Several studies have shown that blood pressure lowering medication does not have much of a beneficial effect on GMV in hypertensive, cognitively normal individuals (Jennings et al., 2012; Raz, Rodrigue, & Acker, 2003). In a study on hypertensive and normotensive individuals, a year long treatment for hypertension did not affect the rate of grey matter atrophy in the anterior cingulate, thalamus and the entorhinal cortex (Jennings et al., 2012). This could be due to the baseline difference between the normotensive and hypertensive participants on BMI, where the average BMI of the hypertensive group fell within the obese range (Jennings et al., 2012). Although the study controlled for the effects of BMI, the negative effects of obesity could have contributed to the deficits found in these regions as has been highlighted in previous studies (Kivipelto et al., 2005; Herrmann et al., 2019). Additionally, the participants were treated for hypertension only for a year, which might not have been a sufficient duration of the medication regime to attenuate the damaging effects of hypertension on GMV (Jennings et al., 2012). Similar findings were observed in a different cross-sectional study which showed lower brain volumes in the prefrontal cortex that were associated with lower performance in executive function in medicated hypertensive individuals (Raz et al., 2003). Hypertensive participants also showed increased WMH in the frontal lobe, alterations that could be responsible for the volumetric deficits observed in this region (Raz et al., 2003). In contrast to the former study, the duration of antihypertensive treatment is not reported in the study by Raz and colleagues (Jennings et al., 2012; Raz et al., 2003). Therefore, it cannot be extrapolated what length of duration of antihypertensive treatment may be required to mitigate the effects of high blood pressure on GMV. Nevertheless, an absence of a beneficial effect of antihypertensive treatment on GMV has been observed in other studies (Alosco et al., 2014; Salerno et al., 1992). It is possible that in the majority of these studies, the antihypertensive treatment was initiated after significant insults were inflicted during the asymptomatic or 'silent' phase of the disease, which could explain the absence of findings of beneficial effects of blood pressure lowering medication in cognitively normal individuals (Sierra et al., 2004; Van Boxtel et al., 2006). Adherence to medication is also an important factor in attenuating the damaging effects of hypertension and several studies have reported medication adherence as a

major problem in assessing the treatment for hypertension (Macquart de Terline et al., 2019; Ramli, Ahmad, & Paraidathathu, 2012; Vrijens et al., 2017).

Examining anti-hypertensive medication type more closely, it appears that different types of antihypertensive treatment could exert differential effects on the brain in AD patients (Jin, 2016b). A cross-sectional study on GMV showed that angiotensin II receptor blockers helped protect against atrophy whereas angiotensin-converting enzyme inhibitors and beta-blockers could increase the risk of cerebral atrophy and cognitive decline (Jin, 2016b). Cognitive impairment associated with beta-blockers has also been indicated in a different study (Burkauskas et al., 2016). It is possible that the detrimental effect of beta-blockers on the brain could be attributed to the property of beta-blockers to increase variability in blood pressure that in turn increases dementia risk (Ma et al., 2019; Rothwell et al., 2010a). Considering the detrimental effect of beta-blockers on cognitive function, a study investigated the association between the risk of all-cause dementia and the use of beta-blockers (Holm et al., 2020). Findings from this study indicated that there was no association between the use of beta-blockers for hypertension and incident AD although use of beta-blockers was associated with higher risk of vascular dementia (Holm et al., 2020). A review suggests that antihypertensive treatment using angiotensin receptor blockers, angiotensin-converting enzyme inhibitors and calcium channel blockers might be effective in combating the vascular and non-vascular elements of AD (Lebouvier et al., 2020). Although this review did take beta-blockers into account, no strong recommendations were made regarding this class of antihypertensive medication (Lebouvier et al., 2020). In support of this, a different study showed impairments in learning in individuals without dementia who were administered with beta-blockers (Burkauskas et al., 2016). Another study suggests that calcium channel blockers and angiotensin-converting enzyme inhibitors could be more beneficial to cognitive function in hypertensive individuals (Amenta et al., 2002). Therefore, the literature is confounded in terms of the beneficial effects of different classes of antihypertensive treatment on the brain and more research is needed to highlight how different classes of antihypertensive drugs could affect cognition and cerebral parameters in individuals with AD.

To our knowledge, only one study has explored the association between hypertension and GMV in patients with AD (García-Alberca et al., 2020). Medical history for the patients was collected regarding history of hypertension and antihypertensive treatment. In this study, the majority of the AD patients with hypertension were on antihypertensive drugs (84%) (García-

Alberca et al., 2020). This study showed higher WMH burden and MTL atrophy in AD patients with hypertension compared to AD patients without hypertension indicating how comorbid hypertension could increase radiological disease severity in AD despite medication (García-Alberca et al., 2020). On the other hand, the work in cognitively normal individuals shows a predominant effect of hypertension in prefrontal, MTL (especially the hippocampus) and subcortical areas. Hippocampal deficits observed in hypertensive individuals could thus indicate how this risk factor could increase the radiological severity of AD by exerting additive detrimental effects in brain regions affected by AD, as highlighted in the study by García-Alberca and colleagues (García-Alberca et al., 2020). Considering that the prefrontal cortices are affected much later in AD, in the presence of hypertension, a more severe radiological phenotype of AD could be observed in patients with the added effect of hypertension. In light of this, a previous longitudinal study has shown that cognitively normal hypertensive individuals have a high probability of future MCI (Reitz et al., 2007b). A different study examining how the presence of cerebrospinal fluid biomarkers of AD and hypertension influences grey matter showed no interactive effects of these two variables (Glodzik et al., 2012). However, the study did show independent and additive effects of the two conditions in the pre-symptomatic AD phase showing how the presence of hypertension could exacerbate the effects of AD (Glodzik et al., 2012). Therefore, hypertension appears to increase the radiological severity of the AD phenotype by promoting grey matter atrophy, especially in known predilection sites for AD (such as the hippocampus).

5.1.1.1.2 White matter Integrity

White matter is particularly susceptible to ischaemic damage, making it highly vulnerable to the negative effects of hypertension and high blood pressure (Wang et al., 2015a). This was highlighted in a study that showed that higher systolic blood pressure was associated with lower FA and increased mean diffusivity in the inferior fronto-occipital fasciculus, genu of the corpus callosum and the anterior thalamic radiations (Maillard et al., 2012). These participants belonged to a younger age group (<40 years), an observation that indicates a detrimental effect of higher systolic blood pressure beginning from the early decades of life (Maillard et al., 2012). This effect could also extend to participants belonging to a wider age range. This hypothesis was supported by the findings from a different study that showed a negative effect of higher mean arterial blood pressure on the frontoparietal white matter and diffusion parameters in individuals between an age range of 43 and 87 years (Salat et al., 2012). Greater

susceptibility of the frontoparietal white matter to the negative effects of high blood pressure was also observed in a different study including older hypertensive participants with an average age of 65 years (Li et al., 2015). This effect was proposed to be mediated by alterations in functional connectivity that could also manifest as executive deficits (Li et al., 2015). Similar associations were found in long-range association tracts connecting frontal and posterior brain regions in hypertensive, cognitively normal older individuals that were linked with poor performance in tasks of memory and executive function (Luo, Tseng, & Chang, 2019). Negative effects of higher blood pressure were also observed in white matter tracts in the cingulum bundle, frontostriatal and frontotemporal regions in another study on elderly individuals (60-86 years) with depression (Hoptman et al., 2009). Since high blood pressure can negatively impact cerebral white matter, chronically elevated blood pressure as seen in hypertension could further exaggerate these effects.

Several other studies have explored the relationship between WMI and hypertension. One of these include a study on normotensive, hypertensive-medicated and hypertensive-unmedicated cognitively healthy individuals (Hannesdottir et al., 2009). In this study, diffusion parameters were associated with poor performance on tasks of executive function in untreated hypertensive participants. Medicated hypertensive patients however, showed poor performance on tasks of memory (Hannesdottir et al., 2009). This pattern of findings indicates that despite medications prescribed to combat the negative effects of hypertension, these effects may still persist. This hypothesis is supported by the findings from a study which show that lower white matter volumes (in addition to GMV) in the prefrontal cortex in hypertensive individuals were also linked with poor performance on tasks of executive function (Raz et al., 2003). Moreover, the presence of WMH coincided with the finding of lower regional parenchymal volumes in the prefrontal cortex (Raz et al., 2003). Participants in this study were medicated for hypertension indicating that in addition to damage to cerebral white matter, hypertension can also have clinical manifestations despite treatment in cognitively normal individuals (Raz et al., 2003).

Findings from a study by McEvoy and colleagues further clarify the relationship between medication for hypertension and brain health. The study showed widespread deficits in WMI in hypertensive patients not medicated for hypertension that persisted in individuals with a shorter disease duration of hypertension who were on antihypertensive treatment (McEvoy et al., 2015). Yet another study showed that medicating for hypertension did not have any beneficial effects on white matter (Haight et al., 2018). Participants on antihypertensive

medication with blood pressure within the normotensive range did not show any associations with WMI. On the other hand, those participants within the hypertensive ranges showed lower WMI, despite antihypertensive treatment (Haight et al., 2018). A variety of factors such as medication adherence, appropriate medication and regular follow-up and evaluation of medical regimens to control blood pressure could modulate the effects of medication on blood pressure and consequently white matter (Fici et al., 2017; Fung et al., 2007). Therefore, it is possible that participants within the hypertensive range exhibiting detriments in WMI might need additional measures for appropriate blood pressure control (Haight et al., 2018). This indicates that despite medication for hypertension, the individual differences in maintaining blood pressure control could have introduced a bias in the literature, where the effects of hypertension medication could be inaccurately reflected in research findings.

Hypertension could also have differential lateralised effects on the cerebral hemispheres, as seen in an experiment by Sabisz and colleagues who showed lower FA in the fornix and projection pathways in the left hemisphere (Sabisz et al., 2019). AD patients tend to experience more detriments in the left hemisphere, highlighting how the negative effects of hypertension could increase the radiological disease severity in AD (Liu et al., 2018). However, other studies do not indicate a predominant effect of hypertension on the white matter in the left hemisphere. In fact, a different study indicated a predominant right-lateralised negative effect of hypertension and pre-hypertension in the superior longitudinal fasciculus and superior thalamic radiation (Suzuki et al., 2017). Studies reviewed in this chapter do not show a preferential effect of hypertension on cerebral hemispheres. Therefore, there does not seem to be a specific susceptibility of cerebral hemispheres to the effects of hypertension.

Hypertension also tends to have effects on the brain similar to those observed in AD. A study using magnetic resonance spectroscopy showed that elderly hypertensive patients had higher myoinositol/creatinine ratio in the cerebral white matter compared to their normotensive counterparts (Catani et al., 2002). This rise in myoinositol/creatinine ratio mirrored the effect that was observed in patients with early AD, a finding that could point towards converging pathways between hypertension and AD that could increase AD severity (Catani et al., 2002). In support of the additive role of hypertension in increasing AD radiological severity, another study examining diffusion tensor imaging parameters and positron emission tomography found variability in WMI associated with lower glucose metabolism in white matter tracts implicated in AD (Chetouani et al., 2018). These white matter tracts included the posterior cingulum and

other white matter tracts in the posterior associative areas and the MTL regions (Chetouani et al., 2018). Moreover, these associations were also linked with poor performance on tests of memory and executive function, deficits that are also commonly observed in AD patients (Chetouani et al., 2018; section 1.3.4.1; section 1.3.4.2). On examining the effect of hypertension in APOE ϵ 4 carriers, a negative effect of hypertension was found in the tracts connecting frontal brain regions to other brain regions (McEvoy et al., 2015). These effects were stronger in hypertensive individuals who were APOE ϵ 4 carriers compared to non-carriers (McEvoy et al., 2015). As it has been exemplified previously, frontal brain regions show detriments in much later stages of AD (section 1.6.1.1, Para 2). This vulnerability of the brain might indicate that the additional burden exerted by hypertension in individuals at a higher risk for AD could increase the radiological severity of the AD phenotype detected in these individuals. So far, no studies have explored the effects of hypertension on WMI in individuals already diagnosed with AD.

5.1.1.1.3 White Matter Hyperintensities

Hypertension can inflict substantial cerebrovascular damage that can result in the accumulation of vascular pathology that can be ‘clinically silent’ for an extended period of time (section 2.2.2.2, Para 1). This damage can begin at the microvascular level as observed in a study that showed that increased BBB permeability was associated with hypertension and a higher volume of WMH, abnormalities that could be detrimental to WMI (Muñoz Maniega et al., 2017). Detriments to WMI mediated by WMH were observed in a study by Haight and colleagues that showed widespread WMH that were associated with lower FA in the tracts in close proximity to these abnormalities (Haight et al., 2018). This study also showed a greater burden of WMH in the white matter tracts in the right hemisphere compared to the left (Haight et al., 2018). Moreover, the detrimental effect of WMH on WMI of the tracts was attenuated by the effects of duration and level of medication for hypertension (Haight et al., 2018). This could indicate that medicating for hypertension could be beneficial in preventing hypertension-related damage that could increase radiological AD severity.

As observed in previous studies, there seems to be a predominant effect of hypertension in the prefrontal brain regions with respect to WMH (Raz et al., 2003). The development of WMH in this brain region could also be linked with poor performance on executive function (Raz et al.,

2003). Apart from prefrontal brain regions, the development of hypertension associated WMH can also be detrimental to other brain regions. This was evidenced in a study that showed higher hippocampal and amygdaloid atrophy in individuals with a higher WMH load (den Heijer et al., 2005). In a different longitudinal study, there was a significant increase in WMH volume (more than twice the volume at baseline) in the frontal and parietal brain regions associated with hypertension (Raz et al., 2007). Although frontal brain regions showed the highest increments in WMH burden, the parietal lobe showed the greatest expansions in the WMH volumes (Raz et al., 2007). Since the temporoparietal regions are affected early in the disease course, this observation could point towards common brain regions affected by early AD and hypertension and how their convergence could exacerbate the AD phenotype. Additionally, hypertension has a profound negative effect on the prefrontal cortex, a brain region affected much later in AD indicating how this comorbidity could increase radiological disease severity in AD patients. Moreover, hypertension is also associated with cerebral microbleeds and lacunes in the subcortical brain regions (Lee et al., 2004).

Only a handful of studies have explored the relationship between WMH and hypertension in AD patients. One of these examined how the presence of hypertension and related WMH could alter patients' response to cholinesterase inhibitors, a common treatment for AD (Connelly, Prentice, & Fowler, 2005; section 1.7, Para 2). Although the presence of hypertension or WMH by themselves did not alter the outcome of cholinesterase inhibitor treatment, the presence of both, hypertension and WMH can significantly influence patients' activities of daily living and social cognition (Connelly et al., 2005). In another study that examined the association between hypertension and AD, hypertensive AD patients presented with higher volumes of WMH and MTL atrophy (García-Alberca et al., 2020). In addition to having higher vascular burden, hypertensive AD patients presented with more severe deficits in cognitive function and had neuropsychiatric symptoms (García-Alberca et al., 2020). Although some patients in this sample were on medication for hypertension, a major proportion of the patients was not, an issue that could have contributed to the magnitude of detriments found (García-Alberca et al., 2020). However, in a different study, individuals treated with antihypertensive drugs with uncontrolled hypertension had higher odds of WMH compared to treated hypertensive individuals with controlled hypertension (Liao et al., 1996). While comorbid hypertension in AD patients could increase clinical and radiological disease severity, the beneficial effect of blood pressure altering medication on cerebral constituents in these patients is debatable. Future studies exploring the effects of medication on WMH could be informative in

determining whether antihypertensive treatment could be beneficial in limiting the clinical and pathological severity of AD in such patients.

5.1.1.2 Functional neuroimaging in hypertension and AD

5.1.1.2.1 Resting-state functional magnetic resonance imaging

Considering that a majority of the negative effects of hypertension have a preference to influence the frontal lobe, a similar pattern of detriments is expected in resting state functional connectivity. This was shown by a study by Li and colleagues that revealed lower functional connectivity between frontoparietal networks specifically in the left inferior frontal lobe, precuneus and inferior parietal lobule (Li et al., 2015). Not only did the study find that the hypertensive participants performed worse on tasks of executive function, but also that altered functional connectivity in the relevant networks could have influenced the WMI of the tracts forming these networks, as examined by the authors using diffusion tensor imaging scans (Li et al., 2015). Altered functional connectivity in anterior and posterior brain regions among hypertensive individuals was also found in a different study (Gu et al., 2019). Therefore, functional connectivity in hypertensive patients seems to be altered mainly in the frontoparietal regions. This loss of functional connectivity is similar to the typical ‘disconnection’ observed in AD, indicating common pathways between hypertension and AD that could increase radiological AD severity (section 1.6.2.1, Para 2). Hypertension can also alter inter-network connectivity as highlighted in a study by Carnevale and colleagues (Carnevale et al., 2019). In this study, compared to normotensive participants, hypertensive individuals showed lower functional connectivity between the dorsal attention network and several other networks that included the sensorimotor network, the visual network and the frontoparietal network (Carnevale et al., 2019). Moreover, altered functional connectivity in the frontoparietal and salience networks was lateralised to the left hemisphere (Carnevale et al., 2019).

While a history of hypertension can increase the risk of MCI, functional connectivity could be affected differentially in hypertensive patients with some level of cognitive impairment (Reitz et al., 2007b). This was demonstrated in a study that examined functional connectivity in hypertensive patients on antihypertensive treatment with and without cognitive impairment (Gu et al., 2019). The findings showed a disconnection within the components of the DMN in cognitively normal hypertensive patients. In contrast, hypertensive patients with cognitive

impairment displayed increased functional connectivity between the DMN subsystems that was associated with poor performance on tests of general cognition (Gu et al., 2019). This contrast in findings and increased functional connectivity in the DMN components among cognitively impaired hypertensive patients could be indicative of maladaptive compensatory mechanisms employed to overcome the cognitive deficits to maintain a certain level of cognitive functioning (Park & Reuter-Lorenz, 2009; Gu et al., 2019). In a different study comparing AD patients with and without hypertension, lower functional connectivity was found between the posterior cingulate gyrus and the anterior cingulate gyrus in the hypertensive patients. Additionally, higher functional connectivity was found between the posterior cingulate gyrus and the inferior parietal lobe (Son et al., 2015). Altered functional connectivity in the posterior cingulate gyrus is observed in very early stages of AD (Zhou et al., 2008; Rami et al., 2012). Thus, it appears that an increased functional connectivity in the posterior components of the DMN might represent a pathophysiological response in cognitively impaired hypertensive patients with abnormal upregulation of activity in these regions reflecting more effortful cognitive functioning. Considering that a further impairment is seen in the components of the DMN as an effect of AD, this observation could be indicative of the additive detrimental effect of comorbid hypertension in AD.

5.1.1.2.2 Perfusion studies

The presence of hypertension can severely affect CBF as has been elucidated in several studies. One such study showed reduced CBF in hypertensive patients in the basal ganglia and frontal cortex (Fujishima et al., 1995). Lower CBF in subcortical structures was also observed in a different study in hypertensive individuals compared to normotensive individuals (Fujii et al., 1990). Therefore, in addition to the frontal lobe, subcortical structures also seem to be susceptible to the negative effects of hypertension, particularly with respect to CBF. The inverse may also be true where ischaemic damage due to hypertension to the basal ganglia could have resulted in lower CBF to this region (Bouma et al., 1992; Pulsinelli, Levy, & Duffy, 1982). The authors of the study by Fujii and colleagues also propose that lower CBF in the hypertensive group could be attributed to antihypertensive treatment in some of the individuals (Fujii et al., 1990). However, previous work has also shown that antihypertensive treatment does not lower CBF, indicating that prolonged periods of high blood pressure could be a factor in reduced CBF observed in hypertensive individuals (Lipsitz et al., 2005). Therefore, the

direction of causality between structural damage due to hypertension and CBF reductions needs to be explored in future studies.

Similar to the observations in functional connectivity studies in hypertensive individuals, CBF is altered in components of the DMN. This is exemplified in a study by Dai and colleagues that compared hypertensive and normotensive participants (Dai et al., 2008). The study showed lower CBF in various regions of the DMN including the anterior cingulate gyrus, left posterior cingulate gyrus and medial precuneus in addition to prefrontal brain regions (Dai et al., 2008). Moreover, the hypertensive participants showed lower CBF in subcortical structures namely the putamen and globus pallidus in addition to the left hippocampus (Dai et al., 2008). While the hippocampus is one of the predominantly affected structures in AD, the left hemisphere is also more susceptible to the effects of AD than the right hemisphere (Thompson et al., 2003; Liu et al., 2018). This susceptibility of the left hippocampus and prefrontal brain regions to reductions in CBF could indicate increased radiological disease severity in AD patients with comorbid hypertension (Dai et al., 2008). Hypertensive individuals in the study were taking antihypertensive drugs and had systolic blood pressure readings approaching hypertensive levels, a finding that could be an indication of poor control of blood pressure in hypertensive participants (Dai et al., 2008).

Vulnerability of CBF in the cingulate gyrus and the prefrontal cortex to the prolonged effects of hypertension was also observed in a different study (Beason-Held et al., 2007). Reduced CBF in the temporal and occipital lobes was found in yet another study on hypertensive individuals (Alosco et al., 2014). Similar to what was observed in the functional connectivity studies, hypertensive patients also appear to exhibit increased perfusion responses. This was observed in a study in which hypertensive patients displayed enhanced CBF in the right hippocampus while performing memory tasks (Jennings et al., 2005). Participants had a minimal lifetime exposure to antihypertensive treatment (<12 months) or did not have a history of pharmacological intervention for hypertension (Jennings et al., 2005). An enhanced CBF signal was also found in parietal brain regions and the thalamus during memory tasks, but this enhancement was far less than that observed in normotensive individuals (Jennings et al., 2005). Therefore, it could be inferred that although the presence of hypertension can increase CBF in the initial stages, reductions in CBF due to prolonged elevation in blood pressure can be observed.

Treatment for hypertension can have variable effects in hypertensive individuals, effects that could also alter the presentation of symptoms. In a study that administered blood pressure lowering medication to mildly hypertensive individuals, those participants who displayed symptoms of cerebrovascular disease consistently displayed incremental decreases in CBF from baseline, even after initiating treatment (Meyer, Rogers, & Mortel, 1985). On the other hand, asymptomatic individuals with mild hypertension displayed increased CBF following treatment, an increase that plateaued in the last year (out of three years) of treatment (Meyer et al., 1985). It is possible that individuals who were symptomatic had already accrued a significant level of irreversible insults during the undiagnosed and asymptomatic phase of hypertension that could have contributed toward future detriments in CBF and cognition despite antihypertensive treatment (Murray et al., 2012; Triantafyllou et al., 2014). However, this study had a small sample size and therefore these results may not be sufficient to extrapolate these findings to the general hypertensive population (Meyer et al., 1985). In a different study on asymptomatic hypertensive individuals, although medicated individuals displayed areas of hypoperfusion, this was less extensive than the hypoperfusion observed in the unmedicated hypertensive individuals (Nobili et al., 1993). Specifically, the unmedicated hypertensive group showed hypoperfusion in the left occipital and right frontoparietal brain regions, an alteration that was attenuated in the medicated group who showed hypoperfusion in the left frontoparietal brain regions only (Nobili et al., 1993). Therefore, hypertensive medication could also alter the pattern of hemispheric perfusion of the brain.

It is possible that the type of medication used to treat hypertension could alter the effect on CBF (Muller et al., 2012). In a longitudinal study by Muller and colleagues, individuals administered with angiotensin receptor blockers did not show a decline in CBF although individuals on other classes of antihypertensive treatment did show a decline in CBF (Muller et al., 2012). The study also showed that individuals with untreated and poorly controlled hypertension and those with high blood pressure measurements exhibited reduced CBF over time (~4 years) (Muller et al., 2012). A different study that used angiotensin-converting enzyme as the only class of administered antihypertensive treatment showed improved CBF after six months of treatment in individuals with uncontrolled hypertension (Lipsitz et al., 2005). This shows that angiotensin converting enzymes could be a potential candidate for treatment of hypertension in AD patients that could improve disease prognosis, although it is difficult to say whether this effect can be observed with other classes of antihypertensive treatment. In support of this, a different study showed that the use of diuretics, angiotensin receptor blockers and

angiotensin converting enzymes was associated with reduced risk of AD dementia (Yasar et al., 2013). However, a different study showed that older individuals (>60 years) prescribed with angiotensin receptor blockers and angiotensin converting enzymes were less likely to develop AD than individuals prescribed with other classes of antihypertensive drugs (Davies et al., 2011). The angiotensin receptor blockers however showed a stronger effect in reducing the likelihood of AD compared to angiotensin converting enzymes (Davies et al., 2011). Therefore, more research is needed to examine the precise effects of different classes of antihypertensive treatment on the brain in AD patients.

The literature examining the effect of comorbid hypertension in AD is limited. However, there are studies that have investigated the effects of blood pressure lowering medication in patients with AD. In one such study, AD patients who had been medicated with nilvadipine (a calcium channel blocker) for six months showed increased CBF in the bilateral hippocampi and stable CBF in the posterior cingulate (de Jong et al., 2019). This observation indicates that antihypertensive treatment to manage cerebral autoregulation (the ability of vessel walls to maintain stability in blood flow with changes in blood pressure) could help preserve CBF or even improve cerebrovascular function in AD patients, especially in brain regions targeted by AD (de Jong et al., 2019). A different study has shown that cerebral autoregulation is not altered due to the presence of AD (Zazulia et al., 2010). Although cerebral autoregulation is not altered in AD, this biological mechanism does undergo age-related decline, which could be even more pronounced in the presence of comorbid hypertension (Zazulia et al., 2010). Therefore, the use of blood pressure lowering medication could not only contribute toward preserving CBF to help reduce AD risk but could also help reduce the clinical and radiological severity of the disease in individuals with abnormal blood pressure.

5.2 Aims and Hypotheses

So far, no study has used blood flow imaging in combination with other multi-modal neuroimaging techniques to take a holistic approach to investigate the effects of blood pressure lowering agents in AD patients. Although antihypertensive treatment in hypertensive individuals could help prevent further cognitive decline and reduce the risk of damage to cerebral constituents, there does not appear to be a substantial beneficial effect of antihypertensive medication in cognitively normal individuals (Dai et al., 2008; Haight et al., 2018; Korf et al., 2004). In fact, some studies show an absence of a protective effect of medication on cognitive decline and risk of dementia in hypertensive individuals (Jennings et al., 2012; Raz et al., 2003). However, medication can be fairly effective in alleviating the negative effects exerted by high blood pressure in AD patients (de Jong et al., 2019). Therefore, the primary aim of this study was to investigate whether AD patients medicated for hypertension had a less severe clinical and radiological AD phenotype than unmedicated AD patients. This will be done by dividing the patients ($N = 133$) into two groups namely AD patients medicated for hypertension (with a medical history of hypertension) and AD patients unmedicated for hypertension. The groups were compared with each other to examine differences in neuroimaging parameters using maps of GMV, WMI and CBF and differences in cognitive function. Among AD patients who have blood pressure measurements within the hypertensive range and who are not medicated for hypertension, it is unclear whether blood pressure can alter cerebral properties and cognitive function. Therefore, the secondary aim of the study was to explore how the variability in pulse pressure could modulate neuroimaging parameters and cognitive function in AD patients who were not medicated for hypertension. Although antihypertensive medication could aid in protecting against future cognitive decline and increasing the clinical severity of the AD phenotype, this protective effect may vary depending on the class of antihypertensive treatment (Holm et al., 2020; Jin, 2016b; Lebouvier et al., 2020; Muller et al., 2012). Studies have shown that the use of angiotensin-converting enzymes, angiotensin receptor blockers could aid in reducing AD risk whereas beta-blockers may be less effective due to their property to increase variations in blood pressure (Davies et al., 2011; Ma et al., 2019; Rothwell et al., 2010b; Yasar et al., 2013). So far, no study has examined how different classes of antihypertensive treatment can modulate cerebral constituents and cognitive function in AD patients. Therefore, a third aim of the study was to examine whether the type of antihypertensive treatment affects neuroimaging parameters and

cognitive function in patients across the AD spectrum. It was hypothesised that the following will be observed:

Primary aim: Medicated vs. Unmedicated AD patients: AD patients who were on antihypertensive treatment ($n = 71$) would present with higher GMV, WMI and CBF parameters and better performance on neuropsychological tests compared to AD patients who were not on antihypertensive treatment ($n = 62$). The differences would primarily be observed in subcortical and frontoparietal and MTL regions.

Secondary aim: Unmedicated AD patients: The association between pulse pressure, neuroimaging parameters and cognition in AD patients who were not on antihypertensive treatment ($n = 71$). Negative associations will be observed between measures of blood pressure and neuroimaging parameters primarily in the frontoparietal and subcortical brain regions. The negative associations found with CBF were predicted to overlap with the negative associations found with brain structure namely GMV and WMI. The extracted signal from these associations would be linked with poor performance on tests of memory and executive function.

Third aim: AD Patients Stratified by Class of Antihypertensive Treatment: The comparison between groups stratified based on the class of antihypertensive treatment into AD patients who were on all classes of antihypertensive treatment except for beta-blockers (Group 1, $n = 34$), AD patients who were on beta-blockers only (Group 2, $n = 13$) and AD patients who were on both, beta-blockers and other classes of antihypertensive treatment (Group 3, $n = 24$). AD patients who were on other classes of antihypertensive treatment other than beta-blockers only (Group 1) and AD patients on both beta-blockers and other classes of antihypertensive treatment (Group 3) would show a less severe radiological and clinical phenotype of AD compared to AD patients on beta-blockers only (Group 2).

5.3 Methods

5.3.1 Participants and participant groups

Details about the study inclusion and exclusion criteria and diagnostic criteria used to classify patients as AD dementia and MCI are outlined in section 4.3.1, Para 1. In addition to the participants included in Chapter 4 from Sheffield, UK, and Kuopio, Finland, as outlined in section 4.3.1, participants who were recruited from the memory clinics in Venice, Italy were also included in this study. Ethics approval for these participants was obtained from the joint ethics committee of the Health Authority Venice and San Camillo IRCCS (Protocol number 2014.08). Patients with mild to moderate AD ($N = 133$) were divided into two groups namely, AD patients medicated for hypertension ($n = 71$) and AD patients unmedicated for hypertension ($n = 62$).

5.3.1.1 Unmedicated AD patients

The 62 AD patients from the unmedicated patient group were included in an analysis to explore associations between pulse pressure, neuroimaging parameters and cognitive function.

5.3.1.2 AD Patients Stratified by Class of Antihypertensive Treatment

A third analysis was performed to examine whether the type of medication differentially altered cerebral properties and cognitive function in AD patients. Therefore, the AD patients medicated for hypertension ($N = 72$) were divided into three groups, depending on the class of antihypertensive medication that they were taking. The three groups were as follows: Group 1 ($n = 34$): Other (all classes of antihypertensive medication except beta-blockers); Group 2 ($n = 13$): beta-blockers; Group 3 ($n = 24$): Both (beta-blockers and other classes of antihypertensives).

5.3.2 Physical assessments

All participants underwent a physical assessment to obtain blood pressure measurements and other biological measures. These were obtained as detailed in section 4.3.2.

5.3.3 Neuropsychological assessment

The neuropsychological assessment was administered as a battery of tests that measured performance on several cognitive domains including tests of memory (prose memory tests, semantic fluency), attention (digit span-forward), executive function (Stroop task, digit span-backward, phonemic fluency), and language (similarities test, test of confrontational naming). For a detailed description of the assessment, please refer to section 4.3.4.

5.3.4 Blood pressure measurements

Pulse pressure was used as a continuous variable to test the associations between blood pressure measurements and neuroimaging parameters in the unmedicated patient group. “Pulse pressure is calculated as the difference between systolic and diastolic blood pressure.” Pulse pressure is often used as an indicator of arterial stiffness which could be used as proxy for the damaging effects of diastolic and systolic blood pressure combined and as an index of arterial stiffness (Martins et al., 2001; Muxfeldt et al., 2008). An increasing difference between systolic and diastolic blood pressure or ambulatory pulse pressure, is associated with greater damage inflicted on the brain (Thorin-Trescases et al., 2018).

5.3.5 Imaging protocol

The imaging protocols for the T1-weighted, T2-weighted, FLAIR, DTI and ASL MRI scans has been specified in section 4.3.5.

5.3.6 Preprocessing

For the procedure carried out for the preprocessing of T1-weighted MRI scans using voxel-based morphometry, please refer to section 4.3.6.1, to section 4.3.6.2 for the preprocessing of DTI data, to section 4.3.6.3 for the preprocessing of the ASL scans and to section 4.3.6.4 for the preprocessing and extraction of WMH values.

5.3.7 Statistical analysis

5.3.7.1 Demographic variables

5.3.7.1.1 Medicated vs Unmedicated AD patients

An independent samples *t*-test was conducted in SPSS to examine the differences between the two groups in terms of their demographic characteristics. For variables that violated the assumptions of parametric data, non-parametric Mann-Whitney *U* tests were used. Chi-square tests were run on the categorical variables to ensure that these variables were independent of one another (Table 5.2).

5.3.7.1.2 Unmedicated AD patients

Statistics for the demographic variables have been reported in Table 5.2.

5.3.7.1.3 Medicated AD patients: Stratified by Class of Antihypertensive medication

A one-way ANOVA was conducted in SPSS to examine the differences between the three groups in terms of their demographic characteristics. For variables that violated the assumptions of parametric data, non-parametric Kruskal-Wallis *H* tests were run to compare the groups on the respective variables. Chi-square tests were run on the categorical variables to ensure that these variables were independent of one another (Table 5.3).

5.3.7.2 Cognitive variables

5.3.7.2.1 Medicated vs Unmedicated AD patients

Similar to what was done with the demographic variables, independent samples *t*-tests were performed in SPSS to compare the medicated and unmedicated groups to examine whether the patients differed on various tests of cognitive function. For data that were not normally distributed, non-parametric Mann-Whitney *U* tests were conducted to assess the differences (Table 5.4).

5.3.7.2.2 Unmedicated AD patients

Statistics for the scores on neuropsychological tests have been reported in Table 5.4.

5.3.7.2.3 *Medicated AD patients: Stratified by Class of Antihypertensive medication*

A one-way ANOVA was conducted in SPSS to examine the differences between the three groups in terms of their demographic variables. For variables that violated the assumptions of parametric data, non-parametric Kruskal-Wallis H tests were used to compare the groups on the respective variables. Chi-square tests were run on the categorical variables to ensure that these variables were independent of each another (Table 5.5).

5.3.7.2.4 *Collinearity analysis*

A collinearity analysis was added to examine whether blood pressure and BMI parameters significantly predicted each other. A linear regression was run between the blood pressure parameters and BMI to assess this.

5.3.7.3 *Voxel-based morphometry*

5.3.7.3.1 *Medicated vs Unmedicated AD patients*

An ANCOVA was run using maps of GMV to examine the differences between medicated and unmedicated AD patients using both, positive and negative contrasts. The analysis was controlled for the effects of age, MMSE, waist circumference and centre as the groups were significantly different from each other with respect to these variables that could have an impact on blood pressure (Table 5.2). The analysis was also controlled for TIV for the reasons specified in section 4.3.7.3. Sex was excluded as a covariate as the groups did not differ in their distributions of this variable. Centre of recruitment was excluded as a covariate as effects of geography need not be considered in evaluating and treating blood pressure in the participants from the specific regions in this study (Duranton et al., 2017). In order to identify the significant clusters, a threshold of $p < .001$ and 1000 voxels was used at the set-level to identify the significant clusters, whereas a family-wise error corrected threshold of $p < .05$ was used at the cluster-level to identify the significant brain regions. Justifications for thresholding decisions are included in section 4.3.7.3

5.3.7.3.2 *Unmedicated AD patients*

A linear regression was carried out between pulse pressure and maps of GMV obtained after performing standard voxel based morphometric procedures. Both, positive and negative correlation contrasts were run. The analysis was controlled for the effects of age, MMSE, TIV,

sex, systolic blood pressure and diagnosis. The analysis controlled for the effects of age and TIV for the reasons specified in section 4.3.7.3. The analysis controlled for the effects of sex as men are more susceptible to hypertension than women, a potential feature that could have confounded the results due to a higher susceptibility of men to hypertension than women (Everett & Zajacova, 2015; Ghosh, Mukhopadhyay, & Barik, 2016). Systolic blood pressure was used as a covariate because the literature often shows a negative effect of greater variability in systolic blood pressure compared to diastolic blood pressure (Eto et al., 2005; Tataschiere et al., 2007; Stevens et al., 2016). Diagnosis was used as a covariate to account for clinical disease severity, whereas MMSE was used to control for the variability in the general level of cognitive functioning (Pezzotti et al., 2008). Centre of recruitment was excluded as a covariate for the reasons specified in section 5.3.7.3.1. For the analysis, a threshold of $p < .001$ and 1000 voxels was used at the set-level to identify clusters that emerged significant. At the cluster-level, a family-wise error corrected rate of $p < .05$ was used to identify significant brain regions. Justifications for thresholding decisions are included in section 4.3.7.3

5.3.7.3.3 *Medicated AD patients: Stratified by Class of Antihypertensive medication*

Independent ANCOVAs were carried out to examine the differences between the three groups using positive and negative contrasts. The analyses were carried out as follows: Other (Group 1) vs beta-blockers (Group 2), Beta blockers (Group 2) vs Both (Group 3) and Other (Group 1) vs Both (Group 3). The analyses were controlled for TIV and white matter hyperintensity volume. A threshold of $p < .001$ and 500 voxels was used at the set-level to identify clusters that emerged significant. Justifications for thresholding decisions are included in section 4.3.7.3. At the cluster level, a family-wise error corrected rate of $p < .05$ was used to identify significant brain regions.

5.3.7.4 Tract-based spatial statistics

The statistical analysis on the different diffusivity maps namely FA, mean diffusivity, radial diffusivity and axial diffusivity was conducted using the ‘randomise’ tool in FSL using both, positive and negative contrasts.

5.3.7.4.1 *Medicated vs Unmedicated AD patients*

Data matrices were created to run the ANCOVA between the AD patients who were medicated and unmedicated for hypertension. Similar to what was done in the voxel-based morphometry

analysis, the analysis included age, MMSE, waist circumference and centre of recruitment as covariates to control for their effects. The first two columns of the matrix were coded so that the number '1' indicated that the participant was assigned to that group and the number '0' indicated that the participant was not. Subsequently, the covariates were entered into the data matrix as outlined in section 4.3.7.4, Para 1. A contrast matrix was then created to compare the groups which consisted of two contrasts to facilitate the testing of a two-tailed hypothesis. The first contrast '1 -1' tested whether the medicated AD patients had higher diffusivity parameters compared to the unmedicated AD patients. On the other hand, the second contrast '-1 1' tested whether medicated AD patients had lower diffusivity parameters compared to the other. Separate statistical analyses were run for each of the diffusivity measures.

5.3.7.4.2 Unmedicated AD patients

Independent data matrices were created to run the linear regression analyses among the two groups. These data matrices contained the main independent variable which was pulse pressure and the covariates which included age, MMSE, TIV, gender, systolic blood pressure and diagnosis. These were identical to the covariates used in the statistical analysis of GMV (section 5.3.7.3). The diagnostic status was converted into a categorical variable to facilitate its inclusion in the matrices, similar to the procedure followed for other categorical variables as specified in section 4.3.7.4, Para 1. Following the data matrices, the contrast matrices to perform the correlation were created as described in section 4.3.7.4, Para 2. Separate statistical analyses were run between each of the diffusivity measures and pulse pressure.

5.3.7.5 Arterial spin labelling

The statistical models for the ASL analysis were analogous to those run in the statistical analyses using voxel-based morphometry and were run using both positive and negative contrasts.

5.3.7.5.1 Medicated vs Unmedicated AD patients

An ANCOVA was run as outlined in section 5.3.7.3.1 using the covariates specified in section 5.3.7.3.1. The analysis was thresholded at $p < .01$ and 500 voxels at the set level and at a family-wise error corrected rate of $p < .05$ at the cluster-level to identify the significant brain regions. Justifications for thresholding decisions are included in section 4.3.7.5.

5.3.7.5.2 Unmedicated AD patients

Linear regression analyses were run between pulse pressure and maps of CBF independently for the unmedicated patient group while controlling for the effects of age, MMSE, TIV, sex, systolic blood pressure and diagnosis as was done in section 5.3.7.3.2. A cluster-forming threshold of $p < .01$ and 1000 voxels was used at the set-level while a family-wise error corrected threshold of $p < .05$ was used at the cluster-level to identify significant brain regions. Justifications for thresholding decisions are included in section 4.3.7.5.

5.3.7.5.3 Medicated AD patients: Stratified by Class of Antihypertensive medication

Independent samples t -tests were run to compare the three groups among one another as specified in section 5.3.7.2.3. To identify significant brain regions of interest, a cluster-forming threshold of $p < .01$ and 1000 voxels was used at the set-level while a family-wise error corrected threshold of $p < .05$ was used at the cluster level. Justifications for thresholding decisions are included in section 4.3.7.5.

5.3.7.6 White Matter Hyperintensities

5.3.7.6.1 Medicated vs Unmedicated AD patients

Non-parametric correlations (Spearman correlation) were run to examine the association between WMH volume and performance on neuropsychological tests and blood pressure measures for the two groups independently.

5.3.7.6.2 Medicated AD patients: Stratified by Class of Antihypertensive medication

For each of the independent groups, correlations were run between WMH volume and performance on neuropsychological tests and blood pressure measures using non-parametric tests (Spearman correlation).

5.3.7.7 Post hoc Analysis Identifying Significant Brain Regions and Exploring Associations With Cognitive Tests

Significant brain regions were identified using the steps detailed in section 4.3.7.6.1. Additionally, the signal was extracted from significant brain regions using the procedure outlined in section 4.3.7.6.2. The extracted signal was then correlated with neuropsychological tests to investigate whether the observed associations were linked with cognitive performance

in each of the analyses. These analyses were performed in SPSS and non-parametric tests were run for the data that were not normally distributed.

5.4 Results

5.4.1 Demographic characteristics

5.4.1.1 Medicated vs Unmedicated AD patients

In terms of their distributions, the demographic variables namely WC, GMV, WMV, CSF and diastolic blood pressure had parametric distributions and independent samples *t* tests were performed to compare the groups. On the other hand, age, years in education, MMSE, BMI, WMH volume, systolic blood pressure and pulse pressure had non-parametric distributions and Mann-Whitney *U* tests were performed to compare the groups. On comparing the groups, the medicated patient group was older than the unmedicated patient group. The medicated AD patient group also had higher MMSE scores, WC and WMH volume compared to the unmedicated group. Conversely, the medicated group had lower number of years in education and GMV compared to the unmedicated group. No group differences were found with respect to BMI, WMV, CSF, TIV, systolic and diastolic blood pressure and pulse pressure. After controlling for the effect of factors that can increase cerebrovascular burden that differed between the groups namely age, WC and the presence of type 2 diabetes, the significant difference in GMV, MMSE and WMH volume did not persist. The statistics for the demographic variables are specified in Table 5.2. Means and standard deviations for variables with non-parametric distributions are included in Appendix B, Table B5.2. The APOE genotypes, and sex were uniformly distributed in the two groups. Within the APOE genotypes, there was no significant difference in the number of APOE ϵ 4 carriers in each group either. However, the groups were not evenly distributed with respect to the centre of recruitment.

Table 5.2 Demographic characteristics of medicated and unmedicated patients with mild to moderate AD reported using means and standard deviations for parametric data and medians and interquartile ranges for non-parametric data

Demographic variable (unit)	Medicated (n = 71)	Unmedicated (n = 62)	Statistic
Parametric tests^a			
	<i>M (SD)</i>	<i>M (SD)</i>	<i>t</i>
WC (cm)	97.05 (13.81)	92.15 (11.52)	-2.21*
GMV (ml)	568.36 (75.98)	596.94 (77.30)	2.15*
WMV (ml)	402.74 (58.86)	412.15 (49.83)	0.99
CSF (ml)	494.56 (145.66)	455.03 (137.62)	-1.61
TIV (ml)	1462.57 (152.50)	1464.12 (152.16)	0.06
BP: Diastolic (mmHg)	79.61 (11.41)	82.31 (10.68)	1.40
Non- Parametric tests^b			
	<i>Mdn (IQR)</i>	<i>Mdn (IQR)</i>	<i>U</i>
Age (years)	76 (68 – 80)	64 (58 – 72)	1054.00***
Education (years)	10 (8 – 13)	12 (10 – 15)	1568.00**
MMSE	26 (24 – 28)	25 (20 – 27)	1653.00*
BMI (kg/m ²)	26.50 (24.13 – 29.43)	24.85 (22.26 – 28.73)	1801.00
WMH volume (ml)	4.14 (1.46 – 9.43)	2.59 (0.61 – 5.77)	1718.50*
BP: Systolic (mmHg)	138 (126 – 158)	143 (133 – 154)	2039.00
Pulse pressure (mmHg)	59 (49 – 74)	61 (49 – 69)	2195.00
Chi square tests^c			
	<i>n</i>	<i>n</i>	<i>χ²</i>
Males/Females	30/41	35/27	2.67
APOE genotype: ε2ε2/ε2ε3/ε3ε3/ε4ε2/ε4ε3/ε4ε4	0/4/30/3/24/5	0/7/19/2/20/11	5.73
APOE ε4 non-carriers/ ε4 carriers	34/33	26/33	0.03
Diagnosis: AD dementia/ AD MCI	20/51	26/36	2.77
Centre (UK/Finland/Italy)	38/19/14	23/34/5	11.64**
Type 2 diabetes/ Obese or overweight	17/46	6/30	4.71*/3.64

* Comparison is significant at 0.05 level (two tailed)

** Comparison is significant at 0.01 level (two tailed)

*** Comparison is significant at 0.001 level (two tailed)

Key: n = sample size; M = mean; SD = standard deviation; t = t -statistic; Mdn = median; IQR = Interquartile range; U = U -statistic; χ^2 = Pearson Chi-square statistic; BP = Blood pressure

^aIndependent samples t tests were run for normally distributed data.

^bNon-parametric Mann-Whitney U tests were run for data that was not normally distributed.

^cPearson Chi-square tests were run to examine the independence of the categorical variables.

Means and standard deviations for non-parametric data have been reported in Appendix B, Table B5.2.

5.4.1.1.1 *Post hoc analysis*

Since the medicated and unmedicated patients did not differ on any measures of blood pressure, a *post hoc* analysis was conducted where the medicated patient group ($N = 71$) was further stratified into normotensive ($n = 33$) and hypertensive ($n = 38$) patients and the unmedicated patient group ($N = 62$) was further divided into groups of hypertensive ($n = 40$) and normotensive patients ($n = 22$). The four groups, namely medicated hypertensive AD patients, medicated normotensive AD patients, unmedicated hypertensive AD patients and unmedicated normotensive AD patients, were then compared on their demographic characteristics (Table 5.2.1). In terms of their distributions, age, WC, GMV, WMV, CSF, TIV, diastolic blood pressure and pulse pressure were normally distributed variables and a one-way ANOVA was used to compare the groups with independent samples *t* tests performed *post hoc* to identify which specific groups differed from one another. On the other hand, years in education, MMSE, BMI, WMH volume and systolic blood pressure were variables that had non-parametric distributions. Kruskal-Wallis *H* tests were performed to examine whether the groups differed from one another and Mann-Whitney *U* tests were performed *post hoc* to identify which specific groups differed from one another. The groups did not differ significantly from one another on MMSE, WC, BMI, GMV, WMV, CSF, TIV and WMH volume. The medicated hypertensive patients were older than the unmedicated hypertensive, $t(76) = 5.40, p < .001$, and unmedicated normotensive patients, $t(58) = 4.52, p < .001$. Similarly, the medicated normotensive patients were older than the unmedicated hypertensive, $t(71) = 3.26, p = .002$, and unmedicated normotensive patients $t(53) = 3.15, p = .003$. No other group differences in age were found. With respect to years in education, medicated hypertensive AD patients had less years in education than medicated normotensive AD patients, $U = 464.00, p = .003$, unmedicated hypertensive AD patients, $U = 437.00, p = .028$, and unmedicated normotensive patients, $U = 172.50, p < .001$. There was no difference in education between any of the other groups.

The medicated hypertensive patients had higher systolic blood pressure than the unmedicated normotensive patients, $U = 25.50, p < .001$, and the medicated normotensive patients, $U = 22.50, p < .001$. Similarly, the unmedicated hypertensive patients had higher systolic blood pressure than the medicated normotensive patients, $U = 46.00, p < .001$, and the unmedicated normotensive patients $U = 35.50, p < .001$. No other group differences in systolic blood pressure were found. Analogous to what was found with systolic blood pressure, medicated

hypertensive patients had higher diastolic blood pressure than the unmedicated normotensive patients, $t(58) = 3.69, p < .001$, and the medicated normotensive patients, $t(69) = 4.45, p < .001$, whereas the unmedicated hypertensive patients had higher diastolic blood pressure than the medicated normotensive patients, $t(71) = 5.98, p < .001$, and the unmedicated normotensive patients, $t(60) = 5.14, p < .001$. With respect to pulse pressure, medicated hypertensive patients had higher pulse pressure than the unmedicated normotensive patients, $t(58) = 5.58, p < .001$, and the medicated normotensive patients, $t(47) = 6.78, p < .001$, whereas the unmedicated hypertensive patients had higher pulse pressure than the medicated normotensive patients, $t(52) = 5.09, p < .001$, and the unmedicated normotensive patients, $t(60) = 3.35, p < .001$. There were no differences in the distribution of AD diagnosis, APOE genotype, sex or the distribution of APOE $\epsilon 4$ carriers across the groups. However, the patients were not uniformly distributed with respect to the centre of recruitment. The statistics for the different demographic variables have been reported in Table 5.2.1. Means and standard deviations for variables with non-parametric distributions are included in Appendix B, Table B5.2.1.

Table 5.2.1 *Post hoc analysis: Demographic characteristics of medicated normotensive and hypertensive AD patients and unmedicated normotensive and hypertensive AD patients reported using means and standard deviations for parametric data and medians and interquartile ranges for non-parametric data*

Demographic variable	Medicated Hypertensive (n = 38)	Medicated Normotensive (n = 33)	Unmedicated Hypertensive (n = 40)	Unmedicated Normotensive (n = 22)	Statistic
Parametric tests^a	M (SD)	M (SD)	M (SD)	M (SD)	F
Age (in years)	75.03 (6.83)	72.24 (9.23)	65.20 (9.13)	63.82 (10.40)	12.32***
WC (in cm)	96.16 (13.31)	98.08 (14.51)	91.40 (11.29)	93.50 (12.06)	1.86
GMV (in ml ³)	571.54 (73.15)	546.70 (80.10)	589.33 (79.28)	610.79 (73.30)	1.94
WMV (in ml ³)	417.93 (64.80)	385.26 (46.21)	412.15 (49.83)	419.37 (42.90)	2.31
CSF (in ml ³)	499.01 (154.98)	489.43 (136.33)	447.76 (130.39)	468.25 (152.17)	1.00
TIV (in ml)	1462.57 (152.50)	1498.39 (150.09)	1445.27 (151.84)	1498.39 (150.09)	1.06
BP: Diastolic (mmHg)	84.55 (11.26)	73.91 (8.70)	86.65 (9.35)	74.41 (8.23)	15.73***
Pulse pressure (mmHg)	73.03 (18.84)	50.85 (6.69)	61.52 (16.64)	52.68 (9.34)	17.02***
Non- Parametric tests^b	Mdn (IQR)	Mdn (IQR)	Mdn (IQR)	Mdn (IQR)	H
Education (years)	9 (7 – 11)	11 (8 – 15)	12 (8 – 15)	12 (11 – 15)	14.74**
MMSE	25 (24 – 28)	27 (24 – 28)	25 (20 – 27)	24 (20 – 27)	7.22
BMI (kg/m ²)	26.00 (24.15 – 27.91)	27.53 (24.11 – 31.58)	24.91 (21.74 – 29.73)	24.85 (23.65 – 28.13)	4.20
WMH volume (ml)	5.87 (1.83 – 10.56)	2.95 (0.90 – 8.52)	2.71 (0.54 – 5.35)	2.34 (0.63 – 7.53)	7.53
BP: Systolic (mmHg)	157 (146 – 169)	126 (119 – 130)	151 (143 – 162)	129 (121 – 135)	85.94***
Chi square tests^c	n	n	n	n	χ²
Males/Females	19/19	11/22	22/18	13/9	4.73
APOE genotype: ε2ε2/ε2ε3/ε3ε3/ε4ε2/ ε4ε3/ε4ε4	3/13/1/16/4/1	1/17/2/8/1/4	4/14/2/9/8	3/5/0/11/3	20.49

APOE ε4 non-carriers/ APOE ε4 carriers	14/21	13/11	18/19	8/14	7.33
Diagnosis: AD dementia/ AD MCI	14/24	6/27	17/23	9/13	5.51
Centre (UK/Finland/Italy)	22/12/4	16/7/10	17/20/3	6/14/2	18.70**

* Comparison is significant at 0.05 level (two tailed)

** Comparison is significant at 0.01 level (two tailed)

*** Comparison is significant at 0.001 level (two tailed)

Key: n = sample size; M = mean; SD = standard deviation; F = F -statistic; Mdn = median; IQR = Interquartile range; H = H -statistic; χ^2 = Chi-square statistic; BP = Blood pressure

^aA one-way ANOVA was run for normally distributed data.

^bNon-parametric Kruskal-Wallis H tests were run for data that was not normally distributed.

^cChi-square tests were run to examine the independence of the categorical variables.

Means and standard deviations for non-parametric data have been reported in Appendix B, Table B5.2.1

5.4.1.2 Medicated AD patients: Stratified by Class of Antihypertensive medication

In terms of their distributions, the variables WC, GMV, WMV, CSF, TIV, systolic blood pressure and diastolic blood pressure had parametric distributions. A one-way ANOVA was performed to compare the groups with independent samples *t* tests performed *post hoc* to identify which specific groups differed from one another. On the other hand, age, years in education, MMSE, BMI, WMH volume and pulse pressure were variables that had non-parametric distributions. Kruskal-Wallis *H* tests were performed to examine whether the groups differed from one another and Mann-Whitney *U* tests were performed *post hoc* to identify which specific groups differed from one another. There was no statistically significant difference between the groups in terms of age, number of years in education, BMI, WC, WMV, TIV, blood pressure measurements (systolic, diastolic and pulse pressure) and also in the distribution of sex, APOE genotype and number of APOE ϵ 4 carriers (Table 5.3) across the groups. However, there was a trend that showed better parameters in the AD patient group on beta-blockers for blood pressure control in addition to being younger and having higher number of years in education. The groups were significantly different on MMSE scores, GMV, CSF and volume of WMH, described as follows. Group 3 had lower MMSE scores than Group 1, $U = 259.00, p = .018$. No other between-group differences were found in terms of MMSE. In terms of GMV, Group 2 had higher GMV than Group 1, $t(45) = 2.71, p = .01$, and Group 3, $t(35) = 2.44, p = .02$, while no differences were observed between Groups 1 and 3. Comparably, Group 2 had lower CSF volumes than Group 1, $t(45) = -2.35, p = .023$, and Group 3, $t(35) = -3.38, p = .002$, while no differences were found between Groups 1 and 3. With respect to the volume of WMH, Group 2 had lower volumes compared to Group 1, $U = 89.00, p = .002$, and Group 3, $U = 66.00, p = .003$. No difference was observed between Group 1 and Group 3 in WMH volume. The voxel-wise analysis for WMI was not carried out in these patient groups as no differences were found between the groups with respect to WMV. The groups were uniformly distributed in terms of sex, centre of recruitment, AD diagnosis and APOE genotype. Within the APOE genotype, the groups also had a uniform distribution of APOE ϵ 4 carriers. The statistics for the different demographic variables have been reported in Table 5.3. Means and standard deviations for variables with non-parametric distributions are included in Appendix B, Table B5.3.

Table 5.3 Demographic characteristics of AD patients on antihypertensive treatment stratified by medication type reported using means and standard deviations for parametric data and medians and interquartile ranges for non-parametric data

Demographic variable	Group 1	Group 2	Group 3	Statistic
	Other (n = 34)	β-blocker (n = 13)	Both (n = 24)	
Parametric tests^a	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>F</i>
WC (in cm)	97.60 (14.19)	94.39 (11.15)	97.71 (14.90)	0.29
GMV (in ml ³)	546.02 (68.77)	621.31 (86.77)	557.15 (70.12)	4.22*
WMV(in ml ³)	402.76 (61.78)	418.50 (48.56)	394.18 (60.18)	0.71
CSF(in ml ³)	514.12 (166.83)	395.08 (117.40)	520.74 (102.81)	4.05*
TIV (in ml ³)	1466.45 (159.47)	1434.89 (118.25)	1472.08 (162.63)	0.27
BP: Systolic (in mmHg)	146.12 (19.54)	135.08 (19.24)	140.88 (21.84)	1.48
BP: Diastolic (in mmHg)	81.12 (9.45)	76.00 (8.10)	79.42 (14.93)	0.95
Non- Parametric tests^b	<i>Mdn (IQR)</i>	<i>Mdn (IQR)</i>	<i>Mdn (IQR)</i>	<i>H</i>
Age (in years)	76 (68 – 80)	71 (59 – 79)	76 (69 – 81)	4.20
Education (in years)	10 (8 –13)	11 (9 – 14)	9 (7 – 13)	1.82
MMSE	28 (24 – 29)	26 (24 – 27)	25 (24 – 26)	6.39*
BMI (kg/m ²)	26.59 (23.71 – 29.71)	27.53 (24.35 – 30.34)	26.26 (24.65 – 29.18)	0.21
WMH volume (ml)	7.46 (1.81 – 18.84)	0.95 (0.39 – 3.11)	3.99 (2.01 – 7.64)	11.78**
Pulse pressure (in mmHg)	63 (51 – 81)	56 (49 – 62)	58 (48 – 73)	0.58
Chi square tests^c	<i>n</i>	<i>n</i>	<i>n</i>	<i>χ²</i>
Males/Females	16/18	4/9	10/14	1.03
APOE genotype: ε2ε2/ε2ε3/ε3ε3/ε4ε2/ε4ε3/ ε4ε4	0/2/13/1/15/1	0/0/6/1/3/1	0/2/11/1/6/3	7.33
APOE ε4 non-carriers/ ε4 carriers	11/17	3/5	13/10	4.35
Diagnosis: AD dementia/AD MCI	9/25	3/10	8/16	5.43
Centre (UK/Finland/Italy)	17/9/8	6/3/4	15/7/2	3.32

Type 2 diabetes/ Obese or overweight	9/20	2/9	6/17	0.66/1.03
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*Comparison is significant at 0.05 level (two tailed)

**Comparison is significant at 0.01 level (two tailed)

Key: n = sample size; M = mean; SD = standard deviation; F = F -statistic; Mdn = median; IQR = Interquartile range; H = H -statistic; χ^2 = Chi-square statistic; BP = Blood pressure

^aA one-way ANOVA was run for normally distributed data.

^bNon-parametric Kruskal-Wallis H tests were run for data that was not normally distributed.

^cPearson Chi-square tests were run to examine the independence of the categorical variables.

Means and standard deviations for non-parametric data have been reported in Appendix B, Table B5.3.

5.4.2 Cognitive tests

5.4.2.1 Medicated vs Unmedicated AD patients

In terms of their distributions, only the similarities test has a parametric distribution whereas the rest of the neuropsychological tests had non-parametric distributions. On comparing the two groups on tests of cognition a significant difference was observed only on the semantic fluency test, where the patients in the medicated AD group performed better than the unmedicated group. The statistics for the respective neuropsychological tests are reported in Table 5.4. Means and standard deviations for variables with non-parametric distributions are included in Appendix B, Table B5.4. There was no difference observed on the prose memory tests (immediate and delayed recall), digit span tasks (forward and backward conditions), phonemic fluency test, similarities test and the Stroop task. After controlling for the effect of WC and the presence of type 2 diabetes *post hoc* using Quade's ANCOVA, medicated AD patients performed better than the unmedicated patient group on the semantic fluency test, $F(1, 131) = 7.11, p = .005$, the prose memory-immediate recall test, $F(1, 125) = 4.06, p = .046$ and the digit span-forward test, $F(1, 125) = 4.43, p = .037$.

Table 5.4 Cognitive profiles of AD patients medicated and unmedicated for hypertension, reported using means and standard deviations for parametric data and medians and interquartile ranges for non-parametric data

Neuropsychological test	Medicated (<i>n</i> = 71)	Unmedicated (<i>n</i> = 62)	Statistic
Parametric tests^a	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>t</i>
Similarities	16.78 (6.47)	16.92 (6.64)	0.12
Non- Parametric tests^b	<i>Mdn</i> (<i>IQR</i>)	<i>Mdn</i> (<i>IQR</i>)	<i>U</i>
Prose Memory-Immediate recall	9 (7 – 12)	7 (4 – 11)	1470.00
Prose Memory-Delayed recall	8 (5 – 13)	6 (2 – 13)	1696.00
Digit Span-Forward	6 (5 – 8)	6 (5 – 7)	1670.00
Digit Span-Backward	4 (3 – 5)	4 (3 – 5)	1954.00
Phonemic Fluency	28 (20 – 38)	24 (19 – 38)	1858.00
Semantic Fluency	17 (14 – 26)	14 (11 – 21)	1567.00**
Confrontational naming test	13 (12 – 15)	14 (12 – 14)	2067.50
Stroop task- error interference	1 (0 – 4)	1 (0 – 5)	1726.00

*Comparison is significant at 0.05 level (two-tailed)

*Comparison is significant at 0.05 level (two tailed)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation; *t* = *t*-statistic; *Mdn* = median; *IQR* = Interquartile range; *U* = *U*-statistic; χ^2 = Pearson Chi-square statistic; BP = Blood pressure

^aIndependent samples *t* tests were run for normally distributed data.

^bNon-parametric Mann-Whitney *U* tests were run for data that was not normally distributed.

Means and standard deviations for non-parametric data have been reported in Appendix B, Table B5.4.

5.4.2.1.1 *Post hoc analysis*

In terms of their distributions, only the similarities test and the prose memory – immediate recall test had parametric distributions whereas the rest of the neuropsychological tests had non-parametric distributions. In the *post hoc* analysis where the medicated and unmedicated AD patients were further divided into hypertensive and normotensive groups, a significant difference was found in performance on the semantic fluency test. The medicated normotensive group had better performance on the semantic fluency test than the unmedicated hypertensive, $U = 415.50, p = .007$, and unmedicated normotensive, $U = 216.50, p = .021$, groups. No other group differences were found in performance on the semantic fluency test or any other neuropsychological tests (Table 5.4.1). Means and standard deviations for variables with non-parametric distributions are included in Appendix B, Table B5.4.1.

Table 5.4.1 *Cognitive profiles of medicated AD patients, unmedicated normotensive AD patients and unmedicated hypertensive AD patients, reported using means and standard deviations for parametric data and medians and interquartile ranges for non-parametric variables*

Neuropsychological test	Medicated Hypertensive (n = 38)	Medicated Normotensive (n = 33)	Unmedicated Hypertensive (n = 40)	Unmedicated Normotensive (n = 22)	Statistic
Parametric tests^a	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>F</i>
Prose Memory - Immediate recall	9.24 (4.02)	9.16 (3.69)	7.81 (4.96)	7.00 (4.72)	1.70
Similarities	17.51 (6.00)	15.94 (6.98)	16.49 (6.29)	14.37 (7.34)	0.49
Non- Parametric tests^b	<i>Mdn (IQR)</i>	<i>Mdn (IQR)</i>	<i>Mdn (IQR)</i>	<i>Mdn (IQR)</i>	<i>H</i>
Prose Memory - Delayed recall	8 (4 – 13)	9 (6 – 13)	6 (3 – 13)	6 (2 – 12)	2.47
Digit Span - Forward	7 (5 – 8)	6 (5 – 8)	6 (5 – 8)	6 (5 – 7)	3.07
Digit Span - Backward	5 (4 – 5)	4 (3 – 5)	4 (3 – 6)	4 (3 – 5)	3.16
Phonemic Fluency	29 (20 – 35)	28 (19 – 43)	23 (20 – 38)	24 (19 – 36)	2.05
Semantic Fluency	16 (13 – 21)	19 (15 – 27)	14 (11 – 21)	15 (10 – 19)	9.57*
Confrontational naming test	13 (11 – 14)	14 (12 – 18)	14 (11 – 14)	13 (12 – 15)	4.87
Stroop task - error interference	1.25 (0 – 4.00)	1.00 (0 – 2.00)	0.50 (0 – 3.25)	1.50 (0.25 – 9.38)	2.38

*Comparison is significant at 0.05 level (two-tailed)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation; *F* = *F*-statistic; *Mdn* = median; *IQR* = Interquartile range; *H* = *H*-statistic; χ^2 = Chi-square statistic

^aA one-way ANOVA was run for normally distributed data.

^bNon-parametric Kruskal-Wallis *H* tests were run for data that was not normally distributed.

Means and standard deviations for non-parametric data have been reported in Appendix B, Table B5.4.1

5.4.2.2 Medicated AD patients: Stratified by Class of Antihypertensive medication

On comparing the three groups on various neuropsychological tests, no significant differences were found between the groups (Table 5.5). Means and standard deviations for variables with non-parametric distributions are included in Appendix B, Table B5.5.

Table 5.5 Cognitive profiles of medicated AD patients stratified by class of antihypertensive treatment reported using means and standard deviations for parametric data and medians and interquartile ranges for non-parametric data.

Neuropsychological test	Group 1	Group 2	Group 3	Statistic
	Other (<i>n</i> = 34)	β-blocker (<i>n</i> = 13)	Both (<i>n</i> = 24)	
Parametric tests ^a	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>F</i>
Prose memory - Delayed recall	8.36 (5.54)	8.23 (3.94)	9.52 (5.81)	0.38
Phonemic Fluency	32.60 (14.00)	33.23 (13.31)	25.38 (9.98)	2.72
Digit Span - Forward	6.91 (1.83)	6.38 (1.33)	6.41 (1.87)	0.71
Similarities	18.18 (6.17)	16.15 (5.71)	15.00 (7.11)	1.72
Non- Parametric tests ^b	<i>Mdn</i> (<i>IQR</i>)	<i>Mdn</i> (<i>IQR</i>)	<i>Mdn</i> (<i>IQR</i>)	<i>H</i>
Prose memory - Immediate recall	9 (5 – 13)	9 (7 – 11)	10 (8 – 13)	1.14
Digit span - Backward	5 (4 – 5)	4 (3 – 6)	4 (3 – 5)	1.82
Semantic fluency	19 (14 – 26)	18 (12 – 32)	16 (13 – 19)	3.50
Confrontational Naming Task	14 (12 – 15)	13 (11 – 17)	12 (11 – 15)	2.81
Stroop task – error interference	1 (0 – 2)	1 (1 – 6.50)	0.50 (0 – 4)	1.30

* Comparison is significant at 0.05 level (two tailed)

Key: β = beta; *n* = sample size; *M* = mean; *SD* = standard deviation; *F* = *F*-statistic; *Mdn* = median; *IQR* = Interquartile range; *H* = *H*-statistic

^aA one-way ANOVA was run for data that was normally distributed.

^bNon-parametric Kruskal-Wallis *H* tests were run for data that was not normally distributed.

Means and standard deviations for non-parametric data have been reported in Appendix B, Table B5.5

5.4.3 Voxel-based morphometry

5.4.3.1 Medicated vs Unmedicated AD patients

No significant differences were found with respect to GMV between AD patients medicated and unmedicated for hypertension in both contrasts.

5.4.3.2 Unmedicated AD patients

There were no correlations found between pulse pressure and GMV in AD patients who were not on blood pressure lowering medication in both contrasts.

5.4.3.3 Medicated AD patients: Stratified by Class of Antihypertensive medication

5.4.3.3.1 Other vs Beta-blocker

Medicated AD patients on antihypertensive medication other than beta-blockers had lower GMV than medicated AD patients on beta-blockers in the occipital lobe, the brainstem, left insula, the temporal brain regions and the superior portion of the cerebellum (Table 5.6, Fig 5.2). The cluster in the occipital lobe was nestled in the midline and extended anteriorly into the middle temporal lobe areas, also covering parts of the left hippocampus. The same cluster extended inferiorly into the superior portions of the cerebellum. The cluster in the anterior temporal regions extended bilaterally from the midline in the anterior midbrain into the temporal poles, extending slightly into the orbitofrontal brain regions. Another cluster in the right temporal lobe was found along the posterolateral borders. Dispersed clusters were found in the left insula and left precentral gyrus as well. The extracted GMV signal was positively correlated with performance on the phonemic fluency test, $r = 0.40$, $p = .005$, the digit span - forward test, $r = 0.34$, $p = .020$, and the similarities test, $r = 0.41$, $p = .004$, and negatively correlated with the error interference score (Stroop test), $r_s = -0.31$, $p = .043$. Additionally, the extracted GMV signal was negatively correlated with WMH volume, $r_s = -0.55$, $p < .001$. There was no correlation between the extracted signal and any of the blood pressure parameters. No significant differences were found using the other contrast.

5.4.3.3.2 Both vs Beta-blocker

Medicated AD patients on beta-blockers and other classes of antihypertensive treatment had lower GMV than medicated AD patients on beta-blockers (Table 5.6, Fig 5.2). One cluster was found in the right superior hippocampus with voxels spilling into the right parahippocampal

gyrus and the right caudate tail. Another cluster was found in the right lateral temporal areas in the superior temporal gyrus, in close proximity to the temporoparietal junction. A third cluster was found in the left hemisphere in the medial portions of the occipital lobe. There was a positive correlation between the extracted GMV signal and performance on the prose memory - delayed recall test, $r = .38$, $p = .023$, digit span - backward test, $r_s = .35$, $p = .038$, and the similarities test, $r = .52$, $p = .001$. The extracted GMV signal was also negatively correlated with WMH volume, $r_s = -.39$, $p = .016$. There was no correlation between the extracted signal and any of the blood pressure parameters. No significant differences were found using the other contrast.

5.4.3.3.3 *Both vs Other*

No significant differences were found between AD patients on beta-blockers and other classes of antihypertensive treatment (Group 3) and AD patients on antihypertensive treatment except for beta-blockers (Group 1) across both contrasts.

Table 5.6 Brain regions showing differences in GMV among AD patients stratified by medication type

Voxels	Cluster level <i>p</i> FWE	Brain region (Brodmann area)	Side	Z-score	MNI coordinates		
					x	y	z
<i>BBlocker > Other</i>							
1722	< .001	Inferior temporal gyrs (20)	R	4.33	52	-40	-27
		Fusiform gyrus (37)	R	4.28	62	-40	-21
		Fusiform gyrus (37)	R	3.9	46	-50	-24
7182	< .001	Cerebellum- anterior lobe	R	4.3	8	-66	-9
		Cuneus (18)	R	4.19	4	-93	27
		Cerebellum- anterior lobe	R	4.06	8	-86	-21
778	0.029	Precentral gyrus (6)	L	4.13	-56	-4	45
		Precentral gyrus (4)	L	4.04	-48	-8	32
		Precentral gyrus (4)	L	3.9	-40	-14	39
922	0.015	Insula (13)	L	4.05	-39	-16	15
		Insula (13)	L	3.89	-40	-10	-8
		Insula (13)	L	3.31	-40	-16	3
2065	< .001	Temporal pole (53)	R	4.00	18	0	-14
		Temporal pole (53)	R	3.91	33	10	-20
		Hippocampus (34)	R	3.75	-22	4	-16
<i>Bblocker > Both</i>							
761	0.018	Hippocampus (34)	R	4.02	38	-34	-3
		Caudate nucleus (48)	R	3.86	27	-36	6
		Parahippocampal gyrus (36)	R	3.26	14	-32	-4
668	0.031	Transverse temporal area (41)	L	4.01	-58	-28	12
		Postcentral gyrus (1)	L	3.54	-44	-22	15
		Superior temporal gyrus (22)	L	3.35	-64	-42	8
852	0.011	Occipital lobe (19)	R	3.74	14	-72	28
		Occipital lobe (18)	R	3.64	2	-58	9
		Occipital lobe (18)	R	3.54	10	-78	22

5.4.4 Tract-based spatial statistics

5.4.4.1 Medicated vs Unmedicated AD patients

There were no significant differences in WMI found between medicated and unmedicated AD patients across both contrasts.

5.4.4.2 Unmedicated AD patients

There was no significant relationship between pulse pressure and any of the diffusivity measures in AD patients who were not on antihypertensive treatment using both contrasts.

5.4.5 Arterial spin labelling

5.4.5.1 Medicated vs Unmedicated AD patients

There were no significant differences in CBF as measured using ASL between medicated and unmedicated AD patients using both contrasts.

5.4.5.2 Unmedicated AD patients

In the AD patients who were not on anti-hypertensive medication, a negative correlation was found between CBF and pulse pressure (Table 5.7, Fig 5.1). This association was located predominantly in the left hemisphere spanning across the subcortical structures. The cluster followed the trajectory of the caudate nucleus for the most part, with some voxels spilling over to the thalamus. In the anterior portions, the cluster extended inferiorly into the basal forebrain and subgenual anterior cingulate region and laterally into the right caudate head. The extracted CBF signal showed a negative correlation with WMH volume, $r_s = -0.46$, $p < .001$. There was no correlation between the extracted signal and any of the blood pressure parameters or neuropsychological test scores. No significant associations were found with the positive correlation contrast.

Table 5.7 Brain regions showing associations between pulse pressure and CBF in unmedicated AD patients.

Voxels	Cluster level <i>p</i> FWE	Brain region (Brodmann area)	Side	Z-score	MNI coordinates		
					x	y	z
1639	.048	Caudate nucleus	L	3.29	-12	24	-4
		Basal forebrain		3.14	0	14	-16
		Thalamus	L	3.10	-16	-26	16
		Caudate nucleus	L	2.99	-12	-14	16
		Thalamus	L	2.89	-22	-34	12
		Caudate nucleus	R	2.86	10	16	-2
		Caudate nucleus	R	2.83	-4	8	2
		Caudate nucleus	L	2.83	4	8	4

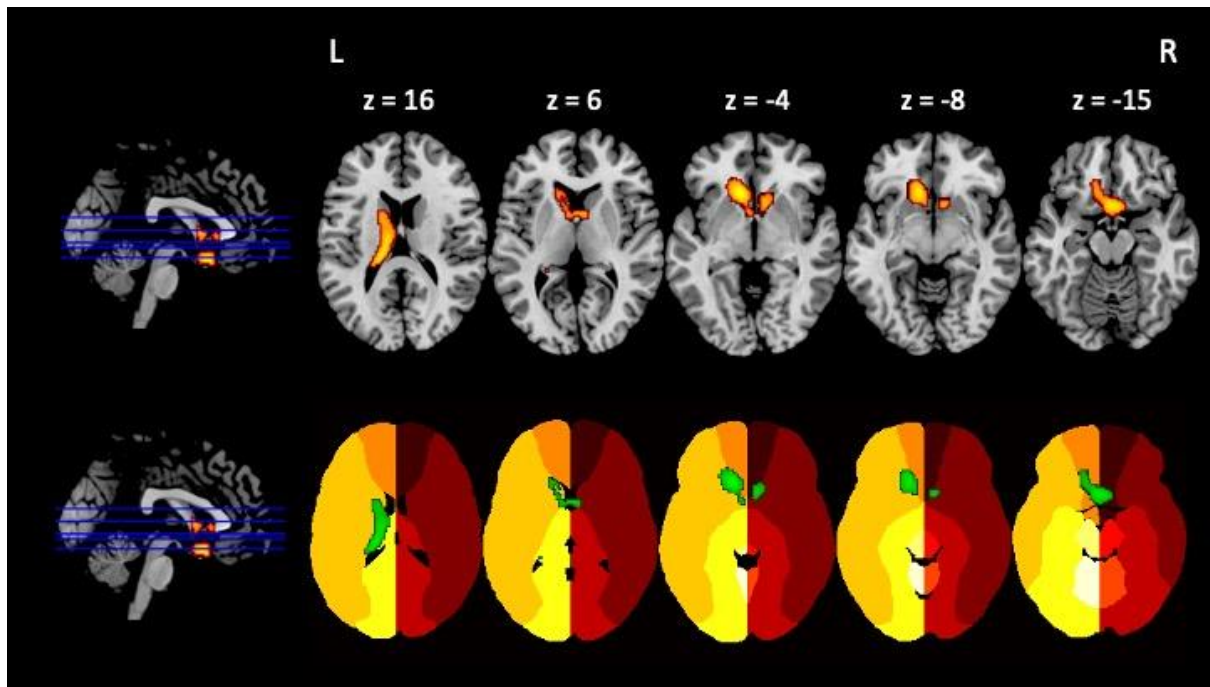


Figure 5.1 *Brain regions showing associations between pulse pressure and CBF in AD patients unmedicated for hypertension*

The image contains axial sections depicting associations observed between pulse pressure and CBF in AD patients unmedicated for hypertension. The sagittal sections on the left represent the location of the axial slices from top to bottom which are subsequently displayed from left to right. Top row: Negative correlations between pulse pressure and CBF found in unmedicated AD patients are represented in orange. Bottom row: Negative correlations between pulse pressure and CBF found in unmedicated AD patients are represented in green mapped onto the vascular territories of major cerebral arteries. These associations were observed across the caudate nucleus, subgenual anterior cingulate and the basal forebrain.

5.4.5.3 Medicated AD patients: Stratified by Class of Antihypertensive medication

5.4.5.3.1 Other vs Beta-blocker

Medicated AD patients on antihypertensive medication other than beta-blockers had lower CBF compared to AD patients who were only on beta-blockers, primarily in periventricular and posterior brain regions (Table 5.8, Fig 5.2). The clusters began bilaterally in the superior parietal white matter and extended inferiorly following the border of the lateral ventricles into the superior hippocampi. In the left hemisphere, the cluster was more widespread than the cluster in the right hemisphere and extended anteriorly into the right insula. Some significant voxels were also found in the midbrain that spilled over into the orbitofrontal area. Additionally, results were also found in the superior portions of the cerebellum. There was a positive correlation between the extracted CBF signal and the semantic fluency test, $r = 0.32$, $p = .026$. The extracted CBF signal was not correlated with WMH volume. However, the extracted CBF signal was negatively correlated with pulse pressure, $r_s = 0.33$, $p = .024$. No differences were detected using the other contrast.

5.4.5.3.2 Both vs Beta-blocker

Medicated AD patients on beta-blockers and other classes of antihypertensive treatment had lower CBF compared to AD patients on beta-blockers (Table 5.8, Fig 5.2). The differences found between these two groups were similar to those found in the comparison above (5.4.5.3.1). Superiorly, clusters were found bilaterally into the parietal lobe, spanning across the precuneus, superior parietal lobule and precentral gyrus. Inferiorly, the clusters extended into the superior hippocampi and parahippocampal white matter bilaterally, following the borders of the lateral ventricles. The voxels also covered structures in the bilateral basal ganglia, posterior corpus callosum, parts of the fornix and the bilateral thalami. These clusters also extended bilaterally into the insulae. Additionally, clusters were found in the midbrain and superior portions of the cerebellum. Anteriorly, significant clusters were located in the prefrontal brain regions spanning across the orbitofrontal, dorsomedial, ventromedial and ventrolateral areas. The extracted CBF signal was not significantly correlated with neuropsychological performance, WMH volume or any of the blood pressure parameters. No differences were observed using the other contrast.

5.4.5.3.3 *Both vs Other*

No significant differences in CBF were found between AD patients on beta-blockers and other classes of antihypertensive treatment and AD patients on antihypertensive treatment except for beta-blockers across both contrasts.

Table 5.8 *Brain regions showing differences in CBF between AD patients stratified by medication type*

Voxels	Cluster level <i>p</i> FWE	Brain region (Brodmann area)	Side	Z-score	MNI coordinates		
					x	y	z
<i>Other < BBlocker</i>							
3096	< .001	Hippocampus (54)	R	4.13	30	-44	0
		Hippocampus (54)	R	3.97	20	-34	8
		Parahippocampal gyrus (WM)	R	3.6	30	-50	26
6948	< .001	Insula (13)	L	3.91	-40	-18	0
		Insula (13)	L	3.89	-42	-8	-6
		Temporal pole (38)	L	3.74	-34	20	-30
<i>Both < Bblocker</i>							
2438	0.002	Superior parietal lobule (7)	R	4.82	4	-50	74
		Superior parietal lobule (5)	L	4.22	-24	-40	74
		Postcentral gyrus	L	3.95	-44	-36	58
14085	< .001	Hippocampus (54)	R	4.79	28	-40	2
		Caudate nucleus (48)	R	4.39	18	-34	14
		Occipital lobe (18)	R	4.21	4	-90	-12
1356	0.035	Orbitofrontal cortex (10)		3.51	0	56	-12
		Dorsolmedial prefrontal cortex (9)	R	3.49	4	62	30
		Dorsolmedial prefrontal cortex (9)	R	3.41	2	58	38

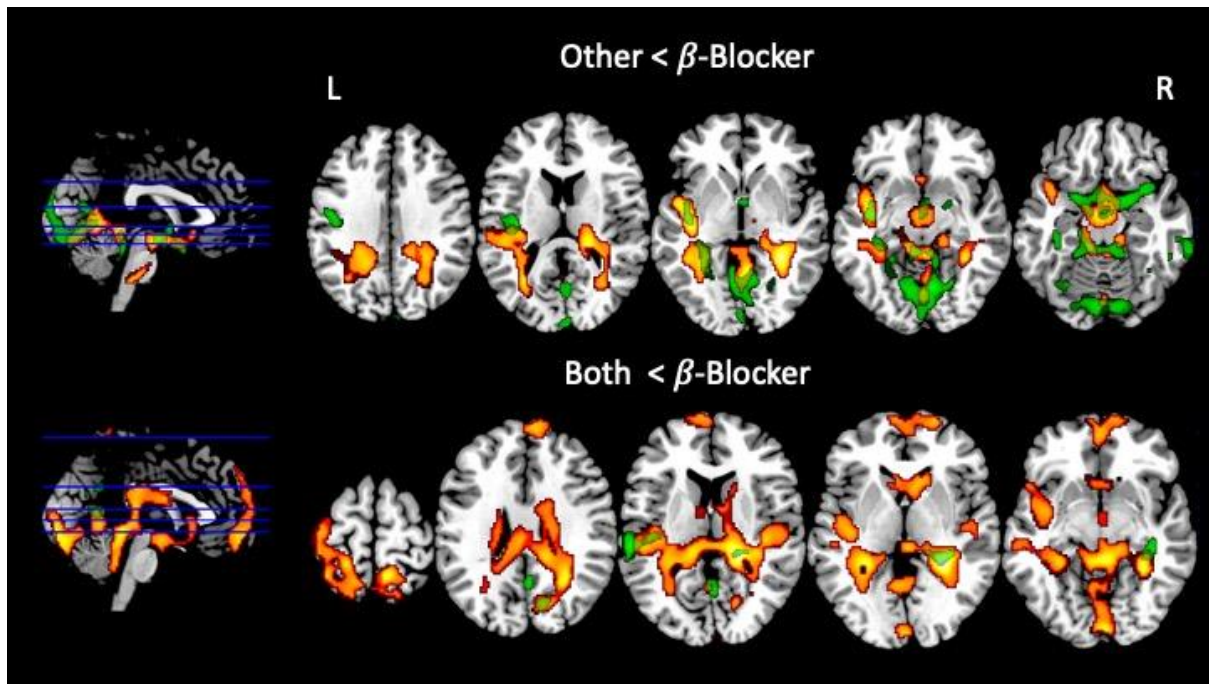


Figure 5.2 Brain regions showing differences between AD patients on different classes of antihypertensive treatment

The two rows contain axial sections depicting comparisons between AD patients on different classes of antihypertensive treatment. Each row begins with a sagittal section representing the location of the axial slices from top to bottom which are subsequently displayed from left to right. Top row: AD patients who were on any class of antihypertensive treatment except for beta-blockers showed lower CBF and GMV in the highlighted regions compared to AD patients who were taking beta-blockers only, for blood pressure control. Differences in GMV are represented in green; while differences in CBF are represented in orange. The z co-ordinates for the axial sections are as follows (from left to right): 34, 14, -2, -8, -16. Bottom row: AD patients who were on any class of antihypertensive treatment and beta-blockers showed lower CBF and GMV in the highlighted regions compared to AD patients who were taking beta-blockers only for blood pressure control. Differences in GMV are represented in green; while differences in CBF are represented in orange. The z co-ordinates for the axial sections are as follows (from left to right): 68, 28, 11, 2, -8.

5.4.6 White Matter Hyperintensities

5.4.6.1 Medicated vs Unmedicated AD patients

A negative correlation was found between WMH volume and scores on the similarities test in AD patients unmedicated for hypertension ($r_s = -.26$, $p = .046$). WMH volume was not significantly correlated with scores on any other neuropsychological test or blood pressure measures. No significant correlations were found with the above variables in the medicated AD patients.

5.4.6.2 Medicated AD patients: Stratified by Class of Antihypertensive medication

There were no significant correlations between WMH volume, cognitive test scores or blood pressure measures in the AD patients on antihypertensive treatment other than beta-blockers (Group 1), AD patients on beta-blockers (Group 2) and in AD patients on both beta-blockers and other classes of antihypertensive treatment (Group 3).

5.4.7 Collinearity analysis

No significant collinearity was found between BMI and blood pressure parameters.

5.5 Discussion

5.5.1 Medicated vs Unmedicated AD patients

The current study is the first to show comparisons of multi-modal neuroimaging variables namely GMV, WMI and CBF between AD patients medicated and unmedicated for hypertension. The study does not show a beneficial effect of blood pressure lowering medication in AD patients (with a medical history of hypertension) on any cerebral properties compared to unmedicated AD patients. One explanation for the absence of a substantial beneficial effect of the use of antihypertensive drugs on cerebral constituents could be due to the similarity in blood pressure readings falling within hypertensive ranges of the medicated and unmedicated AD patients. In addition to hypertensive blood pressure readings, the medicated patients also had a higher number of cardiovascular comorbidities that increase cerebrovascular burden, which could explain the lack of differences in cerebral constituents between the medicated and unmedicated AD patients (Breteler et al., 1994; Yoshita et al., 2006). This was of significance as a difference in GMV and WMH volume was found without controlling for any factors, which did not persist after controlling for the effect of age, WC and presence of type 2 diabetes (factors that can increase cerebrovascular burden). These findings could also indicate that the administration of antihypertensive treatment in AD patients with a medical history of hypertension, could have limited any progressive damage to cerebral constituents, that could have been more extensive, had these patients not been treated appropriately (Haight et al., 2018; Liao et al., 1996).

It is further noteworthy that no significant differences were found in any cerebral properties or cognitive function after dividing the unmedicated and medicated AD patient groups into hypertensive and normotensive groups while performing comparisons *post hoc*. This observation is in contrast with the findings from a previous study that showed detriments in brain structure irrespective of antihypertensive treatment in cognitively normal individuals with blood pressure within the hypertensive range (Haight et al., 2018). The study did not find this detrimental effect in individuals who were on antihypertensive medication with blood pressure in the normotensive range (Haight et al., 2018). A different study showed similar detrimental effects of inappropriate blood pressure control, where individuals treated with antihypertensive drugs with uncontrolled hypertension had higher odds of WMH compared to those who were on antihypertensive medication with controlled hypertension (Liao et al.,

1996). Both of these studies were performed on cognitively normal individuals. Therefore, the level of blood pressure control does not seem to modulate neuroimaging parameters in medicated AD patients in the current study. The absence of a difference between the medicated and unmedicated groups could also imply that the administration of medication in AD patients with a history of hypertension helps prevent hypertensive AD patients from suffering from a more severe radiological AD phenotype by preventing the progressive and additional burden from detriments resulting from chronically elevated blood pressure, regardless of the level of control (Fournier et al., 2009; Fukui et al., 2014; Wharton et al., 2019). It is also possible that the lack of a difference in cerebral parameters and cognitive function between the medicated and unmedicated groups could be due to accumulated age and hypertension-related irreversible insults in AD patients with a history of hypertension prior to commencing antihypertensive treatment (Fan et al., 2019; Mishima et al., 2021). Therefore, early intervention, regular monitoring of blood pressure and medication compliance to maintain blood pressure in the normotensive range, could contribute towards improving protection of the brain to hypertension related detriments and reducing the radiological severity of the AD phenotype (Insel, Reminger, & Hsiao, 2008; McKenney, Munroe, & Wright Jr, 1992; Ngandu et al., 2015).

One explanation for hypertensive blood pressure readings in the medicated group despite antihypertensive treatment could be due the lower level of educational attainment compared to the unmedicated group. The level of educational attainment can affect health literacy and therefore the patients' ability to follow medication regimens consistently (Dhikav, Singh, & Anand, 2013; Levinthal et al., 2008). Studies have shown that lower educational attainment is associated with poor recognition of medication, the dosage schedule and identifying major side effects of the medication (Alkatheri & Albekairy, 2013; Jin, Kim, & Rhie, 2016a; Kripalani et al., 2006). In support of this, *post hoc* analyses conducted in the current study show that the medicated hypertensive patients had the least number of years in education compared to the other three groups (medicated normotensive, unmedicated hypertensive and unmedicated normotensive). Other factors that could have contributed to hypertensive blood pressure readings in the medicated group despite antihypertensive treatment could be poor medication adherence, poor medication regime monitoring and level of cognitive impairment (Cho et al., 2018a).

The presence of comorbidities such as type 2 diabetes and overweight or obesity can cause significant elevations in blood pressure (Adler et al., 2000; Stabouli et al., 2005). The medicated patient group had a higher proportion of patients with comorbidities, which could also explain the lack of a difference found in blood pressure readings and neuroimaging parameters between the medicated and unmedicated groups. However, this inference is not causal as the presence of these comorbidities is not always linked with higher blood pressure readings. Other downstream pathological mechanisms associated with these comorbidities could have played a role in the absence of a difference between the medicated and unmedicated patients (Herrmann et al., 2019; Moulton et al., 2015). Higher age in the medicated group could have also contributed toward higher vascular burden accrued over the lifetime (Lo & Jagust, 2012). On comparing cerebrovascular burden as measured using WMH, no differences were found between the medicated and unmedicated groups after controlling for age, WC and the presence of type 2 diabetes. It is possible that the beneficial effects of antihypertensive medication in the medicated group could have been overshadowed by the detrimental effects from insults accrued with higher age and comorbidities such as obesity and type 2 diabetes.

Another explanation for the hypertensive blood pressure readings in the medicated AD patient group could be due to the cognitive impairment seen in AD patients (Cho et al., 2018a). A study on ~20,000 elderly hypertensive patients showed that poor medication adherence was associated with lower cognitive function in patients without dementia (Cho et al., 2018a). A different study on elderly patients (> 60 years) showed similar findings with less than a third of the patients with cognitive impairment who showed good medication adherence to blood pressure lowering medication regimens (Vinyoles, De la Figuera, & Gonzalez-Segura, 2008). An important factor in good medication adherence is intact memory functions to facilitate planning, organisation and implementation of medication regimens (Hawkins et al., 2012; Hayes et al., 2009). Another important cognitive domain associated with good medication compliance is executive function (Hawkins et al., 2012; Insel et al., 2006; Smith et al., 2017). This cognitive domain is impaired in early AD and deteriorates with disease progression (section 1.3.4.2). Considering that AD patients experience progressive and severe impairments, primarily in the memory domain, in addition to progressive decline in executive function, these patients are highly likely to not comply with medication regimens (section 1.3.4.1). In support of this, past studies have shown that AD patients and patients with dementia are less likely to show medication adherence (Dhikav et al., 2013; El-Saifi et al., 2018; Hudani & Rojas-Fernandez, 2016). Therefore, inappropriate blood pressure control resulting from poor adherence to

medication regimes in AD patients could explain the lack of a difference between medicated and unmedicated patient group profiles in the present study.

However, in spite of having blood pressure readings within the hypertensive range and ranking higher on factors that increase cerebrovascular burden which included higher age, WC and WMH volume, the medicated AD patients had better performance on the MMSE, which measures the general level of cognitive functioning, and on tasks measuring semantic memory compared to the unmedicated AD patients (Pezzotti et al., 2008; section 4.3.4). Both medicated and unmedicated AD patient groups did not statistically differ on any measures of blood pressure. Therefore, antihypertensive treatment in AD patients with a history of hypertension could have the potential to facilitate the preservation of cognitive function, which contradicts studies on cognitively normal individuals and those with cognitive impairment that show detriments in cognitive function despite antihypertensive treatment (García-Alberca et al., 2020; Gu et al., 2019; Hannesdottir et al., 2009; Raz et al., 2003). It is also of significance that preservation is seen in the semantic memory domain, a heavily affected cognitive domain across the AD course (section 1.3.4.1). Higher number of years in education are often associated with better performance on cognitive tests (Beeri et al., 2006b; Bornstein & Suga, 1988). It is noteworthy that performance on cognitive tests was better in the medicated patient group despite having lower number of years in education. However, there was no significant difference in performance on the MMSE after controlling for the effect of factors that are associated with higher cerebrovascular burden namely age, WC and the presence of type 2 diabetes. No significant differences were found in cognitive profiles in the *post hoc* analysis in which medicated and unmedicated groups were further divided into hypertensive and normotensive groups.

Although medicated patients had better performance on tasks of memory, a cognitive domain that is crucial to adherence to medication regimens, this could be explained by a reverse causal effect. Research has shown improvement in the memory domain in individuals who follow complicated medication regimens (Ettenhofer et al., 2010; Gould, McDonald-Miszczak, & King, 1997). In a study by Gould and colleagues, metamemorial variables were identified as predictors of perceived medication adherence (Gould et al., 1997). However, medication adherence was self-reported in this study, which could have impacted the findings (Gould et al., 1997). Contextual cues, often used by individuals taking medication promote habit formation which helps improve memory function and also medication adherence (Gasbarri, et

al., 2014; Stawarz et al., 2016). Therefore, it is possible that the repeated use of the memory domain required for medication adherence could have improved in individuals following medication regimes across their lifetime. The inverse may also be true that antihypertensive treatment in the medicated patient group could have resulted in preservation of memory (Hajjar et al., 2013; Ho, Nation, & ADNI, 2017; Stuhec et al., 2017). It is difficult to distinguish whether the preservation of cognitive function in the medicated patient group could be attributed to the effect of medication or to the repeated use of memory functions required for medication adherence, or a combination of both.

Overall, it appears that medicated AD patients in the current study do not show any differences in cerebral parameters in comparison to the unmedicated group, due to a variety of reasons. Although, there may be some benefits to preserving cognitive function in such patients despite poor blood pressure control and higher prevalence of cardiovascular comorbidities. The higher prevalence of comorbidities, low educational attainment and possibly lower health education and the likelihood of poor adherence to antihypertensive treatment due to low education attainment or AD status, could have all contributed toward masking the beneficial effects of antihypertensive medication in this group. Therefore, it is important that interventions to improve health literacy by educating patients about their conditions, measures to ensure medication adherence and early interventions to modify lifestyle factors to prevent the development of cardiovascular comorbidities could help improve the effectiveness of medications in improving AD prognosis in patients with a medical history of hypertension (Jankowska-Polańska et al., 2016; Ngandu et al., 2015; Wannasirikul et al., 2016).

5.5.2 Unmedicated AD patients

The second aim of the current study was to explore how the variability in pulse pressure could affect cerebral parameters and cognitive function in the unmedicated AD patients. In this analysis, negative associations were found between CBF and pulse pressure. AD patients in this group also had systolic blood pressure within the hypertensive range. Findings from a recent study showed a beneficial effect of administering blood pressure lowering medication in preserving CBF in normotensive patients with mild to moderate AD (~72 years), without a history of hypertension (de Jong et al., 2019). A beneficial effect of the medication (Nilvadipine) was observed on CBF despite a short duration of administration of only six months. Of note, this beneficial effect was seen in brain regions that are typically affected in

AD (de Jong et al., 2019). Similarly, a different study on elderly cognitively normal individuals (> 65 years) showed a beneficial effect of six months of pharmacological reduction of blood pressure on CBF in hypertensive individuals (Lipsitz et al., 2005). The study was also able to establish that long term antihypertensive treatment in otherwise healthy elderly individuals did not result in cerebral hypoperfusion (Lipsitz et al., 2005). This observation could signify that in addition to treating AD patients with a history of hypertension with antihypertensive medication, administering blood pressure lowering agents to AD patients who have blood pressure within the hypertensive range could potentially help protect the brain against damage from high blood pressure, regardless of a history of hypertension, without risking cerebral hypoperfusion (Lipsitz et al., 2005). However, more research is needed to confirm whether there are any substantial benefits to administering antihypertensive treatment to hypertensive AD patients without a prior history of hypertension. The risks of lowering blood pressure in elderly individuals who already experience reductions in blood pressure with higher age, should also be taken into consideration (Satish, Zhang & Goodwin, 2001). Considering that hypertension may involve a prolonged asymptomatic period and that it damages brain regions affected by AD, it is imperative that blood pressure is closely monitored in AD patients to exercise control in a timely manner, before significant damage is inflicted by chronically elevated blood pressure (Friedman et al., 2014; Van Boxtel et al., 2006).

Negative associations were found between pulse pressure and CBF predominantly in the left hemisphere spanning across the caudate nucleus, thalamus and basal forebrain. The fact that these structures lie in the subcortical and deeper brain regions makes them more susceptible to damage from hypertension due to the delicate vasculature supplying these regions (Moody, Bell, & Challa, 1990). Previous studies have shown vulnerability of subcortical structures to the detrimental effects of hypertension (Dai et al., 2008; De Leeuw et al., 1999; Fujii et al., 1990; Lee et al., 2007). The specific susceptibility of the caudate nucleus to the damaging effects of fluctuating high blood pressure and other vascular damage has been detailed in section 6.5.1.1. The finding that the negative correlations were found along the border zones of the arterial territories of major cerebral arteries is of particular significance (Fig 5.1). Brain regions supplied by the terminating and perforating branches of arteries are particularly prone to damage from adverse vascular events as these branches have narrow lumens that increase their susceptibility to fluctuations in blood pressure and embolic events, which can reduce regional CBF (Gutierrez et al., 2015). Patients with hypertension tend to show reductions in lumen diameters and increased wall thickness of cerebral arteries compared to normotensive

counterparts, possibly as a compensation to accommodate for increased blood pressure and to maintain adequate blood flow (Korsgaard et al., 1993; Rizzoni et al., 2001).

Increased arterial wall thickness as seen in arteriosclerosis could also contribute towards damage to deep brain regions due to fluctuations in blood pressure resulting from reduced elasticity to accommodate for such fluctuations (section 2.1.1.2, Para1). This finding thus shows that in unmedicated AD patients with high blood pressure, brain regions that are supplied by the terminating branches of major cerebral arteries are more susceptible to damage. The extracted CBF signal was also linked with higher vascular burden as measured using WMH volume. This could indicate that blood pressure within the hypertensive range in AD patients could exacerbate the vascular dysfunction that is already seen in AD, which could in turn result in a worse disease prognosis. Given the prolonged asymptomatic period of hypertension, and past work that shows preservation of CBF in AD patients without a medical history of hypertension following treatment with antihypertensive drugs, a timely intervention could help reduce the radiological severity of AD (de Jong et al., 2019).

A negative correlation was also observed in the basal forebrain, a critical region in AD pathogenesis (Shinotoh et al., 2000; Teipel et al., 2005). This brain region has a significant role in cholinergic transmission, a mechanism that exhibits considerable impairment in AD (Wilcock et al., 1982). It is also implicated in memory function via its projections to the hippocampus and other brain regions involved in memory (Hasselmo, Wyble, & Wallenstein, 1996; Ikonomic et al., 2003; Power, Vazdarjanova, & McGaugh, 2003). Since in the current study AD patients with a systolic blood pressure in the hypertensive range showed negative associations with pulse pressure and CBF in the basal forebrain, it is possible that negative effects of higher blood pressure in AD could be additive to the cholinergic dysfunction already observed in AD (Davies & Maloney, 1976; Shinotoh et al., 2000). Cholinergic action is also integral in modulating rCBF (Li et al., 2012b; Sato, Sato, & Uchida, 2004). Cholinergic dysfunction observed in early AD combined with the detrimental effects exerted by hypertension could thus have additive effects on altered CBF in AD. These findings highlight how increasing pulse pressure could interact with cerebral parameters to exacerbate the detrimental effects observed in typical AD.

5.5.3 Medicated AD patients stratified by medication type

It is possible that the absence of a significant difference in the cerebral parameters between medicated and unmedicated AD patients could be attributed to the differential effect of the class of blood pressure lowering agents on the brain, as indicated in previous studies (Jin, 2016b; Lebouvier et al., 2020; Muller et al., 2012). In the analysis comparing medicated AD patients stratified by the class of antihypertensive treatment, AD patients on beta-blockers (Group 2) showed higher CBF and GMV compared to the other two groups (Group 1: AD patients on other classes of antihypertensive treatment except beta-blockers and Group 3: AD patients on both, other classes of antihypertensive treatment and beta-blockers). Therefore, within the medicated AD patients, it appears that those patients administered with beta-blockers (Group 2) have a less severe clinical and radiological AD phenotype compared to AD patients on other classes of antihypertensive treatment in combination with (Group 3) and without beta-blockers (Group 1).

Findings from the current study contradict the findings from past studies that have indicated no effect of beta-blockers on cognitive function and a beneficial effect of antihypertensive treatment other than beta-blockers on risk of AD and cerebral constituents in healthy individuals (Burkauskas et al., 2016; Davies et al., 2011; Holm et al., 2020; Jin, 2016b; Lanham et al., 2019; Lebouvier et al., 2020; Muller et al., 2012). Of these studies, reviews conducted on dementia patient samples indicate a beneficial effect of antihypertensive treatments in patients, but a limited benefit from beta-blockers (Lanham et al., 2019; Lebouvier et al., 2020). However, both these reviews were not specific to AD patients. However, in support of findings from the current study, a study by Rosenberg and colleagues showed that use of beta-blockers in AD patients was associated with a delay in their functional decline (Rosenberg et al., 2008). In a different longitudinal study, beta-blocker use was associated with a lower risk of cognitive impairment compared to other classes of antihypertensive treatment (Gelber et al., 2013). However, individuals on beta-blockers who were diagnosed with T2DM and had higher pulse pressure showed increased risk of cognitive decline (Gelber et al., 2013). The findings from the study by Gelber and colleagues are consistent with those from the current study as patients on beta-blockers had the lowest pulse pressure compared to the rest of the groups and had a similar proportion of patients with T2DM as the other two groups (Gelber et al., 2013). Thus, future work and longitudinal studies are needed to establish whether beta-blocker use could be beneficial in protecting the brain from the additional effect of high blood pressure in AD patients.

In the current study, on stratifying the AD patients on antihypertensive treatment by medication type, the patients who were taking beta-blockers (Group 2) had a better prognostic profile of AD than the other two groups with respect to GMV and CSF. The patients who were on beta-blockers not only had the highest GMV and lowest CSF volumes compared to the other groups, but also had the lowest cerebrovascular burden as measured using WMH volume. Lower cerebrovascular burden as measured using WMH volume in this group could be a contributing factor towards preservation of GMV observed in this group (Firbank et al., 2007). In turn, a possible explanation for the lower cerebrovascular burden in this group could be the result of the lower blood pressure readings (Dufouil et al., 2001; Firbank et al., 2007). It is also difficult to extrapolate whether medication adherence in the different groups could be a factor in explaining the differences in pulse pressure found within the groups. Considering that there was no difference in education, which is a significant predictor of medication adherence, it is possible that the use of beta-blockers in AD patients could be beneficial to brain structure and function compared to other classes of antihypertensive treatment or a combination of the two (Alkatheri & Albekairy, 2013). However, given the cross-sectional nature of the data, it is difficult to deduce whether these volumetric differences are an effect of the use of beta-blockers or if these differences were inherently present in the respective patient groups. Future studies that focus on longitudinal effects of beta-blockers in AD patients could thus help shed light on the nature of the effect of this class of antihypertensive medication in the AD brain.

A better AD phenotype in AD patients taking beta-blockers (Group 2) could be attributed to a lower cerebrovascular burden in this group as measured using WMH volume. In turn, an explanation for the lower cerebrovascular burden in this group could be attributed to the significantly lower pulse pressure found in this group compared to the other two groups, as pulse pressure can substantially modulate cerebrovascular burden (Aribisala et al., 2014; Mitchell et al., 2011). A study on rats, however, did not find reductions in pulse pressure with beta-blocker treatment although pulse pressure was reduced with use of other classes of antihypertensive treatment (Christensen, 1991). A study in humans also showed that beta-blocker use did not change structural or functional properties of arteries that could affect pulse pressure (Schiffrin, Deng, & Larochelle, 1994). The same study showed that a converting enzyme inhibitor helped correct structural abnormalities in arterial structure, which aided in lowering pulse pressure (Schiffrin et al., 1994). It is thus unclear as to what mechanisms might have contributed to the observed beneficial effect of use of beta-blockers in AD patients. A study examining neuropathological hallmarks of AD in patients who were taking different

classes of antihypertensive treatment showed no differences in neuropathological burden (Affleck et al., 2020). Rather, the study showed an overall beneficial effect of antihypertensive drug use in AD patients in limiting the spread of AD pathology in patients (Affleck et al., 2020). Additionally, cardiovascular comorbidities were evenly distributed across the three groups. Therefore, it is possible that the presence of these conditions did not influence the level of cerebrovascular burden or blood pressure measurements found in the AD patients on beta-blockers compared to the other two groups.

Findings from the voxel-wise analyses show that medicated AD patients taking beta-blockers (Group 2) showed higher CBF and GMV compared to the AD patients on antihypertensive treatment except for beta-blockers (Group 1) in medial parietal, medial temporal lobe, occipital, cerebellar, orbitofrontal and brainstem regions. There was an overlap in the differences found in CBF and GMV in the left insula, left hippocampus, cerebellum and the brainstem. These brain regions are primarily supplied by the posterior circulation system, except the insula (section 2.1.1.3). This overlap could indicate that beta-blockers could be effective in preserving brain structure and CBF in brain regions that are supplied by the posterior cerebral circulation in AD patients with high blood pressure. The vulnerability of the posterior circulation system to the effects of hypertension has also been found previously (Cates et al., 2012). Assuming that the effect is causal, it is also possible that the overlap could indicate a beneficial effect of higher CBF in preserving GMV in AD patients on beta-blockers. The inverse may also be true where preservation of GMV could have resulted in a co-localised CBF signal (Yu et al., 2017). However, the use of the correction for partial volume effects in the current study might have helped overcome the limitation in inferring that a higher CBF signal is observed independent of the preservation of grey matter, as the partial volume correction helps eliminate signal due to variations in measurements of brain parenchyma (Section 4.3.6.3, Partial Volume Correction). Nevertheless, the directionality of the findings cannot be determined with the cross-sectional design used in the current study.

The overlapping findings of higher CBF and GMV in AD patients on beta-blockers (Group 2) compared to AD patients on other antihypertensive medications except for beta-blockers (Group 1) in the left hippocampus are of particular significance. The hippocampus is one of the brain regions that is significantly affected by AD, in addition to higher susceptibility of the left hemisphere to damage from AD (Donix et al., 2013; Loewenstein et al., 1989; Murphy, Jernigan, & Fennema-Notestine, 2003). The fact that the left hippocampus shows colocalised

patterns of higher CBF and GMV in AD patients with beta-blockers than those on other antihypertensive drugs except for beta-blockers might indicate that beta-blockers could be more effective in protecting the brain from the additional effects of hypertension in AD patients and therefore preventing the occurrence of a more severe radiological AD phenotype. Higher CBF in the patients on beta-blockers was primarily found in periventricular areas spanning across the medial parietal areas to the medial temporal lobe regions extending into the bilateral hippocampi. In AD, there is often a disconnection between the medial parietal areas and the MTL structures (Villain et al., 2008; section 1.6.2.1). This could again indicate that AD patients on beta-blockers may benefit through the preservation of CBF and GMV in brain regions typically affected in AD. It is also of significance that the extracted GMV and CBF signals were associated with better performance on tasks measuring abstract reasoning, attention and executive function. Preservation of GMV and CBF in brain regions that are known neural correlates of these cognitive functions further lends support to the notion that beta-blockers may be effective in protecting the brain against damage from chronically elevated blood pressure (Manns, Hopkins, & Squire, 2003). Therefore, the beneficial effect of beta-blockers could aid in preserving cognitive functions, brain structure and CBF that are impaired in AD.

In the voxel-wise analysis comparing AD patients on beta-blockers (Group 2) and AD patients on both, other classes of antihypertensive treatment and beta-blockers (Group 3), higher CBF and GMV were found in AD patients on beta-blockers only (Group 2) in the parietal, frontal, subcortical, medial temporal lobe, cerebellar and brain stem regions. These differences were similar to the differences found in the group comparison between AD patients on beta-blockers (Group 2) and AD patients on antihypertensive treatments except beta-blockers (Group 1). However, AD patients on beta-blockers showed more extensive patterns of higher CBF, but less extensive patterns in GMV compared to AD patients on both beta-blockers and other classes of antihypertensive drugs. Additionally, most differences in GMV showed an overlap with brain regions exhibiting differences in CBF in this comparison. Furthermore, the extracted GMV signal was linked with better performance on tests measuring long term memory, executive function and abstract reasoning. This could signify that the use of beta-blockers only, to treat high blood pressure in AD patients could be more beneficial in preventing a more severe clinical and radiological AD phenotype compared to other classes of antihypertensive treatment or a combination of the two.

Some group differences were also found in the performance on certain tests of cognition. The MMSE is a test that measures general level of cognitive functioning and is often used as an indicator for measuring the clinical severity of AD (Clark et al., 1999; Teng et al., 1987). Patients who were on any type of antihypertensive treatment except for beta-blockers (Group 1) had better performance on the MMSE compared to AD patients who were on a combination of beta-blockers and other types of antihypertensive treatment (Group 3). Previous work has shown that angiotensin-converting enzyme inhibitors and calcium channel blockers might be more effective than beta-blockers and diuretics to tackle the cognitive complications observed in hypertensive patients (Amenta et al., 2002). It is possible that prolonged use of classes of antihypertensive medication that did not include beta-blockers could have helped preserve a general level of cognitive functioning in these patients (Rozzini et al., 2006; Watfa et al., 2010). However, it is important to note that the baseline differences between the patient groups could be coincidental and that causal inferences cannot be drawn from these findings. Although not statistically significant, the patients in Group 1 had higher number of years in education than Group 3, which could have contributed to this pattern of findings. Nevertheless, Group 1 showed better performance on the MMSE despite presenting with lower parenchymal volumes, higher WMH load and higher blood pressure measurements than Group 3. This pattern of findings could indicate a beneficial effect of all classes of antihypertensive medication excluding beta-blockers, on general cognitive function in AD patients.

5.5.4 Limitations

Given the cross-sectional nature of the data in the current study, it is difficult to draw inferences on the causality of the findings. Therefore, in the comparison of AD patients on different classes of antihypertensive treatment it is difficult to establish whether beta-blocker treatment is associated with a less severe clinical and radiological AD phenotype. Future research with a longitudinal design exploring the effects of beta-blockers on the AD brain is needed, to establish the beneficial effect of beta-blockers. Additionally, single time point measurements of blood pressure are highly variable and may not give an indication of the level of control of blood pressure exerted by the medication (Rothwell et al., 2010a). It is also difficult to determine whether the higher blood pressure readings in the medicated group could be attributed to poor adherence, low educational attainment or poor monitoring or adjustment of medication regimes. Furthermore, it is difficult to isolate the detrimental effects of hypertension even after controlling for the presence of comorbidities. Another limitation of the

study is the lack of information on the duration of the antihypertensive treatment. Without this information, it is difficult to estimate the required duration of medication that could facilitate preservation of brain structure and function in hypertensive AD patients. Due to the prolonged asymptomatic period of hypertension, it is also difficult to identify the exact time frame for disease onset, therefore making inferences about hypertension duration and its effect on the brain remains in contention (Rosen et al., 2006). This is a limitation in most research related to hypertension. Furthermore, in the *post hoc* analysis on the medicated patients, the patient group taking beta-blockers only had only 13 participants, a significantly smaller number of participants in this group compared to the other two groups that had 24 and 34 participants, respectively. Therefore, the smaller sample size limits the inferences that can be drawn from these results.

5.5.5 Conclusions

Results from this study indicate no effect of blood pressure lowering agents in AD patients with a medical history of hypertension compared to AD patients not medicated for hypertension. A possible explanation for the absence of a beneficial effects of antihypertensive treatment in the medicated AD patients could be the similarity in hypertensive blood pressure readings found in both unmedicated and medicated AD patients. However, further breaking down the medicated and unmedicated patient groups into hypertensive and normotensive groups did not change the findings indicating that the level of blood pressure control did not influence the findings. However, a higher burden of cardiovascular comorbidities that increases cerebrovascular burden in the medicated group could offer an explanation for higher levels of blood pressure and an absence of a beneficial effect of blood pressure lowering medication in the medicated AD patients (Gelber et al., 2013; Yoshita et al., 2006). This indicates that primary prevention of modifiable cardiovascular risk factors could be key in improving the prognosis of AD and improving the effect of antihypertensive medication (Ngandu et al., 2015). Additionally, measures to improve blood pressure control through regular monitoring and evaluation of antihypertensive medication regimes and interventions to improve health literacy to increase medication adherence could also aid in preventing a more severe clinical and radiological AD phenotype (Jankowska-Polańska et al., 2016; Yasar et al., 2013).

In patients unmedicated for hypertension, negative correlations were found between pulse pressure and CBF primarily in subcortical structures and in brain regions lying in the border

zones of terminating and perforating branches of major cerebral arteries. Such arteries have delicate structures and are particularly susceptible to the adverse effects of hypertension (Gutierrez et al., 2015). The unmedicated patients had blood pressure readings within the hypertensive range. This could potentially warrant close monitoring of blood pressure in AD patients and administering antihypertensive medication to patients with blood pressure lying within the hypertensive ranges even without a history of hypertension. A previous criticism of lowering blood pressure is general reductions in CBF (which is also observed in AD) which could be detrimental to brain health (Kim et al., 2013; Muller et al., 2012). However, there are some studies that have investigated the effect of hypertensive medication on CBF and these have shown that antihypertensive treatment does not reduce CBF but can instead improve CBF in older individuals and in AD patients (Dai et al., 2008; de Jong et al., 2019). It is possible that the prolonged use of blood pressure lowering medication in hypertensive patients can protect the brain against neuropathological accumulations (such as WMH, A β plaques and NFTs) (Affleck et al., 2020; Dufouil et al., 2001). Nevertheless, baseline clinical disease severity needs to be considered before administering blood pressure lowering medication as this can have differential effects on AD neuropathological deposits in patients with mild and moderate AD (Abdullah et al., 2020). In this study by Abdullah and colleagues, a higher neuropathological burden was observed in AD patients with moderate disease severity treated with nilvadipine, a dihydropyridine calcium channel blocker (Abdullah et al., 2020). It is possible that these effects were observed due to the accumulation of irreversible insults that could not be alleviated even with antihypertensive medication. This, yet again highlights the vitality of early intervention in reducing AD risk to improve disease prognosis. Therefore, it appears that blood pressure lowering medication in hypertensive AD patients could help prevent the formation of AD and vascular pathology while protecting brain structure, CBF and cognitive function in the presence of comorbid hypertension in AD, more so in patients with mild AD.

Another explanation for the absence of a finding of the beneficial effects of antihypertensive treatment in medicated patients compared to unmedicated patients could be the differences in the effects exerted by the class of antihypertensive treatment in AD patients. The current study found a better prognostic profile of AD patients on beta-blockers only (Group 2) compared to AD patients on other classes of antihypertensive treatment except for beta-blockers (Group 1) and a combination of the two (Group 3). This finding is contradictory to findings in cognitively

normal individuals which show a beneficial effect of antihypertensive treatment except for beta-blockers on cerebral constituents and cognitive function (Davies et al., 2011; Holm et al., 2020). However, the findings from the present study are not consistent with observations in previous work on AD patients that do show some beneficial effects of the administration of beta-blockers in AD patients compared to other classes of antihypertensive drugs (Rosenberg et al., 2008).

Chapter 6: The Additional Burden of Type 2

Diabetes on the Brain in AD

6.1 Introduction

The number of individuals diagnosed with Type 2 Diabetes (T2DM) has risen to pandemic proportions, with 451 million recorded cases worldwide and it is estimated that this figure will rise to 693 million by 2045 (Cho et al., 2018b). Major contributors that increase the risk for T2DM include high rates of obesity, sedentary lifestyles (characterised by physical inactivity and consumption of food rich in calorific content), unhealthy diet, lower education and smoking (Bellou et al., 2018). Considering that all these conditions are modifiable, close attention needs to be paid toward early intervention and primary prevention. One of the caveats of the current state for the diagnosis of diabetes is that the pathology has a much earlier onset before any clinical presentations of the disease, similar to what is seen in AD (American Diabetes Association, 2002; Caballero et al., 1999; Parnetti et al., 2019; Troncoso et al., 1998). Therefore, the cascade of mechanisms detrimental to health begins long before T2DM treatment can begin, causing irreversible systemic damage that can contribute toward the development of a variety of diseases, one of which is AD (Bellou et al., 2018; Chornenkyy et al., 2019). AD and T2DM share a plethora of common neurodegenerative mechanisms, which has even resulted in AD being coined ‘Type 3 diabetes’ (de la Monte, Tong, & Wands, 2018). Considering that pathological processes and alterations to cerebral properties commence long before the presentation of clinical symptoms in both diseases and that known risk factors for these diseases are modifiable and the growing number of individuals diagnosed with T2DM and AD, there is an urgent need to increase measures for primary prevention.

6.1.1 Neural correlates of T2DM and AD

As a result of the pathological mechanisms seen in T2DM, there are several downstream effects that can alter the microvasculature and macrovasculature of the brain (Caballero et al., 1999; Stratton et al., 2000). Resultant alterations in the brain can manifest as structural and functional neuronal changes (Moulton et al., 2015; Wu et al., 2017; Xia et al., 2013b). In the presence of AD pathology, the cumulative effects of T2DM and AD could thus significantly deteriorate brain structure and function that could result in a more severe radiological AD phenotype.

6.1.1.1 Structural neuroimaging in T2DM and AD

6.1.1.1.1 Grey Matter Volume

Considering the gross effect of T2DM on brain structure, along with observed global atrophy, there are specific brain regions that are vulnerable to the downstream pathological mechanisms of the disease (Biessels & Reijmer, 2014). The majority of the literature points towards T2DM-related atrophy in the MTL structures and subcortical brain regions (Brundel, Kappelle, & Biessels, 2014; Moulton et al., 2015). The hippocampus (a structure heavily implicated in AD) is influenced by T2DM pathology, as it is more susceptible to damage from downstream hypoxic and hyperglycaemic conditions, relative to other brain regions (Anan et al., 2010; Biessels & Reagan, 2015; den Heijer et al., 2003; Gold et al., 2007; Hayashi et al., 2011; Kamiyama et al., 2010).

Evidence shows that maintaining glycaemic control in T2DM is a recurring challenge and glucose homeostasis has been shown to have an effect on brain structure (section 2.1.2). Several studies have shown a negative effect of hyperglycaemia and poor glycaemic control on GMV. A longitudinal study showed that higher blood glucose was associated with lower global and regional brain volumes in T2DM patients (Walsh et al., 2017). In contrast, a study showed that glycaemic control was not associated with neuroimaging measures although a T2DM diagnosis was associated with these measures (Raffield et al., 2016). It was suggested that the variability in neuroimaging measures found in the study could be attributed to mechanisms grounded in vascular comorbidities seen in T2DM as opposed to glycaemic control (Raffield et al., 2016). Moulton and colleagues expanded on this view by suggesting that hippocampal atrophy may be the result of common neurodegenerative mechanisms between AD and T2DM, and that global and other regional atrophy could be attributed to vascular dysfunction (Moulton et al., 2015). However, a different study showed that glycaemic control could help slow down the progression of grey matter atrophy (Erus et al., 2015). It is possible that the study conducted by Erus and colleagues found an association between blood glucose levels and GMV which was absent in the study by Raffield and colleagues, due to the division of participants into groups according to disease duration which was not done in the latter study (Erus et al., 2015; Raffield et al., 2016). Inclusion of individuals with variable diabetes duration could have therefore dampen the effect of glycaemic control seen on GMV in the study (Raffield et al., 2016).

Insulin is integral to several key processes in the brain and another possible mechanism influencing grey matter atrophy in T2DM is IR (Arnold et al., 2018). Structural changes resulting from IR have previously been observed in AD (Mullins, Mustapic, Goetzl, & Kapogiannis, 2017; Neth & Craft, 2017). In addition to the presence of insulin receptors in the hippocampus, the BBB in the blood vessels surrounding the hippocampus is highly vulnerable to ischemic injury, due to the delicate vasculature supplying this region and the aforementioned vascular dysfunction seen in T2DM and AD (Arnold et al., 2018; De Felice, 2013; Erickson & Banks, 2013). Reduced rCBF to the hippocampus has detrimental effects on hippocampal grey matter, which could indicate why this region is susceptible to T2DM effects (Wirth et al., 2017b). Additionally, IR-mediated reductions in CBF and the depositions of AD-like pathological accumulations in this region can also result in regional and global alterations to GMV (Arnold et al., 2018; Dineley, Jahrling, & Denner, 2014; Hwang & Lee, 2016). Hippocampal atrophy is one of the primary hallmarks of AD and the fact that the hippocampus is particularly vulnerable to the pathological effects of T2DM, could suggest a common link between T2DM and AD (Mattsson et al., 2016).

Apart from exerting regional effects in the hippocampus and MTL regions, T2DM can cause global and regional alterations in other grey matter structures. Studies on patients with T2DM and their age-matched controls found that patients with T2DM had lower GMV in the parieto-occipital areas compared to controls (Ahtiluoto et al., 2010; Nelson et al., 2009). However, these studies used region of interest analyses as opposed to whole brain voxel-based morphometric procedures, limiting the extent of brain areas covered in the analysis. A meta-analysis exploring the effects of T2DM on brain structure identified structural deficits in the basal ganglia, hippocampus, orbitofrontal cortex and the occipital lobe (Moulton et al., 2015). In conjunction with these results, Kumar and colleagues found that AD pathology was associated with volumetric deficits seen in subcortical structures namely, the striatum, putamen and thalamus (de Jong et al., 2008). An explanation for volumetric deficits in the subcortical structures could lie in the susceptibility of these regions to damage inflicted by vascular dysfunction as seen in AD and T2DM. The delicate vasculature of deep brain areas (such as the lenticulostriate arteries that supply the basal ganglia) is highly vulnerable to ischaemic insult and damage to these arteries could result in hypoperfusion-mediated neuronal damage (Kalaria, 2016; Umemura, Kawamura, & Hotta, 2017). In the presence of microvascular and macrovascular complications resulting from T2DM, arteries perforating deep brain regions are

even more susceptible to damage (Gutierrez et al., 2015; Rosner et al., 1984; Soustiel et al., 2001). Atrophy of deep-seated brain regions such as the basal ganglia is also seen in AD, which has also been associated with consequent cognitive impairment (Tuokkola et al., 2019; Yi et al., 2016). A meta-analysis on T2DM found lower GMV in temporal brain regions (Wu et al., 2017). Yet another meta-analysis found lower GMV in the regions implicated in the cortico-striatal limbic networks namely, temporal gyri, the cingulate cortex, precuneus and left basal ganglia extending into the parahippocampal gyrus in individuals with T2DM (Liu et al., 2017). The pattern of atrophy seen in the limbic areas seems to correspond with the ‘disconnection’ of the regions in the DMN typically seen in AD, indicating a concatenation in the patterns of GMV deficits seen in T2DM and AD (section 1.6.1.1; section 1.6.2.1).

Considering the overlap between areas affected by AD and T2DM, a cumulative detrimental effect is expected in individuals affected by both conditions. There is a current gap in the literature where studies using a specific focus on the additional effects of T2DM in AD patients, are lacking. There are several studies that look at grey matter atrophy and associated cognitive impairment or dementia in T2DM patients that again point towards the vulnerability of MTL structures in patients diagnosed with T2DM with mild cognitive impairment (Bruehl et al., 2009; Groeneveld et al., 2018; Roberts et al., 2014; Zhang et al., 2014b). In one study, T2DM patients with cognitive impairment presented with higher grey matter atrophy, especially in the right temporal lobe and subcortical structures than T2DM patients without cognitive impairment (Groeneveld et al., 2018). In conjunction with past studies, hippocampal and whole brain atrophy was proposed to be a downstream effect of neurodegenerative mechanisms while formation of subcortical microbleeds was proposed to be a consequence of vascular dysfunction (Moulton et al., 2015; Roberts et al., 2014). In a different study, MCI patients with T2DM showed lower GMV in the left temporal lobe compared to MCI patients without T2DM (Zhang et al., 2014b). It appears grey matter in the temporal lobe is specifically susceptible to the effects of T2DM in the MCI stages.

Therefore, the overall evidence is suggestive of a negative effect exerted by AD and T2DM, where T2DM can significantly increase the risk of AD or the progression of the disease (Ciudin et al., 2017; Roberts et al., 2014). The additional burden caused by T2DM-mediated changes in GMV that add on to the characteristic deficits seen in AD can amplify the grey matter atrophy observed. Global and regional grey matter changes may be the result of the interaction between several pathological mechanisms, which include IR, glucose dysregulation,

pathological depositions, neurodegeneration and vascular dysfunction, where the majority of the structural changes are attributed to vascular dysfunction. There is considerable overlap between the brain regions affected by the two conditions, which is most evident in the MTL and subcortical structures.

6.1.1.1.2 White Matter Integrity

T2DM has a significant effect on the cerebral macro and microvasculature that cause changes in CBF that specifically influence white matter since it is more prone to vascular insults as opposed to grey matter (Wang et al., 2016). T2DM has a profound and widespread effect on WMI. There are four main indices of diffusivity that measure the anisotropy of water molecules in axons. These indices are a proxy for the diffusion of water molecules along axons and can reveal information about the extent of white matter damage (Alexander et al., 2007). Several studies found associations with various diffusivity indices in the uncinate fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus, cingulum bundle, corpus callosum, fornix, parahippocampal white matter, hippocampal white matter, arcuate fasciculus, thalamic radiations, and the internal and external capsules in T2DM patients, that indicated poor white matter health in these tracts (Hoogenboom et al., 2014; Hsu et al., 2012; Kim et al., 2016; Maillard et al., 2015; Tan et al., 2016; Yau et al., 2014; Zhang et al., 2014a). Most of the above studies used FA as a measure of WMI. The white matter tracts showing reduced white matter health in T2DM coincided with quite a few areas corresponding to the neurodegenerative changes seen in AD (such as the uncinate fasciculus and cingulum bundle), indicating overlapping degenerative patterns in T2DM and AD (section 1.6.1.2). Additionally, damage to the white matter tracts in T2DM has been associated with cognitive deficits in domains of memory, executive function, processing speed and visuospatial processing, most of which may also be presented in AD across different stages (Hoogenboom et al., 2014; Hsu et al., 2012; Kim et al., 2016; Maillard et al., 2015; Tan et al., 2016; Yau et al., 2014; Zhang et al., 2014a; section 1.3.4). However, these studies have variable limitations including small sample sizes, significant differences in participant demographics and lack of corrections for multiple comparisons.

Although the role of the cerebellum is unclear in the pathological presentations of structural deficits in AD and T2DM, studies have previously identified structural white matter deficits in the cerebellum and tracts arising from this structure in the presence of T2DM (Hoogenboom et

al., 2014; Yau et al., 2014; Zhang et al., 2014a). The limited findings in the cerebellum are attributed to the exclusion of this structure from most research analyses due to its limited involvement in AD neurodegeneration and T2DM pathogenesis (Kumar et al., 2008; Reijmer et al., 2013b). Although most studies exploring the effect of T2DM on WMI used FA as a diffusivity index, one of the above studies looking at different diffusivity indices showed lower FA and higher mean diffusivity and axial diffusivity in individuals with T2DM in comparison to controls. These differences were found specifically in the white matter tracts connecting regions of the DMN and also a lot of white matter tracts connecting different regions involved in the limbic system (Tan et al., 2016). This finding was consistently reported in other studies that showed reduced WMI in patients with T2DM in white matter tracts connecting regions of the DMN such as the cingulum bundle and parahippocampal white matter (Hoogenboom et al., 2014; Hsu et al., 2012; Qi et al., 2017). Again, this is representative of the ‘disconnection’ of brain regions typically observed in AD (section 1.6.2.1).

As seen with grey matter, the challenge to achieve optimal glycaemic control in T2DM patients also tends to influence white matter structures. However, there is a fundamental difference in glucose activity between grey matter and white matter, where the rate of cerebral glucose metabolism is three times lower in white matter than grey matter, which could influence the effects T2DM has on white matter (de Graaf et al., 2001; Pan et al., 2000). Previous studies looking at the effect of glucose regulation on WMI have shown that increased levels of fasting blood glucose can cause reductions in WMI, specifically in the inferior longitudinal fasciculus, thalamic radiations, short association fibres and the corpus callosum (Bryan et al., 2014; Weinstein et al., 2015). IR (which affects glucose metabolism) can also alter WMI in the corpus callosum, corona radiata, fornix, and inferior fronto-occipital fasciculus (Nouwen et al., 2017; Ryu, Coutu, Rosas, & Salat, 2014). Reductions in WMI in tracts affected by IR and glucose dysregulation are less frequently associated with those seen in AD, with most studies showing an effect of these mechanisms on frontal lobe white matter (Groeneveld et al., 2018; Hoogenboom et al., 2014; Hsu et al., 2012; Reijmer et al., 2013a). It has been established that T2DM and AD tend to affect MTL structures predominantly while obesity and other vascular comorbidities mediate more frontal lobe damage (Brooks et al., 2013; den Heijer et al., 2003; Jack et al., 1998; Raji et al., 2010; Raz et al., 2003). Therefore, it is possible that other downstream mechanisms of T2DM (such as vascular dysfunction) might also contribute toward the typical pattern of white matter damage seen in the disease, and that this pattern of damage is reflective of more severe neurodegenerative processes in AD. Changes in white

matter mediated by IR and glucose dysregulation might therefore be additional to the white matter damage present in these two conditions independently.

By far, there is no research on WMI in T2DM patients who have already been diagnosed with AD dementia. However, several studies have looked at different forms of mild cognitive impairment in T2DM to look at the effect on WMI (Hoogenboom et al., 2014; Hsu et al., 2012; Tan et al., 2016; Yau et al., 2009). One such study used DTI parameters to look at WMI in diabetic patients with and without MCI and healthy controls. The study found lower FA and higher mean diffusivity and radial diffusivity in diabetic patients with MCI when compared to those without MCI (Xiong et al., 2016). These differences indicated lower integrity of white matter tracts in the frontal lobe (corona radiata and internal and external capsules) and the temporal lobes (posterior thalamic radiations and bilateral hippocampi) in diabetic patients with MCI compared to those without (Xiong et al., 2016). Other studies on T2DM patients with cognitive impairment showed similar findings, with additional reductions in WMI in the uncinate fasciculus, inferior longitudinal fasciculus, cingulum and corpus callosum (Hoogenboom et al., 2014; Reijmer et al., 2013a; Yau et al., 2009). However, a study showed no difference in WMI between T2DM patients with and without MCI indicating inconsistent findings (Groeneveld et al., 2018). Therefore, reduced WMI in the frontal lobe and MTL structures could be indicative of the combined effects of AD and T2DM pathology.

6.1.1.1.3 White Matter Hyperintensities

Considering the vascular complications of T2DM and the formation of micro brain bleeds, a brief glance into research on WMH in T2DM patients is essential. The formation of WMH in T2DM patients has previously been attributed to the macrovascular and microvascular changes that can alter cerebral vasoregulation (Novak et al., 2006). A study that followed up patients with T2DM and healthy controls over a span of four years found higher WMH and grey matter atrophy in both groups with relatively similar rates of progression with a slightly higher rate of progression in T2DM patients. This could be due to the short follow-up period of four years as T2DM-related changes in brain structure were proposed to occur over a longer period of time (De Bresser et al., 2010). Another study found no differences in WMH between controls and individuals with T2DM (Hsu et al., 2012). The average disease duration of T2DM in these individuals was 5.4 years (Hsu et al., 2012). A longer disease duration may be needed to detect

changes in WMH resulting from chronic vascular dysfunction in T2DM. In support of this view, another study showed no association between WMH load and structural deficits seen in T2DM patients (Reijmer et al., 2013a). Diabetes duration in these patients was an average of 8.6 years. However, the average age of the participants was 70 years. Higher age could have weakened the observable harmful effect of T2DM-mediated vascular dysfunction (Reijmer et al., 2013a). In contrast, a different study that looked at WMH in individuals (~66years) with an average diabetes duration of 8 years, found larger WMH volumes in individuals with T2DM (Jongen et al., 2007). Therefore, the harmful effect of WMH in T2DM patients may depend on several factors such as the duration of the disease and age of the participants. A different study proposed that T2DM and WMH might be independent predictors of cognitive decline (Verdelho et al., 2010). Therefore, the additive effect of WMH resulting from chronic vascular dysfunction in T2DM could result in cognitive decline additional to that which is seen in T2DM.

6.1.1.2 Functional neuroimaging in T2DM and AD

6.1.1.2.1 Resting-state functional magnetic resonance imaging (rs-fMRI): The default mode network (DMN)

Functional connectivity is derived from the blood oxygenation level dependent (BOLD) response or how much blood is consumed in response to neuronal activity. Metabolic abnormalities and vascular deficits can have a huge impact on modulating this activity (Binkofski & Seitz, 2004; Duarte et al., 2015). Since T2DM is accompanied by pathological cascades that can impinge on cerebral vascular and metabolic functions, functional connectivity is significantly altered in the disease (Chen et al., 2015a; Hoogenboom et al., 2014; Musen et al., 2012). T2DM seems to exert specific effects on different networks in the brain, mainly regions of the DMN. Studies looking at seed-based connectivity have found reduced connectivity from the hippocampus, posterior cingulate gyrus and thalamus to areas of the DMN, cerebellum, frontal and temporal lobes in T2DM patients (Xiong et al., 2016). Reduced connectivity in these regions also correlated with lower performance on tasks involving memory, executive function, attention, processing speed and visual function (Chen et al., 2014; Chen et al., 2015a; Musen et al., 2012; Zhou et al., 2010a). On the other hand, whole-brain analysis research, without an *a priori* identification of regions of interest has found significant reductions in functional connectivity within the DMN and between the DMN and

other brain regions (Chen et al., 2014; Hoogenboom et al., 2014; Xia et al., 2015a; Xia et al., 2015b; Xia et al., 2013b; Zhou et al., 2010a). These reductions have been hypothesized to be affected by T2DM-related mechanisms such as IR and glucose dysregulation, where functional connectivity in the MTL seems to be particularly vulnerable to IR (Chen et al., 2014; Cui et al., 2015; Hoogenboom et al., 2014; Musen et al., 2012; Xia et al., 2015b; Xia et al., 2015b; Xia et al., 2013b).

As observed in the structural studies, there seems to be a predominant effect of T2DM on the MTL structures. A study looking at hippocampal connectivity within the DMN found lower functional connectivity among T2DM patients between the hippocampus and the frontal lobe (anterior cingulate gyrus, middle frontal gyrus and frontal gyrus), temporal lobe (fusiform gyrus and temporal gyrus) and parietal lobe (precuneus, posterior cingulate gyrus and inferior parietal lobe) (Chen et al., 2014; Xia et al., 2015b). Other studies have found similar disruptions in functional connectivity between the MTL structures and frontal regions and the posterior cingulate gyrus in T2DM patients compared to healthy controls (Zhou et al., 2010a). Reduced functional connectivity in the fronto-temporal areas could thus be explained as a reflection of the prolonged effects of T2DM duration, IR and hyperglycaemia seen in T2DM.

Analogous to lower functional connectivity, higher functional connectivity can also be indicative of underlying neuropathological mechanisms. Increased functional connectivity could be reflective of maladaptive neural mechanisms in response to reduced brain function in other regions or deteriorating brain structure (Chen et al., 2014; Hoogenboom et al., 2014; Musen et al., 2012). These mechanisms could be explained by the maladaptive compensatory neuroplastic changes that could arise in response to deficits in neural structure, disease related brain damage and ischaemic insult (Cui et al., 2016; Park and Reuter-Lorenz, 2009; Xia et al., 2015a). Such increases in functional connectivity were seen in a resting state functional MRI study by Xia and colleagues, where higher neural activity (as measured using amplitude of low frequency fluctuation) was found in the bilateral posterior cerebellar lobe and the right cerebellar culmen, which was decreased in temporal and occipital areas (Xia et al., 2013b).

In addition to alterations in functional connectivity in the DMN, T2DM can also alter connectivity in other brain networks such as attentional networks (Xia et al., 2015a). A study showed that patients with T2DM with MCI seemed to exhibit problems in the executive control network while T2DM patients without MCI and healthy controls showed no alterations in these

networks (Yang et al., 2016). Since the executive control network is implicated in executive function, with components in the frontal lobe, it is possible that other vascular mechanisms as mediated by conditions such as obesity (that can be comorbid in T2DM) might explain the observed deficits (Colosia, Palencia, & Khan, 2013; Daousi et al., 2006; Dong, Lin, & Potenza, 2015; Herrmann et al., 2019). There is evidence that AD patients have deficits in connectivity in the frontal networks implicated in executive function (Menon, 2011; Menon, 2013). It thus appears that reduced functional connectivity is seen between the hippocampus, posterior cingulate gyrus and frontotemporal regions in T2DM patients. This resembles a pattern of ‘disconnection’ between the anterior, inferior and posterior DMN regions also seen in AD, pointing towards common cerebral properties affected by both conditions (Agosta et al., 2012). This could again point towards how the presence of T2DM in AD patients could increase radiological disease severity.

6.1.1.2.2 *Perfusion studies*

T2DM has significant effects on cerebral vascularisation through myriad mechanisms (Fukuda et al., 2015; Groeneveld et al., 2018). These changes can alter rCBF that can have an impact on neural structure and function (Moulton et al., 2015; Xia et al., 2015a). A number of studies have explored the impact of T2DM on CBF using ASL. One such study found lower CBF in T2DM patients in the hippocampus, inferior temporal, inferior parietal and frontal brain regions compared to controls. These reductions in CBF were associated with poor performance on tasks of memory, executive function and processing speed (Bangen et al., 2018). These deficits in cognition and CBF are similar to those presented in AD (section 1.3.4 and 1.6.2.3.1). A different study examined the contribution of cerebral vasoregulation and chronic inflammation to structural atrophy in T2DM using ASL. Higher inflammation and endothelial integrity were associated with volumetric deficits in temporal and parietal regions that were also associated with cognitive deficits (Last et al., 2007). This could point towards how vascular dysfunction in T2DM can negatively influence brain structure. However, the latter study failed to perform a whole brain analysis, which could have enhanced regional effects in CBF changes. Again, temporo-parietal CBF abnormalities are one of the first presentations in AD pointing towards similar brain regions being affected in AD and T2DM (Dai et al., 2008).

In addition to the similarities seen with the typical AD pattern of hypoperfusion in T2DM, the condition can also alter CBF in the subcortical brain regions. A study found hypoperfusion in

T2DM patients compared to controls in subcortical brain regions that was most pronounced in the caudate nucleus and nucleus accumbens without any associated cortical atrophy or deficits in cognitive function (Jansen et al., 2016). The reason for the findings in the CBF reductions in subcortical regions could partly lie in the microvascular architecture irrigating this region. Blood vessels are generally deeper and fewer in number in the subcortical regions, making them more vulnerable to vascular insults (Jansen et al., 2016). Additionally, blood vessels supplying these regions have narrower lumen which exposes these arteries to the detrimental effects of embolic and ischemic events (Gutierrez et al., 2015; Moody et al., 1990; Rosner et al., 1984; Soustiel et al., 2001). A different study examining the effects of CBF on cognition using angiography found no correlation between the two variables in patients with T2DM (Novak et al., 2011). The latter two studies failed to control for partial volume effects, which could explain the absence of cognitive deficits in the presence of hypoperfusion. Failure to control for these effects can distort the CBF signal and therefore influence the association of the signal with cognitive function (Section 4.3.6.3, Partial Volume Effects). Therefore, vascular changes mediated by downstream effects of T2DM seem to alter brain structure and to an extent, cognitive function.

In addition to the vascular complications propagated by T2DM, other associated mechanisms such as IR can influence CBF as well. A study found lower CBF associated with IR in IR patients, but not in patients with T2DM (Rusinek et al., 2015). The absence of hypoperfusion in T2DM patients could be attributed to aggressive medication regimes administered to these patients to control levels of glucose, cholesterol and blood pressure (Rusinek et al., 2015). Findings from another study in cognitively normal asymptomatic individuals with IR showed lower CBF in frontal and temporal brain regions (Hoscheidt et al., 2017). In yet another study, IR mediated hypoperfusion in T2DM patients in the posterior cingulate cortex/precuneus and occipital lobe, was associated with cognitive deficits in visuospatial construction and visual memory, respectively (Cui et al., 2017). These studies show that IR can independently alter CBF that could manifest as cognitive deficits, also highlighting the vital role of insulin in promoting cerebrovascular health. In fact, a study on healthy individuals administered with intranasal insulin showed marked improvements in cerebral parenchymal perfusion (Akintola et al., 2017). Parallel perturbations in glucose homeostasis can also result in detriments to CBF (Desouza, Bolli, & Fonseca, 2010; Loader et al., 2015).

The overall evidence suggests that vascular deficits and other downstream pathological mechanisms resulting from T2DM-related complications can impair CBF and consequently brain structure and function. The CBF deficits in the above studies have been found in brain regions that are predilection sites for hypoperfusion in AD (Bangen et al., 2018; Cui et al., 2017; Jansen et al., 2016; Last et al., 2007). Hypoperfusion in these sites (MTL and medial parietal regions) in T2DM has also been associated with cognitive deficits typically seen in AD (Bangen et al., 2018). The resemblance between the pattern of hypoperfusion in brain regions affected by AD and T2DM independently, again points towards how T2DM can increase the radiological severity of AD. In the presence of both conditions, this might imply that the additional burden resulting from comorbid T2DM could manifest as more severe radiological deficits and accelerated disease progression. Although several studies have examined how lower CBF in T2DM can be associated with cognitive impairment, so far no studies have explored the relationship between CBF and T2DM in MCI or AD patients.

The above neuroimaging evidence shows that T2DM has a clear detrimental effect on brain structure and function. Studies that highlight the effect of comorbid T2DM in AD however, are sparse.

6.2 Aims and Hypotheses

By far, no study has used multi-modal neuroimaging to explore the effects of comorbid T2DM in AD patients. The primary aim of the current chapter is to use multimodal MRI to show that the additional burden caused by vascular dysfunction and other pathological mechanisms seen in T2DM could be linked with damage to brain structure and alterations in cognitive function, that could exacerbate the insults inflicted by AD and normal ageing. This will be done by comparing three groups of participants using maps of GMV, WMI and CBF derived from multimodal MRI scans. The groups were divided as follows: Group 1: AD patients with T2DM, Group 2: AD patients without T2DM, Group 3: Cognitively normal individuals without T2DM. The patient groups consisted of patients across the AD spectrum with MCI or mild to moderate AD dementia. To achieve the primary aim, AD patients with T2DM would be compared with AD patients without T2DM to examine differences in neuroimaging parameters and cognitive function. In order to strengthen the primary aim, the secondary aim of the study was to compare the AD patient group without T2DM to the CN group to verify that the former group represented the typical deficits seen in AD patients. AD patients with T2DM will then be compared with CN individuals to explore whether the additional burden of T2DM in AD would show more extensive deficits in neuroimaging parameters and cognition. Overall, we expected to find structural deficits in regions displaying hypoperfusion. We hypothesised that we would observe the following differences:

AD patients with T2DM vs AD patients without T2DM: AD patients with T2DM would present with lower cerebral indices than AD patients without T2DM. With respect to GMV, these detriments were expected in subcortical and medial temporal lobe regions while differences in WMI were expected in the tracts originating from these regions and tracts across the DMN. Hypoperfusion would be seen in grey matter areas and in the vicinity of white matter tracts connecting these grey matter regions, especially in the limbic and periventricular areas. These deficits would be associated with detriments in domains of memory and executive function.

AD without T2DM vs CN: AD patients without T2DM would present with deficits in all cerebral indices in the MTL regions in addition to other areas typically affected by AD, mainly in regions involved in the DMN such as the medial parietal lobe. These deficits would mainly be associated with detriments in the memory domain.

AD patients with T2DM vs CN: AD patients with T2DM would present with widespread deficits in cerebral indices that would resemble a combination of the effects observed in the former two comparisons. These deficits would be associated with detriments in a variety of cognitive domains, with the strongest associations found in the memory domain.

6.3 Methods

6.3.1 Participants

The present study was designed to compare structural and perfusion differences among 72 participants, 48 of whom were patients across the AD spectrum with and without T2DM, with 24 patients in each group and an independent group of 24 CN individuals. The groups of AD patients (with and without T2DM) contain patients across the AD spectrum. These include patients with MCI and patients with mild to moderate ADD. Initially, 29 AD patients (including MCI) were identified from the database who had T2DM; from this initial sample, 5 patients had to be excluded due to unavailability of scans. Participants from this subset of patient were then used to find participants in the other two groups that were matched for age, sex, centre of recruitment and AD diagnosis (only for the patient groups). Details pertaining to consent, inclusion and exclusion criteria for the study and the diagnostic criteria used to characterise patients as ADD or MCI are specified in section 4.3.1. This study involved participants recruited across Sheffield, UK, Kuopio, Finland and Venice Italy and details about the recruitment for these participants have been included in sections 4.3.1 & 5.3.1. Demographic characteristics of the patients have been included in Table 6.1.

6.3.2 Neuropsychological Assessment

The neuropsychological assessment was administered as a battery of tests that measured performance on several cognitive domains including tests of memory (prose memory tests, semantic fluency), attention (digit span-forward), executive function (stroop task, digit span-backward, phonemic fluency), and language (similarities test, confrontational naming). For a detailed description of the assessment, please refer to section 4.3.4.

6.3.3 Physical Assessment

As specified in the previous experimental chapters, all participants underwent physical assessments (section 4.3.2). The assessment included a health questionnaire pertaining to lifestyles habits that included diet, smoking and physical activity. Part of the assessment also included recording the participants' medications and other medical conditions. Diabetes status for the AD patients that was obtained during these assessments was used to identify AD patients with T2DM in the present study. HbA1c values were not collected at the time of recruitment.

6.3.4 Imaging protocol

The imaging protocol for T1-weighted, T2-weighted, FLAIR, DTI and ASL MRI scans has been specified in section 4.3.5.

6.3.5 Preprocessing

For the procedure carried out for the preprocessing of T1-weighted MRI scans using voxel-based morphometry, please refer to section 4.3.6.1, to section 4.3.6.2 for the preprocessing of DTI data, to section 4.3.6.3 for the preprocessing of the ASL scans and to section 4.3.6.4 for the preprocessing of the FLAIR images to obtain parameters of WMH.

6.3.6 Statistical analysis

6.3.6.1 Demographic variables

The participants across the three groups were matched for age, sex and centre of recruitment. Group comparisons were run in SPSS to compare the three groups to test for differences in demographic characteristics as specified in section 4.3.7.1.

6.3.6.2 Cognitive variables

Group comparisons were run to assess the differences between the three groups on cognitive tests according to the steps outlined in section 4.3.7.2.

6.3.6.3 Voxel-based morphometry

An ANCOVA was run to assess the volumetric differences between AD patients with and without T2DM and CN controlling for TIV. TIV was used as a covariate to account for differences in head size (Groot et al., 2017; Stern, 2009). Sex, centre of recruitment and disease diagnosis were not included as covariates as the participants were matched for these parameters. Blood pressure was not included as a covariate despite the fact that T2DM significantly alters blood pressure as only a single time point measurement was available, and this type of measurement is highly variable through the day and from visit to visit (Lim et al., 2019). The results were thresholded at $p < 0.001$ and 500 voxels at the set level. Justifications for thresholding decisions are included in section 4.3.7.3. Three separate ANCOVAs were run comparing the groups as follows: AD with T2DM vs AD without T2DM, AD without T2DM vs CN and AD with T2DM vs CN. In all the analyses, a threshold of a family-wise error

corrected value of $p < 0.05$ was used to identify significant voxels at the cluster level. Therefore, all results were corrected for multiple testing at the cluster level. Additionally, all the results were checked by applying the family-wise error corrected value of $p < 0.05$ at the set level to examine those results that survived more stringent thresholds. Additionally, two contrasts were run for each of the analyses to test a two-tailed hypothesis.

6.3.6.4 Tract-based spatial statistics

The statistical analyses for the diffusivity measures were run using the ‘randomise’ tool in FSL. First, a data matrix was created containing information about group assignment and covariates used to perform the group comparisons. TIV was included as a covariate and used as a measure of brain reserve (Stern et al., 2018). In fact, Stern and colleagues outline the necessity for using brain reserve as a confounding factor in neuroimaging analysis (Stern et al., 2018). The data matrices to compare the groups were created as specified in section 5.3.7.4.1. The same contrasts and design matrices were used for the comparison of all diffusivity measures across the three groups. The groups were compared as follows: AD with T2DM vs AD without T2DM, AD without T2DM vs CN and AD with T2DM vs CN. Following this analysis, the threshold of the significance map was inverted due to the nature of the output and cluster information was extracted from the results from each of the contrasts. The threshold-free cluster enhanced images were used to mask voxels in the raw images using $p < .05$ (Smith & Nichols, 2009). The MNI co-ordinates of the peaks of the significant white matter tracts were then extracted to identify the white matter tracts as specified in section 4.3.7.6.

6.3.6.5 Arterial spin labelling

Similar to the voxel-based morphometry analysis, an ANCOVA was run to examine perfusion differences across the three groups, controlling for TIV, using the smoothed and normalised perfusion maps obtained from the preprocessing of ASL data using both contrasts. The groups were compared as follows: AD with T2DM vs AD without T2DM, AD without T2DM vs CN and AD with T2DM vs CN. At the set level, a threshold of $p < .001$ and 500 voxels was used to identify clusters that emerged significant. All the analyses were thresholded at a family-wise error corrected value of $p < .05$ to identify significant voxels at the cluster level. Therefore, all results were corrected for multiple comparisons at the cluster level. Justifications for thresholding decisions are included in section 4.3.7.5.

6.3.6.6 WMH

Non-parametric correlations (Spearman correlation) were run to examine the association between WMH volume and performance on neuropsychological tests for the three groups independently.

6.3.6.7 Post hoc analysis

Identification of significant brain regions and signal extractions from these brain regions was done using the methods specified in section 4.3.7.6.2. The extracted signals were then correlated with cognitive tests and WMH volume to examine whether the extracted signal was associated with poor performance in cognitive domains and the extent of vascular burden. These correlations were performed in SPSS and non-parametric tests (Spearman correlations) were performed on those variables that violated the assumptions of normality of distributions.

6.4 Results

6.4.1 Demographic characteristics

In terms of their distributions only MMSE, WC and WMH volume had non-parametric distributions whereas the rest of the demographic variables had non-parametric distribution. After comparing the three groups on their demographic characteristics there were no significant differences in age, BMI and TIV while the groups differed on MMSE, years of education, WC, GMV, WMV, CSF and WMH volume. The analysis revealed that CN had higher years of education than AD patients without T2DM, $t(46) = -2.61, p = .012$, and AD patients with T2DM, $t(46) = -2.71, p = .007$. There was no significant difference in years in education between AD patients with and without T2DM. As expected, CN also had higher MMSE scores than AD patients without T2DM, $U = 101.50, p < 0.001$, and AD patients with T2DM, $U = 116.50, p < 0.001$. There was no significant difference between AD patients with and without T2DM in MMSE. With respect to WC, CN had higher WC than AD patients without T2DM, $U = 116.50, p < 0.001$. There was no significant difference in WC between the two patient groups or between the CN group and AD patients with T2DM.

Additionally, CN had higher GMV than AD patients with T2DM, $t(46) = -5.25, p < 0.001$, and AD patients without T2DM, $t(46) = -3.03, p = .004$, while AD patients without T2DM had higher GMV than AD patients with T2DM, $t(46) = -2.83, p = .007$. There was no significant difference in WMV between the two patient groups, while CN showed higher WMV than AD patients without T2DM, $t(46) = -2.40, p = .021$ and AD patients with T2DM $t(46) = -2.84, p = .007$. AD patients with T2DM had more CSF than CN $t(46) = 2.71, p = .009$. No other significant group differences were found in CSF. Moreover, there was no significant difference in WMH volume between the patient groups while CN had lower WMH volume than AD patients without T2DM, $U = 185.00, p = .034$ and AD patients with T2DM $U = 169.00, p = .014$. The groups were also significantly different in terms of the distribution of APOE genotypes and the number of APOE $\epsilon 4$ carriers. These group differences were expected between the groups. Comparisons between the groups and the respective statistics can be found in Table 6.1. Means and standard deviations for variables with non-parametric distributions are included in Appendix B, Table B6.1. Each group had 8 males and 14 females. Additionally, there were 8 participants from Sheffield (United Kingdom), 13 participants from Kuopio (Finland) and 3 participants from Venice (Italy) in each group.

Table 6.1 Demographic characteristics of AD patients with and without T2DM and CN reported using means and standard deviations for parametric data and medians and interquartile ranges for non-parametric data

Demographic variable	AD with T2DM (<i>n</i> = 24)	AD without T2DM (<i>n</i> = 24)	CN (<i>n</i> = 24)	Statistic
Parametric tests^a	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>F</i>
Age (in years)	71.29 (9.21)	71.58 (8.84)	68.50 (8.60)	0.88
Education (in years)	10.58 (2.77)	10.63 (3.32)	13.29 (3.76)	5.29**
BMI (kg/m ²)	27.72 (5.49)	25.67 (4.10)	28.25 (4.20)	2.07
GMV (in ml ³)	532.61 (70.62)	584.28 (55.09)	639.71 (70.86)	15.84***
WMV (in ml ³)	383.47 (63.11)	398.62 (39.99)	436.611 (66.47)	5.40**
CSF (in ml ³)	525.83 (153.46)	465.92 (130.73)	412.66 (134.89)	3.92*
TIV (in ml ³)	1441.92 (171.28)	1448.82 (131.80)	1488.98 (196.72)	0.55
Non- Parametric tests^b	<i>Mdn</i> (<i>IQR</i>)	<i>Mdn</i> (<i>IQR</i>)	<i>Mdn</i> (<i>IQR</i>)	<i>H</i>
MMSE	26 (24 – 28)	25 (24 – 27)	29 (27 – 29)	19.06***
WC	97 (87 – 110)	95 (86 – 102)	106 (101 – 112)	11.21**
WMH volume (in ml)	4.48 (1.53 – 12.87)	3.30 (1.23 – 9.14)	1.14 (0.29 – 6.24)	7.25*
Chi square tests^c	<i>n</i>	<i>n</i>	<i>n</i>	χ^2
APOE genotype: ε2ε2/ε2ε3/ε3ε3/ε4ε2/ε4ε3/ε4ε4	0/4/9/0/7/2	0/1/8/0/10/3	0/2/19/0/1/0	17.97**
APOE ε4 non-carriers/ ε4 carriers	13/9	9/13	21/1	14.95***

* Comparison is significant at 0.05 level (two tailed)

** Comparison is significant at 0.01 level (two tailed)

*** Comparison is significant at 0.001 level (two tailed)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation; *F* = *F*-statistic; *Mdn* = median; *IQR* = Interquartile range; *H* = *H*-statistic; χ^2 = Chi-square statistic

^aA one-way ANOVA was run for normally distributed data.

^bNon-parametric Kruskal-Wallis *H* tests were run for data that was not normally distributed.

^cChi-square tests were run to examine the independence of the categorical variables.

Means and standard deviations for non-parametric data have been reported in Appendix B, Table B6.1

6.4.2 Cognitive Variables

All the cognitive variables had non-parametric distributions (Table 6.2). Means and standard deviations for variables with non-parametric distributions are included in Appendix B, Table B6.1. On comparing the scores on neuropsychological tests across the three groups, there were no significant differences in the digit span task (forward and backward conditions) and on the Stroop task. On the other hand, significant differences were found in tests of prose memory - immediate recall, prose memory - delayed recall, the similarities test, the verbal fluency tests and the confrontational naming task. On the prose memory - immediate recall test there was no significant difference between AD patients with and without T2DM, while a significant difference was found between CN and AD patients with T2DM, $U = 75.00, p < .001$, and AD patients without T2DM, $U = 81.50, p < .001$, where CN performed better than the patient groups. On the prose memory - delayed recall test, there was no significant difference between AD patients with and without T2DM, whereas CN performed better than AD patients with T2DM, $U = 62.50, p < .001$, and AD patients without T2DM, $U = 72.50, p < .001$.

On the phonemic fluency test, there was no significant difference between the two patient groups whereas, CN performed better than AD patients with T2DM, $U = 104.00, p < .001$, and AD patients without T2DM, $U = 113.50, p = .001$. On the semantic fluency test, there was no significant difference in performance between the two patient groups. However, the CN had better performance on the semantic fluency test than AD patients with T2DM, $U = 154.00, p = .006$, and AD patients without T2DM, $U = 160.00, p = .013$. On the similarities test, there was no significant difference between AD patients with and without T2DM, while CN had better scores compared to AD patients with T2DM, $U = 102.50, p < .001$, and AD patients without T2DM, $U = 83.00, p < .001$. On the task for confrontational naming, CN showed better performance than AD patients with T2DM, $U = 96.50, p < .001$, and AD patients without T2DM, $U = 108.00, p = .002$, while there was no significant difference in performance between the patient groups. No other significant group differences were found. On correlating the scores on the different neuropsychological tests with WMH volume, no significant correlations were found in AD patients with T2DM, in AD patients without T2DM or CN individuals.

Table 6.2 Cognitive profiles of AD patients with and without T2DM and CN, reported and using means and standard deviations for parametric data and medians and interquartile ranges for non-parametric data.

Neuropsychological test	AD with T2DM (n = 24)	AD without T2DM (n = 24)	CN (n = 24)	Statistic
Non- Parametric tests^a	<i>Mdn (IQR)</i>	<i>Mdn (IQR)</i>	<i>Mdn (IQR)</i>	<i>H</i>
Prose Memory-Immediate recall	9 (6 – 12)	9 (4 – 11)	17 (12 – 19)	24.08***
Prose Memory-Delayed recall	7 (4 – 13)	9 (6 – 13)	17 (13 – 20)	27.12***
Digit Span-Forward	6 (5 – 8)	6 (5 – 7)	7 (6 – 8)	3.67
Digit Span-Backward	4 (4 – 6)	4 (4 – 6)	5 (4 – 6)	2.80
Phonemic Fluency	26 (19 – 32)	23 (19 – 35)	40 (32 – 50)	17.83***
Semantic Fluency	18 (13 – 23)	17 (14 – 24)	22 (20 – 28)	9.40**
Similarities	16 (11 – 21)	13 (11 – 20)	25 (19 – 28)	20.96***
Confrontational Naming Task	12 (11 – 15)	14 (12 – 14)	15 (14 – 15)	15.12**
Stroop task-error interference	0 (0 – 1.25)	0.3 (0 – 2)	0 (0 – 0.53)	5.89

* Comparison is significant at 0.05 level (two tailed)

** Comparison is significant at 0.01 level (two tailed)

*** Comparison is significant at 0.001 level (two tailed)

Key: *n* = sample size; *Mdn* = median; *IQR* = Interquartile range; *H* = *H*-statistic

^aNon-parametric Kruskal-Wallis *H* tests were run for data that was not normally distributed.

Means and standard deviations for non-parametric data have been reported in Appendix B, Table B6.1

6.4.3 Voxel-Based Morphometry

6.4.3.1 AD with T2DM vs AD without T2DM

AD patients with T2DM presented with lower GMV than AD patients without T2DM in the bilateral caudate nuclei, thalamus and cerebellum in addition to the lingual gyrus and the fusiform gyrus in the right hemisphere (Table 6.3, Figure 6.1 and 6.4). The significant clusters found in the right caudate nucleus traced the borders of the head of the nucleus rising posteriorly across the body of the caudate and then tapering down partially into the anterior thalamus in the right hemisphere, covering the body and the head of the caudate nucleus. The largest cluster that was found significant rested in the postero-inferior cerebral midline spread across the temporal and occipital areas nestled toward the midline, spanning across the lingual gyrus and the fusiform gyrus. The cluster extended bilaterally from the midline toward the lateral borders of the brain, narrowing gradually until it tapered off. The extension of clusters in the right hemisphere had a few voxels protruding toward the lateral borders. Moreover, the volumetric differences in the cerebellum were observed in lobules V and VIIb in addition to Crus I and Crus II in the right hemisphere. The area tapered down dorsally and was restricted to the inferior regions of the lobules on the right side. Therefore, the two groups presented with a volumetric difference in the bilateral subcortical areas, posterior brain regions and the cerebellum with more GMV deficits in the right hemisphere. No significant results were found using the other contrast. On correlating the GMV signal from significant clusters with tests of cognition, a positive correlation was found between the extracted GMV signal and the test of confrontational naming, $r = .32$, $p = 0.05$. No other significant correlations were found between the extracted GMV signal and neuropsychological tests. There was no significant correlation between the extracted GMV signal and WMH volume either.

Table 6.3 *Regions showing volumetric differences between AD patients with T2DM and AD patients without T2DM*

Voxels (Cluster extent)	Cluster level pFWE	Brain region (Brodmann area)	Side	Z-score	MNI ordinates		
					x	y	z
688	0.039	Anterior thalamus (50)	L	4.22	-10	-8	14
		Caudate nucleus (48)	L	3.71	-14	6	21
		Tail of the caudate nucleus (48)	L	3.55	-18	-26	16
750	0.028	Caudate nucleus (48)	R	4.22	14	16	15
		Caudate nucleus (48)	R	4.10	14	8	21
		Caudate nucleus (48)	R	4.03	15	-2	24
4279	0.000	Fusiform/lingual gyrus (19)	R	4.05	28	-62	-8
		Cerebellum: Crus I	R	3.98	20	-68	-26
		Cerebellum: Lobule V	R	3.86	16	-56	-16
1108	0.005	Cerebellum: Lobule VIIb	R	3.88	34	-70	-50
		Cerebellum: Crus II	R	3.45	42	-62	-45

6.4.3.2 AD without T2DM vs CN

On comparing these two groups AD patients without T2DM presented with lower GMV in the bilateral medial temporal lobe regions, the anterior cingulate gyrus and the medial parietal lobe than CN (Table 6.4, Figure 6.1 and 6.4). The clusters in the bilateral MTL had peak coordinates in the hippocampus extending inferiorly into the entorhinal cortices and the anterior parahippocampal gyrus. Both clusters in the parahippocampal gyrus extended inferiorly toward the inferior temporal gyrus and anteriorly into the temporal pole. The cluster in the anterior cingulate gyrus was relatively smaller and was centred to the midline. The cluster in the parietal lobe was the smallest and was confined to the postero-medial parietal lobe in the precuneus. These areas were restricted to the bilateral medial temporal regions, anterior cingulate gyrus in the prefrontal cortex and the precuneus in the parietal lobe. No significant results were found using the other contrast.

Correlation analyses between the signal extracted from the significant regions from the analysis and scores on cognitive tests showed that there was a positive correlation with the prose memory - immediate recall test, $r_s = 0.68$, $p < .001$, the prose memory - delayed recall test, $r = 0.72$, $p < .001$, the digit span - backward tests, $r_s = 0.35$, $p = .017$, the phonemic fluency test, $r_s = 0.55$, $p < .001$ and the similarities test, $r_s = 0.62$, $p < .001$. No other significant correlations were found between the extracted GMV signal with scores on other neuropsychological tests. Additionally, a negative correlation was found between the extracted GMV signal and WMH volume, $r_s = -0.37$, $p = .009$.

Table 6.4 *Regions showing volumetric grey matter differences between AD patients without T2DM and CN*

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z-score	MNI ordinates		
					x	y	z
4887	0.000	Hippocampus (34)	R	4.97	15	-8	-24
		Hippocampus (34)	R	4.74	26	-6	-12
		Uncus (34)	R	4.31	33	3	-20
1517	0.000	Anterior cingulate gyrus (32)	L	4.53	-4	30	36
		Anterior cingulate gyrus (32)	L	4.06	-2	42	22
		Anterior cingulate gyrus (32)	R	3.81	3	30	26
3528	0.000	Parahippocampal gyrus (36)	L	4.52	-28	-14	-33
		Hippocampus (34)	L	4.33	-18	-4	-32
		Hippocampus (34)	L	4.31	-28	-6	-15
596	0.040	Precuneus (7)	R	4.33	3	-68	39
		Precuneus (7)	L	3.59	-3	-63	46
		Precuneus (7)	L	3.55	-10	-72	45

6.4.3.3 AD with T2DM vs CN

An ANCOVA between AD patients with T2DM and CN revealed widespread volumetric deficits in the group of patients with T2DM (Table 6.5, Figure 6.1 and 6.4). Due to the extent of the results, a more conservative threshold was used to report the results, to increase the specificity of the most significant areas ($p < 0.0001$). This threshold was more conservative than the standard threshold of $p < .001$ used for the GMV analysis across this thesis, for the reasons specified in section 4.3.7.3. Compared to the CN, the patients with T2DM presented with lower GMV in the bilateral temporal lobes, occipital lobes, superior parietal areas, insula, hippocampi, cerebellum and subcortical structures. Specifically, in the frontal lobe, the significant clusters spanned across the anterior cingulate gyrus, the orbitofrontal cortex, Broca's area, insula, inferior frontal gyrus, the middle frontal gyrus, superior frontal gyrus and primary motor cortices. In the parietal lobe, most of the results were contained in the supero-lateral areas spanning across the precuneus, Wernicke's area, angular gyrus, supramarginal gyrus, with some significant voxel protruding medially into the precuneus. Results were significant across most parts of the occipital and MTL with some significant voxels in the later portions of the temporal lobes. Of note, volumetric differences in the MTL were observed in the bilateral hippocampi and parahippocampal gyri (with more significant voxels concentrated anteriorly) that protruded into the temporal poles and amygdaloid bodies. In the subcortical regions, significant voxels were found in the bilateral caudate nuclei and in the left thalamus.

Volumetric differences were more extensive in the left hemisphere. Most of the clusters were concentrated in the postero-inferior parts of the brain, in the temporal, occipital and cerebellar areas. The cluster stretched from the temporo-parietal areas inferiorly into the middle and lateral temporal areas and antero-laterally into the frontal lobe. Extensive areas of the cerebellum were affected in both hemispheres including the cerebellar tonsils anteriorly, sparing only a small portion of the superior cerebellar regions. The results show that extensive brain areas are affected by the cumulative effect of T2DM in AD pathology. No significant results were found using the other contrast.

Correlations with cognitive tests from the extracted signal from the results revealed several different significant correlations. Positive correlations were found between the extracted GMV signal and performance on the prose memory - immediate recall test, $r = 0.59$, $p < 0.001$, the prose memory – delayed recall test, $r = 0.47$, $p = 0.001$, the phonemic fluency test, $r = 0.32$, p

= 0.025 and the similarities test, $r = 0.47$, $p = 0.001$. A negative correlation was also found between the extracted GMV signal and WMH volume, $r_s = -0.43$, $p = 0.003$.

Table 6.5 *Regions showing volumetric grey matter differences between AD patients with T2DM and CN*

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z-score	MNI ordinates		
					x	y	z
64663	0.002	Occipital pole (18)	L	5.58	-8	-96	-9
		Cuneus (19)	L	5.49	-2	-87	32
		Superior parietal lobule/precuneus (7)	L	5.49	-26	-50	64
		Cerebellum: Vermis	L	5.34	-2	-50	-30
		Superior temporal gyrus (22)	R	5.34	54	-40	15
		Parahippocampal gyrus (36)	R	5.05	21	-21	-27
		4646	0.002	Superior frontal gyrus (8)	L	5.47	-6
Anterior cingulate gyrus (32)	L	5.11		-6	48	15	
Orbitofrontal cortex (10)	R	4.66		2	45	-12	
Paracingulate cortex (10)	R	4.58		6	52	3	
Orbitofrontal cortex (10)	L	4.58		-6	45	-6	
		Anterior cingulate gyrus (32)	L	4.57	-4	15	46

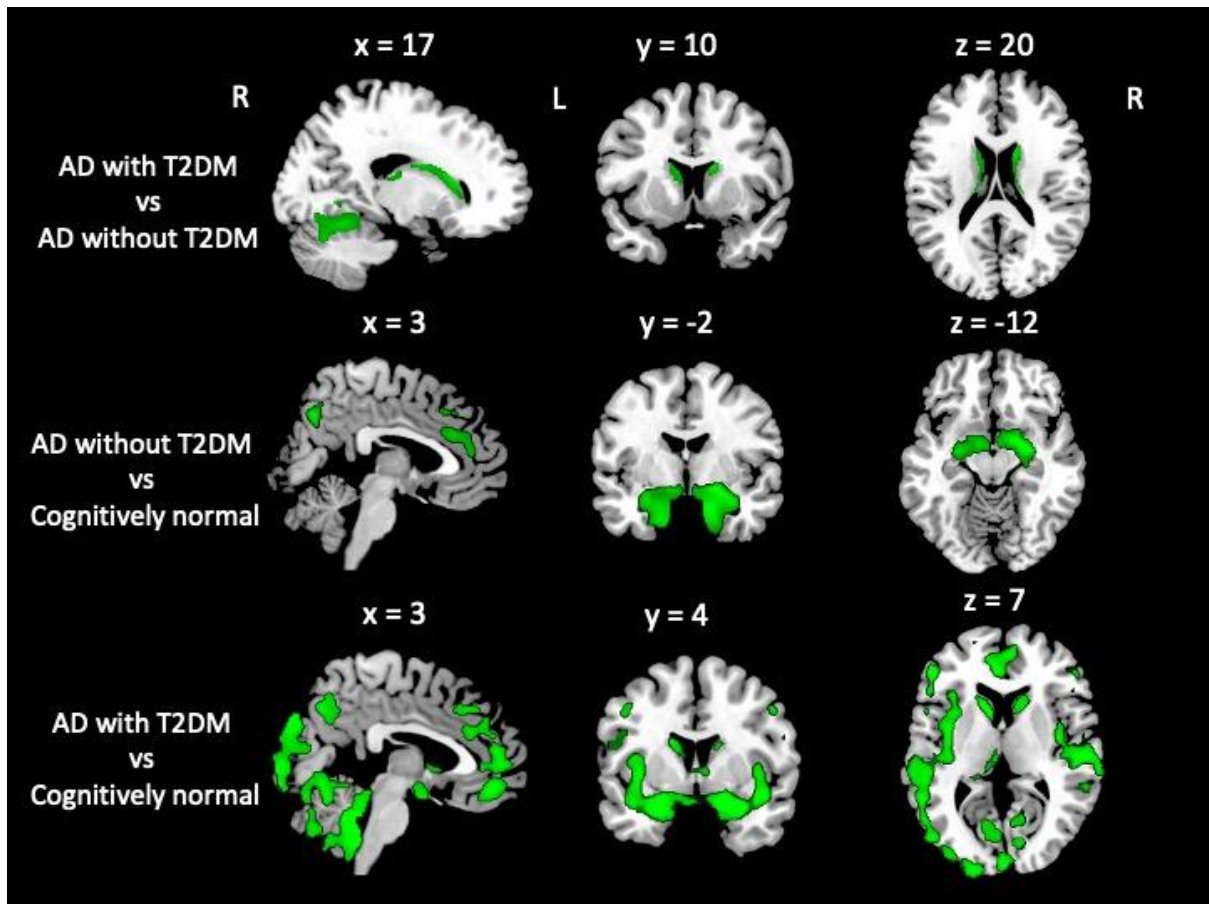


Figure 6.1 Volumetric differences in GMV between AD patients with and without T2DM and CN.

The three rows show volumetric differences displayed in the group comparisons using VBM. Each of the comparisons is represented in the sagittal, coronal and axial orientations from left to right. The ‘x’, ‘y’ and ‘z’ co-ordinates have been reported based on the MNI space. Top row: AD patients with T2DM show lower GMV than AD patients without T2DM in the bilateral caudate nuclei, thalamus, cerebellum and occipital lobe. Middle row: AD patients without T2DM show lower GMV than CN in areas typically affected in AD. Bottom row: AD patients with T2DM show lower GMV in widespread brain regions compared to CN.

6.4.4 Tract-based spatial statistics

6.4.4.1 AD with T2DM vs AD without T2DM

6.4.4.1.1 Fractional anisotropy

AD patients with T2DM showed lower FA than AD patients without T2DM in the cingulum, corpus callosum, superior longitudinal fasciculus, right inferior fronto-occipital fasciculus, right inferior longitudinal fasciculus and right parahippocampal WM (Table 6.6, Figure 6.2 and 6.4). The noticeable effects that were more pronounced in the right hemisphere ran across the anterior cingulum and cingulum body, passing through the posterior cingulum before descending inferiorly into the parahippocampal white matter. None of the extracted average FA values were correlated with neuropsychological tests or WMH volume. No significant results were found using the other contrast.

6.4.4.1.2 Axial Diffusivity

There were no significant differences in axial diffusivity between AD patients with and without T2DM using both contrasts.

6.4.4.1.3 Mean diffusivity

AD patients with T2DM showed higher mean diffusivity than AD patients without T2DM. The differences were widespread across most of the white matter skeleton (Table 6.6, Figure 6.2 and 6.4). The overall results follow the trajectory of the cingulum bilaterally extending inferiorly into the MTL regions along with some significant voxels in the white matter tracts arising from the cerebellum. Other tracts showing differences in mean diffusivity included the corpus callosum, superior longitudinal fasciculus, inferior longitudinal fasciculus, corticospinal tract, inferior fronto-occipital fasciculus, uncinate fasciculus, forceps major, forceps minor and the fornix. None of the extracted average mean diffusivity values were correlated with neuropsychological tests or WMH volume. No significant results were found using the other contrast.

6.4.4.1.4 Radial diffusivity

There were no significant differences in radial diffusivity between AD patients with and without T2DM using both contrasts.

Table 6.6 Differences in diffusion properties of white matter tracts between AD patients with T2DM and AD patients without T2DM.

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z-score	MNI ordinates		
					x	y	z
<i>FA: AD with T2DM < AD without T2DM</i>							
6884	0.028	Superior longitudinal fasciculus	R	4.34	35	-46	26
		Corpus callosum (genu)	L	4.18	-1	19	21
		Inferior fronto-occipital fasciculus	R	4.18	36	-10	-13
		Cingulum (body)	R	4.15	7	-9	31
		Cingulum (body)	R	4.11	8	-7	30
		Superior longitudinal fasciculus	R	3.80	38	-47	25
<i>Mean diffusivity: AD with T2DM > AD without T2DM</i>							
54653	0.005	Superior longitudinal fasciculus	R	5.15	36	-50	26
		Superior longitudinal fasciculus	L	4.90	-35	-28	45
		Superior longitudinal fasciculus	R	4.84	12	-29	60
		Superior longitudinal fasciculus	R	4.80	18	-37	54
		Cerebellar WM (lobules I-IV)	L	4.78	-8	-45	-27

WM: White matter

6.4.4.2 AD without T2DM vs CN

6.4.4.2.1 Fractional Anisotropy

AD patients without T2DM showed no significant differences in WMI as expressed by FA compared to CN using both contrasts.

6.4.4.2.2 Axial diffusivity

AD patients without T2DM showed higher axial diffusivity compared to CN mainly in the anterior white matter tracts. The results extended antero-posteriorly across the superior longitudinal fasciculus and the corpus callosum. Significant voxels were also found in the anterior thalamic radiations, the inferior fronto-occipital fasciculus, uncinate fasciculus, forceps minor and major and subcortical white matter surrounding the thalamus and the striatum. The overall results showed that the axial diffusivity differences between the two groups were mostly located in the anterior and deep brain regions (Table 6.7, Figure 6.2 and 6.4). No significant results were found using the other contrast.

There was a negative correlation between the extracted axial diffusivity signal and the prose memory - immediate recall test, $r_s = -0.56$, $p < .001$, the prose memory - delayed recall test, $r_s = -0.53$, $p < .001$, the digit span - backward tests, $r_s = -0.30$, $p = .047$, the phonemic fluency test, $r_s = -0.44$, $p = .002$ and the similarities test, $r_s = -0.43$, $p = .002$. A positive correlation was found between the extracted axial diffusivity signal and WMH volume, $r_s = 0.56$, $p < .001$.

6.4.4.2.3 Mean diffusivity

The relatively large white matter tracts in which AD patients without T2DM showed higher mean diffusivity than CN were the superior longitudinal fasciculus, cingulum bundle, corpus callosum and inferior fronto-occipital fasciculus. Although the peak co-ordinates did not reflect these results, the significant voxels extended into the left hippocampal and parahippocampal white matter. In the subcortical regions, higher mean diffusivity was found in the striatum, thalamus and the fornix in AD patients. Of note, most of the white tracts showing higher mean diffusivity in AD patients are part of the limbic circuitry. The majority of the differences were concentrated in the white matter tracts in the frontal lobe (Table 6.7, Figure 6.2 and 6.4). No significant results were found using the other contrast.

There was a negative correlation between the extracted mean diffusivity signal and the prose memory - immediate recall test, $r_s = -0.56, p < .001$, the prose memory - delayed recall test, $r_s = -0.49, p = .001$, the phonemic fluency test, $r_s = -0.37, p = .010$ and the similarities test, $r_s = -0.41, p = .004$. A positive correlation was also found between the extracted mean diffusivity signal and WMH volume, $r_s = 0.57, p < .001$.

6.4.4.2.4 Radial diffusivity

AD patients without T2DM showed higher radial diffusivity compared to CN in the white matter tracts restricted to the anterior frontal brain regions. The differences were diffused across the fronto-occipital fasciculus, anterior cingulum and the corpus callosum (Table 6.7, Figure 6.2 and 6.4). No significant results were found using the other contrast.

There was a negative correlation between the extracted radial diffusivity signal and the prose memory - immediate recall test, $r_s = -0.56, p < .001$, the prose memory -delayed recall test, $r_s = -0.50, p < .001$, the phonemic fluency test, $r_s = -0.35, p = .018$, the semantic fluency test, $r_s = -0.29, p = .045$, and the similarities test, $r_s = -0.32, p = .028$. A positive correlation was found between the extracted radial diffusivity signal and WMH volume, $r_s = 0.56, p < .001$.

Table 6.7 Differences in diffusion properties of white matter tracts between AD patients without T2DM and CN.

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z-score	MNI coordinates		
					x	y	z
<i>Axial diffusivity: AD without T2DM > CN</i>							
16661	0.003	Splenium of the corpus callosum	L	5.65	-13	-43	21
		Body of the corpus callosum	L	5.48	-3	-2	28
		Splenium of the corpus callosum	L	4.95	-16	-42	24
		Superior longitudinal fasciculus	R	4.89	31	18	33
		Posterior cingulum	L	4.58	-14	-38	26
		Anterior cingulum	L	4.54	-6	31	11

<i>Mean diffusivity: AD without T2DM > CN</i>							
17177	0.024	Corpus callosum (splenium)	L	4.59	-13	-43	21
		Forceps major	R	4.48	3	-40	13
		Uncinate fasciculus	R	4.38	16	15	-14
		Corpus callosum (genu)	L	4.06	-2	23	-3
		Anterior cingulum	L	3.94	-7	33	10
30	0.049	Inferior fronto-occipital fasciculus	L	2.66	-21	45	-3
		Inferior fronto-occipital fasciculus	L	2.52	-24	43	-2
		Inferior fronto-occipital fasciculus	L	2.51	-22	40	0
<i>Radial diffusivity: AD without T2DM > CN</i>							
4140	0.041	Inferior fronto-occipital fasciculus	R	4.04	20	36	24
		Forceps minor	L	3.94	-2	23	-3
		Forceps minor	L	3.88	-4	23	-4
		Anterior cingulum	R	3.85	17	27	38
		Anterior cingulum	L	3.73	-6	26	-6
		Anterior cingulum	R	3.51	12	39	38
307	0.047	Superior longitudinal fasciculus	R	4.09	42	14	13
		Superior longitudinal fasciculus	R	3.57	37	16	16
202	0.047	Anterior cingulum	L	4.10	-13	3	35
		Superior longitudinal fasciculus	L	3.87	-18	2	36
		Superior longitudinal fasciculus	L	3.82	-16	-8	37

6.4.4.3 AD patients with T2DM vs CN

6.4.4.3.1 Fractional anisotropy

AD patients with T2DM showed lower FA than CN mainly across the white matter tracts connecting brain regions involved in the limbic system. The peak co-ordinates were mostly located in the superior brain regions. The FA differences appeared to follow the trajectory of the cingulum that ran antero-posteriorly, descending down posteriorly into the parahippocampal and hippocampal white matter. The tracts involved in the FA differences between the groups include the inferior longitudinal fasciculus, superior longitudinal fasciculus, cingulum, forceps minor, corpus callosum, inferior fronto-occipital fasciculus and white matter tracts in the striatum (Table 6.8, Figure 6.2 and 6.4). No significant results were found using the other contrast.

On correlating the mean FA signal extracted from the analysis, a positive correlation was found with the prose memory - immediate recall test, $r = 0.54$, $p < 0.001$, the digit span -forward test, $r_s = 0.38$, $p = 0.01$, the similarities test, $r = 0.33$, $p = 0.024$ and the test of confrontational naming, $r_s = 0.37$, $p = 0.014$. The extracted FA signal was also negatively correlated with WMH volume, $r_s = -0.48$, $p = 0.001$.

6.4.4.3.2 Axial diffusivity

AD patients with T2DM showed higher axial diffusivity than CN mainly in the cingulum and subcortical brain regions. The main proportion of the axial diffusivity differences were diffused across the cingulum, with significant voxels spilling over into the superior longitudinal fasciculus, corpus callosum, uncinate fasciculus and the inferior fronto-occipital fasciculus. Although these were not among the peak regions, in the subcortical brain regions, axial diffusivity differences were found in the fornix, external capsule and white matter in the putamen and thalamus (Table 6.8, Figure 6.2 and 6.4). No significant results were found using the other contrast.

On correlating the extracted axial diffusivity signal, a negative correlation was found with the prose memory - immediate recall test, $r_s = -0.43$, $p = 0.002$, the prose memory - delayed recall test, $r_s = -0.34$, $p = 0.02$, the similarities test, $r = -0.52$, $p < 0.001$ and the test of confrontational

naming, $r_s = -0.51$, $p < 0.001$. The extracted axial diffusivity signal was also positively correlated with WMH volume, $r_s = 0.60$, $p < 0.001$.

6.4.4.3.3 Mean diffusivity

The differences in mean diffusivity between the two groups were the most extensive across all the different diffusivity indices. The pattern of differences was spread across the limbic circuitry including some white matter in subcortical and cerebellar regions. Tracts that showed higher mean diffusivity in AD patients with T2DM compared to CN included the corpus callosum, cingulum, superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, forceps major, uncinate fasciculus, the fornix, corticospinal tracts, cerebellar peduncles and thalamic, hippocampal and parahippocampal white matter. Tracts surrounding basal ganglia structures also showed higher mean diffusivity in AD patients with T2DM (Table 6.8, Figure 6.2 and 6.4). No significant results were found using the other contrast.

When correlating neuropsychological tests with the extracted mean diffusivity signal, a negative correlation was found with the prose memory - immediate recall test, $r_s = -0.47$, $p < 0.001$, the prose memory - delayed recall test, $r_s = -0.32$, $p = 0.031$, the semantic fluency test, $r_s = -0.30$, $p = 0.042$ the similarities test, $r = -0.41$, $p = 0.005$ and the test of confrontational naming, $r_s = -0.46$, $p = 0.002$. The extracted mean diffusivity signal was also positively correlated with WMH volume, $r_s = 0.62$, $p < 0.001$.

6.4.4.3.4 Radial diffusivity

AD patients with T2DM showed higher radial diffusivity compared to CN. Although more diffuse than mean diffusivity, the pattern of differences in radial diffusivity resembled those found with mean diffusivity. The pattern seemed to follow the trajectory of the limbic circuitry. Higher radial diffusivity was found across the cingulum, corpus callosum, superior longitudinal fasciculus, anterior thalamic radiation, inferior fronto-occipital fasciculus, cerebellar peduncles, thalamic white matter, parahippocampal and hippocampal white matter and white matter of the striatum (Table 6.8, Figure 6.2 and 6.4). No significant results were found using the other contrast.

When correlating neuropsychological tests with the extracted radial diffusivity signal, a negative correlation was found with the prose memory - immediate recall test, $r_s = -0.53$, $p <$

0.001, the prose memory - delayed recall test, $r_s = -0.41$, $p = 0.004$, the digit span - forward test, $r_s = -0.35$, $p = 0.016$, the phonemic fluency test, $r_s = -0.30$, $p = 0.04$, the semantic fluency test, $r_s = -0.34$, $p = 0.02$ the similarities test, $r = -0.41$, $p = 0.008$ and the test of confrontational naming, $r_s = -0.40$, $p = 0.008$. The extracted radial diffusivity signal was also positively correlated with WMH volume, $r_s = 0.48$, $p = 0.001$.

Table 6.8 Differences in diffusion properties of white matter tracts between AD patients with T2DM and CN.

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z- score	MNI co ordinates		
					x	y	z
<i>Fractional anisotropy: AD with T2DM < CN</i>							
22454	0.007	Posterior cingulum	R	5.29	16	-53	36
		Inferior fronto-occipital fasciculus	L	5.25	-25	-58	29
		Inferior fronto-occipital fasciculus	R	5.02	40	-38	0
		Forceps minor	R	4.74	13	23	19
		Superior longitudinal fasciculus	L	4.71	-42	-42	-3
1116	0.044	Posterior cingulum	R	4.65	12	-57	28
		Superior longitudinal fasciculus	R	4.21	28	-32	47
		Superior longitudinal fasciculus	R	3.61	28	-31	45
		Cingulum (body)	R	3.61	19	-14	40
		Cingulum (body)	R	3.48	18	4	43
<i>Axial diffusivity: AD with T2DM > CN</i>							
21591	0.002	Posterior cingulum	L	5.85	-16	-45	27
		Posterior cingulum	L	5.67	-13	-44	26
		Superior longitudinal fasciculus	R	5.43	41	0	20
		Posterior cingulum	L	5.13	-17	-47	26
		Uncinate fasciculus	R	4.98	35	36	7
		Posterior cingulum	R	4.89	18	-40	33
<i>Mean diffusivity: AD with T2DM > CN</i>							
60750	0.001	Superior longitudinal fasciculus	R	5.62	31	-31	46

		Thalamus	R	5.17	17	-33	9
		Inferior longitudinal fasciculus	L	5.12	-29	-28	-1
		Inferior fronto-occipital fasciculus	L	5.09	-32	-21	-5
		Thalamus	R	5.07	19	-33	7
		Anterior thalamic radiation	R	5.06	28	33	19
<hr/>							
<i>Radial diffusivity : AD with T2DM > CN</i>							
38864	0.002	Anterior thalamic radiation	L	5.45	-18	45	22
		Inferior fronto-occipital fasciculus	L	5.31	-29	-28	-1
		Inferior fronto-occipital fasciculus	L	5.17	-32	-21	-5
		Superior longitudinal fasciculus	R	4.87	36	-24	35
		Cingulum (posterior)	R	4.87	17	-52	36
		Inferior fronto-occipital fasciculus	R	4.80	39	-20	-8
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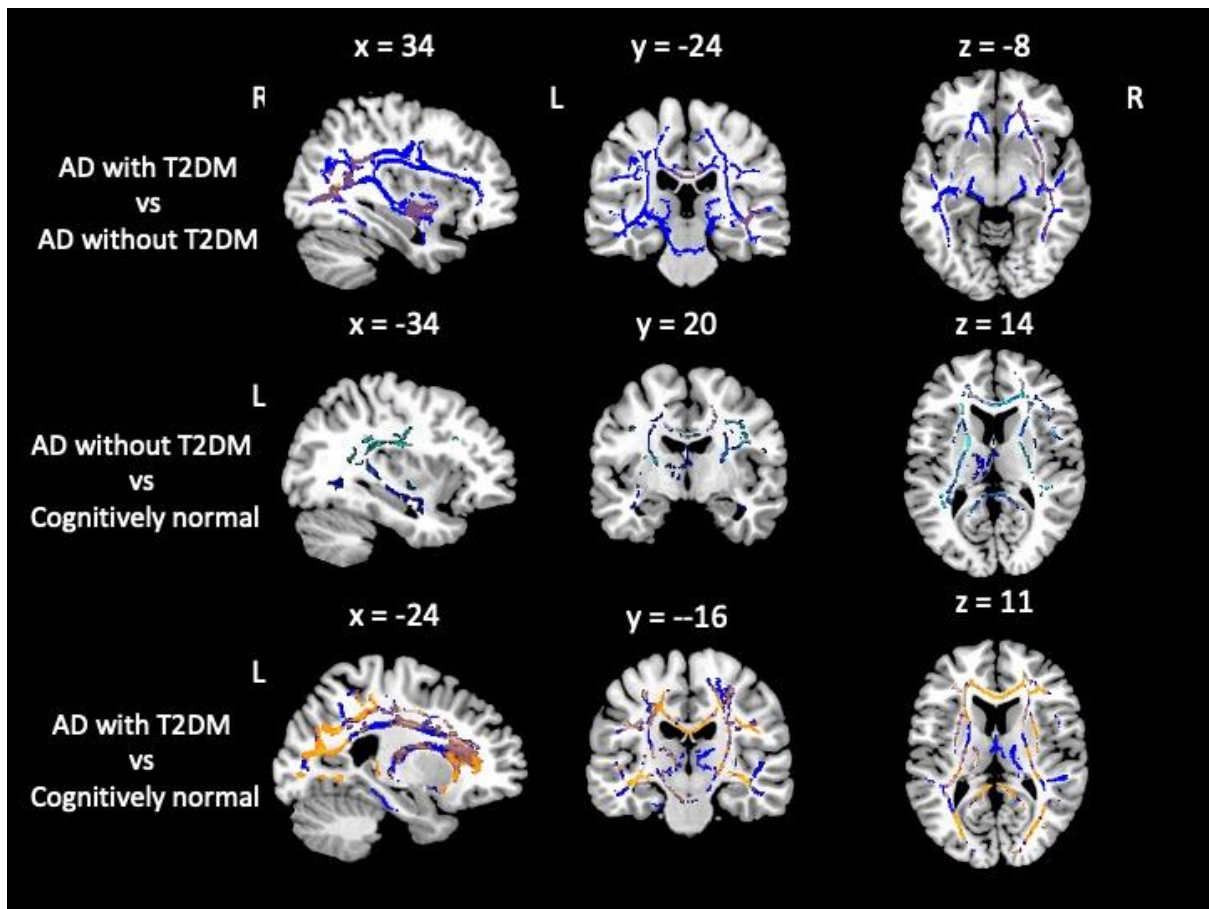


Figure 6.2 Differences in measures of WMI between AD patients with and without T2DM and CN.

The three rows show volumetric differences displayed in the group comparisons using TBSS. Each of the comparisons is represented in the sagittal, coronal and axial orientations from left to right. The 'x', 'y' and 'z' co-ordinates have been reported based on the MNI space. The following colours represent the corresponding diffusivity values: Blue: Mean diffusivity; Yellow: Fractional anisotropy; Turquoise: Axial diffusivity Pink: Radial diffusivity. Top row: AD patients with T2DM show lower WMI than AD patients without T2DM Middle row: AD patients without T2DM show lower WMI than CN in areas affected in AD. Bottom row: AD patients with T2DM show lower WMI in widespread brain regions compared to CN.

6.4.5 Arterial spin labelling

6.4.5.1 AD with T2DM vs AD without T2DM

The ANCOVA between the two patient groups showed that AD patients with T2DM had greater hypoperfusion lateralised to the right hemisphere of the brain compared to AD patients without T2DM. Hypoperfusion was found in areas that roughly overlapped with the areas that showed structural deficits. These areas included the genu of the corpus callosum, anterior cingulate gyrus and the head of the caudate nucleus in anterior brain regions. Additionally, hypoperfusion was seen in the posterior portions of the cingulum bundle. The cluster began in the white matter of the posterior cingulum, dorsolateral to the posterior horn of the right lateral ventricle and continued ventrally into the white matter of the parahippocampal gyrus that also covered a large proportion of the hippocampus. A significant cluster was also found in the cerebellum that was restricted to the medial and anterior cerebellum, mostly covering the cerebellar white matter. Some significant voxels extended into the right cerebellar hemisphere (Table 6.9, Figure 6.3 and 6.4). Applying a more conservative threshold of a family-wise error corrected $p < 0.05$ and 0 voxels at the set-level showed preservation of some voxels in the right parahippocampal gyrus. No significant correlations were found between the extracted perfusion signal, scores on neuropsychological tests and WMH volume. No significant results were found using the other contrast.

Table 6.9 *Regions showing greater hypoperfusion among AD patients with T2DM compared to those without*

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z-score	MNI co ordinates		
					x	y	z
1257	0.001	Hippocampus (28)	R	5.05	40	-24	-14
		Posterior cingulum (WM)	R	3.35	28	-30	24
		Posterior cingulum (WM)	R	3.33	24	-34	26
1117	0.002	Corpus callosum (WM)	R	4.02	18	32	6
		Cingulum (WM)	R	4.02	20	24	22
642	0.017	Cerebellum (WM)	R	3.78	26	-52	-40
		Vermis	R	3.43	2	-44	-42
		Cerebellar peduncle (WM)	R	3.38	-10	-52	-34

WM: white matter

6.4.5.2 AD without T2DM vs CN

AD patients without T2DM showed an atypical pattern of difference in perfusion compared to CN. Hypoperfusion was seen in AD patients only in the left cerebellar hemisphere mostly restricted to the anterior regions. However, on using a less conservative threshold of $p < 0.01$, hypoperfusion was seen in medial and lateral temporal lobes, the prefrontal regions and the cerebellum (Table 6.10, Figure 6.3 and 6.4). A less conservative threshold (of $p < .01$, which was the threshold that was used as the standard across all the CBF analyses) was used to visualise the results to show the typical pattern of hypoperfusion seen in AD patients as the conservative threshold used in the current experimental chapter was less sensitive to detecting this typical pattern. No significant correlations were found between the extracted CBF signal, neuropsychological assessments and WMH volume. No significant results were found using the other contrast.

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z- score	MNI co ordinates		
					x	y	z
9361	<0.001	Supramarginal gyrus (40)	L	4.20	-34	-40	-38
		Inferior temporal gyrus (38)	R	4.05	20	0	-38
		Cerebellum: Lobule VI	R	3.99	36	-40	-40
		Cerebellum: Lobule VIIIB	L	3.77	-20	-46	-50
		Inferior temporal gyrus (37)	R	3.42	64	-44	-18
		Uncus (38)	R	3.29	32	24	-6

Table 6.10 Regions showing hypoperfusion among AD patients without T2DM compared to CN

6.4.5.3 AD with T2DM vs CN

As expected, the ANCOVA between AD patients with T2DM and CN revealed extensive hypoperfusion in the medial temporal lobe structures among AD patients with T2DM compared to CN. The extent of hypoperfusion was spread across the posterior and inferior brain regions, with relative sparing of the anterior and superior posterior brain regions in the frontal and parietal lobes respectively. In the temporal lobes, hypoperfusion was mainly seen in the bilateral parahippocampal gyri and the hippocampi that extended anteriorly into the temporal poles and some lateral temporal areas. Toward the midline, hypoperfusion in AD patients with T2DM was observed in the bilateral caudate nuclei and the fornix. In the frontal lobe, hypoperfusion was seen in patients in the subgenual anterior cingulate gyrus and the genu of the corpus callosum. The analysis also showed hypoperfusion in the cerebellum and parts of the brain stem. Significant clusters were also identified in postero-lateral occipital areas (Table 6.11, Figure 6.3 and 6.4). A *post hoc* analysis conducted using a more conservative threshold of a family-wise error corrected $p < 0.05$ and 0 voxels showed that the significant voxels in the bilateral parahippocampal gyrus and hippocampi survived the correction. A less conservative threshold was used to highlight that the extent of the effects was more severe with reference to the other comparisons. No significant results were found using the other contrast.

As a *post hoc* analysis, correlations were run between the extracted signal from the ANCOVA and cognitive test scores. On correlating the extracted CBF signal with scores on neuropsychological tests, a positive correlation was found with performance on the prose memory - immediate recall test, $r_s = 0.51$, $p < 0.001$, the prose memory - delayed recall test, $r_s = 0.40$, $p = 0.005$, the similarities test, $r_s = 0.33$, $p = 0.024$, and the test of confrontational naming, $r_s = 0.32$, $p = 0.035$. A negative correlation was also found between the extracted CBF signal and WMH volume, $r_s = -0.41$, $p = 0.004$.

Table 6.11 *Regions showing hypoperfusion among AD patients with T2DM compared to CN*

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z-score	MNI ordinates		
					x	y	z
14821	0.000	Hippocampus (36)	L	5.52	-32	-39	-3
		Hippocampus (36)	R	5.39	36	-37	-3
		Hippocampus (36)	R	5.17	40	-28	-9
		Hypothalamus	L	4.94	0	-6	-8
		Thalamus	L	4.86	0	-21	10
		Precentral gyrus (6)	R	4.82	42	-10	43
		Insula (41)	R	4.72	42	-23	16
		Caudate nucleus	L	4.65	-4	7	-7
		Body of the caudate nucleus	L	4.55	-14	-15	17
		Uncus (38)	L	4.43	-32	9	-19
		Nodulus of the cerebellum	L	4.32	4	-50	-34
		Anterior cingulate gyrus	R	4.30	18	29	4
		Pons	R	4.30	16	-21	-24
		Superior temporal gyrus	R	4.29	42	-46	12
		Pons	R	4.27	18	-25	-24
		Precentral gyrus	R	4.15	46	-6	28

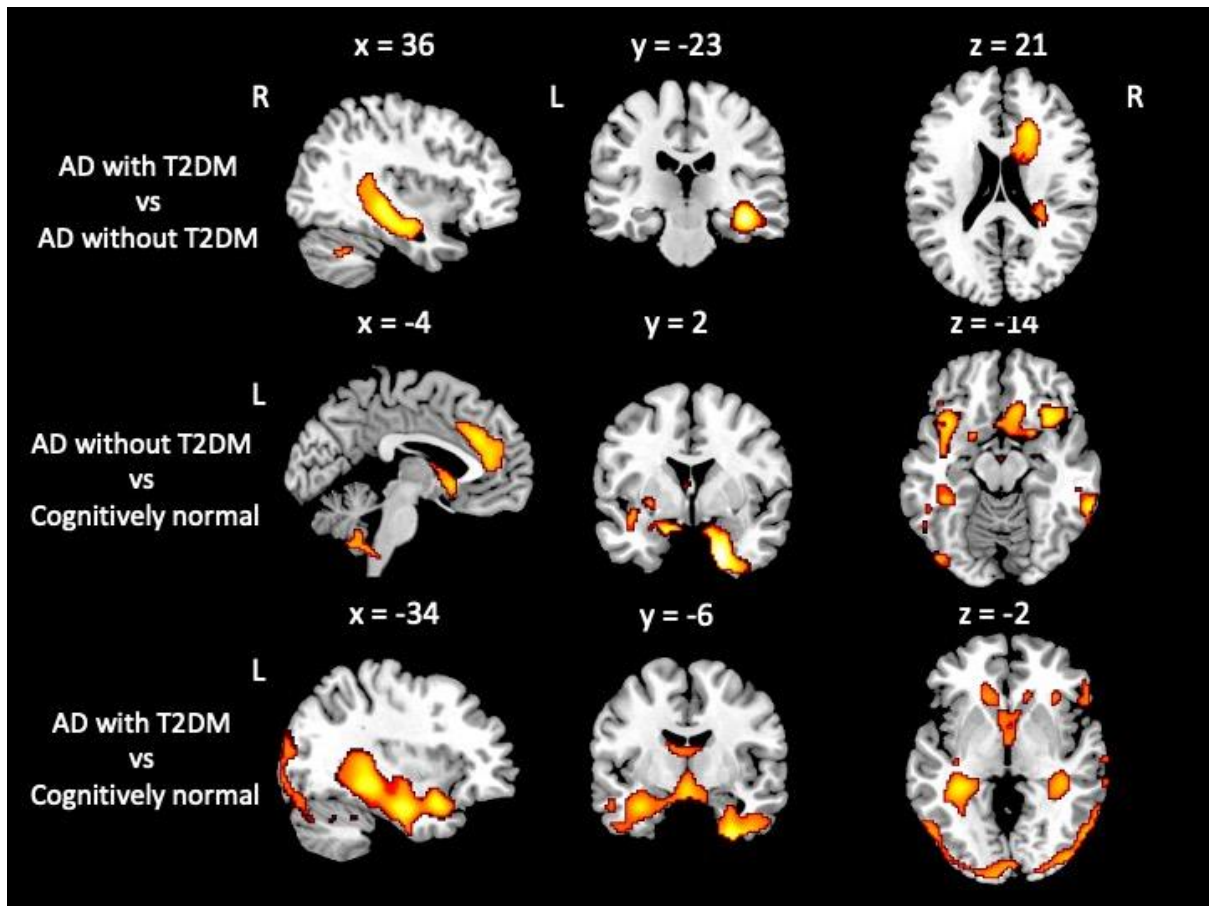


Figure 6.3 Differences in CBF between AD patients with and without T2DM and CN.

The three rows show CBF differences displayed in the group comparisons. Each of the comparisons is represented in the sagittal, coronal and axial orientations from left to right. The 'x', 'y' and 'z' coordinates have been reported based on the MNI space. Top row: AD patients with T2DM show lower CBF than AD patients without T2DM Middle row: AD patients without T2DM show lower CBF than CN. Bottom row: AD patients with T2DM show lower CBF in widespread brain regions compared to CN.

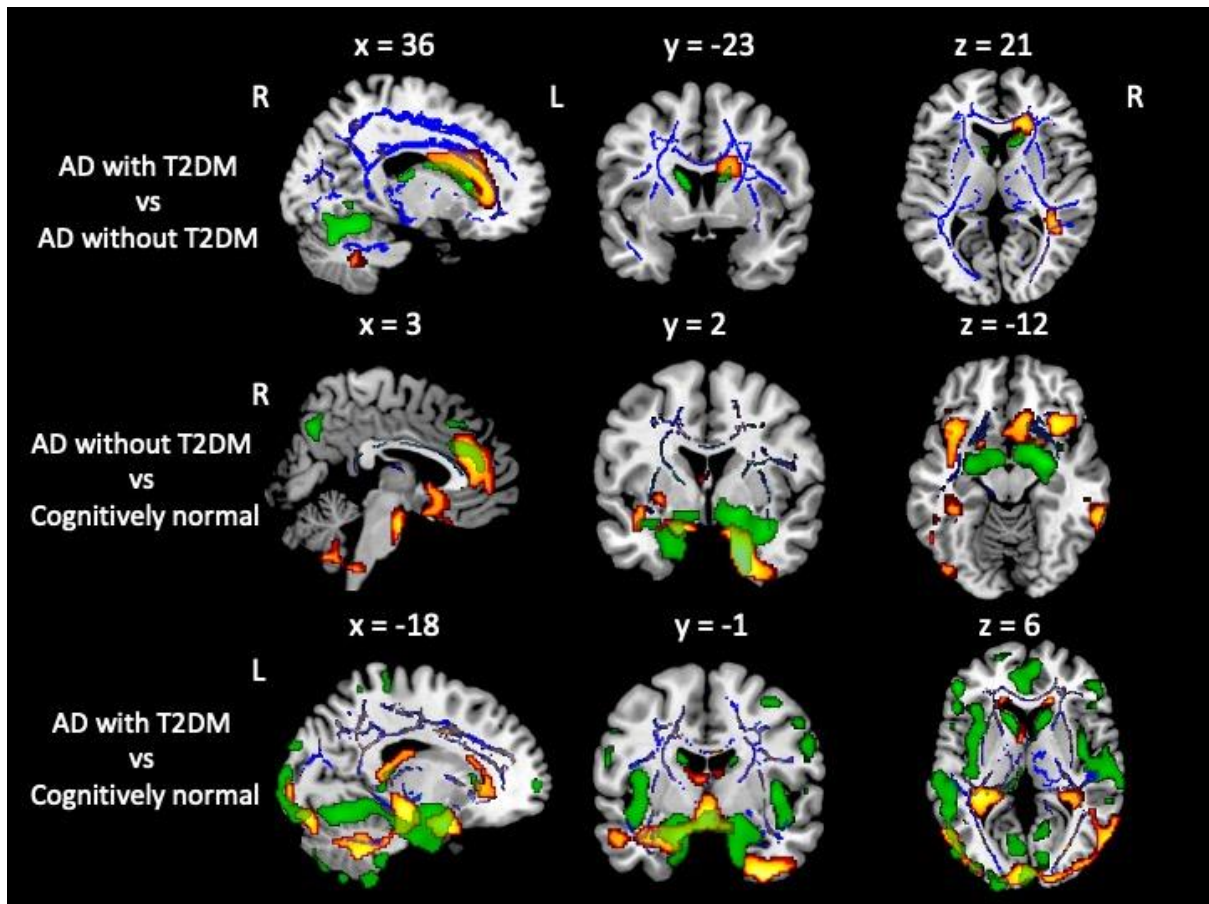


Figure 6.4 Differences in GMV, WMI and CBF between AD patients with and without T2DM and CN.

The three rows show differences in GMV, WMI and CBF observed in the group comparisons. Each of the comparisons is represented in the sagittal, coronal and axial orientations from left to right. The 'x', 'y' and 'z' co-ordinates have been reported based on the MNI space. The following colours represent the corresponding neuroimaging parameters: Green: GMV; Blue: MD; Yellow: FA; Turquoise: DA; Pink: RD; Orange: CBF Top row: AD patients with T2DM show lower parameters of GMV, WMI and CBF than AD patients without T2DM; Middle row: AD patients without T2DM show lower parameters of GMV, WMI and CBF than CN; Bottom row: AD patients with T2DM show lower parameters of GMV, WMI and CBF in widespread brain regions compared to CN.

6.4.6 White Matter Hyperintensities

On correlating the WMH volume with neuropsychological test scores, a positive correlation was found with the Stroop error interference score, $r_s = 0.60$, $p = 0.004$, in AD patients with T2DM. No significant correlations were found between WMH volume and neuropsychological performance in AD patients without T2DM and CN individuals.

6.5 Discussion

This is the first study that makes multi-modal comparisons using four different imaging modalities to explore the effects of T2DM on brain structure (GMV and WMI), CBF and vascular burden (WMH volume). The use of the different neuroimaging modalities aided in providing a more holistic approach to examine the convergent effects of T2DM and AD that helped in the mechanistic interpretation of the findings. It highlights how the presence of comorbid T2DM in AD patients exacerbates the extent of damage inflicted on cerebral constituents. This damage is additional to that already seen in AD patients, contributing toward increased radiological disease severity. Consistent with the hypothesis, AD patients with T2DM presented with structural and perfusion deficits compared to the patients without T2DM in brain regions that overlapped with each other. AD patients without T2DM showed deficits typical of AD when compared to CN, which shows that this group was representative of the AD phenotype. The extent of these deficits was substantially more widespread when comparing the group of AD patients with T2DM to CN and was also consistent with our hypothesis that this comparison would resemble a pattern that is a combination of the differences found in the former two analyses. Most structural deficits were found in the grey matter structures and the white matter tracts that also showed overlapping differences in CBF. These differences could be attributed to microvascular and macrovascular changes seen in AD and T2DM. The co-localisation of the regions showing structural deficits with regions displaying detriments in CBF is in support of the hypothesis that deficits in the brain parenchyma in the presence of AD and T2DM could primarily be a manifestation of vascular dysfunction-mediated attenuation in CBF.

6.5.1 AD patients with T2DM vs AD patients without T2DM

The most prominent deficits in brain structure in AD patients with T2DM were observed in the caudate nuclei, cerebellum, corpus callosum, cingulum, parahippocampal and hippocampal white matter and the inferior fronto-occipital fasciculus compared to AD patients without T2DM. Most of these structures overlapped with the deficits found in CBF. However, differences in FA in the posterior white matter tracts in the parietal and occipital lobes and most differences in mean diffusivity did not co-localise with the differences found in CBF. The differences were mostly lateralised to the right hemisphere except for the differences in GMV, which were bilateral. On using a more conservative threshold ($p < 0.001$), although differences in GMV did not survive significance levels, they approached significance in the right caudate

nucleus and the right cerebellum. The current discussion focuses on the interpretation of the most significant results that were found in the caudate nucleus, parahippocampal gyrus and the cerebellum. Although most of the results found were reflective of structural deficits overlapping with deficits in CBF, the caudate nucleus, parahippocampal gyrus and cerebellum showed the most amount of overlap between structural and CBF deficits. The following sections focus on these particular brain regions to try and extrapolate the mechanisms that underlie these findings.

6.5.1.1 Caudate nucleus

Although a typical brain region to be affected by the pathological mechanisms of T2DM, the stark overlap that was observed between detriments in brain structure and CBF highlights the susceptibility of this brain region to vascular insults in comorbid T2DM and AD. Structural deficits in the head of the caudate nucleus resulting from hypoperfusion in AD patients with T2DM could result from damage to the vascular supply of the basal ganglia. The caudate nucleus receives a major proportion of its blood supply from the anterior cerebral circulation system (Djulejić et al., 2016; Prince & Ahn, 2013). The blood is delivered to the head of the caudate nucleus via deep perforating arteries which are miniscule branches stemming from major cerebral arteries that perfuse deep brain structures such as the basal ganglia (Djulejić et al., 2015). The deep perforating arteries supplying the basal ganglia are known as the lenticulostriate arteries. They stem from the recurrent artery of Heubener (branch of the anterior cerebral artery) and the M1 segment of the middle cerebral artery (Kleine et al., 2017).

Perforating branches of the recurrent artery of Heubener arising from the anterior cerebral artery supply the ventromedial portion of the head of the caudate. The branches of the recurrent artery of Heubener conventionally originate from the proximal A2 segment or alternatively the distal A1 segments of the anterior cerebral artery (Djulejić et al., 2016; Mugikura et al., 2018). The dorsolateral portions of the caudate head and the caudate body on the other hand, are supplied by the lenticulostriate arteries originating from the middle cerebral artery (Antunović et al., 2017; Djulejić et al., 2016). On the other hand, the tail of the caudate nucleus is supplied by the posterior cerebral artery (Djulejić et al., 2016). Therefore, the caudate nucleus receives its blood supply from a variety of major cerebral arteries. Reduced blood supply to the caudate nucleus could therefore be the result of a global reduction in blood supply to cerebral arteries or other mechanisms contributing towards damage to the perforating branches of major cerebral arteries.

Deep perforating arteries generally have a weak vascular tone compared to their parent arteries. They are highly susceptible to damage from the downstream effects of arteriopathies (such as fluctuations in blood pressure) in conditions such as T2DM (Ito et al., 2009). Terminal branches of arteries and their arterioles supplying the deep white matter are highly susceptible to this type of damage (Fernando et al., 2006; Thore et al., 2007). The overlapping pattern of deficits in GMV, WMI and CBF in the caudate nucleus could be indicative of damage and consequent reduction in blood supply from the lenticulostriate arteries arising from the middle cerebral artery and the perforating arteries arising from the recurrent artery of Heubener (part of the anterior cerebral artery), due to T2DM. This was evidenced by a study that used a 7 Tesla MRI scanner to examine lenticulostriate arteries within individuals with and without T2DM that found a lower signal intensity and lower number of stems and branches arising from the deep arteries in individuals with T2DM compared to those without (Yashiro et al., 2018). A different study that examined small infarcts in the caudate nucleus found that these infarcts are commonly found in individuals with symptomatic atherosclerotic pathology, a pathology found in AD and T2DM (Ghaznawi et al., 2017). Reduced CBF due to AD and T2DM mediated damage to arteries could thus offer an explanation for the structural deficits seen in the caudate nucleus. The co-localisation of GMV, WMI and CBF differences in the caudate nucleus lends support to this notion. However, due to the cross-sectional nature of this study, it is difficult to infer the directionality of the findings.

As described earlier, arteriosclerosis is one of the complications of T2DM that can cause the stiffening of arterial walls, reducing their elasticity (Caplan, 2015; Fukuda et al., 2015). Prolonged exposure to variability in the intensity of the pulse pressure as the arterial walls stiffen, makes the delicate microvasculature of the deep perforating arteries more vulnerable to microbleeds (Kario et al., 2004; Kobayashi et al., 1997). Often, these bleeds can be ‘clinically silent,’ where the individual does not exhibit signs of cognitive decline until later stages when there is sufficient accumulation of multiple vascular insults to manifest as cognitive deficits (Stone et al., 2015). This phenomenon could offer a potential explanation for the absence of significantly more severe cognitive deficits in the diabetic AD patients compared to the non-diabetic patients in our present sample, despite structural and CBF differences. Stone and colleagues have proposed that this very phenomenon of the destructive effects exerted by arterial pulse (due to age-related and T2DM-related arterial wall thickening) on the cerebral vasculature, is a catalyst for AD (Stone et al., 2015). Thickening of the media of the deep perforating arteries is also a phenomenon observed in T2DM (Caplan, 2015). This thickening

of arterial walls can alter arterial pressure by restricting autoregulation (Boutouyrie, Beausnier, & Laurent, 2015). Therefore, subcortical ‘silent infarcts’ resulting from inefficient autoregulation could explain the CBF and structural differences seen in subcortical structures.

Another explanation for the pattern of findings detected in the caudate nucleus could be iron accumulation. Iron has a key role in regulating brain functions via mediating processes such as the production of reactive oxygen species, maintenance of axonal integrity and neurotransmitter systems (Ward et al., 2014b). Across ageing, increasing deposits of iron are observed in specific brain regions, with structures in the basal ganglia (putamen, globus pallidus and caudate nucleus) being the most vulnerable to these accumulations (Ramos et al., 2014; Ward et al., 2014b). These accumulations can also be found in the cerebellar nuclei, hippocampus, the cortex and other subcortical regions, with increasing age (Arber et al., 2016; Daugherty & Raz, 2015; Pirpamer et al., 2016). In the past, research has shown that AD and T2DM related pathological cascades can cause increased BBB permeability and inflammation that can result in the excessive accumulation of iron in the interstitial spaces (Butterfield, Di Domenico, & Barone, 2014; Moon, Han, & Moon, 2016). These iron clusters can induce oxidative stress through the generation of reactive oxygen species that are toxic to neural tissue (Dixon & Stockwell, 2014). The presence of reactive oxygen species can initiate a chain reaction that augments the depositions of iron in the interstitial spaces via the breakdown of mitochondrial iron-sulphur cluster proteins (Horowitz & Greenamyre, 2010; Mastroberardino et al., 2009). Disturbed iron homeostasis can in turn hasten neurodegenerative processes, as imbalance of iron concentrations can interfere with mitochondrial function, thus initiating a cascade of events that eventually leads to cell death (Horowitz & Greenamyre, 2010; Mastroberardino et al., 2009). Iron accumulation is also linked with the loss of tight junction proteins and degeneration of endothelial cells, a combination of factors that can result in reduced BBB integrity (Won et al., 2011). Increased BBB permeability due to increased iron accumulation can therefore alter CBF. The susceptibility of the caudate nucleus to the accumulation of excess iron could thus explain the structural and CBF deficits found in this region.

The vulnerability of the caudate nucleus to iron deposits in comorbid AD and T2DM has been supported by previous studies that have found increased iron deposits in the brains of patients diagnosed with AD and T2DM. Using quantitative susceptibility mapping, Moon and colleagues investigated whether excessive iron deposits in the subcortical structures was

associated with dementia (Moon et al., 2016). They found higher iron deposits in the caudate nucleus and putamen in AD patients compared to controls. However, the depositions were not associated with age, clinical disease severity or cognitive function (Moon et al., 2016). In a different study, Yang and colleagues used quantitative susceptibility mapping to examine the pattern of iron depositions in the brain of patients with T2DM. They found that individuals with T2DM showed increased susceptibility to iron deposition in the bilateral caudate head compared to controls, whereas T2DM patients with MCI showed increased susceptibility to iron deposits specifically in the right caudate head (Yang et al., 2018). This provides compelling evidence toward iron toxicity mediated pathology influencing the structural and vascular integrity of the caudate nucleus in comorbid AD and T2DM. The resemblance from the findings of the above studies with the findings from the current study could suggest that iron accumulation may explain the deficits found in the caudate nucleus in the present study, although iron accumulation was not investigated in the current study. Thus, future research is needed in order to understand whether the right caudate nucleus could be susceptible to iron deposits in comorbid AD and T2DM.

Results from the present study are fairly consistent with those found in previous work on patients with T2DM. According to a meta-analysis by Moulton and colleagues, individuals with T2DM presented with subcortical atrophy in comparison with healthy controls (Moulton et al., 2015). Several studies have found specific structural and perfusion deficits in the caudate nucleus of patients with T2DM compared to healthy controls (Chen et al., 2017; Dai et al., 2009; Jansen et al., 2016; Peng et al., 2015; Rofey et al., 2015). Previous research also shows presence of AD pathology in the striatum in early stages of the disease, a finding that could also provide a potential explanation for the structural deficits seen in this region in the present study (Klunk et al., 2007). The combined effect of AD and T2DM pathology could thus have a detrimental effect on the structure and CBF of the caudate nucleus.

6.5.1.2 Parahippocampal gyrus and hippocampus

In the current study, AD patients with T2DM presented with lower WMI and CBF compared to AD patients without T2DM in the parahippocampal gyrus and the hippocampus. Both these brain regions receive their blood supply via the anterior circulation system. The parahippocampal gyrus is supplied by the branches arising from the posterior cerebral artery (that stems from the basilar artery) namely the anterior and posterior temporal arteries (Caplan

& Van Gijn, 2012; Marinković, Milisavljević, & Vučković, 1991). The hippocampus on the other hand is supplied by the anterior choroidal artery (a branch of the internal carotid artery) and branches arising from the posterior cerebral artery that form the majority of the blood supply to the hippocampus (Erdem, Yaşargil, & Roth, 1993). The three main branches that supply the hippocampus (arising from the posterior cerebral artery) are named according to the territory of the hippocampus that they supply, namely anterior, middle and posterior hippocampal arteries (Marinković, Milisavljević, & Puškaš, 1992). The contribution of the anterior choroidal artery toward hippocampal blood supply is highly variable and can depend on the posterior cerebral artery supply (Erdem et al., 1993; Marinković et al., 1992). This variability in the blood supply to the hippocampus and the ‘intrinsic fragility of its vascular network’ could be a factor increasing hippocampal vulnerability to hypoperfusion (Spallazzi et al., 2019). Therefore, in the presence of arteriopathies seen in T2DM, the hippocampus is further prone to damage. Moreover, the hippocampus is highly susceptible to hypoglycaemic damage compared to other brain regions (Dhikav & Anand, 2011). This was further supported by a study examining the association between HbA1c levels and CBF in diabetic patients in different cerebral lobes that found reduced CBF in the temporal lobe, an observation that could indicate a detrimental effect of impaired glucose metabolism in the temporal region (Last et al., 2007). Structural and CBF deficits seen in the MTL regions could thus arise from a number of downstream mechanisms resulting from T2DM and AD.

Past research claims that there is hippocampal involvement in the DMN, albeit this claim has been disputed. Instead, a model where the parahippocampal gyrus acts as a hub for the hippocampal connections to the DMN via a ‘subnetwork’ has been proposed (Ward et al., 2014a). The hippocampus is heavily connected with the parahippocampal gyrus via the entorhinal cortex because the hippocampus has fewer cortical connections compared to the parahippocampal gyrus, which has numerous reciprocal connections with the cortex (Aminoff, Kveraga, & Bar, 2013; Zeidman & Maguire, 2016). Disruptions in the DMN have been reported in both AD and T2DM (section 1.6.2.1 and 6.1.1.2.1). Differential synergistic activations of the DMN and MTL regions are observed during memory encoding and retrieval (Huijbers, Pennartz, Cabeza, & Daselaar, 2011; Vannini et al., 2010). Hippocampal damage due to neuropathological depositions in AD can lead to a loss of connections to the parahippocampal gyrus and consequently from the parahippocampal gyrus to the DMN (Sheline et al., 2010; Zhang et al., 2007b). Congruent with the disconnection hypothesis, a disconnection between these regions is observed in AD (Cui et al., 2015; Zhang et al., 2007b;

Zhou et al., 2015). It is possible that a similar pattern of disconnection might be seen in T2DM as a result of atrophy in the hippocampus. In the present study, hypoperfusion and deficits in WMI extending from the MTL to the posterior cingulum might be indicative of an additional detrimental effect in the underlying disconnection typically seen in AD (section 1.6.2.1). Moreover, recent studies have attempted to establish a link between tau pathology progression along the neurons of anatomically connected brain regions and hypothesised that neurodegeneration spreads via structurally connected networks (De Calignon et al., 2012; Liu et al., 2012a; Pievani et al., 2011). Tau pathology begins in the transentorhinal region (that forms the connection between the parahippocampal gyrus and the hippocampus) before spreading to other brain areas, which could be indicative of the presence of NFT in the parahippocampal gyrus via association with the hippocampus (Dickerson et al., 2001; Khan et al., 2014). Studies have shown that T2DM is linked with higher depositions of tau pathology (Bitel et al., 2012; Jung et al., 2011). Degeneration due to pathology in these regions could thus offer an explanation for the observed deficits in WMI.

The results from the present study are pretty consistent with what has been found in the past. Lower WMI in the MTL structures has previously been shown in AD patients with T2DM (section 6.1.1.1.2). SPECT studies on patients with MCI showed perfusion deficits in the right parahippocampal gyrus (Caroli et al., 2007; Hirao et al., 2005). In one of these studies, amnesic MCI patients who later progressed to AD dementia exhibited hypoperfusion in the right parahippocampal gyrus, left inferior temporal gyrus and left fusiform gyrus (Caroli et al., 2007). A different study found that MCI patients who progressed to AD dementia had hypoperfusion of the bilateral parahippocampal gyrus and right precuneus compared to those who did not progress to dementia (Park et al., 2012). Both these studies proposed that hypoperfusion in the parahippocampal gyrus might be indicative of progression to AD dementia. Atrophy of the right parahippocampal gyrus was observed in studies in patients in later stages of the disease (Burns et al., 2012; Köhler et al., 1998). Lower WMI and CBF in the parahippocampal gyrus and hippocampus found in the present study might, therefore, be an indicator of increased radiological disease severity in AD patients in the presence of T2DM. It is possible that the additional burden of cardiovascular risk factors in later stages of AD has less relative clinical significance on cognition than in earlier stages in individuals with AD and mixed pathologies (O'Brien & Markus, 2014). Therefore, significant changes in cognition resulting from additional vascular burden from comorbidities such as T2DM might be most clinically relevant in prodromal and early disease stages rather than later stages.

It is possible that the deficits in the MTL could be grounded in a theory based on cognitive processes and the interconnected brain networks. The MTL structures have previously been associated with processing of contextual information and memory encoding (Davachi, 2006; Haut et al., 2015; Libby, Hannula, & Ranganath, 2014). Activations in the right parahippocampal gyrus have been associated with encoding of contextual information or episodic memory. Specifically, the anterior parahippocampal gyrus was associated with encoding of information whereas the posterior parahippocampal gyrus was associated with the maintenance of the encoding process (Luck et al., 2010). Baddeley proposed a model where an ‘episodic buffer’ acted as an integrator for the encoding and/or retrieval of episodic memory (Baddeley, 2000; Baddeley, 2003). Luck and colleagues hypothesized that the right parahippocampal gyrus acts as the episodic buffer during memory encoding (Luck et al., 2010). Consistent with the work by Luck and colleagues, the current study finds perfusion and WMI deficits in the right parahippocampal gyrus, indicating a potential disruption in the encoding processes. Past research has indicated that AD and T2DM patients do present with episodic memory deficits (El Haj et al., 2016; Milne et al., 2015; Saxena, 2015). It is possible that impaired glucose metabolism and disease related vascular pathology combined with the deficits in episodic memory could explain the hypoperfusion seen in the right parahippocampal gyrus and hippocampus in AD patients with T2DM.

6.5.1.3 Cerebellum

The cerebellum remains by far the least explored part of the brain, in part due to its exclusion from research analyses (Kumar et al., 2008; Reijmer et al., 2013b). It is implicated in myriad functions namely fine motor movement, vestibulo-ocular response, error monitoring, learning, memory and more (Leggio & Molinari, 2015; Salman & Tsai, 2016). However, its exact role in these functions is still under debate. Nevertheless, the combined effect of T2DM and AD pathology could play some role in modulating cerebellar structure resulting from perfusion deficits. Differences in CBF were particularly observed in the inferior and medial regions of the cerebellum. However, most of the GMV differences in the cerebellum did not overlap with the CBF differences except for the infero-medial regions. These cerebellar regions are supplied by the posterior arterial system, particularly the anterior inferior cerebellar artery and the lateral and medial segments of the posterior inferior cerebellar artery, a branch of the vertebral artery (Gillilan, 1969; Tatu et al., 1996).

As it has been established before, AD and T2DM are accompanied with vascular dysfunction that alters CBF (Dickstein et al., 2010; Wang et al., 2014a). In general, the diameters of the vertebral arteries tend to be asymmetrical with left vertebral arteries presenting with larger diameters than the right vertebral arteries (Jeng & Yip, 2004). This difference in baseline diameters of the vertebral arteries could potentially explain lower blood flow to the right cerebellum via the posterior inferior cerebellar artery. Additionally, atherosclerosis in larger blood vessels leading to embolisms in the connected arteries are a common cause of reduced CBF in the vertebrobasilar arteries (Savitz & Caplan, 2005). The vertebral artery-posterior inferior cerebellar artery junction where the posterior inferior cerebellar artery branches off to supply the cerebellum is highly susceptible to prothrombotic events due to its structure and course (Bertalanffy et al., 2012; Hudgins et al., 1983). Since the posterior inferior cerebellar artery arises from the vertebral artery, occlusions in the respective vertebral artery can lead to reduced blood flow to the ipsilateral region (Amarenco & Hauw, 1990; Gács et al., 1983). The anterior inferior cerebellar artery may also be susceptible to damage due to its angulation from the basilar artery in the presence of arteriopathies. Variability in vertebral artery diameter can also change the angulation of the basilar artery, affecting blood flow, which could in turn cause a reduction in the anterior inferior cerebellar artery blood flow (Jeng & Yip, 2004; Kim, Sohn, & Choi, 2012). Of particular interest, unilateral anterior inferior cerebellar artery infarcts have previously been associated with small artery atherosclerotic disease in patients with diabetes (Amarenco et al., 1993). This could explain part of the hypoperfusion found in areas supplied by the anterior inferior cerebellar artery. However, the evidence supporting the above theories is limited and largely speculative. Also, lower CBF in the cerebellar arteries does not imply a reduction in CBF from other collaterals and it also fails to explain why other areas supplied by the artery do not show differences in CBF.

In conjunction with the vascular dysfunction seen in AD and T2DM, IR (which is seen in both these diseases) might play a role in the structural and functional alterations seen in the cerebellum. Insulin has a neuroprotective role that can protect the brain from apoptosis, vascular insult, A β related toxicity and oxidative stress (Blázquez et al., 2014). There is a high expression of insulin receptors in the cerebellum, striatum, hippocampus, olfactory bulbs and the thalamus (Zahniser et al., 1984). A disturbance in glucose homeostasis resulting from IR can alter brain structure and function and that could potentially explain the deficits in GMV in the cerebellum that do not overlap with hypoperfusion (section 2.1.3). A study looking at the

insulin growth like factor binding ability found very high concentrations of the receptor in the parahippocampal gyrus and a relatively lower concentration in the caudate nucleus and the cerebellum, indicating that IR effects are widespread (Adem et al., 1989). In addition to IR effects, the cerebellum is also susceptible to specific pathological deposits in AD. Although it appears that the cerebellum is relatively spared in terms of neurofibrillary tangle formation, it experiences heavy depositions of A β (Jacobs et al., 2018b; Larner, 1997). Since impaired amyloid clearance is observed as a consequence of insulin dysregulation, the increased amyloid load could be explained by IR (Qiu & Folstein, 2006; Tarasoff-Conway et al., 2015). However, the relative protection against neurofibrillary tangles remains an enigma. AD pathology in the cerebellum is observed in much later stages and it is possible that AD and T2DM related insulin dysregulation play a role in the cerebellar structural deficits seen in the present study.

The present finding of structural and CBF deficits in the cerebellum is unusual, as there is relative preservation of the cerebellum in AD, which could also indicate heightened radiological AD severity in the presence of T2DM (Jacobs et al., 2018b; Larner, 1997). In a longitudinal study comparing MCI groups, where one group progressed to ADD and the other one did not, greater volume loss was observed in the cerebellum of MCI patients who progressed to ADD. The structural atrophic changes were attributed to the susceptibility of the Purkinje cells to ischemic insult (Spulber et al., 2012). In a cross-sectional study comparing healthy controls, MCI and ADD patients, they found differences in cerebellar volumes only between the healthy controls and ADD patients, with the patients presenting with cerebellar GMV deficits (Tabatabaei-Jafari et al., 2017). This pattern of presentation could potentially point toward cerebellar involvement only later in the disease. However, a different study between amnesic MCI and healthy controls found that the patients had lower volumetric deficits compared to controls (Venneri et al., 2011). Therefore, although there seems to be cerebellar involvement in ADD, the pathological mechanisms and the progression of the deficits are still ambiguous.

6.5.1.4 Right lateralised effects

Although past studies have shown a negative effect of T2DM on the brain, a novel finding in the current study is the dominant right-lateralised deficits observed in the comparison between AD patients with and without T2DM in terms of GMV, WMI and CBF. This could potentially be attributed to the course of the internal carotid arteries and their structure before they branch

off in the brain. This structural difference could potentially help shed light on the unilateral detrimental effects seen in the right hemisphere in AD patients with T2DM. The blood is pumped from the heart toward the brain initially through the aorta (Anderson, 2000). It flows upward through the ascending aorta to reach the aortic arch, where it typically trifurcates dorsally into the brachiocephalic artery (also known as the innominate artery), the left subclavian artery and the left common carotid artery (Fig 6.5). The brachiocephalic artery further bifurcates into the right common carotid artery and the right subclavian artery (Jakanani & Adair, 2010; Kadir, 1991). The common carotid and the subclavian arteries give rise to the internal carotid and vertebral arteries that supply the brain, respectively (Netter, 2014).

Since the brachiocephalic artery branches into two main arteries that supply the brain, it has a higher number of bifurcations and larger calibre resulting from a higher influx of blood compared to the left subclavian and left common carotid arteries (Clark et al., 2006). Additionally, the brachiocephalic artery ascends parallel to the direction of the ascending aorta as opposed to the left carotid artery which ascends perpendicular to the aortic arch (Meissner et al., 2004). Hence, the brachiocephalic artery experiences higher wall shear stress compared to the left subclavian and left common carotid arteries making it more prone to wear and tear (Fry, 1973; Huang, Yang, & Lan, 2010). Arteriogenic and atherogenic changes especially due to T2DM that are described earlier, can also influence the walls of these parent arteries and therefore result in alterations in blood flow. These alterations can lead to damage of the collateral blood vessels supplied by the parent arteries (Kim et al., 2011). Additionally, the angles at which the parent arteries ascend, make the ascending arteries to the right more prone to cardiogenic emboli that may eventually enter cerebral hemispheres via the interconnecting arteries and result in cerebrovascular damage (Matsubara et al., 2018; Meissner et al., 2004). In the presence of cardiovascular risk factors that increase atherosclerotic plaque formation, there is a higher circulation of cardiogenic emboli that can occlude blood vessels, thus increasing risk of lower blood flow (Arboix, 2015; Lyaker et al., 2013). These pathological changes in blood flow can ultimately influence the regions that are perfused by the collaterals from these arteries. Therefore, systemic arteriosclerosis and atherosclerotic pathology altering properties of vessel walls in degenerative diseases such as AD and T2DM, can influence cerebral vasculature, particularly in the right hemisphere.

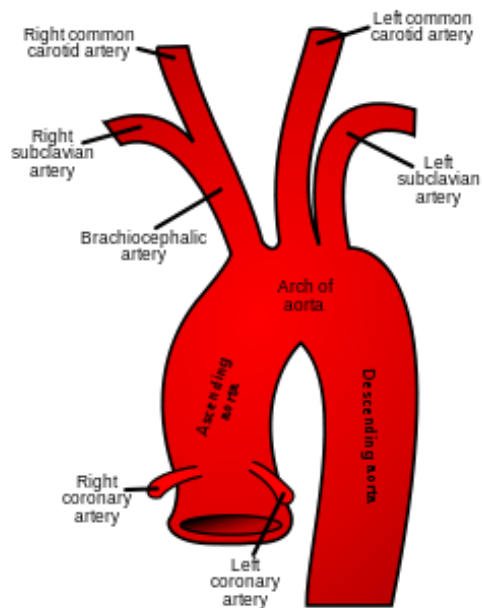


Figure 6.5 Typical trajectory of the brachiocephalic artery (adapted from (Gray, 1878) under the Creative Commons License agreement in Appendix A)

Absence of the cognitive deficits associated with the deficits found in neuroimaging parameters could be attributed to a couple of mechanisms. T2DM is often associated with the development of ‘silent’ infarcts (Kovács et al., 2013). These infarcts are ‘clinically silent’ which means that although individuals may have brain infarcts (that are detectable on MRI), there are no overt or identifiable symptoms presented (Vermeer, Longstreth Jr, & Koudstaal, 2007). Despite the differences observed between AD patients with and without T2DM in brain structure and perfusion, no significant differences were observed in vascular burden. Therefore, it is possible that the extent of the infarcts in the group of AD patients with T2DM was not enough to be associated with cognitive deficits. Another possibility is that in patients already diagnosed with AD, the additional vascular dysfunction caused by the presence of comorbidities such as T2DM does not have as severe an effect on cognitive function as it does in prodromal or earlier disease stages (Esiri et al., 2014; Jellinger, 2001; Lee et al., 2000). Moreover, all the T2DM patients were on medication for glycaemic control, which could have mitigated the deficits seen in cognitive function. Nevertheless, the additional burden can contribute toward altering brain structure and perfusion, which can in turn reduce the available brain reserve, hampering the recruitment of compensatory mechanisms to annul the cognitive deficits (Bischof & Park, 2015; Reuter-Lorenz & Park, 2014). This additional burden can also lead to an accelerated timeline of disease progression and appearance of cognitive deficits with longer disease durations.

Although FA differences were concentrated in the right hemisphere, differences in mean diffusivity were widespread across the cerebral white matter, with the highest concentration of voxels centred around the white matter tracts connecting regions of the DMN. This shows that, although direction dependent diffusion of water molecules (FA) is affected only in the right hemisphere in patients with T2DM, there is widespread restriction of diffusion (mean diffusivity) of water molecules possibly indicating the presence of obstructions (such as miniscule bleeds that are undetected even on MRI or AD pathological formations) restricting their movement. One of the explanations for this phenomenon could be due to the additional vascular dysfunction seen in comorbid AD and T2DM, relative to AD alone. This can lead to the additional build-up of small brain bleeds that could obstruct the diffusion of water molecules in the white matter, similar to the manner in which lesions in multiple sclerosis increase mean diffusivity (Senda et al., 2012). This view is supported by past studies that show that heightened mean diffusivity (and lower FA) is often found in the presence of vascular comorbidities and lesions (Chen et al., 2007; Wang et al., 2015a; Williams et al., 2019b). In two of these studies, APOE status was also associated with higher mean diffusivity and lower FA, indicating that this risk factor for AD could also modulate WMI (Chen et al., 2007; Williams et al., 2019b; Zhou et al., 2011). However, there was no correlation between WMH load and any of the diffusivity measures, indicating that other T2DM-mechanisms could have contributed to the pattern of results.

6.5.2 AD without T2DM vs CN

AD patients without T2DM were compared with the CN group to ensure that the AD patients presented with deficits typical of AD compared to age and gender matched controls. Consistent with previous literature, AD patients without T2DM showed lower GMV in the bilateral MTL areas, the anterior cingulate gyrus and the precuneus in the parietal lobe (section 1.6.1.1). Typically, AD patients show decline in GMV starting in the MTL structures in MCI and prodromal disease stages, with highest atrophy observed in these regions with disease progression (section 1.6). Global atrophy and atrophy of other brain regions (such as the frontal and parietal lobes) is seen with disease progression (section 1.6). Differences in the frontal lobe and parietal lobes were expected, as the group contained patients across the AD spectrum with mild to moderate AD, with varying clinical disease severity. All the significant clusters were positively correlated with tests measuring long term and short term memory (prose memory tests), executive function (phonemic fluency, digit span - backward test) and abstract reasoning

(similarities test). AD patients have shown impaired performance on these domains in the past (Amieva et al., 2008; Di Paola et al., 2007; Izawa et al., 2009; Oda, Yamamoto, & Maeda, 2009; Spaan, Raaijmakers, & Jonker, 2003). Thus, the current AD group without T2DM was representative of the AD phenotype and was appropriate to be compared with AD patients with T2DM to examine how the presence of comorbid T2DM can affect the brain.

Overall, lower WMI integrity was found in the corpus callosum, white matter tracts involved in the limbic circuitry, DMN and subcortical white matter in AD patients without T2DM compared to CN. These findings could indicate that there is extensive damage to various aspects of white matter in AD, especially in the frontal and subcortical brain regions in addition to large callosal fibres in the corpus callosum. According to the neuronal skeletal hypothesis, neurofibrillary tangle pathology tends to spread across structurally and functionally connected brain networks (Cope et al., 2018; Hoenig et al., 2018). It is possible that neuropathological depositions of hyperphosphorylated tau along the white matter tracts seen in AD could contribute toward the disruptions in WMI (Jacobs et al., 2018a; Strain et al., 2018). It appears that lower WMI is seen in AD patients in white matter tracts connecting regions involved in the DMN. Also consistent with the previous literature, lower WMI was expected in the tracts connecting different regions of the DMN and in the subcortical white matter (section 1.6.1.2). Differences in axial diffusivity were found across the corpus callosum, cingulum, subcortical white matter and some white matter tracts in the frontal lobe. These results are mostly consistent with the past literature (Acosta-Cabronero et al., 2010; Shu et al., 2011). In fact, a study by Agosta and colleagues that combined MCI and AD patients showed very similar results to those found in the present study in terms of axial diffusivity (Agosta et al., 2011). Most of the axial diffusivity differences found in the present study were negatively correlated with tests of memory, executive function and abstract reasoning, cognitive domains that are also affected in AD (section 1.3.4). Higher mean diffusivity was found in the white matter tracts in the left MTL regions in addition to inferior frontal regions in the anterior thalamic radiations, thalamic white matter, fornix and uncinate fasciculus. The mean diffusivity differences were more pronounced in the left hemisphere and appeared to involve tracts within the DMN in addition to tracts in the Papez circuit. This is again consistent with the literature as AD has a harsher effect on the left hemisphere in comparison to the right (Thompson et al., 2003; section 1.6.1.1, Para 3). Meanwhile, the differences in radial diffusivity were restricted to frontal brain regions. These findings were mostly consistent with the literature, but differed in the absence of radial diffusivity differences in the MTL between the two groups, which is a

typical finding when comparing AD patients to controls (Agosta et al., 2011; Weiler et al., 2014).

No differences were found in FA between AD patients without T2DM and CN. This is not consistent with past literature as many other studies have found differences in FA between AD patients and controls. One reason for this inconsistent finding could be due to the low sensitivity of FA in detecting AD related differences compared to other DTI measures (Nir et al., 2013). This problem could arise possibly due to the crossing of fibres travelling in different directions in certain brain regions, where the diffusion of water molecules occurs along different directions within the same voxel. Degeneration of fibres in a one particular tract that intersects with white matter tracts that travel in different directions (which changes the direction of diffusion of water molecules), could affect overall FA despite sparing of other tracts crossing the tract displaying lower FA (Reijmer et al., 2012). These results are mostly reflective of those that one would expect to find in typical AD. The variability in the results and their deviation from the typical presentation in AD might arise from the amalgamation of AD patients with dementia and MCI.

In terms of CBF, a typical pattern of difference is seen between CN and AD patients without T2DM in the posterior cingulate and MTL regions (section 1.6.2.3). However, with the uniform threshold that was applied across the results for the comparison of AD patients without T2DM and CN in the present study, only the differences in the cerebellum survived corrections for multiple comparisons. This is an atypical pattern of hypoperfusion for a comparison between AD patients without T2DM and CN. However, lowering the threshold ($p < 0.01$) did reveal a hypoperfusion pattern typical of AD. This difference in the presentation of results due to the level of the threshold could in part be attributed to the extent of vascular contributions or vascular dysfunction seen in the disease. The differences in CBF between AD patients with T2DM compared to CN were far more extensive and widespread than differences found in the comparison between AD patients with and without T2DM. This suggests that the CBF differences between AD patients without T2DM and CN are less severe than the comparisons between the former groups. Therefore, the inherent variability between the three groups in terms of perfusion could warrant the use of alternative thresholds for the interpretation of results. Additionally, lowering the threshold to $p < 0.01$ for all three comparisons shows involvement of the same areas that were found significant using $p < 0.001$ (threshold used in the present study). The comparison between AD patients without T2DM and CN thus shows

that the AD patients included in the current group show a typical AD phenotype compared to CN in terms of differences in GMV, WMI, CBF and cognitive profiles. However, there were some inconsistencies with the existing literature, which could be explained by the variability in the radiological disease severity and profiles in the patient group.

6.5.3 AD patients with T2DM and CN

For the first time, we show the profound effect of comorbid T2DM in AD using multimodal neuroimaging in a comparison between AD patients with T2DM and CN. As predicted, comparisons between these two groups revealed widespread differences in GMV, WMI, CBF and associated cognitive deficits. Consistent with the hypothesis, the results from the current comparison overlapped with the results from the former two comparisons in addition to the involvement of other brain regions. In terms of GMV, the regions that showed differences between the two groups included grey matter structures from the DMN, subcortical structures, lateral and medial frontal lobe, superior and lateral parietal areas, MTL regions, language processing areas (Broca's and Wernicke's areas), insulae, posterior occipital areas and the cerebellum. Using a more conservative threshold showed survival of the results in the temporal poles and the hippocampi, posterior occipital lobes, the cingulate gyrus and parts of the parietal lobe. This presentation of results is consistent with the literature, in that, some of the areas showing volumetric differences are part of the Papez circuit/DMN. The differences in GMV showed associated deficits on tasks measuring memory, executive function and language. These deficits are again consistent with what has been found in the past in AD (section 1.3.4). Additionally, lower GMV was linked with higher vascular burden, which was not found in the comparison between AD patients without T2DM and CN. This could imply that the additional burden of T2DM that is accompanied with vascular complications could have a secondary effect on cognitive function through the modulation of GMV.

Lower WMI was seen mainly in the corpus callosum, white matter tracts connecting grey matter regions of the DMN and subcortical brain regions. Consistent with the Wallerian degeneration hypothesis, WMI was lower in the tracts connecting grey matter regions showing volumetric differences (Coleman, 2005; Stricker et al., 2009; Waller, 1850). Due to the cross-sectional nature of the current study, it is difficult to determine whether GMV differences could explain the differences in WMI or vice-versa. These differences in WMI have also previously been found in comparisons between AD patients with T2DM and CN (section 6.1.1.1.2). With respect to the different diffusivity indices, there were variable results depending on the type of

diffusivity index. Radial diffusivity and FA were lower in the white matter tracts connecting grey matter regions of the DMN, corpus callosum and subcortical brain regions showing that overall direction dependent degeneration of white matter and myelin was found in these regions. On the other hand, mean diffusivity showed widespread differences that resembled the pattern of results found with FA, with voxels spilling over into other large white matter tracts such as the superior longitudinal fasciculus, corticospinal tracts and cerebellothalamic tracts. This shows that pathological processes affecting the brain in comorbid AD and T2DM can have a profound detrimental effect on the integrity of white matter tracts. Axial diffusivity differences were similar to the differences found with FA, but these were mostly restricted to the corpus callosum and the superior portions of the cingulum indicating that axonal integrity is affected the most in these regions in comorbid T2DM and AD. Lower WMI in AD patients with T2DM was associated with lower performance on tasks of short-term memory, attention, abstract reasoning and language.

We expected that the differences in CBF would overlap with the differences found with respect to brain structure. For the most part, an overlap between the CBF differences was found in regions showing differences in brain structure, except in the frontal lobe. The differences in CBF were mostly restricted to inferior and medial brain regions with relative sparing of superior brain regions in the parietal and frontal lobes. Absence of CBF differences in the frontal lobe in the presence of structural deficits could indicate that mechanisms other than lower blood flow could be contributing towards the differences seen. It is possible that this discrepancy could arise from the tendency of shared mechanisms such as IR and glucose dysregulation in comorbid T2DM and AD to target specific brain regions. Differences in CBF were also associated with impaired performance on tasks of episodic and semantic memory.

The extent of the results in the present study highlights that the difference between AD patients with T2DM and CN in terms of cerebral properties and cognitive function is pervasive. The differences not only align with the brain regions showing differences in comparisons between AD patients without T2DM and CN and AD patients with and without T2DM, but they extend beyond the expected differences between the two groups. This could reflect how comorbid T2DM in AD could amplify mechanisms that affect CBF and propagate neurodegenerative processes that can affect myriad brain regions. The fact that these detriments extend beyond those found in the two conditions independently shows that the combination of the pathological processes in comorbid T2DM and AD exert harmful effects on brain regions that are not overtly

vulnerable to these harmful effects. Additionally, the correlations with neuropsychological tests show that cognitive deficits typical of AD are also manifested as a result of comorbid T2DM and AD when compared to controls.

6.5.4 Limitations

The present study was conducted on neuroimaging data that was collected prior to the commencement of the present study, which limits the probability of subsequent monitoring of the patients or gaining additional information pertinent to the research. The present study also uses a cross-sectional design, which restricts the accessibility to patient data that was not acquired at the time of the research appointment with the patient. Such a study design limits the interpretation of the directionality of the findings, as causal effects can only be assumed. Therefore, the overlap of the structural and CBF differences and the interpretation that reduced CBF could be a mechanism propagating structural damage is speculative. Another caveat in this study is the ASL technique which has a low signal to noise ratio, thus reducing the accuracy of the localisation of the brain regions identified with the perfusion deficits. Despite the low signal to noise ratio, we were able to detect CBF differences in areas overlapping with areas exhibiting structural deficits. Additionally, disease duration of T2DM was not collected at the time of recruitment, which could have provided additional insights into the extent of T2DM pathology. Moreover, HbA1c levels were not collected at the time of recruitment, a shortcoming in the study design that limits the inferences that can be drawn from the findings.

6.5.5 Conclusions

This is the first multi-modal MRI study to show that comorbid T2DM in AD can have detrimental effects on brain structure and CBF in a variety of regions, lateralised to the right hemisphere. The considerable degree of convergence in the findings, indicating CBF and structural differences, is particularly novel. Results from the current study suggest that AD and T2DM mediated systemic vascular dysfunction (microvascular and macrovascular changes) resulting in pathological changes in cerebral vasculature may contribute to a majority of the structural deficits observed. These results stress how crucial it is to increase awareness about the ‘silent’ detrimental effects of cardiovascular risk factors in neurodegenerative diseases such as AD, risk factors that could exacerbate the structural and perfusion deficits seen without a clinical manifestation. The silent nature of these detriments also makes them more difficult to detect and prevent. The structural and CBF deficits in AD patients with T2DM could also be representative of increased radiological AD severity in the presence of a comorbidity.

Consequently, there is an urgent need to put in place preventive strategies that could help increase the age of onset or even reduce the incidence of these diseases to improve AD prognosis.

An unexpected finding was the absence of a link with cognitive deficits associated with the detrimental changes seen in the present study when comparing the two AD patient groups with and without T2DM. The cognitive impairment seen as an effect of T2DM therefore, might not be as significant when comparing two pathological subgroups of AD. Moreover, the presence of structural and CBF differences in the absence of a cognitive phenotype is indicative of a reduction in gross brain matter. Consequently, there could be a reduction in the neuroplastic mechanisms that are available in order to compensate for deficits in cognitive function with disease progression (Park et al., 2009). However, increased neuroplastic mechanisms in the presence of disease could help explain why no clinical difference was observed between the patient groups despite a worse radiological phenotype in AD patients with T2DM. The comparison between AD patients with T2DM and CN shows how the presence of a comorbidity in AD could have widespread negative effects that are more extensive than those seen in the comparison between AD patients without T2DM and CN.

Chapter 7: General Discussion

Vascular dysfunction is an established, observable characteristic of AD although it remains unclear whether this dysfunction is observed as an effect of pathological processes seen in AD, the senescence of the vascular system or the presence of comorbidities (Di Marco et al., 2015; Zlokovic, 2011). Using multi-modal neuroimaging, the current thesis highlights that the added effect of certain vascular comorbidities (obesity and T2DM) can in fact increase the radiological severity and in some instances, clinical severity of the AD phenotype in patients. In healthy controls, the presence of these conditions could increase the chances of damage to regions susceptible to AD neurodegeneration and, therefore, could potentially lower the threshold for AD in these individuals. In conjunction with the effect on neuroimaging parameters, experiments from the current thesis show that the presence of modifiable cardiovascular comorbidities and related detriments downstream of these comorbidities, could result in worse cognitive profiles, additional to those already observed in AD (section 1.3.4). This suggests that the presence of obesity and diabetes exacerbates the effects exerted by vascular senescence due to ageing and the pathological processes of AD, that can independently bring about a worse AD phenotype. In addition to the interpretation of the results found in the study, it is also important to account for the thresholding decisions made in the experimental chapters due to the high sensitivity of neuroimaging to weak and diffuse signals (Woo et al., 2014). Using an inappropriate cluster-forming threshold could increase the likelihood of a type I or type II error (Carter, Lesh & Bach, 2016). To reduce the chance of these errors and to improve the replicability of the findings, previously established and more conservative thresholds have been used across the experimental chapters.

Given the irreversible nature of the alterations from AD pathology, its downstream effects, and other non-modifiable risk factors, the modifiable nature of comorbidities such as obesity, hypertension and T2DM make them the crux for AD prevention (Li et al., 2017; Ngandu et al., 2015; Pluta & Ułamek-Kozioł, 2019; Riedel, Thompson, & Brinton, 2016). It is noteworthy that damage from modifiable lifestyle factors can only be mitigated through primary prevention by avoiding the development of the comorbidity, whereas interventions to reduce the prevalence and/or the clinical and radiological severity of these comorbidities would primarily help attenuate any progressive damage without reversing any accumulated damage in the past

(Affleck et al., 2020; Ngandu et al., 2015). Therefore, exploring avenues for early intervention that will aid in reducing the burden exerted by these conditions, could significantly reduce the risk for AD progression and prognosis (Affleck et al., 2020; Ngandu et al., 2015). Although not investigated in the current study, it is possible that findings from the current thesis could suggest that early interventions that implement regimes for weight modifications and medication to restore the individual's biological parameters within the 'normal range' across the lifetime could contribute towards alleviating such detrimental effects (section 4.5.5; section 5.5.5). However, future longitudinal studies introducing interventions to maintain biological parameters within the normal range across the lifetime, particularly beginning from midlife, could help establish the effectiveness of such interventions in reducing AD risk. Such interventions could not only help cater to reducing the risk of AD prognosis and progression but could also reduce the risk of several other diseases (Freisling et al., 2020; Ngandu et al., 2015; Thavendiranathan et al., 2006).

Obesity, hypertension and T2DM often co-occur and effects from each condition can intermingle with effects from a different comorbidity, despite controlling for these factors in statistical models (Colosia et al., 2013; Iglay et al., 2016; Okosun et al., 2001). Taking into account the limitation of our work that the individual effects of these comorbidities cannot be eliminated from the statistical models completely, a detrimental effect of a pathology related to the main variable of interest could play a part in the observed findings across this thesis. The detrimental effect of the additional burden from cardiovascular risk factors in AD patients primarily lies in the subcortical, temporoparietal and frontal brain regions. Although there is involvement of the MTL areas, the primary cause for this effect was presumed to be the pathological burden caused by AD neuropathological depositions in these regions that are typically found in AD patients (Blanken et al., 2017; Braak & Braak 1991). An additional vascular pathological burden found in MTL regions resulting from cardiovascular comorbidities, however, is also likely (Jiménez-Balado et al., 2018; Kril et al., 2002; Schwartz et al., 2010). In fact, a study has shown enlarged perivascular spaces around the hippocampus in hypertensive individuals and MCI patients and this enlargement was aggravated in older patients with poor blood pressure control (Jiménez-Balado et al., 2018).

On the other hand, the susceptibility of the subcortical structures to vascular and structural damage can be attributed to the delicate nature of the arteries supplying these regions and their vulnerability to vascular damage (Moody et al., 1990). These arteries have smaller diameters

and relatively thinner media lining the arterial walls (Moody et al., 1990). Arteries with smaller diameters are more susceptible to vascular damage from arteriopathies observed in the presence of modifiable cardiovascular risk factors, such as atherosclerosis and arteriosclerosis (Gutierrez et al., 2015). Moreover, these perforating arteries bifurcate several times before going on to supply subcortical structures, vascular territories that are downstream from the primary source of blood, which could make such arteries more vulnerable to the cumulative damage exerted by upstream vessels (Rosner et al., 1984; Soustiel et al., 2001). This vulnerability of perforating arteries provides evidence towards how the increasing distance of the tributary artery from the parent artery increases its susceptibility to damage in AD, especially in the presence of a cardiovascular comorbidity. Subcortical structural and vascular damage was a prominent feature in hypertensive and diabetic AD patients, and was also associated with higher anthropometric measures of obesity in cognitively normal individuals and MCI patients to an extent, indicating that vascular dysfunction, specifically fluctuations in blood pressure (seen in hypertension and T2DM) are highly detrimental to these structures in AD.

In addition to the vulnerability of subcortical brain regions to the negative effects of cardiovascular comorbidities, the experiments in the current thesis highlighted that frontal and temporoparietal brain regions are also susceptible to these effects. Of note, these detriments seem to augment the well-known ‘disconnection’ that is observed in AD patients (section 1.6.2.1). This was evident in the associations observed between obesity measures, neuroimaging parameters and cognitive performance in MCI patients and cognitively normal individuals and also in the comparison between AD patients with T2DM, AD patients without T2DM and cognitively normal individuals. The observed associations with obesity measures in MCI were linked with higher vascular burden (as measured using WMH volume), which was not as pronounced in cognitively normal individuals although this latter group had on average higher obesity indices than the MCI patients (section 4.5.2 and 4.5.3). This observation could indicate that in the presence of AD pathology, the additive detrimental effect of overweight might increase radiological and clinical AD severity through the effect of vascular pathological formations in MCI, which may not be as severe in the absence of a neurodegenerative process as in the cognitively healthy group. These pathological WMH formations could be the result of an interaction between AD and overweight-related pathological processes (Kim et al., 2017; Park et al., 2020). A recent study has even shown that WMH burden may mediate the functional connectivity between frontoparietal brain regions (Park et al., 2020). Lower CBF and WMI associated with higher obesity and overweight

measures around periventricular fronto-temporoparietal regions in cognitively normal individuals and MCI patients (no associations found with WMI), also found in the comparison between AD patients with and without T2DM, may suggest that the combined presence of obesity/overweight and T2DM could further contribute toward the characteristic ‘disconnection’ seen in AD (section 1.6.2.1). The fact that the additive effect of overweight, obesity and T2DM affects temporoparietal regions, areas that are heavily affected by neuropathological processes in the course of AD, advocate primary prevention in early decades of life to curb progressive and irreversible insults related to obesity and T2DM in brain regions vulnerable to AD, to reduce AD risk in CN and radiological and clinical disease severity in AD patients (Desikan et al., 2009). Findings of detrimental effects of obesity and T2DM in frontal brain regions, that are affected much later in AD, further support the need for reducing prevalence of cardiovascular risk factors, as this observation is indicative of increased radiological disease severity in AD patients and reduced brain reserve that may lower the threshold for AD in CN (section 1.6 and 4.1.1). This observation could also be attributed to accumulation of AD pathology in temporoparietal regions, as indicated in a study which demonstrated that accumulation of pathology in remote and functionally connected brain regions could affect brain areas that are not known predilection sites for heavy AD pathological accumulations, such as the prefrontal cortex (Klupp et al., 2015).

The majority of the negative effects of cardiovascular risk factors were found in the periventricular regions indicating a higher susceptibility of these regions to conditions that increase vascular burden. Periventricular brain regions are generally supplied by distal branches of major cerebral arteries (De Reuck, 1971). In the presence of metabolic conditions that can significantly alter CBF, these distal arteries are more prone to adverse vascular events. Moreover, the BBB tends to be more permeable around periventricular regions to permit the exchange of substances from the systemic circulation into the central nervous system (Bennett et al., 2009). Considering that the breakdown of the BBB is a central feature seen in AD, obesity, hypertension and T2DM, damage to the BBB in the periventricular areas can further increase permeability that can lead to the extravasation of vessel contents into the brain parenchyma (Kaya et al., 2003; Sweeney et al., 2018; Tucsek et al., 2014). Thus, a breakdown of the BBB can cause aggregations of harmful substances that can promote neurodegenerative processes that can, in turn, increase AD severity and AD risk (Kim et al., 2003; Takechi et al., 2017).

Formations of cerebral amyloid angiopathy pathology seen in AD, hypertension and T2DM in periventricular regions, could further add to the reductions in CBF that could be detrimental to brain structure and cognitive function (Charidimou et al., 2016; Ellis et al., 1996; Holland et al., 2008; Mandybur, 1975; Marnane et al., 2016; Peila et al., 2002). Therefore, this property of periventricular brain regions could make these areas more susceptible to formations of vascular pathology such as WMH. Periventricular WMH have previously been associated with cortical thinning in the frontal lobe, which could explain the cardiovascular comorbidity-related detriments in the frontal lobe across the different studies in this thesis (Seo et al., 2012). The experiments from the thesis also highlight the need to investigate the directionality of white matter and grey matter damage. Since AD is primarily a grey matter disease and the prominent susceptibility of white matter to vascular damage, understanding whether damage to white matter due to the presence of a cardiovascular comorbidity could be a factor in additive detriments observed in grey matter, could highlight some of the mechanisms that foster increased disease severity in AD patients with comorbidities (Agosta et al., 2011; Venkat et al., 2017; section 1.6). Future studies with a longitudinal design that explore the directionality of grey and white matter damage in the presence of a vascular comorbidity in AD could thus shed light on this mechanism.

Although there were several indications of cardiovascular comorbidity-related damage, there was also an indication of a preservative effect on blood flow and brain structure in the temporoparietal brain regions in ADD patients who were within the 'normal' range of biological parameters. This was especially evident in patients with ADD who fell within the normal BMI and WC ranges. In this group, higher values of the normal weight range helped preserve brain structure in the temporoparietal regions, mostly likely due to vascular mechanisms. This observation is supported by evidence from a previous longitudinal study which showed that higher BMI in late-life was associated with reduced risk of AD progression and also with reduced AD risk (Sun et al., 2020). The lateralisation of this preservative effect in the right hemisphere could be explained by the higher susceptibility of the left hemisphere to early AD-related effects which could have spared the right hemisphere from more extensive damage (Liu et al., 2018). Prevention strategies, therefore, could be less effective on core areas affected by pathology very early, but would manifest mostly in regions better preserved in the earliest stages and would spare the right hemisphere from more extensive damage, at least in the early stages of AD.

Additionally, the positive effects observed were primarily found in the vascular territory supplied by the middle cerebral artery, the biggest artery that supplies a wide range of brain structures and is prone to damage from vascular comorbidities (Bustamante et al., 2016; Caplan, 2015; Momjian-Mayor & Baron, 2005). Thus, it appears that the bigger arteries that are more prone to damage may benefit the most from the protective effects of higher body mass in later stages of AD. This positive effect is also consistent with the ‘obesity paradox,’ which states that the relationship between obesity and AD is confounded in the later and clinical stages of the disease due to age and AD-related weight loss (Pegueroles et al., 2018). Therefore, in patients who are at a more advanced disease stage, nutritional interventions to promote weight gain among those patients with very low BMI could help limit progressive detriments to the brain and cognition. A previous study has shown that in cognitively impaired patients admitted for rehabilitation through nutritional and physical activity interventions to improve functional activities, those patients with a BMI below 20 did not show any benefits from the interventions although those patients with a BMI above 20 did benefit from the rehabilitation program (Vassallo et al., 2016). This could indicate early intervention to prevent extensive weight loss and any possible detrimental irreversible brain damage might be advisable in the early stages of AD to ensure effectiveness of nutritional interventions to facilitate weight gain in AD patients in later disease stages.

Pharmacological interventions to attenuate the negative effect of modifiable cardiovascular comorbidities can also help reduce the risk for AD or even lower the level of disease severity. These interventions cannot help in reversing any damage that is already inflicted on the brain but can help limit any progressive damage due to the comorbidity (Fournier et al., 2009; Fukui et al., 2014; Wharton et al., 2019). In support of this statement, a study has shown lower neuropathological burden and slower disease progression in MCI patients taking antihypertensive drugs (Wharton et al., 2019). However, findings in this thesis in the comparison between AD patients on antihypertensive treatment who had a medical history of hypertension and AD patients unmedicated for hypertension do not support this statement. The fact that there were no significant differences in neuroimaging and cognitive parameters could imply that medicating for hypertension had no statistically detectable impact in this patient cohort.

Findings from this thesis did not demonstrate substantial benefits of administering antihypertensive treatment to AD patients, suggesting, however, that the class of

antihypertensive drugs used needs careful consideration. Comparisons on neuroimaging parameters between AD patients on different classes of antihypertensive treatment (with a medical history of hypertension) revealed that AD patients who were taking beta-blockers only, had a better AD phenotype than AD patients on other classes of antihypertensive treatment other than beta-blockers and AD patients on a combination of both beta-blockers and other classes of antihypertensive drugs. Part of an explanation for this observation could lie in the blood pressure measurement differences across the groups where AD patients on beta-blockers only, had the lowest pulse pressure values and blood pressure measurements within the normotensive range compared to the other two groups. However, the cross-sectional nature of the data limits the interpretation of these findings as inferences about the actual effect of beta-blockers cannot be drawn without a history of the medication use and longitudinal effects on the biological parameters. Similarly, with respect to T2DM, the type of medication used could alter the additional burden exerted by the condition, in cases with comorbid T2DM and AD. In AD patients with a history of T2DM who were on glucose-control treatments, an additional detrimental effect of the presence of T2DM was detected, and this detrimental effect was inferred primarily as an effect of vascular dysfunction due to the co-localisation of structural and CBF differences between AD patients with and without T2DM. Therefore, considering other medications that could help lower the vascular burden due to T2DM and its related comorbid conditions, especially in patients with AD who accumulate AD-related pathological depositions that are aggravated in the presence of vascular comorbidities could aid in reducing disease severity in AD patients with comorbid T2DM.

7.1 Limitations

The cross-sectional nature of the data used across the experiments in this thesis limits some of the inferences that can be drawn from the research findings. One such aspect is with respect to the deduction of the direction of the causality of the findings. For instance, with respect to the co-localised pattern of findings of CBF and brain structure, it cannot be inferred whether a reduction in blood flow could explain the findings in brain structure or vice-versa. Future longitudinal studies using multi-modal neuroimaging to examine the effect of comorbidities in AD patients would be helpful in addressing this issue. Another aspect of this limitation is the single time point measurements of blood pressure readings and obesity indices. Blood pressure readings can be highly variable in an individual and there are several factors that could

contribute towards this variability (Kikuya et al., 2008; Rothwell et al., 2010b). Similarly, obesity indices can vary across an individual's lifetime and since the relationship between these measurements and cerebral constituents can change over the life-course, it limits the inferences that can be drawn from the current findings (Pegueroles et al., 2018). Using multiple anthropometric measures taken at regular intervals could help inform some of the inferences that can be drawn from the current findings. Furthermore, the medication history of the study participants was limited to the medications that were prescribed to them at the time of recruitment. A life-long medical history could also help inform some approaches to data analysis to draw meaningful inferences from the findings.

The data used across the different experiments has been collected across various centres in the UK, Italy and Finland. Although this provides a great advantage to studying the effects of cardiovascular risk factors on the brain in varied populations, it can also introduce some limitations in terms of controlling for differences in variability in the population characteristics across the centres. Attempts were made to control for the effects of the centre of recruitment. However, using categorical variables to control for the complexity of multifactorial differences in the different centres might not be sufficient to account for inter-centre variability in variables such as diet and physical composition.

7.2 Conclusions

Although the majority of the findings from this thesis highlights the need for introducing primary prevention measures that could help reduce the prevalence of cardiovascular risk factors through interventions on modifiable risk factors in a timely manner, to reduce AD risk, results from the study on hypertension in AD do not support this conclusion. However, reducing the prevalence of obesity and T2DM could not only help reduce AD risk in healthy individuals, but could also help reduce the radiological and clinical severity of the AD phenotype, as the additional burden from these comorbid cardiovascular risk factors can contribute toward increased brain vulnerability to neurodegeneration in known predilection sites for AD. With respect to pharmacological treatments, future longitudinal studies are needed to examine the effects of different therapeutic drugs used in the treatment of cardiovascular risk factors on cerebral properties, and which specific treatments can aid in

reducing AD risk and clinical and radiological AD severity. Similarly, future work investigating the long-term effects of multi-domain interventions to reduce the prevalence of cardiovascular risk factors to reduce AD risk would go a long way in identifying the most effective measures to reduce AD risk. It is also of note that measures to reduce the severity of cardiovascular comorbidities in order to improve AD prognosis are most effective in early stages of AD, and this highlights the need for exploring new avenues for early identification of individuals at-risk of AD to implement targeted interventions in a timely manner to reduce AD risk.

References

- Aalkjær, C., Boedtkjer, D., & Matchkov, V. (2011). Vasomotion—what is currently thought? *Acta Physiologica*, 202(3), 253-269. <https://doi.org/10.1111/j.1748-1716.2011.02320.x>
- Abad, V. M., García-Polo, P., O'Daly, O., Hernández-Tamames, J. A., & Zelaya, F. (2016). ASAP (Automatic Software for ASL Processing): a toolbox for processing arterial spin labeling images. *Magnetic Resonance Imaging*, 34(3), 334-344. <https://doi.org/10.1016/j.mri.2015.11.002>
- Abarca-Gómez, L., Abdeen, Z. A., Hamid, Z. A., Abu-Rmeileh, N. M., Acosta-Cazares, B., Acuin, C., Adams, R. J., Aekplakorn, W., Afsana, K., Aguilar-Salinas, C., Agyemang, C., Ahmadvand, A., Ahrens, W., Ajlouni, K., Akhteva, N., Al-Hazzaa, H. M., Al-Othman, A. R., Al-Raddadi, R., Al Buhairan, F., ... Ezzati, M. (2017). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128· 9 million children, adolescents, and adults. *The Lancet*, 390(10113), 2627-2642. [https://doi.org/10.1016/S0140-6736\(17\)32129-3](https://doi.org/10.1016/S0140-6736(17)32129-3)
- Abbott, R. D., White, L. R., Ross, G. W., Masaki, K. H., Curb, J. D., & Petrovitch, H. (2004). Walking and dementia in physically capable elderly men. *JAMA*, 292(12), 1447-1453. <https://doi.org/10.1001/jama.292.12.1447>
- Abdi, H. (2007). Bonferroni and Šidák corrections for multiple comparisons. *Encyclopedia of measurement and statistics*, 3, 103-107.
- Abdullah, L., Crawford, F., Tsolaki, M., Börjesson-Hanson, A., Olde Rikkert, M., Pasquier, Wallin, A., Kennelly, S., Ait-Ghezala, G., Paris, D., Hendrix, S., Blennow, K., Lawlor, B., & Mullan, M. (2020). The influence of baseline Alzheimer's disease severity on cognitive decline and CSF biomarkers in the NILVAD trial. *Frontiers in Neurology*, 11, 149. <https://doi.org/10.3389/fneur.2020.00149>
- Abner, E. L., Nelson, P. T., Kryscio, R. J., Schmitt, F. A., Fardo, D. W., Woltjer, R. L., Cairns, N. J., Yu, L., Dodge, H. H., Xiong, C., Masaki, K., Tyas, S. L., Bennett, D. A., Schneider, J. A., & Arvanitakis, Z. (2016). Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology. *Alzheimer's & Dementia*, 12(8), 882-889. <https://doi.org/10.1016/j.jalz.2015.12.006>
- Acharya, N. K., Levin, E. C., Clifford, P. M., Han, M., Tourtellotte, R., Chamberlain, D., Pollaro, M., Coretti, N. J., Kosciuk, M. C., Nagele, E. P., DeMarshall, C., Freeman, T., Shi, Y., Guan, C., Macphee, C. H., Wilensky, R. L., & Nagele, R. G. (2013). Diabetes and hypercholesterolemia increase blood-brain barrier permeability and brain amyloid deposition: beneficial effects of the LpPLA2 inhibitor darapladib. *Journal of Alzheimer's Disease*, 35(1), 179-198. <https://doi.org/10.3233/JAD-122254>
- Acosta-Cabrero, J., Williams, G. B., Pengas, G., & Nestor, P. J. (2010). Absolute diffusivities define the landscape of white matter degeneration in Alzheimer's disease. *Brain*, 133(2), 529-539. <https://doi.org/10.1093/brain/awp257>
- Adem, A., Jossan, S., d'Argy, R., Gillberg, P., Nordberg, A., Winblad, B., & Sara, V. (1989). Insulin-like growth factor 1 (IGF-1) receptors in the human brain: quantitative autoradiographic localization. *Brain Research*, 503(2), 299-303. [https://doi.org/10.1016/0006-8993\(89\)91678-8](https://doi.org/10.1016/0006-8993(89)91678-8)
- Adler, A. I., Stratton, I. M., Neil, H. A. W., Yudkin, J. S., Matthews, D. R., Cull, C. A., Wright, A. D., Turner, R. C., & Holman, R. R. (2000). Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*, 321(7258), 412-419. <https://doi.org/10.1136/bmj.321.7258.412>

- Affleck, A. J., Sachdev, P. S., Stevens, J., & Halliday, G. M. (2020). Antihypertensive medications ameliorate Alzheimer's disease pathology by slowing its propagation. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 6(1), e12060. <https://doi.org/10.1002/trc2.12060>
- Agosta, F., Pievani, M., Geroldi, C., Copetti, M., Frisoni, G. B., & Filippi, M. (2012). Resting state fMRI in Alzheimer's disease: Beyond the default mode network. *Neurobiology of Aging*, 33(8), 1564-1578. <https://doi.org/10.1016/j.neurobiolaging.2011.06.007>
- Agosta, F., Pievani, M., Sala, S., Geroldi, C., Galluzzi, S., Frisoni, G. B., & Filippi, M. (2011). White matter damage in Alzheimer disease and its relationship to gray matter atrophy. *Radiology*, 258(3), 853-863. <https://doi.org/10.1148/radiol.10101284>
- Ahmad, A. A., Taboada, C. B., Gassmann, M., & Ogunshola, O. O. (2011). Astrocytes and pericytes differentially modulate blood—brain barrier characteristics during development and hypoxic insult. *Journal of Cerebral Blood Flow & Metabolism*, 31(2), 693-705. <https://doi.org/10.1038/jcbfm.2010.148>
- Ahmed, S., de Jager, C. A., Haigh, A. M. F. & Garrard, P. (2012). Logopenic aphasia in Alzheimer's disease: Clinical variant or clinical feature. *Journal of Neurology, Neurosurgery and Psychiatry*, 83(11), 1056-1062. <http://dx.doi.org/10.1136/jnnp-2012-302798>
- Ahtiluoto, S., Polvikoski, T., Peltonen, M., Solomon, A., Tuomilehto, J., Winblad, B., Sulkava, R., & Kivipelto, M. (2010). Diabetes, Alzheimer disease, and vascular dementia A population-based neuropathologic study. *Neurology*, 75(13), 1195-1202. <https://doi.org/10.1212/WNL.0b013e3181f4d7f8>
- Akintola, A. A., van Opstal, A. M., Westendorp, R. G., Postmus, I., van der Grond, J., & van Heemst, D. (2017). Effect of intranasally administered insulin on cerebral blood flow and perfusion; A randomized experiment in young and older adults. *Aging (Albany NY)*, 9(3), 790. <https://doi.org/10.18632/aging.101192>
- Akoudad, S., Wolters, F. J., Viswanathan, A., de Bruijn, R. F., van der Lugt, A., Hofman, A., Koudstaal, P. J., Ikram, A. M. & Vernooij, M. K. (2016). Association of cerebral microbleeds with cognitive decline and dementia. *JAMA Neurology*, 73(8), 934-943. <https://doi.org/10.1001/jamaneurol.2016.1017>
- Akushevich, I., Kravchenko, J., Ukraintseva, S., Arbee, K., & Yashin, A. I. (2013). Time trends of incidence of age-associated diseases in the US elderly population: Medicare-based analysis. *Age and Ageing*, 42(4), 494-500. <https://doi.org/10.1093/ageing/aft032>
- Al Rifai, M., DeFilippis, A. P., McEvoy, J. W., Hall, M. E., Acien, A. N., Jones, M. R., Keith, R., Magid, H. S., Rodriguez, C. J., Barr, G. R., Benjamin, E. J., Robertson, R., Bhatnagar, A. & Blaha, M. J. (2017). The relationship between smoking intensity and subclinical cardiovascular injury: The Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*, 258, 119-130. <https://doi.org/10.1016/j.atherosclerosis.2017.01.021>
- Alagiakrishnan, K., & Sclater, A. (2012). Psychiatric disorders presenting in the elderly with type 2 diabetes mellitus. *The American Journal of Geriatric Psychiatry*, 20(8), 645-652. <https://doi.org/10.1097/JGP.0b013e31823038db>
- Alastruey, J., Parker, K., Peiró, J., Byrd, S., & Sherwin, S. J. (2007). Modelling the circle of Willis to assess the effects of anatomical variations and occlusions on cerebral flows. *Journal of Biomechanics*, 40(8), 1794-1805. <https://doi.org/10.1016/j.jbiomech.2006.07.008>
- Albanese, E., Davis, B., Jonsson, P. V., Chang, M., Aspelund, T., Garcia, M., Harris, T., Gudnason, V. & Launer, L. J. (2015). Overweight and obesity in midlife and brain structure and dementia 26 years later: the AGES-Reykjavik study. *American Journal of Epidemiology*, 181(9), 672-679. <https://doi.org/10.1093/aje/kwu331>
- Albert, C. M., Manson, J. E., Cook, N. R., Ajani, U. A., Gaziano, J. M., & Hennekens, C. H. (1999). Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians. *Circulation*, 100(9), 944-950. <https://doi.org/10.1161/01.CIR.100.9.944>

- Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7(3), 270-279. <https://doi.org/10.1016/j.jalz.2011.03.008>
- Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., Fruchart, J., Philip, W., James, T., Loria C. M. & Smith Jr, S. C. (2009). Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*, 120(16), 1640-1645. <https://doi.org/10.1161/CIRCULATIONAHA.109.192644>
- Alberti, K. G., Zimmet, P., Shaw, J. & IDF Epidemiology Task Group (2005). The metabolic syndrome--a new worldwide definition. *Lancet*, 366(9491), 1059-1062. [https://doi.org/10.1016/S0140-6736\(05\)67402-8](https://doi.org/10.1016/S0140-6736(05)67402-8)
- Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics*, 4(3), 316-329. <https://doi.org/10.1016/j.nurt.2007.05.011>
- Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular depression'hypothesis. *Archives of General Psychiatry*, 54(10), 915-922. <https://doi.org/10.1001/archpsyc.1997.01830220033006>
- Alexopoulos, P., Sorg, C., Forschler, A., Grimmer, T., Skokou, M., Wohlschlager, A., Perneczky, R., Zimmer, C., Kurz, A. & Preibisch, C. (2012). Perfusion abnormalities in mild cognitive impairment and mild dementia in Alzheimer's disease measured by pulsed arterial spin labeling MRI. *European Archives of Psychiatry and Clinical Neuroscience*, 262(1), 69-77. <https://doi.org/10.1007/s00406-011-0226-2>
- Aliev, G., Palacios, H. H., Lipsitt, A. E., Fischbach, K., Lamb, B. T., Obrenovich, M. E., Morales, L., Gasimov, E. & Bragin, V. (2009). Nitric oxide as an initiator of brain lesions during the development of Alzheimer disease. *Neurotoxicity Research*, 16(3), 293-305. <https://doi.org/10.1007/s12640-009-9066-5>
- Alkatheri, A. M., & Albekairy, A. M. (2013). Does the patients' educational level and previous counseling affect their medication knowledge? *Annals of Thoracic Medicine*, 8(2), 105. <https://doi.org/10.4103/1817-1737.109823>
- Allen, G., McColl, R., Barnard, H., Ringe, W. K., Fleckenstein, J., & Cullum, C. M. (2005). Magnetic resonance imaging of cerebellar–prefrontal and cerebellar–parietal functional connectivity. *Neuroimage*, 28(1), 39-48. <https://doi.org/10.1016/j.neuroimage.2005.06.013>
- Alosco, M. L., Gunstad, J., Xu, X., Clark, U. S., Labbe, D. R., Riskin-Jones, H. H., Terrero, G., Schwarz, N. F., Walsh, E. G., Poppas, A., Cohen, R. A., & Sweet L. H. (2014). The impact of hypertension on cerebral perfusion and cortical thickness in older adults. *Journal of the American Society of Hypertension*, 8(8), 561-570. <https://doi.org/10.1016/j.jash.2014.04.002>
- Alsop, D. C., Casement, M., de Bazelaire, C., Fong, T., & Press, D. Z. (2008). Hippocampal hyperperfusion in Alzheimer's disease. *NeuroImage*, 42(4), 1267-1274. <https://doi.org/10.1016/j.neuroimage.2008.06.006>
- Alsop, D. C., Dai, W., Grossman, M., & Detre, J. A. (2010). Arterial spin labeling blood flow MRI: its role in the early characterization of Alzheimer's disease. *Journal of Alzheimer's Disease*, 20(3), 871-880. <https://doi.org/10.3233/JAD-2010-091699>
- Alsop, D. C., Detre, J. A., Golay, X., Günther, M., Hendrikse, J., Hernandez-Garcia, L., Lu, H., MacIntosh, B. J., Parkes, L. M., Smits, M., van Osch, M. J., Wang, D. J., Wong, E. C., & Zaharchuk, G. (2015). Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European

- consortium for ASL in dementia. *Magnetic Resonance in Medicine*, 73(1), 102-116.
<https://doi.org/10.1002/mrm.25197>
- Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Reviews*, 16(1), 17-42. <https://doi.org/10.1007/s11065-006-9002-x>
- Alzheimer, A., Förstl, H., & Levy, R. (1991). On certain peculiar diseases of old age. *History of Psychiatry*, 2(5), 71-73.
- Alzheimer, A. (1907). Über eine eigenartige Erkrankung der Hirnrinde. *Allg. Z. Psychiatr.*, 64, 146-148.
- Amarenco, P., & Hauw, J. J. (1990). Cerebellar infarction in the territory of the anterior and inferior cerebellar artery: A clinicopathological study of 20 cases. *Brain*, 113 (1), 139-155.
<https://doi.org/10.1093/brain/113.1.139>
- Amarenco, P., Rosengart, A., DeWitt, L. D., Pessin, M. S., & Caplan, L. R. (1993). Anterior inferior cerebellar artery territory infarcts: Mechanisms and clinical features. *Archives of Neurology*, 50(2), 154-161. <https://doi.org/10.1001/archneur.1993.00540020032014>
- Ambikairajah, A., Tabatabaei-Jafari, H., Walsh, E., Hornberger, M., & Cherbuin, N. (2020). Longitudinal Changes in Fat Mass and the Hippocampus. *Obesity*, 28(7), 1263-1269
<https://doi.org/10.1002/oby.22819>
- Amen, D. G., Wu, J., George, N., & Newberg, A. (2020). Patterns of Regional Cerebral Blood Flow as a Function of Obesity in Adults. *Journal of Alzheimer's Disease*, 77(3), 1331-1337.
<https://doi.org/10.3233/JAD-200655>
- Amenta, F., Mignini, F., Rabbia, F., Tomassoni, D., & Veglio, F. (2002). Protective effect of anti-hypertensive treatment on cognitive function in essential hypertension: analysis of published clinical data. *Journal of the Neurological Sciences*, 203-204, 147-151.
[https://doi.org/10.1016/s0022-510x\(02\)00281-2](https://doi.org/10.1016/s0022-510x(02)00281-2)
- American Diabetes Association (2016). 2. Classification and diagnosis of diabetes. *Diabetes Care*, 39(Supplement 1), S13-S22. <https://doi.org/10.2337/dc16-er09>
- American Diabetes Association (2002). Screening for diabetes. *Diabetes care*, 25(suppl 1), s21-s24.
<https://doi.org/10.2337/diacare.25.2007.S21>
- American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub.
- Amieva, H., Le Goff, M., Millet, X., Orgogozo, J. M., Pérès, K., Barberger-Gateau, P., Jacqmin-Gadda, H., & Dartigues, J. F. (2008). Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. *Annals of Neurology*, 64(5), 492-498.
<https://doi.org/10.1002/ana.21509>
- Aminoff, E. M., Kveraga, K., & Bar, M. (2013). The role of the parahippocampal cortex in cognition. *Trends in Cognitive Sciences*, 17(8), 379-390.
<https://doi.org/10.1016/j.tics.2013.06.009>
- Amlien, I. K., & Fjell, A. M. (2014). Diffusion tensor imaging of white matter degeneration in Alzheimer's disease and mild cognitive impairment. *Neuroscience*, 276, 206-215.
<https://doi.org/10.1016/j.neuroscience.2014.02.017>
- Ammirati, E., Moroni, F., Magnoni, M., Rocca, M.A., Messina, R., Anzalone, N., De Filippis, C., Scotti, I., Besana, F., Spagnolo, P., & Rimoldi, O.E. (2017). Relation between characteristics of carotid atherosclerotic plaques and brain white matter hyperintensities in asymptomatic patients. *Scientific reports*, 7(1), 1-11. <https://doi.org/10.1038/s41598-017-11216-x>
- Amoroso, S., Schmid-Antomarchi, H., Fosset, M., & Lazdunski, M. (1990). Glucose, sulfonylureas, and neurotransmitter release: role of ATP-sensitive K⁺ channels. *Science*, 247(4944), 852-854. <https://doi.org/10.1126/science.2305257>
- Anan, F., Masaki, T., Shimomura, T., Fujiki, M., Umeno, Y., Eshima, N., Saikawa, T., & Yoshimatsu, H. (2010). Abdominal visceral fat accumulation is associated with hippocampus

- volume in non-dementia patients with type 2 diabetes mellitus. *NeuroImage*, 49(1), 57-62.
<https://doi.org/10.1016/j.neuroimage.2009.08.021>
- Anderson, E. A., & Mark, A. L. J. H. (1993). The vasodilator action of insulin. Implications for the insulin hypothesis of hypertension. *Hypertension*, 21(2), 136-141.
<https://doi.org/10.1161/01.HYP.21.2.136>
- Anderson, R. H. (2000). Clinical anatomy of the aortic root. *Heart*, 84(6), 670-673.
<http://dx.doi.org/10.1136/heart.84.6.670>
- Andrews, J. S., Desai, U., Kirson, N. Y., Zichlin, M. L., Ball, D. E., & Matthews, B. R. (2019). Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)*, 5, 354-363.
<https://doi.org/10.1016/j.trci.2019.06.005>
- Anstey, K., Cherbuin, N., Budge, M., & Young, J. (2011). Body mass index in midlife and late-life as a risk factor for dementia: A meta-analysis of prospective studies. *Obesity Reviews*, 12(5), e426-e437. <https://doi.org/10.1111/j.1467-789X.2010.00825.x>
- Anstey, K. J., Ashby-Mitchell, K., & Peters, R. (2017). Updating the evidence on the association between serum cholesterol and risk of late-life dementia: Review and meta-analysis. *Journal of Alzheimer's Disease*, 56(1), 215-228. <https://doi.org/10.3233/JAD-160826>
- Anstey, K. J., Mack, H. A., & Cherbuin, N. (2009). Alcohol consumption as a risk factor for dementia and cognitive decline: Meta-analysis of prospective studies. *The American Journal of Geriatric Psychiatry*, 17(7), 542-555. <https://doi.org/10.1097/JGP.0b013e3181a2fd07>
- Antunović, V., Mirčić, A., Marinković, S., Brigante, L., Mališ, M., Georgievski, B., & Aksić, M. (2017). Clinical Significance of the Cerebral Perforating Arteries. *Prilozi*, 38(3), 19-29.
<https://doi.org/10.2478/prilozi-2018-0003>
- Arai, H., Takahashi, M., Yutani, M., Ikeda, T., Oishi, S., & Miyaoka, H. (2012). Relationship among white matter hyperintensity, arterial stiffness, associated diseases, and lifestyle in late-onset Alzheimer's disease patients. *Kitasato Medical Journal*, 42, 83-90. Retrieved from:
<https://www.kitasato-u.ac.jp/ktms/kaishi/pdf/KMJ42-1/KMJ42-1p083-090.pdf>
- Arber, C., Li, A., Houlden, H., & Wray, S. (2016). Insights into molecular mechanisms of disease in neurodegeneration with brain iron accumulation: Unifying theories. *Neuropathology and Applied Neurobiology*, 42(3), 220-241. <https://doi.org/10.1111/nan.12242>
- Arboix, A. (2015). Cardiovascular risk factors for acute stroke: Risk profiles in the different subtypes of ischemic stroke. *World Journal of Clinical Cases*, 3(5), 418.
<https://doi.org/10.12998/wjcc.v3.i5.418>
- Arenillas, J. F. (2011). Intracranial atherosclerosis: current concepts. *Stroke*, 42(1 Suppl), S20-23.
<https://doi.org/10.1161/STROKEAHA.110.597278>
- Aribisala, B. S., Morris, Z., Eadie, E., Thomas, A., Gow, A., Valdés Hernández, M. C., Royle, N. A., Bastin, M. E., Starr, J., Deary, I. J., & Wardlaw, J. M. (2014). Blood pressure, internal carotid artery flow parameters, and age-related white matter hyperintensities. *Hypertension*, 63(5), 1011-1018. <https://doi.org/10.1161/HYPERTENSIONAHA.113.02735>
- Arita, Y., Kihara, S., Ouchi, N., Takahashi, M., Maeda, K., Miyagawa, J., Hotta, K., Shimomura, I., Nakamura, T., Miyaoka, K., Kuriyama, H., Nishida, M., Yamashita, S., Okubo, K., Matsubara, K., Muraguchi, M., Ohmoto, Y., Funahashi, T., & Matsuzawa, Y. (1999). Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochemical and Biophysical Research Communications*, 257(1), 79-83.
<https://doi.org/10.1006/bbrc.1999.0255>
- Armstrong, K. A., Campbell, S. B., Hawley, C. M., Nicol, D. L., Johnson, D. W., & Isbel, N. M. (2005). Obesity is associated with worsening cardiovascular risk factor profiles and proteinuria progression in renal transplant recipients. *American Journal of Transplantation*, 5(11), 2710-2718. <https://doi.org/10.1111/j.1600-6143.2005.01073.x>

- Arner, P., Bernard, S., Appelsved, L., Fu, K.-Y., Andersson, D., Salehpour, M., Thorell, A., Rydén, M., & Spalding, L. K. (2019). Adipose lipid turnover and long-term changes in body weight. *Nature Medicine*, *25*(9), 1385-1389. <https://doi.org/10.1038/s41591-019-0565-5>
- Arnold, S. E., Arvanitakis, Z., Macauley-Rambach, S. L., Koenig, A. M., Wang, H. Y., Ahima, R. S., Craft, S., Gandy, S., Buettner, C., Stoeckel, L. E., Holtzman, D. M., & Nathan, D. M. (2018). Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nature Reviews Neurology*, *14*, 168-181. <https://doi.org/10.1038/nrneuro.2017.185>
- Arnold, S. E., Hyman, B. T., Flory, J., Damasio, A. R., & Van Hoesen, G. W. (1991). The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cerebral Cortex*, *1*(1), 103-116. <https://doi.org/10.1093/cercor/1.1.103>
- Arruda, A. P., Pers, B. M., Parlakgöl, G., Güney, E., Inouye, K., & Hotamisligil, G. S. (2014). Chronic enrichment of hepatic endoplasmic reticulum-mitochondria contact leads to mitochondrial dysfunction in obesity. *Nature Medicine*, *20*(12), 1427-1435. <https://doi.org/10.1038/nm.3735>
- Ashburner, J. (2010). VBM tutorial. *Tech. rep* Wellcome Trust Centre for Neuroimaging, London, UK.
- Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—The methods. *NeuroImage*, *11*(6), 805-821. <https://doi.org/10.1006/nimg.2000.0582>
- Assaf, Y., & Pasternak, O. (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. *Journal of Molecular Neuroscience*, *34*(1), 51-61. <https://doi.org/10.1007/s12031-007-0029-0>
- Au, R., Massaro, J. M., Wolf, P. A., Young, M. E., Beiser, A., Seshadri, S., D'Agostino, R. B., & DeCarli, C. (2006). Association of white matter hyperintensity volume with decreased cognitive functioning: The Framingham Heart Study. *Archives of Neurology*, *63*(2), 246-250. <https://doi.org/10.1001/archneur.63.2.246>
- Auvity, S., Tonietto, M., Caillé, F., Bodini, B., Bottlaender, M., Tournier, N., Kuhnast, B., & Stankoff, B. (2020). Repurposing radiotracers for myelin imaging: a study comparing 18F-florbetaben, 18F-florbetapir, 18F-flutemetamol, 11C-MeDAS, and 11C-PiB. *European Journal of Nuclear Medicine and Molecular Imaging*, *47*(2), 490-501. <https://doi.org/10.1007/s00259-019-04516-z>
- Baba, H., Nakano, Y., Maeshima, H., Satomura, E., Kita, Y., Suzuki, T., & Arai, H. (2012). Metabolism of amyloid- β protein may be affected in depression. *The Journal of Clinical Psychiatry*, *73*(1), 115-120. <https://doi.org/10.4088/JCP.10m06766>
- Bach, D., Naon, D., Pich, S., Soriano, F. X., Vega, N., Rieusset, J., Laville, M., Guillet, C., Boirie, Y., Wallberg-Henriksson, H., Manco, M., Calvani, M., Castagneto, M., Palacín, M., Mingrone, G., Zierath, J. R., Vidal, H., & Zorzano, A. (2005). Expression of Mfn2, the Charcot-Marie-Tooth neuropathy type 2A gene, in human skeletal muscle: Effects of type 2 diabetes, obesity, weight loss, and the regulatory role of tumor necrosis factor α and interleukin-6. *Diabetes*, *54*(9), 2685-2693. <https://doi.org/10.2337/diabetes.54.9.2685>
- Bachevalier, J., & Vargha-Khadem, F. (2005). The primate hippocampus: Ontogeny, early insult and memory. *Current Opinion in Neurobiology*, *15*(2), 168-174. <https://doi.org/10.1016/j.conb.2005.03.015>
- Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences*, *4*(11), 417-423. [https://doi.org/10.1016/S1364-6613\(00\)01538-2](https://doi.org/10.1016/S1364-6613(00)01538-2)
- Baddeley, A. (2003). Working memory: Looking back and looking forward. *Nature Reviews Neuroscience*, *4*(10), 829. <https://doi.org/10.1038/nrn1201>
- Badhwar, A., Tam, A., Dansereau, C., Orban, P., Hoffstaedter, F., & Bellec, P. (2017). Resting-state network dysfunction in Alzheimer's disease: A systematic review and meta-analysis.

- Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 8, 73-85.
<https://doi.org/10.1016/j.dadm.2017.03.007>
- Baek, K., Morris, L. S., Kundu, P., & Voon, V. (2017). Disrupted resting-state brain network properties in obesity: Decreased global and putaminal cortico-striatal network efficiency. *Psychological Medicine*, 47(4), 585-596. <https://doi.org/10.1017/S0033291716002646>
- Bai, F., Watson, D. R., Yu, H., Shi, Y., Yuan, Y., & Zhang, Z. (2009). Abnormal resting-state functional connectivity of posterior cingulate cortex in amnesic type mild cognitive impairment. *Brain Research*, 1302, 167-174. <https://doi.org/10.1016/j.brainres.2009.09.028>
- Baker, L. D., Cross, D. J., Minoshima, S., Belongia, D., Watson, G. S., & Craft, S. (2011). Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Archives of Neurology*, 68(1), 51-57. <https://doi.org/10.1001/archneurol.2010.225>
- Baker-Nigh, A., Vahedi, S., Davis, E. G., Weintraub, S., Bigio, E. H., Klein, W. L., & Geula, C. (2015). Neuronal amyloid- β accumulation within cholinergic basal forebrain in ageing and Alzheimer's disease. *Brain*, 138(6), 1722-1737. <https://doi.org/10.1093/brain/awv024>
- Ballabh, P., Braun, A., & Nedergaard, M. (2004). The blood-brain barrier: an overview: structure, regulation, and clinical implications. *Neurobiology of Disease*, 16(1), 1-13. <https://doi.org/10.1016/j.nbd.2003.12.016>
- Bamford, J., Sandercock, P., Dennis, M., Warlow, C., & Burn, J. (1991). Classification and natural history of clinically identifiable subtypes of cerebral infarction. *The Lancet*, 337(8756), 1521-1526. [https://doi.org/10.1016/0140-6736\(91\)93206-O](https://doi.org/10.1016/0140-6736(91)93206-O)
- Bang, O. Y., Saver, J., Ovbiagele, B., Choi, Y., Yoon, S., & Lee, K. H. (2007). Adiponectin levels in patients with intracranial atherosclerosis. *Neurology*, 68(22), 1931-1937. <https://doi.org/10.1212/01.wnl.0000263186.20988.9f>
- Bangen, K. J., Werhane, M. L., Weigand, A. J., Edmonds, E. C., Delano-Wood, L., Thomas, K. R., Nation, D. A., Evangelista, N. D., Clark, A. L., Liu, T. T., & Bondi, M. W. (2018). Reduced regional cerebral blood flow relates to poorer cognition in older adults with type 2 diabetes. *Frontiers in Aging Neuroscience*, 10, 270. <https://doi.org/10.3389/fnagi.2018.00270>
- Banks, W. A. (2004). The source of cerebral insulin. *European journal of pharmacology*, 490(1-3), 5-12. <https://doi.org/10.1016/j.ejphar.2004.02.040>
- Banks, W. A., Jaspán, J. B., Huang, W., & Kastin, A. J. (1997). Transport of insulin across the blood-brain barrier: saturability at euglycemic doses of insulin. *Peptides*, 18(9), 1423-1429. [https://doi.org/10.1016/S0196-9781\(97\)00231-3](https://doi.org/10.1016/S0196-9781(97)00231-3)
- Banks, W. A., Kastin, A. J., Huang, W., Jaspán, J. B., & Maness, L. M. (1996). Leptin enters the brain by a saturable system independent of insulin. *Peptides*, 17(2), 305-311. [https://doi.org/10.1016/0196-9781\(96\)00025-3](https://doi.org/10.1016/0196-9781(96)00025-3)
- Baranowska-Bik, A., & Bik, W. (2019). Vascular dysfunction and insulin resistance in aging. *Current Vascular Pharmacology*, 17(5), 465-475. <https://doi.org/10.2174/1570161117666181129113611>
- Baranowska-Bik, A., Bik, W., Styczynska, M., Chodakowska-Zebrowska, M., Barcikowska, M., Wolinska-Witort, E., Kalisz, M., Martynska, L., & Baranowska, B. (2015). Plasma leptin levels and free leptin index in women with Alzheimer's disease. *Neuropeptides*, 52, 73-78. <https://doi.org/10.1016/j.npep.2015.05.006>
- Barbagallo, M., & Dominguez, L. J. (2014). Type 2 diabetes mellitus and Alzheimer's disease. *World Journal of Diabetes*, 5(6), 889. <https://doi.org/10.4239/wjd.v5.i6.889>
- Barnard, N. D., Bush, A. I., Ceccarelli, A., Cooper, J., de Jager, C. A., Erickson, K. I., Fraser, G., Kesler, S., Levin, S. M., Lucey, B., Morris, M., & Squitti, R. (2014). Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. *Neurobiology of Aging*, 35, S74-S78. <https://doi.org/10.1016/j.neurobiolaging.2014.03.033>

- Barnes, D. E., Alexopoulos, G. S., Lopez, O. L., Williamson, J. D., & Yaffe, K. (2006). Depressive symptoms, vascular disease, and mild cognitive impairment: Findings from the Cardiovascular Health Study. *Archives of General Psychiatry*, *63*(3), 273-279. <https://doi.org/10.1001/archpsyc.63.3.273>
- Barnes, D. E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurology*, *10*(9), 819-828. [https://doi.org/10.1016/S1474-4422\(11\)70072-2](https://doi.org/10.1016/S1474-4422(11)70072-2)
- Barnes, D. E., Yaffe, K., Byers, A. L., McCormick, M., Schaefer, C., & Whitmer, R. A. (2012). Midlife vs late-life depressive symptoms and risk of dementia: Differential effects for Alzheimer disease and vascular dementia. *Archives of General Psychiatry*, *69*(5), 493-498. <https://doi.org/10.1001/archgenpsychiatry.2011.1481>
- Barron, A. M., Rosario, E. R., Elteriefi, R., & Pike, C. J. (2013). Sex-specific effects of high fat diet on indices of metabolic syndrome in 3xTg-AD mice: Implications for Alzheimer's disease. *PLoS One*, *8*(10), e78554. <https://doi.org/10.1371/journal.pone.0078554>
- Bartzokis, G. (2004). Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiology of Aging*, *25*(1), 5-18. <https://doi.org/10.1016/j.neurobiolaging.2003.03.001>
- Basser, P. J., & Pierpaoli, C. (2011). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance*, *213*(2), 560-570. <https://doi.org/10.1016/j.jmr.2011.09.022>
- Basta, G. (2008). Receptor for advanced glycation endproducts and atherosclerosis: From basic mechanisms to clinical implications. *Atherosclerosis*, *196*(1), 9-21. <https://doi.org/10.1016/j.atherosclerosis.2007.07.025>
- Basta, G., Lazzarini, G., Massaro, M., Simoncini, T., Tanganelli, P., Fu, C., Kislinger, T., Stern, D. M., Schmidt, A. M., De Caterina, R. (2002). Advanced glycation end products activate endothelium through signal-transduction receptor RAGE: A mechanism for amplification of inflammatory responses. *Circulation*, *105*(7), 816-822. <https://doi.org/10.1161/hc0702.104183>
- Basta, G., Schmidt, A. M., & De Caterina, R. (2004). Advanced glycation end products and vascular inflammation: Implications for accelerated atherosclerosis in diabetes. *Cardiovascular Research*, *63*(4), 582-592. <https://doi.org/10.1016/j.cardiores.2004.05.001>
- Bateman, R. J., Aisen, P. S., De Strooper, B., Fox, N. C., Lemere, C. A., Ringman, J. M., Salloway, S., Sperling, R. A., Windisch, M., & Xiong, C. (2011). Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimer's Research and Therapy*, *3*(1), 1. <https://doi.org/10.1186/alzrt59>
- Bates, S. H., Dundon, T. A., Seifert, M., Carlson, M., Maratos-Flier, E., & Myers, M. G. (2004). LRB-STAT3 signaling is required for the neuroendocrine regulation of energy expenditure by leptin. *Diabetes*, *53*(12), 3067-3073. <https://doi.org/10.2337/diabetes.53.12.3067>
- Baudic, S., Barba, G. D., Thibaudet, M. C., Smagghe, A., Remy, P., & Traykov, L. (2006). Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Archives of Clinical Neuropsychology*, *21*(1), 15-21. <https://doi.org/10.1016/j.acn.2005.07.002>
- Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., & Johns, H. (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimer's & Dementia*, *11*(6), 718-726. <https://doi.org/10.1016/j.jalz.2015.05.016>
- Baumgartner-Parzer, S. M., Wagner, L., Pettermann, M., Grillari, J., Gessl, A., & Waldhäusl, W. (1995). High-glucose-triggered apoptosis in cultured endothelial cells. *Diabetes*, *44*(11), 1323-1327. <https://doi.org/10.2337/diab.44.11.1323>

- Beach, T. G., Wilson, J. R., Sue, L. I., Newell, A., Poston, M., Cisneros, R., Pandya, Y., Esh, C., Connor, D. J., Sabbagh, M., Walker, D. G., & Roher, A. E. (2007). Circle of Willis atherosclerosis: Association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. *Acta Neuropathologica*, *113*(1), 13-21. <https://doi.org/10.1007/s00401-006-0136-y>
- Beal, M. F., Lang, A. E., & Ludolph, A. C. (2005). *Neurodegenerative diseases: Neurobiology, Pathogenesis, and Therapeutics*. Cambridge, UK; New York: Cambridge University Press.
- Beason-Held, L. L., Moghekar, A., Zonderman, A. B., Kraut, M. A., & Resnick, S. M. (2007). Longitudinal changes in cerebral blood flow in the older hypertensive brain. *Stroke*, *38*(6), 1766-1773. <https://doi.org/10.1161/STROKEAHA.106.477109>
- Beenackers, M. A., Kamphuis, C. B., Giskes, K., Brug, J., Kunst, A. E., Burdorf, A., & van Lenthe, F. J. (2012). Socioeconomic inequalities in occupational, leisure-time, and transport related physical activity among European adults: A systematic review. *International Journal of Behavioral Nutrition and Physical Activity*, *9*(1), 1-23. <https://doi.org/10.1186/1479-5868-9-116>
- Beer, J. S., & Ochsner, K. N. (2006). Social cognition: A multi level analysis. *Brain Research*, *1079*(1), 98-105. <https://doi.org/10.1016/j.brainres.2006.01.002>
- Beeri, M., Rapp, M., Silverman, J., Schmeidler, J., Grossman, H., Fallon, J., Purohit, D. P., Perl, D. P., Siddiqui, A., Lesser G., Rosendorff, C., & Haroutunian, V. (2006a). Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers. *Neurology*, *66*(9), 1399-1404. <https://doi.org/10.1212/01.wnl.0000210447.19748.0b>
- Beeri, M., Schmeidler, J., Sano, M., Wang, J., Lally, R., Grossman, H., & Silverman, J. (2006b). Age, gender, and education norms on the CERAD neuropsychological battery in the oldest old. *Neurology*, *67*(6), 1006-1010. <https://doi.org/10.1212/01.wnl.0000237548.15734.cd>
- Beeri, M. S., Silverman, J. M., Davis, K. L., Marin, D., Grossman, H. Z., Schmeidler, J., Purohit, D. P., Perl, D. P., Davidson, M., Mohs, R. C., & Haroutunian, V. (2005). Type 2 diabetes is negatively associated with Alzheimer's disease neuropathology. *The Journals of Gerontology Series A*, *60*(4), 471-475. <https://doi.org/10.1093/gerona/60.4.471>
- Belhadj Slimen, I., Najar, T., Ghram, A., Dabbebi, H., Ben Mrad, M., & Abdrabbah, M. (2014). Reactive oxygen species, heat stress and oxidative-induced mitochondrial damage. A review. *International Journal of Hyperthermia*, *30*(7), 513-523. <https://doi.org/10.3109/02656736.2014.971446>
- Bell, R. D., Winkler, E. A., Sagare, A. P., Singh, I., LaRue, B., Deane, R., & Zlokovic, B. V. (2010). Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. *Neuron*, *68*(3), 409-427. <https://doi.org/10.1016/j.neuron.2010.09.043>
- Bellana, B., Liu, Z. X., Diamond, N. B., Grady, C. L., & Moscovitch, M. (2017). Similarities and differences in the default mode network across rest, retrieval, and future imagining. *Human Brain Mapping*, *38*(3), 1155-1171. <https://doi.org/10.1002/hbm.23445>
- Belleville, S., Chertkow, H., & Gauthier, S. (2007). Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology*, *21*(4), 458-469. <https://doi.org/10.1037/0894-4105.21.4.458>
- Bellew, K. M., Pigeon, J. G., Stang, P. E., Fleischman, W., Gardner, R. M., & Baker, W. W. (2004). Hypertension and the rate of cognitive decline in patients with dementia of the Alzheimer type. *Alzheimer Disease & Associated Disorders*, *18*(4), 208-213.
- Bellou, V., Belbasis, L., Tzoulaki, I., & Evangelou, E. (2018). Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. *PLoS One*, *13*(3). <https://doi.org/10.1371/journal.pone.0194127>
- Bennett, L., Yang, M., Enikolopov, G., & Iacovitti, L. (2009). Circumventricular organs: A novel site of neural stem cells in the adult brain. *Molecular and Cellular Neuroscience*, *41*(3), 337-347. <https://doi.org/10.1016/j.mcn.2009.04.007>

- Benson, D. F., Davis, R. J., & Snyder, B. D. (1988). Posterior cortical atrophy. *Archives of Neurology*, 45(7), 789-793. <https://doi.org/10.1001/archneur.1988.00520310107024>
- Benzinou, M., Creemers, J. W., Choquet, H., Lobbens, S., Dina, C., Durand, E., Guerardel, A., Boutin, P., Jouret, B., Heude, B., Balkau, B., Tichet, J., Marre, M., Potoczna, N., Horber, F., Le Stunff, C., Czernichow, S., Sandbaek, A., Lauritzen, T., ... Froguel, P. (2008). Common nonsynonymous variants in PCSK1 confer risk of obesity. *Nature Genetics*, 40(8), 943. <https://doi.org/10.1038/ng.177>
- Berkman, N. D., Sheridan, S. L., Donahue, K. E., Halpern, D. J., & Crotty, K. (2011). Low health literacy and health outcomes: An updated systematic review. *Annals of Internal Medicine*, 155(2), 97-107. <https://doi.org/10.1016/j.mcn.2009.04.007>
- Bertalanffy, H., Benes, L., Heinze, S., Tirakotai, W., & Sure, U. (2012). Surgical management of aneurysms of the vertebral and posterior inferior cerebellar artery complex. In A. Quiñones-Hinojosa (Ed.). *Schmidek and Sweet Operative Neurosurgical Techniques (Sixth Edition)* (pp. 937-950). WB Saunders. <https://doi.org/10.1016/C2011-1-05132-9>
- Besser, L. M., Gill, D. P., Monsell, S. E., Brenowitz, W., Meranus, D., Kukull, W., & Gustafson, D. R. (2014). Body mass index, weight change, and clinical progression in mild cognitive impairment and Alzheimer's disease. *Alzheimer Disease and Associated Disorders*, 28(1), 36. <https://doi.org/10.1097/WAD.0000000000000005>
- Bettcher, B. M. (2017). Chapter 19: Normal aging of the frontal lobes. In B. L. Miller & J. L. Cumming (Eds.). *The Human Frontal Lobes: Functions and Disorders (Third edition)* (pp. 343-356). The Guilford Press.
- Beyer, F., Kharabian Masouleh, S., Huntenburg, J. M., Lampe, L., Luck, T., Riedel-Heller, S. G., Loeffler, M., Schroeter, M. L., Stumvoll, M., Villringer, A., & Witte, V. (2017). Higher body mass index is associated with reduced posterior default mode connectivity in older adults. *Human Brain Mapping*, 38(7), 3502-3515. <https://doi.org/10.1002/hbm.23605>
- Biessels, G. J., & Reagan, L. P. (2015). Hippocampal insulin resistance and cognitive dysfunction. *Nature Reviews Neuroscience*, 16(11), 660-671. <https://doi.org/10.1038/nrn4019>
- Biessels, G. J., & Reijmer, Y. D. (2014). Brain changes underlying cognitive dysfunction in diabetes: What can we learn from MRI? *Diabetes*, 63(7), 2244-2252.
- Biffi, A., & Greenberg, S. M. (2011). Cerebral amyloid angiopathy: A systematic review. *Journal of Clinical Neurology*, 7(1), 1-9. <https://doi.org/10.3988/jcn.2011.7.1.1>
- Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral cortex*, 19(12), 2767-2796. <https://doi.org/10.1093/cercor/bhp055>
- Binkofski, F. & Seitz, R. J. (2004). Modulation of the BOLD-response in early recovery from sensorimotor stroke. *Neurology*, 63(7), 1223-1229. <https://doi.org/10.1212/01.WNL.0000140468.92212.BE>
- Bischof, G. N., Jessen, F., Fliessbach, K., Dronse, J., Hammes, J., Neumaier, B., Onur, O., Fink, G. R., Kukolja, J., Drzezga, A., van Eimeren, T., & Alzheimer's Disease Neuroimaging Initiative (ADNI) (2016). Impact of tau and amyloid burden on glucose metabolism in Alzheimer's disease. *Annals of Clinical and Translational Neurology* 3(12), 934-939. <https://doi.org/10.1002/acn3.339>
- Bischof, G. N., & Park, D. C. (2015). Obesity and aging: Consequences for cognition, brain structure and brain function. *Psychosomatic Medicine*, 77(6), 697. <https://doi.org/10.1097/PSY.0000000000000212>
- Bitel, C. L., Kasinathan, C., Kaswala, R. H., Klein, W. L., & Frederikse, P. H. (2012). Amyloid- β and tau pathology of Alzheimer's disease induced by diabetes in a rabbit animal model. *Journal of Alzheimer's Disease*, 32(2), 291-305. <https://doi.org/10.3233/JAD-2012-120571>

- Black, C. M., Ritchie, C. W., Wood, R., Jones, E., Ambegaonkar, B. M., Ahir, H., & Khandker, R. K. (2017). The race to diagnose: Disease severity as a factor of Alzheimer's Disease diagnosis. *Alzheimer's & Dementia*, *13*(7), P511. <https://doi.org/10.1016/j.jalz.2017.06.581>
- Blackwell, A. D., Sahakian, B. J., Vesey, R., Semple, J. M., Robbins, T. W., & Hodges, J. R. (2004). Detecting dementia: Novel neuropsychological markers of preclinical Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *17*(1-2), 42-48. <https://doi.org/10.1159/000074081>
- Blanco-Rojas, L., Arboix, A., Canovas, D., Grau-Olivares, M., Morera, J. C. O., & Parra, O. (2013). Cognitive profile in patients with a first-ever lacunar infarct with and without silent lacunes: a comparative study. *BMC Neurology*, *13*(1), 203. <https://doi.org/10.1186/1471-2377-13-203>
- Blanken, A.E., Hurtz, S., Zarow, C., Biado, K., Honarpisheh, H., Somme, J., Brook, J., Tung, S., Kraft, E., Lo, D., Ng, D.W., Vinters, H. V., & Apostolova, L. G. (2017). Associations between hippocampal morphometry and neuropathologic markers of Alzheimer's disease using 7 T MRI. *NeuroImage: Clinical*, *15*, 56-61. <https://doi.org/10.1016/j.nicl.2017.04.020>
- Blasko, I., Kemmler, G., Jungwirth, S., Wichart, I., Krampla, W., Weissgram, S., Jellinger, K., Heinz, Tragl, K. H., & Fischer, P. (2010). Plasma amyloid beta-42 independently predicts both late-onset depression and Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *18*(11), 973-982. <https://doi.org/10.1097/JGP.0b013e3181df48be>
- Blautzik, J., Kotz, S., Brendel, M., Sauerbeck, J., Vettermann, F., Winter, Y., Bartenstein, P., Ishii, K., Rominger, A. & Alzheimer's Disease Neuroimaging Initiative (ADNI) (2018). Relationship between body mass index, ApoE4 status, and PET-based amyloid and neurodegeneration markers in amyloid-positive subjects with normal cognition or mild cognitive impairment. *Journal of Alzheimer's Disease*, *65*(3), 781-791. <https://doi.org/10.3233/JAD-170064>
- Blázquez, E., Velázquez, E., Hurtado-Carneiro, V., & Ruiz-Albusac, J. M. (2014). Insulin in the brain: Its pathophysiological implications for States related with central insulin resistance, type 2 diabetes and Alzheimer's disease. *Frontiers in Endocrinology*, *5*, 161. <https://doi.org/10.3389/fendo.2014.00161>
- Blennerhassett, R., Lillo, P., Halliday, G. M., Hodges, J. R., & Kril, J. J. (2014). Distribution of pathology in frontal variant Alzheimer's disease. *Journal of Alzheimer's Disease*, *39*(1), 63-70. <https://doi.org/10.3233/JAD-131241>
- Blennow, K., Mattsson, N., Schöll, M., Hansson, O., & Zetterberg, H. (2015). Amyloid biomarkers in Alzheimer's disease. *Trends in Pharmacological Sciences*, *36*(5), 297-309. <https://doi.org/10.1016/j.tips.2015.03.002>
- Blumenfeld, H. (2010). *Neuroanatomy through clinical cases*: Sinauer Associates Sunderland.
- Blumenthal, J. A., Babyak, M. A., Sherwood, A., Craighead, L., Lin, P.-H., Johnson, J., Watkins, L. L., Wang, J. T., Kuhn, C., Feinglos, M., & Hinderliter, A. (2010). Effects of the dietary approaches to stop hypertension diet alone and in combination with exercise and caloric restriction on insulin sensitivity and lipids. *Hypertension*, *55*(5), 1199-1205. <https://doi.org/10.1161/HYPERTENSIONAHA.109.149153>
- Bobb, J. F., Schwartz, B. S., Davatzikos, C., & Caffo, B. (2014). Cross-sectional and longitudinal association of body mass index and brain volume. *Human Brain Mapping* *35*(1), 75-88. <https://doi.org/10.1002/hbm.22159>
- Bohnen, N. I., Kaufer, D. I., Hendrickson, R., Ivanco, L. S., Lopresti, B., Davis, J. G., Constantine, G., Mathis, C. A., Moore, R. Y., & DeKosky, S. T. (2005). Cognitive correlates of alterations in acetylcholinesterase in Alzheimer's disease. *Neuroscience Letters*, *380*(1-2), 127-132. <https://doi.org/10.1016/j.neulet.2005.01.031>
- Bondareff, W., & Geinisman, Y. (1976). Loss of synapses in the dentate gyrus of the senescent rat. *American Journal of Anatomy*, *145*(1), 129-136. <https://doi.org/10.1002/aja.1001450110>

- Boots, E. A., Schultz, S. A., Oh, J. M., Larson, J., Edwards, D., Cook, D., Kosciak, R. L., Dowling, M. N., Gallagher, C. L., Carlsson, C. M., Rowley, H. A., Bendlin, B. B., LaRue, A., Asthana, S., Hermann, B. P., Sager, M. A., Johnson, S. C., & Okonkwo, O. C. (2015). Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease. *Brain Imaging and Behaviour*, 9(3), 639-649. <https://doi.org/10.1007/s11682-014-9325-9>
- Bornstein, R. A., & Suga, L. J. (1988). Educational level and neuropsychological performance in healthy elderly subjects. *Developmental Neuropsychology*, 4(1), 17-22.
- Borogovac, A., & Asllani, I. (2012). Arterial spin labeling (ASL) fMRI: Advantages, theoretical constraints and experimental challenges in neurosciences. *International Journal of Biomedical Imaging*, 2012. <https://doi.org/10.1155/2012/818456>
- Borroni, B., Grassi, M., Costanzi, C., Archetti, S., Caimi, L., & Padovani, A. (2006). APOE genotype and cholesterol levels in lewy body dementia and Alzheimer disease: Investigating genotype-phenotype effect on disease risk. *The American Journal of Geriatric Psychiatry*, 14(12), 1022-1031. <https://doi.org/10.1097/01.JGP.0000225088.29353.08>
- Bos, M. J., Koudstaal, P. J., Hofman, A., & Ikram, M. A. (2014). Modifiable etiological factors and the burden of stroke from the Rotterdam study: A population-based cohort study. *PloS Medicine*, 11(4), e1001634. <https://doi.org/10.1371/journal.pmed.1001634>
- Bouma, G. J., Muizelaar, J. P., Stringer, W. A., Choi, S. C., Fatouros, P., & Young, H. F. (1992). Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. *Journal of Neurosurgery*, 77(3), 360-368. <https://doi.org/10.3171/jns.1992.77.3.0360>
- Boutouyrie P., Beaussier H., Laurent S. (2015) Hemodynamic and Mechanical Factors Acting on Arteries. In: Berbari A., Mancina G. (Eds.), *Arterial Disorders*. (93-99). Springer, Cham. https://doi.org/10.1007/978-3-319-14556-3_7
- Boyle, C. P., Raji, C. A., Erickson, K. I., Lopez, O. L., Becker, J. T., Gach, H. M., Longstreth Jr., W. T., Teverovskiy, L., Kuller, L. H., Carmichael, O. T., & Thompson, P. M., (2015). Physical activity, body mass index, and brain atrophy in Alzheimer's disease. *Neurobiology of Aging*, 36, S194-S202. <https://doi.org/10.1016/j.neurobiolaging.2014.05.036>
- Boyles, J., Notterpek, L., & Anderson, L. J. (1990). Accumulation of apolipoproteins in the regenerating and remyelinating mammalian peripheral nerve. Identification of apolipoprotein D, apolipoprotein A-IV, apolipoprotein E, and apolipoprotein A-I. *Journal of Biological Chemistry*, 265(29), 17805-17815. [https://doi.org/10.1016/S0021-9258\(18\)38235-8](https://doi.org/10.1016/S0021-9258(18)38235-8)
- Bozzali, M., Padovani, A., Caltagirone, C., & Borroni, B. (2011). Regional grey matter loss and brain disconnection across Alzheimer disease evolution. *Current Medicinal Chemistry*, 18(16), 2452-2458. <https://doi.org/10.2174/092986711795843263>
- Braak, H., & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica*, 82(4), 239-259.
- Braak, H., & Braak, E. (1997). Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiology of Aging*, 18(4), 351-357. [https://doi.org/10.1016/S0197-4580\(97\)00056-0](https://doi.org/10.1016/S0197-4580(97)00056-0)
- Braak, H., Braak, E., & Kalus, P. (1989). Alzheimer's disease: areal and laminar pathology in the occipital isocortex. *Acta Neuropathologica*, 77(5), 494-506. <https://doi.org/10.1007/BF00687251>
- Braak, H., Del Tredici, K., Schultz, C., & Braak, E. (2000). Vulnerability of select neuronal types to Alzheimer's disease. *Annals New York Academy of Sciences*, 924, 53-61. <https://doi.org/10.1111/j.1749-6632.2000.tb05560.x>
- Brady, A. O., Straight, C. R., & Evans, E. M. (2014). Body composition, muscle capacity, and physical function in older adults: An integrated conceptual model. *Journal of Aging Physical Activity*, 22(3), 441-452. <https://doi.org/10.1123/JAPA.2013-0009>

- Brandt, T., Steinke, W., Thie, A., Pessin, M. S., & Caplan, L. R. J. C. D. (2000). Posterior cerebral artery territory infarcts: Clinical features, infarct topography, causes and outcome. *Cerebrovascular Diseases, 10*(3), 170-182. <https://doi.org/10.1159/000016053>
- Brasure, M., Desai, P., Davila, H., Nelson, V. A., Calvert, C., Jutkowitz, E., Butler, M., Fink, H. A., Ratner, E., Hemmy, L. S., McCarten, J. R., Barclay, T. R., & Kane, R. L. (2018). Physical Activity Interventions in Preventing Cognitive Decline and Alzheimer-Type Dementia: A Systematic Review. *Annals of Internal Medicine, 168*(1), 30-38. <https://doi.org/10.7326/M17-1528>
- Brayne, C., Ince, P. G., Keage, H. A., McKeith, I. G., Matthews, F. E., Polvikoski, T., & Sulkava, R. J. B. (2010). Education, the brain and dementia: neuroprotection or compensation? EClipSE Collaborative Members. *Brain, 133*(8), 2210-2216. <https://doi.org/10.1093/brain/awq185>
- Brendel, M., Pogarell, O., Xiong, G., Delker, A., Bartenstein, P., Rominger, A., & ADNI (2015). Depressive symptoms accelerate cognitive decline in amyloid-positive MCI patients. *European Journal of Nuclear Medicine and Molecular Imaging, 42*(5), 716-724. <https://doi.org/10.1007/s00259-014-2975-4>
- Breteler, M., Van Swieten, J., Bots, M., Grobbee, D., Claus, J., Van Den Hout, J., van Harskamp, F., Tanghe, H. L. J., de Jong, P. T. V. M., van Gijn, J., & Hofman, A. (1994). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. *Neurology, 44*(7), 1246-1246. <https://doi.org/10.1212/WNL.44.7.1246>
- Brickman, A. M., Honig, L. S., Scarmeas, N., Tatarina, O., Sanders, L., Albert, M. S., Brandt, J., Blacker, D., & Stern, Y. (2008). Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. *Archives of Neurology, 65*(9), 1202-1208. <https://doi.org/10.1001/archneur.65.9.1202>
- Brickman, A. M., Zahodne, L. B., Guzman, V. A., Narkhede, A., Meier, I. B., Griffith, E. Y., Provenzano, F. A., Schupf, N., Manly, J. J., Stern, Y., Luchsinger, J. A., Mayeux, R. (2015). Reconsidering harbingers of dementia: Progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. *Neurobiology of Aging, 36*(1), 27-32. <https://doi.org/10.1016/j.neurobiolaging.2014.07.019>
- Brier, M. R., Thomas, J. B., Fagan, A. M., Hassenstab, J., Holtzman, D. M., Benzinger, T. L., Morris, J. C., & Ances, B. M. (2014). Functional connectivity and graph theory in preclinical Alzheimer's disease. *Neurobiology of Aging, 35*(4), 757-768. <https://doi.org/10.1016/j.neurobiolaging.2013.10.081>
- Brier, M. R., Thomas, J. B., Snyder, A. Z., Benzinger, T. L., Zhang, D., Raichle, M. E., Holtzman, D. M., Morris, J. C., & Ances, B. M. (2012). Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression. *The Journal of Neuroscience, 32*(26), 8890-8899. <https://doi.org/10.1523/JNEUROSCI.5698-11.2012>
- Brookmeyer, R., Gray, S., & Kawas, C. (1998). Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *American Journal of Public Health, 88*(9), 1337-1342. <https://doi.org/10.2105/AJPH.88.9.1337>
- Brooks, B. L., Iverson, G. L., & White, T. (2007). Substantial risk of " Accidental MCI" in healthy older adults: Base rates of low memory scores in neuropsychological assessment. *Journal of the International Neuropsychological Society, 13*(3), 490. <https://doi.org/10.10170S1355617707070531>
- Brooks, S. J., Benedict, C., Burgos, J., Kempton, M., Kullberg, J., Nordenskjöld, R., Kilander, L., Nylander, R., Larsson, E-M., Johansson, L., Ahlström, H., Lind, L., & Schiöth, H. B. (2013). Late-life obesity is associated with smaller global and regional gray matter volumes: A voxel-based morphometric study. *International journal of obesity, 37*(2), 230-236. <https://doi.org/10.1038/ijo.2012.13>
- Brooks, T. A., Hawkins, B. T., Huber, J. D., Egleton, R. D., & Davis, T. P. (2005). Chronic inflammatory pain leads to increased blood-brain barrier permeability and tight junction

- protein alterations. *American Journal of Physiology-Heart and Circulatory Physiology*, 289(2), H738-H743. <https://doi.org/10.1152/ajpheart.01288.2004>
- Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. (2009). Default-mode brain dysfunction in mental disorders: a systematic review. *Neuroscience and Biobehavioral Reviews*, 33(3), 279-296. <https://doi.org/10.1016/j.neubiorev.2008.09.002>
- Bruhl, H., Wolf, O. T., Sweat, V., Tirsi, A., Richardson, S., & Convit, A. (2009). Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. *Brain Research*, 1280, 186-194. <https://doi.org/10.1016/j.brainres.2009.05.032>
- Brüel, A., & Oxlund, H. (1996). Changes in biomechanical properties, composition of collagen and elastin, and advanced glycation endproducts of the rat aorta in relation to age. *Atherosclerosis*, 127(2), 155-165. [https://doi.org/10.1016/S0021-9150\(96\)05947-3](https://doi.org/10.1016/S0021-9150(96)05947-3)
- Brundel, M., Kappelle, L. J., & Biessels, G. J. (2014). Brain imaging in type 2 diabetes. *European Neuropsychopharmacology*, 24(12), 1967-1981. <https://doi.org/10.1016/j.euroneuro.2014.01.023>
- Bruner, E. (2018). Human paleoneurology and the evolution of the parietal cortex. *Brain, Behavior and Evolution*, 91, 136-147. <https://doi.org/10.1159/000488889>
- Bruner, E., & Jacobs, H. I. (2013). Alzheimer's disease: the downside of a highly evolved parietal lobe? *Journal of Alzheimer's Disease*, 35(2), 227-240. <https://doi.org/10.3233/JAD-122299>
- Bryan, R. N., Bilello, M., Davatzikos, C., Lazar, R. M., Murray, A., Horowitz, K., Lovato, J., Miller, M. E., Williamson, J., & Launer, L. J. (2014). Effect of diabetes on brain structure: the action to control cardiovascular risk in diabetes MR imaging baseline data. *Radiology*, 272(1), 210-216. <https://doi.org/10.1148/radiol.14131494>
- Buchman, A. S., Wilson, R. S., Bienias, J. L., Shah, R. C., Evans, D. A., & Bennett, D. A. (2005). Change in body mass index and risk of incident Alzheimer disease. *Neurology*, 65(6), 892-897. <https://doi.org/10.1212/01.wnl.0000176061.33817.90>
- Buckner, R. L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron*, 44(1), 195-208. <https://doi.org/10.1016/j.neuron.2004.09.006>
- Budson, A. E., & Price, B. H. (2005). Memory dysfunction. *New England Journal of Medicine*, 352(7), 692-699. <https://doi.org/10.1056/NEJMra041071>
- Bunge, S. A., Klingberg, T., Jacobsen, R. B., & Gabrieli, J. D. E. (2000). A resource model of the neural basis of executive working memory. *Proceedings of the National Academy of Sciences*, 97(7), 3573-3578. <https://doi.org/10.1073/pnas.97.7.3573>
- Burkauskas, J., Noreikaite, A., Bunevicius, A., Brozaitiene, J., Neverauskas, J., Mickuviene, N., & Bunevicius, R. (2016). Beta-1-selective beta-blockers and cognitive functions in patients with coronary artery disease: A cross-sectional study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 28(2), 143-146. <https://doi.org/10.1176/appi.neuropsych.15040088>
- Burke, S. N., & Barnes, C. A. (2006). Neural plasticity in the ageing brain. *Nature Reviews Neuroscience*, 7(1), 30-40. <https://doi.org/10.1038/nrn1809>
- Burns, J. M., Honea, R. A., Vidoni, E. D., Hutfles, L. J., Brooks, W. M., & Swerdlow, R. H. (2012). Insulin is differentially related to cognitive decline and atrophy in Alzheimer's disease and aging. *Biochimica et Biophysica Acta*, 1822(3), 333-339. <https://doi.org/10.1016/j.bbadis.2011.06.011>
- Burns, J. M., Johnson, D. K., Watts, A., Swerdlow, R. H., & Brooks, W. M. (2010). Reduced lean mass in early Alzheimer disease and its association with brain atrophy. *Archives of Neurology*, 67(4), 428-433. <https://doi.org/10.1001/archneurol.2010.38>
- Burns, M. P., Noble, W. J., Olm, V., Gaynor, K., Casey, E., LaFrancois, J., Wang, L., & Duff, K. (2003). Co-localization of cholesterol, apolipoprotein E and fibrillar A β in amyloid plaques.

- Molecular Brain Research*, 110(1), 119-125. [https://doi.org/10.1016/S0169-328X\(02\)00647-2](https://doi.org/10.1016/S0169-328X(02)00647-2)
- Busch, H.-J., Schirmer, S. H., Jost, M., Van Stijn, S., Peters, S. L., Piek, J. J., Bode, C., Buschmann, I. R., & Mies, G. (2011). Leptin augments cerebral hemodynamic reserve after three-vessel occlusion: distinct effects on cerebrovascular tone and proliferation in a nonlethal model of hypoperfused rat brain. *Journal of Cerebral Blood Flow and Metabolism*, 31(4), 1085-1092. <https://doi.org/10.1038/jcbfm.2010.192>
- Bustamante, A., García-Berrocoso, T., Rodriguez, N., Llombart, V., Ribó, M., Molina, C., & Montaner, J. (2016). Ischemic stroke outcome: A review of the influence of post-stroke complications within the different scenarios of stroke care. *European Journal of Internal Medicine*, 29, 9-21. <https://doi.org/10.1016/j.ejim.2015.11.030>
- Butterfield, D. A., Di Domenico, F., & Barone, E. (2014). Elevated risk of type 2 diabetes for development of Alzheimer disease: A key role for oxidative stress in brain. *Biochimica et Biophysica Acta*, 1842(9), 1693-1706.
- Caballero, A. E., Arora, S., Saouaf, R., Lim, S. C., Smakowski, P., Park, J. Y., King, G. L., LoGerfo, F. W., Horton, E. S., & Veves, A. (1999). Microvascular and macrovascular reactivity is reduced in subjects at risk for type 2 diabetes. *Diabetes*, 48(9), 1856-1862. <https://doi.org/10.2337/diabetes.48.9.1856>
- Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, 17(1), 85-100. <https://doi.org/10.1037/0882-7974.17.1.85>
- Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002). A short version of the Stroop test: normative data in an Italian population sample. *Nuova Rivista di Neurologia*, 12(4), 111-115.
- Cahill-Smith, S., & Li, J. M. (2014). Oxidative stress, redox signalling and endothelial dysfunction in ageing-related neurodegenerative diseases: A role of NADPH oxidase 2. *British Journal of Clinical Pharmacology*, 78(3), 441-453. <https://doi.org/10.1111/bcp.12357>
- Cai, X. D., Golde, T. E., & Younkin, S. G. (1993). Release of excess amyloid beta protein from a mutant amyloid beta protein precursor. *Science*, 259(5094), 514-516. <https://doi.org/10.1126/science.8424174>
- Cai, Z., & Xiao, M. (2016). Oligodendrocytes and Alzheimer's disease. *International Journal of Neuroscience*, 126(2), 97-104. <https://doi.org/10.3109/00207454.2015.1025778>
- Cai, Z., Zhao, B., & Ratka, A. (2011). Oxidative stress and beta-amyloid protein in Alzheimer's disease. *Neuromolecular Medicine*, 13(4), 223-250. <https://doi.org/10.1007/s12017-011-8155-9>
- Campbell, N. L., Boustani, M. A., Skopelja, E. N., Gao, S., Unverzagt, F. W., & Murray, M. D. (2012). Medication adherence in older adults with cognitive impairment: A systematic evidence-based review. *The American Journal of Geriatric Pharmacotherapy*, 10(3), 165-177. <https://doi.org/10.1016/j.amjopharm.2012.04.004>
- Campion, D., Dumanchin, C., Hannequin, D., Dubois, B., Belliard, S., Puel, M., Thomas-Anterion, C., Michon, A., Martin, C., Charbonnier, F., Raux, G., Camuzat, A., Penet, C., Mesnage, V., Martinez, M., Clerget-Darpoux, F., Brice, A., & Frebourg, T. (1999). Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *American Journal of Human Genetics*, 65(3), 664-670. <https://doi.org/10.1086/302553>
- Campos-Pena, V., Toral-Rios, D., Becerril-Pérez, F., Sánchez-Torres, C., Delgado-Namorado, Y., Torres-Ossorio, E., Franco-Bocanegra, D., & Carvajal, K. (2017). Metabolic Syndrome as a Risk Factor for Alzheimer's Disease: Is A β a Crucial Factor in Both Pathologies? *Antioxidants and Redox Signaling*, 26(10), 542-560. <https://doi.org/10.1089/ars.2016.6768>
- Caplan, L. R. (2015). Lacunar infarction and small vessel disease: Pathology and pathophysiology. *Journal of Stroke*, 17(1), 2. <https://doi.org/10.5853/jos.2015.17.1.2>
- Caplan, L. R., & Van Gijn, J. (2012). *Stroke syndromes*: Cambridge University Press.

- Capone, C., Faraco, G., Peterson, J. R., Coleman, C., Anrather, J., Milner, T. A., Pickel, V. M., Davisson, R. L., & Iadecola, C. (2012). Central cardiovascular circuits contribute to the neurovascular dysfunction in angiotensin II hypertension. *Journal of Neuroscience*, *32*(14), 4878-4886. <https://doi.org/10.1523/JNEUROSCI.6262-11.2012>
- Carmichael, O., Schwarz, C., Drucker, D., Fletcher, E., Harvey, D., Beckett, L., Jack Jr, C. R., Weiner, M., DeCarli, C., & ADNI. (2010). Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. *Archives of Neurology*, *67*(11), 1370-1378. <https://doi.org/10.1001/archneurol.2010.284>
- Carnevale, D., Mascio, G., D'Andrea, I., Fardella, V., Bell, R. D., Branchi, I., Pallante, F., Zlokovic, B., Yan, S. S., & Lembo, G. (2012). Hypertension induces brain β -amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. *Hypertension*, *60*(1), 188-197. <https://doi.org/10.1161/HYPERTENSIONAHA.112.195511>
- Carnevale, L., Maffei, A., Landolfi, A., Grillea, G., Carnevale, D., & Lembo, G. (2019). A Functional MRI (resting State Functional MRI rs-fMRI) highlights altered connections and altered functional networks in hypertensive patients. *Circulation*, *140*(Suppl_1), A10945-A10945.
- Caroli, A., Testa, C., Geroldi, C., Nobili, F., Barnden, L. R., Guerra, U. P., . . . Frisoni, G. B. (2007). Cerebral perfusion correlates of conversion to Alzheimer's disease in amnesic mild cognitive impairment. *Journal of Neurology*, *254*(12), 1698-1707. <https://doi.org/10.1007/s00415-007-0631-7>
- Carrano, A., Hoozemans, J. J., van der Vies, S. M., Rozemuller, A. J., van Horssen, J., de Vries, H. E. (2011). Amyloid beta induces oxidative stress-mediated blood-brain barrier changes in capillary amyloid angiopathy. *Antioxidants and Redox Signaling*, *15*(5), 1167-1178. <https://doi.org/10.1089/ars.2011.3895>
- Caselli, R. J., Dueck, A. C., Osborne, D., Sabbagh, M. N., Connor, D. J., Ahern, G. L., Baxter, L. C., Rapsak, S. Z., Shi, J., Woodruff, B. K., Locke, D. E. C., Snyder, C. H. (2009). Longitudinal modeling of age-related memory decline and the APOE ϵ 4 effect. *New England Journal of Medicine*, *361*(3), 255-263. <https://doi.org/10.1056/NEJMoa0809437>
- Casscells, W., Vaughn, W., McAllister, H., Willerson, J., Hathorn, B., David, M., Vaughn, W., McAllister, H. K., Willerson, J. T., Krabach, T., & Bearman, G. (1996). Thermal detection of cellular infiltrates in living atherosclerotic plaques: possible implications for plaque rupture and thrombosis. *The Lancet*, *347*(9013), 1447-1449. [https://doi.org/10.1016/S0140-6736\(96\)91684-0](https://doi.org/10.1016/S0140-6736(96)91684-0)
- Casserly, I., & Topol, E. J. (2004). Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. *The Lancet*, *363*(9415), 1139-1146. [https://doi.org/10.1016/S0140-6736\(04\)15900-X](https://doi.org/10.1016/S0140-6736(04)15900-X)
- Castro, G., Areias, M. F. C., Weissmann, L., Quaresma, P. G., Katashima, C. K., Saad, M. J., & Prada, P. O. (2013). Diet-induced obesity induces endoplasmic reticulum stress and insulin resistance in the amygdala of rats. *FEBS Open Bio*, *3*, 443-449. <https://doi.org/10.1016/j.fob.2013.09.002>
- Catani, M., Mecocci, P., Tarducci, R., Howard, R., Pelliccioli, G. P., Mariani, E., Metastasio, A., Benedetti, C., Senin, U., & Cherubini, A. (2002). Proton magnetic resonance spectroscopy reveals similar white matter biochemical changes in patients with chronic hypertension and early Alzheimer's disease. *Journal of the American Geriatrics Society*, *50*(10), 1707-1710. <https://doi.org/10.1046/j.1532-5415.2002.50465.x>
- Cates, M. J., Paton, J. F., Smeeton, N. C., & Wolfe, C. D. (2012). Hypertension before and after posterior circulation infarction: Analysis of data from the South London Stroke Register. *Journal of Stroke and Cerebrovascular Diseases*, *21*(7), 612-618.

- Caulin-Glaser, T., Garcia-Cardena, G., Sarrel, P., Sessa, W. C., & Bender, J. R. (1997). 17β -estradiol regulation of human endothelial cell basal nitric oxide release, independent of cytosolic Ca^{2+} mobilization. *Circulation Research*, *81*(5), 885-892. <https://doi.org/10.1161/01.RES.81.5.885>
- Ceriello, A., Esposito, K., Piconi, L., Ihnat, M. A., Thorpe, J. E., Testa, R., Boemi, M., & Giugliano, D. (2008). Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*, *57*(5), 1349-1354. <https://doi.org/10.2337/db08-0063>
- Cerin, E. & Leslie, E. (2008). How socio-economic status contributes to participation in leisure-time physical activity. *Social Science and Medicine*, *66*(12), 2596-2609. <https://doi.org/10.1016/j.socscimed.2008.02.012>
- Chamorro, A., Saiz, A., Vila, N., Ascaso, C., Blanc, R., Alday, M., & Pujol, J. (1996). Contribution of arterial blood pressure to the clinical expression of lacunar infarction. *Stroke*, *27*(3), 388-392.
- Chan, K. H., Lam, K. S. L., Cheng, O. Y., Kwan, J. S. C., Ho, P. W. L., Cheng, K. K.Y., Chung, S. K., Ho, J. W. M., Guo, V. Y., & Xu, A. (2012). Adiponectin is protective against oxidative stress induced cytotoxicity in amyloid-beta neurotoxicity. *PloS One*, *7*(12), e52354. <https://doi.org/10.1371/journal.pone.0052354>
- Chao, L. L., Buckley, S. T., Kornak, J., Schuff, N., Madison, C., Yaffe, K., Miller, B. L., Kramer, J. H., & Weiner, M. W. (2010). ASL perfusion MRI predicts cognitive decline and conversion from MCI to dementia. *Alzheimer Disease and Associated Disorders*, *24*(1), 19. <https://doi.org/10.1097/WAD.0b013e3181b4f736>
- Chappell, M., MacIntosh, B., & Okell, T. (2018). Introduction to Perfusion Quantification using Arterial Spin Labelling: *Oxford University Press*.
- Charidimou, A., Boulouis, G., Haley, K., Auriel, E., van Etten, E. S., Fotiadis, P., Reijmer, Y., Ayres, A., Vashkevich, A., Dipucchio, Z. Y., Schwab, K. M., Martinez-Ramirez, S., Rosand, J., Viswanathan, A., Greenberg, S. M., & Gurol, M. E. (2016). White matter hyperintensity patterns in cerebral amyloid angiopathy and hypertensive arteriopathy. *Neurology*, *86*(6), 505-511. <https://doi.org/10.1212/WNL.0000000000002362>
- Chee, M. W., Goh, J. O., Venkatraman, V., Tan, J. C., Gutchess, A., Sutton, B., Hebrank, A., Leshikar, E., & Park, D. (2006). Age-related changes in object processing and contextual binding revealed using fMR adaptation. *Journal of Cognitive Neuroscience*, *18*(4), 495-507. <https://doi.org/10.1162/jocn.2006.18.4.495>
- Chen, B., Liao, W. Q., Xu, N., Xu, H., Wen, J. Y., Yu, C. A., Liu, X. Y., Li, C. L., Zhao, S. M., & Campbell, W. (2009). Adiponectin protects against cerebral ischemia-reperfusion injury through anti-inflammatory action. *Brain Research*, *1273*, 129-137. <https://doi.org/10.1016/j.brainres.2009.04.002>
- Chen, J., Zhang, J., Liu, X., Wang, X., Xu, X., Li, H., Cao, B., Yang, Y., Lu, j., & Chen, Z. (2017). Abnormal subcortical nuclei shapes in patients with type 2 diabetes mellitus. *European Radiology*, *27*(10), 4247-4256. <https://doi.org/10.1007/s00330-017-4790-3>
- Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., DeKosky, S. T., & Ganguli, M. (2001). Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. *Archives of General Psychiatry*, *58*(9), 853-858.
- Chen, S.Q., Kang, Z., Hu, X. Q., Hu, B., & Zou, Y. (2007). Diffusion tensor imaging of the brain in patients with Alzheimer's disease and cerebrovascular lesions. *Journal of Zhejiang University*, *8*(4), 242-247.
- Chen, X., Gawryluk, J. W., Wagener, J. F., Ghribi, O., & Geiger, J. D. (2008). Caffeine blocks disruption of blood brain barrier in a rabbit model of Alzheimer's disease. *Journal of Neuroinflammation*, *5*(1), 1-14. <https://doi.org/10.1186/1742-2094-5-12>

- Chen, X., Wen, W., Anstey, K. J., & Sachdev, P. S. (2006). Effects of cerebrovascular risk factors on gray matter volume in adults aged 60–64 years: A voxel-based morphometric study. *Psychiatry Research: Neuroimaging*, *147*(2-3), 105-114.
- Chen, Y., Liu, Z., Zhang, J., Tian, G., Li, L., Zhang, S., Li, X., Chen, K., & Zhang, Z. (2015a). Selectively disrupted functional connectivity networks in type 2 diabetes mellitus. *Frontiers in Aging Neuroscience*, *7*, 233. <https://doi.org/10.3389/fnagi.2015.00233>
- Chen, Y. C., Jiao, Y., Cui, Y., Shang, S. A., Ding, J., Feng, Y., Song, W., Ju, S. H., & Teng, G. J. (2014). Aberrant brain functional connectivity related to insulin resistance in type 2 diabetes: A resting-state fMRI study. *Diabetes Care*, *37*(6), 1689-1696. <https://doi.org/10.2337/dc13-2127>
- Chen, Y. C., Xia, W., Qian, C., Ding, J., Ju, S., & Teng, G. J. (2015b). Thalamic resting-state functional connectivity: Disruption in patients with type 2 diabetes. *Metabolic Brain Disease*, *30*(5), 1227-1236. <https://doi.org/10.1007/s11011-015-9700-2>
- Cheng, C. M., Reinhardt, R. R., Lee, W.-H., Joncas, G., Patel, S. C., & Bondy, C. A. (2000). Insulin-like growth factor 1 regulates developing brain glucose metabolism. *Proceedings of the National Academy of Sciences*, *97*(18), 10236-10241. <https://doi.org/10.1073/pnas.170008497>
- Cheng, D., Huang, R., Lanham, I., Cathcart, H., Howard, M., Corder, E., & Poduslo, S. E. (2005). Functional interaction between APOE4 and LDL receptor isoforms in Alzheimer's disease. *Journal of Medical Genetics*, *42*(2), 129-131. <http://dx.doi.org/10.1136/jmg.2004.024968>
- Cheng, K. K., Lam, K. S., Wang, Y., Huang, Y., Carling, D., Wu, D., Wong, C., & Xu, A. (2007). Adiponectin-induced endothelial nitric oxide synthase activation and nitric oxide production are mediated by APPL1 in endothelial cells. *Diabetes*, *56*(5), 1387-1394. <https://doi.org/10.2337/db06-1580>
- Chételat, G., Desgranges, B., Landeau, B., Mézenge, F., Poline, J., de La Sayette, V., Viader, F., Eustache, F., & Baron, J. C. (2007). Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease. *Brain*, *131*(1), 60-71. <https://doi.org/10.1093/brain/awm288>
- Chetouani, A., Chawki, M. B., Hossu, G., Kearney-Schwartz, A., Chauveau-Beuret, F., Bracard, S., Roch, V., Lebon, V., Marie, P. Y., Benetos, A., Joly, L., & Verger, A. (2018). Cross-sectional variations of white and grey matter in older hypertensive patients with subjective memory complaints. *NeuroImage: Clinical*, *17*, 804-810. <https://doi.org/10.1016/j.nicl.2017.12.024>
- Chilovi, B. V., Conti, M., Zanetti, M., Mazzù, I., Rozzini, L., & Padovani, A. (2009). Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dementia and Geriatric Cognitive Disorders*, *27*(4), 390-398. <https://doi.org/10.1159/000210045>
- Cho, H., Choi, J. Y., Hwang, M. S., Lee, J. H., Kim, Y. J., Lee, H. M., Lyoo, C. H., Ryu, Y. H., & Lee, M. S. (2016). Tau PET in Alzheimer disease and mild cognitive impairment. *Neurology*, *87*(4), 375-383. <https://doi.org/10.1212/WNL.0000000000002892>
- Cho, M. H., Shin, D. W., Chang, S.-A., Lee, J. E., Jeong, S.-M., Kim, S. H., Yun, J. M., & Son, K. (2018a). Association between cognitive impairment and poor antihypertensive medication adherence in elderly hypertensive patients without dementia. *Scientific Reports*, *8*(1), 1-7. <https://doi.org/10.1038/s41598-018-29974-7>
- Cho, N., Shaw, J., Karuranga, S., Huang, Y., da Rocha Fernandes, J., Ohlrogge, A., & Malanda, B. (2018b). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice*, *138*, 271-281.
- Chornenkyy, Y., Wang, W. X., Wei, A., & Nelson, P. T. (2019). Alzheimer's disease and type 2 diabetes mellitus are distinct diseases with potential overlapping metabolic dysfunction upstream of observed cognitive decline. *Brain Pathology*, *29*(1), 3-17. <https://doi.org/10.1111/bpa.12655>

- Chowdhury, U. N., Islam, M. B., Ahmad, S., & Moni, M. A. (2020). Network-based identification of genetic factors in ageing, lifestyle and type 2 diabetes that influence to the progression of Alzheimer's disease. *Informatics in Medicine Unlocked*, *19*, 100309. <https://doi.org/10.1016/j.imu.2020.100309>
- Christensen, K. (1991). Reducing pulse pressure in hypertension may normalize small artery structure. *Hypertension*, *18*(6), 722-727.
- Chuang, S.Y., Chou, P., Hsu, P.F., Cheng, H.M., Tsai, S.T., Lin, I.F., & Chen, C.H. (2006). Presence and progression of abdominal obesity are predictors of future high blood pressure and hypertension. *American Journal of Hypertension*, *19*(8), 788-795. <https://doi.org/10.1016/j.amjhyper.2006.01.010>
- Chuang, Y.-F., An, Y., Bilgel, M., Wong, D. F., Troncoso, J. C., O'Brien, R. J., Breitner, J. C., Ferruci, L., Resnick, S. M., & Thambisetty, M. (2016). Midlife adiposity predicts earlier onset of Alzheimer's dementia, neuropathology and presymptomatic cerebral amyloid accumulation. *Molecular Psychiatry*, *21*(7), 910-915. <https://doi.org/10.1038/mp.2015.129>
- Cifuentes, D., Poittevin, M., Dere, E., Broquères-You, D., Bonnin, P., Benessiano, J., Pocard, M., Mariani, J., Kubis, N., Merkulova-Rainon, T., & Lévy, B. I. (2015). Hypertension accelerates the progression of Alzheimer-like pathology in a mouse model of the disease. *Hypertension*, *65*(1), 218-224. <https://doi.org/10.1161/HYPERTENSIONAHA.114.04139>
- Cilliers, K., & Page, B. J. (2017). Anatomy of the middle cerebral artery: cortical branches, branching pattern and anomalies. *Turkish Neurosurg*, *27*(5), 671-681. <https://doi.org/10.5137/1019-5149.JTN.18127-16.1>
- Citron, M., Oltersdorf, T., Haass, C., McConlogue, L., Hung, A. Y., Seubert, P., Vigo-Pelfrey, C., Lieberburg, I., & Selkoe, D. J. (1992). Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production. *Nature*, *360*(6405), 672-674. <https://doi.org/10.1038/360672a0>
- Ciudin, A., Espinosa, A., Simo-Servat, O., Ruiz, A., Alegret, M., Hernandez, C., Boada, M., & Simo, R. (2017). Type 2 diabetes is an independent risk factor for dementia conversion in patients with mild cognitive impairment. *Journal of Diabetes and its Complications*, *31*(8), 1272-1274. <https://doi.org/10.1016/j.jdiacomp.2017.04.018>
- Clark, C., Campbell, J., Evans, P., & Millward, A. (2006). Prevalence and clinical implications of the inter-arm blood pressure difference: a systematic review. *Journal of Human Hypertension*, *20*(12), 923.
- Clark, C. M., Sheppard, L., Fillenbaum, G. G., Galasko, D., Morris, J. C., Koss, E., Mohs, R., Heyman, A. & CERAD (1999). Variability in annual Mini-Mental State Examination score in patients with probable Alzheimer disease: a clinical perspective of data from the Consortium to Establish a Registry for Alzheimer's Disease. *Archives of Neurology*, *56*(7), 857-862. <https://doi.org/10.1001/archneur.56.7.857>
- Clark, L. R., Berman, S. E., Rivera-Rivera, L. A., Hoscheidt, S. M., Darst, B. F., Engelman, C. D., Rowley, H. A., Carlsson, C. M., Asthana, S., Turski, P., Wieben, O., & Johnson, S. C. (2017). Macrovascular and microvascular cerebral blood flow in adults at risk for Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *7*, 48-55. <https://doi.org/10.1016/j.dadm.2017.01.002>
- Clark, M., Rattigan, S., Clerk, L., Vincent, M., Clark, A., Youd, J., & Newman, J. M. B. (2000). Nutritive and non-nutritive blood flow: Rest and exercise. *Acta Physiologica Scandinavica*, *168*(4), 519-530. <https://doi.org/10.1046/j.1365-201x.2000.00704.x>
- Clark, M. G. (2008). Impaired microvascular perfusion: a consequence of vascular dysfunction and a potential cause of insulin resistance in muscle. *American Journal of Physiology-Endocrinology and Metabolism*, *295*(4), E732-E750.

- Clark, M. G., Wallis, M. G., Barrett, E. J., Vincent, M. A., Richards, S. M., Clerk, L. H., & Rattigan, S. (2003). Blood flow and muscle metabolism: a focus on insulin action. *American Journal of Physiology-Endocrinology and Metabolism*, 284(2), E241-E258.
- Clifford, P. M., Zarrabi, S., Siu, G., Kinsler, K. J., Kosciuk, M. C., Venkataraman, V., D'Andrea, M. R., Dinsmore, S., & Nagele, R. G. (2007). A β peptides can enter the brain through a defective blood-brain barrier and bind selectively to neurons. *Brain Research*, 1142, 223-236. <https://doi.org/10.1016/j.brainres.2007.01.070>
- Clouston, S. A., & Denier, N. (2017). Mental retirement and health selection: Analyses from the US Health and Retirement Study. *Social Science & Medicine*, 178, 78-86. <https://doi.org/10.1016/j.socscimed.2017.01.019>
- Cnop, M., Havel, P. J., Utzschneider, K., Carr, D., Sinha, M., Boyko, E., Retzlaff, B. M., Knopp, R. H., Brunzell, J. D., Kahn, S. E. (2003). Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia*, 46(4), 459-469. <https://doi.org/10.1007/s00125-003-1074-z>
- Cnop, M., Landchild, M. J., Vidal, J., Havel, P. J., Knowles, N. G., Carr, D. R., Wang, F., Hull, R. L., Boyko, E. J., Retzlaff, B. M., Walden, C. E., Knopp, R. H., & Kahn, S. E. (2002). The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations: distinct metabolic effects of two fat compartments. *Diabetes*, 51(4), 1005-1015. <https://doi.org/10.2337/diabetes.51.4.1005>
- Coelho, F. G. d. M., Vital, T. M., Stein, A. M., Arantes, F. J., Rueda, A. V., Camarini, R., Teodorov, E., & Santos-Galduroz, R. F. (2014). Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. *Journal of Alzheimer's Disease*, 39(2), 401-408. <https://doi.org/10.3233/JAD-131073>
- Cohen, J. I., Cazettes, F., & Convit, A. (2011). Abnormal cholesterol is associated with prefrontal white matter abnormalities among obese adults: a diffusion tensor imaging study. *The Neuroradiology Journal*, 24(6), 854-861. <https://doi.org/10.1177/197140091102400604>
- Coimbra, S., Brandão Proença, J., Santos-Silva, A., & Neuparth, M. J. (2014). Adiponectin, leptin, and chemerin in elderly patients with type 2 diabetes mellitus: A close linkage with obesity and length of the disease. *Biomed Research International*, 2014. <https://doi.org/10.1155/2014/701915>
- Coin, A., Bolzetta, F., Rui, M. D., Veronese, N., Granziera, S., Girardi, A., Manzato, E., & Sergi, G. (2012). Nutritional and global indexes of progression in dementia: A 12-month prospective study. *American Journal of Alzheimer's Disease & Other Dementias*, 27(7), 504-508. <https://doi.org/10.1177/1533317512456451>
- Coleman, M. (2005). Axon degeneration mechanisms: commonality amid diversity. *Nature Reviews Neuroscience*, 6(11), 889-898.
- Coleman, M. P., & Freeman, M. R. (2010). Wallerian degeneration, wld^s, and nmnat. *Annual Reviews of Neuroscience*, 33, 245-267. <https://doi.org/10.1146/annurev-neuro-060909-153248>
- Colosia, A. D., Palencia, R., & Khan, S. (2013). Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: A systematic literature review. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 6, 327.
- Comodore-Mensah, Y., Selvin, E., Aboagye, J., Turkson-Ocran, R. A., Li, X., Himmelfarb, C. D., Ahima, R. S., & Cooper, L. A. (2018). Hypertension, overweight/obesity, and diabetes among immigrants in the United States: An analysis of the 2010-2016 National Health Interview Survey. *BMC Public Health*, 18(1), 1-10. <https://doi.org/10.1186/s12889-018-5683-3>
- Conforti, L., Gilley, J., & Coleman, M. P. (2014). Wallerian degeneration: an emerging axon death pathway linking injury and disease. *Nature Reviews Neuroscience*, 15(6), 394-409.

- Connelly, P. J., Prentice, N. P., & Fowler, K. G. (2005). Hypertension, white matter change and response to cholinesterase inhibitors in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *20*(7), 623-628.
- Conner, J. M., Chiba, A. A., & Tuszyński, M. H. (2005). The basal forebrain cholinergic system is essential for cortical plasticity and functional recovery following brain injury. *Neuron*, *46*(2), 173-179. <https://doi.org/10.1016/j.neuron.2005.03.003>
- Conner, S. C., Pase, M. P., Carneiro, H., Raman, M. R., McKee, A. C., Alvarez, V. E., Walker, J. M., Satizabal, C. L., Himali, J. J., Beiser, A., & Seshadri, S. (2019). Mid-life and late-life vascular risk factor burden and neuropathology in old age. *Annals of Clinical and Translational Neurology*, *6*(12), 2403-2412. <https://doi.org/10.1002/acn3.50936>
- Conolly, A., Saunders, C., & Neave, A. (2017). Health Survey for England 2016: Adult overweight and obesity. *Health and Social Care Information Centre*. <http://healthsurvey.hscic.gov.uk/media/63745/HSE2016-Adult-obe.pdf>
- Convit, A., Wolf, O. T., Tarshish, C., & De Leon, M. J. (2003). Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. *Proceedings of the National Academy of Sciences*, *100*(4), 2019-2022. <https://doi.org/10.1073/pnas.0336073100>
- Cooper, R. A. (1978). Influence of increased membrane cholesterol on membrane fluidity and cell function in human red blood cells. *Journal of Supramolecular Structure*, *8*(4), 413-430. <https://doi.org/10.1002/jss.400080404>
- Copani, A., Koh, J.-Y., & Cotman, C. W. (1991). Beta-amyloid increases neuronal susceptibility to injury by glucose deprivation. *Neuroreport*, *2*(12), 763-765. <https://doi.org/10.1097/00001756-199112000-00008>
- Cope, T. E., Rittman, T., Borchert, R. J., Jones, P. S., Vatansever, D., Allinson, K., Passamonti, L., Rodriguez, P. V., Bevan-Jones, W. R., O'Brien, J. T., & Rowe, J. B. (2018). Tau burden and the functional connectome in Alzheimer's disease and progressive supranuclear palsy. *Brain*, *141*(2), 550-567. <https://doi.org/10.1093/brain/awx347>
- Corem, N., Anzi, S., Gelb, S., & Ben-Zvi, A. (2019). Leptin receptor deficiency induces early, transient and hyperglycaemia-independent blood-brain barrier dysfunction. *Scientific Reports*, *9*(1), 1-11. <https://doi.org/10.1038/s41598-019-39230-1>
- Cornford, E. M., Hyman, S., & Swartz, B. E. (1994). The human brain GLUT1 glucose transporter: Ultrastructural localization to the blood—brain barrier endothelia. *Journal of Cerebral Blood Flow & Metabolism*, *14*(1), 106-112. <https://doi.org/10.1038/jcbfm.1994.15>
- Cova, I., Clerici, F., Maggiore, L., Pomati, S., Cucumo, V., Ghiretti, R., Galimberti, D., Scarpini, E., Mariani, C. & Caracciolo, B. (2016). Body mass index predicts progression of mild cognitive impairment to dementia. *Dementia and Geriatric Cognitive Disorders*, *41*(3-4), 172-180.
- Cova, L., Gelosa, P., Mura, E., Mauro, A., Stramba-Badiale, M., Michailidis, G., Colonna, A., El Assawy, N., Pignieri, A., Busca, G., Tremoli, E., Silani, V., Sironi, L., & Zanchetti, A. (2013). Vascular and parenchymal lesions along with enhanced neurogenesis characterize the brain of asymptomatic stroke-prone spontaneous hypertensive rats. *Journal of Hypertension*, *31*(8), 1618-1628. <https://doi.org/10.1097/HJH.0b013e3283619d7f>
- Cox, D. J., Kovatchev, B. P., Gonder-Frederick, L. A., Summers, K. H., McCall, A., Grimm, K. J., & Clarke, W. L. (2005). Relationships between hyperglycemia and cognitive performance among adults with type 1 and type 2 diabetes. *Diabetes Care*, *28*(1), 71-77. <https://doi.org/10.2337/diacare.28.1.71>
- Cox, K. L., Cyarto, E. V., Ellis, K. A., Ames, D., Desmond, P., Phal, P., Sharman, M. J., Szoëke, C., Rowe, C. C., Masters, Colin, L., You, E., Burrows, S., Lai, M, M.Y., & Lautenschlager, N. T. (2019a). A randomized controlled trial of adherence to a 24-month home-based physical activity program and the health benefits for older adults at risk of Alzheimer's disease: The

- AIBL Active-Study. *Journal of Alzheimer's Disease*, 70(s1), S187-S205.
<https://doi.org/10.3233/JAD-180521>
- Cox, S. R., Lyall, D. M., Ritchie, S. J., Bastin, M. E., Harris, M. A., Buchanan, C. R., Fawns-Ritchie, C., Barbu, M. C., de Nooij, L., Reus, L. M., Alloza, C., Shen, X., Neilson, E., Alderson, H. L., Hunter, S., Liewald, D. C., Whalley, H. C., McIntosh, A. M., Lawrie, S. M., ... Deary, I. J. (2019b). Associations between vascular risk factors and brain MRI indices in UK Biobank. *European Heart Journal*, 40(28), 2290-2300. <https://doi.org/10.1093/eurheartj/ehz100>
- Cracchiolo, J. R., Mori, T., Nazian, S. J., Tan, J., Potter, H., & Arendash, G. W. (2007). Enhanced cognitive activity—over and above social or physical activity—is required to protect Alzheimer's mice against cognitive impairment, reduce A β deposition, and increase synaptic immunoreactivity. *Neurobiology of Learning and Memory*, 88(3), 277-294.
<https://doi.org/10.1016/j.nlm.2007.07.007>
- Craft, S., Asthana, S., Schellenberg, G., Baker, L., Cherrier, M., Boyt, A. A., Martins, R. N., Raskind, M., Peskind, E., & Plymate, S. (2000). Insulin effects on glucose metabolism, memory, and plasma amyloid precursor protein in Alzheimer's disease differ according to apolipoprotein-E genotype. *Annals of the New York Academy of Sciences*, 903(1), 222-228.
- Craig, D., Mirakhur, A., Hart, D. J., McIlroy, S. P., & Passmore, A. P. (2005). A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. *The American Journal of Geriatric Psychiatry*, 13(6), 460-468. <https://doi.org/10.1097/00019442-200506000-00004>
- Creager, M. A., Cooke, J. P., Mendelsohn, M. E., Gallagher, S. J., Coleman, S. M., Loscalzo, J., & Dzau, V. J. (1990). Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. *The Journal of Clinical Investigation*, 86(1), 228-234.
<https://doi.org/10.1172/JCI114688>
- Cronk, B. B., Johnson, D. K., Burns, J. M., & Alzheimer's Disease Neuroimaging Initiative (ADNI). (2010). Body mass index and cognitive decline in mild cognitive impairment. *Alzheimer Disease and Associated Disorders*, 24(2), 126.
- Cui, Y., Jiao, Y., Chen, H. J., Ding, J., Luo, B., Peng, C. Y., Ju, S. H., & Teng, G. J. (2015). Aberrant functional connectivity of default-mode network in type 2 diabetes patients. *European Radiology*, 25(11), 3238-3246. <https://doi.org/10.1007/s00330-015-3746-8>
- Cui, Y., Li, S. F., Gu, H., Hu, Y. Z., Liang, X., Lu, C. Q., Cai, Y., Wang, C. X., Yang, Y., & Teng, G. J. (2016). Disrupted Brain Connectivity Patterns in Patients with Type 2 Diabetes. *American Journal of Neuroradiology*, 37(11), 2115-2122.
<https://doi.org/10.3174/ajnr.A4858>
- Cui, Y., Liang, X., Gu, H., Hu, Y., Zhao, Z., Yang, X. Y., Qian, C., Yang, Y., & Teng, G. J. (2017). Cerebral perfusion alterations in type 2 diabetes and its relation to insulin resistance and cognitive dysfunction. *Brain Imaging and Behavior*, 11(5), 1248-1257.
<https://doi.org/10.1007/s11682-016-9583-9>
- Cummings, J. L., & Kaufer, D. (1996). Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. *Neurology*, 47(4), 876-883.
<https://doi.org/10.1212/WNL.47.4.876>
- Cummings, J. L., Tong, G., & Ballard, C. (2019). Treatment combinations for Alzheimer's disease: Current and future pharmacotherapy options. *Journal of Alzheimer's Disease*, 67(3), 779-794.
<https://doi.org/10.3233/JAD-180766>
- Currais, A. (2015). Ageing and inflammation—A central role for mitochondria in brain health and disease. *Ageing Research Reviews*, 21, 30-42. <https://doi.org/10.1016/j.arr.2015.02.001>
- Dahl, A. K., Hassing, L. B., Fransson, E. I., Gatz, M., Reynolds, C. A., & Pedersen, N. L. (2013). Body mass index across midlife and cognitive change in late life. *International Journal of Obesity*, 37(2), 296-302.

- Dai, W., Lopez, O. L., Carmichael, O. T., Becker, J. T., Kuller, L. H., & Gach, H. M. (2008). Abnormal regional cerebral blood flow in cognitively normal elderly subjects with hypertension. *Stroke*, *39*(2), 349-354.
- Dai, W., Lopez, O. L., Carmichael, O. T., Becker, J. T., Kuller, L. H., & Gach, H. M. (2009). Mild cognitive impairment and alzheimer disease: Patterns of altered cerebral blood flow at MR imaging. *Radiology*, *250*(3), 856-866. <https://doi.org/10.1148/radiol.2503080751>.
- Dake, M. D., De Marco, M., Blackburn, D. J., Wilkinson, I. D., Remes, A., Liu, Y., Pikkarainen, M., Hallikainen, M., Soinen, H., & Venneri, A. (2021) Obesity and brain vulnerability in normal and abnormal aging: A multimodal MRI study. *Journal of Alzheimer's Disease Reports*, *5*(1), 65-77. <https://doi.org/10.3233/ADR-200267>
- Dallaire-Theroux, C., Callahan, B. L., Potvin, O., Saikali, S., & Duchesne, S. (2017). Radiological-pathological correlation in Alzheimer's Disease: Systematic review of antemortem magnetic resonance imaging findings. *Journal of Alzheimer's Disease*, *57*(2), 575-601. <https://doi.org/10.3233/JAD-161028>
- Damoiseaux, J. S., & Greicius, M. D. (2009). Greater than the sum of its parts: A review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure & Function*, *213*(6), 525-533. <https://doi.org/10.1007/s00429-009-0208-6>
- Dao, H. H., Essalihi, R., Bouvet, C., & Moreau, P. (2005). Evolution and modulation of age-related medial elastocalcinosis: Impact on large artery stiffness and isolated systolic hypertension. *Cardiovascular Research*, *66*(2), 307-317. <https://doi.org/10.1016/j.cardiores.2005.01.012>
- Daousi, C., Casson, I., Gill, G., MacFarlane, I., Wilding, J., & Pinkney, J. (2006). Prevalence of obesity in type 2 diabetes in secondary care: Association with cardiovascular risk factors. *Postgraduate Medical Journal*, *82*(966), 280-284.
- Daugherty, A. M., & Raz, N. (2015). Appraising the role of iron in brain aging and cognition: Promises and limitations of MRI methods. *Neuropsychology Review*, *25*(3), 272-287.
- Daulatzai, M. A. (2017). Cerebral hypoperfusion and glucose hypometabolism: Key pathophysiological modulators promote neurodegeneration, cognitive impairment, and Alzheimer's disease. *Journal of Neuroscience Research*, *95*(4), 943-972. <https://doi.org/10.1002/jnr.23777>
- Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Current Opinion in Neurobiology*, *16*(6), 693-700.
- Davies, M. J., Richardson, P. D., Woolf, N., Katz, D. R., & Mann, J. (1993). Risk of thrombosis in human atherosclerotic plaques: Role of extracellular lipid, macrophage, and smooth muscle cell content. *Heart*, *69*(5), 377-381. <http://dx.doi.org/10.1136/hrt.69.5.377>
- Davies, N. M., Kehoe, P. G., Ben-Shlomo, Y., & Martin, R. M. (2011). Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *Journal of Alzheimer's Disease*, *26*(4), 699-708.
- Davies, P., & Maloney, A. (1976). Selective loss of central cholinergic neurons in Alzheimer's disease. *The Lancet*, *308*(8000), 1403. [https://doi.org/10.1016/S0140-6736\(76\)91936-X](https://doi.org/10.1016/S0140-6736(76)91936-X)
- Davis, K. L., Mohs, R. C., Marin, D., Purohit, D. P., Perl, D. P., Lantz, M., Austin, G., & Haroutunian, V. (1999). Cholinergic markers in elderly patients with early signs of Alzheimer disease. *JAMA*, *281*(15), 1401-1406. <https://doi.org/10.1001/jama.281.15.1401>
- de Boer, M. P., Meijer, R. I., Newman, J., Stehouwer, C. D., Eringa, E. C., Smulders, Y. M., & Serné, E. H. (2014). Insulin-induced changes in microvascular vasomotion and capillary recruitment are associated in humans. *Microcirculation*, *21*(5), 380-387.
- De Bresser, J., Tiehuis, A. M., Van Den Berg, E., Reijmer, Y. D., Jongen, C., Kappelle, L. J., Mali, W. P., Viergever, M. A., Jan Biessels, G., & Utrecht Diabetic Encephalopathy Study Group (2010). Progression of cerebral atrophy and white matter hyperintensities in patients with type 2 diabetes. *Diabetes Care*, *33*(6), 1309-1314. <https://doi.org/10.2337/dc09-1923>

- de Bruijn, R. F., Bos, M. J., Portegies, M. L., Hofman, A., Franco, O. H., Koudstaal, P. J., & Ikram, M. A. (2015). The potential for prevention of dementia across two decades: The prospective, population-based Rotterdam Study. *BMC, Medicine*, *13*(1), 132. <https://doi.org/10.1186/s12916-015-0377-5>
- de Bruijn, R. F., & Ikram, M. A. (2014). Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC medicine*, *12*(1), 130.
- De Calignon, A., Polydoro, M., Suárez-Calvet, M., William, C., Adamowicz, D. H., Kopeikina, K. J., Pitstick, R., Sahara, N., Ashe, K. H., Carlson, G. A., Spires-Jones, T. L., & Hyman, B. T. (2012). Propagation of tau pathology in a model of early Alzheimer's disease. *Neuron*, *73*(4), 685-697. <https://doi.org/10.1016/j.neuron.2011.11.033>
- De Felice, F. G. (2013). Alzheimer's disease and insulin resistance: Translating basic science into clinical applications. *The Journal of Clinical Investigation*, *123*(2), 531-539.
- de Graaf, R. A., Pan, J. W., Telang, F., Lee, J.-H., Brown, P., Novotny, E. J., Hetherington, H. P., & Rothman, D. L. (2001). Differentiation of glucose transport in human brain gray and white matter. *Journal of Cerebral Blood Flow and Metabolism*, *21*(5), 483-492. <https://doi.org/10.1097/00004647-200105000-00002>
- de Jong, D. L., de Heus, R. A., Rijpma, A., Donders, R., Olde Rikkert, M. G., Günther, M., Lawlor, B. A., van Osch, M. J. P., & Claassen, J. A. H. R. (2019). Effects of nilvadipine on cerebral blood flow in patients with Alzheimer disease: A randomized trial. *Hypertension*, *74*(2), 413-420. <https://doi.org/10.1161/HYPERTENSIONAHA.119.12892>
- de Jong, L., van der Hiele, K., Veer, I., Houwing, J., Westendorp, R., Bollen, E., de Bruin, P. W., Middelkoop, H. A.M., van Buchem, M. A., & van Der Grond, J. (2008). Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: An MRI study. *Brain*, *131*(12), 3277-3285. <https://doi.org/10.1093/brain/awn278>
- De Jongh, R. T., Serné, E. H., IJzerman, R. G., De Vries, G., & Stehouwer, C. D. A. (2004). Impaired microvascular function in obesity: Implications for obesity-associated microangiopathy, hypertension, and insulin resistance. *Circulation*, *109*(21), 2529-2535. <https://doi.org/10.1161/01.CIR.0000129772.26647.6F>
- de Kloet, A. D., Pioquinto, D. J., Nguyen, D., Wang, L., Smith, J. A., Hiller, H., & Sumners, C. (2014). Obesity induces neuroinflammation mediated by altered expression of the renin-angiotensin system in mouse forebrain nuclei. *Physiology and Behavior*, *136*, 31-38. <https://doi.org/10.1016/j.physbeh.2014.01.016>
- de la Monte, S. M., Tong, M., & Wands, J. R. (2018). The 20-year voyage aboard the journal of Alzheimer's disease: Docking at 'Type 3 Diabetes', environmental/exposure factors, pathogenic mechanisms, and potential treatments. *Journal of Alzheimer's Disease*, *62*(3), 1381-1390.
- de la Torre, J. C. (2012). Cerebral hemodynamics and vascular risk factors: setting the stage for Alzheimer's disease. *Journal of Alzheimer's Disease*, *32*(3), 553-567. <https://doi.org/10.1016/10.3233/JAD-2012-120793>
- De Leeuw, F. E., de Groot, J. C., Oudkerk, M., Witteman, J., Hofman, A., Van Gijn, J., & Breteler, M. (2002). Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain*, *125*(4), 765-772.
- De Leeuw, F. E., De Groot, J. C., Oudkerk, M., Witteman, J. C., Hofman, A., Van Gijn, J., & Breteler, M. M. (1999). A follow-up study of blood pressure and cerebral white matter lesions. *Annals of Neurology*, *46*(6), 827-833.
- De Luca, M., Beckmann, C., De Stefano, N., Matthews, P., & Smith, S. M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage*, *29*(4), 1359-1367.
- De Marco, M., Ourselin, S., & Venneri, A. (2019). Age and hippocampal volume predict distinct parts of default mode network activity. *Scientific reports*, *9*(1), 1-9.

- de Montgolfier, O., Pouliot, P., Gillis, M.-A., Ferland, G., Lesage, F., Thorin-Trescases, N., & Thorin, É. (2019). Systolic hypertension-induced neurovascular unit disruption magnifies vascular cognitive impairment in middle-age atherosclerotic LDLr^{-/-}: hApoB^{+/+} mice. *GeroScience*, 41(5), 511-532. <https://doi.org/10.1007/s11357-019-00070-6>
- De Reuck, J. (1971). The human periventricular arterial blood supply and the anatomy of cerebral infarctions. *European Neurology*, 5(6), 321-334.
- De Reuck, J., Deramecourt, V., Cordonnier, C., Leys, D., Pasquier, F., & Muraige, C.A. (2011). Prevalence of small cerebral bleeds in patients with a neurodegenerative dementia: a neuropathological study. *Journal of the Neurological Sciences*, 300(1-2), 63-66. <https://doi.org/10.1016/j.jns.2010.09.031>
- De Smedt, D., Clays, E., Annemans, L., Doyle, F., Kotseva, K., Pająk, A., Prugger, C., Jennings, C., Wood, D., & De Bacquer, D. (2013). Health related quality of life in coronary patients and its association with their cardiovascular risk profile: Results from the EUROASPIRE III survey. *International Journal of Cardiology*, 168(2), 898-903. <https://doi.org/10.1016/j.ijcard.2012.10.053>
- de Vos, L. C., Lefrandt, J. D., Dullaart, R. P., Zeebregts, C. J., & Smit, A. J. (2016). Advanced glycation end products: An emerging biomarker for adverse outcome in patients with peripheral artery disease. *Atherosclerosis*, 254, 291-299.
- Deardorff, W. J., & Grossberg, G. T. (2016). A fixed-dose combination of memantine extended-release and donepezil in the treatment of moderate-to-severe Alzheimer's disease. *Drug Design, Development and Therapy*, 10, 3267. <https://doi.org/10.2147/DDDT.S86463>
- Debette, S., Wolf, C., Lambert, J. C., Crivello, F., Soumaré, A., Zhu, Y. C., Schilling, C., Dufouil, C., Mazoyer, B., Amouyel, P., Tzourio, C., & Elbaz, A. (2014). Abdominal obesity and lower gray matter volume: A Mendelian randomization study. *Neurobiology of Aging*, 35(2), 378-386. <https://doi.org/10.1016/j.neurobiolaging.2013.07.022>
- Declercq, L. D., Vandenberghe, R., Van Laere, K., Verbruggen, A., & Bormans, G. (2016). Drug development in Alzheimer's disease: The contribution of PET and SPECT. *Frontiers in Pharmacology*, 7, 88.
- DeFuria, J., Belkina, A. C., Jagannathan-Bogdan, M., Snyder-Cappione, J., Carr, J. D., Nersesova, Y. R., Markham, D., Strissel, K. J., Watkins, A. A., Zhu, M., Allen, J., Bouchard, J., Toraldo, G., Jasuja, R., Obin, M. S., McDonnell, M. E., Apovian, C., Denis, G. V. & Nikolajczyk, B. S. (2013). B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. *Proceedings of the National Academy of Sciences*, 110(13), 5133-5138. <https://doi.org/10.1073/pnas.1215840110>
- Dekkers, I. A., Jansen, P. R., & Lamb, H. J. (2019). Obesity, brain volume, and white matter microstructure at MRI: A cross-sectional UK biobank study. *Radiology*, 291(3), 763-771. <https://doi.org/10.1148/radiol.2019181012>
- DeKosky, S. T., Ikonomic, M. D., Styren, S. D., Beckett, L., Wisniewski, S., Bennett, D. A., Cochran, E. J., Kordower, J. H., & Mufson, E. J. (2002). Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. *Annals of Neurology*, 51(2), 145-155. <https://doi.org/10.1002/ana.10069>
- DelParigi, A., Chen, K., Salbe, A. D., Reiman, E. M., & Tataranni, P. A. (2005). Sensory experience of food and obesity: A positron emission tomography study of the brain regions affected by tasting a liquid meal after a prolonged fast. *Neuroimage*, 24(2), 436-443. <https://doi.org/10.1016/j.neuroimage.2004.08.035>
- Demir, E. A., Tutuk, O., Dogan, H., & Tumer, C. (2019). Depression in Alzheimer's Disease: The Roles of Cholinergic and Serotonergic Systems. In T. Wisniewski (Ed.), *Alzheimer's Disease*. Codon Publications. <https://doi.org/10.15586/alzheimersdisease.2019.ch14>

- den Heijer, T., Launer, L., Prins, N., Van Dijk, E., Vermeer, S., Hofman, A., Koudstaal, P. J., & Breteler, M. M. B. (2005). Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology*, *64*(2), 263-267. <https://doi.org/10.1212/01.WNL.0000149641.55751.2E>
- den Heijer, T., Vermeer, S. E., van Dijk, E. J., Prins, N. D., Koudstaal, P. J., Hofman, A., & Breteler, M. M. B. (2003). Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia*, *46*(12), 1604-1610. <https://doi.org/10.1007/s00125-003-1235-0>
- Derdeyn, C. P. (2007). Mechanisms of ischemic stroke secondary to large artery atherosclerotic disease. *Neuroimaging Clinics of North America*, *17*(3), 303-311, <https://doi.org/10.1016/j.nic.2007.03.001>
- Desikan, R. S., Cabral, H. J., Fischl, B., Guttman, C. R., Blacker, D., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2009). Temporoparietal MR imaging measures of atrophy in subjects with mild cognitive impairment that predict subsequent diagnosis of Alzheimer disease. *American Journal of Neuroradiology*, *30*(3), 532-538. <https://doi.org/10.3174/ajnr.A1397>
- Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968-980. <https://doi.org/10.1016/j.neuroimage.2006.01.021>
- Desouza, C. V., Bolli, G. B., & Fonseca, V. (2010). Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care*, *33*(6), 1389-1394. <https://doi.org/10.2337/dc09-2082>
- Detre, J. A., Leigh, J. S., Williams, D. S., & Koretsky, A. P. (1992). Perfusion imaging. *Magnetic Resonance in Medicine*, *23*(1), 37-45. <https://doi.org/10.1002/mrm.1910230106>
- Detre, J. A., Rao, H., Wang, D. J., Chen, Y. F., & Wang, Z. (2012). Applications of arterial spin labeled MRI in the brain. *Journal of Magnetic Resonance Imaging*, *35*(5), 1026-1037. <https://doi.org/10.1002/jmri.23581>
- Devaskar, S. U., Giddings, S. J., Rajakumar, P. A., Carnaghi, L. R., Menon, R. K., & Zahm, D. S. (1994). Insulin gene expression and insulin synthesis in mammalian neuronal cells. *Journal of Biological Chemistry*, *269*(11), 8445-8454. [https://doi.org/10.1016/S0021-9258\(17\)37214-9](https://doi.org/10.1016/S0021-9258(17)37214-9)
- Dhikav, V., & Anand, K. (2011). Potential predictors of hippocampal atrophy in Alzheimer's disease. *Drugs & Aging*, *28*(1), 1-11.
- Dhikav, V., Singh, P., & Anand, K. S. (2013). Medication adherence survey of drugs useful in prevention of dementia of Alzheimer's type among Indian patients. *International Psychogeriatrics*, *25*(9), 1409-1413.
- Di Chiara, T., Scaglione, A., Corrao, S., Argano, C., Pinto, A., & Scaglione, R. (2015). Association between low education and higher global cardiovascular risk. *The Journal of Clinical Hypertension*, *17*(5), 332-337.
- Di Marco, L. Y., Venneri, A., Farkas, E., Evans, P. C., Marzo, A., & Frangi, A. F. (2015). Vascular dysfunction in the pathogenesis of Alzheimer's disease - A review of endothelium-mediated mechanisms and ensuing vicious circles. *Neurobiology of Disease*, *82*, 593-606. <https://doi.org/10.1016/j.nbd.2015.08.014>
- Di Paola, M., Macaluso, E., Carlesimo, G., Tomaiuolo, F., Worsley, K., Fadda, L., & Caltagirone, C. (2007). Episodic memory impairment in patients with Alzheimer's disease is correlated with entorhinal cortex atrophy. *Journal of Neurology*, *254*(6), 774-781.
- Diaz-Ruiz, C., Wang, J., Ksiazek-Reding, H., Ho, L., Qian, X., Humala, N., . . . neurology. (2009). Role of Hypertension in Aggravating A Neuropathology of AD Type and Tau-Mediated Motor Impairment. *Cardiovascular Psychiatry and Neurology*, 2009, 107286. <https://doi.org/10.1155/2009/107286>

- Dickerson, B. C., Goncharova, I., Sullivan, M., Forchetti, C., Wilson, R., Bennett, D., & Beckett, L. A. (2001). MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. *Neurobiology of Aging*, *22*(5), 747-754.
- Dickstein, D. L., Walsh, J., Brautigam, H., Stockton Jr, S. D., Gandy, S., & Hof, P. R. (2010). Role of vascular risk factors and vascular dysfunction in Alzheimer's disease. *Mount Sinai Journal of Medicine*, *77*(1), 82-102.
- Dicou, E., Attoub, S., & Gressens, P. (2001). Neuroprotective effects of leptin in vivo and in vitro. *Neuroreport*, *12*(18), 3947-3951.
- Dienel, G. A. (2019). Brain glucose metabolism: Integration of energetics with function. *Physiological Reviews*, *99*(1), 949-1045.
- Dietschy, J. M., & Turley, S. D. (2001). Cholesterol metabolism in the brain. *Current Opinion in Lipidology*, *12*(2), 105-112.
- Dineley, K. T., Jahrling, J. B., & Denner, L. (2014). Insulin resistance in Alzheimer's disease. *Neurobiology of Disease*, *72*, 92-103.
- Ding, Y., Ji, G., Li, G., Zhang, W., Hu, Y., Liu, L., Wang, Y., Hu, C., von Deneen, K. M., Han, Y., Cui, G., Wang, H., Wiers, C. E., Manza, P., Tomasi, D., Volkow, N. D., Nie, Y., Wang, G. J., & Zhang, Y. (2020). Altered interactions among resting-state networks in individuals with obesity. *Obesity*, *28*(3), 601-608. <https://doi.org/10.1002/oby.22731>
- Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., & Reynolds, C. F. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *The British Journal of Psychiatry*, *202*(5), 329-335. <https://doi.org/10.1192/bjp.bp.112.118307>
- Direk, N., Schrijvers, E. M., de Bruijn, R. F., Mirza, S., Hofman, A., Ikram, M. A., & Tiemeier, H. J. J. o. p. r. (2013). Plasma amyloid β , depression, and dementia in community-dwelling elderly. *47*(4), 479-485.
- Dixon, S. J., & Stockwell, B. R. (2014). The role of iron and reactive oxygen species in cell death. *Nature chemical biology*, *10*(1), 9.
- Djulejić, V., Marinković, S., Georgievski, B., Stijak, L., Aksić, M., Puškaš, L., & Milić, I. (2016). Clinical significance of blood supply to the internal capsule and basal ganglia. *Journal of Clinical Neuroscience*, *25*, 19-26.
- Djulejić, V., Marinković, S., Milić, V., Georgievski, B., Rašić, M., Aksić, M., & Puškaš, L. (2015). Common features of the cerebral perforating arteries and their clinical significance. *Acta Neurochirurgica*, *157*(5), 743-754. <https://doi.org/10.1007/s00701-015-2378-8>
- Dong, G., Lin, X., & Potenza, M. N. (2015). Decreased functional connectivity in an executive control network is related to impaired executive function in Internet gaming disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *57*, 76-85.
- Donix, M., Burggren, A. C., Scharf, M., Marschner, K., Suthana, N. A., Siddarth, P., Krupa A. K., Jones, M., Martin-Harris, L., Ercoli, L. M., Miller, K. J., Werner, A., von Kummer, R., Sauera, C., Small, G. W., Holthoff, V. A., & Bookheimer, S. Y. (2013). APOE associated hemispheric asymmetry of entorhinal cortical thickness in aging and Alzheimer's disease. *Psychiatry Research: Neuroimaging*, *214*(3), 212-220. <https://doi.org/10.1016/j.psychresns.2013.09.006>
- Donnelly, L. A., Zhou, K., Doney, A. S. F., Jennison, C., Franks, P. W., & Pearson, E. R. (2018). Rates of glycaemic deterioration in a real-world population with type 2 diabetes. *Diabetologia*, *61*(3), 607-615. <https://doi.org/10.1007/s00125-017-4519-5>
- Donovan, N. J., Locascio, J. J., Marshall, G. A., Gatchel, J., Hanseeuw, B. J., Rentz, D. M., Johnson, K. A., Sperling, R. A., & The Harvard Aging Brain Study (2018). Longitudinal association of amyloid beta and anxious-depressive symptoms in cognitively normal older adults. *The American Journal of Psychiatry*, *175*(6), 530-537. <https://doi.org/10.1176/appi.ajp.2017.17040442>

- dos Santos Matioli, M. N. P., Suemoto, C. K., Rodriguez, R. D., Farias, D. S., da Silva, M. M., Leite, R. E. P., Ferretti-Rebustini, R. E. L., Farfel, J. M., Pasqualucci, C. A., Jacob Filho, W., Arvanitakis, Z., Naslavsky, M. S., Zatz, M., Grinberg, L. T., & Nitrini, R. (2017). Diabetes is not associated with Alzheimer's disease neuropathology. *Journal of Alzheimer's Disease*, *60*(3), 1035-1043. <https://doi.org/10.3233/JAD-170179>
- Doucet, G. E., Rasgon, N., McEwen, B. S., Micali, N., & Frangou, S. (2018). Elevated body mass index is associated with increased integration and reduced cohesion of sensory-driven and internally guided resting-state functional brain networks. *Cerebral Cortex*, *28*(3), 988-997. <https://doi.org/10.1093/cercor/bhx008>
- Dougherty, R. J., Ellingson, L. D., Schultz, S. A., Boots, E. A., Meyer, J. D., Lindheimer, J. B., Van Riper, S., Stegner, A. J., Edwards, D. F., Oh, J. M., Kosciak, R. L., Dowling, M. N., Gallagher, C. L., Carlsson, C. M., Rowley, H. A., Bendlin, B. B., Asthana, S., Hermann, B. P., Sager, M. A., & Cook, D. B. (2016). Meeting physical activity recommendations may be protective against temporal lobe atrophy in older adults at risk for Alzheimer's disease. *Alzheimer's and Dementia: Diagnosis, Assessment and Monitoring*, *4*(1), 14-17. <https://doi.org/10.1016/j.dadm.2016.03.005>
- Drew, B., & Leeuwenburgh, C. (2003). Method for measuring ATP production in isolated mitochondria: ATP production in brain and liver mitochondria of Fischer-344 rats with age and caloric restriction. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *285*(5), R1259-R1267. <https://doi.org/10.1152/ajpregu.00264.2003>
- Driscoll, I., Beydoun, M. A., An, Y., Davatzikos, C., Ferrucci, L., Zonderman, A. B., & Resnick, S. M. (2012). Midlife obesity and trajectories of brain volume changes in older adults. *Human Brain Mapping*, *33*(9), 2204-2210. <https://doi.org/10.1002/hbm.21353>
- Drzezga, A., Lautenschlager, N., Siebner, H., Riemenschneider, M., Willoch, F., Minoshima, S., Schwaiger, M., & Kurz, A. (2003). Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: A PET follow-up study. *European Journal of Nuclear Medicine and Molecular Imaging*, *30*(8), 1104-1113. <https://doi.org/10.1007/s00259-003-1194-1>
- Duan, Y., Dong, S., Gu, F., Hu, Y., & Zhao, Z. (2012). Advances in the pathogenesis of Alzheimer's disease: Focusing on tau-mediated neurodegeneration. *Translational Neurodegeneration*, *1*(1), 24. <https://doi.org/10.1186/2047-9158-1-24>
- Duarte, A., Hayasaka, S., Du, A., Schuff, N., Jahng, G. H., Kramer, J., Miller, B., & Weiner, M. (2006). Volumetric correlates of memory and executive function in normal elderly, mild cognitive impairment and Alzheimer's disease. *Neuroscience Letter*, *406*(1-2), 60-65. <https://doi.org/10.1016/j.neulet.2006.07.029>
- Duarte, J. V., Pereira, J. M., Quendera, B., Raimundo, M., Moreno, C., Gomes, L., Carrilho, F. & Castelo-Branco, M. (2015). Early disrupted neurovascular coupling and changed event level hemodynamic response function in type 2 diabetes: An fMRI study. *Journal of Cerebral Blood Flow & Metabolism*, *35*(10), 1671-1680. <https://doi.org/10.1038/jcbfm.2015.106>
- Dubois, B., & Albert, M. L. (2004). Amnestic MCI or prodromal Alzheimer's disease? *The Lancet Neurology*, *3*(4), 246-248.
- Dubois, B., Feldman, H. H., Jacova, C., Hampel, H., Molinuevo, J. L., Blennow, K., . . . Bateman, R. (2014). Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *The Lancet Neurology*, *13*(6), 614-629.
- Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., Bakardjian, H., Benali, H., Bertram, L., Blennow, K., Broich, K., Cavado, E., Crutch, S., Dartigues, J. F., Duyckaerts, C., Epelbaum, S., Frisoni, G. B., Gauthier, S., Genthon, R., . . . Jack Jr., C. R. (2016a). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's & Dementia*, *12*(3), 292-323. <https://doi.org/10.1016/j.jalz.2016.02.002>

- Dubois, B., Padovani, A., Scheltens, P., Rossi, A., & Dell'Agnello, G. (2016b). Timely Diagnosis for Alzheimer's Disease: A Literature Review on Benefits and Challenges. *Journal of Alzheimer's Disease*, 49(3), 617-631. <https://doi.org/10.3233/JAD-150692>
- Duckrow, R. B., Beard, D. C., & Brennan, R. W. (1985). Regional cerebral blood flow decreases during hyperglycemia. *Annals of Neurology*, 17(3), 267-272.
- Dufouil, C., de Kersaint-Gilly, A., Besancon, V., Levy, C., Auffray, E., Brunnereau, L., Alperovitch, A., & Tzourio, C. (2001). Longitudinal study of blood pressure and white matter hyperintensities: The EVA MRI Cohort. *Neurology*, 56(7), 921-926. <https://doi.org/10.1212/WNL.56.7.921>
- Duranton, F., Kramer, A., Szwarc, I., Bieber, B., Gayraud, N., Jover, B., Vetromile, F., Massy, Z.A., Combe, C., Tentori, F. and Jager, K.J., 2018. Geographical variations in blood pressure level and seasonality in hemodialysis patients. *Hypertension*, 71(2), pp.289-296. <https://doi.org/10.1161/HYPERTENSIONAHA.117.10274>
- Durazzo, T. C., Mattsson, N., Weiner, M. W. & ADNI (2015). Interaction of cigarette smoking history with apoe genotype and age on amyloid level, glucose metabolism, and neurocognition in cognitively normal elders. *Nicotine & Tobacco Research*, 18(2), 204-211. <https://doi.org/10.1093/ntr/ntv075>
- Eckel, R. H., Jakicic, J. M., Ard, J. D., De Jesus, J. M., Miller, N. H., Hubbard, V. S., . . . Millen, B. E. (2014). 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, 63(25 Part B), 2960-2984.
- Edworthy, S., & Devins, G. (1999). Improving medication adherence through patient education distinguishing between appropriate and inappropriate utilization. Patient Education Study Group. *The Journal of Rheumatology*, 26(8), 1793-1801.
- Eelen, G., de Zeeuw, P., Simons, M., & Carmeliet, P. (2015). Endothelial cell metabolism in normal and diseased vasculature. *Circulation Research*, 116(7), 1231-1244. <https://doi.org/10.1161/CIRCRESAHA.116.302855>
- Eguchi, K., Kario, K., & Shimada, K. (2003). Greater impact of coexistence of hypertension and diabetes on silent cerebral infarcts. *Stroke*, 34(10), 2471-2474.
- Ehrlich, D., & Humpel, C. (2012). Chronic vascular risk factors (cholesterol, homocysteine, ethanol) impair spatial memory, decline cholinergic neurons and induce blood-brain barrier leakage in rats in vivo. *Journal of the Neurological Sciences*, 322(1-2), 92-95. <https://doi.org/10.1016/j.jns.2012.07.002>
- Eichner, J. E., Kuller, L. H., Orchard, T. J., Grandits, G. A., McCallum, L. M., Ferrell, R. E., & Neaton, J. D. (1993). Relation of apolipoprotein E phenotype to myocardial infarction and mortality from coronary artery disease. *The American Journal of Cardiology*, 71(2), 160-165.
- Ekblad, L. L., Johansson, J., Helin, S., Viitanen, M., Laine, H., Puukka, P., Jula, A., & Rinne, J. O. (2018). Midlife insulin resistance, APOE genotype, and late-life brain amyloid accumulation. *Neurology*, 90(13), e1150-e1157. <https://doi.org/10.1212/WNL.00000000000005214>
- El Haj, M., Antoine, P., Amouyel, P., Lambert, J.-C., Pasquier, F., & Kapogiannis, D. (2016). Apolipoprotein E (APOE) ε4 and episodic memory decline in Alzheimer's disease: A review. *Ageing Research Reviews*, 27, 15-22.
- El-Saifi, N., Moyle, W., Jones, C., & Tuffaha, H. (2018). Medication adherence in older patients with dementia: a systematic literature review. *Journal of Pharmacy Practice*, 31(3), 322-334.
- Elias, M. F., Wolf, P. A., D'Agostino, R. B., Cobb, J., & White, L. R. (1993). Untreated blood pressure level is inversely related to cognitive functioning: The Framingham Study. *American Journal of Epidemiology*, 138(6), 353-364. <https://doi.org/10.1093/oxfordjournals.aje.a116868>

- Ellis, K. A., Lim, Y. Y., Harrington, K., Ames, D., Bush, A. I., Darby, D., Martins, R. N., Masters, C. L., Rowe, C. C., Savage, G., Szoeker, C., Villemagne, V. L., Maruff, P., & The AIBL Research Group (2013). Decline in cognitive function over 18 months in healthy older adults with high amyloid- β . *Journal of Alzheimer's Disease*, *34*(4), 861-871. <https://doi.org/10.3233/JAD-122170>
- Ellis, R., Olichney, J. M., Thal, L., Mirra, S., Morris, J., Beekly, D., & Heyman, A. (1996). Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: The CERAD experience, Part XV. *Neurology*, *46*(6), 1592-1596.
- Erdem, A., Yaşargil, M. G., & Roth, P. (1993). Microsurgical anatomy of the hippocampal arteries. *Journal of Neurosurgery*, *79*(2), 256-265.
- Erdő, F., Denes, L., & de Lange, E. (2017). Age-associated physiological and pathological changes at the blood–brain barrier: A review. *Journal of Cerebral Blood Flow & Metabolism*, *37*(1), 4-24.
- Erecińska, M., & Dagani, F. (1990). Relationships between the neuronal sodium/potassium pump and energy metabolism. Effects of K⁺, Na⁺, and adenosine triphosphate in isolated brain synaptosomes. *The Journal of General Physiology*, *95*(4), 591-616. <https://doi.org/10.1085/jgp.95.4.591>
- Erickson, M. A., & Banks, W. A. (2013). Blood–brain barrier dysfunction as a cause and consequence of Alzheimer's disease. *Journal of Cerebral Blood Flow & Metabolism*, *33*(10), 1500-1513.
- Erus, G., Battapady, H., Zhang, T., Lovato, J., Miller, M. E., Williamson, J. D., Launer, L. J., Bryan, R. N., & Davatzikos, C. (2015). Spatial patterns of structural brain changes in type 2 diabetic patients and their longitudinal progression with intensive control of blood glucose. *Diabetes Care*, *38*(1), 97-104. <https://doi.org/10.2337/dc14-1196>
- Escott-Price, V., Myers, A., Huentelman, M., Shoai, M., & Hardy, J. (2019). Polygenic risk score analysis of Alzheimer's disease in cases without APOE4 or APOE2 alleles. *The Journal of Prevention of Alzheimer's Disease*, *6*(1), 16-19.
- Esiri, M. M., Joachim, C., Sloan, C., Christie, S., Agacinski, G., Bridges, L. R., Wilcock, G. K., & Smith, A. D. (2014). Cerebral subcortical small vessel disease in subjects with pathologically confirmed Alzheimer disease: A clinicopathologic study in the Oxford Project to Investigate Memory and Ageing (OPTIMA). *Alzheimer Disease & Associated Disorders*, *28*(1), 30-35. <https://doi.org/10.1097/WAD.0b013e31829b72f1>
- Eto, M., Toba, K., Akishita, M., Kozaki, K., Watanabe, T., Kim, S., Hashimoto, M., Ako, J., Iijima, K., Sudoh, N., & Yoshizumi, M., (2005). Impact of blood pressure variability on cardiovascular events in elderly patients with hypertension. *Hypertension research*, *28*(1), 1-7. <https://doi.org/10.1291/hypres.28.1>
- Ettenhofer, M. L., Foley, J., Castellon, S. A., & Hinkin, C. H. (2010). Reciprocal prediction of medication adherence and neurocognition in HIV/AIDS. *Neurology*, *74*(15), 1217-1222.
- Evans, R., Emsley, C., Gao, S., Sahota, A., Hall, K., Farlow, M., & Hendrie, H. (2000). Serum cholesterol, APOE genotype, and the risk of Alzheimer's disease: A population-based study of African Americans. *Neurology*, *54*(1), 240-240. <https://doi.org/10.1212/WNL.54.1.240>
- Everett, B., & Zajacova, A. (2015). Gender differences in hypertension and hypertension awareness among young adults. *Biodemography and Social Biology*, *61*(1), 1-17.
- Ewens, K. G., Jones, M. R., Ankener, W., Stewart, D. R., Urbanek, M., Dunaif, A., Spielman, R. S., Goodarzi, M., & Strauss III, J. F. (2011). FTO and MC4R gene variants are associated with obesity in polycystic ovary syndrome. *PloS One*, *6*(1), e16390. <https://doi.org/10.1371/journal.pone.0016390>
- Fadel, J. R., & Reagan, L. P. (2016). Stop signs in hippocampal insulin signaling: The role of insulin resistance in structural, functional and behavioral deficits. *Current Opinion in Behavioral Sciences*, *9*, 47-54.

- Fan, L. M., Geng, L., Cahill-Smith, S., Liu, F., Douglas, G., McKenzie, C. A., Smith, C., Brooks, G., Channon, K. M., & Li, J. M. (2019). Nox2 contributes to age-related oxidative damage to neurons and the cerebral vasculature. *The Journal of Clinical Investigation*, *129*(8), 3374-3386. <https://doi.org/10.1172/JCI125173>
- Faraco, G., Park, L., Zhou, P., Luo, W., Paul, S. M., Anrather, J., & Iadecola, C. (2016). Hypertension enhances A β -induced neurovascular dysfunction, promotes β -secretase activity, and leads to amyloidogenic processing of APP. *Journal of Cerebral Blood Flow and Metabolism*, *36*(1), 241-252. <https://doi.org/10.1038/jcbfm.2015.79>
- Faria, S. L., Faria, O. P., Menezes, C. S., de Gouvêa, H. R., & de Almeida Cardeal, M. (2012). Metabolic profile of clinically severe obese patients. *Obesity Surgery*, *22*(8), 1257-1262. <https://doi.org/10.1007/s11695-012-0651-y>
- Farmer, M. E., Kittner, S. J., Rae, D. S., Bartko, J. J., & Regier, D. A. (1995). Education and change in cognitive function: The Epidemiologic Catchment Area Study. *Annals of Epidemiology*, *5*(1), 1-7. [https://doi.org/10.1016/1047-2797\(94\)00047-W](https://doi.org/10.1016/1047-2797(94)00047-W)
- Farrall, A. J., & Wardlaw, J. M. (2009). Blood-brain barrier: ageing and microvascular disease—Systematic review and meta-analysis. *Neurobiology of Aging*, *30*(3), 337-352. <https://doi.org/10.1016/j.neurobiolaging.2007.07.015>
- Fernández-Friera, L., Fuster, V., López-Melgar, B., Oliva, B., García-Ruiz, J. M., Mendiguren, J., . . . Fernández-Ortiz, A. J. J. o. t. A. C. o. C. (2017). Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. *70*(24), 2979-2991.
- Fernando, M. S., Simpson, J. E., Matthews, F., Brayne, C., Lewis, C. E., Barber, R., Kalaria, R. N., Forster, G., Esteves, F., Wharton, S. B., Shaw, P. J., O'Brien, J. T., Ince, P. G., & MRC Cognitive Function and Ageing Neuropathology Study Group. (2006). White matter lesions in an unselected cohort of the elderly: Molecular pathology suggests origin from chronic hypoperfusion injury. *Stroke*, *37*(6), 1391-1398. <https://doi.org/10.1161/01.str.0000221308.94473.14>
- Fici, F., Seravalle, G., Koylan, N., Nalbantgil, I., Cagla, N., Korkut, Y., Quarti-Trevano, F., Makel, W., & Grassi, G. (2017). Follow-up of antihypertensive therapy improves blood pressure control: Results of HYT (HYperTension survey) follow-up. *High Blood Pressure & Cardiovascular Prevention*, *24*(3), 289-296. <https://doi.org/10.1007/s40292-017-0208-1>
- Filosa, J. A., Bonev, A. D., Straub, S. V., Meredith, A. L., Wilkerson, M. K., Aldrich, R. W., & Nelson, M. T. (2006). Local potassium signaling couples neuronal activity to vasodilation in the brain. *Nature Neuroscience*, *9*(11), 1397-1403. <https://doi.org/10.1038/nn1779>
- Finkel, T., & Holbrook, N. J. (2000). Oxidants, oxidative stress and the biology of ageing. *Nature*, *408*(6809), 239.
- Firbank, M. J., Wiseman, R. M., Burton, E. J., Saxby, B. K., O'Brien, J. T., & Ford, G. A. (2007). Brain atrophy and white matter hyperintensity change in older adults and relationship to blood pressure. *Journal of Neurology*, *254*(6), 713.
- Firth, N. C., Primativo, S., Marinescu, R.-V., Shakespeare, T. J., Suarez-Gonzalez, A., Lehmann, M., Carton, A., Ocal, D., Pavisic, I., Paterson, R. W., Slattery, C. F., Foulkes, A. J. M., Ridha, B. H., Gil-Néciga, E., Oxtoby, N. P., Young, A. L., Modat, M., Cardoso, M. J., Ourselin, S., . . . Crutch, S. J. (2019). Longitudinal neuroanatomical and cognitive progression of posterior cortical atrophy. *Brain*, *142*(7), 2082-2095. <https://doi.org/10.1093/brain/awz136>
- Fitzpatrick, A. L., Kuller, L. H., Lopez, O. L., Diehr, P., O'Meara, E. S., Longstreth, W., & Luchsinger, J. A. (2009). Midlife and late-life obesity and the risk of dementia: Cardiovascular health study. *Archives of Neurology*, *66*(3), 336-342. <https://doi.org/10.1001/archneurol.2008.582>
- Fleisher, A. S., Podraza, K. M., Bangen, K. J., Taylor, C., Sherzai, A., Sidhar, K., Liu, T. T., Dale, A.M., & Buxton, R. B. (2009). Cerebral perfusion and oxygenation differences in

- Alzheimer's disease risk. *Neurobiology of Aging*, 30(11), 1737-1748.
<https://doi.org/10.1016/j.neurobiolaging.2008.01.012>
- Foerster, M., Marques-Vidal, P., Gmel, G., Daepfen, J.-B., Cornuz, J., Hayoz, D., Pécoud, A., Mooser, V., Waeber, G., Vollenweider, P., Paccaud, F., & Rodondi, N., (2009). Alcohol drinking and cardiovascular risk in a population with high mean alcohol consumption. *The American Journal of Cardiology*, 103(3), 361-368.
<https://doi.org/10.1016/j.amjcard.2008.09.089>
- Fogelholm, M., Kronholm, E., Kukkonen-Harjula, K., Partonen, T., Partinen, M., & Härmä, M. (2007). Sleep-related disturbances and physical inactivity are independently associated with obesity in adults. *International Journal of Obesity*, 31(11), 1713-1721.
<https://doi.org/10.1038/sj.ijo.0803663>
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189-198. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/1202204>
- Fotiadis, P., van Rooden, S., van der Grond, J., Schultz, A., Martinez-Ramirez, S., Auriel, E., van Opstal, A. M., Ayres, A., Schwab, K. M., ADNI., Hedden, T., Rosand, J., Viswanathan, A., Wermer, M., Terwindt, G. M., Sperling, R. A., Polimeni, J. R., Johnson, K. A., ... Gurol, M. E. (2016). Cortical atrophy in patients with cerebral amyloid angiopathy: a case-control study. *Lancet Neurology*, 15(8), 811-819. [https://doi.org/10.1016/S1474-4422\(16\)30030-8](https://doi.org/10.1016/S1474-4422(16)30030-8)
- Fournier, A., Oprisiu-Fournier, R., Serot, J.-M., Godefroy, O., Achard, J.-M., Faure, S., ... Bordet, R. (2009). Prevention of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors. *Expert Review of Neurotherapeutics*, 9(9), 1413-1431.
- Foxe, D., Leyton, C. E., Hodges, J. R., Burrell, J. R., Irish, M., & Piguet, O. (2016). The neural correlates of auditory and visuospatial span in logopenic progressive aphasia and Alzheimer's disease. *Cortex*, 83, 39-50.
- Franklin, S. S., Gustin IV, W., Wong, N. D., Larson, M. G., Weber, M. A., Kannel, W. B., & Levy, D. (1997). Hemodynamic patterns of age-related changes in blood pressure: The Framingham Heart Study. *Circulation*, 96(1), 308-315.
- Frazier, J. A., Chiu, S., Breeze, J. L., Makris, N., Lange, N., Kennedy, D. N., Herbert, M. R., Bent, E. K., B.A., Koneru, V. K., Dieterich, M. E., Hodge, S. M., Rauch, S. L., Grant, P. E., Cohen, B. M., Seidman, L. J., Caviness, V. S., & Biederman, J. (2005). Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. *American Journal of Psychiatry*, 162(7), 1256-1265. <https://doi.org/10.1176/appi.ajp.162.7.1256>
- Frears, E. R., Stephens, D. J., Walters, C. E., Davies, H., & Austen, B. M. (1999). The role of cholesterol in the biosynthesis of β -amyloid. *Neuroreport*, 10(8), 1699-1705.
- Freisling, H., Viallon, V., Lennon, H., Bagnardi, V., Ricci, C., Butterworth, A. S., Sweeting, M., Muller, D., Romieu, I., Bazelle, P., Kvaskoff, M., Arveux, P., Severi, G., Bamia, C., Kühn, T., Kaaks, R., Bergmann, M., Boeing, H., Tjønneland, A., ... Ferrari, P. (2020). Lifestyle factors and risk of multimorbidity of cancer and cardiometabolic diseases: A multinational cohort study. *BMC medicine*, 18(1), 1-11. <https://doi.org/10.1186/s12916-019-1474-7>
- Friedland, R. P., Jagust, W. J., Huesman, R. H., Koss, E., Knittel, B., Mathis, C. A., Ober, B. A., Mazoyer, B. M., & Budinger, T. F. (1989). Regional cerebral glucose transport and utilization in Alzheimer's disease. *Neurology*, 39(11), 1427-1434.
<https://doi.org/10.1212/WNL.39.11.1427>
- Friedman, J. I., Tang, C. Y., de Haas, H. J., Changchien, L., Goliash, G., Dabas, P., Wang, V., Fayad, Z. A., Fuster, V., & Narula, J. (2014). Brain imaging changes associated with risk factors for cardiovascular and cerebrovascular disease in asymptomatic patients. *JACC:Cardiovascular Imaging*, 7(10), 1039-1053.

- Frisoni, G. B., Pievani, M., Testa, C., Sabbatoli, F., Bresciani, L., Bonetti, M., Beltramello, A., Hayashi, K. M., Toga, A. W., & Thompson, P. M. (2007). The topography of grey matter involvement in early and late onset Alzheimer's disease. *Brain*, *130*(Pt 3), 720-730. <https://doi.org/10.1093/brain/awl377>
- Frühbeck, G., & Salvador, J. (2000). Relation between leptin and the regulation of glucose metabolism. *Diabetologia*, *43*(1), 3. <https://doi.org/10.1007/s001250050002>
- Fry, D. (1973). Responses of the arterial wall to certain physical factors. In R. Porter & J. Knight (Eds.). *Atherogenesis: Initiating Factors* (Vol. 12, pp. 93-125): Elsevier Amsterdam.
- Fuhrer, D., Kobayashi, M., & Jiang, H. (2001). Insulin release and suppression by tacrolimus, rapamycin and cyclosporin A are through regulation of the ATP-sensitive potassium channel. *Diabetes, Obesity and Metabolism*, *3*(6), 393-402. <https://doi.org/10.1046/j.1463-1326.2001.00150.x>
- Fujii, H., Takahashi, T., Mukai, T., Tanaka, S., Hosomi, N., Maruyama, H., Sakai, N., & Matsumoto, M. (2017). Modifications of tau protein after cerebral ischemia and reperfusion in rats are similar to those occurring in Alzheimer's disease—Hyperphosphorylation and cleavage of 4- and 3-repeat tau. *Journal of Cerebral Blood Flow and Metabolism* *37*(7), 2441-2457. <https://doi.org/10.1177/0271678X16668889>
- Fujii, K., Sadoshima, S., Okada, Y., Yao, H., Kuwabara, Y., Ichiya, Y., & Fujishima, M. (1990). Cerebral blood flow and metabolism in normotensive and hypertensive patients with transient neurologic deficits. *Stroke*, *21*(2), 283-290.
- Fujishima, M., Ibayashi, S., Fujii, K., & Mori, S. (1995). Cerebral blood flow and brain function in hypertension. *Hypertension Research*, *18*(2), 111-117.
- Fukuda, S., Hirata, A., Nishizawa, H., Nagao, H., Kashine, S., Kimura, T., Inoue, K., Fujishima, Y., Yamaoka, M., Kozawa, J., Kitamura, T., Yasuda, T. Maeda, N., Imagawa, A., Funahashi, T., & Shimomura, I. (2015). Systemic arteriosclerosis and eating behavior in Japanese type 2 diabetic patients with visceral fat accumulation. *Cardiovascular Diabetology*, *14*(1), 1-8. <https://doi.org/10.1186/s12933-015-0174-7>
- Fukui, Y., Yamashita, T., Kurata, T., Sato, K., Lukic, V., Hishikawa, N., Deguchi, K., & Abe, K. (2014). Protective effect of telmisartan against progressive oxidative brain damage and synuclein phosphorylation in stroke-resistant spontaneously hypertensive rats. *Journal of Stroke and Cerebrovascular Diseases*, *23*(6), 1545-1553. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.12.052>
- Fung, V., Huang, J., Brand, R., Newhouse, J. P., & Hsu, J. (2007). Hypertension treatment in a medicare population: adherence and systolic blood pressure control. *Clinical Therapeutics*, *29*(5), 972-984.
- Furst, A. J., Rabinovici, G. D., Rostomian, A. H., Steed, T., Alkalay, A., Racine, C., Miller, B. L., & Jagust, W. J. (2012). Cognition, glucose metabolism and amyloid burden in Alzheimer's disease. *Neurobiology of Aging*, *33*(2), 215-225. <https://doi.org/10.1016/j.neurobiolaging.2010.03.011>
- Furukawa, S., Fujita, T., Shimabukuro, M., Iwaki, M., Yamada, Y., Nakajima, Y., . . . Shimomura, I. (2017). Increased oxidative stress in obesity and its impact on metabolic syndrome. *The Journal of Clinical Investigation*, *114*(12), 1752-1761. <https://doi.org/10.1172/JCI121625>
- Gabriely, I., Ma, X. H., Yang, X. M., Rossetti, L., & Barzilai, N. (2002). Leptin resistance during aging is independent of fat mass. *Diabetes*, *51*(4), 1016-1021. <https://doi.org/10.2337/diabetes.51.4.1016>
- Gács, G., Viñuela, F., Fox, A. J., & Drake, C. G. (1983). Peripheral aneurysms of the cerebellar arteries: Review of 16 cases. *Journal of Neurosurgery*, *58*(1), 63-68.
- Gallagher, M., & Koh, M. T. (2011). Episodic memory on the path to Alzheimer's disease. *Current opinion in neurobiology*, *21*(6), 929-934.

- Gao, L., Maidment, I., Matthews, F. E., Robinson, L., Brayne, C., & Medical Research Council Cognitive Function and Ageing Study. (2018). Medication usage change in older people (65+) in England over 20 years: findings from CFAS I and CFAS II. *Age and Ageing*, *47*(2), 220-225. <https://doi.org/10.1093/ageing/afx158>
- Gao, L., Tian, S., Gao, H., & Xu, Y. (2013). Hypoxia increases A β -induced tau phosphorylation by calpain and promotes behavioral consequences in AD transgenic mice. *Journal of Molecular Neuroscience*, *51*(1), 138-147. <https://doi.org/10.1007/s12031-013-9966-y>
- Gao, S., Zhao, D., Wang, M., Zhao, F., Han, X., Qi, Y., & Liu, J. (2017). Association between circulating oxidized LDL and atherosclerotic cardiovascular disease: a meta-analysis of observational studies. *Canadian Journal of Cardiology*, *33*(12), 1624-1632. <https://doi.org/10.1016/j.cjca.2017.07.015>
- García-García, I., Michaud, A., Dadar, M., Zeighami, Y., Neseliler, S., Collins, D. L., Evans, A. C., & Dagher, A. (2019). Neuroanatomical differences in obesity: Meta-analytic findings and their validation in an independent dataset. *International Journal of Obesity*, *43*(5), 943-951. <https://doi.org/10.1038/s41366-018-0164-4>
- García-Alberca, J. M., Mendoza, S., Gris, E., Royo, J. L., Cruz-Gamero, J. M., & García-Casares, N. (2020). White matter lesions and temporal atrophy are associated with cognitive and neuropsychiatric symptoms in patients with hypertension and Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *35*(11), 1292-1300. <https://doi.org/10.1002/gps.5366>
- García-García, I., Jurado, M. Á., Garolera, M., Segura, B., Sala-Llonch, R., Marqués-Iturria, I., Pueyo, R., Sender-Palacios, M. J., Vernet-Vernet, M., Narberhaus, A., Ariza, M., & Junqué, C. (2013). Alterations of the salience network in obesity: a resting-state fMRI study. *Human Brain Mapping*, *34*(11), 2786-2797. <https://doi.org/10.1002/hbm.22104>
- Gardiner, T., Anderson, H., & Stitt, A. W. (2003). Inhibition of advanced glycation end-products protects against retinal capillary basement membrane expansion during long-term diabetes. *The Journal of Pathology*, *201*(2), 328-333. <https://doi.org/10.1002/path.1429>
- Gardini, S., Cuetos, F., Fasano, F., Ferrari Pellegrini, F., Marchi, M., Venneri, A., & Caffarra, P. (2013). Brain structural substrates of semantic memory decline in mild cognitive impairment. *Current Alzheimer Research*, *10*(4), 373-389. <https://doi.org/10.2174/1567205011310040004>
- Gardini, S., Venneri, A., Sambataro, F., Cuetos, F., Fasano, F., Marchi, M., Girolamo, C., & Caffarra, P. (2015). Increased functional connectivity in the default mode network in mild cognitive impairment: a maladaptive compensatory mechanism associated with poor semantic memory performance. *Journal of Alzheimer's Disease*, *45*(2), 457-470. <https://doi.org/10.3233/JAD-142547>
- Garrison, R., Wilson, P., Castelli, W., Feinleib, M., Kannel, W., & McNamara, P. M. (1980). Obesity and lipoprotein cholesterol in the Framingham offspring study. *Metabolism*, *29*(11), 1053-1060. [https://doi.org/10.1016/0026-0495\(80\)90216-4](https://doi.org/10.1016/0026-0495(80)90216-4)
- Gasbarri, A., Pompili, A., Packard, M. G., & Tomaz, C. (2014). Habit learning and memory in mammals: Behavioral and neural characteristics. *Neurobiology of Learning and Memory*, *114*, 198-208.
- Gatz, M., Mortimer, J. A., Fratiglioni, L., Johansson, B., Berg, S., Reynolds, C. A., & Pederson, N. L. (2006). Potentially modifiable risk factors for dementia in identical twins. *Alzheimer's and Dementia*, *2*(2), 110-117. <https://doi.org/10.1016/j.jalz.2006.01.002>
- Gazdzinski, S., Kornak, J., Weiner, M. W., Meyerhoff, D. J., & Nat, R. (2008). Body mass index and magnetic resonance markers of brain integrity in adults. *Annals of Neurology*, *63*(5), 652-657. <https://doi.org/10.1002/ana.21377>
- Gazzaley, A., Cooney, J. W., Rissman, J., & D'esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience*, *8*(10), 1298-1300.

- Ge, Y., Grossman, R. I., Babb, J. S., Rabin, M. L., Mannon, L. J., & Kolson, D. L. (2002). Age-related total gray matter and white matter changes in normal adult brain. Part II: Quantitative magnetization transfer ratio histogram analysis. *American Journal of Neuroradiology*, *23*(8), 1334-1341.
- Gelber, R. P., Gaziano, J. M., Manson, J. E., Buring, J. E., & Sesso, H. D. (2007). A prospective study of body mass index and the risk of developing hypertension in men. *American Journal of Hypertension*, *20*(4), 370-377.
- Gelber, R. P., Ross, G. W., Petrovitch, H., Masaki, K. H., Launer, L. J., & White, L. R. (2013). Antihypertensive medication use and risk of cognitive impairment: The Honolulu-Asia Aging Study. *Neurology*, *81*(10), 888-895.
- Geldmacher, D. S. (2003). Visuospatial dysfunction in the neurodegenerative diseases. *Frontiers in Bioscience*, *8*, e428-436.
- Ghanavati, E., Salehinejad, M. A., Nejati, V., & Nitsche, M. A. (2019). Differential role of prefrontal, temporal and parietal cortices in verbal and figural fluency: Implications for the supramodal contribution of executive functions. *Scientific reports*, *9*(1), 1-10.
- Ghanem, A., Dörner, J., Schulze-Hagen, L., Müller, A., Wilsing, M., Sinning, J. M., Lütken, J., Frerker, C., Kuck, K. H., Gräff, I., Schild, H., Werner, N., Grube, E., & Nickenig, G. (2017). Subacute subclinical brain infarctions after transcatheter aortic valve implantation negatively impact cognitive function in long-term follow-up. *PloS One*, *12*(1), e0168852. <https://doi.org/10.1371/journal.pone.0168852>
- Ghaznawi, R., de Bresser, J., van der Graaf, Y., Zwartbol, M. H., Witkamp, T. D., Geerlings, M. I., & Hendrikse, J. (2017). Detection and characterization of small infarcts in the caudate nucleus on 7 Tesla MRI: The SMART-MR study. *Journal of Cerebral Blood Flow & Metabolism*, *38*(9), 1609-1617. <https://doi.org/10.1177/0271678X17705974>
- Ghosh, S., Mukhopadhyay, S., & Barik, A. (2016). Sex differences in the risk profile of hypertension: a cross-sectional study. *BMJ Open*, *6*(7). <http://dx.doi.org/10.1136/bmjopen-2015-010085>
- Ghribi, O., Larsen, B., Schrag, M., & Herman, M. M. (2006). High cholesterol content in neurons increases BACE, β -amyloid, and phosphorylated tau levels in rabbit hippocampus. *Experimental Neurology*, *200*(2), 460-467. <https://doi.org/10.1016/j.expneurol.2006.03.019>
- Giacobini, E., & Gold, G. (2013). Alzheimer disease therapy--moving from amyloid-beta to tau. *Nature Reviews Neurology*, *9*(12), 677-686. <https://doi.org/10.1038/nrneurol.2013.223>
- Giada, F., Biffi, A., Agostoni, P., Anedda, A., Belardinelli, R., Carlon, R., Carù, B., D'Andrea, L., Delise, P., De Francesco, A., Fattiroli, F., Guglielmi, R., Guiducci, U., Pelliccia, A., Penco, M., Perticone, F., Thiene, G., Vona, M., & Zeppilli, P. (2008). Exercise prescription for the prevention and treatment of cardiovascular diseases: Part I. *Journal of Cardiovascular Medicine*, *9*(5), 529-544. <https://doi.org/10.2459/JCM.0b013e3282f7ca77>
- Gianaros, P. J., Greer, P. J., Ryan, C. M., & Jennings, J. R. (2006). Higher blood pressure predicts lower regional grey matter volume: Consequences on short-term information processing. *Neuroimage*, *31*(2), 754-765.
- Giannakopoulos, P., Gold, G., von Gunten, A., Hof, P. R., & Bouras, C. (2009). Pathological substrates of cognitive decline in Alzheimer's disease. In P. Giannakopoulos & P. R. Hof (Eds.). *Dementia in clinical practice* (Vol. 24, pp. 20-29): Karger Publishers.
- Giannakopoulos, P., Herrmann, F.R., Bussière, T., Bouras, C., Kövari, E., Perl, D.P., Morrison, J.H., Gold, G. & Hof, P.R. (2003). Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. *Neurology*, *60*(9), 1495-1500. <https://doi.org/10.1212/01.WNL.0000063311.58879.01>
- Giannini, L., Irwin, D., McMillan, C., Ash, S., Wolk, D., Isenberg, A., Rascovsky, K., Trojanowski, J., & Grossman, M. (2016). Clinicopathological correlations of AD neuropathology in the logopenic variant of primary progressive aphasia. *Neurology*, *86*(16 Supplement).

- Giannini, L. A., Irwin, D. J., McMillan, C. T., Ash, S., Rascovsky, K., Wolk, D. A., Van Deerlin, V. M., Lee, E. B., Trojanowski, J. Q., & Grossman, M. (2017). Clinical marker for Alzheimer disease pathology in logopenic primary progressive aphasia. *Neurology*, *88*(24), 2276-2284. <https://doi.org/10.1212/WNL.0000000000004034>
- Gibson, G., & Zhang, H. (2000). Effects of ginkgo biloba (EGb761) on metabolism of reactive oxygen species in fibroblasts from Alzheimer's disease patients and controls. *Advances in Ginkgo biloba Extract Research*, *8*.
- Giles, T. D., Berk, B. C., Black, H. R., Cohn, J. N., Kostis, J. B., Izzo Jr, J. L., & Weber, M. A. (2005). Expanding the definition and classification of hypertension. *The Journal of Clinical Hypertension*, *7*(9), 505-512. <https://doi.org/10.1111/j.1524-6175.2005.04769.x>
- Giles, T. D., Materson, B. J., Cohn, J. N., & Kostis, J. B. (2009). Definition and classification of hypertension: An update. *The Journal of Clinical Hypertension*, *11*(11), 611-614. <https://doi.org/10.1111/j.1751-7176.2009.00179.x>
- Gillilan, L. A. (1969). The arterial and venous blood supplies to the cerebellum of primates. *Journal of Neuropathology & Experimental Neurology*, *28*(2), 295-307.
- Giorgio, A., Santelli, L., Tomassini, V., Bosnell, R., Smith, S., De Stefano, N., & Johansen-Berg, H. (2010). Age-related changes in grey and white matter structure throughout adulthood. *Neuroimage*, *51*(3), 943-951.
- Global Action Against Dementia. (2014). G8 Dementia Summit Declaration. 2013. In London.
- Glöckner, F., Meske, V., Lütjohann, D., & Ohm, T. G. (2011). Dietary cholesterol and its effect on tau protein: A study in apolipoprotein E-deficient and P301L human tau mice. *Journal of Neuropathology & Experimental Neurology*, *70*(4), 292-301. <https://doi.org/10.1097/NEN.0b013e318212f185>
- Glodzik, L., Mosconi, L., Tsui, W., de Santi, S., Zinkowski, R., Pirraglia, E., Rich, K. E., McHugh, P., Li, Y., Williams, S., Ali, F., Zetterberg, H., Blennow, K., Mehta, P., & de Leon, M. J. (2012). Alzheimer's disease markers, hypertension, and gray matter damage in normal elderly. *Neurobiology of aging*, *33*(7), 1215-1227. <https://doi.org/10.1016/j.neurobiolaging.2011.02.012>
- Glowinska, B., Urban, M., Koput, A., & Galar, M. (2003). New atherosclerosis risk factors in obese, hypertensive and diabetic children and adolescents. *Atherosclerosis*, *167*(2), 275-286. [https://doi.org/10.1016/S0021-9150\(03\)00003-0](https://doi.org/10.1016/S0021-9150(03)00003-0)
- Goedert, M., Spillantini, M. G., Potier, M. C., Ulrich, J., & Crowther, R. A. (1989). Cloning and sequencing of the cDNA encoding an isoform of microtubule-associated protein tau containing four tandem repeats: Differential expression of tau protein mRNAs in human brain. *The EMBO Journal*, *8*(2), 393-399.
- Goedert, M. (2015). Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled A β , tau, and α -synuclein. *Science*, *349*(6248).
- Goh, J. O. & Park, D. C. (2009). Neuroplasticity and cognitive aging: The scaffolding theory of aging and cognition. *Restorative Neurology and Neuroscience*, *27*(5), 391-403. <https://doi.org/10.3233/RNN-2009-0493>
- Goh, L. G., Dhaliwal, S. S., Welborn, T. A., Lee, A. H., & Della, P. R. (2014). Anthropometric measurements of general and central obesity and the prediction of cardiovascular disease risk in women: A cross-sectional study. *BMJ Open*, *4*(2). <http://dx.doi.org/10.1136/bmjopen-2013-004138>
- Gold, S. M., Dziobek, I., Sweat, V., Tirsi, A., Rogers, K., Bruehl, H., Tsui, W., Richardson, S., Javier, E., & Convit, A. (2007). Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia*, *50*(4), 711-719. <https://doi.org/10.1007/s00125-007-0602-7>
- Goldin, A., Beckman, J. A., Schmidt, A. M., & Creager, M. A. (2006). Advanced glycation end products: sparking the development of diabetic vascular injury. *Circulation*, *114*(6), 597-605.

- Goldstein, J. M., Seidman, L. J., Makris, N., Ahern, T., O'Brien, L. M., Caviness Jr, V. S., Kennedy, D. N., Faraone, S. V., & Tsuang, M. T. (2007). Hypothalamic abnormalities in schizophrenia: Sex effects and genetic vulnerability. *Biological Psychiatry*, *61*(8), 935-945. <https://doi.org/10.1016/j.biopsych.2006.06.027>
- Gonzalez, C. E., Pacheco, J., Beason-Held, L. L., & Resnick, S. M. (2015). Longitudinal changes in cortical thinning associated with hypertension. *Journal of Hypertension*, *33*(6), 1242.
- Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., Ogar, J.M., Rohrer, J. D., Black, S., Boeve, B. F., Manes, F., Dronkers, N. F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B. L., Knopman, D. S., Hodges, J. R., Mesulam, M. M., & Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, *76*(11), 1006-1014. <https://doi.org/10.1212/WNL.0b013e31821103e6>
- Goto, M., Abe, O., Aoki, S., Hayashi, N., Ohtsu, H., Takao, H., . . . Ohtomo, K. (2015). Longitudinal gray-matter volume change in the default-mode network: utility of volume standardized with global gray-matter volume for Alzheimer's disease: a preliminary study. *Radiol Phys Technol*, *8*(1), 64-72. <https://doi.org/10.1007/s12194-014-0295-9>
- Gottesman, R. F., Mosley, T. H., Knopman, D. S., Hao, Q., Wong, D., Wagenknecht, L. E., Hughes, T. M., Qiao, Y., Dearborn, J., & Wasserman, B. A. (2020). Association of intracranial atherosclerotic disease with brain β -amyloid deposition: Secondary analysis of the ARIC study. *JAMA Neurology*, *77*(3), 350-357. <https://doi.org/10.1001/jamaneurol.2019.4339>
- Gottesman, R. F., Schneider, A. L., Albert, M., Alonso, A., Bandeen-Roche, K., Coker, L., Coresh, J., Knopman, D., Power, M. C., Rawlings, A., Sharrett, A. R., Wruck, L. M., & Mosley, T. H. (2014). Midlife hypertension and 20-year cognitive change: The atherosclerosis risk in communities neurocognitive study. *JAMA Neurology*, *71*(10), 1218-1227. <https://doi.org/10.1001/jamaneurol.2014.1646>
- Gould, O. N., Mcdonald-Miszczak, L., & King, B. (1997). Metacognition and medication adherence: how do older adults remember? *Experimental Aging Research*, *23*(4), 315-342.
- Goyal, M., Menon, B. K., Krings, T., Patil, S., Qazi, E., McTaggart, R. A., Almekhlafi, M. A., Jehan, R., Saver, J., & Jayaraman, M. V. (2016). What constitutes the M1 segment of the middle cerebral artery? *Journal of Neurointerventional Surgery*, *8*(12), 1273-1277. <http://dx.doi.org/10.1136/neurintsurg-2015-012191>
- Graham, D., Gentleman, S., Nicoll, J., Royston, M., McKenzie, J., Roberts, G., & Griffin, W. (1996). Altered β -APP metabolism after head injury and its relationship to the aetiology of Alzheimer's disease. In A. Baethmann, O. S. Kempfski, N. Plesnila & F. Staub (Eds.), *Mechanisms of Secondary Brain Damage in Cerebral Ischemia and Trauma* (pp. 96-102): Springer.
- Grammer, T. B., Hoffmann, M. M., Scharnagl, H., Kleber, M. E., Silbernagel, G., Pilz, S., Tomaschitz, A., Lerchbaum, E., Siekmeier, R., & März, W. (2013). Smoking, apolipoprotein E genotypes, and mortality (the Ludwigshafen Risk and Cardiovascular Health study). *European Heart Journal*, *34*(17), 1298-1305. <https://doi.org/10.1093/eurheartj/ehd001>
- Graner, J. L., Oakes, T. R., French, L. M., & Riedy, G. (2013). Functional MRI in the investigation of blast-related traumatic brain injury. *Frontiers in Neurology*, *4*, 16.
- Gray, H. (1878). *Anatomy of the human body* (Vol. 8): Lea & Febiger.
- Gray, S. M., Meijer, R. I., & Barrett, E. J. (2014). Insulin regulates brain function, but how does it get there? *Diabetes*, *63*(12), 3992-3997.
- Greco, S. J., Bryan, K. J., Sarkar, S., Zhu, X., Smith, M. A., Ashford, J. W., Johnston, J. M., Tezapsidis, N., & Casadesus, G. (2010). Leptin reduces pathology and improves memory in a transgenic mouse model of Alzheimer's disease. *Journal of Alzheimer's Disease*, *19*(4), 1155-1167. <https://doi.org/10.3233/JAD-2010-1308>

- Greco, S. J., Sarkar, S., Johnston, J. M., & Tezapsidis, N. (2009). Leptin regulates tau phosphorylation and amyloid through AMPK in neuronal cells. *Biochemical and Biophysical Research Communications*, *380*(1), 98-104. <https://doi.org/10.1016/j.bbrc.2009.01.041>
- Greenberg, S. M., Bacskai, B. J., Hernandez-Guillamon, M., Pruzin, J., Sperling, R., & van Veluw, S. J. (2020). Cerebral amyloid angiopathy and Alzheimer disease - One peptide, two pathways. *Nature Reviews Neurology*, *16*(1), 30-42. <https://doi.org/10.1038/s41582-019-0281-2>
- Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proceedings of the National Academy of Sciences*, *101*(13), 4637-4642. <https://doi.org/10.1073/pnas.0308627101>
- Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*, *19*(1), 72-78. <https://doi.org/10.1093/cercor/bhn059>
- Grober, E., Hall, C. B., Lipton, R. B., Zonderman, A. B., Resnick, S. M., & Kawas, C. (2008). Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society*, *14*(2), 266-278.
- Groeneveld, O., Reijmer, Y., Heinen, R., Kuijf, H., Koekkoek, P., Janssen, J., Rutten, G., Kappelle, L., Biessels, G., & COG-ID study group. (2018). Brain imaging correlates of mild cognitive impairment and early dementia in patients with type 2 diabetes mellitus. *Nutrition, Metabolism and Cardiovascular Diseases*, *28*(12), 1253-1260. <https://doi.org/10.1016/j.numecd.2018.07.008>
- Groot, C., van Loenhoud, A. C., Barkhof, F., van Berckel, B. N., Koene, T., Teunissen, C. C., Scheltens, P., van der Flier, W. M., & Ossenkoppele, R. (2017). Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease. *Neurology*, *90*(2), e149-e156. <https://doi.org/10.1212/WNL.0000000000004802>
- Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., Gordon, D. J., Krauss, R. M., Savage, P. J., Smith Jr, S. C., Spertus, J. A., & Costa, F. (2005). Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*, *112*(17), 2735-2752. <https://doi.org/10.1161/CIRCULATIONAHA.105.169404>
- Gu, J., Jin, N., Ma, D., Chu, D., Iqbal, K., Gong, C. X., & Liu, F. (2018). Calpain I activation causes GLUT3 proteolysis and downregulation of O-GlcNAcylation in Alzheimer's disease brain. *Journal of Alzheimer's Disease*, *62*(4), 1737-1746. <https://doi.org/10.3233/JAD-171047>
- Gu, Y., Liu, R., Qin, R., Chen, X., Zou, J., Jiang, Y., Ye, Q., Zhang, B., Bai, F., & Xu, Y. (2019). Characteristic changes in the default mode network in hypertensive patients with cognitive impairment. *Hypertension Research*, *42*(4), 530-540. <https://doi.org/10.1038/s41440-018-0176-4>
- Guarino, A., Favieri, F., Boncompagni, I., Agostini, F., Cantone, M., & Casagrande, M. (2018). Executive Functions in Alzheimer Disease: A Systematic Review. *Frontiers in Aging Neuroscience*, *10*, 437. <https://doi.org/10.3389/fnagi.2018.00437>
- Guercio, B. J., Donovan, N. J., Munro, C. E., Aghjayan, S. L., Wigman, S. E., Locascio, J. J., . . . Sperling, R. A. (2015). The Apathy Evaluation Scale: A comparison of subject, informant, and clinician report in cognitively normal elderly and mild cognitive impairment. *Journal of Alzheimer's Disease*, *47*(2), 421-432.
- Guillozet, A. L., Weintraub, S., Mash, D. C., & Mesulam, M. M. (2003). Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Archives of Neurology*, *60*(5), 729-736.

- Gupta, A., & Iadecola, C. (2015). Impaired A β clearance: a potential link between atherosclerosis and Alzheimer's disease. *Frontiers in Aging Neuroscience*, 7, 115.
- Gurrol, M. E., Dierksen, G., Betensky, R., Gidicsin, C., Halpin, A., Becker, A., Carmasin, J., Ayres, A., Schwab, K., Viswanathan, A., Salat, D., Rosand, J., Johnson, K. A., & Greenberg, S. M. (2012). Predicting sites of new hemorrhage with amyloid imaging in cerebral amyloid angiopathy. *Neurology*, 79(4), 320-326. <https://doi.org/10.1212/WNL.0b013e31826043a9>
- Gustafson, D. R., Bäckman, K., Lissner, L., Carlsson, L., Waern, M., Östling, S., Bengtsson, C., & Skoog, I. (2012). Leptin and dementia over 32 years—The prospective population study of women. *Alzheimer's and Dementia*, 8(4), 272-277. <https://doi.org/10.1016/j.jalz.2011.05.2411>
- Gustafson, D. R., Steen, B., & Skoog, I. (2004). Body mass index and white matter lesions in elderly women. An 18-year longitudinal study. *International Psychogeriatrics*, 16(3), 327. <https://doi.org/10.1017/S1041610204000353>
- Gutierrez, J., Cheung, K., Bagci, A., Rundek, T., Alperin, N., Sacco, R. L., . . . Elkind, M. S. (2015). Brain arterial diameters as a risk factor for vascular events. *Journal of the American Heart Association*, 4(8), e002289.
- Haffner, S., Miettinen, H., Mykkänen, L., Karhapää, P., Rainwater, D., & Laakso, M. (1997). Leptin concentrations and insulin sensitivity in normoglycemic men. *International Journal of Obesity*, 21(5), 393-399. <https://doi.org/10.1038/sj.ijo.0800419>
- Haight, T., Bryan, R. N., Erus, G., Hsieh, M.-K., Davatzikos, C., Nasrallah, I., . . . Schreiner, P. (2018). White matter microstructure, white matter lesions, and hypertension: An examination of early surrogate markers of vascular-related brain change in midlife. *NeuroImage: Clinical*, 18, 753-761.
- Hajjar, I., Hart, M., Chen, Y. L., Mack, W., Novak, V., C. Chui, H., & Lipsitz, L. (2013). Antihypertensive therapy and cerebral hemodynamics in executive mild cognitive impairment: results of a pilot randomized clinical trial. *Journal of the American Geriatrics Society*, 61(2), 194-201.
- Hajjar, I., Quach, L., Yang, F., Chaves, P. H., Newman, A. B., Mukamal, K., Longstreth Jr, W., Inzitari, M., & Lipsitz, L. A. (2011). Hypertension, white matter hyperintensities, and concurrent impairments in mobility, cognition, and mood: The Cardiovascular Health Study. *Circulation*, 123(8), 858-865. <https://doi.org/10.1161/CIRCULATIONAHA.110.978114>
- Hall, K., Murrell, J., Ogunniyi, A., Deeg, M., Baiyewu, O., Gao, S., Gureje, O., Dickens, J., Evans, R., Smith-Gamble, V., Unverzagt, F. W., Shen, J., & Hendrie H. (2006). Cholesterol, APOE genotype, and Alzheimer disease: An epidemiologic study of Nigerian Yoruba. *Neurology*, 66(2), 223-227. <https://doi.org/10.1212/01.wnl.0000194507.39504.17>
- Halliday, M. R., Rege, S. V., Ma, Q., Zhao, Z., Miller, C. A., Winkler, E. A., & Zlokovic, B. V. (2016). Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *Journal of Cerebral Blood Flow and Metabolism*, 36(1), 216-227. <https://doi.org/10.1038/jcbfm.2015.44>
- Hämäläinen, A., Tervo, S., Grau-Olivares, M., Niskanen, E., Pennanen, C., Huuskonen, J., Kivipelto, M., Hänninen, T., Tapiola, M., Vanhanen, M., Hallikainen, M., Helkala, E. L., Nissinen, A., Vanninen, R., & Soininen, H. (2007). Voxel-based morphometry to detect brain atrophy in progressive mild cognitive impairment. *NeuroImage*, 37(4), 1122-1131. <https://doi.org/10.1016/j.neuroimage.2007.06.016>
- Hamburg, N. M., Larson, M. G., Vita, J. A., Vasan, R. S., Keyes, M. J., Widlansky, M. E., Fox, S. C., Mitchell, G. F., Levy, D., Meigs, J. B., & Benjamin, E. J. (2008). Metabolic syndrome, insulin resistance, and brachial artery vasodilator function in Framingham Offspring participants without clinical evidence of cardiovascular disease. *The American Journal of Cardiology*, 101(1), 82-88. <https://doi.org/10.1016/j.amjcard.2007.07.053>

- Hamburg, N. M., McMackin, C. J., Huang, A. L., Shenouda, S. M., Widlansky, M. E., Schulz, E., Gokce, N., Ruderman, N. B., Keaney Jr, J. F., & Vita, J. A. (2007). Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 27(12), 2650-2656. <https://doi.org/10.1161/ATVBAHA.107.153288>
- Hamer, M., & Batty, G. D. (2019). Association of body mass index and waist-to-hip ratio with brain structure: UK Biobank study. *Neurology*, 92(6), e594-e600. <https://doi.org/10.1212/WNL.0000000000006879>
- Hamley, I. W. (2012). The Amyloid Beta Peptide: A Chemist's Perspective. Role in Alzheimer's and Fibrillization. *Chemical Reviews*, 112(10), 5147-5192. <https://doi.org/10.1021/cr3000994>
- Han, K., Patel, Y., Lteif, A., Chisholm, R., & Mather, K. J. (2011). Contributions of dysglycaemia, obesity, and insulin resistance to impaired endothelium-dependent vasodilation in humans. *Diabetes/metabolism Research and Reviews*, 27(4), 354-361. <https://doi.org/10.1002/dmrr.1183>
- Hannesdottir, K., Nitkunan, A., Charlton, R. A., Barrick, T., MacGregor, G., & Markus, H. (2009). Cognitive impairment and white matter damage in hypertension: a pilot study. *Acta Neurologica Scandinavica*, 119(4), 261-268.
- Hardy, J. A., & Higgins, G. A. (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science*, 256(5054), 184-186.
- Harik, S. I., & LaManna, J. C. (1988). Vascular Perfusion and Blood-Brain Glucose Transport in Acute and Chronic Hyperglycemia. *Journal of Neurochemistry*, 51(6), 1924-1929.
- Harrison, T. M., La Joie, R., Maass, A., Baker, S. L., Swinnerton, K., Fenton, L., Mellinger, T. J., Edwards, L., Pham, J., Miller, B. L., Rabinovici, G. D., & Jagust, W. J. (2019). Longitudinal tau accumulation and atrophy in aging and alzheimer disease. *Annals of Neurology*, 85(2), 229-240. <https://doi.org/10.1002/ana.25406>
- Harwood, D. G., Kalechstein, A., Barker, W. W., Strauman, S., St. George-Hyslop, P., Iglesias, C., Loewenstein, D., & Duara, R. (2010). The effect of alcohol and tobacco consumption, and apolipoprotein E genotype, on the age of onset in Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 25(5), 511-518. <https://doi.org/10.1002/gps.2372>
- Hashimoto, M., Akishita, M., Eto, M., Ishikawa, M., Kozaki, K., Toba, K., Sagara, Y., Taketani, Y., Orimo, H., & Ouchi, Y. J. C. (1995). Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. *Circulation*, 92(12), 3431-3435. <https://doi.org/10.1161/01.CIR.92.12.3431>
- Hasselbalch, S. G., Knudsen, G. M., Capaldo, B., Postiglione, A., & Paulson, O. B. (2001). Blood-brain barrier transport and brain metabolism of glucose during acute hyperglycemia in humans. *The Journal of Clinical Endocrinology & Metabolism*, 86(5), 1986-1990.
- Hasselmo, M. E., Wyble, B. P., & Wallenstein, G. V. (1996). Encoding and retrieval of episodic memories: Role of cholinergic and GABAergic modulation in the hippocampus. *Hippocampus*, 6(6), 693-708.
- Haut, K. M., van Erp, T. G., Knowlton, B., Bearden, C. E., Subotnik, K., Ventura, J., . . . Cannon, T. D. (2015). Contributions of feature binding during encoding and functional connectivity of the medial temporal lobe structures to episodic memory deficits across the prodromal and first-episode phases of schizophrenia. *Clinical Psychological Science*, 3(2), 159-174.
- Hawkins, L. A., Kilian, S., Firek, A., Kashner, T. M., Firek, C. J., & Silvet, H. (2012). Cognitive impairment and medication adherence in outpatients with heart failure. *Heart & Lung*, 41(6), 572-582.
- Hayakawa, Y., Sasaki, H., Takao, H., Yoshikawa, T., Hayashi, N., Mori, H., . . . Ohtomo, K. (2018). The relationship of waist circumference and body mass index to grey matter volume in community dwelling adults with mild obesity. *Obesity Science & Practice*, 4(1), 97-105.

- Hayashi, K., Kurioka, S., Yamaguchi, T., Morita, M., Kanazawa, I., Takase, H., Wada, A., Kitagaki, H., Nagai, A., Bokura, H., Yamaguchi, S., & Sugimoto, T. (2011). Association of cognitive dysfunction with hippocampal atrophy in elderly Japanese people with type 2 diabetes. *Diabetes Research and Clinical Practice*, *94*(2), 180-185. <https://doi.org/10.1016/j.diabres.2011.07.002>
- Hayden, K. M., Zandi, P. P., Lyketsos, C. G., Khachaturian, A. S., Bastian, L. A., Charoonruk, G., . . . Munger, R. G. (2006). Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. *Alzheimer Disease & Associated Disorders*, *20*(2), 93-100.
- Hayes, T. L., Larimer, N., Adami, A., & Kaye, J. A. (2009). Medication adherence in healthy elders: small cognitive changes make a big difference. *Journal of Aging and Health*, *21*(4), 567-580.
- Hazar, N., Seddigh, L., Rampisheh, Z., & Nojomi, M. (2016). Population attributable fraction of modifiable risk factors for Alzheimer disease: A systematic review of systematic reviews. *Iranian Journal of Neurology*, *15*(3), 164.
- He, Y., Zhai, F., Ma, G., Feskens, E. J., Zhang, J., Fu, P., Van't Veer, P., & Yang, X. (2009). Abdominal obesity and the prevalence of diabetes and intermediate hyperglycaemia in Chinese adults. *Public Health Nutrition*, *12*(8), 1078-1084. <https://doi.org/10.1017/S1368980008003856>
- Head, D., Buckner, R. L., Shimony, J. S., Williams, L. E., Akbudak, E., Conturo, T. E., . . . Snyder, A. Z. (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. *Cerebral Cortex*, *14*(4), 410-423.
- Hedreen, J. C., Struble, R. G., Whitehouse, P. J., & Price, D. L. (1984). Topography of the magnocellular basal forebrain system in human brain. *Journal of Neuropathology and Experimental Neurology*, *43*(1), 1-21. <https://doi.org/10.1097/00005072-198401000-00001>
- Heinzel, S., Liepelt-Scarfone, I., Roeben, B., Nasi-Kordhishti, I., Suenkel, U., Wurster, I., . . . Metzger, F. G. (2014). A neurodegenerative vascular burden index and the impact on cognition. *Frontiers in Aging Neuroscience*, *6*, 161.
- Henderson, S. T., Vogel, J. L., Barr, L. J., Garvin, F., Jones, J. J., & Costantini, L. C. (2009). Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: A randomized, double-blind, placebo-controlled, multicenter trial. *Nutrition and Metabolism*, *6*(1), 31. <https://doi.org/10.1186/1743-7075-6-31>
- Hendrikse, J., Hartkamp, M. J., Hillen, B., Mali, W. P., & van der Grond, J. (2001). Collateral ability of the circle of Willis in patients with unilateral internal carotid artery occlusion: Border zone infarcts and clinical symptoms. *Stroke*, *32*(12), 2768-2773. <https://doi.org/10.1161/hs1201.099892>
- Hendrikse, J., Petersen, E. T., Van Laar, P. J., & Golay, X. (2008). Cerebral border zones between distal end branches of intracranial arteries: MR imaging. *Radiology*, *246*(2), 572-580. <https://doi.org/10.1148/radiol.2461062100>
- Heni, M., Kullmann, S., Preissl, H., Fritsche, A., & Häring, H. U. (2015). Impaired insulin action in the human brain: Causes and metabolic consequences. *Nature Reviews Endocrinology*, *11*(12), 701.
- Heraclides, A. M., Chandola, T., Witte, D. R., & Brunner, E. J. (2012). Work stress, obesity and the risk of Type 2 Diabetes: Gender-specific bidirectional effect in the Whitehall II study. *Obesity*, *20*(2), 428-433.
- Herrmann, M. J., Tesar, A. K., Beier, J., Berg, M., & Warrings, B. (2019). Grey matter alterations in obesity: A meta-analysis of whole-brain studies. *Obesity Reviews*, *20*(3), 464-471. <https://doi.org/10.1111/obr.12799>
- Herrup, K. (2010). Reimagining Alzheimer's disease—an age-based hypothesis. *Journal of Neuroscience*, *30*(50), 16755-16762. <https://doi.org/10.1523/JNEUROSCI.4521-10.2010>

- Heymann, D., Stern, Y., Cosentino, S., Tatarina-Nulman, O., N Dorrejo, J., & Gu, Y. (2016). The association between alcohol use and the progression of Alzheimer's disease. *Current Alzheimer Research*, *13*(12), 1356-1362. <https://doi.org/10.2174/1567205013666160603005035>
- Hildreth, K. L., Van Pelt, R. E., & Schwartz, R. S. (2012). Obesity, insulin resistance, and Alzheimer's disease. *Obesity (Silver Spring)*, *20*(8), 1549-1557. <https://doi.org/10.1038/oby.2012.19>
- Hirai, K., Aliev, G., Nunomura, A., Fujioka, H., Russell, R. L., Atwood, C. S., . . . Smith, M. A. (2001). Mitochondrial abnormalities in Alzheimer's disease. *The Journal of Neuroscience*, *21*(9), 3017-3023. <https://doi.org/10.1523/JNEUROSCI.21-09-03017.2001>
- Hirao, K., Ohnishi, T., Hirata, Y., Yamashita, F., Mori, T., Moriguchi, Y., . . . Yamada, M. (2005). The prediction of rapid conversion to Alzheimer's disease in mild cognitive impairment using regional cerebral blood flow SPECT. *Neuroimage*, *28*(4), 1014-1021.
- Ho, A. J., Raji, C. A., Becker, J. T., Lopez, O. L., Kuller, L. H., Hua, X., . . . Alzheimer's Disease Neuroimaging Initiative. (2010a). Obesity is linked with lower brain volume in 700 AD and MCI patients. *Neurobiology of Aging*, *31*(8), 1326-1339. <https://doi.org/10.1016/j.neurobiolaging.2010.04.006>
- Ho, A. J., Raji, C. A., Saharan, P., DeGiorgio, A., Madsen, S. K., Hibar, D. P., Stein, J. L., Becker, J. T., Lopez, O. L., Toga, A. W., Thompson, P. M., & Alzheimer's Disease Neuroimaging Initiative (2011). Hippocampal volume is related to body mass index in Alzheimer's disease. *Neuroreport*, *22*(1), 10–14. <https://doi.org/10.1097/wnr.0b013e3283412868>
- Ho, A. J., Stein, J. L., Hua, X., Lee, S., Hibar, D. P., Leow, A. D., Dinov, I. D., Toga, A. W., Saykin, A. J., Shen, L., Foroud, T., Pankratz, N., Huentelman, M. J., Craig, D. W., Gerber, J. D., Allen, A. N., Corneveaux, J. J., Stephan, D. A., DeCarli, C. S., DeChairo, B. M., . . . Alzheimer's Disease Neuroimaging Initiative (2010b). A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. *Proceedings of the National Academy of Sciences*, *107*(18), 8404–8409. <https://doi.org/10.1073/pnas.0910878107>
- Ho, J. K., Nation, D. A., & Alzheimer's disease Neuroimaging Initiative (ADNI) (2017). Memory is preserved in older adults taking AT1 receptor blockers. *Alzheimer's Research & Therapy*, *9*(1), 33.
- Ho, L., Qin, W., Pompl, P. N., Xiang, Z., Wang, J., Zhao, Z., . . . Mobbs, C. V. (2004). Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. *The FASEB Journal*, *18*(7), 902-904.
- Ho, Y. S., Yang, X., Yeung, S. C., Chiu, K., Lau, C. F., Tsang, A. W., Mak, J. C., & Chang, R. C. (2012). Cigarette smoking accelerated brain aging and induced pre-Alzheimer-like neuropathology in rats. *PloS one*, *7*(5), e36752. <https://doi.org/10.1371/journal.pone.0036752>
- Hodges, J. R., & Patterson, K. (1995). Is semantic memory consistently impaired early in the course of Alzheimers-Disease - Neuroanatomical and diagnostic implications. *Neuropsychologia*, *33*(4), 441-459. [https://doi.org/10.1016/0028-3932\(94\)00127-B](https://doi.org/10.1016/0028-3932(94)00127-B)
- Hoenig, M.C., Bischof, G.N., Seemiller, J., Hammes, J., Kukolja, J., Onur, Ö.A., Jessen, F., Fliessbach, K., Neumaier, B., Fink, G.R., & van Eimeren, T. (2018). Networks of tau distribution in Alzheimer's disease. *Brain*, *141*(2), 568-581. <https://doi.org/10.1093/brain/awx353>
- Hoeymans, N., Smit, H., Verkleij, H., & Kromhout, D. (1996). Cardiovascular risk factors in relation to educational level in 36 000 men and women in The Netherlands. *European Heart Journal*, *17*(4), 518-525. <https://doi.org/10.1093/oxfordjournals.eurheartj.a014903>
- Hoffman, L. B., Schmeidler, J., Lesser, G. T., Beerli, M. S., Purohit, D. P., Grossman, H. T., & Haroutunian, V. (2009). Less Alzheimer disease neuropathology in medicated hypertensive

- than nonhypertensive persons. *Neurology*, 72(20), 1720–1726.
<https://doi.org/10.1212/01.wnl.0000345881.82856.d5>
- Hofman, A., de Jong, P. T., van Duijn, C. M., & Breteler, M. M. B. (2006). Epidemiology of neurological diseases in elderly people: What did we learn from the Rotterdam Study? *The Lancet*, 5(6), 545-550. [https://doi.org/10.1016/S1474-4422\(06\)70473-2](https://doi.org/10.1016/S1474-4422(06)70473-2)
- Hofman, A., Ott, A., Breteler, M. M., Bots, M. L., Slooter, A. J., van Harskamp, F., Duijn, C. N., Van Broeckhoven, C., & Grobbee, D. E. (1997). Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *The Lancet*, 349(9046), 151-154. [https://doi.org/10.1016/S0140-6736\(96\)09328-2](https://doi.org/10.1016/S0140-6736(96)09328-2)
- Hogenkamp, P. S., Zhou, W., Dahlberg, L. S., Stark, J., Larsen, A. L., Olivo, G., Wiemerslage, L., Larsson, E. M., Sundbom, M., Benedict, C., & Schiöth, H. B. (2016). Higher resting-state activity in reward-related brain circuits in obese versus normal-weight females independent of food intake. *International Journal of Obesity*, 40(11), 1687–1692.
<https://doi.org/10.1038/ijo.2016.105>
- Holland, C. M., Smith, E. E., Csapo, I., Gurol, M. E., Brylka, D. A., Killiany, R. J., . . . Greenberg, S. M. (2008). Spatial distribution of white-matter hyperintensities in Alzheimer disease, cerebral amyloid angiopathy, and healthy aging. *Stroke*, 39(4), 1127-1133.
- Hollander, M., Bots, M., Del Sol, A. I., Koudstaal, P., Witteman, J., Grobbee, D., Hofman, A., & Breteler, M. M. B. (2002). Carotid plaques increase the risk of stroke and subtypes of cerebral infarction in asymptomatic elderly: The Rotterdam study. *Circulation*, 105(24), 2872-2877. <https://doi.org/10.1161/01.CIR.0000018650.58984.75>
- Holm, H., Ricci, F., Di Martino, G., Bachus, E., Nilsson, E., Ballerini, P., . . . Magnusson, M. (2020). Beta-blocker therapy and risk of vascular dementia: A population-based prospective study. *Vascular pharmacology*, 125, 106649.
- Holmes, C., Arranz, M., Collier, D., Powell, J., & Lovestone, S. (2003). Depression in Alzheimer's disease: the effect of serotonin receptor gene variation. *Am J Med Genet B Neuropsychiatr Genet*, 119B(1), 40-43. <https://doi.org/10.1002/ajmg.b.10068>
- Holwerda, T. J., Deeg, D. J., Beekman, A. T., van Tilburg, T. G., Stek, M. L., Jonker, C., & Schoevers, R. A. (2014). Feelings of loneliness, but not social isolation, predict dementia onset: Results from the Amsterdam Study of the Elderly (AMSTEL). *Journal of Neurology, Neurosurgery and Psychiatry*, 85(2), 135-142. <http://dx.doi.org/10.1136/jnnp-2012-302755>
- Hong, K. W., Jin, H. S., Lim, J. E., Kim, S., Go, M. J., & Oh, B. (2010). Recapitulation of two genomewide association studies on blood pressure and essential hypertension in the Korean population. *Journal of Human Genetics* 55(6), 336-341. <https://doi.org/10.1038/jhg.2010.31>
- Hoogenboom, W. S., Marder, T. J., Flores, V. L., Huisman, S., Eaton, H. P., Schneiderman, J. S., Bolo, N. R., Simonson, D. C., Jacobson, A. M., Kubicki, M., Shenton, M. E., & Musen, G. (2014). Cerebral white matter integrity and resting-state functional connectivity in middle-aged patients with type 2 diabetes. *Diabetes*, 63(2), 728-738. <https://doi.org/10.2337/db13-1219>
- Hooijmans, C., Rutters, F., Dederen, P., Gambarota, G., Veltien, A., Van Groen, T., . . . Tanila, H. (2007a). Changes in cerebral blood volume and amyloid pathology in aged Alzheimer APP/PS1 mice on a docosahexaenoic acid (DHA) diet or cholesterol enriched Typical Western Diet (TWD). *Neurobiology of Disease*, 28(1), 16-29.
- Hooijmans, C. R., Graven, C., Dederen, P. J., Tanila, H., van Groen, T., & Kiliaan, A. J. (2007b). Amyloid beta deposition is related to decreased glucose transporter-1 levels and hippocampal atrophy in brains of aged APP/PS1 mice. *Brain Research*, 1181, 93-103.
<https://doi.org/10.1016/j.brainres.2007.08.063>
- Hoptman, M. J., Gunning-Dixon, F. M., Murphy, C. F., Ardekani, B. A., Hrabe, J., Lim, K. O., . . . Alexopoulos, G. S. (2009). Blood pressure and white matter integrity in geriatric depression. *Journal of Affective Disorders*, 115(1-2), 171-176.

- Horowitz, M. P., & Greenamyre, J. T. (2010). Mitochondrial iron metabolism and its role in neurodegeneration. *Journal of Alzheimer's Disease*, *20*(s2), S551-S568.
- Horstmann, A. (2017). It wasn't me; It was my brain—Obesity-associated characteristics of brain circuits governing decision-making. *Physiology and Behaviour*, *176*, 125-133. <https://doi.org/10.1016/j.physbeh.2017.04.001>
- Horwood, N., & Davies, D. C. (1994). Immunolabelling of hippocampal microvessel glucose transporter protein is reduced in Alzheimer's disease. *Virchows Archiv*, *425*(1), 69-72. <https://doi.org/10.1007/BF00193951>
- Hoscheidt, S. M., Kellawan, J. M., Berman, S. E., Rivera-Rivera, L. A., Krause, R. A., Oh, J. M., . . . Carlsson, C. M. (2017). Insulin resistance is associated with lower arterial blood flow and reduced cortical perfusion in cognitively asymptomatic middle-aged adults. *Journal of Cerebral Blood Flow & Metabolism*, *37*(6), 2249-2261.
- Hoshino, T., Kamino, K., & Matsumoto, M. (2002). Gene dose effect of the APOE- ϵ 4 allele on plasma HDL cholesterol level in patients with Alzheimer's disease. *Neurobiology of Aging*, *23*(1), 41-45. [https://doi.org/10.1016/S0197-4580\(01\)00252-4](https://doi.org/10.1016/S0197-4580(01)00252-4)
- Hossain, M. S., Oomura, Y., Fujino, T., & Akashi, K. (2020). Glucose signaling in the brain and periphery to memory. *Neuroscience & Biobehavioral Reviews*, *110*, 100-113.
- Hou, Y., Dan, X., Babbar, M., Wei, Y., Hasselbalch, S. G., Croteau, D. L., & Bohr, V. A. (2019). Ageing as a risk factor for neurodegenerative disease. *Nature Reviews Neurology*, *15*(10), 565-581. <https://doi.org/10.1038/s41582-019-0244-7>
- Hsu, C. L., Voss, M. W., Best, J. R., Handy, T. C., Madden, K., Bolandzadeh, N., & Liu-Ambrose, T. (2015). Elevated body mass index and maintenance of cognitive function in late life: exploring underlying neural mechanisms. *Frontiers in Aging Neuroscience*, *7*, 155. <https://doi.org/10.3389/fnagi.2015.00155>
- Hsu, J. L., Chen, Y. L., Leu, J. G., Jaw, F. S., Lee, C. H., Tsai, Y. F., . . . Leemans, A. (2012). Microstructural white matter abnormalities in type 2 diabetes mellitus: A diffusion tensor imaging study. *Neuroimage*, *59*(2), 1098-1105. <https://doi.org/10.1016/j.neuroimage.2011.09.041>
- Hu, R., & Feng, H. (2017). Lenticulostriate artery and lenticulostriate-artery neural complex: New concept for intracerebral hemorrhage. *Current Pharmaceutical Design*, *23*(15), 2206-2211.
- Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D. S., . . . Mori, S. (2008). Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *Neuroimage*, *39*(1), 336-347.
- Huang, H. W., Guo, M. H., Lin, R. J., Chen, Y. L., Luo, Q., Zhang, Y., & Wong, K. S. (2007). Prevalence and risk factors of middle cerebral artery stenosis in asymptomatic residents in Rongqi County, Guangdong. *Cerebrovascular Diseases*, *24*(1), 111-115.
- Huang, R. F., Yang, T. F., & Lan, Y. K. (2010). Pulsatile flows and wall-shear stresses in models simulating normal and stenosed aortic arches. *Experiments in Fluids*, *48*(3), 497-508.
- Huang, W., Qiu, C., Winblad, B., & Fratiglioni, L. (2002). Alcohol consumption and incidence of dementia in a community sample aged 75 years and older. *Journal of Clinical Epidemiology*, *55*(10), 959-964. [https://doi.org/10.1016/S0895-4356\(02\)00462-6](https://doi.org/10.1016/S0895-4356(02)00462-6)
- Huang, Y., & Mahley, R. W. (2014). Apolipoprotein E: Structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. *Neurobiology of Disease*, *72*, 3-12.
- Huber, J. D., VanGilder, R. L. & Houser, K. A. (2006). Streptozotocin-induced diabetes progressively increases blood-brain barrier permeability in specific brain regions in rats. *American Journal of Physiology-Heart and Circulatory Physiology*, *291*(6), H2660-H2668. <https://doi.org/10.1152/ajpheart.00489.2006>
- Hudani, Z. K., & Rojas-Fernandez, C. H. (2016). A scoping review on medication adherence in older patients with cognitive impairment or dementia. *Research in Social and Administrative Pharmacy*, *12*(6), 815-829.

- Hudgins, R. J., Day, A. L., Quisling, R. G., Rhoton Jr, A. L., Sybert, G. W., & Garcia-Bengochea, F. (1983). Aneurysms of the posterior inferior cerebellar artery: A clinical and anatomical analysis. *Journal of Neurosurgery*, *58*(3), 381-387.
- Hughes, T. F., Borenstein, A.R., Schofield, E., Wu, Y. & Larson, E. B. (2009). Association between late-life body mass index and dementia: The Kame Project. *Neurology*, *72*(20), 1741-1746. <https://doi.org/10.1212/WNL.0b013e3181a60a58>
- Hughes, T. M., Lopez, O. L., Evans, R. W., Kamboh, M. I., Williamson, J. D., Klunk, W. E., Mathis, C. A., Price, J. C., Cohen, A. D., Snitz, B. E., DeKosky, S. T., & Kuller, L. H. (2014). Markers of cholesterol transport are associated with amyloid deposition in the brain. *Neurobiology of Aging*, *35*(4), 802-807. <https://doi.org/10.1016/j.neurobiolaging.2013.09.040>
- Huijbers, W., Pennartz, C. M., Cabeza, R., & Daselaar, S. M. (2011). The hippocampus is coupled with the default network during memory retrieval but not during memory encoding. *PLoS One*, *6*(4), e17463. <https://doi.org/10.1371/journal.pone.0017463>
- Huijts, M., Duits, A., Van Oostenbrugge, R. J., Kroon, A. A., De Leeuw, P. W., & Staals, J. (2013). Accumulation of MRI markers of cerebral small vessel disease is associated with decreased cognitive function. A study in first-ever lacunar stroke and hypertensive patients. *Frontiers in Aging Neuroscience*, *5*, 72. <https://doi.org/10.3389/fnagi.2013.00072>
- Huneau, C., Benali, H., & Chabriat, H. (2015). Investigating Human Neurovascular Coupling Using Functional Neuroimaging: A Critical Review of Dynamic Models. *Frontiers in Neuroscience*, *9*, 467. <https://doi.org/10.3389/fnins.2015.00467>
- Hunter, R. L., Dragicevic, N., Seifert, K., Choi, D. Y., Liu, M., Kim, H. C., Cass, W. A., Sullivan, P. G., & Bing, G. (2007). Inflammation induces mitochondrial dysfunction and dopaminergic neurodegeneration in the nigrostriatal system. *Journal of Neurochemistry*, *100*(5), 1375-1386. <https://doi.org/10.1111/j.1471-4159.2006.04327.x>
- Huntley, J. D., & Howard, R. J. (2010). Working memory in early Alzheimer's disease: A neuropsychological review. *International Journal of Geriatric Psychiatry*, *25*(2), 121-132. <https://doi.org/10.1002/gps.2314>
- Hwang, M. H., & Lee, S. (2016). Insulin resistance: Vascular function and exercise. *Integrative Medicine Research*, *5*(3), 198-203. <https://doi.org/10.1016/j.imr.2016.06.001>
- Iaccarino, L., Chiotis, K., Alongi, P., Almkvist, O., Wall, A., Cerami, C., Bettinardi, V., Gianolli, L., Nordberg, A., & Perani, D. (2017). A cross-validation of FDG-and amyloid-PET biomarkers in mild cognitive impairment for the risk prediction to dementia due to Alzheimer's disease in a clinical setting. *Journal of Alzheimer's Disease*, *59*(2), 603-614. <https://doi.org/10.3233/JAD-170158>
- Iadecola, C. (2004). Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nature Reviews Neuroscience*, *5*(5), 347-360. <https://doi.org/10.1038/nrn1387>
- Iadecola, C. (2010). The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. *Acta Neuropathologica*, *120*(3), 287-296.
- Iadecola, C. (2015). Dangerous leaks: Blood-brain barrier woes in the aging hippocampus. *Neuron*, *85*(2), 231-233. <https://doi.org/10.1016/j.neuron.2014.12.056>
- Iglay, K., Hannachi, H., Joseph Howie, P., Xu, J., Li, X., Engel, S. S., . . . Rajpathak, S. (2016). Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. *Current Medical Research and Opinion*, *32*(7), 1243-1252.
- Ikonomovic, M. D., Mufson, E. J., Wu, J., Cochran, E. J., Bennett, D. A., & DeKosky, S. T. J. (2003). Cholinergic plasticity in hippocampus of individuals with mild cognitive impairment: correlation with Alzheimer's neuropathology. *Journal of Alzheimer's Disease*, *5*(1), 39-48. <https://doi.org/10.3233/JAD-2003-5106>
- Insel, K., Morrow, D., Brewer, B., & Figueredo, A. (2006). Executive function, working memory, and medication adherence among older adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *61*(2), P102-P107.

- Insel, K. C., Reminger, S. L., & Hsiao, C. P. (2008). White matter hyperintensities and medication adherence. *Biological Research for Nursing, 10*(2), 121-127.
- Isaac, V., Sim, S., Zheng, H., Zagorodnov, V., Tai, E. S., & Chee, M. (2011). Adverse Associations between Visceral Adiposity, Brain Structure, and Cognitive Performance in Healthy Elderly. *Frontiers in Aging Neuroscience, 3*, 12. <https://doi.org/10.3389/fnagi.2011.00012>
- Ishii, M., Wang, G., Racchumi, G., Dyke, J. P., & Iadecola, C. (2014). Transgenic mice overexpressing amyloid precursor protein exhibit early metabolic deficits and a pathologically low leptin state associated with hypothalamic dysfunction in arcuate neuropeptide Y neurons. *Journal of Neuroscience, 34*(27), 9096-9106. <https://doi.org/10.1523/JNEUROSCI.0872-14.2014>
- Ismail, Z., Smith, E. E., Geda, Y., Sultzer, D., Brodaty, H., Smith, G., . . . Lyketsos, C. G. (2016). Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. *Alzheimer's & Dementia, 12*(2), 195-202.
- Ito, S., Nagasawa, T., Abe, M., & Mori, T. (2009). Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. *Hypertension Research, 32*(2), 115-121.
- Ito, S., Yanai, M., Yamaguchi, S., Couraud, P. O., & Ohtsuki, S. (2017). Regulation of tight-junction integrity by insulin in an in vitro model of human blood-brain barrier. *Journal of Pharmaceutical Sciences, 106*(9), 2599-2605. <https://doi.org/10.1016/j.xphs.2017.04.036>
- Iwatsubo, T., Odaka, A., Suzuki, N., Mizusawa, H., Nukina, N., & Ihara, Y. (1994). Visualization of A beta 42(43) and A beta 40 in senile plaques with end-specific A beta monoclonals: Evidence that an initially deposited species is A beta 42(43). *Neuron, 13*(1), 45-53.
- Iyo, M., Namba, H., Fukushi, K., Shinotoh, H., Nagatsuka, S., Suhara, T., Sudo, Y., Suzuki, K., & Irie, T. (1997). Measurement of acetylcholinesterase by positron emission tomography in the brains of healthy controls and patients with Alzheimer's disease. *The Lancet, 349*(9068), 1805-1809. [https://doi.org/10.1016/S0140-6736\(96\)09124-6](https://doi.org/10.1016/S0140-6736(96)09124-6)
- Izawa, Y., Urakami, K., Kojima, T., & Ohama, E. (2009). Wechsler Adult Intelligence Scale, (WAIS-III): Usefulness in the early detection of Alzheimer's disease. *Yonago Acta Medica, 52*, 11-20.
- Jack, C. (2016a). Genetics of Alzheimer's Disease. In *Alzheimer's Turning Point* (pp. 75-83): Springer.
- Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Feldman, H. H., Frisoni, G. B., . . . Knopman, D. S. (2016b). A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology, 87*(5), 539-547.
- Jack, C. R., Petersen, R. C., Xu, Y., O'Brien, P. C., Smith, G. E., Ivnik, R. J., . . . Kokmen, E. (1998). Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology, 51*(4), 993-999.
- Jack Jr, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., . . . Karlawish, J. (2018a). NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's and Dementia, 14*(4), 535-562.
- Jack Jr, C. R., Wiste, H. J., Schwarz, C. G., Lowe, V. J., Senjem, M. L., Vemuri, P., . . . Gunter, J. L. (2018b). Longitudinal tau PET in ageing and Alzheimer's disease. *Brain, 141*(5), 1517-1528.
- Jacobs, H. I., Hedden, T., Schultz, A. P., Sepulcre, J., Perea, R. D., Amariglio, R. E., . . . Johnson, K. A. (2018a). Structural tract alterations predict downstream tau accumulation in amyloid-positive older individuals. *Nature Neuroscience, 21*(3), 424-431.
- Jacobs, H. I., Radua, J., Luckmann, H. C., & Sack, A. T. (2013). Meta-analysis of functional network alterations in Alzheimer's disease: Toward a network biomarker. *Neuroscience & Biobehavioral Reviews, 37*(5), 753-765. <https://doi.org/10.1016/j.neubiorev.2013.03.009>
- Jacobs, D. M., Sano, M., Dooneief, G., Marder, K., Bell, K. L., & Stern, Y. (1995). Neuropsychological detection and characterization of preclinical Alzheimer's disease. *Neurology, 45*(5), 957-962. <https://doi.org/10.1212/WNL.45.5.957>

- Jacobs, H. I. L., Hopkins, D. A., Mayrhofer, H. C., Bruner, E., van Leeuwen, F. W., Raaijmakers, W., & Schmahmann, J. D. (2018b). The cerebellum in Alzheimer's disease: Evaluating its role in cognitive decline. *Brain*, *141*(1), 37-47. <https://doi.org/10.1093/brain/awx194>
- Jacobsen, J. S., Wu, C.-C., Redwine, J. M., Comery, T. A., Arias, R., Bowlby, M., Martone, R., Morrison, J. H., Pangalos, M. N., Reinhart, P.H., & Bloom, F. E. (2006). Early-onset behavioral and synaptic deficits in a mouse model of Alzheimer's disease. *Proceedings of the National Academy of Sciences*, *103*(13), 5161-5166. <https://doi.org/10.1073/pnas.0600948103>
- Jacobsen, R., Martinussen, T., Christiansen, L., Jeune, B., Andersen-Ranberg, K., Vaupel, J. W., & Christensen, K. (2010). Increased effect of the ApoE gene on survival at advanced age in healthy and long-lived Danes: Two nationwide cohort studies. *Aging Cell*, *9*(6), 1004-1009. <https://doi.org/10.1111/j.1474-9726.2010.00626.x>
- Jagger, C., Matthews, R., Lindesay, J., Robinson, T., Croft, P., & Brayne, C. (2009). The effect of dementia trends and treatments on longevity and disability: a simulation model based on the MRC Cognitive Function and Ageing Study (MRC CFAS). *Age and Ageing*, *38*(3), 319-325. <https://doi.org/10.1093/ageing/afp016>
- Jagust, W. (2013). Vulnerable neural systems and the borderland of brain aging and neurodegeneration. *Neuron*, *77*(2), 219-234. <https://doi.org/10.1016/j.neuron.2013.01.002>
- Jagust, W., Harvey, D., Mungas, D., & Haan, M. (2005). Central obesity and the aging brain. *Archives of Neurology*, *62*(10), 1545-1548. <https://doi.org/10.1001/archneur.62.10.1545>
- Jagust, W. J., Seab, J. P., Huesman, R. H., Valk, P. E., Mathis, C. A., Reed, B. R., . . . Budinger, T. F. (1991). Diminished glucose transport in Alzheimer's disease: Dynamic PET studies. *Journal of Cerebral Blood Flow and Metabolism*, *11*(2), 323-330. <https://doi.org/10.1038/jcbfm.1991.65>
- Jakanani, G., & Adair, W. (2010). Frequency of variations in aortic arch anatomy depicted on multidetector CT. *Clinical radiology*, *65*(6), 481-487.
- James, D., Kang, S., & Park, S. (2014). Injection of β -amyloid into the hippocampus induces metabolic disturbances and involuntary weight loss which may be early indicators of Alzheimer's disease. *Aging Clinical and Experimental Research*, *26*(1), 93-98. <https://doi.org/10.1007/s40520-013-0181-z>.
- Janelidze, S., Hertze, J., Nägga, K., Nilsson, K., Nilsson, C., Wennström, M., . . . Hansson, O. (2017). Increased blood-brain barrier permeability is associated with dementia and diabetes but not amyloid pathology or APOE genotype. *Neurobiology of Aging*, *51*, 104-112.
- Jang, H., Kwon, H., Yang, J.-J., Hong, J., Kim, Y., Kim, K. W., . . . Lee, K. H. (2017). Correlations between gray matter and white matter degeneration in pure Alzheimer's disease, pure subcortical vascular dementia, and mixed dementia. *Scientific reports*, *7*(1), 1-9.
- Janghorbani, M., Hedley, A. J., Jones, R. B., Zhanpour, M., & Gilmour, W. H. (1993). Gender differential in all-cause and cardiovascular disease mortality. *International Journal of Epidemiology*, *22*(6), 1056-1063. <https://doi.org/10.1093/ije/22.6.1056>
- Jankowska-Polańska, B., Uchmanowicz, I., Dudek, K., & Mazur, G. (2016). Relationship between patients' knowledge and medication adherence among patients with hypertension. *Patient Preference and Adherence*, *10*, 2437.
- Jansen, J. F., van Bussel, F. C., van de Haar, H. J., van Osch, M. J., Hofman, P. A., van Boxtel, M. P., . . . Backes, W. H. (2016). Cerebral blood flow, blood supply, and cognition in Type 2 Diabetes Mellitus. *Scientific Reports*, *6*(1), 10. <https://doi.org/10.1038/s41598-016-0003-6>
- Janson, J., Laedtke, T., Parisi, J. E., O'Brien, P., Petersen, R. C., & Butler, P. C. (2004). Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes*, *53*(2), 474-481.
- Janssen, I., Heymsfield, S. B., & Ross, R. (2002). Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *Journal of the*

American Geriatrics Society, 50(5), 889-896. <https://doi.org/10.1046/j.1532-5415.2002.50216.x>

- Jarrett, J. T., Berger, E. P., & Lansbury, P. T., Jr. (1993). The carboxy terminus of the beta amyloid protein is critical for the seeding of amyloid formation: Implications for the pathogenesis of Alzheimer's disease. *Biochemistry*, 32(18), 4693-4697.
- Jayaraman, A., Lent-Schochet, D., & Pike, C. J. (2014a). Diet-induced obesity and low testosterone increase neuroinflammation and impair neural function. *Journal of Neuroinflammation*, 11(1), 162. <https://doi.org/10.1186/s12974-014-0162-y>
- Jayaraman, A., & Pike, C. J. (2014b). Alzheimer's disease and type 2 diabetes: multiple mechanisms contribute to interactions., *Current Diabetes Reports*, 14(4), 476.
- Jelinek, H. F., Osman, W. M., Khandoker, A. H., Khalaf, K., Lee, S., Almahmeed, W., & Alsafar, H. S. (2017). Clinical profiles, comorbidities and complications of type 2 diabetes mellitus in patients from United Arab Emirates. *BMJ Open Diabetes Research and Care*, 5(1). <http://dx.doi.org/10.1136/bmjdr-2017-000427>
- Jellinger, K. A. (2001). Small concomitant cerebrovascular lesions are not important for cognitive decline in severe Alzheimer disease. *Archives of Neurology*, 58(3), 520-521.
- Jeng, J. S., & Yip, P. K. (2004). Evaluation of vertebral artery hypoplasia and asymmetry by color-coded duplex ultrasonography. *Ultrasound in Medicine and Biology*, 30(5), 605-609.
- Jennings, J., Mendelson, D., Muldoon, M., Ryan, C. M., Gianaros, P., Raz, N., & Aizenstein, H. (2012). Regional grey matter shrinks in hypertensive individuals despite successful lowering of blood pressure. *Journal of Human Hypertension*, 26(5), 295-305.
- Jennings, J., Muldoon, M., Ryan, C., Price, J., Greer, P., Sutton-Tyrrell, K., . . . Meltzer, C. (2005). Reduced cerebral blood flow response and compensation among patients with untreated hypertension. *Neurology*, 64(8), 1358-1365.
- Jeon, S. Y., Byun, M. S., Yi, D., Lee, J. H., Choe, Y. M., Ko, K., Sohn, B. K., Choi, H. J., Lee, J. Y., Lee, D. Y., & KBASE Research Group. (2019). Influence of hypertension on brain amyloid deposition and Alzheimer's disease signature neurodegeneration. *Neurobiology of Aging*, 75, 62-70. <https://doi.org/10.1016/j.neurobiolaging.2018.11.001>
- Jian, M., Kwan, J. S. C., Bunting, M., Ng, R. C. L., & Chan, K. H. (2019). Adiponectin suppresses amyloid- β oligomer (A β O)-induced inflammatory response of microglia via AdipoR1-AMPK-NF- κ B signaling pathway. *Journal of Neuroinflammation*, 16(1), 1-19. <https://doi.org/10.1186/s12974-019-1492-6>
- Jimenez, A., Pegueroles, J., Carmona-Iragui, M., Vilaplana, E., Montal, V., Alcolea, D., . . . Casajoana, A. (2017). Weight loss in the healthy elderly might be a non-cognitive sign of preclinical Alzheimer's disease. *Oncotarget*, 8(62), 104706.
- Jiménez-Balado, J., Riba-Llena, I., Garde, E., Valor, M., Gutiérrez, B., Pujadas, F., & Delgado, P. (2018). Prevalence of hippocampal enlarged perivascular spaces in a sample of patients with hypertension and their relation with vascular risk factors and cognitive function. *Journal of Neurology, Neurosurgery & Psychiatry*, 89(6), 651-656.
- Jin, H., Kim, Y., & Rhie, S. J. (2016a). Factors affecting medication adherence in elderly people. *Patient Preference and Adherence*, 10, 2117.
- Jin, Y. (2016b). *Cross-Sectional Association of Blood Pressure, Antihypertensive Medications, MRI Volumetric Measures and Cognitive Function Scores in an Aging Population* (Publication No. 10801190) [Doctoral dissertation, University of Southern California]. ProQuest Dissertations Publishing.
- Johansson, M. E., Wickman, A., Skøtt, O., Gan, L.-m., & Bergström, G. (2006). Blood pressure is the major driving force for plaque formation in aortic-constricted ApoE $^{-/-}$ mice. *Journal of Hypertension*, 24(10), 2001-2008. <https://doi.org/10.1097/01.hjh.0000244949.65040.de>

- Johnson, J. K., Head, E., Kim, R., Starr, A., & Cotman, C. W. (1999). Clinical and pathological evidence for a frontal variant of Alzheimer disease. *Archives of Neurology*, *56*(10), 1233-1239. <https://doi.org/10.1001/archneur.56.10.1233>
- Johnson, N. A., Jahng, G. H., Weiner, M. W., Miller, B. L., Chui, H. C., Jagust, W. J., . . . Schuff, N. (2005). Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. *Radiology*, *234*(3), 851-859. <https://doi.org/10.1148/radiol.2343040197>
- Johnson, D. K., Wilkins, C. H., & Morris, J. C. (2006). Accelerated weight loss may precede diagnosis in Alzheimer disease. *Archives of neurology*, *63*(9), 1312-1317. doi: <https://doi.org/10.1001/archneur.63.9.1312>
- Jones, D.T., Machulda, M.M., Vemuri, P., McDade, E.M., Zeng, G., Senjem, M.L., Gunter, J.L., Przybelski, S.A., Avula, R.T., Knopman, D.S. & Boeve, B.F. (2011). Age-related changes in the default mode network are more advanced in Alzheimer disease. *Neurology*, *77*(16), 1524-1531. <https://doi.org/10.1212/WNL.0b013e318233b33d>
- Jones, N. R., McCormack, T., Constanti, M., & McManus, R. J. (2020). Diagnosis and management of hypertension in adults: NICE guideline update 2019. *British Journal of General Practice*, *70*(691), 90-91.
- Jongen, C., Van Der Grond, J., Kappelle, L., Biessels, G., Viergever, M., Pluim, J., & Utrecht Diabetic Encephalopathy Study Group. (2007). Automated measurement of brain and white matter lesion volume in type 2 diabetes mellitus. *Diabetologia*, *50*(7), 1509-1516. <https://doi.org/10.1007/s00125-007-0688-y>
- Jonkman, L. E., Kenkhuis, B., Geurts, J. J. G., & van de Berg, W. D. J. (2019). Post-Mortem MRI and Histopathology in Neurologic Disease: A Translational Approach. *Neuroscience Bulletin*, *35*(2), 229-243. <https://doi.org/10.1007/s12264-019-00342-3>
- Josephs, K. A., Dickson, D. W., Murray, M. E., Senjem, M. L., Parisi, J. E., Petersen, R. C., Jack Jr., C. R., & Whitwell, J. L. (2013). Quantitative neurofibrillary tangle density and brain volumetric MRI analyses in Alzheimer's disease presenting as logopenic progressive aphasia. *Brain and Language*, *127*(2), 127-134. <https://doi.org/10.1016/j.bandl.2013.02.003>
- Joubert, S., Gour, N., Guedj, E., Didic, M., Gueriot, C., Koric, L., . . . Ceccaldi, M. (2016). Early-onset and late-onset Alzheimer's disease are associated with distinct patterns of memory impairment. *Cortex*, *74*, 217-232. <https://doi.org/10.1016/j.cortex.2015.10.014>
- Jousilahti, P., Vartiainen, E., Tuomilehto, J., & Puska, P. (1999). Sex, age, cardiovascular risk factors, and coronary heart disease: A prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation*, *99*(9), 1165-1172. <https://doi.org/10.1161/01.CIR.99.9.1165>
- Jung, J., Cloutman, L. L., Binney, R. J., & Lambon Ralph, M. A. (2017). The structural connectivity of higher order association cortices reflects human functional brain networks. *Cortex*, *97*, 221-239. <https://doi.org/10.1016/j.cortex.2016.08.011>
- Jung, H. J., Park, S. S., Mok, J. O., Lee, T. K., Park, C. S., & Park, S. A. (2011). Increased expression of three-repeat isoforms of tau contributes to tau pathology in a rat model of chronic type 2 diabetes. *Experimental neurology*, *228*(2), 232-241. <https://doi.org/10.1016/j.expneurol.2011.01.012>
- Jung, Y., Whitwell, J. L., Duffy, J. R., Strand, E. A., Machulda, M. M., Senjem, M. L., Jack, C. R., Lowe, V. J., & Josephs, K. A. (2016). Regional β -amyloid burden does not correlate with cognitive or language deficits in Alzheimer's disease presenting as aphasia. *European Journal of Neurology*, *23*(2), 313-319. <https://doi.org/10.1111/ene.12761>
- Jurado, M. B., & Rosselli, M. (2007). The elusive nature of executive functions: A review of our current understanding. *Neuropsychology review*, *17*(3), 213-233.
- Jurk, D., Wilson, C., Passos, J. F., Oakley, F., Correia-Melo, C., Greaves, L., Saretzki, G., Fox, C., Lawless, C., Anderson, R., Hewitt, G., Pender, S. L. F., Fullard, N., Nelson, G., Mann, J. van

- de Sluis, B., Mann D. A., & von Zglinicki, T. (2014). Chronic inflammation induces telomere dysfunction and accelerates ageing in mice. *Nature Communications*, 5, 4172. <https://doi.org/10.1038/ncomms5172>
- Kablak-Ziembicka, A., Przewlocki, T., Pieniazek, P., Musialek, P., Motyl, R., Moczulski, Z., & Tracz, W. (2006). Assessment of flow changes in the circle of Willis after stenting for severe internal carotid artery stenosis. *Journal of Endovascular Therapy*, 13(2), 205-213. <https://doi.org/10.1583/05-1700R.1>
- Kadir, S. (1991). *Atlas of normal and variant angiographic anatomy*: WB Saunders Company.
- Kahn, S. E., Cooper, M. E., & Del Prato, S. (2014). Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet*, 383(9922), 1068-1083. [https://doi.org/10.1016/S0140-6736\(13\)62154-6](https://doi.org/10.1016/S0140-6736(13)62154-6)
- Kahn, S. E., Hull, R. L., & Utzschneider, K. M. (2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*, 444(7121), 840-846.
- Kalaria, R. N. (2016). Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer's disease. *Acta Neuropathologica*, 131(5), 659-685.
- Kalaria, R. N., & Harik, S. I. (1989). Reduced glucose transporter at the blood-brain barrier and in cerebral cortex in Alzheimer disease. *Journal of Neurochemistry*, 53(4), 1083-1088. <https://doi.org/10.1111/j.1471-4159.1989.tb07399.x>
- Kalpouzos, G., Chetelat, G., Baron, J. C., Landeau, B., Mevel, K., Godeau, C., Barré, L., Constans, J. M., Viader, F., Eustache, F., & Desgranges, B. (2009). Voxel-based mapping of brain gray matter volume and glucose metabolism profiles in normal aging. *Neurobiology of Aging*, 30(1), 112-124. <https://doi.org/10.1016/j.neurobiolaging.2007.05.019>
- Kamiyama, K., Wada, A., Sugihara, M., Kurioka, S., Hayashi, K., Hayashi, T., Yoshisako, T., Yamamoto, N., Tsuchie, Y., Yamaguchi, S., Sugimoto, T., & Kitagaki, H. (2010). Potential hippocampal region atrophy in diabetes mellitus type 2: A voxel-based morphometry VSRAD study. *Japanese Journal of Radiology*, 28(4), 266-272. <https://doi.org/10.1007/s11604-009-0416-2>
- Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston naming test (2nd edition)*. Lea & Febiger, Philadelphia.
- Karas, G., Burton, E., Rombouts, S., Van Schijndel, R., O'Brien, J., Scheltens, P., McKeith, I. G., Williams, D., Ballard, C., & Barkhof, F. (2003). A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. *Neuroimage*, 18(4), 895-907. [https://doi.org/10.1016/S1053-8119\(03\)00041-7](https://doi.org/10.1016/S1053-8119(03)00041-7)
- Karhunen, L. J., Vanninen, E. J., Kuikka, J. T., Lappalainen, R. I., Tiihonen, J., & Uusitupa, M. I. J. (2000). Regional cerebral blood flow during exposure to food in obese binge eating women. *Psychiatric Research: Neuroimaging*, 99(1), 29-42. [https://doi.org/10.1016/S0925-4927\(00\)00053-6](https://doi.org/10.1016/S0925-4927(00)00053-6)
- Kario, K., Pickering, T. G., Hoshide, S., Eguchi, K., Ishikawa, J., Morinari, M., Hoshide, Y., & Shimada, K. (2004). Morning blood pressure surge and hypertensive cerebrovascular disease: Role of the alpha adrenergic sympathetic nervous system. *American Journal of Hypertension*, 17(8), 668-675. <https://doi.org/10.1016/j.amjhyper.2004.04.001>
- Kasuya, H., Shimizu, T., Nakaya, K., Sasahara, A., Hori, T., & Takakura, K. (1999). Angles between A1 and A2 segments of the anterior cerebral artery visualized by three-dimensional computed tomographic angiography and association of anterior communicating artery aneurysms. *Neurosurgery*, 45(1), 89-94. <https://doi.org/10.1097/00006123-199907000-00021>
- Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., Renbing X., & Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology*, 23(2), 138-144. <https://doi.org/10.1002/ana.410230206>

- Katzmarzyk, P. T., Barreira, T. V., Broyles, S. T., Chaput, J.-P., Fogelholm, M., Hu, G., . . . Maher, C. (2015). Association between body mass index and body fat in 9–11-year-old children from countries spanning a range of human development. *International Journal of Obesity Supplements*, 5(2), S43-S46.
- Kaur, J. (2014). A comprehensive review on metabolic syndrome. *Cardiology Research and Practice*, 2014, 943162. <https://doi.org/10.1155/2014/943162>
- Kawamori, R., Yamasaki, Y., Matsushima, H., Nishizawa, H., Nao, K., Hougaku, H., Maeda, H., Handa, N., Matsumoto, M., & Kamada, T. (1992). Prevalence of Carotid Atherosclerosis in Diabetic Patients Ultrasound high-resolution B-mode imaging on carotid arteries. *Diabetes Care*, 15(10), 1290-1294. <https://doi.org/10.2337/diacare.15.10.1290>
- Kaya, M., Kalayci, R., Küçük, M., Arican, N., Elmas, I., Kudat, H., & Korkut, F. (2003). Effect of losartan on the blood–brain barrier permeability in diabetic hypertensive rats. *Life Sciences*, 73(25), 3235-3244.
- Keage, H. A., Carare, R. O., Friedland, R. P., Ince, P. G., Love, S., Nicoll, J. A., Wharton, S. B., Weller, R. O., & Brayne, C. (2009). Population studies of sporadic cerebral amyloid angiopathy and dementia: A systematic review. *BMC Neurology*, 9, 3. <https://doi.org/10.1186/1471-2377-9-3>
- Kearney, J. (2010). Food consumption trends and drivers. *Philosophical transactions of the royal society B: Biological sciences*, 365(1554), 2793-2807.
- Kelleher, R. J., & Soiza, R. L. (2013). Evidence of endothelial dysfunction in the development of Alzheimer's disease: Is Alzheimer's a vascular disorder? *American Journal of Cardiovascular Disease*, 3(4), 197-226.
- Keller, L., Xu, W., Wang, H.-X., Winblad, B., Fratiglioni, L., & Graff, C. (2011). The obesity related gene, FTO, interacts with APOE, and is associated with Alzheimer's disease risk: A prospective cohort study. *Journal of Alzheimer's Disease*, 23(3), 461-469. <https://doi.org/10.3233/JAD-2010-101068>
- Kelly, A. M., & Garavan, H. (2005). Human functional neuroimaging of brain changes associated with practice. *Cerebral Cortex*, 15(8), 1089-1102. <https://doi.org/10.1093/cercor/bhi005>
- Kestilä, P., Magnussen, C. G., Viikari, J. S., Kähönen, M., Hutri-Kähönen, N., Taittonen, L., Jula, A., Loo, B. M., Pietikäinen, M., Jokinen, E., Lehtimäki, T., Kivimäki, M., Juonala, M., & Raitakari, O. T. (2012). Socioeconomic status, cardiovascular risk factors, and subclinical atherosclerosis in young adults: The cardiovascular risk in Young Finns Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 32(3), 815-821. <https://doi.org/10.1161/ATVBAHA.111.241182>
- Khan, U. A., Liu, L., Provenzano, F. A., Berman, D. E., Profaci, C. P., Sloan, R., Mayeux, R., Duff, K. E., & Small, S. A. (2014). Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. *Nature Neuroscience*, 17(2), 304. <https://doi.org/10.1038/nn.3606>
- Khanna, A., Guo, M., Mehra, M., & Royal III, W. (2013). Inflammation and oxidative stress induced by cigarette smoke in Lewis rat brains. *Journal of Neuroimmunology*, 254(1-2), 69-75. <https://doi.org/10.1016/j.jneuroim.2012.09.006>
- Khemka, V. K., Bagchi, D., Bandyopadhyay, K., Bir, A., Chattopadhyay, M., Biswas, A., Basu, D., & Chakrabarti, S. (2014). Altered serum levels of adipokines and insulin in probable Alzheimer's disease. *Journal of Alzheimer's Disease*, 41(2), 525-533. <https://doi.org/10.3233/JAD-140006>
- Kianoush, S., Yakoob, M. Y., Al-Rifai, M., DeFilippis, A. P., Bittencourt, M. S., Duncan, B. B., Bensenor, I. M., Bhatnagar, A., Lotufo, P. A., & Blaha, M. J. (2017). Associations of cigarette smoking with subclinical inflammation and atherosclerosis: ELSA-Brasil (The Brazilian Longitudinal Study of Adult Health). *Journal of the American Heart Association*, 6(6), e005088. <https://doi.org/10.1161/JAHA.116.005088>

- Kikuya, M., Ohkubo, T., Metoki, H., Asayama, K., Hara, A., Obara, T., Inoue, R., Hoshi, H., Hashimoto, J., Totsune, K., Sato, H., & Imai, Y. (2008). Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: The Ohasama study. *Hypertension*, *52*(6), 1045-1050. <https://doi.org/10.1161/HYPERTENSIONAHA.107.104620>
- Killiany, R. J., Hyman, B. T., Gomez-Isla, T., Moss, M. B., Kikinis, R., Jolesz, F., Jones, T. K., & Albert, M. S. (2002). MRI measures of entorhinal cortex vs hippocampus in preclinical AD. *Neurology*, *58*(8), 1188-1196. <https://doi.org/10.1212/WNL.58.8.1188>
- Kim, C., Sohn, J. H., & Choi, H. C. (2012). Vertebrobasilar angulation and its association with sudden sensorineural hearing loss. *Medical Hypotheses*, *79*(2), 202-203.
- Kim, D. J., Yu, J. H., Shin, M. S., Shin, Y. W., & Kim, M. S. (2016). Hyperglycemia Reduces Efficiency of Brain Networks in Subjects with Type 2 Diabetes. *PLoS One*, *11*(6), e0157268. <https://doi.org/10.1371/journal.pone.0157268>
- Kim, G. W., Gasche, Y., Grzeschik, S., Copin, J.-C., Maier, C. M., & Chan, P. H. (2003). Neurodegeneration in striatum induced by the mitochondrial toxin 3-nitropropionic acid: role of matrix metalloproteinase-9 in early blood-brain barrier disruption? *Journal of Neuroscience*, *23*(25), 8733-8742.
- Kim, H. J., Song, J. M., Kwon, S. U., Kim, B. J., Kang, D. H., Song, J. K., Kim, J. S., & Kang, D. W. (2011). Right-left propensity and lesion patterns between cardiogenic and aortogenic cerebral embolisms. *Stroke*, *42*(8), 2323-2325. <https://doi.org/10.1161/STROKEAHA.111.616573>
- Kim, K., Seo, H., Kwak, M. S., & Kim, D. (2017). Visceral obesity is associated with white matter hyperintensity and lacunar infarct. *International Journal of Obesity*, *41*(5), 683-688. <https://doi.org/10.1038/ijo.2017.13>
- Kim, S. M., Kim, M. J., Rhee, H. Y., Ryu, C. W., Kim, E. J., Petersen, E. T., & Jahng, G. H. (2013). Regional cerebral perfusion in patients with Alzheimer's disease and mild cognitive impairment: Effect of APOE epsilon4 allele. *Neuroradiology*, *55*(1), 25-34. <https://doi.org/10.1007/s00234-012-1077-x>
- Kinnunen, K. M., Cash, D. M., Poole, T., Frost, C., Benzinger, T. L. S., Ahsan, R. L., Leung, K. K., Cardoso, M. J., Modat, M., Malone, I. B., Morris, J. C., Bateman, R. J., Marcus, D. S., Goate, A., Salloway, S. P., Correia, S., Sperling, R. A., Chhatwal, K. P., Mayeux, R. P. ... Dominantly Inherited Alzheimer Network (DIAN)(2018). Presymptomatic atrophy in autosomal dominant Alzheimer's disease: A serial magnetic resonance imaging study. *Alzheimer's & Dementia*, *14*(1), 43-53. <https://doi.org/10.1016/j.jalz.2017.06.2268>
- Kirova, A. M., Bays, R. B., & Lagalwar, S. (2015). Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *Biomed Research International*, *2015*, 748212. <https://doi.org/10.1155/2015/748212>
- Kiuchi, K., Nejima, J., Takano, T., Ohta, M., & Hashimoto, H. (2001). Increased serum concentrations of advanced glycation end products: A marker of coronary artery disease activity in type 2 diabetic patients. *Heart*, *85*(1), 87-91.
- Kivimäki, M., Luukkonen, R., Batty, G.D., Ferrie, J.E., Pentti, J., Nyberg, S.T., Shipley, M.J., Alfredsson, L., Fransson, E.I., Goldberg, M. & Knutsson, A. (2018). Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimer's & Dementia*, *14*(5), 601-609. <https://doi.org/10.1016/j.jalz.2017.09.016>
- Kivipelto, M., Helkala, E.-L., Laakso, M. P., Hänninen, T., Hallikainen, M., Alhainen, K., Soininen, H., Tuomilehto, J., & Nissinen, A. (2001). Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ*, *322*(7300), 1447-1451. <https://doi.org/10.1136/bmj.322.7300.1447>
- Kivipelto, M., Mangialasche, F., & Ngandaisu, T. (2018). Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nature Reviews Neurology*, *14*(11), 653-666. <https://doi.org/10.1038/s41582-018-0070-3>

- Kivipelto, M., Ngandu, T., Fratiglioni, L., Viitanen, M., Kåreholt, I., Winblad, B., Helkala, E. L., Tuomilehto, J., Soininen, H., & Nissinen, A. (2005). Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Archives of Neurology*, *62*(10), 1556-1560. <https://doi.org/10.1001/archneur.62.10.1556>
- Kivipelto, M., Rovio, S., Ngandu, T., Kåreholt, I., Eskelinen, M., Winblad, B., Hachinski, V., Cedazo-Minguez, A., Soininen, H., Tuomilehto, J., & Nissinen, A. (2008). Apolipoprotein E ϵ 4 magnifies lifestyle risks for dementia: A population-based study. *Journal of Cellular and Molecular Medicine*, *12*(6b), 2762-2771. <https://doi.org/10.1111/j.1582-4934.2008.00296.x>
- Kivipelto, M., Solomon, A., Ahtiluoto, S., Ngandu, T., Lehtisalo, J., Antikainen, R., . . . Laatikainen, T. (2013). The Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER): Study design and progress. *Alzheimer's & Dementia*, *9*(6), 657-665.
- Kleine, J. F., Beller, E., Zimmer, C., & Kaesmacher, J. (2017). Lenticulostriate infarctions after successful mechanical thrombectomy in middle cerebral artery occlusion. *Journal of Neurointerventional Surgery*, *9*(3), 234-239.
- Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., . . . Langstrom, B. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of Neurology*, *55*(3), 306-319. <https://doi.org/10.1002/ana.20009>
- Klunk, W. E., Price, J. C., Mathis, C. A., Tsopelas, N. D., Lopresti, B. J., Ziolkowski, S. K., . . . Ikonomic, M. D. (2007). Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees. *Journal of Neuroscience*, *27*(23), 6174-6184.
- Klupp, E., Grimmer, T., Tahmasian, M., Sorg, C., Yakushev, I., Yousefi, B. H., Drzezga, A., & Förster, S. (2015). Prefrontal hypometabolism in Alzheimer disease is related to longitudinal amyloid accumulation in remote brain regions. *Journal of Nuclear Medicine*, *56*(3), 399-404. <https://doi.org/10.2967/jnumed.114.149302>
- Knafo, S., Alonso-Nanclares, L., Gonzalez-Soriano, J., Merino-Serrais, P., Feraud-Espinosa, I., Ferrer, I., & DeFelipe, J. (2009). Widespread changes in dendritic spines in a model of Alzheimer's disease. *Cerebral Cortex*, *19*(3), 586-592. <https://doi.org/10.1093/cercor/bhn111>
- Knopman, D. S., Haeblerlein, S. B., Carrillo, M. C., Hendrix, J. A., Kerchner, G., Margolin, R., . . . & Siemers, E. (2018). The National Institute on Aging and the Alzheimer's Association research framework for Alzheimer's disease: perspectives from the research roundtable. *Alzheimer's & Dementia*, *14*(4), 563-575. <https://doi.org/10.1016/j.jalz.2018.03.002>
- Knopman, D. S., Petersen, R. C., & Jack, C. R. (2019). A brief history of “Alzheimer disease”: Multiple meanings separated by a common name. *Neurology*, *92*(22), 1053-1059. <https://doi.org/10.1212/WNL.00000000000007583>
- Knouff, C., Briand, O., Lestavel, S., Clavey, V., Altenburg, M., & Maeda, N. (2004). Defective VLDL metabolism and severe atherosclerosis in mice expressing human apolipoprotein E isoforms but lacking the LDL receptor. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, *1684*(1-3), 8-17. <https://doi.org/10.1016/j.bbalip.2004.03.004>
- Ko, K. R., Ngai, A., & Winn, H. R. (1990). Role of adenosine in regulation of regional cerebral blood flow in sensory cortex. *American Journal of Physiology-Heart and Circulatory Physiology*, *259*(6), H1703-H1708. <https://doi.org/10.1152/ajpheart.1990.259.6.H1703>
- Kobayashi, S., Okada, K., Koide, H., Bokura, H., & Yamaguchi, S. (1997). Subcortical silent brain infarction as a risk factor for clinical stroke. *Stroke*, *28*(10), 1932-1939.
- Koch, C., Augustine, R. A., Steger, J., Ganjam, G. K., Benzler, J., Pracht, C., Lowe, C., Schwartz, M. W., Shepherd, P. R., Anderson, G. M., Grattan, D. R., & Tups, A. (2010). Leptin rapidly improves glucose homeostasis in obese mice by increasing hypothalamic insulin sensitivity. *Diabetes*, *59*(12), 16180-16187. <https://doi.org/10.1523/JNEUROSCI.3202-10.2010>
- Koch, W., Teipel, S., Mueller, S., Benninghoff, J., Wagner, M., Bokde, A. L., Hampel, H., Coates, U., Resier, M., & Meindl, T. (2012). Diagnostic power of default mode network resting state

- fMRI in the detection of Alzheimer's disease. *Neurobiology of Aging*, 33(3), 466-478.
<https://doi.org/10.1016/j.neurobiolaging.2010.04.013>
- Koepsell, T. D., Kurland, B. F., Harel, O., Johnson, E. A., Zhou, X. H., & Kukull, W. A. (2008). Education, cognitive function, and severity of neuropathology in Alzheimer disease. *Neurology*, 70(19 Part 2), 1732-1739. <https://doi.org/10.1212/01.wnl.0000284603.85621.aa>
- Köhler, S., Black, S., Sinden, M., Szekely, C., Kidron, D., Parker, J., L., Foster, J. K., Moscovitch, M., Wincour, G., Szalai, J., & Bronskill, M. J. (1998). Memory impairments associated with hippocampal versus parahippocampal-gyrus atrophy: An MR volumetry study in Alzheimer's disease. *Neuropsychologia*, 36(9), 901-914.
- Kojima, S., Funahashi, T., Sakamoto, T., Miyamoto, S., Soejima, H., Hokamaki, J., Kajiwara, I., Sugiyama, S., Yoshimura, M., Fujimoto, K., Miyao, Y., Suefuji, H., Kitagawa, A., Ouchi, N., Kihara, S., Matsuzawa, Y., & Ogawa, H. (2003). The variation of plasma concentrations of a novel, adipocyte derived protein, adiponectin, in patients with acute myocardial infarction. *Heart*, 89(6), 667-667. <http://dx.doi.org/10.1136/heart.89.6.667>
- Konan, L. M., Reddy, V., & Mesfin, F. B. (2020). Neuroanatomy, Cerebral Blood Supply. In StatPearls. StatPearls Publishing.
- Korf, E. S., White, L. R., Scheltens, P., & Launer, L. J. (2004). Midlife blood pressure and the risk of hippocampal atrophy: The Honolulu Asia Aging Study. *Hypertension*, 44(1), 29-34.
- Korsgaard, N., Aalkjaer, C., Heagerty, A. M., Izzard, A. S., & Mulvany, M. J. (1993). Histology of subcutaneous small arteries from patients with essential hypertension. *Hypertension*, 22(4), 523-526.
- Kotsis, V., Tsioufis, K., Antza, C., Seravalle, G., Coca, A., Sierra, C., Lurbe, E., Stabouli, S., Jelakovic, B., Redon, J., Redon, P., Nilsson, P. M., Jordan, J., Micic, D., Finer, N., Leitner, D. R., Toplak, H., Tokgozoglu, L., Athyros, Vasilios., ... Guido, G. (2018). Obesity and cardiovascular risk: A call for action from the European society of hypertension working group of obesity, diabetes and the high-risk patient and european association for the study of obesity part B obesity-induced cardiovascular disease, early prevention strategies and future research directions. *Journal of Hypertension*, 36(7), 1441-1455.
<https://doi.org/10.1097/HJH.0000000000001731>
- Kovács, K. R., Czuriga, D., Bereczki, D., Bornstein, N. M., & Csiba, L. (2013). Silent brain infarction—a review of recent observations. *International Journal of Stroke*, 8(5), 334-347.
- Kril, J., Patel, S., Harding, A., & Halliday, G. (2002). Patients with vascular dementia due to microvascular pathology have significant hippocampal neuronal loss. *Journal of Neurology, Neurosurgery & Psychiatry*, 72(6), 747-751.
- Kripalani, S., Henderson, L. E., Chiu, E. Y., Robertson, R., Kolm, P., & Jacobson, T. A. (2006). Predictors of medication self-management skill in a low-literacy population. *Journal of General Internal Medicine*, 21(8), 852-856.
- Kugiyama, K., Yasue, H., Ohgushi, M., Motoyama, T., Kawano, H., Inobe, Y., Hirashima, O., & Sugiyama, S. (1996). Deficiency in nitric oxide bioactivity in epicardial coronary arteries of cigarette smokers. *Journal of the American College of Cardiology*, 28(5), 1161-1167.
- Kuiper, J. S., Zuidersma, M., Voshaar, R. C. O., Zuidema, S. U., van den Heuvel, E. R., Stolk, R. P., & Smidt, N. (2015). Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Reviews*, 22, 39-57.
<https://doi.org/10.1016/j.arr.2015.04.006>
- Kuk, J. L., Saunders, T. J., Davidson, L. E., & Ross, R. (2009). Age-related changes in total and regional fat distribution. *Ageing Research Reviews*, 8(4), 339-348.
- Kullmann, S., Callaghan, M. F., Heni, M., Weiskopf, N., Scheffler, K., Häring, H. U., Fritsche, A., Veit, R., & Preissl, H. (2016). Specific white matter tissue microstructure changes associated with obesity. *Neuroimage*, 125, 36-44. <https://doi.org/10.1016/j.neuroimage.2015.10.006>

- Kullmann, S., Heni, M., Fritsche, A., & Preissl, H. (2015). Insulin action in the human brain: evidence from neuroimaging studies. *Journal of Neuroendocrinology*, 27(6), 419-423.
- Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Häring, H. U., Fritsche, A., & Preissl, H. (2012). The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity. *Human Brain Mapping*, 33(5), 1052-1061. <https://doi.org/10.1002/hbm.21268>
- Kumar, A., Haroon, E., Darwin, C., Pham, D., Ajilore, O., Rodriguez, G., & Mintz, J. (2008). Gray matter prefrontal changes in type 2 diabetes detected using MRI. *Journal of Magnetic Resonance Imaging*, 27(1), 14-19.
- Kumar, A., & Singh, A. (2015). A review on Alzheimer's disease pathophysiology and its management: An update. *Pharmacological Reports*, 67(2), 195-203. <https://doi.org/10.1016/j.pharep.2014.09.004>
- Kume, K., Hanyu, H., Sato, T., Hirao, K., Shimizu, S., Kanetaka, H., Sakurai, H., & Iwamoto, T. (2011). Vascular risk factors are associated with faster decline of Alzheimer disease: A longitudinal SPECT study. *Journal of Neurology*, 258(7), 1295-1303. <https://doi.org/10.1007/s00415-011-5927-y>
- Kurth, F., Levitt, J. G., Phillips, O. R., Luders, E., Woods, R. P., Mazziotta, J. C., Toga, A. W., & Narr, K. L. (2013). Relationships between gray matter, body mass index, and waist circumference in healthy adults. *Human Brain Mapping*, 34(7), 1737-1746. <https://doi.org/10.1002/hbm.22021>
- Kusters, P., Seijkens, T., Bürger, C., Legein, B., Winkels, H., Gijbels, M., Barthels, C., Bennett, R., Beckers, L., Atzler, D., Biessen, E., Brocker, T., Weber, C., Gerdes, N., & Lutgens, E. (2017). Constitutive CD40 signaling in dendritic cells limits atherosclerosis by provoking inflammatory bowel disease and ensuing cholesterol malabsorption. *The American Journal of Pathology*, 187(12), 2912-2919. <https://doi.org/10.1016/j.ajpath.2017.08.016>
- Kyle, U. G., Genton, L., Hans, D., Karsegard, L., Slosman, D. O., & Pichard, C. (2001). Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. *European Journal of Clinical Nutrition*, 55(8), 663-672. <https://doi.org/10.1038/sj.ejcn.1601198>
- Lacroix, M. C., Badonnel, K., Meunier, N., Tan, F., Poupon, C. S. L., Durieux, D., Monnerie, R., Baly, C., Congar, P., Salesse, R., & Caillol, M. (2008). Expression of insulin system in the olfactory epithelium: first approaches to its role and regulation. *Journal of Neuroendocrinology*, 20(10), 1176-1190. <https://doi.org/10.1111/j.1365-2826.2008.01777.x>
- Lakka, T. A., Lakka, H.-M., Salonen, R., Kaplan, G. A., & Salonen, J. T. (2001). Abdominal obesity is associated with accelerated progression of carotid atherosclerosis in men. *Atherosclerosis*, 154(2), 497-504. [https://doi.org/10.1016/S0021-9150\(00\)00514-1](https://doi.org/10.1016/S0021-9150(00)00514-1)
- Lam, B., Masellis, M., Freedman, M., Stuss, D. T., Black, S. E. (2013). Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. *Alzheimer's Research & Therapy*, 5(1), 1-14. <https://doi.org/10.1186/alzrt155>
- Lam, C. S., Borlaug, B. A., Kane, G. C., Enders, F. T., Rodeheffer, R. J., & Redfield, M. M. (2009). Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation*, 119(20), 2663. <https://doi.org/10.1161/CIRCULATIONAHA.108.838698>
- Lambert, M. P., Barlow, A., Chromy, B. A., Edwards, C., Freed, R., Liosatos, M., Morgan, T. E., Rozovsky, I., Trommer, B., Viola, K. L., Wals, P., Zhang, C., Finch, C. E., Krafft, G. A., & Klein, W. L., (1998). Diffusible, nonfibrillar ligands derived from A β 1-42 are potent central nervous system neurotoxins. *Proceedings of the National Academy of Sciences*, 95(11), 6448-6453. <https://doi.org/10.1073/pnas.95.11.6448>
- Lampe, L., Zhang, R., Beyer, F., Huhn, S., Kharabian Masouleh, S., Preusser, S., Bazin, P. L., Schroeter, M. L., Villringer, A., & Witte, A. V. (2019). Visceral obesity relates to deep white

- matter hyperintensities via inflammation. *Annals of Neurology*, 85(2), 194-203.
<https://doi.org/10.1002/ana.25396>
- Lanctôt, K. L., Amatniek, J., Ancoli-Israel, S., Arnold, S. E., Ballard, C., Cohen-Mansfield, J., Ismail, Z., Lyketsos, C., Miller, D. S., Musiek, E., Osorio, R. S., Rosenberg, P. B., Satlin, A., Steffens, D., Tariot, P., Bain, L. J., Carrillo, M. C., Hendrix, J. A., Jurgens, H., & Boot, B. (2017). Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 3(3), 440-449. <https://doi.org/10.1016/j.trci.2017.07.001>
- Landau, S. M., Thomas, B. A., Thurfjell, L., Schmidt, M., Margolin, R., Mintun, M., Pontecorvo, M., Baker, S. L., Jagust, W. J. & Alzheimer's Disease Neuroimaging Initiative (ADNI). (2014). Amyloid PET imaging in Alzheimer's disease: a comparison of three radiotracers. *European Journal of Nuclear Medicine and Molecular Imaging*, 41(7), 1398-1407.
<https://doi.org/10.1007/s00259-014-2753-3>
- Lane, C. A., Barnes, J., Nicholas, J. M., Sudre, C. H., Cash, D. M., Parker, T. D., Malone, I. B., Lu, K., James, S. N., Keshavan, A., Murray-Smith, H., Wong, A., Buchanan, S. M., Keuss, S. E., Gordon, E., Coath, W., Barnes, A., Dickson, J., Modat, M., ... Schott, J. M. (2019). Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): An epidemiological study. *The Lancet Neurology*, 18(10), 942-952.
[https://doi.org/10.1016/S1474-4422\(19\)30228-5](https://doi.org/10.1016/S1474-4422(19)30228-5)
- Lang, P., Hasselwander, S., Li, H., & Xia, N. (2019). Effects of different diets used in diet-induced obesity models on insulin resistance and vascular dysfunction in C57BL/6 mice. *Scientific Reports*, 9(1), 1-14. <https://doi.org/10.1038/s41598-019-55987-x>
- Langballe, E. M., Ask, H., Holmen, J., Stordal, E., Saltvedt, I., Selbæk, G., Fikseanet, A., Bergh, S., Nafstad, P., & Tambs, K. (2015). Alcohol consumption and risk of dementia up to 27 years later in a large, population-based sample: the HUNT study, Norway. *European Journal of Epidemiology*, 30(9), 1049-1056. <https://doi.org/10.1007/s10654-015-0029-2>
- Lanham, D., Ali, S., Davis, D., & Rawle, M. J. (2019). Beta-Blockers for the Secondary Prevention of Myocardial Infarction in People with Dementia: A Systematic Review. *Journal of Alzheimer's Disease*, 71(4), 1105-1114. <https://doi.org/10.3233/JAD-190503>
- Lanoiselee, H. M., Nicolas, G., Wallon, D., Rovelet-Lecrux, A., Lacour, M., Rousseau, S., Richard, A. C., Pasquier, F., Rollin-Sillaire, A., Martinaud, O., Quillard-Muraine, M., de la Sayette, V., Boutoleau-Bretonniere, C., Etcharry-Bouyx, F., Chauviré, V., Sarazin, M., le Ber, I., Epelbaum, S., Jonveaux, T., ... Collaborators of the CNR-MAJ project (2017). APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. *PLoS Medicine*, 14(3), e1002270.
<https://doi.org/10.1371/journal.pmed.1002270>
- Lanz, T., Carter, D., & Merchant, K. M. (2003). Dendritic spine loss in the hippocampus of young PDAPP and Tg2576 mice and its prevention by the ApoE2 genotype. *Neurobiology of Disease*, 13(3), 246-253. [https://doi.org/10.1016/S0969-9961\(03\)00079-2](https://doi.org/10.1016/S0969-9961(03)00079-2)
- Laogun, A., & Gosling, R. G. (1982). In vivo arterial compliance in man. *Clinical Physics and Physiological Measurement*, 3(3), 201. <https://doi.org/10.1088/0143-0815/3/3/004>
- Larner, A. J. (1997). The cerebellum in Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, 8(4), 203-209. <https://doi.org/10.1159/000106632>
- Last, D., Alsop, D. C., Abduljalil, A. M., Marquis, R. P., de Bazelaire, C., Hu, K., Cavallerano, J. & Novak, V. (2007). Global and regional effects of type 2 diabetes on brain tissue volumes and cerebral vasoreactivity. *Diabetes Care*, 30(5), 1193-1199. <https://doi.org/10.2337/dc06-2052>
- Launer, L. J., Petrovitch, H., Ross, G. W., Markesbery, W., & White, L. R. (2008). AD brain pathology: Vascular origins?: Results from the HAAS autopsy study. *Neurobiology of Aging*, 29(10), 1587-1590. <https://doi.org/10.1016/j.neurobiolaging.2007.03.008>

- Launer, L. J., Ross, G. W., Petrovitch, H., Masaki, K., Foley, D., White, L. R., & Havlik, R. J. (2000). Midlife blood pressure and dementia: the Honolulu–Asia aging study☆. *Neurobiology of Aging* 21(1), 49-55. [https://doi.org/10.1016/S0197-4580\(00\)00096-8](https://doi.org/10.1016/S0197-4580(00)00096-8)
- Lavie, C. J., Milani, R. V., & Ventura, H. O. (2009). Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *Journal of the American College of Cardiology* 53(21), 1925-1932. <https://doi.org/10.1016/j.jacc.2008.12.068>
- Law, L. L., Rol, R. N., Schultz, S. A., Dougherty, R. J., Edwards, D. F., Kosciak, R. L., Gallagher, C. L., Carlsson, C. M., Bendlin, B. B., Zetterberg, H., Blennow, K., Asthana, S., Sager, M. A., Hermann, B. P., Johnson, S. C., Cook, D. B., & Okonkwo, O. C (2018). Moderate intensity physical activity associates with CSF biomarkers in a cohort at risk for Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 10(1), 188-195. <https://doi.org/10.1016/j.dadm.2018.01.001>
- Lebouvier, T., Chen, Y., Duriez, P., Pasquier, F., & Bordet, R. (2020). Antihypertensive agents in Alzheimer's disease: Beyond vascular protection. *Expert Review of Neurotherapeutics*, 20(2), 175-187. <https://doi.org/10.1080/14737175.2020.1708195>
- Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: Concepts and applications. *Journal of Magnetic Resonance Imaging*, 13(4), 534-546. <https://doi.org/10.1002/jmri.1076>
- Lee, A. T., Richards, M., Chan, W. C., Chiu, H. F., Lee, R. S., & Lam, L. C. W. (2015). Intensity and types of physical exercise in relation to dementia risk reduction in community-living older adults. *Journal of the American Medical Directors Association*, 16(10), 899. e891-899. e897. <https://doi.org/10.1016/j.jamda.2015.07.012>
- Lee, F. Y. J., Li, Y., Yang, E. K., Yang, S. Q., Lin, H. Z., Trush, M. A., Dannenberg, A. J., & Diehl, A. M. (1999). Phenotypic abnormalities in macrophages from leptin-deficient, obese mice. *Journal of Physiology-Cell Physiology*, 276(2), C386-C394. <https://doi.org/10.1152/ajpcell.1999.276.2.C386>
- Lee, J. H., Olichney, J. M., Hansen, L. A., Hofstetter, C. R., & Thal, L. J. (2000). Small concomitant vascular lesions do not influence rates of cognitive decline in patients with Alzheimer disease. *Archives of Neurology*, 57(10), 1474-1479. <https://doi.org/10.1001/archneur.57.10.1474>
- Lee, S. B., Kim, J. H., Cho, M. H., Choe, E. S., Kim, K. S., & Shim, S. M. (2017). Impact of commercial cigarette smoke condensate on brain tissue co-cultured with astrocytes and blood–brain barrier endothelial cells. *Journal of Toxicology and Environmental Health, Part A*, 80(10-12), 533-541. <https://doi.org/10.1080/15287394.2017.1355863>
- Lee, S. H., Kim, S. M., Kim, N., Yoon, B. W., & Roh, J. K. (2007). Cortico-subcortical distribution of microbleeds is different between hypertension and cerebral amyloid angiopathy. *Journal of the Neurological Sciences*, 258(1-2), 111-114. <https://doi.org/10.1016/j.jns.2007.03.008>
- Lee, S. H., Bae, H. J., Ko, S. B., Kim, H., Yoon, B. W., & Roh, J. K. (2004). Comparative analysis of the spatial distribution and severity of cerebral microbleeds and old lacunes. *Journal of Neurology, Neurosurgery & Psychiatry*, 75(3), 423-427. <https://doi.org/10.1136/jnnp.2003.015990>
- Lee, T. H., Feng, S. H., Lin, C. H., Hwang, Y. H., Huang, C. L., & Hwang, P.P. (2003). Ambient salinity modulates the expression of sodium pumps in branchial mitochondria-rich cells of Mozambique tilapia, *Oreochromis mossambicus*. *Zoological Science*, 20(1), 29-36. <https://doi.org/10.2108/zsj.20.29>
- Lee, V. M., Goedert, M., & Trojanowski, J. Q. (2001). Neurodegenerative tauopathies. *Annual Review of Neuroscience*, 24, 1121-1159. <https://doi.org/10.1146/annurev.neuro.24.1.1121>
- Leggio, M., & Molinari, M., (2015). Cerebellar sequencing: a trick for predicting the future. *Cerebellum*, 14(1), 35-38. <https://doi.org/10.1007/s12311-014-0616-x>

- Leiva, A. M., Martínez, M. A., Cristi-Montero, C., Salas, C., Ramirez-Campillo, R., Aguilar-Farías, N., & Celis-Morales, C. (2017). Sedentary lifestyle is associated with metabolic and cardiovascular risk factors independent of physical activity. *Revista Medica de Chile*, *145*(4), 458-467. <https://doi.org/10.4067/S0034-98872017000400006>
- Lemieux, S., Despres, J., Moorjani, S., Nadeau, A., Theriault, G., Prud'Homme, D., Tremblay, A., Bouchard, C., & Lupien, P. J. (1994). Are gender differences in cardiovascular disease risk factors explained by the level of visceral adipose tissue? *Diabetologia*, *37*(8), 757-764. <https://doi.org/10.1007/BF00404332>
- Lennon, M. J., Makkar, S. R., Crawford, J. D., & Sachdev, P. S. (2019). Midlife hypertension and Alzheimer's disease: A systematic review and meta-analysis. *Journal of Alzheimer's Disease*, *71*(1), 307-316. <https://doi.org/10.3233/JAD-190474>
- Leroi, I., Voulgari, A., Breitner, J. C., & Lyketsos, C. G. (2003). The epidemiology of psychosis in dementia. *The American Journal of Geriatric Psychiatry*, *11*(1), 83-91. <https://doi.org/10.1097/00019442-200301000-00011>
- Letra, L., Matafome, P., Rodrigues, T., Duro, D., Lemos, R., Baldeiras, I., Patrício, M., Castelo-Branco, M., Caetano, G., Seíça, R., & Santana, I. (2019). Association between adipokines and biomarkers of Alzheimer's disease: A cross-sectional study. *Journal of Alzheimer's Disease*, *67*(2), 725-735. <https://doi.org/10.3233/JAD-180669>
- Levinthal, B. R., Morrow, D. G., Tu, W., Wu, J., & Murray, M. D. (2008). Cognition and health literacy in patients with hypertension. *Journal of General Internal Medicine*, *23*(8), 1172. <https://doi.org/10.1007/s11606-008-0612-2>
- Levy, D., Ehret, G. B., Rice, K., Verwoert, G. C., Launer, L. J., Dehghan, A., Glazer, N. L., Morrison, A. C., Johnson, A. D., Aspelund, T., Aulchenko, Y., Lumley, T., Köttgen, A., Vasan, R. S., Rivadeneira, F., Eiriksdottir, G., Guo, X., Arking, D. E., Mitchell, G. F., ... van Duijn, C. M. (2009). Genome-wide association study of blood pressure and hypertension. *Nature Genetics*, *41*(6), 677-687. <https://doi.org/10.1038/ng.384>
- Levy-Lahad, E., & Bird, T. D. (1996). Genetic factors in Alzheimer's disease: a review of recent advances. *Ann Neurol*, *40*(6), 829-840. doi:10.1002/ana.410400604
- Lezak, M. D., Howieson, D. B., Loring, D. W., & Fischer, J. S. (2004). *Neuropsychological Assessment*: Oxford University Press, USA.
- Li, G., Shofer, J. B., Petrie, E. C., Yu, C.-E., Wilkinson, C. W., Figlewicz, D. P., Shutes-David, A., Zhang, J., Montine, T. J., Raskind, M. A., Quinn, J. F., Galasko, D. R., & Peskind, E. R. (2017). Cerebrospinal fluid biomarkers for Alzheimer's and vascular disease vary by age, gender, and APOE genotype in cognitively normal adults. *Alzheimer's Research & Therapy*, *9*(1), 1-9. <https://doi.org/10.1186/s13195-017-0271-9>
- Li, H., Dhanasekaran, P., Alexander, E. T., Rader, D. J., Phillips, M. C., & Lund-Katz, S. (2013). Molecular mechanisms responsible for the differential effects of apoE3 and apoE4 on plasma lipoprotein-cholesterol levels. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *33*(4), 687-693. <https://doi.org/10.1161/ATVBAHA.112.301193>
- Li, J., Deng, J., Sheng, W., & Zuo, Z. (2012a). Metformin attenuates Alzheimer's disease-like neuropathology in obese, leptin-resistant mice. *Pharmacology Biochemistry and Behavior*, *101*(4), 564-574. <https://doi.org/10.1016/j.pbb.2012.03.002>
- Li, L., Cao, D., Garber, D. W., Kim, H., & Fukuchi, K. (2003). Association of aortic atherosclerosis with cerebral β -amyloidosis and learning deficits in a mouse model of Alzheimer's disease. *The American Journal of Pathology*, *163*(6), 2155-2164. [https://doi.org/10.1016/S0002-9440\(10\)63572-9](https://doi.org/10.1016/S0002-9440(10)63572-9)
- Li, L., Zhang, X., Yang, D., Luo, G., Chen, S., & Le, W. (2009). Hypoxia increases A β generation by altering β - and γ -cleavage of APP. *Neurobiology of Aging*, *30*(7), 1091-1098. <https://doi.org/10.1016/j.neurobiolaging.2007.10.011>

- Li, W., Antuono, P. G., Xie, C., Chen, G., Jones, J. L., Ward, B. D., Franczak, M. B., Goveas, J. S., & Li, S. J. (2012b). Changes in regional cerebral blood flow and functional connectivity in the cholinergic pathway associated with cognitive performance in subjects with mild Alzheimer's disease after 12-week donepezil treatment. *Neuroimage*, *60*(2), 1083-1091. <https://doi.org/10.1016/j.neuroimage.2011.12.077>
- Li, W., Ma, D., Liu, M., Liu, H., Feng, S., Hao, Z., Wu, B., & Zhang, S. (2008a). Association between metabolic syndrome and risk of stroke: a meta-analysis of cohort studies. *Cerebrovascular Diseases*, *25*(6), 539-547. <https://doi.org/10.1159/000131672>
- Li, X., Liang, Y., Chen, Y., Zhang, J., Wei, D., Chen, K., Shu, N., Reiman, E. M. & Zhang, Z. (2015). Disrupted frontoparietal network mediates white matter structure dysfunction associated with cognitive decline in hypertension patients. *Journal of Neuroscience*, *35*(27), 10015-10024. <https://doi.org/10.1523/JNEUROSCI.5113-14.2015>
- Li, Y., Rinne, J. O., Mosconi, L., Pirraglia, E., Rusinek, H., DeSanti, S., Kempainen, N., Någren, K., Kim, B. C., Tsui, W., & de Leon M. J. (2008b). Regional analysis of FDG and PIB-PET images in normal aging, mild cognitive impairment, and Alzheimer's disease. *European Journal of Nuclear Medicine and Molecular Imaging*, *35*(12), 2169-2181. <https://doi.org/10.1007/s00259-008-0833-y>
- Liao, D., Cooper, L., Cai, J., Toole, J. F., Bryan, N. R., Hutchinson, R. G., & Tyroler, H. A. (1996). Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control: The ARIC Study. *Stroke*, *27*(12), 2262-2270. <https://doi.org/10.1161/01.STR.27.12.2262>
- Liao, Q., Zheng, Z., Xiu, S., Chan, P. (2018). Waist circumference is a better predictor of risk for frailty than BMI in the community-dwelling elderly in Beijing. *Aging Clinical and Experimental Research*, *30*(11), 1319-1325. <https://doi.org/10.1007/s40520-018-0933-x>
- Libby, L. A., Hannula, D. E., & Ranganath, C. (2014). Medial temporal lobe coding of item and spatial information during relational binding in working memory. *Journal of Neuroscience*, *34*(43), 14233-14242. <https://doi.org/10.1523/JNEUROSCI.0655-14.2014>
- Lieb, W., Beiser, A. S., Vasan, R. S., Tan, Z. S., Au, R., Harris, T. B., Roubenoff, R., Auerbach, S., DeCarli, C., Wolf, P. A., & Seshadri, S. (2009). Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. *JAMA*, *302*(23), 2565-2572. <https://doi.org/10.1001/jama.2009.1836>
- Lieberman, M. D., & Cunningham, W. A. (2009). Type I and Type II error concerns in fMRI research: re-balancing the scale. *Social cognitive and affective neuroscience*, *4*(4), 423-428. <https://doi.org/10.1093/scan/nsp052>
- Lin, F., Lo, R. Y., Cole, D., Ducharme, S., Chen, D. G., Mapstone, M., Porsteinsson, A., & Alzheimer's Disease Neuroimaging Initiative (2014). Longitudinal effects of metabolic syndrome on Alzheimer and vascular related brain pathology. *Dementia and Geriatric Cognitive Disorders Extra*, *4*(2), 184-194. <https://doi.org/10.1159/000363285>
- Lin, Y. T., Seo, J., Gao, F., Feldman, H. M., Wen, H. L., Penney, J., Cam, H. P., Gjonjeska, E., Raja, W. K., Cheng, J., Rueda, R., Kritskiy, O., Abdurrob, F., Peng, Z., Milo, B., Yu, C. J., Elmsaouri, S., Dey, D., Ko, T., Yankner, B. A., ... Tsai, L. H. (2018). APOE4 Causes Widespread Molecular and Cellular Alterations Associated with Alzheimer's Disease Phenotypes in Human iPSC-Derived Brain Cell Types. *Neuron*, *98*(6), 1141-1154.e7. <https://doi.org/10.1016/j.neuron.2018.05.008>
- Lindström, M., Hanson, B. S. & Östergren, P.O. (2001). Socioeconomic differences in leisure-time physical activity: the role of social participation and social capital in shaping health related behaviour. *Social Science & Medicine*, *52*(3), 441-451. [https://doi.org/10.1016/S0277-9536\(00\)00153-2](https://doi.org/10.1016/S0277-9536(00)00153-2)
- Lips, M. A., Wijngaarden, M. A., van der Grond, J., van Buchem, M. A., de Groot, G. H., Rombouts, S. A., Pijl, H., & Veer, I. M. (2014). Resting-state functional connectivity of brain regions

- involved in cognitive control, motivation, and reward is enhanced in obese females. *The American Journal of Clinical Nutrition*, 100(2), 524–531.
<https://doi.org/10.3945/ajcn.113.080671>
- Lipsitz, L. A., Gagnon, M., Vyas, M., Iloputaife, I., Kiely, D. K., Sorond, F., Serrador, J., Cheng, D. M., Babikian, V., & Cupples, L. A. (2005). Antihypertensive therapy increases cerebral blood flow and carotid distensibility in hypertensive elderly subjects. *Hypertension*, 45(2), 216–221. <https://doi.org/10.1161/01.HYP.0000153094.09615.11>
- Liu, H., Zhang, L., Xi, Q., Zhao, X., Wang, F., Wang, X., Men, W., & Lin, Q. (2018). Changes in Brain Lateralization in Patients with Mild Cognitive Impairment and Alzheimer's Disease: A Resting-State Functional Magnetic Resonance Study from Alzheimer's Disease Neuroimaging Initiative. *Frontiers in Neurology*, 9, 3.
<https://doi.org/10.3389/fneur.2018.00003>
- Liu, J., Liu, T., Wang, W., Ma, L., Ma, X., Shi, S., Gong, Q., & Wang, M. (2017). Reduced Gray Matter Volume in Patients with Type 2 Diabetes Mellitus. *Frontiers in Aging Neuroscience*, 9, 161. <https://doi.org/10.3389/fnagi.2017.00161>
- Liu, L., Drouet, V., Wu, J. W., Witter, M. P., Small, S. A., Clelland, C., & Duff, K. (2012a). Trans-synaptic spread of tau pathology in vivo. *PLoS One*, 7(2), e31302.
<https://doi.org/10.1371/journal.pone.0031302>
- Liu, S. Y., Chen, C. L., Yang, T. T., Huang, W. C., Hsieh, C. Y., Shen, W. J., Tsai, T. T., Shieh, C. C., & Lin, C. F. (2012b). Albumin prevents reactive oxygen species-induced mitochondrial damage, autophagy, and apoptosis during serum starvation. *Apoptosis*, 17(11), 1156–1169.
<https://doi.org/10.1007/s10495-012-0758-6>
- Liu, Y., Liu, F., Iqbal, K., Grundke-Iqbal, I., & Gong, C. X. (2008). Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer disease. *FEBS Letters*, 582(2), 359–364. <https://doi.org/10.1016/j.febslet.2007.12.035>
- Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Larson, E. B., Ritchie, K., Rockwood, K., Sampson, E. L., ... Mukadam, N. (2017). Dementia Prevention, Intervention, and Care. *The Lancet*, 390(10113), 2673–2734.
[https://doi.org/10.1016/S0140-6736\(17\)31363-6](https://doi.org/10.1016/S0140-6736(17)31363-6)
- Lo, R. Y., & Jagust, W. J. (2012). Vascular burden and Alzheimer disease pathologic progression. *Neurology*, 79(13), 1349–1355. <https://doi.org/10.1212/WNL.0b013e31826c1b9d>
- Loader, J., Montero, D., Lorenzen, C., Watts, R., Méziat, C., Reboul, C., Stewart, S., & Walther, G. (2015). Acute hyperglycemia impairs vascular function in healthy and cardiometabolic diseased subjects: Systematic review and meta-analysis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 35(9), 2060–2072. <https://doi.org/10.1161/ATVBAHA.115.305530>
- Loewenstein, D. A., Barker, W. W., Chang, J. Y., Apicella, A., Yoshii, F., Kothari, P., Levin, B., & Duara, R. (1989). Predominant left hemisphere metabolic dysfunction in dementia. *Archives of Neurology*, 46(2), 146–152. <https://doi.org/10.1001/archneur.1989.00520380046012>
- Lofgren, I., Herron, K., Zern, T., West, K., Patalay, M., Shachter, N. S., Koo, S. I., & Fernandez, M. L. (2004). Waist circumference is a better predictor than body mass index of coronary heart disease risk in overweight premenopausal women. *The Journal of Nutrition*, 134(5), 1071–1076. <https://doi.org/10.1093/jn/134.5.1071>
- Lönnqvist, F., Wennlund, A., & Arner, P. (1997). Relationship between circulating leptin and peripheral fat distribution in obese subjects. *International Journal of Obesity*, 21(4), 255–260.
<https://doi.org/10.1038/sj.ijo.0800394>
- Lopez, O. L., Klunk, W. E., Mathis, C., Coleman, R. L., Price, J., Becker, J. T., Aizenstein, H. J., Snitz, B., Cohen, A., Ikonomic, M., McDade, E., DeKosky, S. T., Weissfeld, L., & Kuller, L. H. (2014). Amyloid, neurodegeneration, and small vessel disease as predictors of dementia

- in the oldest-old. *Neurology*, 83(20), 1804–1811.
<https://doi.org/10.1212/WNL.0000000000000977>
- Lowe, V. J., Wiste, H. J., Senjem, M. L., Weigand, S. D., Therneau, T. M., Boeve, B. F., Josephs, K. A., Fang, P., Pandey, M. K., Murray, M. E., Kantarci, K., Jones, D. T., Vemuri, P., Graff-Radford, J., Schwarz, C. G., Machulda, M. M., Mielke, M. M., Roberts, R. O., Knopman, D. S., Petersen, R. C., ... Jack, C. R., Jr (2018). Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia. *Brain*, 141(1), 271–287.
<https://doi.org/10.1093/brain/awx320>
- Luchsinger, J., Reitz, C., Honig, L. S., Tang, M. X., Shea, S., & Mayeux, R. (2005). Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*, 65(4), 545-551.
<https://doi.org/10.1212/01.wnl.0000172914.08967.dc>
- Luchsinger, J. A., Tang, M. X., Siddiqui, M., Shea, S., & Mayeux, R. (2004). Alcohol intake and risk of dementia. *Journal of the American Geriatrics Society*, 52(4), 540–546.
<https://doi.org/10.1111/j.1532-5415.2004.52159.x>
- Luck, D., Danion, J. M., Marrer, C., Pham, B. T., Gounot, D., & Foucher, J. (2010). The right parahippocampal gyrus contributes to the formation and maintenance of bound information in working memory. *Brain and Cognition*, 72(2), 255–263.
<https://doi.org/10.1016/j.bandc.2009.09.009>
- Ludwig, D. S. (2011). Technology, diet, and the burden of chronic disease. *JAMA*, 305(13), 1352-1353. <https://doi.org/10.1001/jama.2011.380>
- Lukács, A., Horváth, E., Máté, Z., Szabó, A., Virág, K., Papp, M., Sándor, J., Ádány, R., & Paulik, E. (2019). Abdominal obesity increases metabolic risk factors in non-obese adults: a Hungarian cross-sectional study. *BMC Public Health*, 19(1), 1533.
<https://doi.org/10.1186/s12889-019-7839-1>
- Luo, D. H., Tseng, W. Y. I., & Chang, Y. L. (2019). White matter microstructure disruptions mediate the adverse relationships between hypertension and multiple cognitive functions in cognitively intact older adults. *NeuroImage*, 197, 109-119.
<https://doi.org/10.1016/j.neuroimage.2019.04.063>
- Lyaker, M. R., Tulman, D. B., Dimitrova, G. T., Pin, R. H., & Papadimos, T. J. (2013). Arterial embolism. *International Journal of Critical Illness and Injury Science*, 3(1), 77–87.
<https://doi.org/10.4103/2229-5151.109429>
- Ma, H. R., Pan, P. L., Sheng, L. Q., Dai, Z. Y., Wang, G. D., Luo, R., Chen, J. H., Xiao, P. R., Zhong, J. G., & Shi, H. C. (2017). Aberrant pattern of regional cerebral blood flow in Alzheimer's disease: A voxel-wise meta-analysis of arterial spin labeling MR imaging studies. *Oncotarget*, 8(54), 93196–93208. <https://doi.org/10.18632/oncotarget.21475>
- Ma, L., Wang, J., & Li, Y. (2015). Insulin resistance and cognitive dysfunction. *Clinica Chimica acta*, 444, 18-23. <https://doi.org/10.1016/j.cca.2015.01.027>
- Ma, T., Hoeffler, C. A., Capetillo-Zarate, E., Yu, F., Wong, H., Lin, M. T., Tampellini, D., Klann, E., Blitzer, R. D., & Gouras, G. K. (2010). Dysregulation of the mTOR pathway mediates impairment of synaptic plasticity in a mouse model of Alzheimer's disease. *PloS One*, 5(9), e12845. <https://doi.org/10.1371/journal.pone.0012845>
- Ma, Y., Wolters, F. J., Chibnik, L. B., Licher, S., Ikram, M. A., Hofman, A., & Ikram, M. K. (2019). Variation in blood pressure and long-term risk of dementia: A population-based cohort study. *PLoS Medicine*, 16(11), e1002933. <https://doi.org/10.1371/journal.pmed.1002933>
- MacIntosh, B. J., Shirzadi, Z., Atwi, S., Detre, J. A., Dolui, S., Bryan, R. N., Launer, L. J., & Swardfager, W. (2020). Metabolic and vascular risk factors are associated with reduced cerebral blood flow and poorer midlife memory performance. *Human Brain Mapping*, 41(4), 855-864. <https://doi.org/10.1002/hbm.24844>

- Macpherson, H., Formica, M., Harris, E., & Daly, R. M. (2017). Brain functional alterations in Type 2 Diabetes—A systematic review of fMRI studies. *Frontiers in Neuroendocrinology*, *47*, 34-46. <https://doi.org/10.1016/j.yfrne.2017.07.001>
- Macquart de Terline, D., Kane, A., Kramoh, K. E., Ali Toure, I., Mipinda, J. B., Diop, I. B., Nhavoto, C., Balde, D. M., Ferreira, B., Dèdonougbo Houenassi, M., Ikama, M. S., Kingue, S., Kouam Kouam, C., Takombe, J. L., Limbole, E., Mfeukeu Kuate, L., N'guetta, R., Damorou, J. M., Sesso, Z., Sidy Ali, A., ... Antignac, M. (2019). Factors associated with poor adherence to medication among hypertensive patients in twelve low and middle income Sub-Saharan countries. *PloS One*, *14*(7), e0219266. <https://doi.org/10.1371/journal.pone.0219266>
- Maillard, P., Carmichael, O. T., Reed, B., Mungas, D., & DeCarli, C. (2015). Cooccurrence of vascular risk factors and late-life white-matter integrity changes. *Neurobiology of Aging*, *36*(4), 1670-1677. <https://doi.org/10.1016/j.neurobiolaging.2015.01.007>
- Maillard, P., Seshadri, S., Beiser, A., Himali, J. J., Au, R., Fletcher, E., Carmichael, O., Wolf, P. A., & DeCarli, C. (2012). Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: A cross-sectional study. *The Lancet Neurology*, *11*(12), 1039-1047. [https://doi.org/10.1016/S1474-4422\(12\)70241-7](https://doi.org/10.1016/S1474-4422(12)70241-7)
- Makris, N., Goldstein, J. M., Kennedy, D., Hodge, S. M., Caviness, V. S., Faraone, S. V., Tsuang, M. T., & Seidman, L. J. (2006). Decreased volume of left and total anterior insular lobule in schizophrenia. *Schizophrenia Research*, *83*(2-3), 155–171. <https://doi.org/10.1016/j.schres.2005.11.020>
- Malek-Ahmadi, M., Beach, T., Obradov, A., Sue, L., Belden, C., Davis, K., Walker, D. G., Lue, L., Adem, A., & Sabbagh, M. (2013). Increased Alzheimer's disease neuropathology is associated with type 2 diabetes and ApoE ε4 carrier status. *Current Alzheimer Research*, *10*(6), 654-659. <https://doi.org/10.2174/15672050113109990006>
- Malloy, S. I., Altenburg, M. K., Knouff, C., Lanningham-Foster, L., Parks, J. S., & Maeda, N. (2004). Harmful effects of increased LDLR expression in mice with human APOE* 4 but not APOE* 3. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *24*(1), 91-97. <https://doi.org/10.1161/01.ATV.0000094963.07902.FB>
- Mamotte, C. D., Sturm, M., Foo, J. I., van Bockxmeer, F. M., & Taylor, R. R. (1999). Comparison of the LDL-receptor binding of VLDL and LDL from apoE4 and apoE3 homozygotes. *American Journal of Physiology-Endocrinology and Metabolism*, *276*(3), E553-E557. <https://doi.org/10.1152/ajpendo.1999.276.3.E553>
- Mandybur, T. (1975). The incidence of cerebral amyloid angiopathy in Alzheimer's disease. *Neurology*, *25*(2), 120-120. <https://doi.org/10.1212/WNL.25.2.120>
- Manninen, H., Tulla, H., Vanninen, R., & Ronkainen, A. (2008). Endangered cerebral blood supply after closure of left subclavian artery: postmortem and clinical imaging studies. *The Annals of Thoracic Surgery*, *85*(1), 120-125. <https://doi.org/10.1016/j.athoracsur.2007.08.035>
- Manns, J. R., Hopkins, R. O., & Squire, L. R. (2003). Semantic memory and the human hippocampus. *Neuron*, *38*(1), 127-133. [https://doi.org/10.1016/S0896-6273\(03\)00146-6](https://doi.org/10.1016/S0896-6273(03)00146-6)
- Mardh, S., Nagga, K., & Samuelsson, S. (2013). A longitudinal study of semantic memory impairment in patients with Alzheimer's disease. *Cortex*, *49*(2), 528-533. <https://doi.org/10.1016/j.cortex.2012.02.004>
- Marini, S., Merino, J., Montgomery, B. E., Malik, R., Sudlow, C. L., Dichgans, M., Florez, J. C., Rosand, J., Gill, D., Anderson, C. D., & International Stroke Genetics Consortium (2020). Mendelian Randomization Study of Obesity and Cerebrovascular Disease. *Annals of Neurology*, *87*(4), 516–524. <https://doi.org/10.1002/ana.25686>
- Marinković, S., Milisavljević, M., & Puškaš, L. (1992). Microvascular anatomy of the hippocampal formation. *Surgical Neurology*, *37*(5), 339-349. [https://doi.org/10.1016/0090-3019\(92\)90001-4](https://doi.org/10.1016/0090-3019(92)90001-4)

- Marinković, S. V., Milisavljević, M. M., & Vučković, V. D. (1991). Experimental and clinical studies: Microvascular anatomy of the uncus and the parahippocampal gyrus. *Neurosurgery*, 29(6), 805-814. <https://doi.org/10.1227/00006123-199112000-00001>
- Marks, B., Katz, L., Styner, M., & Smith, J. K. (2011). Aerobic fitness and obesity: relationship to cerebral white matter integrity in the brain of active and sedentary older adults. *British Journal of Sports Medicine*, 45(15), 1208-1215. <https://doi.org/10.1136/bjsm.2009.068114>
- Marnane, M., Al-Jawadi, O. O., Mortazavi, S., Pogorzelec, K. J., Wang, B. W., Feldman, H. H., Hsiung, G. Y., & Alzheimer's Disease Neuroimaging Initiative (2016). Periventricular hyperintensities are associated with elevated cerebral amyloid. *Neurology*, 86(6), 535–543. <https://doi.org/10.1212/WNL.0000000000002352>
- Maroules, C. D., Khera, A., Ayers, C., Goel, A., Peshock, R. M., Abbara, S., & King, K. S. (2014). Cardiovascular outcome associations among cardiovascular magnetic resonance measures of arterial stiffness: The Dallas heart study. *Journal of Cardiovascular Magnetic Resonance*, 16(1), 33. <https://doi.org/10.1186/1532-429X-16-33>
- Marqués-Iturria, I., Scholtens, L. H., Garolera, M., Pueyo, R., García-García, I., González-Tartiere, P., Segura, B., Junqué, C., Sender-Palacios, M. J., Vernet-Vernet, M., Sánchez-Garre, C., de Reus, M. A., Jurado, M. A., & van den Heuvel, M. P. (2015). Affected connectivity organization of the reward system structure in obesity. *NeuroImage*, 111, 100–106. <https://doi.org/10.1016/j.neuroimage.2015.02.012>
- Martinelli, L. M. B., Mizutani, B. M., Mutti, A., D'elia, M. P. B., Coltro, R. S., & Matsubara, B. B. (2008). Quality of life and its association with cardiovascular risk factors in a community health care program population. *Clinics*, 63(6), 783-788. <https://doi.org/10.1590/s1807-59322008000600013>
- Martins, D., Nelson, K., Pan, D., Tareen, N., & Norris, K. (2001). The effect of gender on age-related blood pressure changes and the prevalence of isolated systolic hypertension among older adults: data from NHANES III. *The Journal of Gender-Specific Medicine : JGSM : The Official Journal of the Partnership for Women's Health at Columbia*, 4(3), 10–20.
- Marwarha, G., Dasari, B., Prasanthi, J. R., Schommer, J., & Ghribi, O. (2010). Leptin reduces the accumulation of A β and phosphorylated tau induced by 27-hydroxycholesterol in rabbit organotypic slices. *Journal of Alzheimer's Disease*, 19(3), 1007-1019. <https://doi.org/10.3233/JAD-2010-1298>
- Mastroberardino, P. G., Hoffman, E. K., Horowitz, M. P., Betarbet, R., Taylor, G., Cheng, D., Na, H. M., Gutekunst, C. A., Gearing, M., Trojanowski, J. Q., Anderson, M., Chu, C. T., Peng, J., & Greenamyre, J. T. (2009). A novel transferrin/TfR2-mediated mitochondrial iron transport system is disrupted in Parkinson's disease. *Neurobiology of Disease*, 34(3), 417–431. <https://doi.org/10.1016/j.nbd.2009.02.009>
- Mather, K., Anderson, T. J., & Verma, S. (2001). Insulin action in the vasculature: physiology and pathophysiology. *Journal of Vascular Research*, 38(5), 415-422. <https://doi.org/10.1159/000051074>
- Matsubara, S., Koga, M., Ohara, T., Iguchi, Y., Minatoya, K., Tahara, Y., Fukuda, T., Miyazaki, Y., Kajimoto, K., Sakamoto, Y., Makita, N., Tokuda, N., Nagatsuka, K., Ando, Y., & Toyoda, K. (2018). Cerebrovascular imaging of cerebral ischemia in acute type A aortic dissection. *Journal of the Neurological Sciences*, 388, 23–27. <https://doi.org/10.1016/j.jns.2018.02.044>
- Matsuda, H., Kanetaka, H., Ohnishi, T., Asada, T., Imabayashi, E., Nakano, S., Katoh, A., & Tanaka, F. (2002). Brain SPET abnormalities in Alzheimer's disease before and after atrophy correction. *European Journal of Nuclear Medicine and Molecular Imaging*, 29(11), 1502-1505. <https://doi.org/10.1007/s00259-002-0930-2>
- Matsumoto, K., Sera, Y., Nakamura, H., Ueki, Y., Miyake, S. (2002). Correlation between common carotid arterial wall thickness and ischemic stroke in patients with type 2 diabetes mellitus.

- Metabolism-Clinical and Experimental* 51(2), 244-247.
<https://doi.org/10.1053/meta.2002.28971>
- Matsumoto, Y., Yanase, D., Noguchi-Shinohara, M., Ono, K., Yoshita, M., & Yamada, M. (2007). Blood-brain barrier permeability correlates with medial temporal lobe atrophy but not with amyloid- β protein transport across the blood-brain barrier in Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, 23(4), 241-245. <https://doi.org/10.1159/000100019>
- Matsuzaki, T., Sasaki, K., Tanizaki, Y., Hata, J., Fujimi, K., Matsui, Y., Sekita, A., Suzuki, S. O., Kanba, S., Kiyohara, Y. & Iwaki, T. (2010). Insulin resistance is associated with the pathology of Alzheimer disease: the Hisayama study. *Neurology*, 75(9), 764-770. <https://doi.org/10.1212/WNL.0b013e3181eee25f>
- Matthews, F. E., Arthur, A., Barnes, L. E., Bond, J., Jagger, C., Robinson, L., & Brayne, C. (2013). A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: Results of the Cognitive Function and Ageing Study I and II. *Lancet*, 382(9902), 1405-1412. [https://doi.org/10.1016/S0140-6736\(13\)61570-6](https://doi.org/10.1016/S0140-6736(13)61570-6)
- Matthews, F. E., Stephan, B. C., Robinson, L., Jagger, C., Barnes, L. E., Arthur, A., & Brayne, C. (2016). A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. *Nature Communications*, 7(1), 1-8. <https://doi.org/10.1038/ncomms11398>
- Mattsson, N., Schott, J. M., Hardy, J., Turner, M. R., & Zetterberg, H. (2016). Selective vulnerability in neurodegeneration: insights from clinical variants of Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 87(9), 1000-1004. <https://doi.org/10.1136/jnnp-2015-311321>
- Mauvais-Jarvis, F. (2018). Gender differences in glucose homeostasis and diabetes. *Physiology & Behavior*, 187, 20-23. <https://doi.org/10.1016/j.physbeh.2017.08.016>
- Mayer, F., Di Pucchio, A., Lacorte, E., Bacigalupo, I., Marzolini, F., Ferrante, G., Minardi, V., Masocco, M., Canevelli, M., Di Fiandra, T., & Vanacore, N. (2018). An Estimate of Attributable Cases of Alzheimer Disease and Vascular Dementia due to Modifiable Risk Factors: The Impact of Primary Prevention in Europe and in Italy. *Dementia and Geriatric Cognitive Disorders Extra*, 8(1), 60-71. <https://doi.org/10.1159/000487079>
- McCarron, M. O., & Nicoll, J. A. (2004). Cerebral amyloid angiopathy and thrombolysis-related intracerebral haemorrhage. *Lancet Neurology*, 3(8), 484-492. [https://doi.org/10.1016/S1474-4422\(04\)00825-7](https://doi.org/10.1016/S1474-4422(04)00825-7)
- McEvoy, L. K., Fennema-Notestine, C., Eyler, L. T., Franz, C. E., Hagler Jr, D. J., Lyons, M. J., Panizzon, M. S., Rinker, D. A., Dale, A. M., & Kremen, W. S. (2015). Hypertension-related alterations in white matter microstructure detectable in middle age. *Hypertension*, 66(2), 317-323. <https://doi.org/10.1161/HYPERTENSIONAHA.115.05336>
- McGill Jr, H. C., McMahan, C. A., Herderick, E. E., Zieske, A. W., Malcom, G. T., Tracy, R. E., & Strong, J. P. (2002). Obesity accelerates the progression of coronary atherosclerosis in young men. *Circulation*, 105(23), 2712-2718. <https://doi.org/10.1161/01.CIR.0000018121.67607.CE>
- McGrath, E. R., Beiser, A. S., DeCarli, C., Plourde, K. L., Vasan, R. S., Greenberg, S. M., & Seshadri, S. (2017). Blood pressure from mid-to late life and risk of incident dementia. *Neurology*, 89(24), 2447-2454. <https://doi.org/10.1212/WNL.0000000000004741>
- McKenney, J. M., Munroe, W. P., & Wright Jr, J. T. (1992). Impact of an electronic medication compliance aid on long-term blood pressure control. *The Journal of Clinical Pharmacology*, 32(3), 277-283. <https://doi.org/10.1002/j.1552-4604.1992.tb03837.x>
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the

- auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34(7), 939-944. <https://doi.org/10.1212/WNL.34.7.939>
- McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr, Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7(3), 263–269. <https://doi.org/10.1016/j.jalz.2011.03.005>
- McMonagle, P., Deering, F., Berliner, Y., & Kertesz, A. (2006). The cognitive profile of posterior cortical atrophy. *Neurology*, 66(3), 331-338. <https://doi.org/10.1212/01.wnl.0000196477.78548.db>
- Mehran, A. E., Templeman, N. M., Brigidi, G. S., Lim, G. E., Chu, K. Y., Hu, X., Botezelli, J. D., Asadi, A., Hoffman, B. G., Kieffer, T. J., Bamji, S. X., Clee, S. M., & Johnson, J. D. (2012). Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. *Cell Metabolism*, 16(6), 723–737. <https://doi.org/10.1016/j.cmet.2012.10.019>
- Meijer, R. I., de Boer, M. P., Groen, M. R., Eringa, E. C., Rattigan, S., Barrett, E. J., Smulders, Y. M., & Serné, E. H. (2012). Insulin-induced microvascular recruitment in skin and muscle are related and both are associated with whole-body glucose uptake. *Microcirculation*, 19(6), 494-500. <https://doi.org/10.1111/j.1549-8719.2012.00174.x>
- Meissner, I., Khandheria, B. K., Sheps, S. G., Schwartz, G. L., Wiebers, D. O., Whisnant, J. P., Covalt, J. L., Petterson, T. M., Christianson, T. J. H., & Agmon, Y. (2004). Atherosclerosis of the aorta: Risk factor, risk marker, or innocent bystander?: A prospective population-based transesophageal echocardiography study. *Journal of the American College of Cardiology*, 44(5), 1018-1024. <https://doi.org/10.1016/j.jacc.2004.05.075>
- Meltzer, H., Bebbington, P., Dennis, M. S., Jenkins, R., McManus, S., & Brugha, T. S. (2013). Feelings of loneliness among adults with mental disorder. *Social Psychiatry and Psychiatric Epidemiology*, 48(1), 5-13. <https://doi.org/10.1007/s00127-012-0515-8>
- Mendez, M. F., Ghajaranian, M., & Perryman, K. M. (2002). Posterior cortical atrophy: Clinical characteristics and differences compared to Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, 14(1), 33-40. <https://doi.org/10.1159/000058331>
- Meneilly, G. S., & Tessier, D. M. (2016). Diabetes, dementia and hypoglycemia. *Canadian Journal of Diabetes*, 40(1), 73-76. <https://doi.org/10.1016/j.jcjd.2015.09.006>
- Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, 15(10), 483-506. <https://doi.org/10.1016/j.tics.2011.08.003>
- Menon, V. (2013). Developmental pathways to functional brain networks: Emerging principles. *Trends in Cognitive Sciences*, 17(12), 627-640. <https://doi.org/10.1016/j.tics.2013.09.015>
- Menzies, F. M., Fleming, A., Caricasole, A., Bento, C. F., Andrews, S. P., Ashkenazi, A., Füllgrabe, J., Jackson, A., Jimenez Sanchez, M., Karabiyik, C., Licitra, F., Lopez Ramirez, A., Pavel, M., Puri, C., Renna, M., Ricketts, T., Schlotawa, L., Vicinanza, M., Won, H., Zhu, Y., ... Rubinsztein, D. C. (2017). Autophagy and Neurodegeneration: Pathogenic Mechanisms and Therapeutic Opportunities. *Neuron*, 93(5), 1015-1034. <https://doi.org/10.1016/j.neuron.2017.01.022>
- Meredith, J. E., Jr, Sankaranarayanan, S., Guss, V., Lanzetti, A. J., Berisha, F., Neely, R. J., Slemmon, J. R., Portelius, E., Zetterberg, H., Blennow, K., Soares, H., Ahljiyanian, M., & Albright, C. F. (2013). Characterization of novel CSF Tau and ptau biomarkers for Alzheimer's disease. *PloS One*, 8(10), e76523. <https://doi.org/10.1371/journal.pone.0076523>

- Mergenthaler, P., Lindauer, U., Dienel, G. A., & Meisel, A. (2013). Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends in Neurosciences*, *36*(10), 587-597. <https://doi.org/10.1016/j.tins.2013.07.001>
- Mesulam, M., Wicklund, A., Johnson, N., Rogalski, E., Léger, G. C., Rademaker, A., Weintraub, S., & Bigio, E. H. (2008). Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. *Annals of Neurology*, *63*(6), 709-719. <https://doi.org/10.1002/ana.21388>
- Mesulam, M. (1986). Alzheimer plaques and cortical cholinergic innervation. *Neuroscience*, *17*(1), 275-276. [https://doi.org/10.1016/0306-4522\(86\)90242-3](https://doi.org/10.1016/0306-4522(86)90242-3)
- Mesulam, M. M., Mufson, E. J., Levey, A. I., & Wainer, B. H. (1983). Cholinergic innervation of cortex by the basal forebrain: Cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *The Journal of Comparative Neurology*, *214*(2), 170-197. <https://doi.org/10.1002/cne.902140206>
- Mesulam, M. M. (2001). Primary progressive aphasia. *Annals of Neurology*, *49*(4), 425-432. <https://doi.org/10.1002/ana.91>
- Mevel, K., Chetelat, G., Eustache, F., & Desgranges, B. (2011). The default mode network in healthy aging and Alzheimer's disease. *International Journal of Alzheimer's Disease*, *2011*, 535816. <https://doi.org/10.4061/2011/535816>
- Meyer, J. S., Rogers, R. L., & Mortel, K. F. (1985). Prospective analysis of long term control of mild hypertension on cerebral blood flow. *Stroke*, *16*(6), 985-990. <https://doi.org/10.1161/01.STR.16.6.985>
- Mickes, L., Wixted, J. T., Fennema-Notestine, C., Galasko, D., Bondi, M. W., Thal, L. J., & Salmon, D. P. (2007). Progressive impairment on neuropsychological tasks in a longitudinal study of preclinical Alzheimer's disease. *Neuropsychology*, *21*(6), 696. <https://doi.org/10.1037/0894-4105.21.6.696>
- Mielke, M. M., Zandi, P., Sjögren, M., Gustafson, D., Östling, S., Steen, B., & Skoog, I. (2005). High total cholesterol levels in late life associated with a reduced risk of dementia. *Neurology*, *64*(10), 1689-1695.
- Miller, A. W., Tulbert, C., Puskar, M., & Busija, D. W. (2002). Enhanced endothelin activity prevents vasodilation to insulin in insulin resistance. *Hypertension*, *40*(1), 78-82. <https://doi.org/10.1161/01.HYP.0000022806.87281.62>
- Miller, C. D., Phillips, L. S., Ziemer, D. C., Gallina, D. L., Cook, C. B., & El-Kebbi, I. M. (2001). Hypoglycemia in patients with type 2 diabetes mellitus. *Archives of Internal Medicine*, *161*(13), 1653-1659. <https://doi.org/10.1001/archinte.161.13.1653>
- Milne, N., Bruce, D., Starkstein, S., Nelson, M., Davis, W., Pierson, R., & Bucks, R. (2015). Hippocampal asymmetry is associated with cognitive decline in Type 2 diabetes. In Conference Abstract: *XII International Conference on Cognitive Neuroscience (ICON-XII)*, (Vol. 292). <https://doi.org/10.3389/conf.fnhum>
- Minet, A. D., & Gaster, M. (2010). ATP synthesis is impaired in isolated mitochondria from myotubes established from type 2 diabetic subjects. *Biochemical and Biophysical Research Communications*, *402*(1), 70-74. <https://doi.org/10.1016/j.bbrc.2010.09.115>
- Minokoshi, Y., Haque, M. S., & Shimazu, T. (1999). Microinjection of leptin into the ventromedial hypothalamus increases glucose uptake in peripheral tissues in rats. *Diabetes*, *48*(2), 287-291. <https://doi.org/10.2337/diabetes.48.2.287>
- Minuz, P., Patrignani, P., Gaino, S., Degan, M., Menapace, L., Tommasoli, R., Seta, F., Capone, M. L., Tacconelli, S., Palatresi, S., Bencini, C., Del Vecchio, C., Mansueto, G., Arosio, E., Santonastaso, C. L., Lechi, A., Morganti, A., & Patrono, C. (2002). Increased oxidative stress and platelet activation in patients with hypertension and renovascular disease. *Circulation*, *106*(22), 2800-2805. <https://doi.org/10.1161/01.CIR.0000039528.49161.E9>

- Mishima, E., Funayama, Y., Suzuki, T., Mishima, F., Nitta, F., Toyohara, T., Kikuchi, K., Kunikata, H., Hashimoto, J., Miyazaki, M., Harigae, H., Nakazawa, T., Ito, S., & Abe, T. (2021). Concurrent analogous organ damage in the brain, eyes, and kidneys in malignant hypertension: Reversible encephalopathy, serous retinal detachment, and proteinuria. *Hypertension Research*, *44*(1), 88–97. <https://doi.org/10.1038/s41440-020-0521-2>
- Misra, A., Arora, N., Mondal, S., Pandey, R. M., Jaikhan, B., Peshin, S., Chaudhary, D., Saluja, T., Singh, P., Chandna, S., Luthra, K., & Vikram, N. K. (2001). Relation between plasma leptin and anthropometric and metabolic covariates in lean and obese diabetic and hyperlipidaemic Asian Northern Indian subjects. *Diabetes, Nutrition & Metabolism*, *14*(1), 18–26.
- Mitchell, G. F., van Buchem, M. A., Sigurdsson, S., Gotal, J. D., Jonsdottir, M. K., Kjartansson, Ó., Garcia, M., Aspelund, T., Harris, T. B., Gudnason, V., & Launer, L. J. (2011). Arterial stiffness, pressure and flow pulsatility and brain structure and function: The Age, Gene/Environment Susceptibility–Reykjavik study. *Brain*, *134*(11), 3398–3407. <https://doi.org/10.1093/brain/awr253>
- Mitchell, T. W., Mufson, E. J., Schneider, J. A., Cochran, E. J., Nissanov, J., Han, L. Y., Bienias, J. L., Lee, V. M., Trojanowski, J. Q., Bennett, D. A., & Arnold, S. E. (2002). Parahippocampal tau pathology in healthy aging, mild cognitive impairment, and early Alzheimer's disease. *Annals of Neurology*, *51*(2), 182–189. <https://doi.org/10.1002/ana.10086>
- Miyashita, Y., Koide, N., Ohtsuka, M., Ozaki, H., Itoh, Y., Oyama, T., Uetake, T., Ariga, K., & Shirai, K. (2004). Beneficial effect of low carbohydrate in low calorie diets on visceral fat reduction in type 2 diabetic patients with obesity. *Diabetes Research and Clinical Practice*, *65*(3), 235–241. <https://doi.org/10.1016/j.diabres.2004.01.008>
- Miyata, T., Wada, Y., Cai, Z., Iida, Y., Horie, K., Yasuda, Y., Maeda, K., Kurokawa, K., & De Zeeuw, C. V. Y. (1997). Implication of an increased oxidative stress in the formation of advanced glycation end products in patients with end-stage renal failure. *Kidney International*, *51*(4), 1170–1181. <https://doi.org/10.1038/ki.1997.160>
- Miyazaki, H., Matsuoka, H., Cooke, J. P., Usui, M., Ueda, S., Okuda, S., & Imaizumi, T. (1999). Endogenous nitric oxide synthase inhibitor: A novel marker of atherosclerosis. *Circulation*, *99*(9), 1141–1146. <https://doi.org/10.1161/01.CIR.99.9.1141>
- Mohamed-Ali, V., Goodrick, S., Rawesh, A., Katz, D., Miles, J., Yudkin, J., Klein, S., & Coppack, S. W. (1997). Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor- α , in vivo. *The Journal of Clinical Endocrinology & Metabolism*, *82*(12), 4196–4200. <https://doi.org/10.1210/jcem.82.12.4450>
- Mohan, A., & Vanneste, S. (2017). Adaptive and maladaptive neural compensatory consequences of sensory deprivation—From a phantom percept perspective. *Progress in Neurobiology*, *153*, 1–17. <https://doi.org/10.1016/j.pneurobio.2017.03.010>
- Mole, J. P., Fasano, F., Evans, J., Sims, R., Hamilton, D. A., Kidd, E., & Metzler-Baddeley, C. (2020). Genetic risk of dementia modifies obesity effects on white matter myelin in cognitively healthy adults. *Neurobiology of Aging*, *94*, 298–310. <https://doi.org/10.1016/j.neurobiolaging.2020.06.014>
- Molinuevo, J. L., Gómez-Anson, B., Monte, G. C., Bosch, B., Sánchez-Valle, R., & Rami, L. (2011). Neuropsychological profile of prodromal Alzheimer's disease (Prd-AD) and their radiological correlates. *Archives of Gerontology and Geriatrics*, *52*(2), 190–196. <https://doi.org/10.1016/j.archger.2010.03.016>
- Momjian-Mayor, I., & Baron, J. C. (2005). The pathophysiology of watershed infarction in internal carotid artery disease: Review of cerebral perfusion studies. *Stroke*, *36*(3), 567–577. <https://doi.org/10.1161/01.STR.0000155727.82242.e1>
- Monnier, L., Mas, E., Ginet, C., Michel, F., Villon, L., Cristol, J. P., & Colette, C. (2006). Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic

- hyperglycemia in patients with type 2 diabetes. *JAMA*, 295(14), 1681-1687.
<https://doi.org/10.1001/jama.295.14.1681>
- Moody, D., Bell, M., & Challa, V. (1990). Features of the cerebral vascular pattern that predict vulnerability to perfusion or oxygenation deficiency: An anatomic study. *American Journal of Neuroradiology*, 11(3), 431-439.
- Moon, Y., Han, S. H., & Moon, W. J. (2016). Patterns of brain iron accumulation in vascular dementia and Alzheimer's dementia using quantitative susceptibility mapping imaging. *Journal of Alzheimer's Disease*, 51(3), 737-745.
- Moore, T. J., Conlin, P. R., Ard, J., Svetkey, L. P., & DASH Collaborative Research Group. (2001). DASH (Dietary Approaches to Stop Hypertension) diet is effective treatment for stage 1 isolated systolic hypertension. *Hypertension*, 38(2), 155-158.
<https://doi.org/10.1161/01.HYP.38.2.155>
- Moran, M., Mufson, E., & Gomez-Ramos, P. (1993). Colocalization of cholinesterases with β amyloid protein in aged and Alzheimer's brains. *Acta Neuropathologica*, 85(4), 362-369.
<https://doi.org/10.1007/BF00334445>
- Morbelli, S., Drzezga, A., Perneczky, R., Frisoni, G. B., Caroli, A., van Berckel, B. N., Ossenkoppele, R., Guedj, E., Didic, M., Brugnolo, A., Sambuceti, G., Pagani, M., Salmon, E., & Nobili, F. (2012). Resting metabolic connectivity in prodromal Alzheimer's disease. A European Alzheimer Disease Consortium (EADC) project. *Neurobiology of Aging*, 33(11), 2533–2550. <https://doi.org/10.1016/j.neurobiolaging.2012.01.005>
- Morbiducci, U., Kok, A. M., Kwak, B. R., Stone, P. H., Steinman, D. A., & Wentzel, J. J. (2016). Atherosclerosis at arterial bifurcations: Evidence for the role of haemodynamics and geometry. *Thrombosis and Haemostasis*, 115(3), 484–492. <https://doi.org/10.1160/TH15-07-0597>
- Moreno-Gonzalez, I., Edwards III, G., Salvadores, N., Shahnawaz, M., Diaz-Espinoza, R., & Soto, C. (2017). Molecular interaction between type 2 diabetes and Alzheimer's disease through cross-seeding of protein misfolding. *Molecular Psychiatry*, 22(9), 1327-1334.
<https://doi.org/10.1038/mp.2016.230>
- Moreno-Gonzalez, I., Estrada, L. D., Sanchez-Mejias, E., & Soto, C. (2013). Smoking exacerbates amyloid pathology in a mouse model of Alzheimer's disease. *Nature Communications*, 4(1), 1-10. <https://doi.org/10.1038/ncomms2494>
- Mori, S., Wakana, S., Van Zijl, P. C., & Nagae-Poetscher, L. (2005). *MRI atlas of human white matter*: Elsevier Science.
- Mori, S., & Zhang, J. (2006). Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron*, 51(5), 527-539. <https://doi.org/10.1016/j.neuron.2006.08.012>
- Morisky, D. E., Levine, D. M., Green, L. W., Shapiro, S., Russell, R. P., & Smith, C. R. (1983). Five-year blood pressure control and mortality following health education for hypertensive patients. *American Journal of Public Health*, 73(2), 153-162.
- Morita-Tsuzuki, Y., Bouskela, E., & Hardebo, J. (1993). Effects of nitric oxide synthesis blockade and angiotensin II on blood flow and spontaneous vasomotion in the rat cerebral microcirculation. *Acta Physiologica Scandinavica*, 148(4), 449-454.
<https://doi.org/10.1111/j.1748-1716.1993.tb09581.x>
- Moroz, N., Tong, M., Longato, L., Xu, H., & de la Monte, S. M. (2008). Limited Alzheimer-type neurodegeneration in experimental obesity and type 2 diabetes mellitus. *Journal of Alzheimer's Disease*, 15(1), 29-44. <https://doi.org/10.3233/JAD-2008-15103>
- Morris, M. C., Tangney, C. C., Wang, Y., Sacks, F. M., Bennett, D. A., Aggarwal, N. T. (2015). MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimer's and Dementia*, 11(9), 1007-1014. <https://doi.org/10.1016/j.jalz.2014.11.009>
- Morton, G. J., Gelling, R. W., Niswender, K. D., Morrison, C. D., Rhodes, C. J., & Schwartz, M. W. (2005). Leptin regulates insulin sensitivity via phosphatidylinositol-3-OH kinase signaling in

- mediobasal hypothalamic neurons. *Cell Metabolism*, 2(6), 411-420.
<https://doi.org/10.1016/j.cmet.2005.10.009>
- Moser, V. A., & Pike, C. J. (2017). Obesity Accelerates Alzheimer-Related Pathology in APOE4 but not APOE3 Mice. *eNeuro*, 4(3), ENEURO.0077-17.2017.
<https://doi.org/10.1523/ENEURO.0077-17.2017>
- Moulton, C. D., Costafreda, S. G., Horton, P., Ismail, K., & Fu, C. H. (2015). Meta-analyses of structural regional cerebral effects in type 1 and type 2 diabetes. *Brain Imaging and Behavior*, 9(4), 651-662. <https://doi.org/10.1007/s11682-014-9348-2>
- Moustafa, R. R., Izquierdo-Garcia, D., Jones, P. S., Graves, M. J., Fryer, T. D., Gillard, J. H., Warburton, E. A., & Baron, J. C. (2010). Watershed infarcts in transient ischemic attack/minor stroke with $\geq 50\%$ carotid stenosis: Hemodynamic or embolic? *Stroke*, 41(7), 1410-1416. <https://doi.org/10.1161/STROKEAHA.110.580415>
- Mrak, R. (2009). Alzheimer-type neuropathological changes in morbidly obese elderly individuals. *Clinical Neuropathology*, 28(1), 40-45. <https://doi.org/10.5414/npp28040>
- Mudau, M., Genis, A., Lochner, A., & Strijdom, H. (2012). Endothelial dysfunction: the early predictor of atherosclerosis. *Cardiovascular Journal of Africa*, 23(4), 222.
<https://doi.org/10.5830/CVJA-2011-068>
- Mueller, K., Anwander, A., Möller, H. E., Horstmann, A., Lepsien, J., Busse, F., Mohammadi, S., Schroeter, M. L., Stumvoll, M., Villringer, A., & Pleger, B. (2011). Sex-dependent influences of obesity on cerebral white matter investigated by diffusion-tensor imaging. *PLoS One*, 6(4), e18544. <https://doi.org/10.1371/journal.pone.0018544>
- Mueller, K., Sacher, J., Arelin, K., Holiga, Š., Kratzsch, J., Villringer, A., & Schroeter, M. L. (2012). Overweight and obesity are associated with neuronal injury in the human cerebellum and hippocampus in young adults: A combined MRI, serum marker and gene expression study. *Translational Psychiatry*, 2(12), e200-e200. <https://doi.org/10.1038/tp.2012.121>
- Mugikura, S., Kikuchi, H., Fujimura, M., Mori, E., Takahashi, S., & Takase, K. (2018). Subcallosal and Heubner artery infarcts following surgical repair of an anterior communicating artery aneurysm: A causal relationship with postoperative amnesia and long-term outcome. *Japanese Journal of Radiology*, 36(2), 81-89. <https://doi.org/10.1007/s11604-017-0703-2>
- Muller, M., van der Graaf, Y., Visseren, F. L., Mali, W. P. T. M., Geerlings, M. I., & The SMART Study Group. (2012). Hypertension and longitudinal changes in cerebral blood flow: The SMART-MR study. *Annals of Neurology*, 71(6), 825-833. <https://doi.org/10.1002/ana.23554>
- Mullins, R. J., Mustapic, M., Goetzl, E. J., & Kapogiannis, D. (2017). Exosomal biomarkers of brain insulin resistance associated with regional atrophy in Alzheimer's disease. *Human Brain Mapping*, 38(4), 1933-1940. <https://doi.org/10.1002/hbm.23494>
- Muniyappa, R., & Quon, M. J. (2007). Insulin action and insulin resistance in vascular endothelium. *Current Opinion in Clinical Nutrition & Metabolic Care*, 10(4), 523-530.
<https://doi.org/10.1097/MCO.0b013e32819f8ecd>
- Muñoz Maniega, S., Chappell, F. M., Valdés Hernández, M. C., Armitage, P. A., Makin, S. D., Heye, A. K., Thrippleton, M. J., Sakka, E., Shuler, K., Dennis, M. S., & Wardlaw, J. M. (2017). Integrity of normal-appearing white matter: Influence of age, visible lesion burden and hypertension in patients with small-vessel disease. *Journal of Cerebral Blood Flow & Metabolism*, 37(2), 644-656. <https://doi.org/10.1177/0271678X16635657>
- Murphy, C. (2019). Olfactory and other sensory impairments in Alzheimer disease. *Nature Reviews Neurology*, 15(1), 11-24. <https://doi.org/10.1038/s41582-018-0097-5>
- Murphy, C., Jernigan, T. L., & Fennema-Notestine, C. (2003). Left hippocampal volume loss in Alzheimer's disease is reflected in performance on odor identification: A structural MRI study. *Journal of the International Neuropsychological Society*, 9(3), 459-471.
<https://doi.org/10.1017/s1355617703930116>

- Murray, M. E., Graff-Radford, N. R., Ross, O. A., Petersen, R. C., Duara, R., & Dickson, D. W. (2011). Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: A retrospective study. *The Lancet Neurology*, *10*(9), 785-796. [https://doi.org/10.1016/S1474-4422\(11\)70156-9](https://doi.org/10.1016/S1474-4422(11)70156-9)
- Murray, A. D., Staff, R. T., McNeil, C. J., Salarirad, S., Starr, J. M., Deary, I. J., & Whalley, L. J. (2012). Brain lesions, hypertension and cognitive ageing in the 1921 and 1936 Aberdeen birth cohorts. *Age*, *34*(2), 451-459. <https://doi.org/10.1007/s11357-011-9233-5>
- Musen, G., Jacobson, A. M., Bolo, N. R., Simonson, D. C., Shenton, M. E., McCartney, R. L., Flores, V. L., & Hoogenboom, W. S. (2012). Resting-state brain functional connectivity is altered in type 2 diabetes. *Diabetes*, *61*(9), 2375-2379. <https://doi.org/10.2337/db11-1669>
- Muxfeldt, E. S., Fiszman, R., Castelpoggi, C. H., & Salles, G. F. (2008). Ambulatory arterial stiffness index or pulse pressure: Which correlates better with arterial stiffness in resistant hypertension? *Hypertension Research*, *31*(4), 607-613. <https://doi.org/10.1291/hypres.31.607>
- Nah, H. W., Kang, D. W., Kwon, S. U., & Kim, J. S. (2010). Diversity of single small subcortical infarctions according to infarct location and parent artery disease: Analysis of indicators for small vessel disease and atherosclerosis. *Stroke*, *41*(12), 2822-2827. <https://doi.org/10.1161/STROKEAHA.110.599464>
- Naimi, T. S., Brown, D. W., Brewer, R. D., Giles, W. H., Mensah, G., Serdula, M. K., Mokdad, A. H., Hungerford, D. W., Lando, J., Naimi, S., & Stroup, D. F. (2005). Cardiovascular risk factors and confounders among nondrinking and moderate-drinking U.S. adults. *American Journal of Preventive Medicine*, *28*(4), 369-373. <https://doi.org/10.1016/j.amepre.2005.01.011>
- Nakajima, K., & Tanaka, A. (2018). Atherogenic postprandial remnant lipoproteins; VLDL remnants as a causal factor in atherosclerosis. *Clinica Chimica Acta*, *478*, 200-215. <https://doi.org/10.1016/j.cca.2017.12.039>
- Nam, K. W., Kwon, H., Kwon, H. M., Park, J. H., Jeong, H. Y., Kim, S. H., Jeong, S. M., Kim, H. J., & Hwang, S. S. (2019). Abdominal fatness and cerebral white matter hyperintensity. *Journal of the Neurological Sciences*, *404*, 52-57. <https://doi.org/10.1016/j.jns.2019.07.016>
- Nanchahal, K., Ashton, W. D., & Wood, D. A. (2000). Alcohol consumption, metabolic cardiovascular risk factors and hypertension in women. *International Journal of Epidemiology*, *29*(1), 57-64. <https://doi.org/10.1093/ije/29.1.57>
- Nation, D. A., Preis, S. R., Beiser, A., Bangen, K. J., Delano-Wood, L., Lamar, M., Libon, D. J., Seshadri, S., Wolf, P. A., & Au, R. (2016). Pulse Pressure Is Associated With Early Brain Atrophy and Cognitive Decline: Modifying Effects of APOE-ε4. *Alzheimer Disease and Associated Disorders*, *30*(3), 210-215. <https://doi.org/10.1097/WAD.0000000000000127>
- National Institute for Health and Care Excellence (NICE) (2016). Obesity: Identification, assessment and management of overweight and obesity in children, young people and adults (CG189). 2016.
- Nazarian, A., Arbeev, K. G., Yashkin, A. P., & Kulminski, A. M. (2019). Genetic heterogeneity of Alzheimer's disease in subjects with and without hypertension. *GeroScience*, *41*(2), 137-154. <https://doi.org/10.1007/s11357-019-00071-5>
- Negrean, M., Stirban, A., Stratmann, B., Gawlowski, T., Horstmann, T., Götting, C., Kleesiek, K., Mueller-Roesel, M., Koschinsky, T., Uribarri, J., Vlassara, H., & Tschoepe, D. (2007). Effects of low- and high-advanced glycation endproduct meals on macro- and microvascular endothelial function and oxidative stress in patients with type 2 diabetes mellitus. *The American Journal of Clinical Nutrition*, *85*(5), 1236-1243. <https://doi.org/10.1093/ajcn/85.5.1236>
- Nelson, A. R., Sweeney, M. D., Sagare, A. P., & Zlokovic, B. V. (2016). Neurovascular dysfunction and neurodegeneration in dementia and Alzheimer's disease. *Biochimica et Biophysica Acta*

- (BBA) - *Molecular Basis of Disease*, 1862(5), 887-900.
<https://doi.org/10.1016/j.bbadis.2015.12.016>
- Nelson, P. T., Smith, C. D., Abner, E. A., Schmitt, F. A., Scheff, S. W., Davis, G. J., Keller, J. N., Jicha, G. A., Davis, D., Wang-Xia, W., Hartman, A., Katz, D. G., & Markesbery, W. R. (2009). Human cerebral neuropathology of Type 2 diabetes mellitus. *Biochimica et Biophysica Acta*, 1792(5), 454–469. <https://doi.org/10.1016/j.bbadis.2008.08.005>
- Neth, B. J., & Craft, S. (2017). Insulin resistance and Alzheimer's disease: Bioenergetic linkages. *Frontiers in Aging Neuroscience*, 9, 345. <https://doi.org/10.3389/fnagi.2017.00345>
- Netter, F. H. (2014). *Atlas of Human Anatomy, Professional Edition E-Book: including NetterReference. com Access with Full Downloadable Image Bank*: Elsevier Health Sciences.
- Neufer, P. D., Bamman, M. M., Muoio, D. M., Bouchard, C., Cooper, D. M., Goodpaster, B. H., Booth, F. W., Kohrt, W. M., Gerszten, R. E., Mattson, M. P., Hepple, R. T., Kraus, W. E., Reid, M. B., Bodine, S. C., Jakicic, J. M., Fleg, J. L., Williams, J. P., Joseph, L., Evans, M., Maruvada, P., ... Laughlin, M. R. (2015). Understanding the Cellular and Molecular Mechanisms of Physical Activity-Induced Health Benefits. *Cell Metabolism*, 22(1), 4–11. <https://doi.org/10.1016/j.cmet.2015.05.011>
- Neuenschwander, M., Ballon, A., Weber, K. S., Norat, T., Aune, D., Schwingshackl, L., & Schlesinger, S. (2019). Role of diet in type 2 diabetes incidence: Umbrella review of meta-analyses of prospective observational studies. *BMJ (Clinical research ed.)*, 366, 12368. <https://doi.org/10.1136/bmj.12368>
- Ng, R. C., & Chan, K. H. (2017). Potential Neuroprotective Effects of Adiponectin in Alzheimer's Disease. *International Journal of Molecular Sciences*, 18(3), 592. <https://doi.org/10.3390/ijms18030592>
- Ng, R. C., Cheng, O. Y., Jian, M., Kwan, J. S., Ho, P. W., Cheng, K. K., Yeung, P. K., Zhou, L. L., Hoo, R. L., Chung, S. K., Xu, A., Lam, K. S., & Chan, K. H. (2016). Chronic adiponectin deficiency leads to Alzheimer's disease-like cognitive impairments and pathologies through AMPK inactivation and cerebral insulin resistance in aged mice. *Molecular Neurodegeneration*, 11(1), 71. <https://doi.org/10.1186/s13024-016-0136-x>
- Ngandu, T., Lehtisalo, J., Solomon, A., Levälähti, E., Ahtiluoto, S., Antikainen, R., Bäckman, L., Hänninen, T., Jula, A., Laatikainen, T., Lindström, J., Mangialasche, F., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T., Tuomilehto, J., Soininen, H., & Kivipelto, M. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *The Lancet*, 385(9984), 2255-2263. [https://doi.org/10.1016/S0140-6736\(15\)60461-5](https://doi.org/10.1016/S0140-6736(15)60461-5)
- Nguyen, N. T., Magno, C. P., Lane, K. T., Hinojosa, M. W., & Lane, J. S. (2008). Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: Findings from the National Health and Nutrition Examination Survey, 1999 to 2004. *Journal of the American College of Surgeons*, 207(6), 928-934. <https://doi.org/10.1016/j.jamcollsurg.2008.08.022>
- Nicholson, A. M., & Ferreira, A. (2009). Increased membrane cholesterol might render mature hippocampal neurons more susceptible to β -amyloid-induced calpain activation and tau toxicity. *Journal of Neuroscience*, 29(14), 4640-4651. <https://doi.org/10.1523/JNEUROSCI.0862-09.2009>
- Nicolas, S., Cazareth, J., Zarif, H., Guyon, A., Heurteaux, C., Chabry, J., & Petit-Paitel, A. (2017). Globular adiponectin limits microglia pro-inflammatory phenotype through an AdipoR1/NF- κ B signaling pathway. *Frontiers in Cellular Neuroscience*, 11, 352. <https://doi.org/10.3389/fncel.2017.00352>
- Niedowicz, D. M., Reeves, V. L., Platt, T. L., Kohler, K., Beckett, T. L., Powell, D. K., Lee, T. L., Sexton, T. R., Song, E. S., Brewer, L. D., Latimer, C. S., Kraner, S. D., Larson, K. L., Ozcan,

- S., Norris, C. M., Hersh, L. B., Porter, N. M., Wilcock, D. M., & Murphy, M. P. (2014). Obesity and diabetes cause cognitive dysfunction in the absence of accelerated β -amyloid deposition in a novel murine model of mixed or vascular dementia. *Acta Neuropathologica Communications*, 2, 64. <https://doi.org/10.1186/2051-5960-2-64>
- Niedowicz, D. M., Studzinski, C. M., Weidner, A. M., Platt, T. L., Kingry, K. N., Beckett, T. L., Bruce-Keller, A. J., Keller, J. N., & Murphy, M. P. (2013). Leptin regulates amyloid β production via the γ -secretase complex. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1832(3), 439-444. <https://doi.org/10.1016/j.bbadis.2012.12.009>
- Nielsen, J. K., Djurhuus, C. B., Gravholt, C. H., Carus, A. C., Granild-Jensen, J., Orskov, H., & Christiansen, J. S. (2005). Continuous glucose monitoring in interstitial subcutaneous adipose tissue and skeletal muscle reflects excursions in cerebral cortex. *Diabetes*, 54(6), 1635-1639. <https://doi.org/10.2337/diabetes.54.6.1635>
- Niyya, Y., Abumiya, T., Yamagishi, S., Takino, J., & Takeuchi, M. (2012). Advanced glycation end products increase permeability of brain microvascular endothelial cells through reactive oxygen species-induced vascular endothelial growth factor expression. *Journal of Stroke and Cerebrovascular Diseases*, 21(4), 293-298. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2010.09.002>
- Nir, T. M., Jahanshad, N., Villalon-Reina, J. E., Toga, A. W., Jack, C. R., Weiner, M. W., Thompson, P. M., & Alzheimer's Disease Neuroimaging Initiative (ADNI) (2013). Effectiveness of regional DTI measures in distinguishing Alzheimer's disease, MCI, and normal aging. *NeuroImage: Clinical*, 3, 180-195. <https://doi.org/10.1016/j.nicl.2013.07.006>
- Nobili, F., Rodriguez, G., Marenco, S., De Carli, F., Gambaro, M., Castello, C., Pontremoli, R., & Rosadini, G. (1993). Regional cerebral blood flow in chronic hypertension. A correlative study. *Stroke*, 24(8), 1148-1153. <https://doi.org/10.1161/01.STR.24.8.1148>
- Norberg, M., Stenlund, H., Lindahl, B., Andersson, C., Eriksson, J. W., & Weinehall, L. (2007). Work stress and low emotional support is associated with increased risk of future type 2 diabetes in women. *Diabetes Research and Clinical Practice*, 76(3), 368-377. <https://doi.org/10.1016/j.diabres.2006.09.002>
- Nordberg, A. (2004). PET imaging of amyloid in Alzheimer's disease. *Lancet Neurology*, 3(9), 519-527. [https://doi.org/10.1016/S1474-4422\(04\)00853-1](https://doi.org/10.1016/S1474-4422(04)00853-1)
- Nortley, R., Korte, N., Izquierdo, P., Hirunpattarasilp, C., Mishra, A., Jaunmuktane, Z., Kyrargyri, V., Pfeiffer, T., Khennouf, L., Madry, C., Gong, H., Richard-Loendt, A., Huang, W., Saito, T., Saido, T. C., Brandner, S., Sethi, H., & Attwell, D. (2019). Amyloid β oligomers constrict human capillaries in Alzheimer's disease via signaling to pericytes. *Science*, 365(6450), eaav9518. <https://doi.org/10.1126/science.aav9518>
- Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *Lancet Neurology*, 13(8), 788-794. [https://doi.org/10.1016/S1474-4422\(14\)70136-X](https://doi.org/10.1016/S1474-4422(14)70136-X)
- Notkola, I. L., Sulkava, R., Pekkanen, J., Erkinjuntti, T., Ehnholm, C., Kivinen, P., Tuomilehto, J., & Nissinen, A. (1998). Serum total cholesterol, apolipoprotein E {FC12} e4 allele, and Alzheimer's disease. *Neuroepidemiology*, 17(1), 14-20. <https://doi.org/10.1159/000026149>
- Nouwen, A., Chambers, A., Chechlacz, M., Higgs, S., Blissett, J., Barrett, T. G., & Allen, H. A. (2017). Microstructural abnormalities in white and gray matter in obese adolescents with and without type 2 diabetes. *NeuroImage: Clinical*, 16, 43-51. <https://doi.org/10.1016/j.nicl.2017.07.004>
- Novak, V., Last, D., Alsop, D. C., Abduljalil, A. M., Hu, K., Lepicovsky, L., Cavigliaro, J., & Lipsitz, L. A. (2006). Cerebral blood flow velocity and periventricular white matter hyperintensities in type 2 diabetes. *Diabetes Care*, 29(7), 1529-1534. <https://doi.org/10.2337/dc06-0261>

- Novak, V., Zhao, P., Manor, B., Sejdic, E., Alsop, D., Abduljalil, A., Roberson, P. K., Munshi, M., & Novak, P. (2011). Adhesion molecules, altered vasoreactivity, and brain atrophy in type 2 diabetes. *Diabetes care*, *34*(11), 2438-2441. <https://doi.org/10.2337/dc11-0969>
- Nowotny, K., Jung, T., Höhn, A., Weber, D., & Grune, T. (2015). Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. *Biomolecules*, *5*(1), 194-222. <https://doi.org/10.3390/biom5010194>
- Nyberg, L., & Pudas, S. (2019). Successful Memory Aging. *Annual Review of Psychology*, *70*, 219–243. <https://doi.org/10.1146/annurev-psych-010418-103052>
- O'Brien, J. T., & Markus, H. S. (2014). Vascular risk factors and Alzheimer's disease. *BMC Medicine*, *12*, 218. <https://doi.org/10.1186/s12916-014-0218-y>
- O'Neill, S., & O'driscoll, L. (2015). Metabolic syndrome: A closer look at the growing epidemic and its associated pathologies. *Obesity Reviews*, *16*(1), 1-12. <https://doi.org/10.1111/obr.12229>
- O'Sullivan, M., Jones, D. K., Summers, P., Morris, R., Williams, S., & Markus, H. (2001). Evidence for cortical “disconnection” as a mechanism of age-related cognitive decline. *Neurology*, *57*(4), 632-638. <https://doi.org/10.1212/WNL.57.4.632>
- Oda, H., Yamamoto, Y., & Maeda, K. (2009). The neuropsychological profile in dementia with Lewy bodies and Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *24*(2), 125-131. <https://doi.org/10.1002/gps.2078>
- Ogawa, Y., Kaneko, Y., Sato, T., Shimizu, S., Kanetaka, H., & Hanyu, H. (2018). Sarcopenia and muscle functions at various stages of Alzheimer disease. *Frontiers in Neurology*, *9*, 710. <https://doi.org/10.3389/fneur.2018.00710>
- Ogino, E., Manly, J. J., Schupf, N., Mayeux, R., & Gu, Y. (2019). Current and past leisure time physical activity in relation to risk of Alzheimer's disease in older adults. *Alzheimer's and Dementia*, *15*(12), 1603-1611. <https://doi.org/10.1016/j.jalz.2019.07.013>
- Ohayon, J., Gharib, A. M., Garcia, A., Heroux, J., Yazdani, S. K., Malvè, M., Tracqui, P., Martinez, M. A., Doblare, M., Finet, G., & Pettigrew, R. I. (2011). Is arterial wall-strain stiffening an additional process responsible for atherosclerosis in coronary bifurcations?: an in vivo study based on dynamic CT and MRI. *American journal of physiology: Heart and Circulatory Physiology*, *301*(3), H1097–H1106. <https://doi.org/10.1152/ajpheart.01120.2010>
- Okamura, N., Harada, R., Furumoto, S., Arai, H., Yanai, K., & Kudo, Y. (2014). Tau PET imaging in Alzheimer's disease. *Current neurology and neuroscience reports*, *14*(11), 500.
- Okosun, I. S., Chandra, K. D., Choi, S., Christman, J., Dever, G. A., & Prewitt, T. E. (2001). Hypertension and type 2 diabetes comorbidity in adults in the United States: risk of overall and regional adiposity. *Obesity research*, *9*(1), 1-9. <https://doi.org/10.1038/oby.2001.1>
- Ondrejcek, T., Klyubin, I., Hu, N. W., Barry, A. E., Cullen, W. K., & Rowan, M. J. (2010). Alzheimer's disease amyloid beta-protein and synaptic function. *Neuromolecular Medicine*, *12*(1), 13–26. <https://doi.org/10.1007/s12017-009-8091-0>
- Oomura, Y., Hori, N., Shiraishi, T., Fukunaga, K., Takeda, H., Tsuji, M., Matsumiya, T., Ishibashi, M., Aou, S., Li, X. L., Kohno, D., Uramura, K., Sougawa, H., Yada, T., Wayner, M. J., & Sasaki, K. (2006). Leptin facilitates learning and memory performance and enhances hippocampal CA1 long-term potentiation and CaMK II phosphorylation in rats. *Peptides*, *27*(11), 2738–2749. <https://doi.org/10.1016/j.peptides.2006.07.001>
- Ossenkoppele, R., Schonhaut, D. R., Schöll, M., Lockhart, S. N., Ayakta, N., Baker, S. L., O'Neil, J. P., Janabi, M., Lazaris, A., Cantwell, A., Vogel, J., Santos, M., Miller, Z. A., Bettcher, B. M., Vessel, K. A., Kramer, J. H., Gorno-Tempini, M. L., Miller, B. L., Jagust, W. J., & Rabinovici, G. D. (2016). Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain*, *139*(Pt 5), 1551-1567. <https://doi.org/10.1093/brain/aww027>
- Osuka, K., Watanabe, Y., Yasuda, M., & Takayasu, M. (2012). Adiponectin activates endothelial nitric oxide synthase through AMPK signaling after subarachnoid hemorrhage. *Neuroscience Letters*, *514*(1), 2-5. <https://doi.org/10.1016/j.neulet.2011.12.041>

- Ott, A., Breteler, M. M., Van Harskamp, F., Claus, J. J., Van Der Cammen, T. J., Grobbee, D. E., & Hofman, A. (1995). Prevalence of Alzheimer's disease and vascular dementia: Association with education. The Rotterdam study. *BMJ*, *310*(6985), 970-973. <https://doi.org/10.1136/bmj.310.6985.970>
- Ott, A., Slioter, A., Hofman, A., van Harskamp, F., Witteman, J., Van Broeckhoven, C., van Duijn, C. M., & Breteler, M. M. B. (1998). Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: The Rotterdam Study. *The Lancet*, *351*(9119), 1840-1843. [https://doi.org/10.1016/S0140-6736\(97\)07541-7](https://doi.org/10.1016/S0140-6736(97)07541-7)
- Ott, A., Stolk, R., Van Harskamp, F., Pols, H., Hofman, A., & Breteler, M. J. N. (1999). Diabetes mellitus and the risk of dementia: The Rotterdam Study. *53*(9), 1937-1937.
- Ott, M., Gogvadze, V., Orrenius, S., & Zhivotovsky, B. (2007). Mitochondria, oxidative stress and cell death. *Apoptosis*, *12*(5), 913-922. <https://doi.org/10.1007/s10495-007-0756-2>
- Owen-Smith, A. A., Smith, D. H., Rand, C. S., Tom, J. O., Laws, R., Waterbury, A., Williams, A., & Vollmer, W. M. (2016). Difference in effectiveness of medication adherence intervention by health literacy level. *The Permanente Journal*, *20*(3), 15-200. <https://doi.org/10.7812/TPP/15-200>
- Padilha, H. G., Crispim, C. A., Zimberg, I. Z., De-Souza, D. A., Waterhouse, J., Tufik, S., & de-Mello, M. T. (2011). A link between sleep loss, glucose metabolism and adipokines. *Brazilian Journal of Medical and Biological Research*, *44*(10), 992-999. <https://doi.org/10.1590/s0100-879x2011007500113>
- Pan, J., Stein, D. T., Telang, F., Lee, J., Shen, J., Brown, P., Cline, G., Mason, G. F., Shulman, G. I., Rothman, D. L., & Hetherington, H. P. (2000). Spectroscopic imaging of glutamate C4 turnover in human brain. *Magnetic Resonance in Medicine*, *44*(5), 673-679. [https://doi.org/10.1002/1522-2594\(200011\)44:5<673::AID-MRM3>3.0.CO;2-L](https://doi.org/10.1002/1522-2594(200011)44:5<673::AID-MRM3>3.0.CO;2-L)
- Panagiotakos, D. B., Pitsavos, C. E., Chrysohoou, C. A., Skoumas, J., Toutouza, M., Belegirinos, D., Toutouzas, P. K., & Stefanadis, C. (2004). The association between educational status and risk factors related to cardiovascular disease in healthy individuals: The ATTICA study. *Annals of Epidemiology*, *14*(3), 188-194. [https://doi.org/10.1016/S1047-2797\(03\)00117-0](https://doi.org/10.1016/S1047-2797(03)00117-0)
- Pancani, T., Anderson, K. L., Brewer, L. D., Kadish, I., DeMoll, C., Landfield, P. W., Blalock, E. M., Porter, N. M., & Thibault, O. (2013). Effect of high-fat diet on metabolic indices, cognition, and neuronal physiology in aging F344 rats. *Neurobiology of Aging*, *34*(8), 1977-1987. <https://doi.org/10.1016/j.neurobiolaging.2013.02.019>
- Panegyres, P. K., & Chen, H. Y. (2013). Differences between early and late onset Alzheimer's disease. *American Journal of Neurodegenerative Disease*, *2*(4), 300.
- Paneni, F., Costantino, S., & Cosentino, F. (2014). Molecular mechanisms of vascular dysfunction and cardiovascular biomarkers in type 2 diabetes. *Cardiovascular Diagnosis and Therapy*, *4*(4), 324. <https://doi.org/10.3978/j.issn.2223-3652.2014.08.02>
- Pannacciulli, N., Del Parigi, A., Chen, K., Le, D. S. N., Reiman, E. M., & Tataranni, P. A. (2006). Brain abnormalities in human obesity: A voxel-based morphometric study. *NeuroImage*, *31*(4), 1419-1425. <https://doi.org/10.1016/j.neuroimage.2006.01.047>
- Papageorgiou, I., Astrakas, L. G., Xydis, V., Alexiou, G. A., Bargiotas, P., Tzarouchi, L., Zikou, A. K., Kiortsis, D. N., & Argyropoulou, M. I. (2017). Abnormalities of brain neural circuits related to obesity: A diffusion tensor imaging study. *Magnetic Resonance Imaging*, *37*, 116-121. <https://doi.org/10.1016/j.mri.2016.11.018>
- Papp, K. V., Mormino, E. C., Amariglio, R. E., Munro, C., Dagley, A., Schultz, A. P., Johnson, K. A., Sperling, R. A., & Rentz, D. M. (2016). Biomarker validation of a decline in semantic processing in preclinical Alzheimer's disease. *Neuropsychology*, *30*(5), 624. <https://doi.org/10.1037/neu0000246>
- Pararasa, C., Bailey, C. J., & Griffiths, H. R. (2015). Ageing, adipose tissue, fatty acids and inflammation. *Biogerontology*, *16*(2), 235-248. <https://doi.org/10.1007/s10522-014-9536-x>

- Pardo, J. V., Lee, J. T., Sheikh, S. A., Surerus-Johnson, C., Shah, H., Munch, K. R., Carlis, J. V., Lewis, S. M., Kuskowski, M. A., & Dysken, M. W. (2007). Where the brain grows old: Decline in anterior cingulate and medial prefrontal function with normal aging. *NeuroImage*, 35(3), 1231-1237. <https://doi.org/10.1016/j.neuroimage.2006.12.044>
- Park, B., Byeon, K., Lee, M. J., Kim, S. H., & Park, H. (2020). The orbitofrontal cortex functionally links obesity and white matter hyperintensities. *Scientific Reports*, 10(1), 1-11. <https://doi.org/10.1038/s41598-020-60054-x>
- Park, D. C., & Reuter-Lorenz, P. (2009). The Adaptive Brain: Aging and Neurocognitive Scaffolding. *Annual Review of Psychology*, 60, 173-196. <https://doi.org/10.1146/annurev.psych.59.103006.093656>
- Park, K. W., Yoon, H. J., Kang, D. Y., Kim, B. C., Kim, S., & Kim, J. W. (2012). Regional cerebral blood flow differences in patients with mild cognitive impairment between those who did and did not develop Alzheimer's disease. *Psychiatry Research: Neuroimaging*, 203(2-3), 201-206. <https://doi.org/10.1016/j.psychresns.2011.12.007>
- Parnetti, L., Chipi, E., Salvadori, N., D'Andrea, K., & Eusebi, P. (2019). Prevalence and risk of progression of preclinical Alzheimer's disease stages: A systematic review and meta-analysis. *Alzheimer's Research & Therapy*, 11(1), 7. <https://doi.org/10.1186/s13195-018-0459-7>
- Pasha, E. P., Birdsill, A., Parker, P., Elmenshawy, A., Tanaka, H., & Haley, A. P. (2017). Visceral adiposity predicts subclinical white matter hyperintensities in middle-aged adults. *Obesity Research & Clinical Practice*, 11(2), 177-187. <https://doi.org/10.1016/j.orcp.2016.04.003>
- Pasi, M., Boulouis, G., Fotiadis, P., Auriel, E., Charidimou, A., Haley, K., Ayres, A., Schwab, K. M., Goldstein, J. N., Rosand, J., Viswanathan, A., Pantoni, L., Greenberg, S. M., & Gurol, M. E. (2017). Distribution of lacunes in cerebral amyloid angiopathy and hypertensive small vessel disease. *Neurology*, 88(23), 2162-2168. <https://doi.org/10.1212/WNL.0000000000004007>
- Patching, S. G. (2017). Glucose transporters at the blood-brain barrier: Function, regulation and gateways for drug delivery. *Molecular Neurobiology*, 54(2), 1046-1077. <https://doi.org/10.1007/s12035-015-9672-6>
- Patel, C., Ghanim, H., Ravishankar, S., Sia, C. L., Viswanathan, P., Mohanty, P., & Dandona, P. (2007). Prolonged reactive oxygen species generation and nuclear factor- κ B activation after a high-fat, high-carbohydrate meal in the obese. *The Journal of Clinical Endocrinology & Metabolism*, 92(11), 4476-4479. <https://doi.org/10.1210/jc.2007-0778>
- Patterson, C. (2018). World Alzheimer Report 2018: the state of the art of dementia research: New frontiers. *Alzheimer's Disease International (ADI): London, UK*.
- Paul, K. C., Jerrett, M., & Ritz, B. (2018). Type 2 Diabetes Mellitus and Alzheimer's Disease: Overlapping Biologic Mechanisms and Environmental Risk Factors. *Current Environmental Health Reports*, 5(1), 44-58. <https://doi.org/10.1007/s40572-018-0176-1>
- Peditizi, E., Peters, R., & Beckett, N. (2016). The risk of overweight/obesity in mid-life and late life for the development of dementia: A systematic review and meta-analysis of longitudinal studies. *Age and Ageing*, 45(1), 14-21. <https://doi.org/10.1093/ageing/afv151>
- Pegueroles, J., Jiménez, A., Vilaplana, E., Montal, V., Carmona-Iragui, M., Pané, A., Alcolea, D., Videla, L., Casajoana, A., Clarimón, J., Ortega, E., Vidal, J., Blesa, R., Lleó, A., Fortea, J., & Alzheimer's Disease Neuroimaging Initiative (2018). Obesity and Alzheimer's disease, does the obesity paradox really exist? A magnetic resonance imaging study. *Oncotarget*, 9(78), 34691-34698. <https://doi.org/10.18632/oncotarget.26162>
- Peila, R., Rodriguez, B. L., & Launer, L. J. (2002). Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes*, 51(4), 1256-1262. <https://doi.org/10.2337/diabetes.51.4.1256>

- Peng, B., Chen, Z., Ma, L., & Dai, Y. (2015). Cerebral alterations of type 2 diabetes mellitus on MRI: A pilot study. *Neuroscience Letters*, *606*, 100-105. <https://doi.org/10.1016/j.neulet.2015.08.030>
- Penninx, B. W., Beekman, A. T., Honig, A., Deeg, D. J., Schoevers, R. A., van Eijk, J. T., & van Tilburg, W. (2001). Depression and cardiac mortality: Results from a community-based longitudinal study. *Archives of General Psychiatry*, *58*(3), 221-227. <https://doi.org/10.1001/archpsyc.58.3.221>
- Peppiatt, C. M., Howarth, C., Mobbs, P., & Attwell, D. (2006). Bidirectional control of CNS capillary diameter by pericytes. *Nature*, *443*(7112), 700-704. <https://doi.org/10.1038/nature05193>
- Perego, L., Pizzocri, P., Corradi, D., Maisano, F., Paganelli, M., Fiorina, P., Barbieri, M., Morabito, A., Paolisso, G., Folli, F., & Pontiroli, A. E. (2005). Circulating leptin correlates with left ventricular mass in morbid (grade III) obesity before and after weight loss induced by bariatric surgery: a potential role for leptin in mediating human left ventricular hypertrophy. *The Journal of Clinical Endocrinology and Metabolism*, *90*(7), 4087-4093. <https://doi.org/10.1210/jc.2004-1963>
- Pereira-Pedro, A. S., Bruner, E., Gunz, P., & Neubauer, S. (2020). A morphometric comparison of the parietal lobe in modern humans and Neanderthals. *Journal of Human Evolution*, *142*, 102770. <https://doi.org/10.1016/j.jhevol.2020.102770>
- Pérez Pérez, A., Ybarra Muñoz, J., Blay Cortés, V., & de Pablos Velasco, P. (2007). Obesity and cardiovascular disease. *Public Health Nutrition*, *10*(10A), 1156-1163. <https://doi.org/10.1017/S1368980007000651>
- Perez-Gonzalez, R., Alvira-Botero, M., Robayo, O., Antequera, D., Garzon, M., Martín-Moreno, A. M., Brera, B., de Ceballos, M. L., & Carro, E. (2014). Leptin gene therapy attenuates neuronal damages evoked by amyloid- β and rescues memory deficits in APP/PS1 mice. *Gene Therapy*, *21*(3), 298-308. <https://doi.org/10.1038/gt.2013.85>
- Perichart-Perera, O., Balas-Nakash, M., Schiffman-Selechnik, E., Barbato-Dosal, A., & Vadillo-Ortega, F. (2007). Obesity increases metabolic syndrome risk factors in school-aged children from an urban school in Mexico City. *Journal of the American Dietetic Association*, *107*(1), 81-91. <https://doi.org/10.1016/j.jada.2006.10.011>
- Perl, D. P. (2010). Neuropathology of Alzheimer's disease. *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine*, *77*(1), 32-42. <https://doi.org/10.1002/msj.20157>
- Perneckzy, R., Kempermann, G., Korczyn, A.D., Matthews, F.E., Ikram, M.A., Scarmeas, N., Chetelat, G., Stern, Y., & Ewers, M. (2019). Translational research on reserve against neurodegenerative disease: consensus report of the International Conference on Cognitive Reserve in the Dementias and the Alzheimer's Association Reserve, Resilience and Protective Factors Professional Interest Area working groups. *BMC Medicine*, *17*(1), 1-15. <https://doi.org/10.1186/s12916-019-1283-z>
- Perneckzy, R., Wagenpfeil, S., Lunetta, K., Cupples, L., Green, R., DeCarli, C., Farrer, L. A., & Kurz, A. (2010). Head circumference, atrophy, and cognition: Implications for brain reserve in Alzheimer disease. *Neurology*, *75*(2), 137-142. <https://doi.org/10.1212/WNL.0b013e3181e7ca97>
- Perry, E. K., Gibson, P. H., Blessed, G., Perry, R. H., & Tomlinson, B. E. (1977). Neurotransmitter enzyme abnormalities in senile dementia: Choline acetyltransferase and glutamic acid decarboxylase activities in necropsy brain tissue. *Journal of the Neurological Sciences*, *34*(2), 247-265. [https://doi.org/10.1016/0022-510X\(77\)90073-9](https://doi.org/10.1016/0022-510X(77)90073-9)
- Perry, E. K., Tomlinson, B. E., Blessed, G., Bergmann, K., Gibson, P. H., & Perry, R. H. (1978). Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *BMJ*, *2*(6150), 1457-1459. <https://doi.org/10.1136/bmj.2.6150.1457>

- Perry, R., Candy, J., Perry, E., Thompson, J., & Oakley, A. E. (1984). The substantia innominata and adjacent regions in the human brain: Histochemical and biochemical observations. *Journal of Anatomy*, 138(Pt 4), 713.
- Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease. A critical review. *Brain*, 122 (Pt 3), 383-404. <https://doi.org/10.1093/brain/122.3.383>
- Petersen, R. C. (2001). Mild cognitive impairment: transition from aging to Alzheimer's disease. In K. Iqbal, S. S. Sisodia, B. Winbald (Eds.) *Alzheimer's Disease: Advances in Etiology, Pathogenesis and Therapeutics*, 141-151. John Wiley & Sons, Ltd. <https://doi.org/10.1002/0470846453>
- Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology*, 56(3), 303-308. <https://doi.org/10.1001/archneur.56.3.303>
- Pezzotti, P., Scalmana, S., Mastromattei, A., & Di Lallo, D. (2008). The accuracy of the MMSE in detecting cognitive impairment when administered by general practitioners: A prospective observational study. *BMC Family Practice*, 9(1), 29. <https://doi.org/10.1186/1471-2296-9-29>
- Phan, T. G., Donnan, G. A., Wright, P. M., & Reutens, D. C. (2005). A digital map of middle cerebral artery infarcts associated with middle cerebral artery trunk and branch occlusion. *Stroke*, 36(5), 986-991. <https://doi.org/10.1161/01.STR.0000163087.66828.e9>
- Piaceri, I., Nacmias, B., & Sorbi, S. (2013). Genetics of familial and sporadic Alzheimer's disease. *Frontiers in Bioscience (Elite Ed)*, 5(1), 167-177.
- Piepoli, M. F., Hoes, A. W., Agewall, S., Albus, C., Brotons, C., Catapano, A. L., Cooney, M. T., Corrà, U., Cosyns, B., Deaton, C., Graham, I., Hall, M. S., Hobbs, F., Løchen, M. L., Löllgen, H., Marques-Vidal, P., Perk, J., Prescott, E., Redon, J., Richter, D. J., ... ESC Scientific Document Group (2016). 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European Heart Journal*, 37(29), 2315–2381. <https://doi.org/10.1093/eurheartj/ehw106>
- Pierpaoli, C., Barnett, A., Pajevic, S., Chen, R., Penix, L., Virta, A., & Basser, P. (2001). Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *NeuroImage*, 13(6), 1174-1185. <https://doi.org/10.1006/nimg.2001.0765>
- Pievani, M., de Haan, W., Wu, T., Seeley, W. W., & Frisoni, G. B. (2011). Functional network disruption in the degenerative dementias. *Lancet Neurology*, 10(9), 829-843. [https://doi.org/10.1016/S1474-4422\(11\)70158-2](https://doi.org/10.1016/S1474-4422(11)70158-2)
- Pini, L., Pievani, M., Bocchetta, M., Altomare, D., Bosco, P., Cavedo, E., Galluzzi, S., Marizzoni, M., & Frisoni, G. B. (2016). Brain atrophy in Alzheimer's Disease and aging. *Ageing Research Reviews*, 30, 25-48. <https://doi.org/10.1016/j.arr.2016.01.002>
- Pirpamer, L., Hofer, E., Gesierich, B., De Guio, F., Freudenberger, P., Seiler, S., Duering, M., Jouvent, E., Duchesnay, E., Dichgans, M., Ropele, S., & Schmidt, R. (2016). Determinants of iron accumulation in the normal aging brain. *Neurobiology of Aging*, 43, 149–155. <https://doi.org/10.1016/j.neurobiolaging.2016.04.002>
- Pischon, T., Girman, C. J., Hotamisligil, G. S., Rifai, N., Hu, F. B., & Rimm, E. B. (2004). Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA*, 291(14), 1730-1737. <https://doi.org/10.1001/jama.291.14.1730>
- Platt, T. L., Beckett, T. L., Kohler, K., Niedowicz, D. M., & Murphy, M. P. (2016). Obesity, diabetes, and leptin resistance promote tau pathology in a mouse model of disease. *Neuroscience*, 315, 162-174. <https://doi.org/10.1016/j.neuroscience.2015.12.011>

- Pluta R., Ułamek M., Januszewski S. (2006) Micro-blood-brain barrier openings and cytotoxic fragments of amyloid precursor protein accumulation in white matter after ischemic brain injury in long-lived rats. In: Hoff J.T., Keep R.F., Xi G., Hua Y. (Eds.) *Brain Edema XIII. Acta Neurochirurgica Supplementum*, vol 96. Springer, Vienna. https://doi.org/10.1007/3-211-30714-1_57
- Pluta, R., & Ułamek-Kozioł, M. (2019). The role of degenerative pathways in the development of irreversible consequences after brain ischemia. *Neural Regeneration Research*, 14(6), 982. <https://doi.org/10.4103/1673-5374.250574>
- Poirier, J., Hess, M., May, P. C., & Finch, C. E. (1991). Cloning of hippocampal poly (A) RNA sequences that increase after entorhinal cortex lesion in adult rat. *Molecular Brain Research*, 9(3), 191-195. [https://doi.org/10.1016/0169-328X\(91\)90002-F](https://doi.org/10.1016/0169-328X(91)90002-F)
- Poldrack, R. A. (2000). Imaging brain plasticity: Conceptual and methodological issues - A theoretical review. *NeuroImage*, 12(1), 1-13. <https://doi.org/10.1006/nimg.2000.0596>
- Popkin, B. M. (2015). Nutrition transition and the global diabetes epidemic. *Current Diabetes Reports*, 15(9), 64. <https://doi.org/10.1007/s11892-015-0631-4>
- Power, A. E., Vazdarjanova, A., & McGaugh, J. L. (2003). Muscarinic cholinergic influences in memory consolidation. *Neurobiology of Learning and Memory*, 80(3), 178-193. [https://doi.org/10.1016/S1074-7427\(03\)00086-8](https://doi.org/10.1016/S1074-7427(03)00086-8)
- Power, B. D., Alfonso, H., Flicker, L., Hankey, G. J., Yeap, B. B., & Almeida, O. P. (2011). Body adiposity in later life and the incidence of dementia: The health in men study. *PLoS One*, 6(3), e17902. <https://doi.org/10.1371/journal.pone.0017902>
- Prakash, R. S., Erickson, K. I., Colcombe, S. J., Kim, J. S., Voss, M. W., & Kramer, A. F. (2009). Age-related differences in the involvement of the prefrontal cortex in attentional control. *Brain and Cognition*, 71(3), 328-335. <https://doi.org/10.1016/j.bandc.2009.07.005>
- Prandoni, P., Ciammaichella, M., Mumoli, N., Zanatta, N., Visonà, A., Avruscio, G., Camporese, G., Bucherini, E., Bova, C., Imberti, D., Benedetti, R., Rossetto, V., Noventa, F., Milan, M., & Veritas Investigators (2017). An association between residual vein thrombosis and subclinical atherosclerosis: Cross-sectional study. *Thrombosis Research*, 157, 16–19. <https://doi.org/10.1016/j.thromres.2017.06.036>
- Preische, O., Schultz, S. A., Apel, A., Kuhle, J., Kaeser, S. A., Barro, C., Gräber, S., Kuder-Buletta, E., LaFougere, C., Laske, C., Vöglein, J., Levin, J., Masters, C. L., Martins, R., Schofield, P. R., Rossor, M. N., Graff-Radford, N. R., Salloway, S., Ghetti, B., Ringman, J. M., ... Dominantly Inherited Alzheimer Network (2019). Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. *Nature Medicine*, 25(2), 277–283. <https://doi.org/10.1038/s41591-018-0304-3>
- Price, A. J., Crampin, A. C., Amberbir, A., Kayuni-Chihana, N., Musicha, C., Tafatatha, T., Branson, K., Lawlor, D. A., Mwaiyeghele, E., Nkhwazi, L., Smeeth, L., Pearce, N., Munthali, E., Mwangomba, B. M., Mwansambo, C., Glynn, J. R., Jaffar, S., & Nyirenda, M. (2018). Prevalence of obesity, hypertension, and diabetes, and cascade of care in sub-Saharan Africa: A cross-sectional, population-based study in rural and urban Malawi. *The Lancet, Diabetes & Endocrinology*, 6(3), 208-222. [https://doi.org/10.1016/S2213-8587\(17\)30432-1](https://doi.org/10.1016/S2213-8587(17)30432-1)
- Prince, E. A., & Ahn, S. H. (2013). Basic vascular neuroanatomy of the brain and spine: what the general interventional radiologist needs to know. *Seminars in Interventional Radiology*, 30(3), 234–239. <https://doi.org/10.1055/s-0033-1353475>
- Prince, M., Comas-Herrera, A., Knapp, M., Guerchet, M., & Karagiannidou, M. (2016) World Alzheimer report 2016: Improving healthcare for people living with dementia: Coverage, quality and costs now and in the future. Alzheimer's Disease International (ADI), London, UK.

- Profenno, L. A., Porsteinsson, A. P., & Faraone, S. V. (2010). Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. *Biological Psychiatry*, *67*(6), 505-512. <https://doi.org/10.1016/j.biopsych.2009.02.013>
- Pu, Y., Lan, L., Leng, X., Wong, L. K., & Liu, L. (2017). Intracranial atherosclerosis: From anatomy to pathophysiology. *International Journal of Stroke*, *12*(3), 236-245. <https://doi.org/10.1177/1747493016685716>
- Puente, E. C., Silverstein, J., Bree, A. J., Musikantow, D. R., Wozniak, D. F., Maloney, S., Daphna-Iken, D., & Fisher, S. J. (2010). Recurrent moderate hypoglycemia ameliorates brain damage and cognitive dysfunction induced by severe hypoglycemia. *Diabetes*, *59*(4), 1055-1062. <https://doi.org/10.2337/db09-1495>
- Pugazhenthii, S., Qin, L., & Reddy, P. H. (2017). Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1863*(5), 1037-1045. <https://doi.org/10.1016/j.bbadis.2016.04.017>
- Pulsinelli, W. A., Levy, D. E., & Duffy, T. E. (1982). Regional cerebral blood flow and glucose metabolism following transient forebrain ischemia. *Annals of Neurology*, *11*(5), 499-509. <https://doi.org/10.1002/ana.410110510>
- Punthakee, Z., Goldenberg, R., & Katz, P. (2018). Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. *Canadian Journal of Diabetes*, *42*, S10-S15. <https://doi.org/10.1016/j.jcjd.2017.10.003>
- Qi, D., Wang, A., Chen, Y., Chen, K., Zhang, S., Zhang, J., Li, X., Ai, L., & Zhang, Z. (2017). Default mode network connectivity and related white matter disruption in type 2 diabetes mellitus patients concurrent with amnesic mild cognitive impairment. *Current Alzheimer Research*, *14*(11), 1238-1246. <https://doi.org/10.2174/1567205014666170417113441>
- Qi, Z., Wu, X., Wang, Z., Zhang, N., Dong, H., Yao, L., & Li, K. (2010). Impairment and compensation coexist in amnesic MCI default mode network. *NeuroImage*, *50*(1), 48-55. <https://doi.org/10.1016/j.neuroimage.2009.12.025>
- Qiu, C., Winblad, B., & Fratiglioni, L. (2005). Risk factors for dementia and Alzheimer's disease--findings from a community-based cohort study in Stockholm, Sweden. *Zhonghua liu xing bing xue za zhi= Zhonghua liuxingbingxue zazhi*, *26*(11), 882.
- Qiu, C., Xu, W., & Fratiglioni, L. (2010). Vascular and psychosocial factors in Alzheimer's disease: Epidemiological evidence toward intervention. *Journal of Alzheimer's Disease*, *20*(3), 689-697. <https://doi.org/10.3233/JAD-2010-091663>
- Qiu, W. Q., & Folstein, M. F. (2006). Insulin, insulin-degrading enzyme and amyloid- β peptide in Alzheimer's disease: Review and hypothesis. *Neurobiology of Aging*, *27*(2), 190-198. <https://doi.org/10.1016/j.neurobiolaging.2005.01.004>
- Quental, N. B., Brucki, S. M., & Bueno, O. F. (2013). Visuospatial function in early Alzheimer's disease--the use of the Visual Object and Space Perception (VOSP) battery. *PLoS One*, *8*(7), e68398. <https://doi.org/10.1371/journal.pone.0068398>
- Rabinovici, G. D., Jagust, W. J., Furst, A. J., Ogar, J. M., Racine, C. A., Mormino, E. C., O'Neil, J. P., Lal, R. A., Dronkers, N. F., Miller, B. L., & Gorno-Tempini, M. L. (2008). Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia. *Annals of Neurology*, *64*(4), 388-401. <https://doi.org/10.1002/ana.21451>
- Racchi, M., Sironi, M., Caprera, A., König, G., & Govoni, S. (2001). Short-and long-term effect of acetylcholinesterase inhibition on the expression and metabolism of the amyloid precursor protein. *Molecular Psychiatry*, *6*(5), 520-528.
- Radanovic, M., Pereira, F. R., Stella, F., Aprahamian, I., Ferreira, L. K., Forlenza, O. V., & Busatto, G. F. (2013). White matter abnormalities associated with Alzheimer's disease and mild cognitive impairment: A critical review of MRI studies. *Expert Review of Neurotherapeutics*, *13*(5), 483-493. <https://doi.org/10.1586/ern.13.45>

- Rader, D. J., Alexander, E. T., Weibel, G. L., Billheimer, J., & Rothblat, G. H. (2009). The role of reverse cholesterol transport in animals and humans and relationship to atherosclerosis. *Journal of Lipid Research*, 50(Supplement), S189-S194. <https://doi.org/10.1194/jlr.R800088-JLR200>
- Rafalowska, J., Barcikowska, M., Wen, G., & Wisniewski, H. M. (1988). Laminar distribution of neuritic plaques in normal aging, Alzheimer's disease and Down's syndrome. *Acta Neuropathologica*, 77(1), 21-25.
- Raffaitin, C., Gin, H., Empana, J. P., Helmer, C., Berr, C., Tzourio, C., Portet, F., Dartigues, J. F., Alperovitch, A., & Barberger-Gateau, P. (2009). Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: The Three-City Study. *Diabetes Care*, 32(1), 169–174. <https://doi.org/10.2337/dc08-0272>
- Raffield, L. M., Cox, A. J., Freedman, B. I., Hugenschmidt, C. E., Hsu, F. C., Wagner, B. C., Xu, J., Maldjian, J. A., & Bowden, D. W. (2016). Analysis of the relationships between type 2 diabetes status, glycemic control, and neuroimaging measures in the Diabetes Heart Study Mind. *Acta Diabetologica*, 53(3), 439–447. <https://doi.org/10.1007/s00592-015-0815-z>
- Rafii, S., Butler, J. M., & Ding, B. S. (2016). Angiocrine functions of organ-specific endothelial cells. *Nature*, 529(7586), 316. <https://doi.org/10.1038/nature17040>
- Rahman, A., Akterin, S., Flores-Morales, A., Crisby, M., Kivipelto, M., Schultzberg, M., & Cedazo-Mínguez, A. (2005). High cholesterol diet induces tau hyperphosphorylation in apolipoprotein E deficient mice. *FEBS Letters*, 579(28), 6411-6416. <https://doi.org/10.1016/j.febslet.2005.10.024>
- Rahmoune, H., Thompson, P. W., Ward, J. M., Smith, C. D., Hong, G., & Brown, J. (2005). Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. *Diabetes*, 54(12), 3427-3434. <https://doi.org/10.2337/diabetes.54.12.3427>
- Raichle, M. E. (2015). The brain's default mode network. *Annual Reviews of Neuroscience*, 38, 433-447. <https://doi.org/10.1146/annurev-neuro-071013-014030>
- Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, 98(2), 676-682. <https://doi.org/10.1073/pnas.98.2.676>
- Raj, M., Sundaram, K., Paul, M., Deepa, A., & Kumar, R. K. (2007). Obesity in Indian children: Time trends and relationship with hypertension. *National Medical Journal of India*, 20(6), 288.
- Raji, C. A., Ho, A. J., Parikshak, N. N., Becker, J. T., Lopez, O. L., Kuller, L. H., Hua, X., Leow, A. D., Toga, A. W., & Thompson, P. M. (2010). Brain structure and obesity. *Human Brain Mapping*, 31(3), 353-364. <https://doi.org/10.1002/hbm.20870>
- Rami, L., Sala-Llonch, R., Solé-Padullés, C., Fortea, J., Olives, J., Lladó, A., Peña-Gómez, C., Balasa, M., Bosch, B., Antonell, A., Sanchez-Valle, R., Bartrés-Faz, D., & Molinuevo, J. L. (2012). Distinct functional activity of the precuneus and posterior cingulate cortex during encoding in the preclinical stage of Alzheimer's disease. *Journal of Alzheimer's Disease*, 31(3), 517–526. <https://doi.org/10.3233/JAD-2012-120223>
- Ramli, A., Ahmad, N. S., & Paraidathathu, T. (2012). Medication adherence among hypertensive patients of primary health clinics in Malaysia. *Patient preference and adherence*, 6, 613. <https://doi.org/10.2147/PPA.S34704>
- Ramos, P., Santos, A., Pinto, N. R., Mendes, R., Magalhães, T., & Almeida, A. (2014). Iron levels in the human brain: A post-mortem study of anatomical region differences and age-related changes. *Journal of Trace Elements in Medicine and Biology*, 28(1), 13-17. <https://doi.org/10.1016/j.jtemb.2013.08.001>
- Randriamboavonjy, V., Schrader, J., Busse, R., & Fleming, I. (2004). Insulin induces the release of vasodilator compounds from platelets by a nitric oxide–G kinase–VAMP-3–dependent

- pathway. *The Journal of Experimental Medicine*, 199(3), 347-356.
<https://doi.org/10.1084/jem.20030694>
- Rapp, M. A., Schnaider-Beeri, M., Purohit, D. P., Perl, D. P., Haroutunian, V., & Sano, M. (2008). Increased neurofibrillary tangles in patients with Alzheimer disease with comorbid depression. *The American Journal of Geriatric Psychiatry*, 16(2), 168-174.
<https://doi.org/10.1097/JGP.0b013e31816029ec>
- Rask-Madsen, C., Li, Q., Freund, B., Feather, D., Abramov, R., Wu, I. H., Chen, K., Yamamoto-Hiraoka, J., Goldenbogen, J., Sotiropoulos, K. B., Clermont, A., Gerald, P., Dall'Osso, C., Wagers, A. J., Huang, P. L., Reikhter, M., Scalia, R., Kahn, C. R., & King, G. L. (2010). Loss of insulin signaling in vascular endothelial cells accelerates atherosclerosis in apolipoprotein E null mice. *Cell metabolism*, 11(5), 379–389. <https://doi.org/10.1016/j.cmet.2010.03.013>
- Raškeliene, V., Babarskienė, M. R., Macijauskienė, J., & Šeškevičius, A. (2009). Impact of duration and treatment of arterial hypertension on health-related quality of life. *Medicine*, 45(5), 405.
<https://doi.org/10.3390/medicina45050051>
- Rathi, Y., Pasternak, O., Savadjiev, P., Michailovich, O., Bouix, S., Kubicki, M., Westin, C. F., & Shenton, M. E. (2014). Gray matter alterations in early aging: a diffusion magnetic resonance imaging study. *Human Brain Mapping*, 35(8), 3841-3856. <https://doi.org/10.1002/hbm.22441>
- Rauch, U., Osende, J. I., Fuster, V., Badimon, J. J., Fayad, Z., & Chesebro, J. H. (2001). Thrombus formation on atherosclerotic plaques: Pathogenesis and clinical consequences. *Annals of Internal Medicine*, 134(3), 224-238. <https://doi.org/10.7326/0003-4819-134-3-200102060-00014>
- Rawlings, A. M., Sharrett, A. R., Mosley, T. H., Ballew, S. H., Deal, J. A., & Selvin, E. (2017). Glucose peaks and the risk of dementia and 20-year cognitive decline. *Diabetes Care*, 40(7), 879-886. <https://doi.org/10.2337/dc16-2203>
- Raz, L., Bhaskar, K., Weaver, J., Marini, S., Zhang, Q., Thompson, J. F., Espinoza, C., Iqbal, S., Maphis, N. M., Weston, L., Sillerud, L. O., Caprihan, A., Pesko, J. C., Erhardt, E. B., & Rosenberg, G. A. (2019). Hypoxia promotes tau hyperphosphorylation with associated neuropathology in vascular dysfunction. *Neurobiology of Disease*, 126, 124–136.
<https://doi.org/10.1016/j.nbd.2018.07.009>
- Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., & Acker, J. D. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral Cortex*, 15(11), 1676-1689.
<https://doi.org/10.1093/cercor/bhi044>
- Raz, N., Rodrigue, K. M., & Acker, J. D. (2003). Hypertension and the brain: Vulnerability of the prefrontal regions and executive functions. *Behavioral Neuroscience*, 117(6), 1169.
<https://doi.org/10.1037/0735-7044.117.6.1169>
- Raz, N., Rodrigue, K. M., Kennedy, K. M., & Acker, J. D. (2007). Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology*, 21(2), 149.
<https://doi.org/10.1037/0894-4105.21.2.149>
- Reed, B., Villeneuve, S., Mack, W., DeCarli, C., Chui, H. C., & Jagust, W. (2014). Associations between serum cholesterol levels and cerebral amyloidosis. *JAMA*, 71(2), 195-200.
<https://doi.org/10.1001/jamaneurol.2013.5390>
- Rehm, J., Hasan, O. S., Black, S. E., Shield, K. D., & Schwarzingler, M. (2019). Alcohol use and dementia: A systematic scoping review. *Alzheimer's Research & Therapy*, 11(1), 1-11.
<https://doi.org/10.1186/s13195-018-0453-0>
- Reijmer, Y. D., Brundel, M., De Bresser, J., Kappelle, L. J., Leemans, A., Biessels, G. J., & Utrecht Vascular Cognitive Impairment Study Group (2013a). Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes: A diffusion tensor imaging study. *Diabetes Care*, 36(1), 137-144. <https://doi.org/10.2337/dc12-0493>

- Reijmer, Y. D., Leemans, A., Brundel, M., Kappelle, L. J., & Biessels, G. J. (2013b). Disruption of the cerebral white matter network is related to slowing of information processing speed in patients with type 2 diabetes. *Diabetes*, *62*(6), 2112-2115. <https://doi.org/10.2337/db12-1644>
- Reijmer, Y. D., Leemans, A., Heringa, S. M., Wielaard, I., Jeurissen, B., Koek, H. L., & Biessels, G. J. (2012). Improved sensitivity to cerebral white matter abnormalities in Alzheimer's disease with spherical deconvolution based tractography. *PLoS One*, *7*(8). <https://doi.org/10.1371/journal.pone.0044074>
- Reiman, E. M., Chen, K., Langbaum, J. B., Lee, W., Reschke, C., Bandy, D., Alexander, G. E., & Caselli, R. J. (2010). Higher serum total cholesterol levels in late middle age are associated with glucose hypometabolism in brain regions affected by Alzheimer's disease and normal aging. *NeuroImage*, *49*(1), 169-176.
- Reisberg, B., Franssen, E. H., Hasan, S. M., Monteiro, I., Boksay, I., Souren, L. E., Kenowsky, S., Auer, S. R., Elahi, S., & Kluger, A. (1999). Retrogenesis: Clinical, physiologic, and pathologic mechanisms in brain aging, Alzheimer's and other dementing processes. *European Archives of Psychiatry and Clinical Neuroscience*, *249* Suppl 3, 28-36. <https://doi.org/10.1007/pl00014170>
- Reitz, C., den Heijer, T., van Duijn, C., Hofman, A., & Breteler, M. M. B. (2007a). Relation between smoking and risk of dementia and Alzheimer disease: The Rotterdam Study. *Neurology*, *69*(10), 998-1005. <https://doi.org/10.1212/01.wnl.0000271395.29695.9a>
- Reitz, C., Tang, M.-X., Manly, J., Mayeux, R., & Luchsinger, J. A. (2007b). Hypertension and the risk of mild cognitive impairment. *Archives of Neurology*, *64*(12), 1734-1740. <https://doi.org/10.1001/archneur.64.12.1734>
- Reitz, C., Tosto, G., Mayeux, R., & Luchsinger, J. A. (2012). Genetic variants in the Fat and Obesity Associated (FTO) gene and risk of Alzheimer's disease. *PloS, One*, *7*(12), e50354. <https://doi.org/10.1371/journal.pone.0050354>
- Resnick, S. M., Sojkova, J., Zhou, Y., An, Y., Ye, W., Holt, D. P., Dannals, R. F., Mathis, C. A., Klunk, W. E., Ferrucci, L., Kraut, M. A., & Wong, D. F. (2010). Longitudinal cognitive decline is associated with fibrillar amyloid-beta measured by [¹¹C]PiB. *Neurology*, *74*(10), 807-815. <https://doi.org/10.1212/WNL.0b013e3181d3e3e9>
- Reuter-Lorenz, P. A., & Park, D. C. (2014). How Does it STAC Up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology Review*, *24*(3), 355-370. <https://doi.org/10.1007/s11065-014-9270-9>
- Richard, E., Van den Heuvel, E., van Charante, E. P. M., Achthoven, L., Vermeulen, M., Bindels, P. J., & Van Gool, W. A. (2009). Prevention of dementia by intensive vascular care (PreDIVA): A cluster-randomized trial in progress. *Alzheimer Disease & Associated Disorders*, *23*(3), 198-204. <https://doi.org/10.1097/WAD.0b013e31819783a4>
- Richards, O. C., Raines, S. M., & Attie, A. D. (2010). The role of blood vessels, endothelial cells, and vascular pericytes in insulin secretion and peripheral insulin action. *Endocrine Reviews*, *31*(3), 343-363. <https://doi.org/10.1210/er.2009-0035>
- Richter, C. (1995). Oxidative damage to mitochondrial DNA and its relationship to ageing. *The International Journal of Biochemistry & Cell Biology*, *27*(7), 647-653. [https://doi.org/10.1016/1357-2725\(95\)00025-K](https://doi.org/10.1016/1357-2725(95)00025-K)
- Riedel, B. C., Thompson, P. M., & Brinton, R. D. (2016). Age, APOE and sex: triad of risk of Alzheimer's disease. *The Journal of Steroid Biochemistry and Molecular Biology*, *160*, 134-147. <https://doi.org/10.1016/j.jsbmb.2016.03.012>
- Riederer, J. W., Shott, M. E., Deguzman, M., Pryor, T. L., & Frank, G. K. W. (2016). Understanding neuronal architecture in obesity through analysis of white matter connection strength. *Frontiers in Human Neuroscience*, *10*, 271. <https://doi.org/10.3389/fnhum.2016.00271>

- Ring, C., Burns, V. E., & Carroll, D. (2002). Shifting hemodynamics of blood pressure control during prolonged mental stress. *Psychophysiology*, *39*(5), 585-590. <https://doi.org/10.1111/1469-8986.3950585>
- Ritter, M. A., Droste, D., Hegedüs, K., Szepesi, R., Nabavi, D., Csiba, L., & Ringelstein, E. B. (2005). Role of cerebral amyloid angiopathy in intracerebral hemorrhage in hypertensive patients. *Neurology*, *64*(7), 1233-1237. <https://doi.org/10.1212/01.WNL.0000156522.93403.C3>
- Rius-Pérez, S., Tormos, A., Pérez, S., & Taléns-Visconti, R. (2018). Vascular pathology: Cause or effect in Alzheimer disease? *Neurología (English Edition)*, *33*(2), 112-120. <https://doi.org/10.1016/j.nrleng.2015.07.008>
- Rizzoni, D., Porteri, E., Guelfi, D., Muiesan, M. L., Valentini, U., Cimino, A., Girelli, A., Rodella, L., Bianchi, R., Sleiman, I., & Rosei, E. A. (2001). Structural alterations in subcutaneous small arteries of normotensive and hypertensive patients with non-insulin-dependent diabetes mellitus. *Circulation*, *103*(9), 1238-1244. <https://doi.org/10.1161/01.CIR.103.9.1238>
- Roberts, R. O., Knopman, D. S., Geda, Y. E., Cha, R. H., Pankratz, V. S., Baertlein, L., Boeve, B. F., Tangalos, E. G., Ivnik, R. J., Mielke, M. M., & Petersen, R. C. (2014). Association of diabetes with amnesic and nonamnesic mild cognitive impairment. *Alzheimer's & Dementia*, *10*(1), 18-26. <https://doi.org/10.1016/j.jalz.2013.01.001>
- Rodríguez-Flores, M., Rodríguez-Saldaña, J., Cantú-Brito, C., Aguirre-García, J., & Alejandro, G. G. (2013). Prevalence and severity of atherosclerosis in different arterial territories and its relation with obesity. *Cardiovascular Pathology*, *22*(5), 332-338. <https://doi.org/10.1016/j.carpath.2013.01.008>
- Rofey, D. L., Arslanian, S. A., El Nokali, N. E., Verstynen, T., Watt, J. C., Black, J. J., Sax, R., Krall, J. S., Proulx, C., Dillon, M., & Erickson, K. I. (2015). Brain volume and white matter in youth with type 2 diabetes compared to obese and normal weight, non-diabetic peers: A pilot study. *International Journal of Developmental Neuroscience*, *46*, 88-91. <https://doi.org/10.1016/j.ijdevneu.2015.07.003>
- Roher, A. E., Debbins, J. P., Malek-Ahmadi, M., Chen, K., Pipe, J. G., Maze, S., Belden, C., Maarouf, C. L., Thiyyagura, P., Mo, H., Hunter, J. M., Kokjohn, T. A., Walker, D. G., Kruchowsky, J. C., Belohlavek, M., Sabbagh, M. N., & Beach, T. G. (2012). Cerebral blood flow in Alzheimer's disease. *Vascular Health and Risk Management*, *8*, 599-611. <https://doi.org/10.2147/VHRM.S34874>
- Roher, A. E., Esh, C., Kokjohn, T. A., Kalback, W., Luehrs, D. C., Seward, J. D., Sue, L. I., & Beach, T. G. (2003). Circle of willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *23*(11), 2055-2062. <https://doi.org/10.1161/01.ATV.0000095973.42032.44>
- Roher, A. E., Tyas, S. L., Maarouf, C. L., Daus, I. D., Kokjohn, T. A., Emmerling, M. R., Garami, Z., Belohlavek, M., Sabbagh, M. N., Sue, L. I., & Beach, T. G. (2011). Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia. *Alzheimer's & Dementia*, *7*(4), 436-444. <https://doi.org/10.1016/j.jalz.2010.08.228>
- Romero, J. R., Preis, S. R., Beiser, A., DeCarli, C., Viswanathan, A., Martinez-Ramirez, S., Kase, C. S., Wolf, P. A., & Seshadri, S. (2014). Risk factors, stroke prevention treatments, and prevalence of cerebral microbleeds in the Framingham Heart Study. *Stroke*, *45*(5), 1492-1494. <https://doi.org/10.1161/STROKEAHA.114.004130>
- Rosen, B. D., Saad, M. F., Shea, S., Nasir, K., Edvardsen, T., Burke, G., Jerosch-Herold, M., Arnett, D. K., Lai, S., Bluemke, D. A., & Lima, J. A. (2006). Hypertension and smoking are associated with reduced regional left ventricular function in asymptomatic individuals: The Multi-Ethnic Study of Atherosclerosis. *Journal of the American College of Cardiology*, *47*(6), 1150-1158. <https://doi.org/10.1016/j.jacc.2005.08.078>

- Rosenberg, A., Mangialasche, F., Ngandu, T., Solomon, A., & Kivipelto, M. (2019). Multidomain Interventions to Prevent Cognitive Impairment, Alzheimer's Disease, and Dementia: From FINGER to World-Wide FINGERS. *The Journal of Prevention of Alzheimer's Disease*, 7, 29-36. <https://doi.org/10.14283/jpad.2019.41>
- Rosenberg, P. B., Mielke, M. M., Appleby, B. S., Oh, E. S., Geda, Y. E., & Lyketsos, C. G. (2013). The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. *The American Journal of Geriatric Psychiatry*, 21(7), 685-695. <https://doi.org/10.1016/j.jagp.2013.01.006>
- Rosenberg, P. B., Mielke, M. M., Tschanz, J., Cook, L., Corcoran, C., Hayden, K. M., Norton, M., Rabins, P. V., Green, R. C., Welsh-Bohmer, K. A., Breitner, J. C., Munger, R., & Lyketsos, C. G. (2008). Effects of cardiovascular medications on rate of functional decline in Alzheimer disease. *The American Journal of Geriatric Psychiatry*, 16(11), 883-892. <https://doi.org/10.1097/JGP.0b013e318181276a>
- Rosenberg, P. B., Nowrangi, M. A., & Lyketsos, C. G. (2015). Neuropsychiatric symptoms in Alzheimer's disease: What might be associated brain circuits? *Molecular Aspects of Medicine*, 43-44, 25-37. <https://doi.org/10.1016/j.mam.2015.05.005>
- Rosner, S. S., Rhoton, A. L., Ono, M., & Barry, M. (1984). Microsurgical anatomy of the anterior perforating arteries. *Journal of Neurosurgery*, 61(3), 468-485. <https://doi.org/10.3171/jns.1984.61.3.0468>
- Rosvall, L., Rizzuto, D., Wang, H.-X., Winblad, B., Graff, C., & Fratiglioni, L. (2009). APOE-related mortality: Effect of dementia, cardiovascular disease and gender. *Neurobiology of Aging*, 30(10), 1545-1551. <https://doi.org/10.1016/j.neurobiolaging.2007.12.003>
- Rothwell, P. M., Howard, S. C., Dolan, E., O'Brien, E., Dobson, J. E., Dahlöf, B., Poulter, N. R., & Sever, P. S. (2010a). Effects of β blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *The Lancet Neurology*, 9(5), 469-480. [https://doi.org/10.1016/S1474-4422\(10\)70066-1](https://doi.org/10.1016/S1474-4422(10)70066-1)
- Rothwell, P. M., Howard, S. C., Dolan, E., O'Brien, E., Dobson, J. E., Dahlöf, B., Sever, P. S., & Poulter, N. R. (2010b). Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *The Lancet*, 375(9718), 895-905. [https://doi.org/10.1016/S0140-6736\(10\)60308-X](https://doi.org/10.1016/S0140-6736(10)60308-X)
- Rottenberg, H. (1973). The mechanism of energy-dependent ion transport in mitochondria. *The Journal of Membrane Biology*, 11(1), 117-137. <https://doi.org/10.1007/BF01869816>
- Rouch, L., Cestac, P., Hanon, O., Cool, C., Helmer, C., Bouhanick, B., Chamontin, B., Dartigues, J. F., Vellas, B., & Andrieu, S. (2015). Antihypertensive drugs, prevention of cognitive decline and dementia: A systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. *CNS drugs*, 29(2), 113-130. <https://doi.org/10.1007/s40263-015-0230-6>
- Rousset, O., Rahmim, A., Alavi, A., & Zaidi, H. (2007). Partial volume correction strategies in PET. *PET clinics*, 2(2), 235-249. <https://doi.org/10.1016/j.cpet.2007.10.005>
- Rovio, S., Kåreholt, I., Helkala, E.-L., Viitanen, M., Winblad, B., Tuomilehto, J., Soininen, H., Nissinen, A., & Kivipelto, M. (2005). Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *The Lancet Neurology*, 4(11), 705-711. [https://doi.org/10.1016/S1474-4422\(05\)70198-8](https://doi.org/10.1016/S1474-4422(05)70198-8)
- Rowan, M. J., Klyubin, I., Wang, Q., & Anwyl, R. (2005). Synaptic plasticity disruption by amyloid beta protein: Modulation by potential Alzheimer's disease modifying therapies. *Biochemical Society Transactions*, 33(Pt 4), 563-567. <https://doi.org/10.1042/BST0330563>
- Rowe, C. C., Ng, S., Ackermann, U., Gong, S. J., Pike, K., Savage, G., Cowie, T. F., Dickinson, K. L., Maruff, P., Darby, D., Smith, C., Woodward, M., Merory, J., Tochon-Danguy, H., O'Keefe, G., Klunk, W. E., Mathis, C. A., Price, J. C., Masters, C. L., & Villemagne, V. L.

- (2007). Imaging beta-amyloid burden in aging and dementia. *Neurology*, 68(20), 1718–1725. <https://doi.org/10.1212/01.wnl.0000261919.22630.ea>
- Roy, S., Trudeau, K., Roy, S., Behl, Y., Dhar, S., & Chronopoulos, A. (2010). New insights into hyperglycemia-induced molecular changes in microvascular cells. *Journal of Dental Research*, 89(2), 116-127. <https://doi.org/10.1177/0022034509355765>
- Rozzini, L., Chilovi, B. V., Bertolotti, E., Conti, M., Rio, I. D., Trabucchi, M., & Padovani, A. (2006). Angiotensin converting enzyme (ACE) inhibitors modulate the rate of progression of amnesic mild cognitive impairment. *International Journal of Geriatric Psychiatry*, 21(6), 550-555. <https://doi.org/10.1002/gps.1523>
- Rubenstein, J., & Rakic, P. (2013). *Neural circuit development and function in the brain: comprehensive developmental neuroscience* (Vol. 3): Academic Press.
- Ruitenbergh, A., van Swieten, J. C., Witteman, J. C., Mehta, K. M., van Duijn, C. M., Hofman, A., & Breteler, M. M. B. (2002). Alcohol consumption and risk of dementia: The Rotterdam Study. *The Lancet*, 359(9303), 281-286. [https://doi.org/10.1016/S0140-6736\(02\)07493-7](https://doi.org/10.1016/S0140-6736(02)07493-7)
- Rusanen, M., Rovio, S., Ngandu, T., Nissinen, A., Tuomilehto, J., Soininen, H., & Kivipelto, M. (2010). Midlife smoking, apolipoprotein E and risk of dementia and Alzheimer's disease: A population-based cardiovascular risk factors, aging and dementia study. *Dementia and Geriatric Cognitive Disorders*, 30(3), 277-284. <https://doi.org/10.1159/000320484>
- Rusinek, H., Endo, Y., De Santi, S., Frid, D., Tsui, W.-H., Segal, S., Convit, A., & De Leon, M. J. (2004). Atrophy rate in medial temporal lobe during progression of Alzheimer disease. *Neurology*, 63(12), 2354-2359. <https://doi.org/10.1212/01.WNL.0000148602.30175.AC>
- Rusinek, H., Ha, J., Yau, P. L., Storey, P., Tirsi, A., Tsui, W. H., Frosch, O., & Convit, A. (2015). Cerebral perfusion in insulin resistance and type 2 diabetes. *Journal of Cerebral Blood Flow & Metabolism*, 35(1), 95-102. <https://doi.org/10.1038/jcbfm.2014.173>
- Ryan, S. M., & Kelly, Á. M. (2016). Exercise as a pro-cognitive, pro-neurogenic and anti-inflammatory intervention in transgenic mouse models of Alzheimer's disease. *Ageing Research Reviews*, 27, 77-92. <https://doi.org/10.1016/j.arr.2016.03.007>
- Ryu, S. H., Jung, H. Y., Lee, K. J., Moon, S. W., Lee, D. W., Hong, N., Kee, B. S., Kim, D. H., Han, C., & Lee, C. U. (2017). Incidence and Course of Depression in Patients with Alzheimer's Disease. *14*(3), 271. <https://doi.org/10.4306/pi.2017.14.3.271>
- Ryu, S. Y., Coutu, J. P., Rosas, H. D., & Salat, D. H. (2014). Effects of insulin resistance on white matter microstructure in middle-aged and older adults. *Neurology*, 82(21), 1862-1870. <https://doi.org/10.1212/WNL.0000000000000452>
- Sabisz, A., Naumczyk, P., Marcinkowska, A., Graff, B., Gąsecki, D., Glińska, A., Witkowska, M., Jankowska, A., Konarzewska, A., Kwela, J., Jodzio, K., Szurowska, E., & Narkiewicz, K. (2019). Aging and hypertension - Independent or intertwined white matter impairing factors? Insights from the quantitative diffusion tensor imaging. *Frontiers in Aging Neuroscience*, 11, 35. <https://doi.org/10.3389/fnagi.2019.00035>
- Sabri, O., Hellwig, D., Schreckenberger, M., Schneider, R., Kaiser, H. J., Wagenknecht, G., Mull, M., & Buell, U. (2000). Influence of diabetes mellitus on regional cerebral glucose metabolism and regional cerebral blood flow. *Nuclear Medicine Communications*, 21(1), 19-29. <https://doi.org/10.1097/00006231-200001000-00005>
- Sacks, F. M., Svetkey, L. P., Vollmer, W. M., Appel, L. J., Bray, G. A., Harsha, D., Obarzanek, E., Conlin, P. R., Miller, E. R., 3rd, Simons-Morton, D. G., Karanja, N., Lin, P. H., & DASH-Sodium Collaborative Research Group (2001). Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *The New England Journal of Medicine*, 344(1), 3–10. <https://doi.org/10.1056/NEJM200101043440101>

- Sadanand, S., Balachandar, R. & Bharath, S. (2016). Memory and executive functions in persons with type 2 diabetes: a meta-analysis. *Diabetes/metabolism Research and Reviews*, 32(2), 132-142. <https://doi.org/10.1002/dmrr.2664>
- Saeki, N., & Rhoton, A. L. (1977). Microsurgical anatomy of the upper basilar artery and the posterior circle of Willis. *Journal of Neurosurgery*, 46(5), 563-578. <https://doi.org/10.3171/jns.1977.46.5.0563>
- Safar, M. E., O'Rourke, M. F., & Frohlich, E. D. (2014). *Blood pressure and arterial wall mechanics in cardiovascular diseases*. Springer, London. <https://doi.org/10.1007/978-1-4471-5198-2>
- Saher, G., Brügger, B., Lappe-Siefke, C., Möbius, W., Tozawa, R.-i., Wehr, M. C., Wieland, F., Ishibashi, S., & Nave, K. A. (2005). High cholesterol level is essential for myelin membrane growth. *Nature Neuroscience*, 8(4), 468-475. <https://doi.org/10.1038/nn1426>
- Saji, N., Kimura, K., Shimizu, H., & Kita, Y. (2012). Association between silent brain infarct and arterial stiffness indicated by brachial-ankle pulse wave velocity. *Internal Medicine*, 51(9), 1003-1008. <https://doi.org/10.2169/internalmedicine.51.6852>
- Sala-Llonch, R., Bartrés-Faz, D., & Junqué, C. (2015). Reorganization of brain networks in aging: A review of functional connectivity studies. *Frontiers in Psychology*, 6, 663. <https://doi.org/10.3389/fpsyg.2015.00663>
- Salat, D. H., Kaye, J. A., & Janowsky, J. S. (1999). Prefrontal gray and white matter volumes in healthy aging and Alzheimer disease. *Archives of Neurology*, 56(3), 338-344. <https://doi.org/10.1001/archneur.56.3.338>
- Salat, D. H., Williams, V. J., Leritz, E. C., Schnyer, D. M., Rudolph, J. L., Lipsitz, L. A., McGlinchey, R. E., & Milberg, W. P. (2012). Inter-individual variation in blood pressure is associated with regional white matter integrity in generally healthy older adults. *NeuroImage*, 59(1), 181-192. <https://doi.org/10.1016/j.neuroimage.2011.07.033>
- Salerno, J. A., Murphy, D., Horwitz, B., DeCarli, C., Haxby, J. V., Rapoport, S. I., & Schapiro, M. B. (1992). Brain atrophy in hypertension. A volumetric magnetic resonance imaging study. *Hypertension*, 20(3), 340-348. <https://doi.org/10.1161/01.HYP.20.3.340>
- Salimi, S., Irish, M., Foxe, D., Hodges, J. R., Pigué, O., & Burrell, J. R. (2017). Can visuospatial measures improve the diagnosis of Alzheimer's disease?. *Alzheimer's & Dementia (Amsterdam, Netherlands)*, 10, 66–74. <https://doi.org/10.1016/j.dadm.2017.10.004>
- Salman, M. S., & Tsai, P. (2016). The role of the pediatric cerebellum in motor functions, cognition and behavior: A clinical perspective. *Neuroimaging Clinics of North America*, 26(3), 317. <https://doi.org/10.1016/j.nic.2016.03.003>
- Salmon, E., Van der Linden, M., Collette, F., Delfiore, G., Maquet, P., Degueldre, C., Luxen, A., & Franck, G. (1996). Regional brain activity during working memory tasks. *Brain*, 119(5), 1617-1625. <https://doi.org/10.1093/brain/119.5.1617>
- Salo, K. I., Scharfen, J., Wilden, I. D., Schubotz, R. I., & Holling, H. (2019). Confining the concept of vascular depression to late-onset depression: A meta-analysis of MRI-defined hyperintensity burden in major depressive disorder and bipolar disorder. *Frontiers in Psychology*, 10, 1241. <https://doi.org/10.3389/fpsyg.2019.01241>
- Salomone, S., Caraci, F., Leggio, G. M., Fedotova, J., & Drago, F. (2012). New pharmacological strategies for treatment of Alzheimer's disease: focus on disease modifying drugs. *British Journal of Clinical Pharmacology*, 73(4), 504-517. <https://doi.org/10.1111/j.1365-2125.2011.04134.x>
- Salzar, R. S., Thubrikar, M. J., & Eppink, R. T. (1995). Pressure-induced mechanical stress in the carotid artery bifurcation: A possible correlation to atherosclerosis. *Journal of Biomechanics*, 28(11), 1333-1340. [https://doi.org/10.1016/0021-9290\(95\)00005-3](https://doi.org/10.1016/0021-9290(95)00005-3)
- Samara, A., Murphy, T., Strain, J., Rutlin, J., Sun, P., Neyman, O., Sreevalsan, N., Shimony, J. S., Ances, B. M., Song, S. K., Hershey, T., & Eisenstein, S. A. (2020). Neuroinflammation and

- White Matter Alterations in Obesity Assessed by Diffusion Basis Spectrum Imaging. *Frontiers in Human Neuroscience*, 13, 464. <https://doi.org/10.3389/fnhum.2019.00464>
- Sanchez, A., Tripathy, D., Luo, J., Yin, X., Martinez, J., & Grammas, P. (2013). Neurovascular unit and the effects of dosage in VEGF toxicity: role for oxidative stress and thrombin. *Journal of Alzheimer's Disease*, 34(1), 281-291. <https://doi.org/10.3233/JAD-121636>
- Sasaki, N., Fukatsu, R., Tsuzuki, K., Hayashi, Y., Yoshida, T., Fujii, N., Koike, T., Wakayama, I., Yanagihara, R., Garruto, R., Amano, N., & Makita, Z. (1998). Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. *The American Journal of Pathology*, 153(4), 1149-1155. [https://doi.org/10.1016/S0002-9440\(10\)65659-3](https://doi.org/10.1016/S0002-9440(10)65659-3)
- Satish, S., Zhang, D. D., & Goodwin, J. S. (2001). Clinical significance of falling blood pressure among older adults. *Journal of Clinical Epidemiology*, 54(9), 961-967. [https://doi.org/10.1016/S0895-4356\(01\)00360-2](https://doi.org/10.1016/S0895-4356(01)00360-2)
- Sato, A., Sato, Y., & Uchida, S. (2004). Activation of the intracerebral cholinergic nerve fibers originating in the basal forebrain increases regional cerebral blood flow in the rat's cortex and hippocampus. *Neuroscience Letters*, 361(1-3), 90-93. <https://doi.org/10.1016/j.neulet.2004.01.004>
- Sato, K., Ogoh, S., Hirasawa, A., Oue, A., & Sadamoto, T. (2011). The distribution of blood flow in the carotid and vertebral arteries during dynamic exercise in humans. *The Journal of Physiology*, 589(11), 2847-2856. <https://doi.org/10.1113/jphysiol.2010.204461>
- Sato, S., Toyoda, K., Uehara, T., Toratani, N., Yokota, C., Moriwaki, H., Naritomi, H., & Minematsu, K. (2008). Baseline NIH Stroke Scale Score predicting outcome in anterior and posterior circulation strokes. *Neurology*, 70(24 Part 2), 2371-2377. <https://doi.org/10.1212/01.wnl.0000304346.14354.0b>
- Sattler, C., Toro, P., Schönknecht, P., & Schröder, J. (2012). Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. *Psychiatric Research*, 196(1), 90-95. <https://doi.org/10.1016/j.psychres.2011.11.012>
- Savitz, S. I., & Caplan, L. R. (2005). Vertebrobasilar disease. *New England Journal of Medicine*, 352(25), 2618-2626. <https://doi.org/10.1056/NEJMra041544>
- Savoirdo, M., Bracchi, M., Passerini, A., & Visciani, A. (1987). The vascular territories in the cerebellum and brainstem: CT and MR study. *American Journal of Neuroradiology*, 8(2), 199-209.
- Sawicka, K., Szczyrek, M., Jastrzebska, I., Prasal, M., Zwolak, A., & Daniluk, J. (2011). Hypertension—The silent killer. *Journal of Pre-Clinical and Clinical Research*, 5(2).
- Saxena, S. (2015). *Episodic memory performance and associated grey matter volume in older adults with type 2 diabetes mellitus* (<https://hdl.handle.net/2144/13980>) [Doctoral dissertation, Boston University]. Boston University Theses and Dissertations.
- Scarmeas, N., Albert, S., Manly, J., & Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 77(3), 308-316. <http://dx.doi.org/10.1136/jnnp.2005.072306>
- Scarmeas, N., Luchsinger, J. A., Schupf, N., Brickman, A. M., Cosentino, S., Tang, M. X., & Stern, Y. (2009). Physical activity, diet, and risk of Alzheimer disease. *JAMA*, 302(6), 627-637. <https://doi.org/10.1001/jama.2009.1144>
- Schäfer, M., Kheyfets, V. O., Schroeder, J. D., Dunning, J., Shandas, R., Buckner, J. K., Browning, J., Hertzberg, J., Hunter, K. S., & Fenster, B. E. (2016). Main pulmonary arterial wall shear stress correlates with invasive hemodynamics and stiffness in pulmonary hypertension. *Pulmonary Circulation*, 6(1), 37-45. <https://doi.org/10.1086/685024>
- Schultz, B., Later, W., Heller, M., Peters, A., Müller, M. J., & Bosy-Westphal, A. (2012). Impact of age on leptin and adiponectin independent of adiposity. *British Journal of Nutrition*, 108(2), 363-370. <https://doi.org/10.1017/S0007114511005605>

- Scheltens, P., Blennow, K., Breteler, M. M., de Strooper, B., Frisoni, G. B., Salloway, S., & Van der Flier, W. M. (2016). Alzheimer's disease. *The Lancet*, *388*(10043), 505-517. [https://doi.org/10.1016/S0140-6736\(15\)01124-1](https://doi.org/10.1016/S0140-6736(15)01124-1)
- Schiffrin, E. L. (2004). Vascular stiffening and arterial compliance: Implications for systolic blood pressure. *American Journal of Hypertension*, *17*(S3), 39S-48S. <https://doi.org/10.1016/j.amjhyper.2004.08.019>
- Schiffrin, E. L., Deng, L. Y., & Larochelle, P. (1994). Effects of a beta-blocker or a converting enzyme inhibitor on resistance arteries in essential hypertension. *Hypertension*, *23*(1), 83-91. <https://doi.org/10.1161/01.HYP.23.1.83>
- Schmid, N. S., Taylor, K. I., Foldi, N. S., Berres, M., & Monsch, A. U. (2013). Neuropsychological signs of Alzheimer's disease 8 years prior to diagnosis. *Journal of Alzheimer's Disease*, *34*(2), 537-546. <https://doi.org/10.3233/JAD-121234>
- Schmidt, P., Gaser, C., Arsic, M., Buck, D., Förschler, A., Berthele, A., Hoshi, M., Ilg, R., Schmid, V. J., Zimmer, C., Hemmer, B., & Mühlau, M. (2012). An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. *NeuroImage*, *59*(4), 3774-3783. <https://doi.org/10.1016/j.neuroimage.2011.11.032>
- Schrijvers, E. M., Verhaaren, B. F., Koudstaal, P. J., Hofman, A., Ikram, M. A., & Breteler, M. M. B. (2012). Is dementia incidence declining? Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology*, *78*(19), 1456-1463. <https://doi.org/10.1212/WNL.0b013e3182553be6>
- Schutz, D. D., Busetto, L., Dicker, D., Farpour-Lambert, N., Pryke, R., Toplak, H., Widmer, D., Yumuk, V., & Schutz, Y. (2019). European practical and patient-centred guidelines for adult obesity management in primary care. *Obesity Facts*, *12*(1), 40-66. <https://doi.org/10.1159/000496183>
- Schwartz, E., Wicinski, B., Schmeidler, J., Haroutunian, V., & Hof, P. (2010). Cardiovascular risk factors affect hippocampal microvasculature in early AD. *Translational Neuroscience*, *1*(4), 292-299. <https://doi.org/10.2478/v10134-010-0040-9>
- Scuteri, A. (2012). Brain injury as end-organ damage in hypertension. *The Lancet Neurology*, *11*(12), 1015-1017. [https://doi.org/10.1016/S1474-4422\(12\)70265-X](https://doi.org/10.1016/S1474-4422(12)70265-X)
- Sequist, E. R., Tkac, I., Damberg, G., Thomas, W., & Gruetter, R. (2005). Brain glucose concentrations in poorly controlled diabetes mellitus as measured by high-field magnetic resonance spectroscopy. *Metabolism*, *54*(8), 1008-1013. <https://doi.org/10.1016/j.metabol.2005.02.018>
- Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*, *27*(9), 2349-2356. <https://doi.org/10.1523/JNEUROSCI.5587-06.2007>
- Segal, K. R., Landt, M., & Klein, S. (1996). Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. *Diabetes*, *45*(7), 988-991. <https://doi.org/10.2337/diab.45.7.988>
- Segura, B., Jurado, M., Freixenet, N., Falcon, C., Junqué, C., & Arboix, A. (2009). Microstructural white matter changes in metabolic syndrome: A diffusion tensor imaging study. *Neurology*, *73*(6), 438-444. <https://doi.org/10.1212/WNL.0b013e3181b163cd>
- Seijkens, T., Hoeksema, M. A., Beckers, L., Smeets, E., Meiler, S., Levels, J., Tjwa, M., de Winther, M. P., & Lutgens, E. (2014). Hypercholesterolemia-induced priming of hematopoietic stem and progenitor cells aggravates atherosclerosis. *The FASEB Journal*, *28*(5), 2202-2213. <https://doi.org/10.1096/fj.13-243105>
- Selim, M., Jones, R., Novak, P., Zhao, P., & Novak, V. (2008). The effects of body mass index on cerebral blood flow velocity. *Clinical Autonomic Research*, *18*(6), 331. <https://doi.org/10.1007/s10286-008-0490-z>

- Selkoe, D. J. (2015). Alzheimer disease. In R. N. Rosenberg & J. M. Pascual (Eds.), *Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease (Fifth Edition)* (pp. 753-768): Elsevier.
- Selkoe, D. J. (1991). The molecular pathology of Alzheimer's disease. *Neuron*, 6(4), 487-498. [https://doi.org/10.1016/0896-6273\(91\)90052-2](https://doi.org/10.1016/0896-6273(91)90052-2)
- Senda, J., Watanabe, H., Tsuboi, T., Hara, K., Watanabe, H., Nakamura, R., Ito, M., Atsuta, N., Tanaka, F., Naganawa, S., & Sobue, G. (2012). MRI mean diffusivity detects widespread brain degeneration in multiple sclerosis. *Journal of the Neurological Sciences*, 319(1-2), 105-110. <https://doi.org/10.1016/j.jns.2012.04.019>
- Seo, D. C., Choe, S., & Torabi, M. R. (2017). Is waist circumference $\geq 102/88$ cm better than body mass index ≥ 30 to predict hypertension and diabetes development regardless of gender, age group, and race/ethnicity? Meta-analysis. *Preventive Medicine*, 97, 100-108. <https://doi.org/10.1016/j.ypmed.2017.01.012>
- Seo, S. W., Lee, J. M., Im, K., Park, J. S., Kim, S. H., Kim, S. T., Ahn, H. J., Chin, J., Cheong, H. K., Weiner, M. W., & Na, D. L. (2012). Cortical thinning related to periventricular and deep white matter hyperintensities. *Neurobiology of Aging*, 33(7), 1156-1167. <https://doi.org/10.1016/j.neurobiolaging.2010.12.003>
- Serné, E. H., IJzerman, R. G., Gans, R. O., Nijveldt, R., De Vries, G., Evertz, R., Donker, A. J., & Stehouwer, C. D. (2002). Direct evidence for insulin-induced capillary recruitment in skin of healthy subjects during physiological hyperinsulinemia. *Diabetes*, 51(5), 1515-1522. <https://doi.org/10.2337/diabetes.51.5.1515>
- Serrano-Pozo, A., Qian, J., Muzikansky, A., Monsell, S. E., Montine, T. J., Frosch, M. P., Betensky, R. A., & Hyman, B. T. (2016). Thal amyloid stages do not significantly impact the correlation between neuropathological change and cognition in the Alzheimer disease continuum. *Journal of Neuropathology & Experimental Neurology*, 75(6), 516-526. <https://doi.org/10.1093/jnen/nlw026>
- Serrano-Pozo, A., William, C.M., Ferrer, I., Uro-Coste, E., Delisle, M.B., Maura, C.A., Hock, C., Nitsch, R.M., Masliah, E., Growdon, J.H., & Frosch, M.P. (2010). Beneficial effect of human anti-amyloid- β active immunization on neurite morphology and tau pathology. *Brain*, 133(5), 1312-1327. <https://doi.org/10.1093/brain/awq056>
- Servello, A., Fioretti, A., Gualdi, G., Di Biasi, C., Pittalis, A., Sollaku, S., Pavaci, S., Tortorella, F., Fusetti, M., Valenti, M., Masedu, F., Cacciafesta, M., Marigliano, V., Ettorre, E., & Pagliarella, M. (2015). Olfactory Dysfunction, Olfactory Bulb Volume and Alzheimer's Disease: Is There a Correlation? A Pilot Study1. *Journal of Alzheimer's Disease*, 48(2), 395-402. <https://doi.org/10.3233/JAD-150232>
- Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., Ling, Y., O'Gorman, J., Qian, F., Arastu, M., Li, M., Chollate, S., Brennan, M. S., Quintero-Monzon, O., Scannevin, R. H., Arnold, H. M., Engber, T., ... Sandrock, A. (2016). The antibody aducanumab reduces A β plaques in Alzheimer's disease. *Nature*, 537(7618), 50-56. <https://doi.org/10.1038/nature19323>
- Sexton, C. E., Kalu, U. G., Filippini, N., Mackay, C. E., & Ebmeier, K. P. (2011). A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, 32(12), 2322 e2325-2318. <https://doi.org/10.1016/j.neurobiolaging.2010.05.019>
- Shabir, O., Moll, T. A., Matuszyk, M. M., Eyre, B., Dake, M. D., Berwick, J., & Francis, S. E. (2020). Preclinical models of disease and multimorbidity with focus upon cardiovascular disease and dementia. *Mechanisms of Ageing and Development*, 192, 111361. <https://doi.org/10.1016/j.mad.2020.111361>

- Shafto, M. A., & Tyler, L. K. (2014). Language in the aging brain: the network dynamics of cognitive decline and preservation. *Science*, *346*(6209), 583-587. <https://doi.org/10.1126/science.1254404>
- Shao, B., & Bayraktutan, U. (2014). Hyperglycaemia promotes human brain microvascular endothelial cell apoptosis via induction of protein kinase C- β I and prooxidant enzyme NADPH oxidase. *Redox Biology*, *2*, 694-701. <https://doi.org/10.1016/j.redox.2014.05.005>
- Shaw, M. E., Abhayaratna, W. P., Anstey, K. J., & Cherbuin, N. (2017). Increasing body mass index at midlife is associated with increased cortical thinning in Alzheimer's disease-vulnerable regions. *Journal of Alzheimer's Disease*, *59*(1), 113-120. <https://doi.org/10.3233/JAD-170055>
- Sheen, Y. J., & Sheu, W. H. (2016). Association between hypoglycemia and dementia in patients with type 2 diabetes. *Diabetes Research and Clinical Practice*, *116*, 279-287. <https://doi.org/10.1016/j.diabres.2016.04.004>
- Sheline, Y. I., Raichle, M. E., Snyder, A. Z., Morris, J. C., Head, D., Wang, S., & Mintun, M. A. (2010). Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. *Biological Psychiatry*, *67*(6), 584-587. <https://doi.org/10.1016/j.biopsych.2009.08.024>
- Shen, L.-J., Yang, S.-B., Lv, Q.-W., Zhang, G.-H., Zhou, J., Guo, M., Huang, H. B., Li, Z., & Yang, C. S. (2014). High plasma adiponectin levels in patients with severe traumatic brain injury. *Clinica Chimica Acta*, *427*, 37-41. <https://doi.org/10.1016/j.cca.2013.09.047>
- Shimizu, F., Sano, Y., Tominaga, O., Maeda, T., Abe, M., & Kanda, T. (2013). Advanced glycation end-products disrupt the blood-brain barrier by stimulating the release of transforming growth factor- β by pericytes and vascular endothelial growth factor and matrix metalloproteinase-2 by endothelial cells in vitro. *Neurobiology of Aging*, *34*(7), 1902-1912. <https://doi.org/10.1016/j.neurobiolaging.2013.01.012>
- Shinotoh, H., Namba, H., Fukushi, K., Nagatsuka, S. I., Tanaka, N., Aotsuka, A., Ota, T., Tanada, S., & Irie, T. (2000). Progressive loss of cortical acetylcholinesterase activity in association with cognitive decline in Alzheimer's disease: A positron emission tomography study. *Annals of Neurology*, *48*(2), 194-200. [https://doi.org/10.1002/1531-8249\(200008\)48:2<194::AID-ANA9>3.0.CO;2-X](https://doi.org/10.1002/1531-8249(200008)48:2<194::AID-ANA9>3.0.CO;2-X)
- Shirwany, N. A., & Zou, M. H. (2010). Arterial stiffness: A brief review. *Acta Pharmacologica Sinica*, *31*(10), 1267. <https://doi.org/10.1038/aps.2010.123>
- Shoghi-Jadid, K., Small, G. W., Agdeppa, E. D., Kepe, V., Ercoli, L. M., Siddarth, P., P., Read, S., Satyamurthy, N., Petric, A., Huang, S.C., & Barrio, J.R., (2002). Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *10*(1), 24-35. <https://doi.org/10.1097/00019442-200201000-00004>
- Shott, M. E., Cornier, M.-A., Mittal, V. A., Pryor, T. L., Orr, J. M., Brown, M. S., & Frank, G. K. W. (2015). Orbitofrontal cortex volume and brain reward response in obesity. *International Journal of Obesity*, *39*(2), 214-221. <https://doi.org/10.1038/ijo.2014.121>
- Shu, N., Wang, Z., Qi, Z., Li, K., & He, Y. (2011). Multiple diffusion indices reveals white matter degeneration in Alzheimer's disease and mild cognitive impairment: A tract-based spatial statistics study. *Journal of Alzheimer's Disease*, *26*(s3), 275-285. <https://doi.org/10.3233/JAD-2011-0024>
- Sierra, C., De La Sierra, A., Salameo, M., Sobrino, J., Gómez-Angelats, E., & Coca, A. (2004). Silent cerebral white matter lesions and cognitive function in middle-aged essential hypertensive patients. *American Journal of Hypertension*, *17*(6), 529-534. <https://doi.org/10.1016/j.amjhyper.2004.02.014>
- Siervo, M., Lara, J., Chowdhury, S., Ashor, A., Oggioni, C., & Mathers, J. C. (2015). Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: A

- systematic review and meta-analysis. *British Journal of Nutrition*, 113(1), 1-15.
<https://doi.org/10.1017/S0007114514003341>
- Silha, J. V., Krsek, M., Skrha, J. V., Sucharda, P., Nyomba, B. L., & Murphy, L. J. (2003). Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance. *European Journal of Endocrinology*, 149(4), 331–335.
<https://doi.org/10.1530/eje.0.1490331>
- Silva, E. A., Flexa, F., & Zanella, M. T. (2009). Impact of abdominal fat and insulin resistance on arterial hypertension in non-obese women. *Arquivos Brasileiros de Endocrinologia & Metabologia*, 53(3), 340-343. <https://doi.org/10.1590/S0004-27302009000300007>
- Silvah, J. H., Marchini, J. S., Lima, C. M. M., Nicoletti, C. F., Santos, L. A., Itikawa, E., Trevisan, A. C., Pitella, F. A., Kato, M., Junior, N. I., Frantz, F. G., Cunha, S. F. C., Buchpiguel, C. A., & Wichert-Ana, L. (2020). Regional cerebral blood flow at rest in obesity. *Nutrition*, 79-80, 110888.
- Singh, R., & Tubbs, R. S. (2018). Histological verification of atherosclerosis due to bends and bifurcations in carotid arteries predicted by hemodynamic model. *Jornal Vascular Brasileiro*, 17(4), 280-289. <https://doi.org/10.1590/1677-5449.004118>
- Sipahi, I., Tuzcu, E. M., Schoenhagen, P., Wolski, K. E., Nicholls, S. J., Balog, C., Crowe, T. D., & Nissen, S. E. (2006). Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis. *Journal of the American College of Cardiology*, 48(4), 833-838. <https://doi.org/10.1016/j.jacc.2006.05.045>
- Small, S. A., Schobel, S. A., Buxton, R. B., Witter, M. P., & Barnes, C. A. (2011). A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nature Reviews Neuroscience*, 12(10), 585-601. <https://doi.org/10.1038/nrn3085>
- Smith, D., Lovell, J., Weller, C., Kennedy, B., Winbolt, M., Young, C., & Ibrahim, J. (2017). A systematic review of medication non-adherence in persons with dementia or cognitive impairment. *PLoS One*, 12(2), e0170651. <https://doi.org/10.1371/journal.pone.0170651>
- Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, 31(4), 1487-1505. <https://doi.org/10.1016/j.neuroimage.2006.02.024>
- Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, 44(1), 83-98. <https://doi.org/10.1016/j.neuroimage.2008.03.061>
- Sobngwi, E., Mbanya, J. N., Unwin, N., Kengne, A., Fezeu, L., Minkoulou, E., Aspray, T. J., & Alberti, K. G. M. M. (2002). Physical activity and its relationship with obesity, hypertension and diabetes in urban and rural Cameroon. *International Journal of Obesity*, 26(7), 1009-1016. <https://doi.org/10.1038/sj.ijo.0802008>
- Sofi, F., Cesari, F., Abbate, R., Gensini, G. F., & Casini, A. (2008). Adherence to Mediterranean diet and health status: Meta-analysis. *BMJ*, 337, a1344. <https://doi.org/10.1136/bmj.a1344>
- Solomon, A., Dobranici, L., Kåreholt, I., Tudose, C., & Lăzărescu, M. (2011). Comorbidity and the rate of cognitive decline in patients with Alzheimer dementia. *International Journal of Geriatric Psychiatry*, 26(12), 1244-1251. <https://doi.org/10.1002/gps.2670>
- Solomon, A., Kåreholt, I., Ngandu, T., Winblad, B., Nissinen, A., Tuomilehto, J., Soininen, H., & Kivipelto, M. (2007). Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. *Neurology*, 68(10), 751-756.
<https://doi.org/10.1212/01.wnl.0000256368.57375.b7>
- Son, S. J., Kim, J., Lee, E., Park, J. Y., Namkoong, K., Hong, C. H., Ku, J., Kim, E., & Oh, B. H. (2015). Effect of hypertension on the resting-state functional connectivity in patients with Alzheimer's disease (AD). *Archives of Gerontology and Geriatrics*, 60(1), 210-216.
<https://doi.org/10.1016/j.archger.2014.09.012>

- Song, J., Choi, S.-M., Whitcomb, D. J., Kim, B. C. J. C. d., & disease. (2017). Adiponectin controls the apoptosis and the expression of tight junction proteins in brain endothelial cells through AdipoR1 under beta amyloid toxicity. *8*(10), e3102-e3102.
- Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dismyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *NeuroImage*, *17*(3), 1429-1436. <https://doi.org/10.1006/nimg.2002.1267>
- Song, Z., Cai, L., Guo, L., Tsukamoto, Y., Yutani, C., & Li, X. A. (2010). Accumulation and expression of serum amyloid P component in human atherosclerotic lesions. *Atherosclerosis*, *211*(1), 90-95. <https://doi.org/10.1016/j.atherosclerosis.2010.01.046>
- Soro-Paavonen, A., Watson, A. M., Li, J., Paavonen, K., Koitka, A., Calkin, A. C., Barit, D., Coughlan, M. T., Drew, B. G., Lancaster, G. I., Thomas, M., Forbes, J. M., Nawroth, P. P., Bierhaus, A., Cooper, M. E., & Jandeleit-Dahm, K. A. (2008). Receptor for advanced glycation end products (RAGE) deficiency attenuates the development of atherosclerosis in diabetes. *Diabetes*, *57*(9), 2461–2469. <https://doi.org/10.2337/db07-1808>
- Soustiel, J. F., Levy, E., Bibi, R., Lukaschuk, S., & Manor, D. (2001). Hemodynamic consequences of cerebral vasospasm on perforating arteries: a phantom model study. *Stroke*, *32*(3), 629-635. <https://doi.org/10.1161/01.STR.32.3.629>
- Spaan, P. E., Raaijmakers, J. G., & Jonker, C. (2003). Alzheimer's disease versus normal ageing: A review of the efficiency of clinical and experimental memory measures. *Journal of Clinical and Experimental Neuropsychology*, *25*(2), 216-233. <https://doi.org/10.1076/jcen.25.2.216.13638>
- Spallazzi, M., Dobisch, L., Becke, A., Berron, D., Stucht, D., Oeltze-Jafra, S., Caffarra, P., Speck, O., & Düzel, E. (2019). Hippocampal vascularization patterns: A high-resolution 7 Tesla time-of-flight magnetic resonance angiography study. *NeuroImage: Clinical*, *21*, 101609. <https://doi.org/10.1016/j.nicl.2018.11.019>
- Sparks, D. L., Scheff, S. W., Liu, H., Landers, T. M., Coyne, C. M., & Hunsaker III, J. C. (1995). Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension. *Journal of the Neurological Sciences*, *131*(2), 162-169. [https://doi.org/10.1016/0022-510X\(95\)00105-B](https://doi.org/10.1016/0022-510X(95)00105-B)
- Spieker, E. A., Kochunov, P., Rowland, L. M., Sprooten, E., Winkler, A. M., Olvera, R. L., Almasy, L., Duggirala, R., Fox, P. T., Blangero, J., Glahn, D. C., & Curran, J. E. (2015). Shared genetic variance between obesity and white matter integrity in Mexican Americans. *Frontiers in Genetics*, *6*, 26. <https://doi.org/10.3389/fgene.2015.00026>
- Spinelli, M., Fusco, S., Mainardi, M., Scala, F., Natale, F., Lapenta, R., Mattera, A., Rinaudo, M., Li Puma, D. D., Ripoli, C., Grassi, A., D'Ascenzo, M., & Grassi, C. (2017). Brain insulin resistance impairs hippocampal synaptic plasticity and memory by increasing GluA1 palmitoylation through FoxO3a. *Nature Communications*, *8*(1), 2009. <https://doi.org/10.1038/s41467-017-02221-9>
- Špolcová, A., Mikulášková, B., Kršková, K., Gajdošechová, L., Zórad, Š., Olszanecki, R., Suski, M., Bujak-Giżycka, B., Železná, B., & Maletínská, L. (2014). Deficient hippocampal insulin signaling and augmented Tau phosphorylation is related to obesity-and age-induced peripheral insulin resistance: a study in Zucker rats. *BMC Neuroscience*, *15*(1), 111. <https://doi.org/10.1186/1471-2202-15-111>
- Spulber, G., Niskanen, E., MacDonald, S., Kivipelto, M., Ferreira Padilla, D., Julkunen, V., Hallikainen, M., Vanninen, R., Wahlund, L. O., & Soininen, H. (2012). Evolution of global and local grey matter atrophy on serial MRI scans during the progression from MCI to AD. *Current Alzheimer Research*, *9*(4), 516-524. <https://doi.org/10.2174/156720512800492486>
- Srikanth, V., Maczurek, A., Phan, T., Steele, M., Westcott, B., Juskiw, D., & Münch, G. (2011). Advanced glycation endproducts and their receptor RAGE in Alzheimer's disease. *Neurobiology of Aging*, *32*(5), 763-777. <https://doi.org/10.1016/j.neurobiolaging.2009.04.016>

- Stabouli, S., Kotsis, V., Papamichael, C., Constantopoulos, A., & Zakopoulos, N. (2005). Adolescent obesity is associated with high ambulatory blood pressure and increased carotid intimal-medial thickness. *The Journal of Pediatrics*, *147*(5), 651-656. <https://doi.org/10.1016/j.jpeds.2005.06.008>
- Stanaway, J. D., Afshin, A., Gakidou, E., Lim, S. S., Abate, D., Abate, K. H., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, M., Abebe, Z., Abera, S. F., Abil, O. Z., Abraha, H. N., ... Murray, C. J. L. (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1923-1994. [https://doi.org/10.1016/S0140-6736\(18\)32225-6](https://doi.org/10.1016/S0140-6736(18)32225-6)
- Stanek, K. M., Grieve, S. M., Brickman, A. M., Korgaonkar, M. S., Paul, R. H., Cohen, R. A., & Gunstad, J. J. (2011). Obesity is associated with reduced white matter integrity in otherwise healthy adults. *Obesity*, *19*(3), 500-504. <https://doi.org/10.1038/oby.2010.312>
- Starks, E. J., Patrick O'Grady, J., Hoscheidt, S. M., Racine, A. M., Carlsson, C. M., Zetterberg, H., Blennow, K., Okonkwo, O. C., Puglielli, L., Asthana, S., Dowling, N. M., Gleason, C. E., Anderson, R. M., Davenport-Sis, N. J., DeRungs, L. M., Sager, M. A., Johnson, S. C., & Bendlin, B. B. (2015). Insulin Resistance is Associated with Higher Cerebrospinal Fluid Tau Levels in Asymptomatic APOEε4 Carriers. *Journal of Alzheimer's Disease*, *46*(2), 525–533. <https://doi.org/10.3233/JAD-150072>
- Starr, J. M., Farrall, A. J., Armitage, P., McGurn, B., & Wardlaw, J. (2009). Blood–brain barrier permeability in Alzheimer's disease: A case–control MRI study. *Psychiatry Research: Neuroimaging*, *171*(3), 232-241. <https://doi.org/10.1016/j.pscychresns.2008.04.003>
- Stawarz, K., Rodríguez, M. D., Cox, A. L., & Blandford, A. (2016). Understanding the use of contextual cues: Design implications for medication adherence technologies that support remembering. *Digital health*, *2*, 2055207616678707. <https://doi.org/10.1177/2055207616678707>
- Stead, T., Rastogi, V., Penumudi, R., Lamb, D., Williamson, J., & Hedna, V. (2015). Hemispheric differences in malignant middle cerebral artery stroke. *Neurology*, *84*(14 supplement), P2. 288.
- Stegenga, H., Haines, A., Jones, K., & Wilding, J. (2014). Identification, assessment, and management of overweight and obesity: Summary of updated NICE guidance. *BMJ*, *349*, g6608. <https://doi.org/10.1136/bmj.g6608>
- Steinarsson, A. O., Rawshani, A., Gudbjornsdottir, S., Franzen, S., Svensson, A. M., & Sattar, N. (2018). Short-term progression of cardiometabolic risk factors in relation to age at type 2 diabetes diagnosis: A longitudinal observational study of 100,606 individuals from the Swedish National Diabetes Register. *Diabetologia*, *61*(3), 599-606. <https://doi.org/10.1007/s00125-017-4532-8>
- Stephan, K., Friston, K., & Squire, L. (2009). Functional connectivity. In L. R. Squire (Ed.), *Encyclopedia of Neuroscience* (pp. 391-397). Elsevier.
- Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015-2028. <https://doi.org/10.1016/j.neuropsychologia.2009.03.004>
- Stern, Y., Albert, S., Tang, M. X., & Tsai, W. Y. (1999). Rate of memory decline in AD is related to education and occupation: Cognitive reserve?. *Neurology*, *53*(9), 1942-1942. <https://doi.org/10.1212/WNL.53.9.1942>
- Stern, Y., Arenaza-Urquijo, E. M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W. S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., & the Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain

- maintenance. *Alzheimer's & Dementia*, 16(9), 1305–1311.
<https://doi.org/10.1016/j.jalz.2018.07.219>
- Stern, Y., Gurland, B., Tatemichi, T. K., Tang, M. X., Wilder, D., & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA*, 271(13), 1004-1010. <https://doi.org/10.1001/jama.1994.03510370056032>
- Stevens, S. L., Wood, S., Koshiaris, C., Law, K., Glasziou, P., Stevens, R. J., & McManus, R. J. (2016). Blood pressure variability and cardiovascular disease: Systematic review and meta-analysis. *BMJ*, 354, i4098. <https://doi.org/10.1136/bmj.i4098>
- Stice, E., Figlewicz, D. P., Gosnell, B. A., Levine, A. S., & Pratt, W. E. (2013). The contribution of brain reward circuits to the obesity epidemic. *Neuroscience & Biobehavioral Reviews*, 37(9), 2047-2058. <https://doi.org/10.1016/j.neubiorev.2012.12.001>
- Stolp, H., Dziegielewska, K., Ek, C., Potter, A., & Saunders, N. (2005). Long-term changes in blood–brain barrier permeability and white matter following prolonged systemic inflammation in early development in the rat. *European Journal of Neuroscience*, 22(11), 2805-2816. <https://doi.org/10.1111/j.1460-9568.2005.04483.x>
- Stone, J., Johnstone, D. M., Mitrofanis, J., & O'Rourke, M. (2015). The mechanical cause of age-related dementia (Alzheimer's disease): the brain is destroyed by the pulse. *Journal of Alzheimer's Disease*, 44(2), 355-373. <https://doi.org/10.3233/JAD-141884>
- Stopford, C. L., Thompson, J. C., Neary, D., Richardson, A. M., & Snowden, J. S. (2012). Working memory, attention, and executive function in Alzheimer's disease and frontotemporal dementia. *Cortex*, 48(4), 429-446. <https://doi.org/10.1016/j.cortex.2010.12.002>
- Strain, J. F., Smith, R. X., Beaumont, H., Roe, C. M., Gordon, B. A., Mishra, S., Adeyemo, B., Christensen, J. J., Su, Y., Morris, J. C., Benzinger, T. L. S., & Ances, B. M. (2018). Loss of white matter integrity reflects tau accumulation in Alzheimer disease defined regions. *Neurology*, 91(4), e313-e318. <https://doi.org/10.1212/WNL.0000000000005864>
- Stranahan, A. M., Hao, S., Dey, A., Yu, X., & Baban, B. (2016). Blood–brain barrier breakdown promotes macrophage infiltration and cognitive impairment in leptin receptor-deficient mice. *Journal of Cerebral Blood Flow & Metabolism*, 36(12), 2108-2121. <https://doi.org/10.1177/0271678X16642233>
- Strassburger, T. L., Lee, H. C., Daly, E. M., Szczepanik, J., Krasuski, J. S., Mentis, M. J., Salerno, J. A., DeCarli, C., Schapiro, M. B., & Alexander, G. E. (1997). Interactive effects of age and hypertension on volumes of brain structures. *Stroke*, 28(7), 1410-1417. <https://doi.org/10.1161/01.STR.28.7.1410>
- Stratton, I. M., Adler, A. I., Neil, H. A. W., Matthews, D. R., Manley, S. E., Cull, C. A., Hadden, D., Turner, R. C., & Holman, R. R. (2000). Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ*, 321(7258), 405-412. <https://doi.org/10.1136/bmj.321.7258.405>
- Stricker, N. H., Schweinsburg, B. C., Delano-Wood, L., Wierenga, C. E., Bangen, K. J., Haaland, K. Y., Frank, L. R., Salmon, D. P., & Bondi, M. W. (2009). Decreased white matter integrity in late-myelinating fiber pathways in Alzheimer's disease supports retrogenesis. *NeuroImage*, 45(1), 10-16. <https://doi.org/10.1016/j.neuroimage.2008.11.027>
- Strickland, S. (2018). Blood will out: Vascular contributions to Alzheimer's disease. *The Journal of Clinical Investigation*, 128(2), 556-563. <https://doi.org/10.1172/JCI97509>
- Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology: General*, 18(6), 643. <https://doi.org/10.1037/0096-3445.121.1.15>
- Stuhec, M., Keuschler, J., Serra-Mestres, J., & Isetta, M. (2017). Effects of different antihypertensive medication groups on cognitive function in older patients: A systematic review. *European Psychiatry*, 46, 1-15. <https://doi.org/10.1016/j.eurpsy.2017.07.015>
- Sugimoto, T., Ono, R., Murata, S., Saji, N., Matsui, Y., Niida, S., Toba, K., & Sakurai, T. J. C. A. R. (2016). Prevalence and associated factors of sarcopenia in elderly subjects with amnesic

- mild cognitive impairment or Alzheimer disease. *Current Alzheimer Research*, 13(6), 718-726. <https://doi.org/10.2174/1567205013666160211124828>
- Suh, Y. H., & Checler, F. (2002). Amyloid precursor protein, presenilins, and alpha-synuclein: molecular pathogenesis and pharmacological applications in Alzheimer's disease. *Pharmacological Reviews*, 54(3), 469-525. <https://doi.org/10.1124/pr.54.3.469>
- Sun, M. K., & Alkon, D. L. (2004). Cerebral hypoperfusion and amyloid-induced synergistic impairment of hippocampal CA1 synaptic efficacy and spatial memory in young adult rats. *Journal of Alzheimer's Disease*, 6(4), 355-366. <https://doi.org/10.3233/JAD-2004-6402>
- Sun, Z., Wang, Z. T., Sun, F. R., Shen, X. N., Xu, W., Ma, Y. H., Dong, Q., Tan, L., Yu, J. T., & Alzheimer's Disease Neuroimaging Initiative (2020). Late-life obesity is a protective factor for prodromal Alzheimer's disease: A longitudinal study. *Aging*, 12(2), 2005–2017. <https://doi.org/10.18632/aging.102738>
- Sutoo, D. e., & Akiyama, K. (2003). Regulation of brain function by exercise. *Neurobiology of Disease*, 13(1), 1-14. [https://doi.org/10.1016/S0969-9961\(03\)00030-5](https://doi.org/10.1016/S0969-9961(03)00030-5)
- Suzanne, M. (2012). Metabolic derangements mediate cognitive impairment and Alzheimer's disease: Role of peripheral insulin resistance diseases. *Panminerva Medicine*, 54(3), 171.
- Suzuki, H., Gao, H., Bai, W., Evangelou, E., Glocker, B., O'Regan, D. P., Elliott, P., & Matthews, P. M. (2017). Abnormal brain white matter microstructure is associated with both pre-hypertension and hypertension. *PLoS One*, 12(11), e0187600. <https://doi.org/10.1371/journal.pone.0187600>
- Suzuki, N., Cheung, T. T., Cai, X. D., Odaka, A., Otvos, L., Jr., Eckman, C., Golde, T. E., & Younkin, S. G. (1994). An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (beta APP717) mutants. *Science*, 264(5163), 1336-1340. <https://doi.org/10.1126/science.8191290>
- Sweeney, M. D., Ayyadurai, S., & Zlokovic, B. V. (2016). Pericytes of the neurovascular unit: Key functions and signaling pathways. *Nature Neuroscience*, 19(6), 771-783. <https://doi.org/10.1038/nn.4288>
- Sweeney, M. D., Sagare, A. P., & Zlokovic, B. V. (2018). Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nature Reviews Neurology*, 14(3), 133-150. <https://doi.org/10.1038/nrneuro.2017.188>
- Swislocki, A. L., Hoffman, B. B., & Reaven, G. M. (1989). Insulin resistance, glucose intolerance and hyperinsulinemia in patients with hypertension. *American Journal of Hypertension*, 2(6_Pt_1), 419-423. <https://doi.org/10.1093/ajh/2.6.419>
- Tabatabaei-Jafari, H., Walsh, E., Shaw, M. E., Cherbuin, N., & Alzheimer's Disease Neuroimaging Initiative (ADNI) (2017). The cerebellum shrinks faster than normal ageing in Alzheimer's disease but not in mild cognitive impairment. *Human Brain Mapping*, 38(6), 3141-3150. <https://doi.org/10.1002/hbm.23580>
- Tahara, N., Yamagishi, S., Matsui, T., Takeuchi, M., Nitta, Y., Kodama, N., Mizoguchi, M., & Imaizumi, T. (2012). Serum levels of advanced glycation end products (AGEs) are independent correlates of insulin resistance in nondiabetic subjects. *Cardiovascular Therapeutics*, 30(1), 42–48. <https://doi.org/10.1111/j.1755-5922.2010.00177.x>
- Tahir, R. A., Haider, S., Kole, M., Griffith, B., & Marin, H. (2019). Anterior cerebral artery: Variant anatomy and pathology. *Journal of Vascular and Interventional Neurology*, 10(3), 16.
- Takahashi, H., Ishii, K., Hosokawa, C., Hyodo, T., Kashiwagi, N., Matsuki, M., Ashikaga, R., & Murakami, T. (2014). Clinical Application of 3D Arterial Spin-Labeled Brain Perfusion Imaging for Alzheimer Disease: Comparison with Brain Perfusion SPECT. *American Journal of Neuroradiology*, 35(5), 906-911. <https://doi.org/10.3174/ajnr.A3780>
- Takechi, R., Lam, V., Brook, E., Giles, C., Fimognari, N., Mooradian, A., Al-Salami, H., Coulson, S. H., Nesbit, M., & Mamo, J. C. (2017). Blood-brain barrier dysfunction precedes cognitive decline and neurodegeneration in diabetic insulin resistant mouse model: An implication for

- causal link. *Frontiers in Aging Neuroscience*, 9, 399.
<https://doi.org/10.3389/fnagi.2017.00399>
- Taki, Y., Goto, R., Evans, A., Zijdenbos, A., Neelin, P., Lerch, J., Sato, K., Ono, S., Kinomura, S., Nakagawa, M., Sugiura, M., Watanabe, J., Kawashima, R., & Fukuda, H. (2004). Voxel-based morphometry of human brain with age and cerebrovascular risk factors. *Neurobiology of Aging*, 25(4), 455–463. <https://doi.org/10.1016/j.neurobiolaging.2003.09.002>
- Talbot, K., Wang, H. Y., Kazi, H., Han, L. Y., Bakshi, K. P., Stucky, A., Fuino, R. L., Kawaguchi, K. R., Samoyedny, A. J., Wilson, R. S., Arvanitakis, Z., Schneider, J. A., Wolf, B. A., Bennett, D. A., Trojanowski, J. Q., & Arnold, S. E. (2012). Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *The Journal of Clinical Investigation*, 122(4), 1316–1338. <https://doi.org/10.1172/JCI59903>
- Taler, V., & Phillips, N. A. (2008). Language performance in Alzheimer's disease and mild cognitive impairment: a comparative review. *Journal of Clinical and Experimental Neuropsychology*, 30(5), 501–556. <https://doi.org/10.1080/13803390701550128>
- Tan, E. C., Hilmer, S. N., Garcia-Ptacek, S., & Bell, J. S. (2018). Current approaches to the pharmacological treatment of Alzheimer's disease. *Australian Journal of General Practice*, 47(9), 586–592. <https://doi.org/10.31128/AJGP-05-18-4586>
- Tan, X., Fang, P., An, J., Lin, H., Liang, Y., Shen, W., Leng, X., Zhang, C., Zheng, Y., & Qiu, S. (2016). Micro-structural white matter abnormalities in type 2 diabetic patients: a DTI study using TBSS analysis. *Neuroradiology*, 58(12), 1209–1216. <https://doi.org/10.1007/s00234-016-1752-4>
- Tang-Wai, D. F., Graff-Radford, N., Boeve, B. F., Dickson, D. W., Parisi, J. E., Crook, R., Caselli, R. J., Knopman, D. S., & Petersen, R. C. (2004). Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. *Neurology*, 63(7), 1168–1174. <https://doi.org/10.1212/01.WNL.0000140289.18472.15>
- Tarasoff-Conway, J. M., Carare, R. O., Osorio, R. S., Glodzik, L., Butler, T., Fieremans, E., Axel, L., Rusinek, H., Nicholson, C., Zlokovic, B. V., Frangione, B., Blennow, K., Ménard, J., Zetterberg, H., Wisniewski, T., & de Leon, M. J. (2015). Clearance systems in the brain—implications for Alzheimer disease. *Nature Reviews Neurology*, 11(8), 457–470. <https://doi.org/10.1038/nrneurol.2015.119>
- Tarr, D., Graham, D., Roy, L. A., Holmes, W. M., McCabe, C., Mhairi Macrae, I., Muir, K. W., & Dewar, D. (2013). Hyperglycemia accelerates apparent diffusion coefficient-defined lesion growth after focal cerebral ischemia in rats with and without features of metabolic syndrome. *Journal of Cerebral Blood Flow and Metabolism*, 33(10), 1556–1563. <https://doi.org/10.1038/jcbfm.2013.107>
- Tatasciore, A., Renda, G., Zimarino, M., Soccio, M., Bilo, G., Parati, G., Schillaci, G., & De Caterina, R. (2007). Awake systolic blood pressure variability correlates with target-organ damage in hypertensive subjects. *Hypertension*, 50(2), 325–332. <https://doi.org/10.1161/HYPERTENSIONAHA.107.090084>
- Tatu, L., Moulin, T., Bogousslavsky, J., & Duvernoy, H. (1996). Arterial territories of human brain: brainstem and cerebellum. *Neurology*, 47(5), 1125–1135. <https://doi.org/10.1212/WNL.47.5.1125>
- Teipel, S., Grothe, M. J., & Alzheimer's disease Neuroimaging initiative (ADNI) (2016). Does posterior cingulate hypometabolism result from disconnection or local pathology across preclinical and clinical stages of Alzheimer's disease? *European Journal of Nuclear Medicine and Molecular Imaging*, 43(3), 526–536. <https://doi.org/10.1007/s00259-015-3222-3>
- Teipel, S., Heinsen, H., Amaro Jr, E., Grinberg, L. T., Krause, B., Grothe, M., & Alzheimer's disease Neuroimaging initiative (ADNI) (2014). Cholinergic basal forebrain atrophy predicts amyloid

- burden in Alzheimer's disease. *Neurobiology of Aging*, 35(3), 482-491.
<https://doi.org/10.1016/j.neurobiolaging.2013.09.029>
- Teipel, S. J., Flatz, W. H., Heinsen, H., Bokde, A. L., Schoenberg, S. O., Stöckel, S., Dietrich, O., Reiser, M. F., Möller, H. J., & Hampel, H. (2005). Measurement of basal forebrain atrophy in Alzheimer's disease using MRI. *Brain*, 128(Pt 11), 2626-2644.
<https://doi.org/10.1093/brain/awh589>
- Teng, E. L., Chui, H. C., Schneider, L. S., & Metzger, L. E. (1987). Alzheimer's dementia: performance on the Mini-Mental State Examination. *Journal of Consulting and Clinical Psychology*, 55(1), 96. <https://doi.org/10.1037/0022-006X.55.1.96>
- Terry, R. D., Masliah, E., Salmon, D. P., Butters, N., DeTeresa, R., Hill, R., Hansen, L. A., & Katzman, R. (1991). Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Annals of Neurology*, 30(4), 572-580.
<https://doi.org/10.1002/ana.410300410>
- Thal, D. R., Ghebremedhin, E., Orantes, M., & Wiestler, O. D. (2003). Vascular pathology in Alzheimer disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. *Journal of Neuropathology & Experimental Neurology*, 62(12), 1287-1301. <https://doi.org/10.1093/jnen/62.12.1287>
- Thal, D. R., Rüb, U., Orantes, M., & Braak, H. (2002). Phases of A β -deposition in the human brain and its relevance for the development of AD. *Neurology*, 58(12), 1791-1800.
<https://doi.org/10.1212/WNL.58.12.1791>
- Thavendiranathan, P., Bagai, A., Brookhart, M. A., & Choudhry, N. K. (2006). Primary prevention of cardiovascular diseases with statin therapy: A meta-analysis of randomized controlled trials. *Archives of Internal Medicine*, 166(21), 2307-2313.
<https://doi.org/10.1001/archinte.166.21.2307>
- Thomann, P. A., Dos Santos, V., Toro, P., Schönknecht, P., Essig, M., & Schröder, J. (2009). Reduced olfactory bulb and tract volume in early Alzheimer's disease—A MRI study. *Neurobiology of Aging*, 30(5), 838-841. <https://doi.org/10.1016/j.neurobiolaging.2007.08.001>
- Thompson, P. M., Hayashi, K. M., de Zubicaray, G., Janke, A. L., Rose, S. E., Semple, J., Herman, D., Hong, M. S., Dittmer, S. S., Doddrell, D. M., & Toga, A. W. (2003). Dynamics of gray matter loss in Alzheimer's disease. *The Journal of Neuroscience*, 23(3), 994-1005.
<https://doi.org/10.1523/JNEUROSCI.23-03-00994.2003>
- Thore, C. R., Anstrom, J. A., Moody, D. M., Challa, V. R., Marion, M. C., & Brown, W. R. (2007). Morphometric analysis of arteriolar tortuosity in human cerebral white matter of preterm, young, and aged subjects. *Journal of Neuropathology & Experimental Neurology*, 66(5), 337-345. <https://doi.org/10.1097/nen.0b013e3180537147>
- Thorin-Trescases, N., de Montgolfier, O., Pinçon, A., Raignault, A., Caland, L., Labbé, P., & Thorin, E. (2018). Impact of pulse pressure on cerebrovascular events leading to age-related cognitive decline. *American Journal of Physiology-Heart and Circulatory Physiology*, 314(6), H1214-H1224. <https://doi.org/10.1152/ajpheart.00637.2017>
- Tiehuis, A. M., Vincken, K. L., van den Berg, E., Hendrikse, J., Manschot, S. M., Mali, W. P., Kappelle, L. J., & Biessels, G. J. (2008). Cerebral perfusion in relation to cognitive function and type 2 diabetes. *Diabetologia*, 51(7), 1321-1326. <https://doi.org/10.1007/s00125-008-1041-9>
- Tobler, H. G., & Edwards, J. E. (1988). Frequency and location of atherosclerotic plaques in the ascending aorta. *The Journal of Thoracic and Cardiovascular Surgery*, 96(2), 304-306.
[https://doi.org/10.1016/S0022-5223\(19\)35275-4](https://doi.org/10.1016/S0022-5223(19)35275-4)
- Toga, A. W., Thompson, P. M., & Sowell, E. R. (2006). Mapping brain maturation. *Trends in Neuroscience*, 29(3), 148-159. <https://doi.org/10.1016/j.tins.2006.01.007>
- Toledo, J. B., Arnold, S. E., Raible, K., Brettschneider, J., Xie, S. X., Grossman, M., Monsell, S. E., Kukull, W. A., & Trojanowski, J. Q. (2013). Contribution of cerebrovascular disease in

- autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain*, 136(9), 2697-2706. <https://doi.org/10.1093/brain/awt188>
- Tölle, M., Reshetnik, A., Schuchardt, M., Höhne, M., & van der Giet, M. (2015). Arteriosclerosis and vascular calcification: Causes, clinical assessment and therapy. *European Journal of Clinical Investigation*, 45(9), 976-985. <https://doi.org/10.1111/eci.12493>
- Tondelli, M., Wilcock, G. K., Nichelli, P., De Jager, C. A., Jenkinson, M., & Zamboni, G. (2012). Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. *Neurobiology of Aging*, 33(4), 825. e825-825. e836. <https://doi.org/10.1016/j.neurobiolaging.2011.05.018>
- Toro, P., Degen, C., Pierer, M., Gustafson, D., Schröder, J., & Schönknecht, P. (2014). Cholesterol in mild cognitive impairment and Alzheimer's disease in a birth cohort over 14 years. *European Archives of Psychiatry and Clinical Neuroscience*, 264(6), 485-492. <https://doi.org/10.1007/s00406-013-0468-2>
- Torromino, G., Maggi, A., & De Leonibus, E. (2020). Estrogen-dependent hippocampal wiring as a risk factor for age-related dementia in women. *Progress in Neurobiology*, 101895. <https://doi.org/10.1016/j.pneurobio.2020.101895>
- Tran, L., Langlais, P. R., Hoffman, N., Roust, L., & Katsanos, C. S. (2019). Mitochondrial ATP synthase β -subunit production rate and ATP synthase specific activity are reduced in skeletal muscle of humans with obesity. *Experimental Physiology*, 104(1), 126-135. <https://doi.org/10.1113/EP087278>
- Triantafyllou, A., Anyfanti, P., Zabulis, X., Gavriilaki, E., Karamaounas, P., Gkaliagkousi, E., Petidis, K., Pырpasopoulou, A., Girasis, C., Aslanidis, S. & Douma, S. (2014). Accumulation of microvascular target organ damage in newly diagnosed hypertensive patients. *Journal of the American Society of Hypertension*, 8(8), 542-549. <https://doi.org/10.1016/j.jash.2014.04.008>
- Trifunovic, A., & Larsson, N. G. (2008). Mitochondrial dysfunction as a cause of ageing. *Journal of Internal Medicine*, 263(2), 167-178. <https://doi.org/10.1111/j.1365-2796.2007.01905.x>
- Tromp, D., Dufour, A., Lithfous, S., Pebayle, T., & Despres, O. (2015). Episodic memory in normal aging and Alzheimer disease: Insights from imaging and behavioral studies. *Ageing Research Reviews*, 24(Pt B), 232-262. <https://doi.org/10.1016/j.arr.2015.08.006>
- Troncoso, J. C., Cataldo, A. M., Nixon, R. A., Barnett, J. L., Lee, M. K., Checler, F., Fowler, D. R., Smialek, J. E., Crain, B., Martin, L. J., & Kawas, C. H. (1998). Neuropathology of preclinical and clinical late-onset Alzheimer's disease. *Annals of Neurology*, 43(5), 673-676. <https://doi.org/10.1002/ana.410430519>
- Tropeano, A.-I., Boutouyrie, P., Katsahian, S., Laloux, B., & Laurent, S. (2004). Glucose level is a major determinant of carotid intima-media thickness in patients with hypertension and hyperglycemia. *Journal of Hypertension*, 22(11), 2153-2160. [10.1097/00004872-200411000-00018](https://doi.org/10.1097/00004872-200411000-00018)
- Tsai, J. C., Perrella, M. A., Yoshizumi, M., Hsieh, C. M., Haber, E., Schlegel, R., & Lee, M. E. (1994). Promotion of vascular smooth muscle cell growth by homocysteine: A link to atherosclerosis. *Proceedings of the National Academy of Sciences*, 91(14), 6369-6373. <https://doi.org/10.1073/pnas.91.14.6369>
- Tsai, P. H., Teng, E., Liu, C. & Mendez, M. F. (2011). Posterior cortical atrophy: Evidence for discrete syndromes of early-onset Alzheimer's disease. *American Journal of Alzheimer's Disease & Other Dementias*, 26(5), 413-418. <https://doi.org/10.1177/1533317511418955>
- Tucsek, Z., Toth, P., Sosnowska, D., Gautam, T., Mitschelen, M., Koller, A., Szalai, G., Sonntag, W. E., Ungvari, Z., & Csiszar, A. (2014). Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: Effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. *Journals of Gerontology Series A*, 69(10), 1212-1226. <https://doi.org/10.1093/gerona/glt177>

- Tuokkola, T., Karrasch, M., Koikkalainen, J., Parkkola, R., Lötjönen, J., Löyttyniemi, E., Hurme, S., & Rinne, J. O. (2019). Association between deep gray matter changes and neurocognitive function in mild cognitive impairment and Alzheimer's disease: A tensor-based morphometric MRI study. *Dementia and Geriatric Cognitive Disorders*, *48*(1-2), 68-78. <https://doi.org/10.1159/000502476>
- Turnbull, F. M., Abraira, C., Anderson, R. J., Byington, R. P., Chalmers, J. P., Duckworth, W. C., Evans, G. W., Gerstein, H. C., Holman, R. R., Moritz, T. E., Neal, B. C., Ninomiya, T., Patel, A. A., Paul, S. K., Traver, F., & Woodward, M. (2009). Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia*, *52*(11), 2288–2298. <https://doi.org/10.1007/s00125-009-1470-0>
- Tyler, L. K., Shafto, M. A., Randall, B., Wright, P., Marslen-Wilson, W. D., & Stamatakis, E. A. (2010). Preserving syntactic processing across the adult life span: The modulation of the frontotemporal language system in the context of age-related atrophy. *Cerebral Cortex*, *20*(2), 352-364. <https://doi.org/10.1093/cercor/bhp105>
- Ullrich, C., Pirchl, M., & Humpel, C. (2010). Hypercholesterolemia in rats impairs the cholinergic system and leads to memory deficits. *Molecular and Cellular Neuroscience*, *45*(4), 408-417. <https://doi.org/10.1016/j.mcn.2010.08.001>
- Umemura, T., Kawamura, T., & Hotta, N. (2017). Pathogenesis and neuroimaging of cerebral large and small vessel disease in type 2 diabetes: A possible link between cerebral and retinal microvascular abnormalities. *Journal of Diabetes Investigation*, *8*(2), 134-148. <https://doi.org/10.1111/jdi.12545>
- Une, K., Takei, Y., Tomita, N., Asamura, T., Ohru, T., Furukawa, K., & Arai, H. (2011). Adiponectin in plasma and cerebrospinal fluid in MCI and Alzheimer's disease. *European Journal of Neurology*, *18*(7), 1006-1009. <https://doi.org/10.1111/j.1468-1331.2010.03194.x>
- Unger, R. H. (2005). Longevity, lipotoxicity and leptin: The adipocyte defense against feasting and famine. *Biochimie*, *87*(1), 57-64. <https://doi.org/10.1016/j.biochi.2004.11.014>
- United Nations, Department of Economic and Social Affairs, Population Division. (2015). *World population ageing 2015*. https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf
- Uribarri, J., Cai, W., Peppas, M., Goodman, S., Ferrucci, L., Striker, G., & Helen Vlassara (2007). Circulating glycotoxins and dietary advanced glycation endproducts: Two links to inflammatory response, oxidative stress, and aging. *The Journals of Gerontology: Series A*, *62*(4), 427-433. <https://doi.org/10.1093/gerona/62.4.427>
- Vagelatos, N. T., & Eslick, G. D. (2013). Type 2 diabetes as a risk factor for Alzheimer's disease: The confounders, interactions, and neuropathology associated with this relationship. *Epidemiologic Reviews*, *35*(1), 152-160. <https://doi.org/10.1093/epirev/mxs012>
- Valenzuela, M., Brayne, C., Sachdev, P., Wilcock, G., Matthews, F., & Medical Research Council Cognitive Function and Ageing Study (2011). Cognitive lifestyle and long-term risk of dementia and survival after diagnosis in a multicenter population-based cohort. *American Journal of Epidemiology*, *173*(9), 1004–1012. <https://doi.org/10.1093/aje/kwq476>
- Valotassiou, V., Malamitsi, J., Papatriantafyllou, J., Dardiotis, E., Tsougos, I., Psimadas, D., Alexiou, S., Hadjigeorgiou, G., & Georgoulas, P. (2018). SPECT and PET imaging in Alzheimer's disease. *Annals of Nuclear Medicine*, *32*(9), 583–593. <https://doi.org/10.1007/s12149-018-1292-6>
- van Andel, M., van Schoor, N. M., Korten, N. C., Comijs, H. C., Heijboer, A. C., & Drent, M. L. (2021). The association between high-molecular-weight adiponectin, ghrelin and leptin and age-related cognitive decline: Results from longitudinal aging study Amsterdam. *The Journals of Gerontology. Series A*, *76*(1), 131–140. <https://doi.org/10.1093/gerona/glaa126>

- Van Boxtel, M., Henskens, L., Kroon, A., Hofman, P., Gronenschild, E., Jolles, J., & de Leeuw, P. (2006). Ambulatory blood pressure, asymptomatic cerebrovascular damage and cognitive function in essential hypertension. *Journal of Human Hypertension*, *20*(1), 5-13. <https://doi.org/10.1038/sj.jhh.1001934>
- van de Wall, E., Leshan, R., Xu, A. W., Balthasar, N., Coppari, R., Liu, S. M., Jo, Y. H., MacKenzie, R. G., Allison, D. B., Dun, N. J., Elmquist, J., Lowell, B. B., Barsh, G. S., de Luca, C., Myers, M. G., Jr, Schwartz, G. J., & Chua, S. C., Jr (2008). Collective and individual functions of leptin receptor modulated neurons controlling metabolism and ingestion. *Endocrinology*, *149*(4), 1773–1785. <https://doi.org/10.1210/en.2007-1132>
- Van der Auwera, I., Wera, S., Van Leuven, F., & Henderson, S. T. (2005). A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. *Nutrition & Metabolism*, *2*(1), 28. <https://doi.org/10.1186/1743-7075-2-28>
- Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., & Beekman, A. (2007). Depression and the risk for cardiovascular diseases: Systematic review and meta-analysis. *International Journal of Geriatric Psychiatry*, *22*(7), 613-626. <https://doi.org/10.1002/gps.1723>
- Van Deurs, B. (1976). Observations on the blood-brain barrier in hypertensive rats, with particular reference to phagocytic pericytes. *Journal of Ultrastructure Research*, *56*(1), 65-77. [https://doi.org/10.1016/S0022-5320\(76\)80141-4](https://doi.org/10.1016/S0022-5320(76)80141-4)
- van Dijk, E. J., Breteler, M. M., Schmidt, R., Berger, K., Nilsson, L.-G. r., Oudkerk, M., Pajak, A., Sans, S., de Ridder, M., Dufouil, C., Fuhrer, R., Giampaoli, S., Launer, L. J., & Hofman A. (2004). The association between blood pressure, hypertension, and cerebral white matter lesions: Cardiovascular determinants of dementia study. *Hypertension*, *44*(5), 625-630. <https://doi.org/10.1161/01.HYP.0000145857.98904.20>
- Van Dyken, P., & Lacoste, B. (2018). Impact of metabolic syndrome on neuroinflammation and the blood–brain barrier. *Frontiers in Neuroscience*, *12*, 930. <https://doi.org/10.3389/fnins.2018.00930>
- van Himbergen, T. M., Beiser, A. S., Ai, M., Seshadri, S., Otokozaawa, S., Au, R., Thongtang, N., Wolf, P. A., & Schaefer, E. J. (2012). Biomarkers for insulin resistance and inflammation and the risk for all-cause dementia and alzheimer disease: results from the Framingham Heart Study. *Archives of neurology*, *69*(5), 594–600. <https://doi.org/10.1001/archneurol.2011.670>
- VanderLaan, P. A., Reardon, C. A., & Getz, G. S. (2004). Site specificity of atherosclerosis: Site-selective responses to atherosclerotic modulators. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *24*(1), 12-22. <https://doi.org/10.1161/01.ATV.0000105054.43931.f0>
- Vanhanen, M., Kivipelto, M., Koivisto, K., Kuusisto, J., Mykkänen, L., Helkala, E. L., Hänninen, T., Kervinen, K., Kesäniemi, Y. A., Laakso, M. P., & Soininen, H. (2001). APOE-ε4 is associated with weight loss in women with AD: A population-based study. *Neurology*, *56*(5), 655-659. <https://doi.org/10.1212/WNL.56.5.655>
- Vanhanen, M., Koivisto, K., Moilanen, L., Helkala, E., Hänninen, T., Soininen, H., Kervinen, K., Kesäniemi, Y. A., Laakso, M., & Kuusisto, J. (2006). Association of metabolic syndrome with Alzheimer disease: A population-based study. *Neurology*, *67*(5), 843-847. <https://doi.org/10.1212/01.wnl.0000234037.91185.99>
- Vannini, P., O'brien, J., O'keefe, K., Pihlajamäki, M., Laviolette, P., & Sperling, R. (2010). What goes down must come up: Role of the posteromedial cortices in encoding and retrieval. *Cerebral Cortex*, *21*(1), 22-34. <https://doi.org/10.1093/cercor/bhq051>
- Vassallo, M., Poynter, L., Sharma, J., & Kwan, J. (2016). Nutritional risk, body mass index and rehabilitation outcome in cognitively impaired vs. cognitively normal patients. *European Geriatric Medicine*, *7*(2), 122-126. <https://doi.org/10.1016/j.eurger.2016.01.010>

- Veglio, F., Paglieri, C., Rabbia, F., Bisbocci, D., Bergui, M., & Cerrato, P. (2009). Hypertension and cerebrovascular damage. *Atherosclerosis*, *205*(2), 331-341. <https://doi.org/10.1016/j.atherosclerosis.2008.10.028>
- Veldsman, M., Tai, X.-Y., Nichols, T., Smith, S., Peixoto, J., Manohar, S., & Husain, M. (2020). Cerebrovascular risk factors impact frontoparietal network integrity and executive function in healthy ageing. *Nature Communications*, *11*(1), 1-10. <https://doi.org/10.1038/s41467-020-18201-5>
- Venkat, P., Chopp, M., Zacharek, A., Cui, C., Zhang, L., Li, Q., Lu, M., Zhang, T., Liu, A., & Chen, J. (2017). White matter damage and glymphatic dysfunction in a model of vascular dementia in rats with no prior vascular pathologies. *Neurobiology of Aging*, *50*, 96-106. <https://doi.org/10.1016/j.neurobiolaging.2016.11.002>
- Venneri, A., Gorgoglione, G., Toraci, C., Nocetti, L., Panzetti, P., & Nichelli, P. (2011). Combining neuropsychological and structural neuroimaging indicators of conversion to Alzheimer's disease in amnesic mild cognitive impairment. *Current Alzheimer Research*, *8*(7), 789-797. <https://doi.org/10.2174/156720511797633160>
- Venneri, A., Jahn-Carta, C., de Marco, M., Quaranta, D., & Marra, C. (2018). Diagnostic and prognostic role of semantic processing in preclinical Alzheimer's disease. *Biomarkers in Medicine*, *12*(6), 637-651. <https://doi.org/10.2217/bmm-2017-0324>
- Verclytte, S., Lopes, R., Lenfant, P., Rollin, A., Semah, F., Leclerc, X., Pasquier, F., & Delmaire, C. (2016). Cerebral hypoperfusion and hypometabolism detected by arterial spin labeling MRI and FDG-PET in early-onset Alzheimer's Disease. *Journal of Neuroimaging*, *26*(2), 207-212. <https://doi.org/10.1111/jon.12264>
- Verdelho, A., Madureira, S., Moleiro, C., Ferro, J., Santos, C., Erkinjuntti, T., Pantoni, L., Fazekas, F., Visser, M., Waldemar, G., Wallin, A., Hennerici, M., & Inzitari, D. (2010). White matter changes and diabetes predict cognitive decline in the elderly: The LADIS study. *Neurology*, *75*(2), 160-167. <https://doi.org/10.1212/WNL.0b013e3181e7ca05>
- Verdon, C.-M., Fossati, P., Verny, M., Dieudonné, B., Teillet, L., & Nadel, J. (2007). Social cognition: An early impairment in dementia of the Alzheimer type. *Alzheimer's Disease & Associated Disorders*, *21*(1), 25-30. <https://doi.org/10.1097/WAD.0b013e318032487a>
- Vermeer, S. E., Longstreth Jr, W. T., & Koudstaal, P. J. (2007). Silent brain infarcts: A systematic review. *The Lancet Neurology*, *6*(7), 611-619. [https://doi.org/10.1016/S1474-4422\(07\)70170-9](https://doi.org/10.1016/S1474-4422(07)70170-9)
- Verplaetse, T. L., Cosgrove, K. P., Tanabe, J., & McKee, S. A. (2021). Sex/gender differences in brain function and structure in alcohol use: A narrative review of neuroimaging findings over the last 10 years. *Journal of Neuroscience Research*, *99*(1), 309-323. <https://doi.org/10.1002/jnr.24625>
- Villain, N., Desgranges, B., Viader, F., De La Sayette, V., Mézenge, F., Landeau, B., Baron, J. C., Eustache, F., & Chételat, G. (2008). Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. *Journal of Neuroscience*, *28*(24), 6174-6181. <https://doi.org/10.1523/JNEUROSCI.1392-08.2008>
- Villemagne, V. L., Mulligan, R. S., Pejoska, S., Ong, K., Jones, G., O'Keefe, G., Gordon Chan, J., Young, K., Tochon-Danguy, H., Masters, C. L., & Rowe, C. C. (2012). Comparison of 11 C-PiB and 18 F-florbetaben for A β imaging in ageing and Alzheimer's disease. *European Journal of Nuclear Medicine and Molecular Imaging*, *39*(6), 983-989. <https://doi.org/10.1007/s00259-012-2088-x>
- Villeneuve, S., Belleville, S., Massoud, F., Bocti, C., & Gauthier, S. (2009). Impact of vascular risk factors and diseases on cognition in persons with mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, *27*(4), 375-381. <https://doi.org/10.1159/000209965>

- Vinters, H. V., Wang, Z. Z., & Secor, D. L. (1996). Brain parenchymal and microvascular amyloid in Alzheimer's disease. *Brain Pathology*, *6*(2), 179-195. <https://doi.org/10.1111/j.1750-3639.1996.tb00799.x>
- Vinyoles, E., De la Figuera, M., & Gonzalez-Segura, D. (2008). Cognitive function and blood pressure control in hypertensive patients over 60 years of age: COGNIPRES study. *Current Medical Research and Opinion*, *24*(12), 3331-3340. <https://doi.org/10.1185/03007990802538724>
- Virdis, A., Ghiadoni, L., Pinto, S., Lombardo, M., Petraglia, F., Gennazzani, A., Buralli, S., Taddei, S., & Salvetti, A. (2000). Mechanisms responsible for endothelial dysfunction associated with acute estrogen deprivation in normotensive women. *Circulation*, *101*(19), 2258-2263. <https://doi.org/10.1161/01.CIR.101.19.2258>
- Vlassara, H., & Uribarri, J. (2014). Advanced glycation end products (AGE) and diabetes: cause, effect, or both? *Current Diabetes Reports*, *14*(1), 453. <https://doi.org/10.1007/s11892-013-0453-1>
- Vogel, A., Waldorff, F. B. & Waldemar, G. (2010). Impaired awareness of deficits and neuropsychiatric symptoms in early Alzheimer's disease: The Danish Alzheimer Intervention Study (DAISY). *Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(1), 93-99. <https://doi.org/10.1176/jnp.2010.22.1.93>
- Vokonas, P. S., Kannel, W. B., & Cupples, L. A. (1988). Epidemiology and risk of hypertension in the elderly: the Framingham Study. *Journal of hypertension. Supplement*, *6*(1), S3-S9.
- Vrijens, B., Antoniou, S., Burnier, M., de la Sierra, A., & Volpe, M. (2017). Current situation of medication adherence in hypertension. *Frontiers in Pharmacology*, *8*, 100. <https://doi.org/10.3389/fphar.2017.00100>
- Vuorinen, M., Solomon, A., Rovio, S., Nieminen, L., Kåreholt, I., Tuomilehto, J., Soininen, H., & Kivipelto, M. (2011). Changes in vascular risk factors from midlife to late life and white matter lesions: A 20-year follow-up study. *31*(2), 119-125. <https://doi.org/10.1159/000323810>
- Wakana, S., Caprihan, A., Panzenboeck, M. M., Fallon, J. H., Perry, M., Gollub, R. L., Hua, K., Zhang, J., Jiang, H., Dubey, P., Blitz, A., van Zijl, P., & Mori, S. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage*, *36*(3), 630-644. <https://doi.org/10.1016/j.neuroimage.2007.02.049>
- Walker, J. M., Dixit, S., Saulsberry, A. C., May, J. M., & Harrison, F. E. (2017). Reversal of high fat diet-induced obesity improves glucose tolerance, inflammatory response, β -amyloid accumulation and cognitive decline in the APP/PSEN1 mouse model of Alzheimer's disease. *Neurobiology of Disease*, *100*, 87-98.
- Walker, K. A., Sharrett, A. R., Wu, A., Schneider, A., Albert, M., Lutsey, P. L., Bandeen-Roche, K., Coresh, J., Gross, A. L., Windham, B. G., Knopman, D. S., Power, M. C., Rawlings, A. M., Mosley, T. H., & Gottesman, R. F. (2019). Association of Midlife to Late-Life Blood Pressure Patterns With Incident Dementia. *JAMA*, *322*(6), 535-545. <https://doi.org/10.1001/jama.2019.10575>
- Wallace, S. M., Yasmin, McEniery, C. M., Maki-Petaja, K. M., Booth, A. D., Cockcroft, J. R., & Wilkinson, I. B. (2007). Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction. *Hypertension*, *50*(1), 228-233. <https://doi.org/10.1161/HYPERTENSIONAHA.107.089391>
- Waller, A. V. (1850). XX. Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibres. *Philosophical Transactions of the Royal Society of London*, *140*, 423-429. <https://doi.org/10.1098/rstl.1850.0021>
- Walsh, D. M., Klyubin, I., Fadeeva, J. V., Cullen, W. K., Anwyl, R., Wolfe, M. S., Rowan M. J., & Selkoe, D. J. (2002). Naturally secreted oligomers of amyloid β protein potently inhibit

- hippocampal long-term potentiation in vivo. *Nature*, 416(6880), 535-539.
<https://doi.org/10.1038/416535a>
- Walsh, E., Shaw, M., Sachdev, P., Anstey, K., & Cherbuin, N. (2017). Brain atrophy in ageing: Estimating effects of blood glucose levels vs. other type 2 diabetes effects. *Diabetes & Metabolism*, 44(1), 80-83. <https://doi.org/10.1016/j.diabet.2017.06.004>
- Walther, K., Birdsill, A. C., Glisky, E. L., & Ryan, L. (2010). Structural brain differences and cognitive functioning related to body mass index in older females. *Human Brain Mapping*, 31(7), 1052-1064. <https://doi.org/10.1002/hbm.20916>
- Waltz, J. A., Knowlton, B. J., Holyoak, K. J., Boone, K. B., Back-Madruga, C., McPherson, S., Masterman, D., Chow, T., Cummings, J. L., & Miller, B. L. (2004). Relational integration and executive function in Alzheimer's disease. *Neuropsychology*, 18(2), 296.
<https://doi.org/10.1037/0894-4105.18.2.296>
- Wang, F., Guo, X., Shen, X., Kream, R. M., Mantione, K. J., & Stefano, G. B. (2014a). Vascular dysfunction associated with type 2 diabetes and Alzheimer's disease: A potential etiological linkage. *Medical Science Monitor Basic Research*, 20, 118.
<https://doi.org/10.12659/MSMBR.891278>
- Wang, F., Zhao, M., Han, Z., Li, D., Zhang, S., Zhang, Y., Kong, X., Zhang, Q., & Lei, P (2017). Long-term subclinical hyperglycemia and hypoglycemia as independent risk factors for mild cognitive impairment in elderly people. *The Tohoku Journal of Experimental Medicine*, 242(2), 121-128. <https://doi.org/10.1620/tjem.242.121>
- Wang, H., & Eckel, R. H. (2014b). What are lipoproteins doing in the brain? *Trends in Endocrinology & Metabolism*, 25(1), 8-14. <https://doi.org/10.1016/j.tem.2013.10.003>
- Wang, H. W., Pasternak, J. F., Kuo, H., Ristic, H., Lambert, M. P., Chromy, B., Krafft, G. A., & Trommer, B. L. (2002a). Soluble oligomers of β amyloid (1-42) inhibit long-term potentiation but not long-term depression in rat dentate gyrus. *Brain Research*, 924(2), 133-140. [https://doi.org/10.1016/S0006-8993\(01\)03058-X](https://doi.org/10.1016/S0006-8993(01)03058-X)
- Wang, H. X., Karp, A., Winblad, B., & Fratiglioni, L. (2002b). Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: A longitudinal study from the Kungsholmen project. *American Journal of Epidemiology*, 155(12), 1081-1087.
<https://doi.org/10.1093/aje/155.12.1081>
- Wang, J., Zhang, Y., Wolf, R. L., Roc, A. C., Alsop, D. C., & Detre, J. A. (2005). Amplitude-modulated continuous arterial spin-labeling 3.0-T perfusion MR imaging with a single coil: Feasibility study. *Radiology*, 235(1), 218-228. <https://doi.org/10.1148/radiol.2351031663>
- Wang, L., Goldstein, F. C., Veledar, E., Levey, A. I., Lah, J. J., Meltzer, C. C., Holder, C. A., & Mao, H. (2009). Alterations in cortical thickness and white matter integrity in mild cognitive impairment measured by whole-brain cortical thickness mapping and diffusion tensor imaging. *American Journal of Neuroradiology*, 30(5), 893-899.
<https://doi.org/10.3174/ajnr.A1484>
- Wang, R., Fratiglioni, L., Laukka, E. J., Lövdén, M., Kalpouzos, G., Keller, L., Graff, C., Salami, A., Bäckman, L., & Qiu, C. (2015a). Effects of vascular risk factors and APOE ϵ 4 on white matter integrity and cognitive decline. *Neurology*, 84(11), 1128-1135.
<https://doi.org/10.1212/WNL.0000000000001379>
- Wang, W. Y., Yu, J. T., Liu, Y., Yin, R. H., Wang, H. F., Wang, J., Tan, L., Radua, J., & Tan, L. (2015b). Voxel-based meta-analysis of grey matter changes in Alzheimer's disease. *Translational neurodegeneration*, 4, 6. <https://doi.org/10.1186/s40035-015-0027-z>
- Wang, Y., Liu, G., Hong, D., Chen, F., Ji, X., & Cao, G. (2016). White matter injury in ischemic stroke. *Progress in Neurobiology*, 141, 45-60.
<https://doi.org/10.1016/j.pneurobio.2016.04.005>
- Wannasirikul, P., Termsirikulchai, L., Sujirarat, D., Benjakul, S., & Tanasugarn, C. (2016). Health literacy, medication adherence, and blood pressure level among hypertensive older adults

- treated at primary health care centers. *Southeast Asian Journal of Tropical Medicine and Public Health*, 47(1), 109.
- Ward, A. M., Schultz, A. P., Huijbers, W., Van Dijk, K. R., Hedden, T., & Sperling, R. A. (2014a). The parahippocampal gyrus links the default-mode cortical network with the medial temporal lobe memory system. *Human Brain Mapping*, 35(3), 1061-1073. <https://doi.org/10.1002/hbm.22234>
- Ward, R. J., Zucca, F. A., Duyn, J. H., Crichton, R. R., & Zecca, L. (2014b). The role of iron in brain ageing and neurodegenerative disorders. *The Lancet Neurology*, 13(10), 1045-1060. [https://doi.org/10.1016/S1474-4422\(14\)70117-6](https://doi.org/10.1016/S1474-4422(14)70117-6)
- Wardlaw J. M. (2005). What causes lacunar stroke? *Journal of Neurology, Neurosurgery, and Psychiatry*, 76(5), 617–619. <https://doi.org/10.1136/jnnp.2004.039982>
- Wardle, J., & Steptoe, A. (2003). Socioeconomic differences in attitudes and beliefs about healthy lifestyles. *Journal of Epidemiology & Community Health*, 57(6), 440-443. <http://dx.doi.org/10.1136/jech.57.6.440>
- Warren, M. W., Hynan, L. S., Weiner, M. F., & The Texas Alzheimer's Research and Care Consortium. (2012). Lipids and adipokines as risk factors for Alzheimer's disease. *Journal of Alzheimer's Disease*, 29(1), 151-157. <https://doi.org/10.3233/JAD-2012-111385>
- Wasserthal, J., Neher, P., & Maier-Hein, K. H. (2018). TractSeg-Fast and accurate white matter tract segmentation. *NeuroImage*, 183, 239-253. <https://doi.org/10.1016/j.neuroimage.2018.07.070>
- Watfa, G., Rossignol, P., Kearney-Schwartz, A., Fay, R., Bracard, S., Felblinger, J., Boivin, J. M., Lacolley, P., Zannad, F., & Benetos, A. (2010). Use of calcium channel blockers is associated with better cognitive performance in older hypertensive patients with subjective memory complaints. *Journal of Hypertension*, 28(12), 2485–2493. <https://doi.org/10.1097/HJH.0b013e32833e4108>
- Watson, T. C., Becker, N., Apps, R., & Jones, M. W. (2014). Back to front: Cerebellar connections and interactions with the prefrontal cortex. *Frontiers in Systems Neuroscience*, 8, 4. <https://doi.org/10.3389/fnsys.2014.00004>
- Webb, A. J., Simoni, M., Mazzucco, S., Kuker, W., Schulz, U., & Rothwell, P. M. (2012). Increased cerebral arterial pulsatility in patients with leukoaraiosis: Arterial stiffness enhances transmission of aortic pulsatility. *Stroke*, 43(10), 2631-2636. <https://doi.org/10.1161/STROKEAHA.112.655837>
- Weber, C., & Noels, H. (2011). Atherosclerosis: current pathogenesis and therapeutic options. *Nature Medicine*, 17(11), 1410-1422. <https://doi.org/10.1038/nm.2538>
- Wechsler, D. (1958). *The measurement and appraisal of adult intelligence*. Williams & Wilkins Co. <https://doi.org/10.1037/11167-000>
- Wechsler, D. (1981). *Wechsler adult intelligence scale-revised (WAIS-R)*. Psychological Corporation.
- Wechsler, D. (1987). *Wechsler Memory Scale-Revised*. The Psychological Corporation.
- Weiler, M., de Campos, B. M., Nogueira, M. H., Damasceno, B. P., Cendes, F., & Balthazar, M. L. (2014). Structural connectivity of the default mode network and cognition in Alzheimer's disease. *Psychiatry Research: Neuroimaging*, 223(1), 15-22. <https://doi.org/10.1016/j.psychresns.2014.04.008>
- Weinstein, G., Maillard, P., Himali, J. J., Beiser, A. S., Au, R., Wolf, P. A., Seshadri, S., & DeCarli, C. (2015). Glucose indices are associated with cognitive and structural brain measures in young adults. *Neurology*, 84(23), 2329-2337. <https://doi.org/10.1212/WNL.0000000000001655>
- Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, 2(4), a006171. <https://doi.org/10.1101/cshperspect.a006171>

- Weiss, D., Kools, J. J., & Taylor, W. R. (2001). Angiotensin II–induced hypertension accelerates the development of atherosclerosis in apoE-deficient mice. *Circulation*, *103*(3), 448-454. <https://doi.org/10.1161/01.CIR.103.3.448>
- Wellhoener, P., Fruehwald-Schultes, B., Kern, W., Dantz, D., Kerner, W., Born, J., Fehm, H. L., & Peters, A. (2000). Glucose metabolism rather than insulin is a main determinant of leptin secretion in humans. *The Journal of Clinical Endocrinology & Metabolism*, *85*(3), 1267-1271. <https://doi.org/10.1210/jcem.85.3.6483>
- Welsh, K. A., Butters, N., Mohs, R. C., Beekly, D., Edland, S., Fillenbaum, G., & Heyman, A. (1994). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology*, *44*(4), 609-614. <https://doi.org/10.1212/WNL.44.4.609>
- Weuve, J., Kang, J. H., Manson, J. E., Breteler, M. M., Ware, J. H., & Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *JAMA*, *292*(12), 1454-1461. <https://doi.org/10.1001/jama.292.12.1454>
- Wharton, W., Zhao, L., Steenland, K., Goldstein, F. C., Schneider, J. A., Barnes, L. L., Gearing, M., & Yasar, S. (2019). Neurofibrillary tangles and conversion to mild cognitive impairment with certain antihypertensives. *Journal of Alzheimer's Disease*, *70*(1), 153-161. <https://doi.org/10.3233/JAD-190011>
- White, P., Goodhardt, M., Keet, J., Hiley, C., Carrasco, L., Williams, I., & Bowen, D. M. (1977). Neocortical cholinergic neurons in elderly people. *The Lancet*, *309*(8013), 668-671. [https://doi.org/10.1016/S0140-6736\(77\)92114-6](https://doi.org/10.1016/S0140-6736(77)92114-6)
- Whitmer, R. A., Gunderson, E. P., Quesenberry, C. P., Zhou, J., & Yaffe, K. (2007). Body mass index in midlife and risk of Alzheimer disease and vascular dementia. *Current Alzheimer Research*, *4*(2), 103-109. <https://doi.org/10.2174/156720507780362047>
- Whitmer, R. A., Karter, A. J., Yaffe, K., Quesenberry, C. P., & Selby, J. V. (2009). Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA*, *301*(15), 1565-1572. <https://doi.org/10.1001/jama.2009.460>
- Whitmer, R. A., Sidney, S., Selby, J., Johnston, S. C., & Yaffe, K. (2005). Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*, *64*(2), 277-281. <https://doi.org/10.1212/01.WNL.0000149519.47454.F2>
- Whitwell, J. L., Dickson, D. W., Murray, M. E., Weigand, S. D., Tosakulwong, N., Senjem, M. L., Knopman, D. S., Boeve, B. F., Parisi, J. E., Petersen, R. C., Jack Jr, C. R., & Josephs, K. A. (2012). Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study. *Lancet Neurology*, *11*(10), 868-877. [https://doi.org/10.1016/S1474-4422\(12\)70200-4](https://doi.org/10.1016/S1474-4422(12)70200-4)
- Whitwell, J. L., Jack Jr, C. R., Kantarci, K., Weigand, S. D., Boeve, B. F., Knopman, D. S., Drubach, D. A., Tang-Wai, D. F., Petersen, R. C., & Josephs, K. A. (2007). Imaging correlates of posterior cortical atrophy. *Neurobiology of Aging*, *28*(7), 1051-1061. <https://doi.org/10.1016/j.neurobiolaging.2006.05.026>
- Wiegmann, C., Mick, I., Brandl, E. J., Heinz, A., & Gutwinski, S. (2020). Alcohol and Dementia—What is the Link? A Systematic Review. *Neuropsychiatric Disease and Treatment*, *16*, 87. <https://doi.org/10.2147/NDT.S198772>
- Wilcock, G., Esiri, M., Bowen, D., & Smith, C. C. T. (1982). Alzheimer's disease: correlation of cortical choline acetyltransferase activity with the severity of dementia and histological abnormalities. *Journal of the Neurological Sciences*, *57*(2-3), 407-417. [https://doi.org/10.1016/0022-510X\(82\)90045-4](https://doi.org/10.1016/0022-510X(82)90045-4)
- Willette, A. A., Johnson, S. C., Birdsill, A. C., Sager, M. A., Christian, B., Baker, L. D., . . . dementia. (2015). Insulin resistance predicts brain amyloid deposition in late middle-aged adults. *11*(5), 504-510. e501.

- Willeumier, K. C., Taylor, D. V., & Amen, D. G. (2011). Elevated BMI is associated with decreased blood flow in the prefrontal cortex using SPECT imaging in healthy adults. *Obesity, 19*(5), 1095-1097. <https://doi.org/10.1038/oby.2011.16>
- Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D., Coca, A., De Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S., Kreutz, R., Laurent, S., Lip, G., ... Desormais, I. (2018). 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *Blood Pressure, 27*(6), 314–340. <https://doi.org/10.1080/08037051.2018.1527177>
- Williams, B., Mancia, G., Spiering, W., Rosei, E. A., Azizi, M., Burnier, M., Clement, D. L., Coca, A., de Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S. E., Kreutz, R., Laurent, S., Lip, G., ... Desormais, I. (2019a). 2018 ESC/ESH Guidelines for the management of arterial hypertension [2018 ESC/ESH Guidelines for the management of arterial hypertension]. *Kardiologia Polska, 77*(2), 71–159. <https://doi.org/10.5603/KP.2019.0018>
- Williams, O. A., An, Y., Beason-Held, L., Huo, Y., Ferrucci, L., Landman, B. A., & Resnick, S. M. (2019b). Vascular burden and APOE ε4 are associated with white matter microstructural decline in cognitively normal older adults. *NeuroImage, 188*, 572-583. <https://doi.org/10.1016/j.neuroimage.2018.12.009>
- Wilson, R. S., Krueger, K. R., Arnold, S. E., Schneider, J. A., Kelly, J. F., Barnes, L. L., Tang, Y., & Bennett, D. A. (2007). Loneliness and risk of Alzheimer disease. *Archives of General Psychiatry, 64*(2), 234–240. <https://doi.org/10.1001/archpsyc.64.2.234>
- Wilson, R. S., Leurgans, S. E., Boyle, P. A., & Bennett, D. A. (2011). Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. *Archives of Neurology, 68*(3), 351-356. <https://doi.org/10.1001/archneurol.2011.31>
- Win, K. T., Pluta, J., Yushkevich, P., Irwin, D. J., McMillan, C. T., Rascovsky, K., Wolk, D., & Grossman, M. (2017). Neural correlates of verbal episodic memory and lexical retrieval in logopenic variant primary progressive aphasia. *Frontiers in Neuroscience, 11*, 330. <https://doi.org/10.3389/fnins.2017.00330>
- Wirth, M., Bejanin, A., La Joie, R., Arenaza-Urquijo, E. M., Gonneaud, J., Landeau, B., . . . Desgranges, B. (2017a). Regional patterns of gray matter volume, hypometabolism, and beta-amyloid in groups at risk of Alzheimer's disease. *Neurobiology of Aging, 63*, 140-151. <https://doi.org/10.1016/j.neurobiolaging.2017.10.023>
- Wirth, M., Pichet Binette, A., Brunecker, P., Köbe, T., Witte, A. V., & Flöel, A. (2017b). Divergent regional patterns of cerebral hypoperfusion and gray matter atrophy in mild cognitive impairment patients. *Journal of Cerebral Blood Flow & Metabolism, 37*(3), 814-824. <https://doi.org/10.1177/0271678X16641128>
- Wolf, A. B., Braden, B. B., Bimonte-Nelson, H., Kusne, Y., Young, N., Engler-Chiurazzi, E., Garcia, A. N., Walker, D. G., Moses, G. S., Tran, H., LaFerla, F., Lue, L., Emerson Lombardo, N., & Valla, J. (2012). Broad-based nutritional supplementation in 3xTg mice corrects mitochondrial function and indicates sex-specificity in response to Alzheimer's disease intervention. *Journal of Alzheimer's Disease, 32*(1), 217–232. <https://doi.org/10.3233/JAD-2012-120478>
- Wolf, H., Julin, P., Gertz, H. J., Winblad, B., & Wahlund, L. O. (2004). Intracranial volume in mild cognitive impairment, Alzheimer's disease and vascular dementia: evidence for brain reserve? *International Journal of Geriatric Psychiatry, 19*(10), 995–1007. <https://doi.org/10.1002/gps.1205>
- Wolffenbuttel, B. H., Boulanger, C. M., Crijns, F. R., Huijberts, M. S., Poitevin, P., Swennen, G. N., Vasan S., Egan, J. J., Ulrich, P., Cerami, & Lévy, B. I. (1998). Breakers of advanced glycation end products restore large artery properties in experimental diabetes. *Proceedings*

- of the National Academy of Sciences, 95(8), 4630-4634.
<https://doi.org/10.1073/pnas.95.8.4630>
- Wolk, D. A., Dickerson, B. C., & Alzheimer's Disease Neuroimaging Initiative (ADNI). (2010). Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. *Proceedings of the National Academy of Sciences*, 107(22), 10256-10261. <https://doi.org/10.1073/pnas.1001412107>
- Won, S. M., Lee, J. H., Park, U. J., Gwag, J., Gwag, B. J., & Lee, Y. B. (2011). Iron mediates endothelial cell damage and blood-brain barrier opening in the hippocampus after transient forebrain ischemia in rats. *Experimental & molecular medicine*, 43(2), 121-128.
<https://doi.org/10.3858/emm.2011.43.2.020>
- Wong, E. C. (2005). Quantifying CBF with pulsed ASL: Technical and pulse sequence factors. *Journal of Magnetic Resonance Imaging*, 22(6), 727-731. <https://doi.org/10.1002/jmri.20459>
- Wong, S., Janssen, I., & Ross, R. (2003). Abdominal adipose tissue distribution and metabolic risk. *Sports Medicine*, 33(10), 709-726. <https://doi.org/10.2165/00007256-200333100-00001>
- Woo, C. W., Krishnan, A., & Wager, T. D. (2014). Cluster-extent based thresholding in fMRI analyses: pitfalls and recommendations. *Neuroimage*, 91, 412-419.
<https://doi.org/10.1016/j.neuroimage.2013.12.058>
- Woodward, M., Brodaty, H., Boundy, K., Ames, D., Blanch, G., & Balshaw, R. (2010a). Does executive impairment define a frontal variant of Alzheimer's disease? *International Psychogeriatrics*, 22(8), 1280-1290. <https://doi.org/10.1017/S1041610210001596>
- Woodward, M., Jacova, C., Black, S. E., Kertesz, A., Mackenzie, I. R., Feldman, H., & ACCORD Investigator Group (2010b). Differentiating the frontal variant of Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 25(7), 732-738.
<https://doi.org/10.1002/gps.2415>
- Wu, G., Lin, L., Zhang, Q., & Wu, J. (2017). Brain gray matter changes in type 2 diabetes mellitus: A meta-analysis of whole-brain voxel-based morphometry study. *Journal of Diabetes and its Complications*, 31(12), 1698-1703. <https://doi.org/10.1016/j.jdiacomp.2017.09.001>
- Wu, K. Y., Hsiao, I. T., Chen, C. S., Chen, C. H., Hsieh, C. J., Wai, Y. Y., Chang, C. J., Tseng, H. J., Yen, T. C., Liu, C. Y., & Lin, K. J. (2014). Increased brain amyloid deposition in patients with a lifetime history of major depression: Evidenced on 18F-florbetapir (AV-45/Amyvid) positron emission tomography. *European Journal of Nuclear Medicine and Molecular Imaging*, 41(4), 714-722. <https://doi.org/10.1007/s00259-013-2627-0>
- Xia, C. F., Arteaga, J., Chen, G., Gangadharmath, U., Gomez, L. F., Kasi, D., Lam, C., Liang, Q., Liu, C., Mocharla, V. P., Mu, F., Sinha, A., Su, H., Szardenings, A. K., Walsh, J. C., Wang, E., Yu, C., Zhang, W., Zhao, T., & Kolb, H. C. (2013a). [(18)F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease. *Alzheimer's & Dementia*, 9(6), 666-676. <https://doi.org/10.1016/j.jalz.2012.11.008>
- Xia, W., Wang, S., Rao, H., Spaeth, A. M., Wang, P., Yang, Y., Huang, R., Cai, R., & Sun, H. (2015a). Disrupted resting-state attentional networks in T2DM patients. *Scientific Reports*, 5, 11148. <https://doi.org/10.1038/srep11148>
- Xia, W., Wang, S., Spaeth, A. M., Rao, H., Wang, P., Yang, Y., Huang, R., Cai, R., & Sun, H. (2015b). Insulin resistance-associated interhemispheric functional connectivity alterations in T2DM: A resting-state fMRI study. *BioMed Research International*, 719076.
<https://doi.org/10.1155/2015/719076>
- Xia, W., Wang, S., Sun, Z., Bai, F., Zhou, Y., Yang, Y., Wang, P., Huang, Y., & Yuan, Y. (2013b). Altered baseline brain activity in type 2 diabetes: A resting-state fMRI study. *Psychoneuroendocrinology*, 38(11), 2493-2501.
<https://doi.org/10.1016/j.psyneuen.2013.05.012>
- Xiang, L., Dearman, J., Abram, S. R., Carter, C., & Hester, R. L. (2008). Insulin resistance and impaired functional vasodilation in obese Zucker rats. *American journal of physiology*.

- American Journal of Physiology-Heart and Circulatory Physiology*, 294(4), H1658–H1666.
<https://doi.org/10.1152/ajpheart.01206.2007>
- Xie, S. X., Libon, D. J., Wang, X., Massimo, L., Moore, P., Vesely, L., Khan, A., Chatterjee, A., Coslett, H. B., Hurtig, H. I., Liang, T. W., & Grossman, M. (2010). Longitudinal patterns of semantic and episodic memory in frontotemporal lobar degeneration and Alzheimer's disease. *Journal of the International Neuropsychological Society*, 16(2), 278–286.
<https://doi.org/10.1017/S1355617709991317>
- Xiong, Y., Sui, Y., Xu, Z., Zhang, Q., Karaman, M. M., Cai, K., Anderson, T. M., Zhu, W., Wang, J., & Zhou, X. J. (2016). A Diffusion Tensor Imaging Study on White Matter Abnormalities in Patients with Type 2 Diabetes Using Tract-Based Spatial Statistics. *American Journal of Neuroradiology*, 37(8), 1462–1469. <https://doi.org/10.3174/ajnr.A4740>
- Xu, G., Antuono, P. G., Jones, J., Xu, Y., Wu, G., Ward, D., & Li, S. J. (2007). Perfusion fMRI detects deficits in regional CBF during memory-encoding tasks in MCI subjects. *Neurology*, 69(17), 1650-1656. <https://doi.org/10.1212/01.wnl.0000296941.06685.22>
- Xu, J., Patassini, S., Rustogi, N., Riba-Garcia, I., Hale, B. D., Phillips, A. M., Waldvogel, H., Haines, R., Bradbury, P., Stevens, A., Faull, R., Dowsey, A. W., Cooper, G., & Unwin, R. D. (2019). Regional protein expression in human Alzheimer's brain correlates with disease severity. *Communications Biology*, 2, 43. <https://doi.org/10.1038/s42003-018-0254-9>
- Xu, W., Atti, A., Gatz, M., Pedersen, N., Johansson, B., & Fratiglioni, L. (2011). Midlife overweight and obesity increase late-life dementia risk: a population-based twin study. *Neurology*, 76(18), 1568-1574. <https://doi.org/10.1212/WNL.0b013e3182190d09>
- Xu, W., Wang, H., Wan, Y., Tan, C., Li, J., Tan, L., & Yu, J. T. (2017). Alcohol consumption and dementia risk: a dose-response meta-analysis of prospective studies. *European Journal of Epidemiology*, 32(1), 31–42. <https://doi.org/10.1007/s10654-017-0225-3>
- Xu, X., Hilal, S., Collinson, S. L., Chong, E. J. Y., Ikram, M. K., Venketasubramanian, N., & Chen, C. L. H. (2015). Association of magnetic resonance imaging markers of cerebrovascular disease burden and cognition. *Stroke*, 46(10), 2808-2814.
<https://doi.org/10.1161/STROKEAHA.115.010700>
- Yakushev, I., Schreckenberger, M., Müller, M. J., Schermuly, I., Cumming, P., Stoeter, P., Gerhard, A., & Fellgiebel, A. (2011). Functional implications of hippocampal degeneration in early Alzheimer's disease: a combined DTI and PET study. *European Journal of Nuclear Medicine and Molecular Imaging*, 38(12), 2219-2227. <https://doi.org/10.1007/s00259-011-1882-1>
- Yamauchi, T., Kamon, J., Waki, H., Imai, Y., Shimozawa, N., Hioki, K., Uchida, S., Ito, Y., Takakuwa, K., Matsui, J., Takata, M., Eto, K., Terauchi, Y., Komeda, K., Tsunoda, M., Murakami, K., Ohnishi, Y., Naitoh, T., Yamamura, K., Ueyama, Y., ... Kadowaki, T. (2003). Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. *The Journal of Biological Chemistry*, 278(4), 2461–2468.
<https://doi.org/10.1074/jbc.M209033200>
- Yang, Q., Zhou, L., Liu, C., Liu, D., Zhang, Y., Li, C., Shang, Y., Wei, X., Li, C., & Wang, J. (2018). Brain iron deposition in type 2 diabetes mellitus with and without mild cognitive impairment-an in vivo susceptibility mapping study. *Brain Imaging and Behavior*, 12(5), 1479–1487. <https://doi.org/10.1007/s11682-017-9815-7>
- Yang, S. Q., Xu, Z. P., Xiong, Y., Zhan, Y. F., Guo, L. Y., Zhang, S., Jiang, R. F., Yao, Y. H., Qin, Y. Y., Wang, J. Z., Liu, Y., & Zhu, W. Z. (2016). Altered intranetwork and internetwork functional connectivity in type 2 diabetes mellitus with and without cognitive impairment. *Scientific Reports*, 6, 32980. <https://doi.org/10.1038/srep32980>
- Yasar, S., Xia, J., Yao, W., Furberg, C. D., Xue, Q. L., Mercado, C. I., Fitzpatrick, A. L., Fried, L. P., Kawas, C. H., Sink, K. M., Williamson, J. D., DeKosky, S. T., Carlson, M. C., & Ginkgo Evaluation of Memory (GEM) Study Investigators (2013). Antihypertensive drugs decrease

- risk of Alzheimer disease: Ginkgo Evaluation of Memory Study. *Neurology*, 81(10), 896–903. <https://doi.org/10.1212/WNL.0b013e3182a35228>
- Yashiro, S., Kameda, H., Chida, A., Todate, Y., Hasegawa, Y., Nagasawa, K., Uwano, I., Sasaki, M., Ogasawara, K., & Ishigaki, Y. (2018). Evaluation of Lenticulostriate Arteries Changes by 7 T Magnetic Resonance Angiography in Type 2 Diabetes. *Journal of Atherosclerosis and Thrombosis*, 25(10), 1067–1075. <https://doi.org/10.5551/jat.43869>
- Yatawara, C., Lee, D., Ng, K. P., Chander, R., Ng, D., Ji, F., Shim, H. Y., Hilal, S., Venketasubramanian, N., Chen, C., Zhou, J., & Kandiah, N. (2019). Mechanisms Linking White Matter Lesions, Tract Integrity, and Depression in Alzheimer Disease. *The American Journal of Geriatric Psychiatry*, 27(9), 948–959. <https://doi.org/10.1016/j.jagp.2019.04.004>
- Yau, P. L., Javier, D., Tsui, W., Sweat, V., Bruehl, H., Borod, J. C., & Convit, A. (2009). Emotional and neutral declarative memory impairments and associated white matter microstructural abnormalities in adults with type 2 diabetes. *Psychiatry Research*, 174(3), 223–230. <https://doi.org/10.1016/j.psychres.2009.04.016>
- Yau, P. L., Kluger, A., Borod, J. C., & Convit, A. (2014). Neural substrates of verbal memory impairments in adults with type 2 diabetes mellitus. *Journal of Clinical and Experimental Neuropsychology*, 36(1), 74–87. <https://doi.org/10.1080/13803395.2013.869310>
- Yi, H. A., Möller, C., Dieleman, N., Bouwman, F. H., Barkhof, F., Scheltens, P., van der Flier, W. M., & Vrenken, H. (2016). Relation between subcortical grey matter atrophy and conversion from mild cognitive impairment to Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 87(4), 425–432. <https://doi.org/10.1136/jnnp-2014-309105>
- Yin, R. H., Tan, L., Liu, Y., Wang, W. Y., Wang, H. F., Jiang, T., Radua, J., Zhang, Y., Gao, J., Canu, E., Migliaccio, R., Filippi, M., Gorno-Tempini, M. L., & Yu, J. T. (2015). Multimodal voxel-based meta-analysis of white matter abnormalities in Alzheimer's disease. *Journal of Alzheimer's Disease*, 47(2), 495–507. <https://doi.org/10.3233/JAD-150139>
- Yoshita, M., Fletcher, E., Harvey, D., Ortega, M., Martinez, O., Mungas, D. M., Reed, B. R., & DeCarli, C. (2006). Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology*, 67(12), 2192–2198. <https://doi.org/10.1212/01.wnl.0000249119.95747.1f>
- Yoshiura, T., Hiwatashi, A., Yamashita, K., Ohyagi, Y., Monji, A., Takayama, Y., Nagao, E., Kamano, H., Noguchi, T., & Honda, H. (2009). Simultaneous measurement of arterial transit time, arterial blood volume, and cerebral blood flow using arterial spin-labeling in patients with Alzheimer disease. *American Journal of Neuroradiology*, 30(7), 1388–1393. <https://doi.org/10.3174/ajnr.A1562>
- Young, E. A., Haskett, R. F., Murphy-Weinberg, V., Watson, S. J., & Akil, H. (1991). Loss of glucocorticoid fast feedback in depression. *Archives of General Psychiatry*, 48(8), 693–699. <https://doi.org/10.1001/archpsyc.1991.01810320017003>
- Yu, Y. P., & Tan, L. (2016). The vulnerability of vessels involved in the role of embolism and hypoperfusion in the mechanisms of ischemic cerebrovascular diseases. *BioMed Research International*, 8531958. <https://doi.org/10.1155/2016/8531958>
- Yu, X., Yang, L., Song, R., Jiaerken, Y., Yang, J., Lou, M., Jiang, Q., & Zhang, M. (2017). Changes in structure and perfusion of grey matter tissues during recovery from ischaemic subcortical stroke: A longitudinal MRI study. *European Journal of Neuroscience*, 46(7), 2308–2314. <https://doi.org/10.1111/ejn.13669>
- Yudkin, J. S., Stehouwer, C., Emeis, J. & Coppack, S. W. (1999). C-reactive protein in healthy subjects: Associations with obesity, insulin resistance, and endothelial dysfunction: A potential role for cytokines originating from adipose tissue? *Arteriosclerosis, Thrombosis and Vascular Biology*, 19(4), 972–978. <https://doi.org/10.1161/01.ATV.19.4.972>

- Zafrilla, P., Mulero, J., Xandri, J. M., Santo, E., Caravaca, G., & Morillas, J. M. (2006). Oxidative stress in Alzheimer patients in different stages of the disease. *Current Medicinal Chemistry*, *13*(9), 1075–1083. <https://doi.org/10.2174/092986706776360978>
- Zahniser, N. R., Goens, M. B., Hanaway, P. J., & Vinych, J. V. (1984). Characterization and regulation of insulin receptors in rat brain. *Journal of Neurochemistry*, *42*(5), 1354-1362. <https://doi.org/10.1111/j.1471-4159.1984.tb02795.x>
- Zakzanis, K. K., Graham, S. J., & Campbell, Z. (2003). A meta-analysis of structural and functional brain imaging in dementia of the Alzheimer's type: A neuroimaging profile. *Neuropsychology Review*, *13*(1), 1-18. <https://doi.org/10.1023/A:1022318921994>
- Zaletel, J., Barlovic, D. P., & Prezelj, J. (2010). Adiponectin-leptin ratio: a useful estimate of insulin resistance in patients with Type 2 diabetes. *Journal of Endocrinological Investigation*, *33*(8), 514-518. <https://doi.org/10.1007/BF03346639>
- Zarins, C. K., Giddens, D. P., Bharadvaj, B., Sottiurai, V. S., Mabon, R. F., & Glagov, S. (1983). Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. *Circulation Research*, *53*(4), 502-514. <https://doi.org/10.1161/01.RES.53.4.502>
- Zazulia, A. R., Videen, T. O., Morris, J. C., & Powers, W. J. (2010). Autoregulation of cerebral blood flow to changes in arterial pressure in mild Alzheimer's disease. *Journal of Cerebral Blood Flow & Metabolism*, *30*(11), 1883-1889. <https://doi.org/10.1038/jcbfm.2010.135>
- Zeidman, P., & Maguire, E. A. (2016). Anterior hippocampus: The anatomy of perception, imagination and episodic memory. *Nature Reviews Neuroscience*, *17*(3), 173. <https://doi.org/10.1038/nrn.2015.24>
- Zeki Al Hazzouri, A., Stone, K. L., Haan, M. N. & Yaffe, K. (2013). Leptin, mild cognitive impairment, and dementia among elderly women. *The Journals of Gerontology: Series A*, *68*(2), 175-180. <https://doi.org/10.1093/gerona/gls155>
- Zhang, B., Tian, D., Yu, C., Zhang, J., Tian, X., von Deneen, K. M., Zang, Y., Walter, M., & Liu, Y. (2015). Altered baseline brain activities before food intake in obese men: a resting state fMRI study. *Neuroscience Letters*, *584*, 156-161. <https://doi.org/10.1016/j.neulet.2014.10.020>
- Zhang, F., Wang, S., Signore, A. P., & Chen, J. (2007a). Neuroprotective effects of leptin against ischemic injury induced by oxygen-glucose deprivation and transient cerebral ischemia. *Stroke*, *38*(8), 2329-2336. <https://doi.org/10.1161/STROKEAHA.107.482786>
- Zhang, F., Zhong, R., Li, S., Fu, Z., Cheng, C., Cai, H., & Le, W. (2017a). Acute hypoxia induced an imbalanced M1/M2 activation of microglia through NF-κB signaling in Alzheimer's disease mice and wild-type littermates. *9*, 282. <https://doi.org/10.3389/fnagi.2017.00282>
- Zhang, H. Y., Wang, S. J., Liu, B., Ma, Z. L., Yang, M., Zhang, Z. J., & Teng, G. J. (2010). Resting brain connectivity: changes during the progress of Alzheimer disease. *Radiology*, *256*(2), 598-606. <https://doi.org/10.1148/radiol.10091701>
- Zhang, J., Tian, L., Zhang, L., Cheng, R., Wei, R., He, F., Li, J., Luo, B., & Ye, X. (2019). Relationship between white matter integrity and post-traumatic cognitive deficits: A systematic review and meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *90*(1), 98-107. <http://dx.doi.org/10.1136/jnnp-2017-317691>
- Zhang, J., Wang, Y., Wang, J., Zhou, X., Shu, N., Wang, Y., & Zhang, Z. (2014a). White matter integrity disruptions associated with cognitive impairments in type 2 diabetic patients. *Diabetes*, *63*(11), 3596-3605. <https://doi.org/10.2337/db14-0342>
- Zhang, N., Gordon, M. L., & Goldberg, T. E. (2017b). Cerebral blood flow measured by arterial spin labeling MRI at resting state in normal aging and Alzheimer's disease. *Neuroscience and Biobehavioral Reviews*, *72*, 168-175. <https://doi.org/10.1016/j.neubiorev.2016.11.023>
- Zhang, R., Beyer, F., Lampe, L., Luck, T., Riedel-Heller, S. G., Loeffler, M., Schroeter, M. L., Stumvoll, M., Villringer, A., & Witte, A. V. (2018). White matter microstructural variability

- mediates the relation between obesity and cognition in healthy adults. *NeuroImage*, 172, 239–249. <https://doi.org/10.1016/j.neuroimage.2018.01.028>
- Zhang, S., Chai, R., Yang, Y. Y., Guo, S. Q., Wang, S., Guo, T., Xu, S. F., Zhang, Y. H., Wang, Z. Y., & Guo, C. (2017c). Chronic diabetic states worsen Alzheimer neuropathology and cognitive deficits accompanying disruption of calcium signaling in leptin-deficient APP/PS1 mice. *Oncotarget*, 8(27), 43617–43634. <https://doi.org/10.18632/oncotarget.17116>
- Zhang, Y., Schuff, N., Jahng, G.-H., Bayne, W., Mori, S., Schad, L., . . . Yaffe, K. (2007b). Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. *Neurology*, 68(1), 13-19. <https://doi.org/10.1212/01.wnl.0000250326.77323.01>
- Zhang, Y., Zhang, X., Zhang, J., Liu, C., Yuan, Q., Yin, X., Wei, L., Cui, J., Tao, R., Wei, P., & Wang, J. (2014b). Gray matter volume abnormalities in type 2 diabetes mellitus with and without mild cognitive impairment. *Neuroscience Letters*, 562, 1-6. <https://doi.org/10.1016/j.neulet.2014.01.006>
- Zhao, G., Etherton, T. D., Martin, K. R., West, S. G., Gillies, P. J., & Kris-Etherton, P. M. (2004). Dietary α -linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. *The Journal of Nutrition*, 134(11), 2991-2997. <https://doi.org/10.1093/jn/134.11.2991>
- Zhao, Z., Nelson, A. R., Betsholtz, C., & Zlokovic, B. V. (2015). Establishment and dysfunction of the blood-brain barrier. *Cell*, 163(5), 1064-1078. <https://doi.org/10.1016/j.cell.2015.10.067>
- Zhou, B., Yao, H., Wang, P., Zhang, Z., Zhan, Y., Ma, J., Xu, K., Wang, L., An, N., Liu, Y., & Zhang, X. (2015). Aberrant functional connectivity architecture in Alzheimer's disease and mild cognitive impairment: A whole-brain, data-driven analysis. *BioMed Research International*, 495375. <https://doi.org/10.1155/2015/495375>
- Zhou, H., Lu, W., Shi, Y., Bai, F., Chang, J., Yuan, Y., Teng, G., & Zhang, Z. (2010a). Impairments in cognition and resting-state connectivity of the hippocampus in elderly subjects with type 2 diabetes. *Neuroscience Letters*, 473(1), 5-10. <https://doi.org/10.1016/j.neulet.2009.12.057>
- Zhou, J., Greicius, M. D., Gennatas, E. D., Growdon, M. E., Jang, J. Y., Rabinovici, G. D., Kramer, J. H., Weiner, M., Miller, B. L., & Seeley, W. W. (2010b). Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain*, 133(Pt 5), 1352-1367. <https://doi.org/10.1093/brain/awq075>
- Zhou, X., Zhang, J., Chen, Y., Ma, T., Wang, Y., Wang, J., & Zhang, Z. (2014). Aggravated cognitive and brain functional impairment in mild cognitive impairment patients with type 2 diabetes: A resting-state functional MRI study. *Journal of Alzheimer's Disease*, 41(3), 925-935. <https://doi.org/10.3233/JAD-132354>
- Zhou, Y., Dougherty, J. H., Jr., Hubner, K. F., Bai, B., Cannon, R. L., & Hutson, R. K. (2008). Abnormal connectivity in the posterior cingulate and hippocampus in early Alzheimer's disease and mild cognitive impairment. *Alzheimer's & Dementia*, 4(4), 265-270. <https://doi.org/10.1016/j.jalz.2008.04.006>
- Zhou, Y., Xu, Q., Qin, L. D., Qian, L. J., Cao, W. W., & Xu, J. R. (2011). A primary study of diffusion tensor imaging-based histogram analysis in vascular cognitive impairment with no dementia. *Clinical Neurology and Neurosurgery*, 113(2), 92-97. <https://doi.org/10.1016/j.clineuro.2010.09.007>
- Zhou, Y., Wu, K., Shen, H., Zhang, J., Deng, H. W., & Zhao, L. J. (2019). Geographical differences in osteoporosis, obesity, and sarcopenia related traits in white American cohorts. *Scientific Reports*, 9(1), 1-8. <https://doi.org/10.1038/s41598-019-48734-9>
- Zhuang, L., Sachdev, P. S., Trollor, J. N., Reppermund, S., Kochan, N. A., Brodaty, H., & Wen, W. (2013). Microstructural white matter changes, not hippocampal atrophy, detect early amnesic mild cognitive impairment. *PLoS One*, 8(3), e58887. <https://doi.org/10.1371/journal.pone.0058887>

- Zhuang, Q.-S., Zheng, H., Gu, X.-D., Shen, L., & Ji, H. F. (2017). Detecting the genetic link between Alzheimer's disease and obesity using bioinformatics analysis of GWAS data. *Oncotarget*, 8(34), 55915. <https://doi.org/10.18632/oncotarget.19115>
- Zimmet, P., Collins, V., De Courten, M., Hodge, A., Collier, G. R., Dowse, G., K., Alberti, K. G. M. M., Tuomilehto, J., Hemraj, F., Gareeboo, H., & Chitson, P. (1998). Is there a relationship between leptin and insulin sensitivity independent of obesity? A population-based study in the Indian Ocean nation of Mauritius. *International Journal of Obesity*, 22(2), 171-177. <https://doi.org/10.1038/sj.ijo.0800559>
- Zink, D. N., Miller, J. B., Caldwell, J. Z., Bird, C., & Banks, S. J. (2018). The relationship between neuropsychological tests of visuospatial function and lobar cortical thickness. *Journal of Clinical and Experimental Neuropsychology*, 40(5), 518-527. <https://doi.org/10.1080/13803395.2017.1384799>
- Zlokovic, B. V. (2010). Neurodegeneration and the neurovascular unit. *Nature Medicine*, 16(12), 1370-1371. <https://doi.org/10.1038/nm1210-1370>
- Zlokovic, B. V. (2011). Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nature Reviews Neuroscience*, 12(12), 723-738. <https://doi.org/10.1038/nrn3114>
- Zobel, E. H., Hansen, T. W., Rossing, P., & von Scholten, B. J. (2016). Global changes in food supply and the obesity epidemic. *Current Obesity Reports*, 5(4), 449-455. <https://doi.org/10.1007/s13679-016-0233-8>
- Zonneveld, H. I., Loehrer, E. A., Hofman, A., Niessen, W. J., Lugt, A. v. d., Krestin, G. P., Ikram, M. A., & Vernooij, M. W. (2015). The bidirectional association between reduced cerebral blood flow and brain atrophy in the general population. *Journal of Cerebral Blood Flow & Metabolism*, 35(11), 1882-1887. <https://doi.org/10.1038/jcbfm.2015.157>
- Zorzano, A., Liesa, M., & Palacín, M. (2009). Mitochondrial dynamics as a bridge between mitochondrial dysfunction and insulin resistance. *Archives of Physiology and Biochemistry*, 115(1), 1-12. <https://doi.org/10.1080/13813450802676335>
- Zoungas, S., Woodward, M., Li, Q., Cooper, M. E., Hamet, P., Harrap, S., Heller, S., Marre, M., Patel, A., Poulter, N., Williams, B., Chalmers, J., & ADVANCE Collaborative Group (2014). Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia*, 57(12), 2465-2474. <https://doi.org/10.1007/s00125-014-3369-7>

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3 messages

Manmohi Dhananjay Dake <m.dake@sheffield.ac.uk>
To: Kate Sully <katesully@blueyonder.co.uk>

5 October 2020 at 19:19

Hi Kate,

Hope you are doing well. It was so wonderful working with you on the festival of the mind project. I thought that it would be great if I could include a picture of Corpus as my cover page in my PhD thesis and wanted to ask for your permission if I could?

Thank you

Best wishes
Mo

--

Manmohi Dake

PhD Student

The Translational Neuropsychology Group, The Department of Neuroscience
Royal Hallamshire Hospital, N floor, Room N132
Glossop Road, Sheffield, S10 2JF
Email: m.dake@sheffield.ac.uk

Kate Sully <katesully@blueyonder.co.uk>
To: Manmohi Dhananjay Dake <m.dake@sheffield.ac.uk>

5 October 2020 at 20:28

Hi Mo

I am ok thanks and yes of course use the image and I will share the drop box pics with you from James as they are really good quality.

Good luck with your thesis!

Cheers

Kate

[Quoted text hidden]

Fig. 1.1 Stages of the progression of AD pathology

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2 messages

Manmohi Dhananjay Dake <m.dake@sheffield.ac.uk>
To: mg@mrc-lmb.cam.ac.uk

10 November 2020 at 16:24

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Best wishes
Manmohi Dake

—

Manmohi Dake

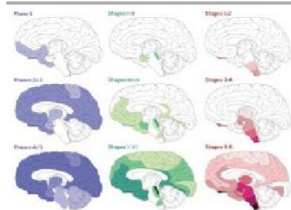
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The Translational Neuropsychology Group, The Department of Neuroscience

Royal Hallamshire Hospital, N floor, Room N132

Glossop Road, Sheffield, S10 2JF

Email: m.dake@sheffield.ac.uk



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Michel Goedert <mg@mrc-lmb.cam.ac.uk>
To: Manmohi Dhananjay Dake <m.dake@sheffield.ac.uk>

10 November 2020 at 21:03

Dear Manmohi,

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Michel

On 10 Nov 2020, at 10:55, Manmohi Dhananjay Dake <m.dake@sheffield.ac.uk> wrote:

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Fig 1.2 *The default mode network*

Fig 2.1 *Cerebral blood supply*

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Fig 2.2 *Shared mechanisms between obesity, T2DM and hypertension that contribute toward increasing AD severity in AD patients or reducing the threshold for AD in healthy individuals*

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





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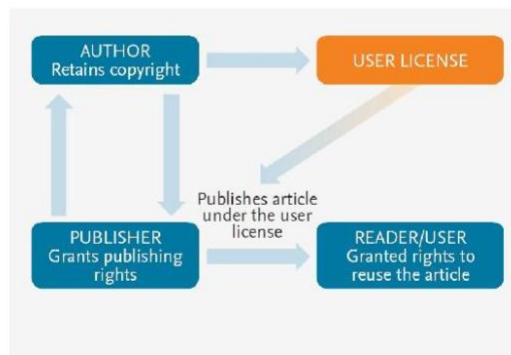
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Appendix B

Means and standard deviations of non-parametric data across the chapters

Table B4.2 *Demographic characteristics of ADD, MCI and CN groups reported using means and standard deviations for non-parametric data.*

Demographic variable	ADD	MCI	CN
(units)	(n = 47)	(n = 68)	(n = 57)
Statistics	M (SD)	M (SD)	M (SD)
Education (in years)	11.28 (3.74)	11.78 (3.75)	14.39 (3.30)
MMSE	21.53 (4.68)	26.03 (2.52)	28.11 (1.62)
BMI (kg/m ²)	25.54 (3.89)	27.37 (5.36)	28.07 (5.09)
WMV (ml)	383.47 (63.11)	398.62 (39.99)	436.611 (66.47)
WMH volume (ml)	9.18 (11.90)	6.64 (7.94)	3.02 (3.55)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation

Table B4.3 *Cognitive profiles of CN and patients with MCI and ADD reported using means and standard deviations for non-parametric data.*

Neuropsychological test	ADD	MCI	CN
	(n = 47)	(n = 68)	(n = 57)
Statistics	M (SD)	M (SD)	M (SD)
Prose Memory-Immediate recall	6.32 (4.37)	10.13 (4.10)	15.91 (3.27)
Prose Memory-Delayed recall	5.20 (4.77)	10.23 (5.45)	17.81 (3.41)
Digit Span-Forward	6.47 (1.72)	6.72 (1.80)	6.80 (1.83)
Digit Span-Backward	4.00 (1.60)	4.75 (1.79)	5.45 (1.48)
Semantic Fluency	12.83 (6.50)	17.85 (5.54)	21.54 (5.28)
Phonemic Fluency	24.38 (12.74)	31.51 (12.95)	44.53 (14.31)
Similarities	14.61 (7.37)	18.22 (6.34)	24.23 (4.37)
Confrontational Naming Test	11.78 (2.57)	12.80 (1.93)	14.38 (0.80)
Stroop-error interference	7.31 (9.38)	3.85 (13.45)	0.50 (1.75)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation

Table B5.2 Demographic characteristics of medicated and unmedicated patients with mild to moderate AD reported using means and standard deviations.

Demographic variable	Medicated (<i>n</i> = 71)	Unmedicated (<i>n</i> = 62)
Statistics	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)
Age (in years)	73.73 (8.10)	64.71 (9.54)
Education (in years)	10.48 (3.87)	12.18 (3.44)
MMSE	25.31 (3.63)	23.48 (4.39)
BMI (in kg/m ²)	27.31 (5.19)	25.47 (4.10)
WMH volume (in ml)	8.53 (11.36)	5.17 (7.61)
Blood pressure: Systolic (in mmHg)	142.32 (20.44)	143.82 (18.09)
Pulse pressure (in mmHg)	62.72 (18.22)	61.52 (16.64)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation

Table B5.2.1 Post hoc analysis: Demographic characteristics of medicated normotensive and hypertensive AD patients and unmedicated normotensive and hypertensive AD patients

Demographic variable	Medicated Hypertensive (<i>n</i> = 38)	Medicated Normotensive (<i>n</i> = 33)	Unmedicated Hypertensive (<i>n</i> = 40)	Unmedicated Normotensive (<i>n</i> = 22)
Statistics	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)
Education (in years)	9.61 (3.48)	11.48 (4.69)	11.93 (3.68)	12.64 (2.99)
MMSE	25.08 (3.26)	25.58 (4.06)	23.50 (4.47)	23.45 (4.34)
BMI (in kg/m ²)	26.51 (4.10)	28.22 (6.15)	25.38 (4.25)	25.64 (3.91)
Lesion volume (in ml)	9.98 (12.34)	6.85 (10.03)	5.00 (7.11)	5.47 (8.61)
Blood pressure: Systolic (in mmHg)	157.58 (14.75)	124.76 (8.21)	153.03 (14.42)	127.09 (10.49)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation

Table B5.3 Demographic characteristics of AD patients on antihypertensive treatment stratified by medication type reported using means and standard deviations for non-parametric variables

Demographic variable	Group 1	Group 2	Group 3
	Other (<i>n</i> = 34)	β-blocker (<i>n</i> = 13)	Both (<i>n</i> = 24)
Statistics	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)
Age (in years)	74.94 (7.54)	68.85 (9.43)	74.67 (7.42)
Education ⁺ (in years)	10.79 (4.24)	11.15 (3.89)	9.67 (3.26)
MMSE	25.97 (3.66)	25.92 (2.14)	24.04 (3.99)
BMI (kg/m ²)	26.91 (4.78)	27.22 (4.52)	27.92 (6.15)
WMH volume (ml)	12.11 (13.96)	2.15 (2.85)	6.91 (8.00)
Pulse pressure (in mmHg)	65.00 (18.09)	59.08 (16.36)	61.46 (19.62)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation

Table B5.4 Cognitive profiles of AD patients medicated and unmedicated for hypertension, reported using means and standard deviations for non-parametric variables

Neuropsychological test	Medicated	Unmedicated
	(<i>n</i> = 71)	(<i>n</i> = 62)
Statistics	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)
Prose Memory-Immediate recall	9.20 (3.84)	7.53 (4.85)
Prose Memory-Delayed recall	8.72 (5.33)	7.42 (5.39)
Digit Span-Forward	6.65 (1.75)	6.19 (1.68)
Digit Span-Backward	4.34 (1.86)	4.32 (1.51)
Phonemic Fluency	30.27 (12.96)	27.18 (12.02)
Semantic Fluency	19.34 (8.34)	15.54 (6.40)
Confrontational naming test	13.47 (3.36)	13.08 (2.69)
Stroop task- error interference	3.80 (7.81)	4.40 (7.71)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation

Table B5.4.1 *Cognitive profiles of medicated AD patients, unmedicated normotensive AD patients and unmedicated hypertensive AD patients, reported using with means and standard deviations for non-parametric data*

Neuropsychological test	Medicated Hypertensive (n = 38)	Medicated Normotensive (n = 33)	Unmedicated Hypertensive (n = 40)	Unmedicated Normotensive (n = 22)
Statistics	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
Prose Memory-Delayed recall	8.68 (5.59)	8.78 (5.10)	7.86 (5.60)	6.60 (5.01)
Digit Span-Forward	6.67 (1.71)	6.63 (1.83)	6.18 (1.86)	6.20 (1.28)
Digit Span-Backward	4.58 (1.54)	4.03 (1.45)	4.51 (2.09)	4.00 (1.30)
Phonemic Fluency	30.37 (12.20)	30.15 (13.98)	27.79 (12.09)	26.05 (12.10)
Semantic Fluency	18.26 (8.07)	20.58 (8.59)	15.68 (6.72)	15.29 (5.90)
Confrontational naming test	12.82 (2.91)	14.25 (3.72)	12.89 (3.00)	13.41 (2.06)
Stroop task- error interference	3.86 (6.76)	2.82 (5.05)	3.87 (6.57)	5.95 (8.70)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation

Table B5.5 Cognitive profiles of medicated AD patients stratified by class of antihypertensive treatment reported using means and standard deviations for non-parametric data.

Neuropsychological test	Group 1 Other (n = 34)	Group 2 β-blocker (n = 13)	Group 3 Both (n = 24)
Statistics	M (SD)	M (SD)	M (SD)
Logical Memory-Immediate recall	9.15 (4.27)	8.62 (2.73)	9.61 (3.82)
Digit Span-Backward	4.58 (1.64)	4.23 (1.59)	4.00 (1.23)
Semantic Fluency	20.71 (8.46)	21.54 (10.39)	16.21 (6.06)
Confrontational Naming Task	13.94 (3.46)	13.85 (3.74)	12.57 (2.94)
Stroop task-error	3.55 (6.58)	3.81 (5.83)	2.71 (5.18)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation

Table B6.1 Demographic characteristics and cognitive profiles of AD patients with and without T2DM and CN, reported using means and standard deviations for non-parametric data.

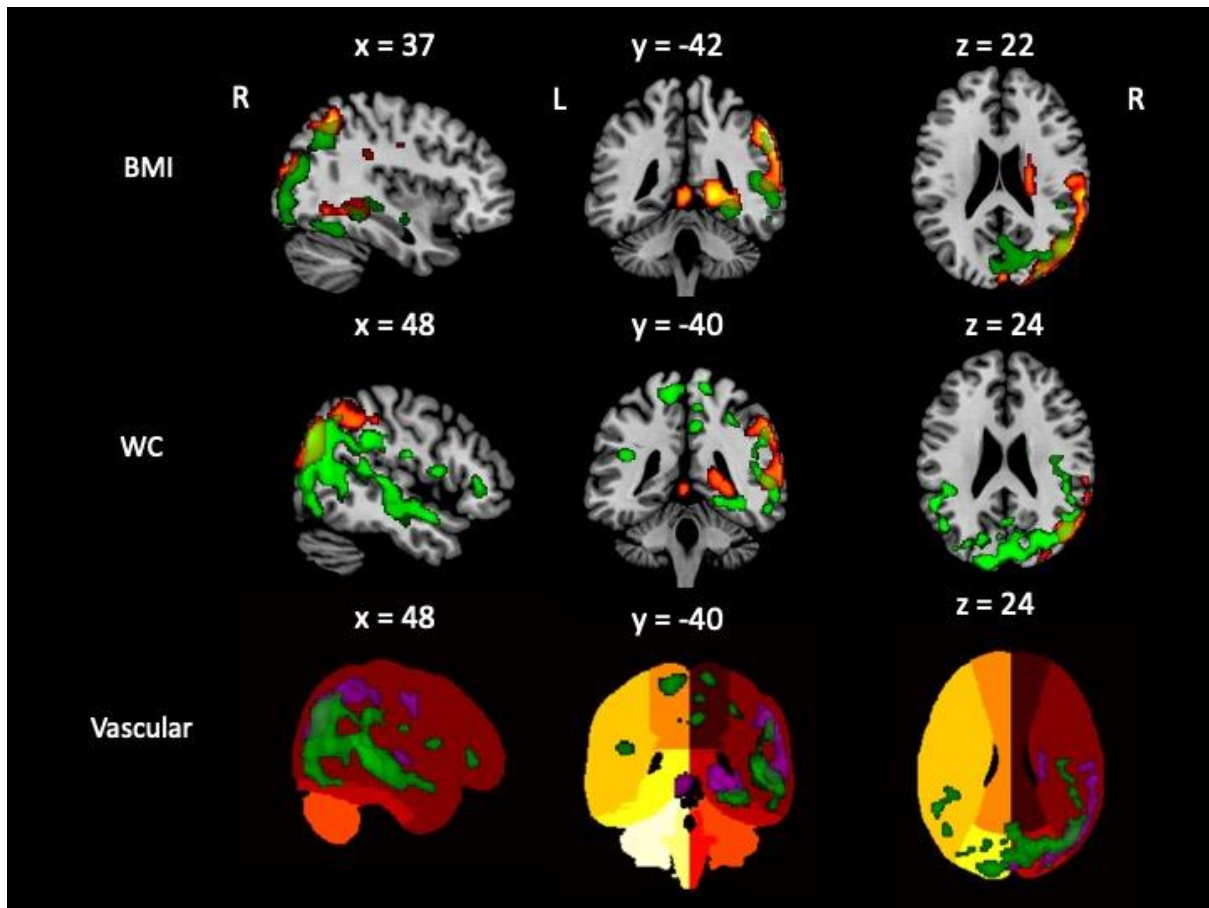
Demographic variable	AD with T2DM (<i>n</i> = 24)	AD without T2DM (<i>n</i> = 24)	CN (<i>n</i> = 24)
Statistics	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)
MMSE	25.88 (2.29)	25.33 (2.63)	28.17 (1.31)
WC	99.25 (16.46)	97.79 (10.06)	104.33 (10.48)
Lesion volume (ml)	9.18 (11.90)	6.64 (7.94)	3.02 (3.55)
Neuropsychological test			
Logical Memory-Immediate recall	8.92 (3.23)	8.59 (4.74)	15.21 (4.08)
Logical Memory-Delayed recall	7.67 (4.76)	8.59 (5.14)	16.17 (4.83)
Digit Span-Forward	6.30 (1.94)	6.32 (1.43)	7.00 (1.45)
Digit Span-Backward	4.52 (1.28)	4.91 (1.48)	5.35 (1.58)
Phonemic Fluency	26.29 (10.72)	27.30 (11.68)	40.96 (12.52)
Semantic Fluency	17.38 (6.28)	18.30 (6.57)	23.88 (8.10)
Similarities	16.70 (5.82)	15.52 (5.81)	23.50 (4.63)
Confrontational Naming Task	12.55 (2.40)	12.95 (1.93)	14.96 (2.05)
Stroop task-error	1.22 (2.22)	1.06 (1.34)	0.29 (0.72)

Key: *n* = sample size; *M* = mean; *SD* = standard deviation

Appendix C

Supplementary results and images

Fig C.1 *Overlap of positive correlations found between obesity measures and neuroimaging parameters in patients with ADD*



The three rows show positive correlations between obesity measures and neuroimaging parameters in patients with AD dementia. Each of the associations is represented in the sagittal, coronal and axial orientations from left to right. The 'x', 'y' and 'z' co-ordinates have been reported based on the MNI space. Top row: Positive associations found between BMI and GMV around the right temporoparietal junction. Correlations with GMV are represented in green whereas correlations with CBF are depicted in orange. Middle row: Positive associations found between WC and GMV around the right temporoparietal junction. Correlations with GMV are represented in green whereas correlations with CBF are depicted in orange. Bottom row: Positive associations found between obesity measures and GMV and CBF around the right temporoparietal junction mapped onto the vascular territories of major cerebral arteries. Correlations with GMV are represented in green whereas correlations with CBF are depicted in purple.

Appendix D

D.1 Obesity and brain vulnerability in normal and abnormal aging: A multimodal MRI study

Extracts from chapter 4 have been published in the form of a journal article. Full text from the article can be found via the following link: <https://content.iospress.com/articles/journal-of-alzheimers-disease-reports/adr200267>

and has also been included below:

Journal of Alzheimer's Disease Reports 5 (2021) 65–77
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IOS Press

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Research Report

Obesity and Brain Vulnerability in Normal and Abnormal Aging: A Multimodal MRI Study

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Abstract.

Background: How the relationship between obesity and MRI-defined neural properties varies across distinct stages of cognitive impairment due to Alzheimer's disease is unclear.

Objective: We used multimodal neuroimaging to clarify this relationship.

Methods: Scans were acquired from 47 patients clinically diagnosed with mild Alzheimer's disease dementia, 68 patients with mild cognitive impairment, and 57 cognitively healthy individuals. Voxel-wise associations were run between maps of gray matter volume, white matter integrity, and cerebral blood flow, and global/visceral obesity.

Results: Negative associations were found in cognitively healthy individuals between obesity and white matter integrity and cerebral blood flow of temporo-parietal regions. In mild cognitive impairment, negative associations emerged in frontal, temporal, and brainstem regions. In mild dementia, a positive association was found between obesity and gray matter volume around the right temporoparietal junction.

Conclusion: Obesity might contribute toward neural tissue vulnerability in cognitively healthy individuals and mild cognitive impairment, while a healthy weight in mild Alzheimer's disease dementia could help preserve brain structure in the presence of age and disease-related weight loss.

Keywords: Alzheimer's disease, body mass index, neuroimaging, overweight

INTRODUCTION

Obesity significantly increases vascular risk and has been identified as a risk factor for Alzheimer's disease (AD) [1]. The potential involvement of vas-

cular factors in AD etiology has received increased scrutiny [2]. A recent meta-analysis on 1.3 million individuals showed that higher body mass index (BMI) is associated with increased dementia risk when measured earlier than 20 years before diagnosis [3]. Earlier evidence had also suggested that risk is greater for midlife obesity than old age obesity [4]. This could be due to the pathological cascade of obesity-mediated mechanisms that can induce neuroinflammation, blood-brain barrier

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breakdown, production of reactive oxygen species, and microglial activation [5]. These mechanisms can promote the build-up of AD pathology while simultaneously accelerating neuronal damage. Overall, the available evidence suggests common neurodegenerative pathways between the two conditions [5]. However, meta-analytical evidence also shows that higher BMI is associated with lower dementia risk when measured later than 10 years before diagnosis [3]. Body fat-mediated mechanisms may modify, therefore, AD risk across disease stages differently.

Although obesity has an overall negative effect on neural health, cerebral constituents have a variable susceptibility to AD and obesity. Patients in the early stages of AD typically present with reduced cerebral blood flow (CBF) in the posteromedial parietal areas, reduced white matter integrity (WMI) and neuronal loss in mediotemporal areas, extending to other brain regions with disease progression [6]. In contrast, obesity seems to affect frontal brain regions among older individuals, i.e., > 65 years of age, while temporal areas are more vulnerable to obesity-related damage in midlife, i.e., > 40 years of age [7, 8]. Since both AD and obesity can significantly alter cerebral constituents, that an interaction between these pathologies can exacerbate the above effects is not surprising, with higher age playing a catalytic role [1]. Although the prevalence of both obesity and AD rates have risen in the past decades, few studies have explored the association between brain structure, perfusion and obesity in patients across the clinical spectrum of AD, and the evidence is largely restricted to brain volume [9, 10]. It is, therefore, a clinical priority to examine the link between obesity, a prevalent but modifiable risk factor [1, 11], and brain properties.

Research has shown conflicting evidence surrounding the effects of obesity on the brain across various stages of life and disease [1, 3]. Given the uncertainty, a characterization of the neural phenotype associated with obesity that can be stratified using cognitive status would be extremely valuable in the management of patient body-fat composition to reduce damage to the brain, in clinical settings. The present study investigated the relationship between structural and perfusion brain parameters and indices of obesity across three diagnostic groups: patients with mild AD dementia (ADD), patients with mild cognitive impairment (MCI), and cognitively healthy individuals (CH). By analyzing multimodal brain images containing information about gray matter volume (GMV), WMI, and CBF, a holistic approach was

used to examine the interplay between obesity and cognitive staging in the cognitively healthy to AD dementia continuum.

MATERIALS AND METHODS

Participants

Datasets from 172 participants recruited as part of the VPH-DARE@IT EU-funded project coordinated by the University of Sheffield, Department of Neuroscience (<http://www.vph-dare.eu/>) were included in this study. Experimental procedures complied with the declaration of Helsinki and written informed consent was obtained from all participants. Ethical approval was obtained from the Yorkshire and Humber Regional Ethics Committee, RefNo: 12/YH/0474 for the participants from the Sheffield (UK) cohort and from the ethics committee of the Northern Savo- nia Hospital District for the participants from Kuopio (Finland). The participants were divided into patients with a clinical diagnosis of ADD ($n = 47$)¹, patients with a diagnosis of MCI ($n = 68$) and CH ($n = 57$), following established clinical diagnostic procedures. Specifically, diagnoses of ADD or MCI due to AD were reached based on clinical criteria [12, 13]. Diagnoses were formulated following a consensus among a senior neurologist, a senior clinical neuropsychologist and a neuroradiologist. In addition, MCI patients also had clinical follow ups at regular intervals for at least 4 years to confirm their diagnosis. Cerebrospinal fluid biomarkers were available for a proportion of the sample (14 ADD and 20 MCI).

The presence of MRI abnormalities, any major medical condition or any etiological entity that could account for the presence of cognitive impairment were exclusion criteria (see [14] for a comprehensive list). All demographic characteristics, including specific details on age ranges and averages, are listed in Table 1.

Indices of obesity

Anthropometric measurements were obtained to calculate obesity indices. Quetelet's index was used to calculate BMI (kg/m^2) as an index of global obesity. Waist circumference in centimeters (WC) was used as an index of abdominal obesity [15, 16].

¹This number was reduced to 45 in the WMI analysis due to two unavailable diffusion scans.

body mass index; WC, waist circumference; GMV, gray matter volume; MMSE, Mini-Mental State Examination.

Table 1
Demographic characteristics and cognitive profiles of the three diagnostic groups

Variable	ADD (<i>n</i> = 47)			
	MCI (<i>n</i> = 68)			
	CH (<i>n</i> = 57)			
Statistic				
Demographic variables				
<i>Parametric tests</i> [§]	<i>mean (SD)</i>	<i>mean (SD)</i>	<i>mean (SD)</i>	<i>F</i>
Age (y)	68.09 (9.88)	68.56 (9.45)	66.51 (11.11)	0.67
Education ^{%x} (y)	10.91 (3.26)	11.78 (3.74)	14.44 (3.29)	15.22
WC (cm)	92.11 (10.95)	96.08 (14.39)	96.32 (13.33)	1.69
GMV ^{&%x} (ml)	569.30 (77.26)	605.37 (74.34)	636.19 (70.40)	11.52***
CSF ^{&x} (ml)	525.83 (153.46)	465.92 (130.73)	412.66 (134.89)	6.68**
TIV (ml)	1491.17 (163.41)	1454.14 (143.54)	1495.70 (173.28)	1.24
<i>Non-Parametric tests</i> ⁺	<i>median (IQR)</i>	<i>median (IQR)</i>	<i>median (IQR)</i>	<i>H</i>
MMSE ^{&%x}	21 (17 – 25)	26 (25 – 28)	28 (27 – 29)	69.11***
BMI [§] (kg/m ²)	24.82 (22.86 – 28.37)	26.76 (23.40 – 26.76)	27.54 (24.94 – 31.01)	7.87*
WMV (ml)	416.04 (369.51 – 416.04)	407.54 (370.71 – 446.86)	430.34 (381.55 – 469.56)	4.08
WMH volume (ml) ^{%x}	3.53 (1.83 – 7.79)	6.64 (0.64 – 7.86)	3.02 (0.22 – 3.55)	11.44**
<i>Chi square tests</i> [#]	<i>n</i>	<i>n</i>	<i>n</i>	<i>χ²</i>
Males/Females	29/18	31/37	26/31	3.54
APOE genotype: <i>e2e2/e2e3/e3e3/e4e2/e4e3/e4e4</i>	0/6/13/0/16/11	0/3/28/5/28/4	0/7/38/2/9/1	36.96***
APOE <i>e4</i> non-carriers/ <i>e4</i> carriers	19/27	31/37	45/12	19.15***
Centre (UK/Finland)	24/23	29/39	38/19	7.27*
Neuropsychological measures				
<i>Parametric tests</i> [§]	<i>mean (SD)</i>	<i>mean (SD)</i>	<i>mean (SD)</i>	<i>F</i>
Category Fluency ^{&%x}	12.63 (6.50)	17.85 (5.54)	21.54 (5.28)	30.83***
<i>Non-Parametric tests</i> ⁺	<i>M (IQR)</i>	<i>M (IQR)</i>	<i>M (IQR)</i>	<i>H</i>
Prose Memory-Immediate recall ^{&%x}	6 (2.25 – 9)	10 (8 – 13)	17 (14 – 19)	84.41***
Prose Memory-Delayed recall ^{&%x}	4 (2 – 8)	11 (6 – 14)	18 (16 – 20)	96.54***
Similarities ^{%x}	13.5 (8 – 21)	17 (12 – 23)	25 (21.5 – 27.5)	45.37***
Letter Fluency ^{&%x}	22 (13 – 32)	28.5 (20 – 44)	45 (32.5 – 55)	45.01***
Digit Span-Forward	6 (5 – 8)	6 (5 – 8)	7 (5 – 8)	0.72
Digit Span-Backward ^{%x}	4 (3 – 5)	5 (3.75 – 6)	5 (4 – 6)	19.08***
Boston Naming Test ^{%x}	12 (10–14)	13 (12 – 14)	15 (14 – 15)	47.32***
Stroop task-error ^{%x}	2.5 (0 – 14.5)	0.50 (0 – 2)	0 (0 – 0)	29.47***

*Comparison is significant at 0.05 level (two tailed);
 **Comparison is significant at 0.01 level (two tailed);
 ***Comparison is significant at 0.001 level (two tailed);
 Normality of data was tested using the Shapiro-Wilk Test of Normality. F, F-statistic; H, H-statistic; IQR, Interquartile range; SD, standard deviation; χ^2 , Chi-square statistic; [§]A one-way ANOVA was run for data that were normally distributed. The F-statistic is reported. ⁺Non-parametric Kruskal-Wallis H tests were run for data that were not normally distributed. The H statistic is reported. [&]Significant difference between ADD and MCI; [%]Significant difference between MCI and CH; ^x Significant difference between CH and ADD; ADD, Alzheimer's disease dementia; MCI, mild cognitive impairment; CH, cognitively healthy; BMI,

MRI acquisition and preprocessing

The imaging protocol included a T1-weighted and a T2-weighted anatomical image, a diffusion-weighted image for the analysis of WMI and a pseudo-continuous arterial spin labelling (pCASL) sequence for the modelling of blood flow. All images were acquired using a Philips Ingenia 3T scanner. T1-weighted images were acquired with the following specifications: voxel size $0.94 \times 0.94 \times 1.00 \text{ mm}^3$, matrix size $256 \times 256 \text{ mm}^2$, repetition time 8.2 ms, echo time 3.84 ms, flip angle 8° field of view $240 \times 240 \times 70 \text{ mm}$. T2-weighted images features were as follows: voxel size $0.532 \times 0.532 \times 4.000 \text{ mm}^3$, matrix size $432 \times 432 \text{ mm}^2$, repetition time 3000 ms, echo time 80 ms, flip angle 8° field of view $230 \times 140 \times 5 \text{ mm}$. Diffusion-weighted images followed instead these technical parameters: 32 directions, voxel size 2.5 mm^3 isotropic, matrix size $96 \times 96 \text{ mm}^2$, repetition time 3 s, echo time 98 ms, flip angle 90° , field of view $240 \times 120 \times 40 \text{ mm}$. Finally, pCASL imaging acquisition consisted of two consecutive sequences: an M0 estimation tag, followed by a pseudo-continuous ASL sequence: voxel size $3 \times 3 \times 8 \text{ mm}^3$ with inter-slice 1 mm gap, matrix size $80 \times 80 \text{ mm}^2$, repetition time 4 s, echo time 14 s, flip angle 40° field of view $240 \times 135 \times 240 \text{ mm}$, number of label/control pairs 73, labelling gap 20 s, labelling duration 1.65 s, post-labelling delay time 1.525 s.

Gray matter volume

T1-weighted scans were preprocessed and analyzed using voxel-based morphometry within the Statistical Parametric Mapping (SPM) 12 software (The Wellcome Centre for Human Neuroimaging, London, UK) running in MATLAB (Mathworks Inc., Natick, MA, USA). A tissue-class probabilistic segmentation was initially run to separate gray matter (GM), white matter (WM), and cerebrospinal fluid for each scan within its native space, according to the most updated version of the standard voxel-based morphometry procedures [17]. GM maps were then registered and normalized to the standard template for “European” brains and were then smoothed with an 8 mm full-width at half-maximum Gaussian kernel.

White matter integrity

Fractional anisotropy (FA) of diffusion-weighted images was selected as the WMI index. FA provides information about the motional anisotropy of

water molecules and is the most widely used measure of WMI [18, 19]. Each image was preprocessed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library v5.0.8 (FSL, <http://www.fmrib.ox.ac.uk/fsl>). The FSL Diffusion Toolbox was used to correct for eddy currents and motion artifacts. A fractional-intensity threshold of 0.5 was applied to the resultant image in order to strip the skull and generate a binary mask using the Brain Extraction Tool. This mask was fitted with the diffusion-tensor model at each voxel to calculate FA maps. Tract-based spatial statistics [20] was then applied, where FA maps were initially eroded to eliminate outliers. The most representative FA map was then identified and used as a reference for non-linear registration. Subsequent to the affine alignment to the standard Montreal Neurological Institute (MNI) space, an average of the FA maps was computed. The resultant ‘average’ FA map was then skeletonized and each FA image was projected onto the skeleton.

Cerebral blood flow

pCASL sequences were acquired to obtain maps of CBF. pCASL images are usually obtained by applying multiple radiofrequency pulses to reduce the duration of application of the pulse in a continuous arterial-spin-labelling sequence, successfully combining the advantages of continuous and pulsed arterial-spin-labelling sequences [21]. The current acquisition included a pCASL image and an M0 estimation image, which contain the information about the CBF quantification and calibration, respectively. The M0 and pCASL images were used to generate CBF maps in Nordic Ice (<https://www.nordicneurolab.com/en/HelpAll/nordicICE>). The maps were sequentially co-registered with the T2-weighted and then the T1-weighted images to maximize inter-tissue demarcation and to increase the accuracy of the anatomical correspondence of the CBF signal. Images were then modified to increase the signal from the brain parenchyma and to reduce the contribution to the signal from the cerebrospinal fluid. Therefore, only voxels with CBF values enclosing more than 50% of GM and WM were included in the analysis. Next, a partial volume correction (PVC) was performed under the assumption that the perfusion of WM accounts for 40% of the perfusion of GM [22], as illustrated below for voxel “i”.

$$PVC_{i_{CBF}} = \frac{i_{CBF} \times (i_{GM} + i_{WM} > 0.5)}{i_{GM} + (0.4 \times i_{WM})}$$

The resultant partial volume corrected images were then normalized using the standard template for “European” brains in SPM 12 and smoothed using a 10 × 10 × 12 full-width at half-maximum Gaussian kernel.

Statistical analysis

Multiple regression models were run using GMV, WMI, and CBF maps to examine the associations between these brain parameters and obesity. For all three diagnostic groups, independent models were run using the indices of obesity (BMI and WC) as predictors, controlling for the confounding effects of age, the Mini-Mental State Examination (MMSE) score as an index of clinical severity, total intracranial volume as an index of brain reserve [23], recruitment centre and sex. The MMSE was not included in the analysis of cognitively healthy participants given its limited numerical variability, i.e., a variance of just 2.6 (Table 1). All analyses were carried out voxel-by-voxel and statistical thresholds were applied. Voxel-based-morphometry models were thresholded at a cluster-forming threshold of $p < 0.001$. The analysis of skeletonized FA maps was run using the FMRIB Software Library (v5.0.8) using the ‘randomise’ command and implementing 5000 permutations via a threshold-free cluster enhancement. Finally, given the smaller size of the acquisition matrix for CBF maps, a more lenient cluster-forming threshold of $p < 0.01$ was used for these analyses. For all inferential models, only results surviving a family-wise error-corrected value of $p < 0.05$ at the cluster level were considered significant.

To contextualize the pattern of findings in relation to clinical profiles, we extracted the average signal from clusters showing significant results and correlated it with scores on neuropsychological tests. All results surviving at $p < 0.01$ were considered as significant. The neuropsychological tests measured lexical abilities (Boston Naming test), semantic memory (Category Fluency test), executive function (Letter Fluency test, Digit Span test - backwards, Stroop Error Interference test), long-term memory (Prose Memory test - immediate and delayed recall), short-term memory (Digit Span test-forward), and verbal reasoning (the Similarities subtest of the Wechsler Adult Intelligence Scale) [14, 24].

RESULTS

There were no significant group differences in age, total intracranial volume, and WC. Cognitively healthy participants ranked the highest when it came to measurements of years of education, MMSE, BMI, and GMV, while MCI and ADD patients ranked lower than the cognitively healthy participants, in that order (Table 1). With respect to cognitive profiles, all groups had significant differences between their scores with ADD patients scoring the lowest, cognitively healthy participants performing the highest and MCI patients having an intermediate performance (Table 1), with the exception of the Digit Span test – forward.

Body mass index

In ADD patients, there was a positive association between BMI and GMV in right posterolateral areas, particularly around the temporoparietal junction. This cluster spanned across the junction and a large proportion of the occipital lobe that tapered down anteriorly toward the hippocampus (Table 2). No significant associations were found between BMI and measures of WMI. Although the results from the CBF analysis did not reach significance, the trend of association observed in these analyses overlapped with the areas exhibiting BMI-related positive associations with GMV.

In the MCI patients, higher BMI was associated with lower GMV in the occipital and frontal lobes bilaterally, and the right cerebellum and with lower CBF in the brainstem, frontoparietal and medial temporal areas (Tables 2 and 3). Left frontal volumes showed a positive correlation with performance on the Letter Fluency test. No significant associations were found between BMI and measures of WMI.

In the cognitively healthy participants, GMV was negatively associated with BMI in inferior frontal, occipital, subcortical, and cerebellar regions, bilaterally (Table 2). Additionally, higher BMI was associated with lower FA in the superior longitudinal fasciculus, fronto-occipital tracts, optic radiations, middle cerebellar peduncle, cingulum, parahippocampal/hippocampal fibers and fornix (Table 4). BMI was also negatively associated with CBF in the bilateral fronto-occipital tracts and in the superior portions of the parahippocampal fibers (Table 3). Regional signal extracted from the three analyses revealed a positive correlation with performance on the Category Fluency test, Prose Memory

(immediate and delayed recall) and the Similarities test.

Waist circumference

In ADD patients, WC was positively associated with GMV in the areas around the temporoparietal junction and in the right cerebellar hemisphere. No significant associations were found between WC and measures of WMI. Similar to BMI, the pattern of association observed in the CBF analysis overlapped with the areas exhibiting WC-related positive associations with GMV (Table 2, Fig. 1).

In the MCI group, a negative association was found between WC and GMV in bilateral inferior frontal, occipital, and cerebellar regions (Table 2, Fig. 1). A positive association was found between the extracted GMV signal from these regions and performance on the Letter Fluency and Digit Span - forward tests. No significant associations were found between WC and measures of WMI. A negative association was found between WC and CBF in the bilateral hippocampi, parts of the brainstem and frontoparietal regions, concentrated more in the right hemisphere (Table 4, Fig. 1).

In the cognitively healthy group, there was a negative correlation between GMV and WC in the bilateral occipital lobes, cerebellum and midline structures (Table 2, Fig. 1). Tracts showing a negative association between FA and WC included the inferior fronto-occipital fasciculus, cingulum, fornix, and anterior thalamic radiations (Table 4, Fig. 1). Cognitively healthy participants also showed a negative association between CBF and WC in the bilateral frontal lobes that extended backward toward the parietal lobe, joining at the midline and then extending inferiorly into the temporal lobes. This negative association was also observed in the cerebellum and parts of the brainstem (Table 3, Fig. 1). Positive correlations were found between regional neural signals and performance on the Category Fluency test, Prose Memory-immediate and delayed recall and the Similarities test.

DISCUSSION

In this study, evidence from multimodal neuroimaging suggests variable associations between indices of obesity and the brain across three diagnostic statuses. The three groups had substantial baseline differences in the distribution of their obesity indices. The distribution of the cognitively healthy group

fell in part within the obese range; that of the MCI group fell in the overweight range, while the distribution of the ADD group was within the normal range. Group differences may be among the drivers of the associations found. These differences could be a factor of age and disease-related weight alterations, where the trends of body mass distributions seen in this study are consistent with the existing literature [3, 25]. The findings indicate that higher indices of obesity within the overweight and obese ranges are linked to reduced brain structure and CBF parameters in cognitively healthy participants and MCI patients. In contrast, higher indices of body mass within the normal range are linked to higher retention of GMV parameters in ADD patients. This trend could be linked to downstream mechanisms resulting from circulating hormones associated with body fat (including sex hormones), age-related changes in body fat accumulation and the interaction between AD and obesity [26–28].

Negative associations between GMV and obesity in the MCI and cognitively healthy groups were identified in frontal, occipital, cerebellar and deep brain regions, albeit the negative associations found in the MCI group were less extensive than those in the cognitively healthy group. This almost entirely replicated the results of a meta-analysis on GM and obesity [29]. The only discrepancy was in the occipital lobe, where a negative association was found between obesity and GMV in this region in cognitively healthy participants and MCI patients in our study, as opposed to a positive correlation [29]. The GM areas showing negative associations in the cognitively healthy group are connected by WM tracts that exhibit a negative association between WMI and indices of obesity [30]. Past literature has indicated that a loss of structural connectivity can lead to reductions in GM density [31]. If this inference in WMI were causal, WM disconnections could explain the negative associations found within the GM. Additionally, obesity has an element of metabolic dysfunction that fosters systemic inflammatory processes that, as evidence from other neurological conditions shows, are detrimental to both GM and WM [e.g. 32]. The mechanisms and directionality of the relationship between GM and WM damage still need additional study and clarification. A negative association between WMI and obesity in the corpus callosum, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, fornix, and cingulum was found only in the cognitively healthy sample. This is in accordance with the previous literature [19, 33, 34]. The absence of a neg-

Table 2
Regions showing associations between obesity and GMV across the three diagnostic groups

Voxels (Cluster extent)	Cluster level <i>p</i> FWE	Brain region	Side	Z-score	MNI coordinates		
					x	y	z
<i>AD: Positive correlation</i>							
<i>BMI</i>							
16986	<0.001	Superior parietal lobule (BA 7)	R	5.64	40	-58	42
		Cuneus (BA 18)	R	4.91	22	-88	18
		Middle temporal gyrus (BA 39)	R	4.76	57	-44	6
		Superior temporal gyrus (BA 22)	R	4.76	44	-33	10
634	0.04	Superior temporal gyrus (BA 39)	L	3.89	-46	-61	22
		Superior temporal gyrus (BA 39)	L	3.83	-50	-53	28
<i>WC</i>							
13284	<0.001	Superior parietal lobule (BA 7)	R	6.11	42	-58	39
		Superior parietal lobule (BA 7)	L	4.70	-24	-62	47
		Superior occipital gyrus (BA 19)	R	4.39	38	-73	22
		Superior temporal gyrus (BA 22)	R	4.16	55	-48	8
905	0.01	Inferior frontal gyrus (BA 44)	R	4.30	44	6	11
		Insula (BA 13)	R	4.08	32	-13	17
787	0.02	Cerebellum: Posterior lobe	R	4.05	28	-52	-40
<i>MCI: Negative correlation</i>							
<i>BMI</i>							
2618	<0.001	Middle occipital gyrus (BA 19)	R	4.85	50	-80	-1
1318	0.001	Cerebellum: Posterior lobe	R	4.76	48	-75	-23
870	0.01	Inferior frontal gyrus (BA 47)	L	4.67	-50	36	-15
2545	<0.001	Inferior occipital gyrus (BA 19)	L	4.42	-39	-91	-6
639	0.04	Inferior frontal gyrus (BA 47)	R	4.32	50	26	-15
<i>WC</i>							
1178	0.002	Inferior frontal gyrus (BA 47)	L	5.29	-48	32	-16
4662	<0.001	Inferior occipital gyrus (BA 18)	R	4.77	48	-82	-3
		Cerebellum: Posterior lobe	R	4.71	40	-74	-40
615	0.04	Cerebellum: Posterior lobe	L	3.88	-40	-77	-33
611	0.04	Inferior frontal gyrus (BA 47)	R	4.50	53	27	-11
1872	<0.001	Inferior occipital gyrus (BA 18)	L	4.49	-38	-91	-8
1478	0.001	Precentral gyrus (BA 6)	L	4.24	-57	4	20
<i>CH: Negative correlation</i>							
<i>BMI</i>							
1701	<0.001	Thalamus: Ventral anterior nucleus	L	3.60	-12	-12	18
1029	0.001	Posterior lobe of the cerebellum	R	4.43	36	-81	-35
543	0.02	Posterior lobe of the cerebellum	L	4.27	-36	-81	-38
1015	0.001	Anterior cingulate gyrus (BA 24)	L	4.36	-3	16	21
631	0.01	Inferior occipital gyrus (BA 18)	L	4.34	-38	-91	-9
1218	<0.001	Inferior frontal gyrus (BA 47)	R	3.94	50	40	-15
1386	<0.001	Insula	L	4.19	-36	14	1
879	0.002	Inferior frontal gyrus (BA 47)	L	3.92	-46	44	-16
793	<0.001	Inferior occipital gyrus (BA 18)	R	3.89	39	-91	-6
<i>WC</i>							
1506	<0.001	Inferior occipital gyrus (BA 19)	L	4.40	-36	-92	-9
1451	<0.001	Thalamus	L	4.05	-12	-11	19
704	0.01	Anterior cingulate gyrus (BA 24)	L	4.48	-2	17	19
821	0.003	Insula (BA 13)	L	4.28	-42	-10	-5

ADD, Alzheimer's disease dementia; BMI, body mass index; GMV, gray matter volume; CH, cognitively healthy; L, left; MCI, mild cognitive impairment; MNI, Montreal Neurological Institute; *p*FWE, Family-wise error corrected *p* value; R, Right; WC, waist circumference.

ative association between obesity indices and WMI in MCI patients might be due to lower obesity rates seen in this group, which could explain the more attenuated neural effects mediated by obesity compared to cognitively healthy participants.

These findings suggest that being on the higher end of the obesity spectrum may be detrimental to brain structure. Our findings also indicate that there might

be a resilient effect of higher body-fat store within the normal weight range in advanced disease stages, as reflected by the positive correlation between GMV and normal body mass in ADD patients. A parallel pattern of association was also found in the analysis of CBF in the same regions (although it did not survive the predetermined threshold of significance), suggesting that a relative preservation of vascular

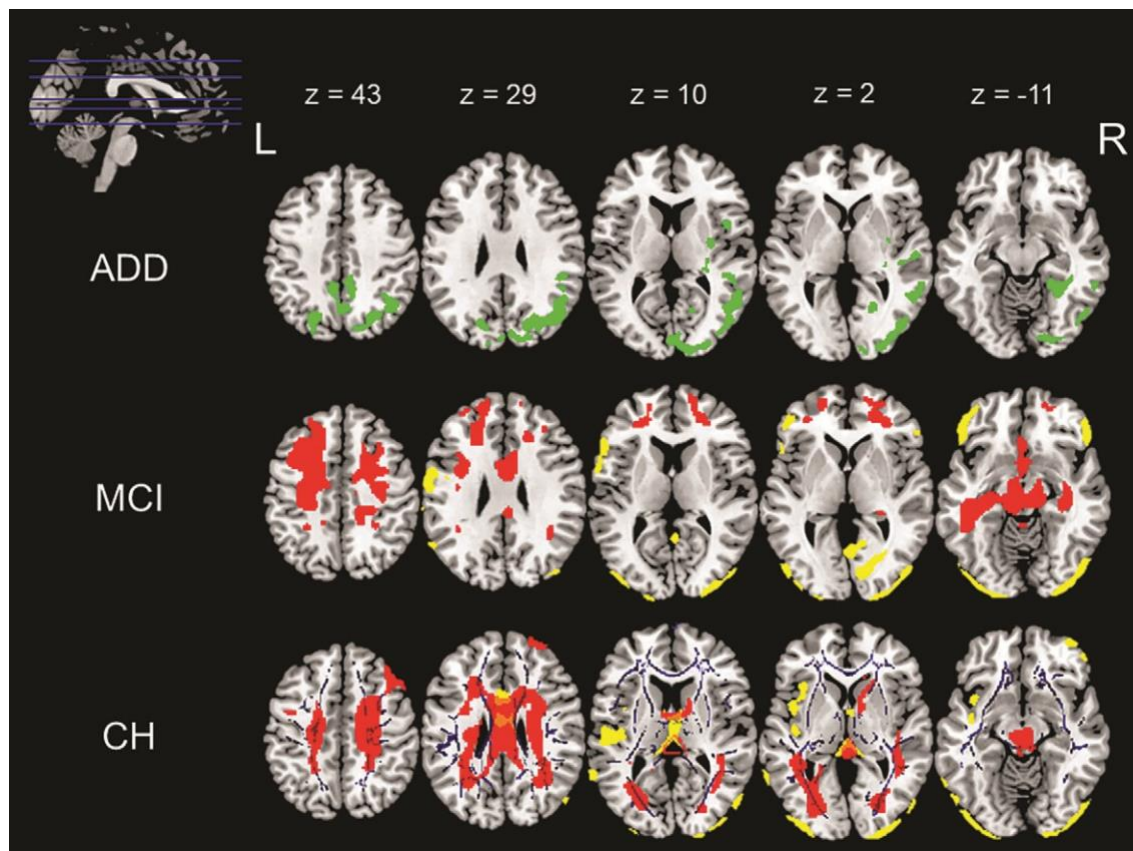


Fig. 1. Associations with waist circumference across the three diagnostic groups namely ADD, MCI, and CH. The above image shows various positive and negative correlations between different neuroimaging indices and waist circumference. The image in the top left corner shows the axial slices chosen in the image and the MNI coordinates for these slices are listed in the same row. The slices going from top to bottom have been arranged from left to right across the three rows of images. These MNI co-ordinates also correspond to the column that they represent. First row (ADD): The green overlay represents a positive correlation found between GMV and WC in ADD patients. Middle row (MCI): The yellow overlay represents a negative correlation between GMV and WC and the red overlay represents a negative correlation between CBF and WC in MCI patients. Last row (CH): The yellow overlay represents a negative correlation between GMV and WC, the red overlay represents a negative correlation between CBF and WC and the blue overlay represents a negative correlation between WMI and WC in CH.

function might be contributing to the associations found with GMV. Furthermore, the association could be attributed to the availability of sufficient resources to cope with neural damage as a result of retaining a healthy body mass in later disease stages. Therefore, in the presence of natural age and disease-related weight loss, having a healthy weight and better nutrition could help preserve brain structure [19, 35, 36], or even mitigate disease progression as suggested by nutrition interventional studies in mice [37, 38]. This could imply that interventions that aid ADD patients to maintain a healthy body weight could help alleviate some of the neural susceptibility caused by body-mass reductions clinically observed in later disease stages [25]. Our study is limited by its cross-sectional

design, and we can only speculate about how body-fat composition can modulate disease onset. Since the ADD group fell within the normal weight range, we cannot draw inferences on the effects of being overweight or obese in the dementia stage. This is a limitation for most studies due to the pattern of weight loss usually seen in disease and aging. Future longitudinal studies can potentially offer complementary evidence.

Considerable variation across the three groups was found in the associations with CBF. In cognitively healthy participants, a negative association with CBF was mainly seen in WM regions, specifically in the fronto-occipital tracts, corpus callosum and the posterior ends of the cingulum, most of which also

Table 3
Regions showing a negative association between obesity and CBF across CH and MCI groups

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z-score	MNI coordinates		
					x	y	z
<i>MCI: Negative correlation</i>							
<i>BMI</i>							
4529	<0.001	Inferior fronto-occipital fasciculus	L	3.77	-28	39	11
		Middle frontal gyrus (BA 6)	L	3.39	-34	5	27
		Corticospinal tract	L	3.67	-22	-23	45
2555	0.002	Midbrain	L	3.68	-6	-28	-9
		Inferior longitudinal fasciculus/ Parahippocampal gyrus	L	3.52	-42	-32	-9
3266	<0.001	Superior longitudinal fasciculus	R	3.42	22	0	42
		Precuneus (BA 39)	R	3.32	28	-65	29
<i>WC</i>							
5626	<0.001	Hippocampus	R	5.23	36	-11	-16
		Thalamus	R	3.77	12	-16	-4
		Hippocampus	L	3.52	-28	-22	-11
10179	<0.001	Anterior cingulate gyrus (BA 32)	L	4.64	-20	31	28
		Corticospinal tracts	L	4.44	-22	-23	47
		Middle frontal gyrus (BA 6)	R	3.75	28	-13	49
		Superior longitudinal fasciculus	R	3.53	36	-43	33
<i>CH: Negative correlation</i>							
<i>BMI</i>							
2365	0.01	Superior longitudinal fasciculus	L	3.23	-26	-14	36
		Parahippocampal gyrus (BA 36)	L	2.83	-24	-47	2
2546	0.01	Superior longitudinal fasciculus	R	3.33	22	-8	39
		Parahippocampal gyrus (BA 36)	R	2.84	42	-31	-2
<i>WC</i>							
1879	0.04	Posterior lobe of the cerebellum	L	4.55	-10	-54	-39
		Posterior lobe of the cerebellum	R	2.70	20	-70	-34
13608	<0.001	Superior longitudinal fasciculus	R	3.73	32	-47	30
		Superior longitudinal fasciculus	L	3.72	-28	-51	30
		Superior longitudinal fasciculus	L	3.56	-42	-33	0
		Superior longitudinal fasciculus	R	3.43	42	-39	6

BMI, body mass index; CBF, cerebral blood flow; CH, cognitively healthy; L, left; MCI, mild cognitive impairment; MNI, Montreal Neurological Institute; pFWE, Family-wise error corrected *p* value; R, right; WC, waist circumference.

Table 4
Regions showing a negative association between obesity and FA in CH

Voxels (Cluster extent)	Cluster level pFWE	Brain region	Side	Z-score	MNI coordinates		
					x	y	z
<i>BMI</i>							
54045	0.001	Fornix	L	7.75	-28	-27	-4
		Fornix	L	7.13	-28	-29	-1
		Superior longitudinal fasciculus/ Inferior fronto-occipital fasciculus	L	6.90	-37	34	6
		Cingulum	R	6.66	9	-5	34
		Inferior fronto-occipital fasciculus	R	6.62	26	29	-10
		Superior longitudinal fasciculus	L	6.62	36	14	18
<i>WC</i>							
55438	0.001	Anterior thalamic radiation	L	7.49	-28	-30	0
		Inferior fronto-occipital fasciculus	R	7.47	26	29	-10
		Fornix	L	7.05	-29	-26	-3
		Cingulum	R	6.92	9	-5	34
		Inferior fronto-occipital fasciculus	L	6.85	-35	-55	0
		Inferior fronto-occipital fasciculus	L	6.80	-37	34	6

BMI, body mass index; FA, fractional anisotropy; CH, cognitively healthy; L, left; MNI, Montreal Neurological Institute; pFWE, Family-wise error corrected *p* value; R, right; WC, waist circumference.

showed negative correlations with WMI. In MCI patients, the negative association with CBF was concentrated in the frontal lobe and extended to the brainstem, cerebellum, and medial temporal lobes. Of note, in the present study the MCI group showed more extensive negative associations with CBF in the left hemisphere, while loss of function among obese cognitively healthy participants seems to be more right lateralized [39]. This discrepancy might be due to the asymmetry of AD-related neurodegeneration, which is harsher in the left hemisphere [40]. The right-sided association in MCI might result from an interaction between AD and the right-sided susceptibility to obesity [41]. In addition, some regions displaying negative associations with obesity are in close proximity to cerebral watershed sites, making them particularly vulnerable to the effects of vascular pathology [42, 43]. The more inferior areas correspond to the system involved in reward behavior, which are often affected in obese individuals [44]. Of these, the mediotemporal lobes and certain brainstem nuclei are centrally affected in AD as well [45]. Therefore, down-regulation of neural parameters in MCI patients might manifest as an amalgamation of detriments resulting from the presence of AD pathology and being overweight. This may accelerate the progression rate toward ADD.

The negative associations with CBF that were found in the groups of cognitively healthy participants and MCI patients in the parietal lobe are particularly of note. This territory acts as a central hub that integrates several brain regions, making it a region with high metabolic demands and, as a consequence, particularly prone to damage [46–48]. Furthermore, the parietal lobe is supplied by the terminating branches of the posterior and middle cerebral arteries, making the medial parietal areas more vulnerable to hypoperfusion as terminating arterial branches are more susceptible to ischemic damage than major arteries [42, 43, 49]. Such a combination of factors confers a certain susceptibility to the parietal lobe to the effects of metabolic conditions such as obesity.

Past research has consistently indicated that medioparietal hypometabolism and hypoperfusion are among the earliest indicators of AD [6]. Disruptions in medioparietal function possibly reflecting a deficit of input from medial temporal areas often leads to a ‘disconnection’ between areas of the default mode network, a phenomenon commonly seen in AD, even in early disease stages [50]. In the present study, negatively correlated maps of CBF

and WMI extended from temporal to medioparietal areas and even some anterior areas in cognitively healthy participants. This pattern partly resembled the map of ‘disconnection’ typically seen in AD. This convergence again points toward common pathophysiological pathways between AD and obesity. Additionally, the down-regulation of cerebral indices can reduce the amount of brain tissue available for compensatory mechanisms, thus accelerating progression from cognitively healthy to MCI, or even from MCI to ADD [51]. Therefore, this finding in the cognitively healthy sample could potentially offer an explanation for how obesity could promote pathophysiological cascades, fostering greater damage to cerebral constituents.

The areas exhibiting negative correlations with obesity among cognitively healthy participants, were associated with worse performance on tests of memory and reasoning. This indicates that damage to brain areas with high metabolic demands (e.g., the medioparietal lobe) could result in the manifestation of cognitive symptoms in the presence of metabolic disorders as those often associated with obesity. The fact that these areas of cognition are also affected early on in AD offers an explanation for how obesity may contribute toward AD risk [6]. Although a similar association was found between regional neural indices and obesity, correlations with test performance in the MCI group revealed disruptions in performance on tasks of executive functioning. This finding might reflect the presence of greater variability in scores in executive tasks at the MCI level, since the slope of decline in executive function is not as steep as the slope of decline in memory and reasoning tasks, allowing statistical effects to emerge. This might also reflect obesity-mediated effects, as loss of executive function has been established as a cognitive deficit associated with obesity [7].

In conclusion, our study found diminished CBF, structural, and cognitive measures associated with obesity in cognitively healthy participants that resemble neural changes typically induced by AD, while those in MCI patients resemble changes typically associated with obesity and AD. This could point toward susceptible pathways that are shared between AD and obesity and toward the initiation of a pathological cascade pushing the brain over the threshold for potential progression from cognitively healthy to MCI and from MCI to ADD [51]. However, this relationship may change in individuals in later disease stages, where having a higher body weight remaining within the normal range may contribute

to preservation of brain structure in the presence of aging and disease related insults. It is noteworthy that these results were consistent across the two different anthropometric indices of obesity.

These findings are of central importance for the characterization and management of patients with AD or, more generally, patients referred to a neurological examination. Although obesity is mentioned among the risk factors for AD, its exact effects on the brain are still undetermined. These findings highlight multi-component mechanisms associated with obesity, involving diagnosis-dependent properties of GMV, WMI, and CBF. This evidence emphasizes the urgent need to introduce early interventions that advocate lifestyle assessment and remediation across the lifespan. It also highlights the importance of primary prevention strategies based on modulation of lifestyle factors such as obesity in midlife as an effective strategy to achieve a reduction of AD related dementia with advancing age [52].

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CONFLICT OF INTEREST

HS reports consultation fees from ACImmune, and MERCK and Novo Nordisk not related to this work. AV has received consultation fees from MERCK and Biogen not related to this work. The other authors have no conflicts of interest to report.

REFERENCES

- [1] Alford S, Patel D, Perakakis N, Mantzoros CS (2018) Obesity as a risk factor for Alzheimer's disease: Weighing the evidence. *Obes Rev* **19**, 269-280.
- [2] Santos CY, Snyder PJ, Wu WC, Zhang M, Echeverria A, Alber J (2017) Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. *Alzheimers Dement (Amst)* **7**, 69-87.
- [3] Kivimäki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, Shipley MJ, Alfredsson L, Fransson EI, Goldberg M, Knutsson A, Koskenvuo M, Kuosma E, Nordin M, Suominen SB, Theorell T, Vuoksima E, Westerholm P, Westerlund H, Zins M, Kivipelto M, Vahtera J, Kaprio J, Singh-Manoux A, Jokela M (2018) Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement* **14**, 601-609.
- [4] Pedditzi E, Peters R, Beckett N (2016) The risk of overweight/obesity in mid-life and late life for the development of dementia: A systematic review and meta-analysis of longitudinal studies. *Age Ageing* **45**, 14-21.
- [5] Pugazhenti S, Qin L, Reddy PH (2017) Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. *Biochim Biophys Acta Mol Basis Dis* **1863**, 1037-1045.
- [6] Ruan Q, D'Onofrio G, Sancarlo D, Bao Z, Greco A, Yu Z (2016) Potential neuroimaging biomarkers of pathologic brain changes in mild cognitive impairment and Alzheimer's disease: A systematic review. *BMC Geriatr* **16**, 104.
- [7] Lowe CJ, Reichelt AC, Hall PA (2019) The prefrontal cortex and obesity: A health neuroscience perspective. *Trends Cogn Sci* **23**, 349-361.
- [8] Willette AA, Kapogiannis D (2015) Does the brain shrink as the waist expands? *Ageing Res Rev* **20**, 86-97.
- [9] Boyle CP, Raji CA, Erickson KI, Lopez OL, Becker JT, Gach HM, Longstreth Jr WT, Teverovskiy L, Kuller LH, Carmichael OT, Thompson PM (2015) Physical activity, body mass index, and brain atrophy in Alzheimer's disease. *Neurobiol Aging* **36**, S194-S202.
- [10] Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, Lee S, Hibar D, Dinov ID, Stein JL, Jack Jr CR, Weiner MW, Toga AW, Thompson PM, Cardiovascular Health Study, for the Alzheimer's Disease Neuroimaging Initiative (2010) Obesity is linked with lower brain volume in 700 AD and MCI patients. *Neurobiol Aging* **31**, 1326-1339.
- [11] World Health Organization (2020) Obesity and overweight fact sheet. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>, Last updated April 1, 2020, Accessed on June 1, 2020.
- [12] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.
- [13] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic

- guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 270-279.
- [14] Jones SA, De Marco M, Manca R, Bell SM, Blackburn DJ, Wilkinson ID, Soininen H, Venneri A (2019) Altered frontal and insular functional connectivity as pivotal mechanisms for apathy in Alzheimer's disease. *Cortex* **119**, 100-110.
- [15] Hamer M, Batty GD (2019) Association of body mass index and waist-to-hip ratio with brain structure: UK Biobank study. *Neurology* **92**, e594-e600.
- [16] Janowitz D, Wittfeld K, Terock J, Freyberger HJ, Hegenscheid K, Völzke H, Habes M, Hosten N, Friedrich N, Nauck M, Domanska G, Grabe HJ (2015) Association between waist circumference and gray matter volume in 2344 individuals from two adult community-based samples. *Neuroimage* **122**, 149-157.
- [17] Ashburner J, Friston KJ (2000) Voxel-based morphometry—the methods. *Neuroimage* **11**, 805-821.
- [18] Assaf Y, Pasternak O (2008) Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. *J Mol Neurosci* **34**, 51-61.
- [19] Kullmann S, Schweizer F, Veit R, Fritsche A, Preissl H (2015) Compromised white matter integrity in obesity. *Obes Rev* **16**, 273-281.
- [20] Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TEJ (2006) Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage* **31**, 1487-1505.
- [21] Silva AC, Kim SG (1999) Pseudo-continuous arterial spin labeling technique for measuring CBF dynamics with high temporal resolution. *Magn Reson Med* **42**, 425-429.
- [22] Kim SM, Kim MJ, Rhee HY, Ryu CW, Kim EJ, Petersen ET, Jahng GH (2013) Regional cerebral perfusion in patients with Alzheimer's disease and mild cognitive impairment: Effect of APOE epsilon4 allele. *Neuroradiology* **55**, 25-34.
- [23] van Loenhoud AC, Groot C, Vogel JW, van der Flier WM, Ossenkoppele R (2018) Is intracranial volume a suitable proxy for brain reserve? *Alzheimers Res Ther* **10**, 91.
- [24] Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, Heyman A (1994) The Consortium to Establish a Registry for Alzheimer's disease (CERAD). Part V. a normative study of the neuropsychological battery. *Neurology* **44**, 609-614.
- [25] Jimenez A, Pegueroles J, Carmona-Iragui M, Vilaplana E, Montal V, Alcolea D, Videla L, Illán-Gala I, Pané A, Casajoana A, Belbin O, Clarimón J, Moizé V, Vidal J, Lleó A, Fortea J, Blesa R, for the Alzheimer's Disease Neuroimaging Initiative (2017) Weight loss in the healthy elderly might be a non-cognitive sign of preclinical Alzheimer's disease. *Oncotarget* **8**, 104706-104716.
- [26] Arner P, Bernard S, Appelsved L, Fu KY, Andersson DP, Salehpour M, Thorell A, Rydén M, Spalding KL (2019) Adipose lipid turnover and long-term changes in body weight. *Nat Med* **25**, 1385-1389.
- [27] Doherty GH (2011) Obesity and the ageing brain: Could leptin play a role in neurodegeneration? *Curr Gerontol Geriatr Res* **2011**, 708154.
- [28] Profenno LA, Porsteinsson AP, Faraone SV (2010) Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. *Biol Psychiatry* **67**, 505-512.
- [29] Herrmann MJ, Tesar AK, Beier J, Berg M, Warrings B (2019) Grey matter alterations in obesity: A meta-analysis of whole-brain studies. *Obes Rev* **20**, 464-471.
- [30] Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PCM, Mori S (2004) Fiber tract-based atlas of human white matter anatomy. *Radiology* **230**, 77-87.
- [31] Jacobs HI, Van Boxtel MPJ, Jolles J, Verhey FRJ, Uylings HBM (2012) Parietal cortex matters in Alzheimer's disease: An overview of structural, functional and metabolic findings. *Neurosci Biobehav Rev* **36**, 297-309.
- [32] Calabrese M, Magliozzi R, Ciccarelli O, Geurts JGG, Reynolds R, Martin R (2015) Exploring the origins of grey matter damage in multiple sclerosis. *Nat Rev Neurosci* **16**, 147-158.
- [33] Kullmann S, Callaghan MF, Heni M, Weiskopf N, Scheffler K, Häring HU, Fritsche A, Veit R, Preissl H (2016) Specific white matter tissue microstructure changes associated with obesity. *Neuroimage* **125**, 36-44.
- [34] van Bloemendaal L, Ijzerman RG, Ten Kulve JS, Barkhof F, Diamant M, Veltman DJ, van Duinkerken E (2016) Alterations in white matter volume and integrity in obesity and type 2 diabetes. *Metab Brain Dis* **31**, 621-629.
- [35] Dahl AK, Löppönen M, Isoaho R, Berg S, Kivela SL (2008) Overweight and obesity in old age are not associated with greater dementia risk. *J Am Geriatr Soc* **56**, 2261-2266.
- [36] Luchsinger JA, Cheng D, Tang MX, Schupf N, Mayeux R (2012) Central obesity in the elderly is related to late-onset Alzheimer disease. *Alzheimer Dis Assoc Disord* **26**, 101-105.
- [37] Wahl D, Cogger VC, Solon-Biet SM, Waern RVR, Gokarn R, Pulpitel T, de Cabo R, Mattson MP, Raubenheimer D, Simpson SJ, Le Couteur DG (2016) Nutritional strategies to optimise cognitive function in the aging brain. *Ageing Res Rev* **31**, 80-92.
- [38] Van der Auwera I, Wera S, Van Leuven F, Henderson ST (2005) A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. *Nutr Metab* **2**, 28.
- [39] Alonso-Alonso M, Pascual-Leone A (2007) The right brain hypothesis for obesity. *JAMA* **297**, 1819-1822.
- [40] Minkova L, Habich A, Peter J, Kaller CP, Eickhoff SB, Klöppel S (2017) Gray matter asymmetries in aging and neurodegeneration: A review and meta-analysis. *Hum Brain Mapp* **38**, 5890-5904.
- [41] Vainik U, Baker TE, Dadar M, Zeighami Y, Michaud A, Zhang Y, Garcia Alanis JC, Mistic B, Collins DL, Dagher A (2018) Neurobehavioral correlates of obesity are largely heritable. *Proc Natl Acad Sci USA* **115**, 9312-9317.
- [42] Kapasi A, Leurgans SE, James BD, Boyle PA, Arvanitakis Z, Nag S, Bennett DA, Buchman AS, Schneider JA (2018) Watershed microinfarct pathology and cognition in older persons. *Neurobiol Aging* **70**, 10-17.
- [43] Suter OC, Sunthorn T, Kraftsik R, Straubel J, Darekar P, Khalili K, Miklossy J (2002) Cerebral hypoperfusion generates cortical watershed microinfarcts in Alzheimer disease. *Stroke* **33**, 1986-1992.
- [44] Russo SJ, Nestler EJ (2013) The brain reward circuitry in mood disorders. *Nat Rev Neurosci* **14**, 609-625.
- [45] Wierenga CE, Hays CC, Zlatar ZZ (2014) Cerebral blood flow measured by arterial spin labeling MRI as a preclinical marker of Alzheimer's disease. *J Alzheimers Dis* **42**, S411-S419.
- [46] Jung J, Cloutman LL, Binney RJ, Lambon Ralph MA (2017) The structural connectivity of higher order association cortices reflects human functional brain networks. *Cortex* **97**, 221-239.
- [47] Sala-Llloch R, Bartrés-Faz D, Junqué C (2015) Reorganization of brain networks in aging: A review of functional connectivity studies. *Front Psychol* **6**, 663.

- [48] Bruner E, Jacobs HIJ (2013) Alzheimer's disease: The downside of a highly evolved parietal lobe? *J Alzheimers Dis* **35**, 227-240.
- [49] Weis S, Sonnberger M, Dunzinger A, Voglmayr E, Aichholzer M, Kleiser R, Strasser P (2019) Arterial supply of the brain. In: *Imaging Brain Diseases*, Weis S, Sonnberger M, Dunzinger A, Voglmayr E, Aichholzer M, Kleiser R, Strasser P, eds. Springer, pp. 191-209.
- [50] Lacalle-Aurioles M, Navas-Sanchez FJ, Aleman-Gomez Y, Olazarán J, Guzmán-De-Villoria JA, Cruz-Orduña I, Mateos-Pérez JM, Desco M (2016) The disconnection hypothesis in Alzheimer's disease studied through multi-modal magnetic resonance imaging: Structural, perfusion, and diffusion tensor imaging. *J Alzheimers Dis* **50**, 1051-1064.
- [51] Neth BJ, Graff-Radford J, Mielke MM, Przybelski SA, Lesnick TG, Schwarz CG, Reid RI, Senjem ML, Lowe VJ, Machulda MM, Petersen RC, Jack Jr CR, Knopman DS, Vemuri P (2019) Relationship between risk factors and brain reserve in late middle age: Implications for cognitive aging. *Front Aging Neurosci* **11**, 355.
- [52] Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L (2011) Midlife overweight and obesity increase late-life dementia risk: A population-based twin study. *Neurology* **76**, 1568-1574.

D.2 *Preclinical models of disease and multimorbidity with focus upon cardiovascular disease and dementia*

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