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Cognitive and neuroimaging approaches to preclinical markers for Alzheimer's Disease.

By

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"If a man has lost a leg or an eye, he knows he has lost a leg or an eye; but if he has lost a self—himself—he cannot know it, because he is no longer there to know it."

- Oliver Sacks, The Man Who Mistook His Wife for a Hat and Other Clinical Tales

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Abstract

In the absence of disease modifying therapies, early diagnosis of Alzheimer's disease (AD) is imperative not only for drug development but also for the timely application of pharmaceutical and behavioural treatments that may ameliorate rapid decline and improve quality of life for both patients and caregivers. The present research, therefore, applied psychological and neuroimaging approaches for the identification of cognitive markers of the earliest stages of AD physiological degradation. Specifically, the first experiments focussed on clarifying neural correlates of semantic memory decline in prodromal and dementia stages of disease. These studies not only identified a significant relationship between semantic memory performance and discrete structural alterations, within structures known to be affected at the initial stages of the AD pathological cascade, but further confirmed that a quick and simple verbal fluency test may provide a meaningful marker for very early neurodegeneration. Experiments three and four applied a more novel graph theoretical approach to the quantification of AD cognitive change. Experiment three aimed to elucidate neuropsychological profiles characteristic of the various stages of ageing and disease. The topology of networks reflecting cognitive performance were outlined and compared revealing notable differences in network structure relating to age that were further altered in the presence of disease. These findings specifically highlighted a central role for semantic processing and abstract reasoning in neuropsychological performance among healthy older adults, which appeared to be lost among patient groups. Finally, experiment four sought to investigate underlying alterations in brain structural networks that may account for the differences seen in ageing and disease at the cognitive level. Findings indicated that, even in prodromal AD, significant differences in network topology, relating to volumetric covariance, are apparent when compared with healthy age-related change, and such differences in structural relationships may account, to some extent, for the observable contrast in neuropsychological profile.

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List of Abbreviations

AD: Alzheimer's Disease; **Aβ**: Amyloid Beta; **aMCI**: Amnestic Mild Cognitive Impairment; **aMCI-md**: Multi-Domain Amnestic Mild Cognitive Impairment; **aMCI-sd**: Single Domain Amnestic Mild Cognitive Impairment; **AMPA**: A-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid; **aMTL**: Anterior Medial Temporal Lobe **ApoE-ε4**: Apolipoprotein-E ε4 allele; **APP**: Amyloid Precursor Protein; **ARIA-E**: Amyloid-Related Imaging Abnormalities-Effusion Type; **ATL**: Anterior Temporal Lobe; **aMTL**: Anterior Medial Temporal Lobe; **BA**: Brodmann's Area; **BOLD**: Blood-Oxygen Level Dependant; **CDR**: Clinical Dementia Rating; **CSF**: Cerebrospinal Fluid; **DMN**: Default Mode Network; **DTI**: Diffusion Tensor Imaging; **ERC**: Entorhinal Cortex; **FDR**: False Discovery Rate; **FLAIR**: Fluid-Attenuated Inversion Recovery; **fMRI**: Functional Magnetic Resonance Imaging; **frPSI**: Failure to Recover from Proactive Semantic Interference; **FWE**: Family Wise Error; **GDS**: Global Deterioration Scale; **GSK3**: Glycogen Synthase Kinase-3; **IFOF**: Inferior Fronto-Occipital Fasciculus; **LASSI-L**: Loewenstein-Acevedo Scale for Semantic Interference and Learning; **lv-PPA**: Logopenic Variant Primary Progressive Aphasia; **MAP**: Microtubule Associated Protein; **MCI**: Mild Cognitive Impairment; **MCI-na**: Non-Amnestic Mild Cognitive Impairment; **MDRS**: Mattis Dementia Rating Scale; **md-MCI-na**: Multi-Domain Non-Amnestic Mild Cognitive Impairment; **MNI**: Montreal Neurological Institute; **MRI**: Magnetic Resonance Imaging; **MMSE**: Mini Mental State Examination; **MTL**: Medial Temporal Lobe; **NFL**: Neurofilament Light; **NFT**: Neurofibrillary Tangle; **NINCDS-ADRDA**: National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association; **NMDA**: N-methyl-d-aspartate; **NP**: Neuritic Plaque; **NT**: Neuropil Thread; **PACC**, Preclinical Alzheimer's Cognitive Composite; **PCA**: Posterior Cortical Atrophy; **PCC**: Posterior Cingulate Cortex; **PET**: Positron Emission Tomography; **PRC**: Perirhinal Cortex; **PSEN1**: Presenilin 1; **PSEN2**: Presenilin 2; **PSI**: Proactive Semantic Interference; **P-tau**: Hyperphosphorylated Tau; rCBF: Regional Cerebral Blood Flow; **ROI**: Region of Interest; **rTMS**: Repetitive Transcranial Magnetic Stimulation; **SCD**: Subjective Cognitive Decline; **SD**: Standard Deviation; **sd-MCI-na**: Single Domain Non-Amnestic Mild Cognitive Impairment; **SMA**: Supplementary Motor Area; **SPECT**: Single Photon Emission Computed Tomography; **T2D**: Type 2 Diabetes; **TMS**: Transcranial Magnetic Stimulation; **T-tau**: Total Tau; **VBM**: Voxel Based Morphometry; **VTA**: Ventral Tegmental Area

Chapter 1 | Alzheimer's Disease

1.1. General Introduction

Throughout the developing world, one of the biggest issues facing health services is the question of how to accommodate and care for an ever-growing population of older people. In the UK, ever increasing life expectancies are set to continue rising, with females born in 2015 expected to live an average of 82.8 years and males 73.4, a 4 and 5.7-year increase respectively, compared with those born in 1991 (Office for National Statistics, 2017). With this increase in life expectancy comes an increase in geriatric disease that has shifted the burden of our national health service, from heart diseases as the leading cause of death in both males and females in 2001, towards Alzheimer's disease (AD) and dementias as the leading cause of death in females and second most common in males in 2015 (Patel, 2016). As this continues, the rates of older people living with dementia in the UK is expected to increase from 850,000 as of 2015, to around 1 million by 2025, and further double to a possible 2 million by the year 2050, a rate of increase that is reflected by a global rise in prevalence from 36 million in 2010 to 115 million by 2050 (Prince *et al*., 2015). However, evidence from the Cognitive Function and Ageing studies I and II has suggested that the incidence of dementia among older populations may have dropped considerably in recent years, particularly among men, as a result of primary prevention of comorbidities that would otherwise exacerbate and accelerate the consequences of AD neurodegeneration (Matthews *et al*., 2013; Matthews *et al*., 2016).

Accounting for around ⅔ of all dementia cases in the UK, AD is a neurodegenerative disease that primarily affects individuals over the age of 65 (Alzheimer's Research UK, May 2016). Characterised by the spread of pathological protein deposits, and devastating losses of brain tissue, the clinical phenotype of AD is easily identified by significant declines in cognitive function, marked, in particular, by deficits in memory but ultimately affecting a wide range of cognitive domains (McKhann *et al*., 2011). The primary cause of the neurodegeneration and dementia in AD remains a topic of much debate; however, a great deal of research now exists outlining the histopathological, neurological and clinical hallmarks of this disease. As a debilitating condition affecting a large number of individuals and their caregivers, the efforts to develop early diagnostic techniques and provide disease

modifying therapies in AD have only increased in recent years in an attempt to address what is quickly becoming a global health crisis (Prince *et al*., 2015).

1.2. Risk Factors

A lack of understanding as to the primary cause of disease onset in AD has led to a large component of research focussing primarily on the risk factors associated with lifestyle and genetics that may have significant roles in triggering the subsequent disease processes (Livingston *et al*., 2017). Ageing remains the primary risk factor associated with the development of dementia, with the prevalence of disease among older populations having been shown to double every five years after the age of 50 (Nichols *et al*., 2019), likely reflecting a greater vulnerability to co-morbidities such as diabetes, hearing loss and hypertension that may also impact on a person's risk for cognitive decline in later life (Livingston *et al*., 2017). Senescence may also interact negatively with a number of modifiable lifestyle factors outlined by a *Lancet* Commission Report as potentially accounting for around 35% of dementia cases, including low levels of education, hypertension, obesity, physical inactivity, smoking, social isolation and late-life depression (Livingston *et al*., 2017). Despite the known genetic component of AD, elimination of the Apolipoprotein-E ε4 allele (ApoE-ε4), as a genetic risk factor, from a Cox model including a number of modifiable risk factors, such as those listed above, found only a 7.1% reduction in incidence in comparison with the highest reduction, at 18.1%, that was attributed to increasing measures of crystallised intelligence in adulthood (Ritchie *et al*., 2010). Given that the majority of AD cases are thought to be sporadic (Bettens, Sleegers & Van Broeckhoven, 2013), understanding modifiable risk factors and implementing lifestyle interventions and preventative measures is of the upmost importance, having the potential for a very large effect on delaying onset and reducing the prevalence of disease in an ageing population (Barnes & Yaffe, 2011).

1.2.1. Lifestyle Factors

As previously mentioned, a growing number of health and lifestyle factors in early life have been associated with later dementia development. Awareness of modifiable risk factors, such as smoking status and obesity etc., is particularly vital given the ease with which such risks may be addressed in the individual and the significant impact they have on dementia prevalence in the population (Livingston *et al*., 2017). Many of the lifestyle factors

that have been identified have been directly related to vascular health. The mechanisms through which cardiovascular factors contribute to cognitive decline are varied and have been found to influence AD development through concomitant vascular dementia, comorbid neuronal damage by cerebrovascular diseases or by directly influencing AD pathogenesis through the pathological accumulation of materials such as amyloid beta (Aβ) (Schneider *et al*., 2007; Jellinger, 2010; Marchesi, 2011; Sagare, Bell & Zlokovic, 2012; Janota, Lemere & Brito, 2016). Conditions impacting vascular health that may be present in mid-life such as hypertension, diabetes, obesity, atherosclerosis and hypercholesterolemia have all been identified as significant risk-factors for dementia in late-life (Hofman *et al*., 1997; Arvanitakis *et al*., 2004; Kivipelto *et al*., 2006; Gottesman *et al*., 2017). Some clinico-pathological studies have suggested that the main contribution to dementia from vascular disease is through co-morbid brain damage caused by multiple infarcts, white matter lesions and small or large vessel disease as opposed to a direct influence on AD pathogenesis (Richardson *et al*., 2012; Kapasi & Schneider, 2016). Diabetes, in particular, has been shown to be one of the greatest mid-life risk-factors for dementia, with one study finding the hazard ratio for dementia associated with diabetes being almost as high as that found for the presence of the ApoE-ε4 genotype, the greatest known genetic risk-factor for late-onset AD (Liu *et al*., 2013; Gottesman *et al*., 2017). This may be explained by the presence of related disorders and AD risk factors, particularly associated with type 2 diabetes (T2D), such as metabolic dysfunction, hypoglycaemia and obesity, as well as lifestyle factors such as inactivity and poor nutrition (Haan, 2006; Jayaraman & Pike, 2014; Lee *et al*., 2018). As a preventable and modifiable condition, a much larger body of literature has explored the role of T2D in cognitive decline and AD than the role of type 1 diabetes, although the mechanisms of type 1 have been suggested to contribute to cognitive dysfunction to a potentially greater extent (Biessels, Deary & Ryan, 2008). Hyperinsulinemia, insulin resistance and hypoglycaemia, as hallmarks of T2D, have all been suggested to contribute to neurodegeneration to greater or lesser extents (Lee *et al*., 2018; Hegde, Dhurandhara & Reddy, 2019). Furthermore, a number of common abnormalities associated with both AD and T2D have led to the conclusion that shared disruptions to particular molecular pathways may explain the exacerbation of AD progression in those with T2D in a way which, unlike other vascular pathologies, involves a direct influence on AD pathogenesis (Zhao & Townsend, 2009). For example, normal insulin receptor signalling should induce the phosphorylation of glycogen synthase kinase-3 (GSK3) and its α and β subunits, inhibiting its activation. In the presence of insulin resistance or hyperinsulinemia however, abnormal insulin receptor

functioning can lead to the disinhibition of GSK3 and thereby affect the production of both Aβ and Tau, the accumulation of which mark the two prominent proteinopathies characteristic of AD (Zhao & Townsend, 2009; Hegde, Dhurandhara & Reddy, 2019). GSK3α mediates the activity of presenilin 1 (a secretase involved in the cleavage of the amyloid precursor protein) thereby promoting the production of Aβ. GSK3β plays a role in the phosphorylation of Tau, potentially contributing to the formation of neurofibrillary tangles, an intracellular lesion associated with AD progression (Braak & Braak, 1991).

Further modifiable risks associated with the development of AD dementia include a range of cognitive, social and psychiatric factors such as low education levels and cognitive reserve, loneliness and social isolation or a history of depression (Fratiglioni, Paillard-Borg & Winblad, 2004; Stern, 2006; Ownby *et al*., 2006; Wilson *et al*., 2007). Higher levels of education and cognitive reserve, along with increased physical activity, have been described by Baumgart *et al*., (2015) as being the most compelling and robust, in terms of evidence within the literature, modifiable factors that may decrease a person's chance of cognitive decline and dementia in later life. Cognitive reserve is a concept that refers to one's ability to adapt their cognitive processes and use compensatory mechanisms to complete tasks successfully, despite the presence of brain damage (Stern, 2002). Having a higher cognitive reserve, which may be measured through formal years of education, occupation, literacy or intelligence, would therefore allow for greater levels of brain damage to be sustained before the appearance of significant functional decline (Stern, 2002; 2009). In accordance with the reserve model, many studies have demonstrated that high education levels, as a proxy for cognitive reserve, are associated with a reduced incidence and prevalence of dementia, including both AD and vascular dementia (Meng & D'Arcy, 2012). Such findings demonstrate that interventions relating to education in early life, but also increased occupational complexity, a healthy social-life and more complex leisure activities may provide an avenue for preventative measures and health policies aimed at reducing dementia incidence (Meng & D'Arcy, 2012).

1.2.2. Genetic Factors

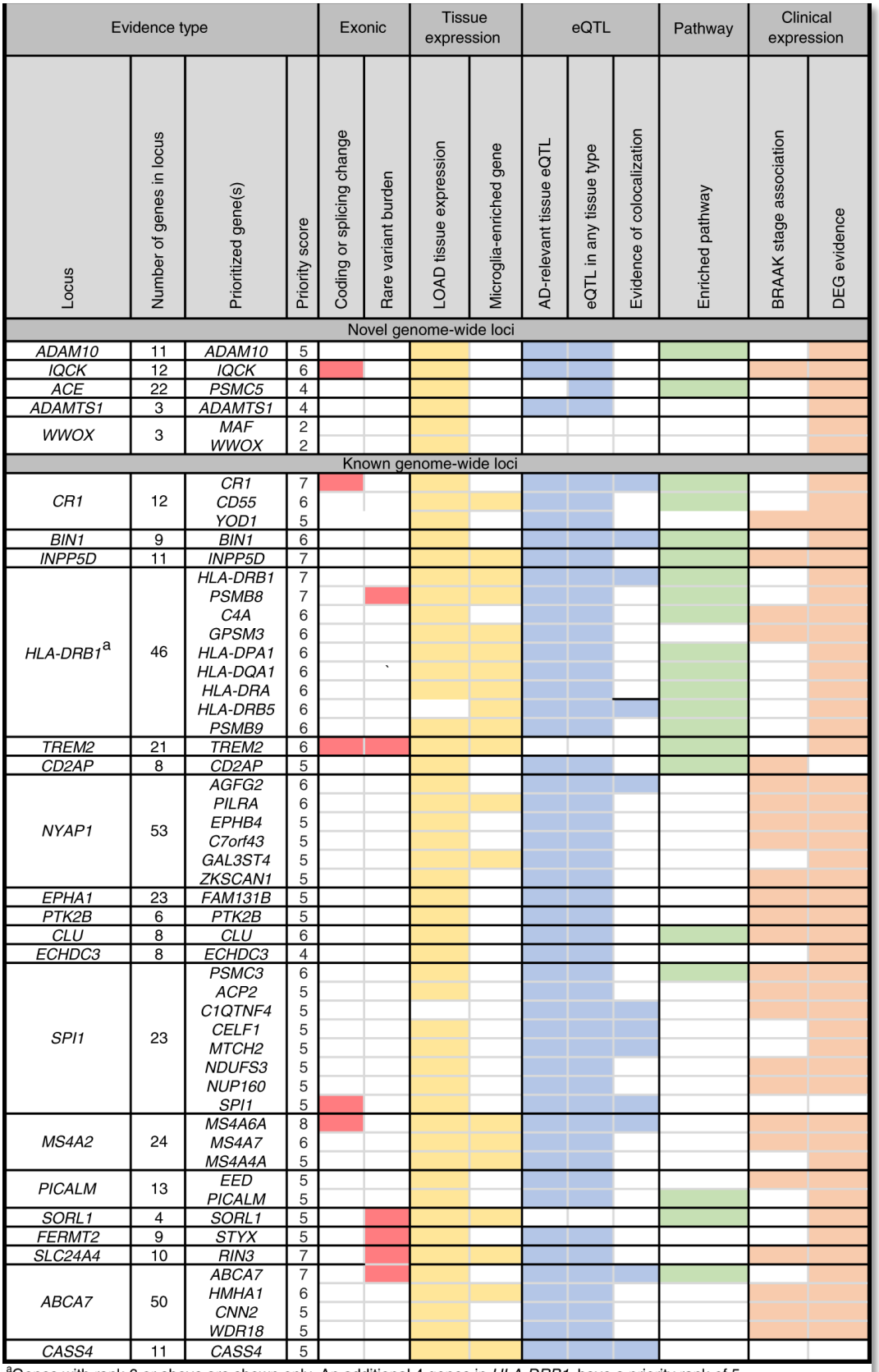
Despite the fact that the majority of AD cases are thought to occur sporadically within the population, as a multifactorial disease, with only a small percentage of early-onset (i.e. patients under the age of 65) forms being attributable to autosomal dominant genetic mutations (Bettens, Sleegers & Van Broeckhoven, 2013), the high hereditability of late-onset

AD (Gatz *et al*., 2006) has led to a large body of work to identify the genes associated with the development of the disease in later life.

Although representing a small portion of AD cases, the causes of early-onset forms of familial AD have been well characterised as being a result of mutations in one of three genes encoding either the amyloid precursor protein (APP) or the γ-secretase proteins presenilin 1 (PSEN1) or presenilin 2 (PSEN2) (Bettens, Sleegers & Van Broeckhoven, 2013). Each of these genes expresses a high penetrance and all are directly related to the synthesis of amyloid in the brain, a pathway that has high pathological significance in AD that will be explored further in later sections. In particular, mutations in PSEN1/2, account for the majority of cases of autosomal dominant forms of early onset familial AD (Bekris *et al*., 2010). However, AD pathology and dementia have also been found to be present in almost all individuals with Down syndrome over the age of 40 (Mann, 1988); a fact that has been explained as being a result of the triplication of the APP gene located on chromosome 21, suggesting that simply having extra copies of this gene, even in the absence of missense mutations, is sufficient to induce neurotoxic production of Aβ (Lott & Head, 2019).

Among late-onset sporadic disease, the greatest known genetic risk factor relates to the polymorphic alleles of the ApoE gene, with the frequency of the ApoE-ε4 allele being significantly higher among AD patients than in healthy individuals, at around 40% (Farrer *et al*., 1997; Liu *et al*., 2013). For carriers of a single ε4 allele, the lifetime risk of developing AD has been estimated as ~25% by age 85 and >50% by age 85 for carriers of a double ε4 allele (Genin *et al*., 2011). In contrast however, the ε2 allele appears to represent a protective factor in the development of AD, with carriers of ApoE ε2/ε2 or ε2/ε3 demonstrating not only a lower risk than those who carry a copy of the ε4 allele, but also than carriers of ε3/ε3 (Farrer *et al*., 1997). The presence of ApoE-ε4 has been linked to accelerated deposition of AD pathological materials in early life (Bussy *et al*., 2019), accelerated cognitive declines in preclinical cohorts (Caselli *et al*., 2004; Albert *et al*., 2014) and a moderately increased risk of progression to AD type dementia among patients considered as having a mild cognitive impairment (Elias-Sonnenschein *et al*., 2011). However, variations in the ApoE allele are far from representative of a causal factor in the development of late-life AD and dementia and, therefore, although a significant risk factor, remain just one aspect of a multitude of factors impacting the onset and progression of disease. Large scale meta-analyses have recently identified an array of genetic loci that may be associated with sporadic AD in addition to ApoE, meaning genetic factors are now thought to account for around 53% of the phenotypic variance (Lambert *et al*., 2013; Ridge *et al*., 2016; Kunkle *et al*., 2019). The currently known

AD associated genes, however, still only account for around 31% of the genetic variance in late-onset AD, leaving a majority of the risk associated with genetic factors uncharacterised (Ridge *et al*., 2016). A list of the genetic loci identified by the most recent meta-analysis (Kunkle *et al*., 2019) can be found in ***Fig 1.1***.



Evidence type				Exonic		Tissue expression		eQTL			Pathway	Clinical expression	
Locus	Number of genes in locus	Prioritized gene(s)	Priority score	Coding or splicing change	Rare variant burden	LOAD tissue expression	Microglia-enriched gene	AD-relevant tissue eQTL	eQTL in any tissue type	Evidence of colocalization	Enriched pathway	BRAAK stage association	DEG evidence
Novel genome-wide loci													
ADAM10	11	*ADAM10*	5										
IQCK	12	*IQCK*	6										
ACE	22	*PSMC5*	4										
ADAMTS1	3	*ADAMTS1*	4										
WWOX	3	*MAF*	2										
		WWOX	2										
Known genome-wide loci													
CR1	12	*CR1*	7										
		CD55	6										
		YOD1	5										
BIN1	9	*BIN1*	6										
INPP5D	11	*INPP5D*	7										
HLA-DRB1[a]	46	*HLA-DRB1*	7										
		PSMB8	7										
		C4A	6										
		GPSM3	6										
		HLA-DPA1	6										
		HLA-DQA1	6										
		HLA-DRA	6										
		HLA-DRB5	6										
		PSMB9	6										
TREM2	21	*TREM2*	6										
CD2AP	8	*CD2AP*	5										
NYAP1	53	*AGFG2*	6										
		PILRA	6										
		EPHB4	5										
		C7orf43	5										
		GAL3ST4	5										
		ZKSCAN1	5										
EPHA1	23	*FAM131B*	5										
PTK2B	6	*PTK2B*	5										
CLU	8	*CLU*	6										
ECHDC3	8	*ECHDC3*	4										
SPI1	23	*PSMC3*	6										
		ACP2	5										
		C1QTNF4	5										
		CELF1	5										
		MTCH2	5										
		NDUFS3	5										
		NUP160	5										
		SPI1	5										
MS4A2	24	*MS4A6A*	8										
		MS4A7	6										
		MS4A4A	5										
PICALM	13	*EED*	5										
		PICALM	5										
SORL1	4	*SORL1*	5										
FERMT2	9	*STYX*	5										
SLC24A4	10	*RIN3*	7										
ABCA7	50	*ABCA7*	7										
		HMHA1	6										
		CNN2	5										
		WDR18	5										
CASS4	11	*CASS4*	5										

[a]Genes with rank 6 or above are shown only. An additional 4 genes in *HLA-DRB1* have a priority rank of 5.

Figure 1.1. *Taken from Kunkle et al., (2019). Table showing all known genetic loci associated with an increased risk of developing late-life AD as identified by recent meta-analysis. A full description can be found in Kunkle et al., 2019. Permission to reproduce this figure can be found in Appendix A.*

1.3. Neuropathology of AD

1.3.1. Pathological Protein Accumulation

Histopathology associated with AD development has been well established in the field and is distinguished primarily by the accumulation of two distinct intra and extracellular proteinopathies (Arnold *et al*., 1991; Braak & Braak, 1991; Hardy & Higgins, 1992; Perl, 2010). Extracellularly, there occurs a build-up of senile plaques comprised of the aggregated peptide of APP; Aβ. Otherwise known as amyloid plaques, this particular proteinopathy occurs very early in the disease process, likely predating the presence of other, intracellular pathologies (Hardy & Selkoe, 2002; Jack *et al*., 2013). For this reason, for almost 30 years, the amyloid hypothesis of AD has maintained that the cortical deposition of Aβ is the primary event in AD pathogenesis leading to the development of dementia (Selkoe & Hardy, 2016). Despite much research supporting this theory (Selkoe & Hardy, 2016) and the demonstration of distinct phases of Aβ deposition by Thal *et al*. (2002), accumulation of Aβ within the cortex is not generally considered appropriate or useful in terms of staging the pathological cascade of AD. According to the seminal histopathological paper by Braak and Braak (1991), the reasons for this lie in the fact that the size, shape and distribution of amyloid plaques rarely manifest in a consistent manner between individuals, limiting the potential application of Aβ deposition for pathological staging.

The second pathological material, more appropriate for disease staging, involves hyperphosphorylation of tau protein: the major microtubule associated protein in adult neurons (Grundke-Iqbal *et al*., 1986). Abnormal phosphorylation of this protein in AD leads to the intracellular accumulation of three distinct types of neurofibrillary changes outlined by Braak and Braak (1991): neurofibrillary tangles (NFTs), neuropil threads (NTs) and neuritic plaques (NPs). As with amyloid plaques, high inter-individual variation exists in the density, distribution and presentation of NPs. Furthermore, the presence of such plaques appears to occur only after the initial appearance of NFTs and NTs making this neurofibrillary change again limited in its application to disease staging. NFTs and NTs however, both demonstrate restricted variability across individuals, with a distribution pattern that is highly common and characteristic of disease. Given the relative consistency of this pattern of distribution, Braak and Braak (1991) were able to demonstrate how the deposition of these particular neurofibrillary changes may be used to track the progression of the AD neuropathological cascade and differentiate this progression into six distinct stages, which have since been

confirmed by more recent biomarker imaging (Schöll *et al*., 2016). According to this model, the first two stages of tau deposition involve the initial distribution of neurofibrillary changes within transentorhinal regions of the anterior medial temporal lobes (aMTLs) lying rostral to the hippocampus. These areas, comprising the perirhinal (PRC), transentorhinal and entorhinal (ERC) cortices are affected in these initial stages by neurofibrillary pathology with very little involvement of hippocampal regions. As pathology spreads, the next two stages, III and IV, known as the limbic stages, describe the moment in which pathology intensifies within hippocampal regions, with densities increasing in the transentorhinal cortices and progressing from CA1 areas throughout the hippocampus proper. At this stage, there still remains a lack of involvement of isocortical areas. The final stages, V and VI, are further characterised by severe changes within hippocampal regions as well as extended involvement of surrounding medial temporal lobes (MTLs) and most importantly, progression of pathology within subcortical as well as isocortical regions. These stages are, therefore, known as the 'isocortical' stages. More recent histopathological research by Braak and collegues has since indicated that the first stages of pathological tau deposition may occur sub-cortically, even before the involvement of the aMTLs, in areas such as the locus coeruleus (Braak *et al*., 2011; Braak & Del Tredici, 2011; Braak & Del Tredici, 2015).

Of the proteinopathies known to be present in AD, NFTs have been found to correlate the most strongly with neuronal loss and subsequent cortical atrophy, the primary pathological correlate of cognitive decline (Jack *et al*., 2002; Giannakapoulos *et al*., 2003; Whitwell *et al*., 2008; Serrano-Pozo *et al*., 2011). Although the role of NFTs in cell death remains relatively poorly understood, with conflicting evidence existing in support of as well as refuting a causal role of NFTs in neuronal loss (Serrano-Pozo *et al*., 2011), the distribution and quantity of NFTs within the cortex has been found to be significantly correlated with cognitive function and dementia duration in AD patients (Nelson *et al*., 2012; Bejanin *et al*., 2017). It is, therefore, theoretically possible to assume a somewhat predictable relationship exists between this measure of neuropathology and the progressive cognitive decline present in symptomatic AD. Importantly however, considerable evidence from *in vivo* studies has now been successful in demonstrating the presence of a lengthy preclinical disease phase during which underlying pathology is detectable despite the absence of observable cognitive decline (Jack *et al*., 2010; Braak & Del Tredici, 2015). Newly developed imaging techniques such as amyloid positron emission tomography (PET) and structural magnetic resonance imaging (MRI) along with cerebrospinal fluid (CSF) markers of Aβ and tau led to the development of a model by Jack *et al*., (2010) that suggests that proteinopathies may be

present even decades prior to subsequent cognitive decline and clinical diagnosis. It is this preclinical stage of AD that is arguably the most significant to research (Sperling *et al*., 2011). Development of a marker sensitive to this stage of disease will be imperative to successful application of disease modifying agents in the future.

1.3.1.1. Amyloid Hypothesis

What is often thought of as a leading model of AD pathogenesis began in 1984 when Glenner and Wong first introduced the concept that the accumulation of Aβ may represent a causal factor in the subsequent cascade of pathological events associated with AD (Glenner & Wong, 1984). Since then, the amyloid hypothesis has been the subject of much debate within the field owing to a number of controversies including but not limited to, the examples of amyloidosis in healthy individuals, weak associations between the presence of amyloid and clinical symptoms and the failure of a multitude of experimental drug trials (Chételat *et al*., 2013; Morris, Clark & Vissel, 2014; Panza *et al*., 2019).

In brief, the amyloid cascade hypothesis, as it is otherwise known, describes the theory that significant aggregation of the Aβ protein within the brain leads to the ensuing deposition of neurofibrillary tangles, cell loss and degradation of the brain parenchyma, vascular damage and ultimate devastation of cognitive function resulting in dementia (Hardy & Higgins, 1992) (See ***Fig. 1.2***). Accumulation of Aβ is thought to occur primarily as a result of inaccurate cleavage of the APP protein. Despite the precise biological function of APP being poorly understood, this transmembrane protein has been implicated in adult synaptic function, neuronal plasticity and neuroprotection (Müller, Deller & Korte, 2017). The non-amyloidogenic cycle of APP sees the end of its biological function within the cell marked by the cleavage of the protein by a γ- and a β-secretase. The amyloid cascade hypothesis is largely based on the compelling observations that familial forms of AD are associated with autosomal-dominant mutations in genes that encode either APP directly or the γ-secretase proteins, PSEN1 and PSEN2, responsible for APP cleavage. Since the inception of the hypothesis in the 1990s, a wealth of work in familial AD has demonstrated increases in extracellular concentrations of Aβ associated with genetic mutations in APP and PSEN1/2 (Selkoe & Hardy, 2016). In particular, mutations in PSEN1/2, accounting for the majority of cases of autosomal dominant forms of early onset familial AD (Bekris *et al*., 2010), have been found to contribute to excess extracellular Aβ through altered APP cleavage leading to an increased ratio of longer, more self-aggregating Aβ peptides such as the 42-amino acid

isoform Aβ42, relative to shorter peptides such as Aβ40 (Chavez-Gutierrez *et al*., 2012; Okochi *et al*., 2013; Fernandez *et al*., 2014).

Despite the compelling evidence from genetic studies such as these, as mentioned previously, early-onset familial AD only accounts for a small percentage of AD cases, with the rest being classed as sporadic or late-onset (Bettens, Sleegers & Van Broeckhoven., 2013). Furthermore, within familial cases themselves, only around 13% can be explained by mutations in the APP or PSEN1/2 genes (Campion *et al*., 1999). While a small percentage of familial AD may, therefore, be explained in terms of these mutations resulting in increased relative production of Aβ42, sporadic disease relies on the notion that a failure to clear excess Aβ successfully leads to gradually rising levels of Aβ42 aggregation that triggers the pathogenic cascade of AD, leading to dementia later in life (Mawuenyega *et al*., 2010; Selkoe & Hardy, 2016). Twin studies have however, demonstrated extremely high heritability of even the sporadic form of the disease, reaching as high as 79% (Gatz *et al*., 2006), suggesting a strong genetic component and both the increased production and reduced clearance of Aβ in AD (Mawuenyega *et al*., 2010) has since been linked to the inherited form of the ApoE allele, ApoE-ε4 (Zhao *et al*., 2018). The significant links between ApoE and Aβ production, in particular the evidence surrounding the role of ApoE and its receptors in the efficient clearance of Aβ (Zhao *et al*., 2018), therefore, provides compelling evidence that modulation of the relative levels of Aβ peptides within the brain is likely a significant, if not causal factor in the development of AD among those with a genetic predisposition, suggesting that the amyloid hypothesis may explain not only familial cases of AD, but also a large proportion of those considered to be sporadic.

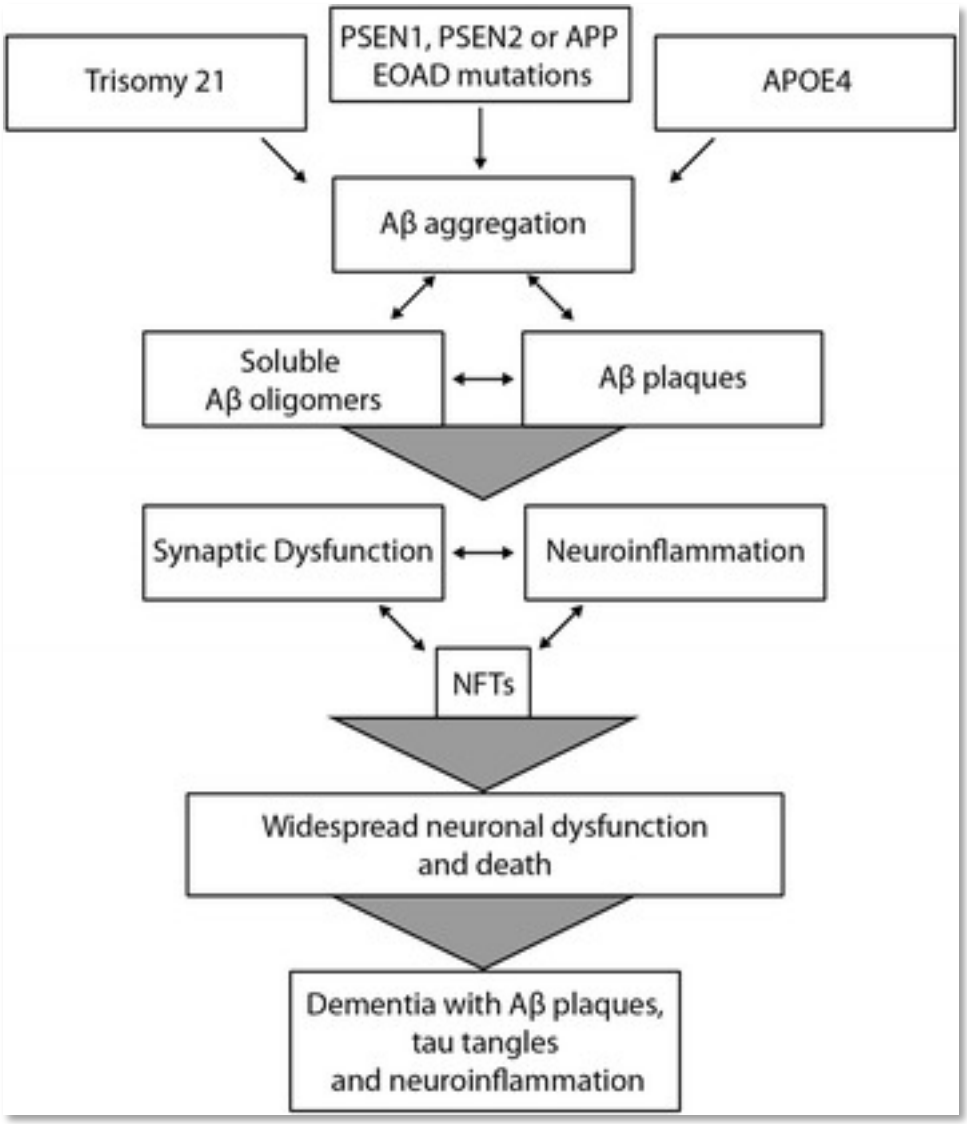


Figure 1.2. *Taken from Morris, Clark & Vissel (2014) Figure showing an outline of the pathways underlying the amyloid hypothesis. Permissions to reuse this figure can be found in Appendix B.*

Of great importance to the amyloid hypothesis has been the debate as to the toxicity of Aβ and whether the extracellular plaques or the soluble Aβ oligomers are the primary neurotoxic entity contributing to AD pathogenesis. In Selkoe's 2011 article it is argued that both have a role to play in neuronal and synaptic loss, although in highly distinctive ways and at differing stages of the process, with plaques themselves exerting somewhat indirect effects on the surrounding neuronal processes, potentially through acting as a reservoir for more neuro- and synaptotoxic oligomers (Koffie *et al*., 2009; Mucke & Selkoe, 2012). For a considerable time, senile plaques were thought to constitute one of the main aberrant features of Aβ accumulation, owing to the results of mouse model investigations that found that such plaques are associated with dendritic changes, synaptic loss and neuritic dystrophy in areas of cortex in their immediate vicinity (Tsai *et al*., 2004; Dong *et al*., 2007; Spires-Jones *et al*.,

2007). More recently however, the hypothesis that neuronal changes and synapse loss in areas surrounding fibrillar plaques may be due to the presence of soluble Aβ oligomers within and surrounding the plaques themselves (Koffie *et al*., 2009) has been supported by the considerable evidence that Aβ oligomers are sufficient to induce synaptic loss and disrupt synaptic plasticity in the absence of senile plaques (Shankar *et al*., 2008; Li & Selkoe, 2020). The selective targeting of Aβ oligomers to hippocampal neurons and the subsequent prevention of long-term potentiation, a well-established physiological substrate of learning and memory (Lynch, 2004), within these neurons is thought to explain the significant decline of memory function early in the course of AD (Lacor *et al*., 2004). Such evidence suggests that cognitive changes associated with AD are far more strongly correlated with the presence of this form of Aβ than fibrillar amyloid plaques (Lue *et al*., 1999; McLean *et al*., 1999). Moreover, the concentration of Aβ oligomers within halo-like formations surrounding plaques (Koffie *et al*., 2009) has been found to distinguish the brains of individuals with dementia from those without, going some way to explain the criticism that, when examined at autopsy, many so-called healthy individuals present with a high burden of senile plaques, without any evidence of cognitive decline in life (Esparza *et al*., 2013). Such a finding could indicate a protective effect of the plaques in the initial stages of the disease in which plaques prevent excessive diffusion of the more neurotoxic soluble oligomers throughout the extracellular space through their role as a binding site.

Although the exact mechanism of how oligomeric forms of Aβ disrupt synaptic function and therefore contribute to cognitive decline is still yet to be confirmed, alterations in synaptic plasticity by this form of Aβ likely represent an early event in the pathogenesis of AD, particularly given the accumulation of Aβ in the preclinical stages of disease (Hardy & Selkoe, 2002; Jack *et al*., 2010), and support the hypothesis that Aβ constitutes a primary pathological material responsible for the disruption of brain function in AD.

Although the amyloid hypothesis has many strong theoretical underpinnings, perhaps the main criticism of the approach to treat amyloid as a therapeutic target is the systematic failure of a multitude of anti-amyloid clinical trials (Cummings, 2018; Lahiri *et al*., 2019). Several approaches including immunotherapies and inhibitors of both β-secretase and γ-secretase have been adopted by drug trials attempting to develop a treatment for AD. To date however, despite having some success in the blocking of Aβ production or the removal of plaques and even soluble Aβ, no trials have definitively shown significant slowing or cessation of cognitive decline in patients. Some inhibitors of APP γ-secretase and the β-site-APP-cleaving enzyme 1 (BACE1), an aspartyl protease that, in conjunction with γ-secretase,

cleaves APP, forming the residual isoforms Aβ40 and Aβ42, intended to impede the production of nascent Aβ, have even been found to exacerbate cognitive decline among some individuals (Panza *et al*, 2019).

While previous trials may have failed due to the flaws in the safety of the drugs themselves, such as semagacestat, a γ-secretase inhibitor for which phase III trials were halted due to increases in the incidence of skin cancer among participants (Doody *et al*., 2013), one of the most recent disappointments in the field of Aβ targeting chemotherapies was the failure of a phase III trial testing the efficacy of the monoclonal antibody aducanumab that selectively binds to both soluble Aβ and Aβ fibrils (Selkoe, 2019). Despite having shown significant promise in an early phase trial in which administration of aducanumab was found to produce unequivocal decreases in amyloid plaques within all the examined brain regions, to the extent that almost half of the patients receiving the highest dose demonstrated negative amyloid PET scans after 12 months (Sevigny *et al*., 2016), the clinical findings regarding cognitive change were far less robust. Of the four clinical scales measuring cognitive decline only two, the Mini Mental State Examination (MMSE) and the Clinical Dementia Rating Scale (CDR) indicated a slowing of decline relative to the placebo group at follow-up after a year. Furthermore, of the 16 observations (4 cognitive scales across 4 dose groups), only 3 were statistically significant, with 2 of these being in the highest dose group and significance levels not being corrected for multiple comparisons. Regardless, this early trial solidified the use of aducanumab as an effective treatment for the removal of cortical amyloid and two phase III trials were planned to assess the clinical efficacy of the drug with the primary outcome measure being a significant slowing of cognitive decline as measured by the CDR. In March of 2019 however, the pharmaceutical company Biogen announced the cessation of both trials (ENGAGE and EMERGE) after they were each deemed futile due to a failure to reach 20% conditional power (i.e. a 20% probability that either would show statistically significant differences in CDR measured cognitive decline by the end of the trial, given the results found at the time of the futility analysis) (Schneider, 2020). Following this announcement however, in October 2019 Biogen retracted its previous statement, now claiming that the futility analyses were misleading and presenting a plan to seek regulatory approval for aducanumab from the U.S. Food and Drug Administration (FDA). In light of new findings that took into account additional participants in each trial who had now completed the treatment, Biogen announced that the EMERGE trial had in fact demonstrated a 23% ($p<0.031$) improvement relative to the placebo group on the primary outcome of the CDR (Schneider, 2020). The use of this finding as an argument for approval

of the drug by the FDA has received a reasonable amount of criticism however, with questions being raised as to the validity of the results presented. As Schneider outlines in a 2020 article published in *The Lancet Neurology*, a number of issues exist when taking these results as statistically and, in particular, clinically significant, including the potential statistical exaggeration of treatment effects owing to multiple *post-hoc* analyses on a subset of participants that was 40% smaller than the originally planned sample size. Furthermore, the effect is small. What is described by Biogen as a 23% relative difference to the placebo group amounted to an absolute difference of around 0.4 CDR points according to Schneider, which puts into question the true clinical relevance of the findings. What Schneider outlines in his article on the trials is that with the current evidence it is unclear whether the findings presented by Biogen are strong enough to eliminate the possibilities that the same findings could not be attributable to a worsening on the CDR among the placebo group, or even that had the so-called 'successful' EMERGE trial continued to its intended completion, these results would not have potentially regressed to the mean, given that the fluctuation of interim results during drug trials are a common occurrence, which may be at odds with the true effect. Further issues in the aducanumab trials was the finding that more than 33% of the participants presented with amyloid-related imaging abnormalities (effusion type, ARIA-E) including cerebral oedema, most notably in patients who were carriers of ApoE-ε4 (Schneider, 2020; Aisen *et al*., 2020). Although some research now suggests that such ARIA-E relating to amyloid antibody therapies may be relatively safe and easy to manage, it remains to be a significant concern in the pursuit of antibody treatments given the considerable uncertainty that continues to surround the mechanisms and the individual patient susceptibility (Aisen *et al*., 2020).

The initial halt of the aducanumab trials has not reduced the enthusiasm for the amyloid hypothesis however, with many researchers retaining a high degree of faith in the anti-amyloid approach to disease modifying therapies, in particular in the utilisation of monoclonal antibodies, in light of the positive results of the EMERGE trial (Aisen *et al*., 2020). These moderate and controversial results among many more failed and discontinued trials owing to adverse effects, however, have left other researchers stressing the need to focus elsewhere, if not dismissing the amyloid-dominant approach altogether, emphasising a need to enhance the approach by similarly addressing further adverse disease related events such as tauopathy and neuroinflammation (Panza *et al*., 2019; Gauthier *et al*., 2020). This viewpoint is principally fuelled by the ongoing explanation that the failure of anti-amyloid trials can largely be attributed to the administration of drugs at a late stage of disease in

which these further adverse events have already been triggered, making the removal of Aβ no longer sufficient to curtail neurodegeneration (Selkoe, 2019). Recent approaches have therefore included the possibility of addressing so-called 'downstream' pathologies as a means to prevent further neuronal damage including anti-tau and anti-neuroinflammatory therapies (Gauthier *et al*., 2020).

Whether deposition of Aβ is the primary event in the neurodegenerative cascade responsible for AD may not yet be definitively proven and there are still many mechanistic gaps in the theoretical outline of the hypothesis, not least the lack of understanding surrounding the normal physiological functions of APP and its Aβ peptides (Coronel *et al*., 2018). However, the wealth of genetic and biochemical evidence that has been collated over the last 30 years suggests that Aβ likely does play both a very significant and very early role in the emergence of AD pathology. What has been made evident over the past 15+ years however, with each failing drug trial, is that amyloid clearance may not, at least when administered in isolation, be the ground-breaking treatment that will modify the effects of disease to a clinically relevant level.

1.3.1.2. Tauopathy

Aside from the accumulation of Aβ, the second proteinopathy associated with AD is the hyperphosphorylation of the tau protein (Grunde-Iqbal *et al*., 1986). As described previously, this particular proteinopathy is associated with the development of three distinct lesions: NFTs, NPs, and NTs. As the major microtubule associated protein (MAP) of mature neurons (Iqbal *et al*., 2010), tau is primarily responsible for the formation of microtubules and the stabilisation of their structure through its interaction with tubulin (Weingarten *et al*., 1975). The toxic properties of tau deposition in AD have, therefore, been demonstrated as a failure of this abnormally hyperphosphorylated tau to bind to tubulin and promote the assembly of microtubules (Lindwall & Cole, 1984). According to a 2010 paper by Iqbal and colleagues, as much as 40% of abnormally phosphorylated tau in the brains of AD patients is found within the cytosol of the cell, having not aggregated into tangles. This cytosolic tau may actively inhibit microtubule assembly and disrupt their structural formation. Additionally, the abnormal tau has been found to sequester both normal tau as well as the two other MAPs, MAP1 A/B and MAP 2 (Alonso, Grundke-Iqbal & Iqbal, 1996; Alonso *et al*., 1997), resulting in the further destruction and breakdown of microtubule formation. Both aggregation of the abnormal tau protein into NTs, NFTs and later NPs as well as the

sequestration of normally phosphorylated tau and other MAPs are, therefore, characteristic of the tauopathy associated with AD. As a major structural component of the neuron, the disruption of microtubule assembly by hyperphosphorylated tau is thought to be a primary event in AD leading to neuronal structural collapse and subsequent death. Evidence to support this theory is largely related to the findings that this type of proteinopathy is most closely related to the neuronal loss and structural atrophy seen in AD brains (Jack *et al*., 2002; Giannakapoulos *et al*., 2003; Whitwell *et al*., 2008; Serrano-Pozo *et al*., 2011). For this reason, deposition of tau has received considerable attention as potentially reflecting the primary pathological process associated with cognitive decline in these patients (Nelson *et al*., 2012; Bejanin *et al*., 2017).

Just as the deposition of Aβ is thought to begin as early as decades prior to a diagnosis of dementia (Jack *et al*., 2009; Jack *et al*., 2010), the deposition of abnormal tau has also been detected in the brains of healthy individuals several decades before the expected development of cognitive symptoms (Braak *et al*., 2011; Braak & Del Tredici, 2011; Braak & Del Tredici, 2014; Braak & Del Tredici, 2015). Given the extent of the literature into the mechanisms of tau pathology in AD and the consistent disappointment of anti-amyloid trials, recent work into disease modifying therapies has seen an increase in focus towards tau-targeting treatments (Congdon & Sigurdsson, 2018). As tau is both known to be directly toxic to neurons as well as able to mediate the effects of Aβ (Ittner & Götz, 2011), the reduction or removal of tau from the brains of AD patients makes for a compelling therapeutic approach. Many approaches to anti-tau therapies have been trialled, including aggregation inhibitors, microtubule stabilizers and immunotherapies, with some initial success in studies using animal models often failing to translate to human participants (Congdon & Sigurdsson, 2018). For example, the tau aggregation inhibitor methylene blue appeared to be a promising agent for clinical trials when studies using transgenic mouse models found it to be successful in both reducing the levels of pathological tau aggregates and promoting some improvements in cognitive function (Panza *et al*., 2016). Since then, however, despite some initially promising results from a phase II trial (Wischik *et al*., 2015), as with the aducanumab anti-amyloid trials, subsequent phase III trials with methylene blue have failed to demonstrate any significant clinical benefits in slowing the progression of disease, with any claims by the authors to the contrary being challenged due to potential methodological issues (Gauthier *et al*., 2016; Congdon & Sigurdsson, 2018). Recent experimental work that has sought to explain the failure of these trials has suggested that, despite the ability of methylene blue to inhibit the formation of NFTs, the lack of effect this agent has on the formation of granular

tau oligomers is likely responsible for its lack of efficacy in modifying disease (Soeda *et al*., 2019). Far from being novel, the suggestion that NFTs may not actually be the primary tau pathology responsible for cell death in AD has been around for many years, with several studies indicating that soluble forms of hyperphosphorylated tau within the cytosol, which appear upstream of NFT aggregations, may be the primary cause of microtubule degradation and consequent neurodegeneration (Iqbal *et al*., 1994; Wittmann *et al*., 2001; Santacruz *et al*., 2005; Alonso *et al*., 2006; Li *et al*., 2007; Kimura *et al*., 2007; Iqbal, Alonso & Grundke-Iqbal, 2008; Iqbal *et al*., 2010). Aggregation inhibitors that are primarily effective in the clearance of NFTs, therefore, may be inadequate for slowing the damage caused by the presence of hyperphosphorylated tau prior to and in tandem with NFT formation.

An alternative approach that has become perhaps the most widely researched tau treatment target in recent years is tau immunotherapy (Congdon & Sigurdsson, 2018). Just as immunotherapy to clear pathological amyloid has shown some promise despite the failure of the aducanumab trials (Aisen *et al*., 2020), tau immunotherapy studies have shown some promise in cell and mouse models, as outlined by Congdon and Sigurdsson in their 2018 review. The failure of anti-amyloid treatments has often been attributed to the inefficacy of such agents in the symptomatic phase of disease, owing to the ongoing effects of tau deposition and neuroinflammation (Selkoe, 2019). In particular, tau deposition is known to tightly correlate with cognitive performance (Nelson *et al*., 2012; Bejanin *et al*., 2017) and so it is logical to assume the possibility that anti-tau immunotherapies may stand a better chance at improving cognition or slowing the course of decline. Many of these trials are still ongoing (Ceyzériat *et al*., 2020) and, therefore, limited results are currently available. However, early findings from the Phase II ADAMANT trial testing the safety of the vaccine AADvac1, which reached its conclusion in September 2019, demonstrated that around 98% of patients generated antibodies against tau in response to the treatment, with no apparent adverse effects. Furthermore, although not the primary outcome measure, a trend was observed that suggested a reduction of AD biomarkers and there was even some indication of an effect of treatment on cognition (Axon Neuroscience SE, 2019). Given these encouraging results, along with the evidence from animal models demonstrating the reduction of a number of tau pathologies, as well as improvement in the behavioural phenotype (Novak *et al*., 2019), the biotech company Axon who were behind the initial trials, will likely seek a larger Phase III trial of AADvac1 in the near future. To date, however, no Phase III trial has been conducted testing the efficacy of tau immunotherapies in the modification of AD neurodegeneration and so it is unclear whether the initial findings of the ADAMANT trial will lead to any further

success in later testing or whether the anti-climax of the aducanumab and methylene blue trials will once again be felt in the field of AD therapeutic development. The current sentiment in the literature therefore, as expressed by a number of authors (Congdon & Sigurdsson, 2018; Ceyzériat *et al*., 2020; Schneider, 2020), is that the answer to successful implementation of disease modifying therapies in AD is likely to involve a combined approach combatting the accumulation and propagation of both tau and Aβ pathologies.

1.3.2. Vascular Changes, Neuroinflammation and Senescence

Further to the hallmark proteinopathies, AD is also characterised by a range of additional pathological changes involving neuroinflammation and vascular pathologies, as well as age related mechanisms, that have given rise to alternative theories of AD pathogenesis. As outlined in previous sections, two large risk factors associated with AD development include both ageing itself as well as the presence of vascular disease. Vascular abnormalities associated with AD include a range of macro and microscopic changes from decreases in regional blood flow, white matter lesions, macro and micro infarcts as well as disruptions of the blood brain barrier and cerebral amyloid angiopathy (Kapasi & Schneider, 2016). Given the extent of the vascular injury present within AD patients, the "vascular hypothesis of AD" has been proposed by some authors who claim that pathological vascular changes may occur prior to, and subsequently promote, later neurodegenerative progression in a two hit process in which ageing and vascular risk factors first contribute to dysfunction of the cerebral vasculature before leading to the accumulation of Aβ within the brain parenchyma and the surrounding blood vessels (Sagare *et al*., 2012; Kelleher & Soiza, 2013; Janota, Lemere & Brito, 2016). Overlapping with the amyloid hypothesis, studies that support the vascular hypothesis of AD have demonstrated evidence that cerebrovascular dysfunction may be associated with impaired clearance of Aβ, an increased influx of peripheral Aβ through a compromised blood brain barrier and even overexpression of APP (Janota, Lemere & Brito, 2016). Despite going a step further to explain the initial deposition of pathological Aβ accumulation as resulting from a primary vascular aetiology, the vascular hypothesis of AD, therefore, fundamentally supports the notion that elevated levels of Aβ within the brain are the dominant cause of subsequent neurodegenerative processes and cognitive decline.

Rather than providing an explanation for the emergence of pathological materials associated with neurodegeneration, the neuroinflammatory response in AD is of particular

interest to researchers as a well-defined mechanism, central to the pathogenesis of the disease, which may exacerbate its progression and, therefore, represent a potential target for therapeutics (Akiyama *et al*., 2000; Morales *et al*., 2014; Kinney *et al*., 2018). Non-specific to AD, a chronic neural inflammatory response has been identified as a principal feature of a range of neurodegenerative aetiologies (Kinney *et al*., 2018). Despite providing a protective response in the early stages of disease, through the accumulation of phagocytic microglia and subsequent promotion of Aβ clearance, as disease progresses and the immune response is sustained, proinflammatory cytokines and associated neurotoxins, that continue to be released by microglia, serve to downregulate Aβ-binding receptors and Aβ-degrading enzymes resulting in reduced clearance and increased accumulation of this protein within the brain (Hickman, Allison & El Khoury, 2008). As the microglia are continually recruited to address the accumulation of Aβ, the cycle continues, exacerbating both the neuroinflammation itself and the subsequent neurodegeneration (Kinney *et al*., 2018). Further evidence has suggested an interaction of known vascular risk factors, such as obesity, and neuroinflammation, with one study revealing that obesity in ageing mice is associated with greater levels of systemic neuroinflammation, exacerbating damage to the blood-brain barrier (Tucsek *et al*., 2014).

In light of limited progress in the development of disease modifying therapies, greater attention has also been placed on the hallmarks of human biological senescence that mediate a range of age-related neurodegenerative conditions (Hou *et al*., 2019). Not only does ageing represent the primary risk factor for the development of AD dementia, but histopathological studies at autopsy have further revealed that the deposition of AD related proteins within the brains of those showing no signs of cognitive decline before death is relatively common among the elderly (Elobeid *et al*., 2016). The complex relationship between pathological deposits and cognitive decline remains unclear, with further population-based studies in the oldest-old (i.e. aged 90 and over) finding that almost half of the individuals in this age group may either fulfil the neuropathological criteria for AD or display a mix of pathologies despite not meeting the criteria for dementia, while a further 12% of those diagnosed with dementia are found to be free of pathological markers (Kawas *et al*., 2015). A possible explanation of these findings is that the presence of pathology in the absence of cognitive decline may represent a preclinical stage of neurodegeneration (Dubois *et al*., 2016). It may also seem a compelling argument, however, to explain AD and other age-related dementias as the result of an accelerated form of the normal ageing process at the extreme end of a continuum of brain health associated with increased age. As outlined in two reviews by Wyss-Coray (2016) and Hou *et al*., (2019) however, such a conclusion fails to acknowledge the evident

disparities between the ageing process and specific diseases in terms of both the brain regions affected by structural change and the cognitive profiles associated with each process. Instead, both highlight the importance of accounting for core senescent changes that show significant interactions with disease processes including DNA damage, mitochondrial dysfunction, cell ageing, inflammation and immune dysregulation. A holistic approach to disease modifying treatment may, therefore, require the inclusion of combined strategies that target some aspects of the ageing process known to play significant roles in disease onset and progression.

1.3.3. Deficits in Neurotransmission

A further significant aspect of AD pathogenesis is synaptic dysfunction and the disruption of neurotransmission. Impairments to neurotransmission have been identified in AD within numerous systems including GABAergic, glutamatergic, cholinergic, serotonergic and dopaminergic circuits, among others (Nava-Mesa *et al*., 2014; Li *et al*., 2016a; Jha *et al*., 2017). Both Aβ and hyperphosphorylated tau protein have been found to be toxic to synaptic transmission and plasticity in AD (Nava-Mesa *et al*., 2014; Guerrero-Muñoz, Gerson, & Castillo-Carranza, 2015; Jha *et al*., 2017). Further mechanisms implicated in synaptic loss and neurotoxicity in AD, as reviewed by Jha *et al*., (2017), include oxidative stress, mitochondrial dysfunction and alterations in redox signalling, as well as the effect of impaired neurotransmitter activity on the activity of synaptic proteins, transcription factors and Ca2+ regulation causing disruption to neuronal homeostasis. Aberrant synaptic transmission within the cholinergic system in particular, and the selective vulnerability of cholinergic neurons to AD pathology, represent one of the only pathological processes for which pharmaceutical amelioration has proved beneficial in symptomatic treatment (Hampel *et al*., 2018; Long & Holtzman, 2019). Alterations to cholinergic transmission in AD are characterised by a reduction in the synaptic release of acetylcholine, reduced choline uptake and the downregulation of cholinergic receptor expression (Schliebs & Arendt, 2011).

Research has further identified an Aβ mediated imbalance in excitatory and inhibitory neurotransmission in AD, resulting from alterations in both glutamatergic and GABAergic functioning (Nava-Mesa *et al*., 2014). In particular, alterations in excitatory transmission by glutamatergic neurons in AD has been related to an effect of Aβ accumulation on N-methyl-d-aspartate (NMDA) and/or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors that has been suggested to result in excitotoxicity and

subsequent cell death (Greenamyre *et al*., 1988; Parameshwaran, Dhanasekaran & Suppiramaniam, 2008). As such, the only pharmaceutical intervention currently available for AD other than cholinesterase inhibitors is memantine, a non-competitive glutamatergic NMDA antagonist (Long & Holtzman, 2019).

More recent investigations have further implicated the dopaminergic system as an early target of AD related neural dysfunction, finding a significant decrease in levels of dopamine among AD patients relative to controls (Pan *et al*., 2019). In particular, areas of the mesocorticolimbic dopaminergic pathway, such as the ventral tegmental area (VTA) of the midbrain, have demonstrated evidence of very early dopaminergic neuronal loss in AD, resulting in decreased dopamine innervation to the hippocampus (Nobili *et al*., 2017; De Marco & Venneri, 2018). Due to its numerous cortical connections particularly with the nucleus accumbens, amygdala, hippocampus, and medial prefrontal cortices (Morales & Margolis, 2017), such impairments in dopaminergic transmission within the VTA have the potential to contribute to a range of behavioural or psychiatric symptoms relating to these areas. However, in AD it is the VTA-hippocampal pathway that appears particularly afflicted (Nobili *et al*., 2017), a finding that is reflected by evidence showing a particular relationship between both VTA volume and VTA-hippocampal connectivity and AD specific cognitive indices such as memory function (De Marco & Venneri, 2018).

Given the role that neurotransmitter modulation has played in the development of symptomatic treatment in AD, it is an unsurprising fact that scientists continue to explore this line of research and the complex interactions between AD pathogenesis and synaptic function, particularly relating to transmission, in an effort to develop further treatments and potential disease modifying therapies (Nava-Mesa *et al*., 2014; Kandimalla & Reddy, 2017; Jha *et al*., 2017).

1.4. Diagnosis

To date, a definitive diagnosis of AD may only be achieved *post-mortem* through confirmation of the presence of characteristic pathological hallmarks within the brain tissue. Currently therefore, patients considered as presenting with the disease may be delineated as ‘possible’ or ‘probable’ AD contingent upon a range of assessments including clinical phenotype, neuroimaging markers and the presence of protein biomarkers on imaging, in the CSF or in the blood (McKhann *et al*., 2011).

1.4.1. Clinical Features

Although diagnostic criteria for AD and prodromal stages of disease in research settings have moved towards the involvement of biomarkers, allowing for the detection of underlying proteinopathies, even in the absence of pronounced cognitive decline (Jack *et al*., 2018), neuropsychological measures still remain the gold standard for clinical AD diagnosis (McKhann *et al*., 2011). Dubois *et al*., (2007) highlight episodic memory decline as the most prominent deficit affecting patients presenting with AD pathology, stating that patients will be considered as probable AD following a gradual and progressive decline in episodic memory function as reported by themselves or trusted informants over a 6-month period. This deficit should be apparent on cognitive testing and be either in isolation or associated with other cognitive changes only apparent at the onset of decline or that have manifested as suspected disease advances. Similarly, McKhann *et al*., (2011) also highlight the importance of an amnestic presentation; however, language, visuospatial and executive presentations on cognitive examination are also considered as evidence for a probable AD diagnosis when an individual meets the wider criteria for dementia and shows an insidious onset and progressive worsening of cognition.

1.4.1.1. Cognitive Assessment

Clinically, a diagnosis of dementia due to AD is usually considered as '*probable'* or '*possible*' AD as per McKhann *et al*.'s 2011 diagnostic criteria. This is due to the fact that biomarker evaluation, in the 2011 guidelines, are considered an additional criterion that may be informative but not crucial to diagnosis in a clinical setting. Therefore, biomarker validation is not a routine part of clinical practice and instead pathological confirmation of AD remains an aspect of examination at autopsy. Instead, patient history and objective cognitive assessment remain the core methods of clinical evaluation.

A diagnosis of probable AD dementia first requires the patient to meet the criteria for the wider syndrome of dementia. This, therefore, requires evidence from a patient's history, a trusted informant or neuropsychological testing that the patient suffers from a cognitive or behavioural impairment in a minimum of two domains ranging from memory, judgement and reasoning, visuospatial abilities, language function or changes in personality, mood or general disposition. These changes must represent a decline from their previous levels of functioning, must significantly interfere with their ability to function during activities of daily

life and cannot be explained by psychiatric disorders or delirious episodes (McKhann *et al*., 2011). A large number of short-form, bedside cognitive screening assessments exist for the purposes of defining dementia and disease severity, the most widely used of which being the MMSE (Folstein, Folstein & McHugh, 1975). This five to 10-minute cognitive screening assessment was originally devised by Folstein, Folstein and McHugh to provide a brief, objective examination tool to differentiate organic disease from functional psychiatric disorders. Although the authors do not propose that the MMSE alone provides a comprehensive diagnostic tool, it has been widely accepted across the world as providing a standardised measure for the severity of disease in a given individual and the progression of cognitive decline across time. The MMSE was even recommended as an aid to clinical examination in the 1984 guidelines for clinical AD diagnosis (McKhann *et al*., 1984). Today, scores on the MMSE may provide some evidence to clinicians when defining prodromal AD, usually marked by conditions such as Mild Cognitive Impairment (MCI), from AD dementia. The cut-off for clinically normal performance on the MMSE is usually considered to be around twenty-four out of a possible 30 (Folstein, Folstein & McHugh, 1975; Creavin *et al*., 2016) with a score below 24 indicating significant cognitive impairment and possible dementia. However, recent research into the diagnostic utility of the MMSE in cognitively impaired populations have since suggested that a cut-off closer to 27/30 may be more informative when detecting those with MCI or cognitive complaints, particularly in those with higher levels of education (O-Bryant *et al*., 2008; Spering *et al*., 2012). Nevertheless, the MMSE has a number of flaws, in particular the significant effect of age and levels of education on scores and so, despite having demonstrated some utility in tracking cognitive decline (Han *et al*., 2000), this brief screening test may be primarily considered an effective tool for the ruling out of dementia in primary care settings, rather than a nuanced diagnostic tool for detecting cognitive change, particularly at the MCI stage (Mitchell, 2009). Other rating scales are more often implemented in research settings when assessing dementia severity. This includes the CDR (Hughes *et al*., 1982; Morris, 1997) and the Global Deterioration Scale (GDS, Reisberg *et al*., 1982). The CDR classifies individuals as normal (CDR 0), questionable dementia (CDR 0.5) or as having dementia ranging from mildly (CDR 1) to severely (CDR 3) affected. Generally, a CDR of 0.5 would be considered a criterion for MCI diagnosis, however, similarly to the GDS, which classifies a rating of 3 as indicating some cognitive decline, there is inevitably some over-lap, with patients classified as CDR 0.5 or GDS 3 likely to fall under either MCI or AD dementia diagnosis depending on core clinical criteria. Petersen was, therefore, careful to highlight the issues with these rating

scales in his 2007 guidelines for MCI diagnosis (Petersen, 2004), stating that such rating scales, while potentially useful in certain settings (such as research) should not be confused with clinical criteria.

Neuropsychological evaluation for the diagnosis of AD extends far beyond simple screening tests such as the MMSE. McKhann *et al*., (2011) recommend extended neuropsychological testing when the patient history or bedside screening examination does not provide a confident diagnosis. As previously mentioned, the absence of biomarker testing in common clinical practise leaves neuropsychological evaluation, along with brain imaging measures, as the most effective clinical tool for differential diagnosis and prognosis in suspected AD patients.

It has been well established that one of the most profound deficits affecting patients with AD, even in the earliest stages of disease, is a significant and progressive decline in episodic memory function relating to selective involvement of limbic structures in the initial stages of pathological progression (Grober & Buschke, 1987; Braak & Braak 1991; Salmon & Bondi, 1991, Welsh *et al*., 1991, Welsh *et al*., 1992; Locascio *et al*., 1995; Jack *et al*. 1997; de Toledo-Morrell *et al*. 2000; Lemos *et al*., 2017). Consistent with the finding that the spread of pathological materials first occurs in medial temporal structures such as the ERC and hippocampus (Braak & Braak, 1991), an abundance of neuropsychological studies have since focussed on the aspects of mnemonic cognition that may be exploited to best distinguish cases of AD, even in the earliest stages, from healthy ageing. Such research has demonstrated that a number of changes including deficits in delayed recall, inability to access '*to-be-remembered'* information, impaired recognition memory, ineffective semantic encoding and an increased susceptibility to intrusion errors can all differentiate AD patients from healthy ageing, even in the milder stages of disease (Salmon & Bondi, 2009). Diagnostic criteria have, therefore, recommended the use of list learning and delayed recall tests, and in particular the Free and Cued Selective Reminding Test, which controls for the effects of attention and other cognitive functions, to identify best the amnestic syndrome typical of AD (Dubois *et al*., 2014; Lemos *et al*., 2017).

Despite previous theories that episodic memory function was the only cognitive domain affected prior to the significant spread of pathological changes in the wider neocortex (Grady *et al*., 1988; Locascio *et al*., 1995; Hodges & Patterson, 1995), it has now been recognised that more subtle changes in semantic memory and concept formation may be among the first recognisable signs of impairment in patients at the preclinical stages of disease (Amieva *et al*., 2008). Declines in non-memory domains such as attention, abstract

reasoning, language and visuospatial abilities have also all been recognised as core features of the dementia syndrome in AD (Salmon & Bondi, 2009). However, changes in these areas are often thought of as secondary to the amnestic presentation of the disease, occurring only once pathological changes have reached a more global level (Grady *et al*., 1988; Locascio *et al*., 1995; Salmon & Bondi, 2009). In a 2002 study by Salmon and colleagues, which analysed the neuropsychological profiles of ninety-eight pathologically confirmed AD cases, authors suggested that, in the earliest stages (i.e., MMSE ≥ 24), AD may be characterised by impairments not only in episodic memory but also semantic knowledge and certain executive functions. Several more recent articles have since confirmed the existence of executive dysfunction in MCI patients (Bäckman *et al*., 2005), especially affecting working memory (Kirova, Bays & Lagalwar, 2015), selective attention (Belleville, Chertkow & Gauthier, 2007) and inhibitory processes (Bélanger, Belleville & Gauthier, 2010). Given the heterogenous nature of the disease, particularly in the early stages, research into non-memory functions that may be affected early in the course of disease, even in the absence of significant memory decline, serves to inform diagnostic protocols, particularly in patients presenting with MCI, and improve differential diagnoses in a patient cohort who may go on to develop a number of differing forms of dementia (Petersen, 2004).

1.4.1.2. Mild Cognitive Impairment

As the focus of research has begun to shift towards the very earliest stages of disease, it has become increasingly apparent that a rather long period of cognitive decline exists, outside the range of normal ageing, prior to the emergence of clinically definable dementia. The need to define this period of recognisable transitioning from healthy to pathological ageing has, therefore, become increasingly significant. The most commonly used term to describe this stage is mild cognitive impairment or MCI (Petersen, Doody & Kurz, 2001).

I. Diagnosis

Patients presenting with MCI are described as presenting with a reasonable level of cognitive decline, outside the range of normal ageing, that has not yet progressed to dementia or caused significant impairment in activities of daily living (Petersen, 2004). In more recent years, MCI has gained considerable attention as its own recognisable pathological condition and diagnostic entity (Petersen, 2004).

II. Subtypes and Prognostic Outcome

A diagnosis of MCI may apply to a highly heterogeneous group of individuals with a varying range of underlying aetiologies and cognitive deficits. Four recognised clinical subtypes, outlined by Petersen (2004), cover the varying presentations that an MCI diagnosis may refer to. The most common presentation of MCI involves a significant memory impairment beyond the typical boundaries for a given individual's age group. This can manifest despite having relatively intact functionality of other cognitive domains, as in single domain amnestic MCI (aMCI) or in conjunction with a number of similar level deficits in other cognitive domains, such as executive functions, language or visuospatial skills, as in multi-domain amnestic MCI (md-MCI + a). Less common variants of MCI include multi domain non-amnestic (md-MCI – a) where, although patients present with impairments on a range of cognitive tests, their memory function appears intact and the least common, single-domain MCI (sd-MCI) in which patients present with a significant cognitive decline in only one area, other than that of memory (Petersen, 2004).

Given the heterogeneous nature of MCI as a diagnosis, not all MCI patients will necessarily go on to develop dementia and many will go on to present with neurodegenerative dementias of aetiologies other than AD (Petersen *et al*., 2001; Petersen, 2004; Busse *et al*., 2006; Petersen & Negash, 2008). However, in AD research, MCI diagnosis has become an important delineation thought to represent a prodromal stage of the disease (Albert *et al*., 2011). In particular, amnestic forms of MCI are most often thought to be the manifestation of the earliest stages of AD, being significantly more likely than those with a non-amnestic profile, who may represent early forms of differing neurodegenerative aetiologies, to go on to progress to dementia of the Alzheimer's type (Busse *et al*., 2006; Petersen *et al*., 2001; Petersen, 2004; Petersen & Negash, 2008). Both aMCI and md-MCI + a are thought to represent the very earliest stages of the disease process (Petersen, 2004), with around 12% of patients presenting with a significant memory impairment progressing to AD dementia per year (Petersen & Morris, 2003). Recommendations from the National Institute on Aging-Alzheimer's Association (Albert *et al*., 2011), therefore, describe MCI due to AD as representing the symptomatic predementia phase of disease and, provided clinical evaluation suggests a neurodegenerative aetiology, patients who present with a significant episodic memory deficit abnormal for their age group may be considered as MCI due to AD (Albert *et al*., 2011).

1.4.2. Atypical Alzheimer Syndromes

As highlighted in previous sections, AD dementia, although often characterised primarily as an amnestic condition, ultimately affects, even in the earliest stages, a multitude of cognitive functions (Salmon & Bondi, 2009). Furthermore, a number of atypical forms exist, usually occurring in early-onset AD but also present in the late-onset population, with up to as many as 25% of all AD cases demonstrating an atypical clinical profile and pattern of NFT pathology (Balasa *et al*., 2011; Murray *et al*., 2011; Jones & Thompson, 2017). In these cases, the onset of the disease may occur within a range of brain areas other than the MTLs, resulting in markedly different clinical phenotypes. Three well described atypical AD syndromes include: logopenic aphasia, a form of primary progressive aphasia associated with significant declines in language function; posterior cortical atrophy (PCA), in which the onset of pathology within the occipital lobes leads to a significant visual disorder and finally the frontal onset of AD marked by deficits in executive function and behavioural change (Dubois *et al*., 2014).

The term logopenic aphasia, later termed logopenic variant primary progressive aphasia (lv-PPA, Gorno-Tempini *et al*., 2011), was first used by Gorno-Tempini and colleagues (2004) to distinguish patients with a form of primary progressive aphasia that did not present as either typically non-fluent or semantic in nature. The results of that study demonstrated that the slow speech, impairments in sentence repetition and comprehension deficits that characterised the condition were accompanied by significant atrophy of the left posterior temporoparietal regions, as opposed to the pattern of degradation within frontoinsular or anterior temporal structures that are typical of primary non-fluent aphasia and semantic dementia respectively (Gorno-Tempini *et al*., 2004). These neuroimaging findings, therefore, likely explain the absence of significant declines in motor speech functions or single word comprehension deficits in lv-PPA, found by the study, which again are more characteristic of the more typical forms of PPA. Since then, lv-PPA has been further defined as a condition, most often relating to AD pathology (Mesulam *et al*., 2008), that can be described primarily as a disorder of verbal short-term and working memory and naming, likely attributable to disruptions to the phonological system caused by degradation of regions surrounding the temporoparietal junction (Gorno-Tempini *et al*., 2008; Leyton *et al*., 2012; Foxe *et al*., 2013; Ossenkopple *et al*., 2016).

First described in a paper by Benson, Davis and Snyder in 1988, PCA describes a condition marked by considerable occipitoparietal atrophy that leads to characteristic declines

in a range of high order visual functions and, in particular, visuoperceptual and visuospatial deficits (Crutch *et al*., 2012; 2017). The age of onset in PCA tends to be earlier than in typical AD, with the suggested onset of symptoms being between the early 50s to early 60s (Mendez, Ghajarania & Perryman, 2002; Jones & Thompson, 2017). Despite the existence of non-AD related PCA syndromes, it is thought that, as in lv-PPA, the majority of PCA cases occur as a result of AD pathology (Tang-Wai *et al*., 2004; Seguin *et al*., 2011; Crutch *et al*., 2017). The exact prevalence of PCA among patients with AD pathology is not entirely clear. However, studies have suggested that a possible 5% of diagnosed AD cases may refer to a visual presentation (Snowden *et al*., 2007).

Finally, the frontal variant of AD remains the least well characterised of the focal AD variants, with accurate diagnosis being extremely difficult without the application of biomarker imaging (Jones & Thompson, 2017). Described initially by Johnson *et al*., (1999), the frontal variant of AD is characterised by a clinical syndrome in which frontally mediated functions are disproportionately affected, outside the range of typical AD, thought to result from a more severe build-up of pathology within frontal regions (Dickerson *et al*., 2011). Although considered a rare form of atypical AD, studies have since demonstrated the existence of pathologically confirmed cases of AD whose clinical presentation more closely resembles that of frontotemporal dementia, with the presence of either behavioural disturbance or a significant executive dysfunction that appears dominant to the additional memory impairment (Forman *et al*., 2006; Dickerson *et al*., 2011; Ossenkoppele *et al*., 2015).

Now included within diagnostic criteria (Dubois *et al*., 2014), each of these atypical forms of AD may be recognised, through neuropsychological testing, by the deficits that mark the spread of pathology within the distinct brain regions they primarily affect. In particular, the burden of tau pathology, within distinct areas, has been shown to relate to domain specific deficits among differing clinical subtypes (Ossenkoppele *et al*., 2019; Petersen *et al*., 2019), as opposed to the distribution of amyloid, that appears to remain similar across focal variants (Rosenbloom *et al*., 2011). In the past year, a paper published in *Nature Medicine* was further able to identify distinct variations in the forms phosphorylated tau present among a group of pathologically confirmed atypical AD patients that provides a possible explanation for the variable effects of AD pathology among these subtypes (Dujardin *et al*., 2020).

Given the significant symptomatic overlap between these atypical AD syndromes and differing aetiologies, such as specific forms of frontotemporal dementia, a compelling

argument is made for the implementation of routine biomarker imaging as a part of clinical evaluation, in light of the difficulties of differential neuropsychological diagnosis.

1.4.3. Neuroimaging

Several neuroimaging techniques may be applied to patients with AD, each providing a variety of information regarding spread of pathological material, brain structure and brain function. Clinically, neuroimaging was traditionally considered an additional procedure in the diagnostic process, implemented in order to rule out any possible brain trauma or lesion causing cognitive decline that may be surgically treatable. In the UK, computed tomography and MRI are still used primarily for this exclusionary purpose within clinical settings. However, advances in imaging techniques have allowed for more nuanced identification of specific structural and functional changes associated with disease that can provide complementary information to support a diagnosis, particularly in research environments (Dubois *et al*., 2007; McKhann *et al*., 2011; Johnson *et al*., 2012). Specifically, diagnostic guidelines for research purposes stipulate that accepted supportive features of AD, as measured by neuroimaging, include the presence of significant MTL atrophy evidenced on structural MRI, particularly in the hippocampus and surrounding ERC, but also specific functional changes such as reduced glucose metabolism in temporo-parietal regions, evidenced by PET (Dubois *et al*., 2007; McKhann *et al*., 2011). Hippocampal atrophy in particular, has been shown to be a highly effective marker for distinguishing AD from healthy ageing in even the very early stages of disease (Jack *et al*., 1997). Furthermore, enlargement of the ventricles, particularly in the temporal horn, as well as relative sparing of the primary motor, sensory and visual cortices are considered to be highly stereotypical of an AD-type aetiology and have been found to be recognisable early on in the course of disease (Brun & Englund, 1981; Thompson *et al*., 2003; Dickerson *et al*., 2009, 2011; Serrano-Pozo *et al*., 2011).

1.4.3.1. Structural Imaging

As discussed previously, AD is associated with a number of macrostructural changes primarily affecting temporal regions before spreading throughout the cortex and sub-cortical structures. In line with the Braak staging of NFT deposition, structural changes assessed by MRI demonstrate a reliable pattern of progression beginning within hippocampal pathways, including the rhinal cortices, further hippocampal complex and posterior cingulate/precuneus,

before spreading to the posterior temporal lobe and the wider temporoparietal association cortex. Finally, atrophy of the frontal regions occurs in a later stage of disease, with relative sparing of the cerebellum, primary motor, somatosensory and visual cortices until the final stages (Baron *et al*., 2001; Scahill *et al*., 2002; Thompson *et al*., 2003; Whitwell *et al*., 2007a; Whitwell *et al*., 2008a; Whitwell, 2010; Schwarz *et al*., 2016; Gordon *et al*., 2018). This apparently inexorable relationship between the appearance of pathological materials and subsequent atrophic change has, in recent years, allowed for accurate assessment of the staging and progression of disease through the use of structural imaging (Frisoni *et al*., 2010). Rates of structural change in a number of cortical regions, including the hippocampus, ERC, whole temporal lobe and even the whole brain, have further been demonstrated to correlate highly with indices of cognitive decline throughout the course of disease (Scheltens *et al*., 1992; Fox *et al*., 1999; Thompson *et al*., 2003; Sluimer *et al*., 2008; Dickerson *et al*., 2009; Vemuri *et al*., 2009; Frisoni *et al*., 2010). Synaptic loss indicated by the presence of atrophy, as opposed to the accumulation of proteinopathies, particularly in the MCI to dementia stages, is therefore considered the best neural correlate for cognitive impairment in AD (Jack *et al*., 2009; Sluimer *et al*., 2010; Serrano-Pozo *et al*., 2011). Longitudinal studies have further demonstrated considerable predictive power of structural changes in predicting progression to dementia among MCI patients (Korf *et al*., 2004; Whitwell *et al*., 2008b; Lan *et al*., 2017).

Aside from complementing positive AD identification, structural neuroimaging is also often used to exclude any other possible causes of dementia or comorbid conditions, both when assessing patients clinically, but also characterising patients for research. In particular, the properties of structural MRI mean that certain sequences can be attuned to specific tissue properties (Grover *et al*., 2015). Lesions in the white matter, for example, can be detected using the fluid-attenuated inversion recovery (FLAIR) MRI sequence that produces a T2-weighted image in which the white matter appears darker than the grey matter, allowing for the visualisation of bright hyperintensities suggestive of a lesion (Hajnal et a., 1992). A high volume or number of such white matter hyperintensities in older individuals is usually indicative of vascular damage, which, when present with cognitive decline, could potentially reflect a primary vascular degenerative aetiology (De Leeuw *et al*., 2001). Such findings are usually considered an exclusionary criterion within research studies or drug trials (Rollin-Sillaire *et al*., 2013). However, the comorbidity of vascular pathology with AD means that such imaging techniques may be beneficial in clinical settings for patient treatment and personalised medicine (Kapasi & Schneider, 2016).

To date, much of the research pertaining to macrostructural changes in AD has focussed on MRI indices of cortical integrity, including grey matter volume, cortical thickness and surface area (Apostolova & Thompson, 2008). However, changes in the integrity of white matter networks have been identified in AD even in the preclinical stages (Fischer *et al*., 2015). At the microstructural level, the techniques of diffusion tensor imaging (DTI) have identified differences in white matter integrity not only among MCI cohorts (Chua *et al*., 2008; Pievani *et al*., 2010; Wang *et al*., 2012; Selnes *et al*., 2012; Nir *et al*., 2013; Yu, Lam & Lee, 2017; Wen *et al*., 2019), but even in patients who may be considered as being in a preclinical stage of the disease (Selnes *et al*., 2012; Adluru *et al*., 2014; Kantarci *et al*., 2014; Li *et al*., 2015). Specifically, fractional anisotropy, a measure that indicates to what degree the diffusion of water along axons is constrained to one direction, appears decreased across the spectrum of AD, suggesting the possible breakdown of myelin and axonal integrity. Mean diffusivity however, a measure that indicates the average diffusivity of water molecules in any direction, is often found to increase in AD cohorts, potentially reflecting a loss of cellular boundaries such as myelin sheaths or cell membranes (Pievani *et al*., 2010; Sexton *et al*., 2011; Wang *et al*., 2012; Selnes *et al*., 2012; Nir *et al*., 2013; Adluru *et al*., 2014; Kantarci *et al*., 2014; Li *et al*., 2015; Yu, Lam & Lee, 2017; Wen *et al*., 2019). Such microstructural changes have been found to correlate with cortical degradation, accumulation of tau and even clinical disease severity in AD (Rose *et al*., 2006; Lee *et al*., 2015; Kantarci *et al*., 2017). Given its early presentation and tight relationship with disease severity measures, microstructural measurements of white matter integrity are now considered to reflect a potentially effective imaging biomarker for AD diagnosis (Selnes *et al*., 2013).

1.4.3.2. Functional Imaging

Despite the initial structural changes within the MTLs, functional imaging studies of AD and MCI patients have consistently demonstrated a predominant breakdown of functional processes in widespread brain regions. Of the known functional changes associated with AD, the most well-established diagnostic hallmark is marked by findings from PET and single photon emission computed tomography (SPECT) imaging showing a significant decrease in glucose metabolism and cerebral perfusion within areas of the precuneus and posterior cingulate cortex (PCC), occurring at a very early stage of disease (Minoshima *et al*., 1997; Kogure *et al*., 2000; Bradley *et al*., 2002). For many years, researchers have suggested that

significant changes in blood flow and glucose consumption within these regions may be explained as indicators of brain dysfunction, occurring as a result of disconnection between these areas and areas of the MTLs significantly affected by neurodegeneration (Jobst *et al*., 1992; Meguro *et al*., 2001; Matsuda *et al*., 2002). More recent studies assessing white matter integrity have since evidenced a measurable breakdown of the cingulum bundle in AD, connecting the PCC with the hippocampus and parahippocampal gyrus, that is significantly correlated with both hippocampal atrophy and hypometabolism of both the PCC and a number of other structures associated with the Papez circuit (Zhang *et al*., 2007; Villain *et al*., 2008; Villain *et al*., 2010). Furthermore, evidence from AD and MCI patients has demonstrated a shift in the relationship between hippocampal atrophy and PCC hypometabolism in relation to increases in disease severity. In a study by Teipel and colleagues (2016), it was found that, in the earliest stages of MCI, PCC hypometabolism was exclusively related to hippocampal atrophy, while in the later stages a significant relationship was also found with local atrophy of the PCC itself. In AD dementia patients the correlation between hippocampal atrophy and PCC volume was lost entirely, therefore supporting the disconnection hypothesis of PCC hypometoblism in AD. Hypometabolism of the PCC has been found to identify individuals with MCI who are likely to progress to AD dementia and has been found to be present within preclinical cohorts with a family history of AD or carrying the ApoE-ε4 allele (Reiman *et al*., 1996; Chételat *et al*., 2003; Reiman *et al*., 2004). As such, reduced glucose metabolism within the PCC and surrounding regions, evidenced by PET, is now considered a supporting factor for the diagnosis of AD, particularly in research settings (Dubois *et al*., 2007; McKhann *et al*., 2011).

Aside from metabolic imaging and assessment of cerebral blood flow, another functional imaging modality that has shown characteristic changes in AD is blood-oxygen level dependant functional MRI (BOLD fMRI). One of the most consistent findings in this area is the functional disruption seen within the default mode network (DMN) within AD patients when compared with healthy older individuals (Greicius *et al*., 2004). Originally described by Raichle in 2001, the DMN reflects a collection of brain regions that show significant simultaneous decreases in activation when the brain is actively engaged in goal-directed tasks, despite being collectively active at rest. A wealth of research has since related a wide range of introspective and self-referential processes, including free thinking, the remembering of past events, visualisation of the future, as well as social cognition processes such as Theory of Mind (a process that involves the interpretation of others intentions or beliefs), to the activation of the DMN (Buckner & Carroll, 2007; Spreng, Mar & Kim, 2009;

Buckner & DiNicola, 2019). Recent evaluations of the DMN speculate that the network may be an amalgamation of several distinct sub-networks that are more or less related to the functions of the DMN listed above (Buckner & DiNicola, 2019). In particular, a clear distinction may be made between anterior and posterior regions of the DMN, with a posterior network, including the PCC, precuneus and inferior parietal lobules as core hubs to which all region of the DMN are connected (Buckner, Andrews-Hanna & Schacter, 2008; Fransson & Marrelec, 2008). As Buckner and colleagues outline in their 2008 paper, the hippocampal formation and surrounding cortex, including the parahippocampal gyrus, represent another subsystem of the DMN in which activation demonstrates significant correlations with activity within the core posterior hubs, despite showing no correlation with other, more anterior subsystems. In AD, it is this observed coactivation of the hippocampal regions and the PCC that has been shown to be significantly reduced when compared with healthy controls, with this difference alone successfully distinguishing AD patients from healthy older adults with a sensitivity and specificity of 77% and 85%, respectively (Greicius *et al*., 2004). Changes in DMN activation, as measured by resting-state fMRI, therefore support the disconnection hypothesis reflected by early PET studies (Minoshima *et al*., 1997; Kogure *et al*., 2000; Bradley *et al*., 2002) and further reinforce the findings of structural imaging that indicate such disconnection occurs as an early pathological event, through evidence from MCI patients who were found to show a similar reduction in functional connectivity between the hippocampus and PCC (Bai *et al*., 2008; Zhou *et al*., 2008).

1.4.3.3. Biomarker Imaging

As discussed previously, the AD biomarker widely understood to be the best proxy for the progression of structural change and cognitive decline is the deposition of hyperphosphorylated tau protein (Jack *et al*., 2002; Giannakapoulos *et al*., 2003; Csernansky *et al*., 2004; Whitwell *et al*., 2008a; Serrano-Pozo *et al*., 2011; Nelson *et al*., 2012; Bejanin *et al*., 2017). Initially demonstrated by histopathological studies (Arrigada *et al*., 1992), patterns of tau deposition and their relationship to structural change and cognitive decline have now been confirmed by multiple clinicopathological *post-mortem* studies (Nelson *et al*., 2012), as well as more recent studies utilising biomarker imaging techniques *in vivo* such as PET tau. Using radiotracers designed to bind to NFTs, such studies have indicated a significant relationship between both global cognitive status and Braak staging, but furthermore specific deficits such as memory impairment have been associated with the deposition of NFTs within

select brain regions of the MTLs (Cho *et al*., 2016; Schöll *et al*., 2016; Ossenkoppele *et al*., 2016; Bejanin *et al*., 2017). PET imaging, therefore, has played a significant role in recent years in the identification and staging of AD *in vivo*, with the original Braak staging of tau deposition preserving its utility as a measure of disease severity and progression (Schöll *et al*., 2016).

Amyloid imaging has been arguably less consistent. Despite now being widely considered an essential aspect of AD diagnosis (Dubois *et al*., 2014; Jack *et al*., 2018), amyloid PET imaging has revealed a pattern of spread that appears to be relatively independent of cortical structure, function and cognitive decline (Jagust *et al*., 2009; Chételat *et al*., 2013; Chételat, 2013; Jack *et al*., 2013; Besson *et al*., 2015). Amyloid positivity as a biomarker for AD has, therefore, most successfully been considered a descriptive marker, indicating the presence of AD pathology, without necessarily offering diagnostic or prognostic information for an individual's disease severity (Besson *et al*., 2015; Chételat *et al*., 2013; Jack *et al*., 2016) that may best be established through volumetric MRI or functional imaging (Dubois *et al*., 2014).

1.4.4. Cerebrospinal Fluid Biomarkers

Recent advances in AD diagnosis have further seen the arrival of CSF and blood biomarkers, indicating the presence of elevated AD pathology. The deposition of tau may be measured in the CSF by levels of either total tau (T-tau) or hyperphosphorylated tau (P-tau), while the presence of pathological Aβ is measured by the level of Aβ42 or the Aβ42/Aβ40 ratio (Olsson *et al*., 2016). Both T-tau and P-tau are usually found to be elevated in the CSF of AD patients, whereas CSF levels of Aβ42 are consistently found to be lower than those of healthy controls, a signature that is also consistent within prodromal disease (Blennow *et al*., 2010; Olsson *et al*., 2016). Low levels of CSF Aβ42, in spite of high amyloid burden evidenced by PET imaging, are thought to reflect the inhibitory effect of amyloid plaques on the transportation of Aβ42 from the brain to the CSF (Fagan *et al*., 2006; Koffie *et al*., 2009). High levels of T- and P-tau, however, are a reflection of neuronal degeneration and tau hyperphosphorylation and tangle formation, respectively (Blennow *et al*., 2010). A meta-analysis by Olsson and colleagues (2016), revealed that each of these core CSF biomarkers were highly successful in differentiating both AD patients from healthy controls, as well as discriminating those considered as MCI due to AD from MCI patients who were considered to be stable. Furthermore, CSF levels of neurofilament light (NFL), a neurofilament subtype

forming a crucial component for the structure of the neuronal cytoskeleton (Zetterberg, 2016), also demonstrated a significant association with the presence of disease in both dementia and MCI patients. Neurofilaments are particularly abundant within large calibre myelinated axons (Friede & Samorajski, 1970; Trojanowski, Walkenstein & Lee, 1986) that form the fibres constituting a number of white matter tracts that are particularly vulnerable to AD pathology (Rose *et al*., 2000; Medina *et al*., 2006; Stebbins & Murphy, 2009). Correlations between white matter lesions and levels of NFL within the CSF have been identified in a number of neuropathologies, which in accordance with the presence of this protein within large myelinated axons, have been interpreted as a breakdown of axonal integrity resulting in the leakage of this structural protein into the extracellular fluid (Srögren *et al*., 2001; Bergman *et al*., 2016). Despite a lack of disease specificity, increased levels of NFL within AD patients have further supported the existence of significant white matter damage and axonal destruction as a prominent aspect of this pathology and further implicated a utility of this measure as a general diagnostic tool for neurodegeneration (Olsson *et al*., 2016).

The utility of CSF biomarkers in AD diagnosis has been consistently demonstrated by a number of studies, and such markers have even been suggested to provide effective prognostic tools for the prediction of dementia development among prodromal disease groups and possibly even future cognitive decline among healthy adults (Blennow *et al*., 2010; Buchhave *et al*., 2012). However, one of the greatest limitations around CSF markers and their use in clinical settings is the invasive procedure of the lumbar puncture. Despite showing utility in differential diagnosis, where a clinical evaluation may not be sufficient (Koopman *et al*., 2009; Paterson *et al*., 2018), the positive predictive value of CSF biomarkers among preclinical cohorts is limited (Blennow *et al*., 2010). As such, along with biomarker neuroimaging, these remain representative of an additive rather than core component of diagnostic protocols in neurodegenerative disease, where cognitive testing may provide adequate evidence for pathological decline without the need for more invasive or expensive procedures, particularly in light of the absence of disease modifying treatments.

1.4.5. Blood Biomarkers

The high costs associated with PET biomarker neuroimaging and the invasive, time-consuming nature of the lumbar punctures needed for CSF collection, make both options limited in their use as routine screening tools for neurodegenerative causes of cognitive

decline. As such, in recent years, there has been an increase in research towards non-invasive procedures for the detection of biomarkers in the blood (Blennow, 2017). Recent technological advances in ultrasensitive analysis techniques, have made it possible to detect very low concentrations of AD related proteins in the blood plasma or serum (Andreasson, Blennow & Zetterberg, 2016).

Current research has demonstrated the most robust findings when using NFL as a blood-based biomarker, evidencing its accuracy in reflecting neurodegeneration in AD as well as other neurodegenerative conditions and its high correlations with CSF and longitudinal measures of disease severity (Zetterberg, 2019). However, blood NFL markers are limited by a lack of disease specificity and therefore, a combination of NFL with tau markers, that in the CSF show a surprising specificity for AD, even when compared with other tauopathies (Zetterberg, 2017), and plasma Aβ markers, where a reduced Aβ42/40 ratio has shown some promise in terms of diagnostic accuracy, could provide a way forward for blood biomarker testing (Zetterberg, 2019). At present however, research into blood-based biomarkers particularly for tau and Aβ, despite showing considerable promise, is still in the nascent stages and more replication studies are needed to determine the efficacy of such markers as reliable diagnostic tools.

1.6. Treatments and Therapies

Despite a multitude of trials testing potential disease modifying therapies for AD, today only four pharmacological treatments exist that have been approved by the FDA (Long & Holtzman, 2019). Furthermore, these symptomatic treatments fail to address the underlying cause of the neurodegenerative process and as such prevention strategies aimed at the amelioration of potential risk factors for this multifactorial disease remain an important aspect of geriatric health care for the preservation of cognition in ageing (Livingston *et al*., 2017).

1.6.1. Pharmacological Therapies

Current pharmacological treatments for AD are limited to one of two medications: cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), developed to block the effects of acetylcholinesterase, the enzyme responsible for the degradation and clearance of acetylcholine from the synapse and memantine, an NMDA receptor modulator that, despite its exact mechanisms being unclear, is thought to reduce the toxicity of glutamate released by

dying neurons (Greenamyre *et al*., 1988; Long & Holtzman, 2019). The efficacy of cholinesterase inhibitors in the symptomatic treatment of AD reflects the selective degeneration and synaptic dysfunction seen among neurons of the cholinergic system, particularly within the basal forebrain, in AD pathology. Now considered a core feature of the disease, cholinergic selectivity of AD pathology was first recognised many years ago and is thought to contribute significantly to the clinical manifestation of AD neurodegeneration, as outlined by the cholinergic hypothesis (Ferreira-Vieira *et al*., 2016; Hampel *et al*., 2018). Areas of the cholinergic basal forebrain provide the majority of cholinergic innervation to the rest of the cerebral cortex and hippocampus, playing a critical role in attention and memory functions (Ferreira-Vieira *et al*., 2016; Agostinelli, Geerling & Scammell, 2019; Hampel *et al*., 2018). Neuronal loss within the nucleus basalis of Meynert is particularly devastating in AD (Schliebs & Arendt, 2006) and tau related cytopathology of cholinergic neurons in this region has been found by histopathological investigations to occur at the earliest stages of disease, potentially before cognitive deficits, and to correlate significantly with memory function (Mesulam *et al*., 2004). Subsequent investigations have since shown that atrophy within the basal forebrain of prodromal AD patients may predict later ERC atrophy and furthermore, such atrophy may be present even preceding ERC involvement and cognitive decline in preclinical individuals testing positive for Aβ (Schmitz & Spreng, 2016). The success of cholinesterase inhibitors in the amelioration of AD symptoms is, therefore, likely to reflect the maintenance of cholinergic functional pathways between the MTLs and the basal forebrain in the presence of significant synaptic and neuronal loss. Such drugs, however, are thought not to provide a means to mediate disease progression in AD, as evidenced by the short window of efficacy (ranging from around 1-3 years), they provide for a given individual before no longer exerting any significant positive effects (Sun *et al*., 2008; Howard *et al*., 2012; Ferreira-Vieira *et al*., 2016). Furthermore, evidence suggests that cholinesterase inhibitors are most effective in late-stage disease, with studies finding little to no effects for individuals in the MCI stage (Hampel *et al*., 2018). However, recent evidence from the Hippocampus Study, demonstrated a significant impact of donepezil treatment in the reduction of atrophy rates within a number of brain regions vulnerable in AD including both the hippocampus and the basal forebrain (Cavedo *et al*., 2016). In particular, these trials found that patients in a prodromal stage of disease receiving donepezil showed hippocampal atrophy rates that were almost half that of the placebo group (Dubois *et al*., 2015). Follow-up investigations have since confirmed a distinct effect of donepezil treatment on reducing atrophy rates within the nucleus basalis of Meynert and the medial septum-diagonal band of

Broca complex, an area of the basal forebrain known to provide particular cholinergic innervation to hippocampal structures (Cavedo *et al*., 2017; Agostinelli, Geerling & Scammell, 2019). These recent findings, therefore, suggest that, despite the limited clinical effects of cholinesterase inhibitors in the prodromal stages of AD, the administration of such drugs at these early stages may provide a means to slow the progression of disease to some extent and, therefore, delay the onset of dementia (Hampel *et al*., 2018).

1.6.2. Non-Pharmacological Therapies

Despite the success of cholinesterase inhibitors and memantine in ameliorating some of the cognitive symptoms associated with AD at a late stage of disease, the absence of clinically effective disease modifying treatments means that a significant aspect of research in AD therapeutics, particularly for the earliest stages, is centred around non-pharmacological methods for the delay or slowing of further cognitive decline. The most widely researched interventions in this area, summarised in a review by Zucchella *et al*. (2018), include exercise and motor rehabilitation, cognitive stimulation, behavioural and psychological therapies, assistive technologies, art and music therapy and virtual reality or gaming. Despite Zuchella and colleagues' conclusion, pointing out a number of inconsistencies regarding the efficacy and clinical relevance of these methods, particularly in light of the significant variability of outcome measures included in non-pharmacological clinical trials (Couch *et al*., 2020), the positive outcomes of these types of interventions include improvements in cognitive ability, daily functioning, quality of life and reduction in care-giver burden (Zuchella *et al*., 2018) and as such these methods should not be ignored, particularly where their implementation is relatively simple and cost-effective.

Chapter 2 | Semantic Memory and the Temporal Lobes in Alzheimer's Disease

2.1. Introduction

As highlighted in the first chapter, clinical diagnosis of Alzheimer's disease (AD) and even prodromal AD in the form of mild cognitive impairment (MCI), continues to rely heavily on the presence of a significant decline in episodic memory function (Dubois *et al*., 2007; Albert *et al*., 2011). A component of declarative memory, first described by Cohen and Squire (1980), episodic memory has since been defined in terms of the recall of past events, relying heavily on contextual cues and experience (Tulving, 2002). The likely reason for this marker, lies in the fact that significant dysfunction of episodic memory reflects the moment in which pathological material accumulates significantly within the medial temporal lobes (MTLs) and specifically, hippocampal complex, the hallmark of AD related cortical degradation. The hippocampus is widely acknowledged as the cortical area responsible for sustaining episodic memory (Eichenbaum, 2001), and so an impairment in this cognitive function reliably informs clinicians of significant pathological involvement in this area, consistent with an AD diagnosis. This focus on episodic processing, however, is highly problematic for the pursuit of earlier AD diagnosis. Given the findings of histopathological studies, it is clear that there is an extensive preclinical phase of disease in which pathology is present within discrete subhippocampal structures, such as the perirhinal cortex (PRC), entorhinal cortex (ERC) and transentorhinal cortex, prior to hippocampal involvement and subsequent diagnosis (Braak & Braak, 1991; Jack *et al*., 2010). To focus on episodic memory, particularly as a marker of prodromal disease, is to undermine potential neuropsychological markers that may be more sensitive to the very earliest pathological changes associated with AD. It is imperative therefore, that research explores a greater range of neuropsychological changes detectable in patients in the earliest stages of disease, in order to develop clinical markers more accurate in their exposure of underlying sub-hippocampal pathology (Venneri, Mitolo & De Marco, 2016).

2.1.1. Declarative Memory in Healthy Ageing and Alzheimer's Disease

First described by Tulving (1972), declarative memory includes two types of explicit memory processes. The first, episodic memory, as previously described, involves the retrieval

of past events including the contextual details of the experience and awareness of self in the reliving and remembering of that event (Tulving, 2002). The second however, semantic memory, refers to general knowledge of the world that is context-free in nature (Tulving, 1972; Didic *et al*., 2011). This type of memory may include the memory of facts, names, places and faces that are independent of one's own experience (Levy, Bayley & Squire, 2004; Tulving, 1972).

A further limitation surrounding the continued use of episodic memory function as a marker for AD and MCI, lies in the fact that these declarative memory processes differentially decline in the course of normal ageing (Rönnlund *et al*., 2005). It has been well established that, in later life, episodic memory function begins to show considerable decline even in healthy ageing, where semantic memory shows a much less pronounced decline and may even be facilitated by increasing age (Levine *et al*., 2002; Rönnlund *et al*., 2005). A study by Levine *et al*., (2002) demonstrated this phenomenon using the autobiographical interview to measure personal remote memory recall. The scoring system for this particular measure allows for the researcher to separate qualitatively the nature of the memories recalled, whether they present as a truly episodic, re-experiencing of autobiographical events or whether they are more semanticised recollection. The results showed a significant difference in the nature of memories retrieved between age groups, with older adults producing less contextual details relating to events, locations, perceptions and personal thoughts or emotions, specific to the recalled event, in favour of more general semantic details. A further imaging study by Spreng *et al*., (2018) was able to replicate these results, finding that more semanticised recollection in older adults related to a shift in the dynamics of functional brain networks. Their findings suggest an adaptive capacity in the ageing brain to promote the utilisation of 'crystallised cognition', such as accumulated general knowledge, as a compensatory mechanism in the presence of declining 'fluid cognition', in this case represented by episodic memory function.

In the context of AD then, episodic memory decline does not represent a neuropsychological marker specific to disease processes. Instead, a large body of literature suggests that functional decline in episodic memory, at least in terms of retrieval deficits, are common in old age (Levine *et al*., 2002). In contrast, retrieval of semantic information appears to be well preserved in an ageing population (Levine *et al*., 2002). It is well established that not all MCI patients will convert to dementia, with some even reverting to normal cognition (Petersen, 2004). Therefore, the value of semantic memory tasks lies in the potential to distinguish the so-called 'converters' from the 'non-converters' in a prodromal

cohort, where episodic memory impairment is a core diagnostic component that, given its presence in normal ageing (Rönnlund *et al*., 2005), may be less specific in detecting truly abnormal pathological changes.

2.1.2. Semantic Memory Deficits in Early Alzheimer's Disease

Semantic memory deficits have generally been overlooked in AD progression. Early studies in this area had suggested that AD pathology primarily affects the episodic memory system with relative sparing of brain areas supporting semantic memory function (Graham & Hodges, 1997). This view is in line with the theory that episodic and semantic variants of declarative memory are, at least in part, cognitively and neurally dissociable (Vargha-Khadem *et al*., 1997; Graham & Hodges, 1997; Snowden, Griffiths & Neary, 1996) and so significant degradation of hippocampal areas seen in AD would lead to episodic dysfunction with little effect on the semantic memory system. However, there is now a growing body of research that has demonstrated that, contrary to these previous findings, a significant semantic memory impairment is present in AD, even in the earliest stages of disease, prior to the onset of dementia.

Didic *et al*., (2011) hypothesised that the progressive degradation of the MTLs, seen in the earliest stages of AD, may explain how the emergence of a semantic memory deficit may be present and yet overlooked prior to a subsequent severe episodic memory decline. According to their review, Didic and colleagues propose the existence of two distinct, anatomically separable networks within the MTL. The network first affected by AD pathology in Braak stages I and II, lies anteriorly to the hippocampal formation and is comprised of the transentorhinal cortex, PRC and ERC. A posterior hippocampal network, comprised of the hippocampus and posterior portions of the parahippocampal gyrus, is affected in the later stages of disease, Braak stages 3 and 4. The hypotheses outlined in this review, suggest that the "anterior MTL network" is important for sustaining 'context-free' or semantic memory while the "posterior MTL network" contributes mainly to context-rich episodic or spatial memory. It has been well documented that pathology within this "anterior MTL network" occurs as early as years or even decades prior to a formal AD diagnosis (Jack *et al*., 2010). Previously, these stages of disease were thought to have little clinical presentation; however, Didic and colleagues suggest that damage to these discrete areas of the MTL may have a clinical presentation that is simply easier to disguise and compensate for, than the severe episodic memory decline that occurs later in the disease process. Unlike

episodic memory decline, a semantic memory impairment is unlikely to result in a lack of independence for an individual and the types of complaints resulting from a semantic memory deficit, such as word finding or naming difficulties, can easily be overcome in a world in which any information is readily accessible.

2.1.2.1. Evidence of the Semantic Deficit in Neuropathologically Confirmed Cases

A growing body of behavioural research, including compelling evidence from retrospective case studies, has further supported Didic *et al*.'s theory that a semantic memory decline will be present in the first stages of disease. A seminal paper by Snowdon *et al*., (1996) used longitudinal data, along with neuropathological examination at autopsy, to study the linguistic traits of a group of nuns and how a semantic measure such as this may relate to subsequently confirmed AD related pathology. Autobiographical diaries, written, on average, sixty-two years prior to death, were collected from a cohort consisting of 74 nuns. Linguistic ability was assessed using what was referred to by researchers as 'idea density'. Using the final ten sentences of each diary, idea density was calculated as the mean number of ideas expressed every 10 words. Results of this study demonstrated a significant correlation between this semantically mediated linguistic measure and the presence of neurofibrillary tangles in frontal, temporal and parietal lobes. Participants whose writing contained low levels of idea density, therefore, were significantly more likely to meet neuropathological criteria for AD at *post-mortem*. The results of this early paper suggest that poorer linguistic ability earlier in life may reflect a marker characterising a distinct course of cognitive and neurological development more susceptible to the development of AD pathology in old age.

More recent work looking at similar measures of semantic functioning comes from Garrard *et al*., (2005) and Le *et al*., (2011), who both examined the writings of author Iris Murdoch in retrospective case studies aiming to assess the linguistic changes notable in her work prior to her AD diagnosis. Garrard *et al*., (2005) looked at the writing styles from three of Murdoch's works to assess the syntactical and semantic properties of her writing from her early career, in her first book Under the Net (1954), through the height of her success, in a book widely considered one of her most accomplished works, The Sea, The Sea (1978) and finally in the last book she wrote, Jackson's Dilemma (1995). According to the authors, while writing Jackson's Dilemma, Murdoch was likely already experiencing the initial stages of AD pathology, Braak stage I (Garrard *et al*., 2005), with proteinopathies spreading

throughout the transentorhinal regions. It was hypothesised by researchers that this early manifestation of AD pathology may provide an explanation for the notable linguistic changes present in Murdoch's final work, which had been harshly reviewed by critics. A range of textual analysis methods were used to quantify the linguistic properties within each book, assessing both syntactical and structural changes as well as differences in vocabulary and lexical selection. The results showed that, despite no differences being apparent across the works in terms of structure or syntax, a significant difference was found in lexical traits and vocabulary between Murdoch's final work and the previous two books, particularly compared to The Sea, The Sea, that authors believe indicates that the effect is unlikely to reflect a simple change in literary style. This study, therefore, provided objective evidence of a significant restriction in Murdoch's use of vocabulary by her final work, suggesting that the transentorhinal stage of AD that Murdoch was thought to present with at the time of writing Jackson's Dilemma, is coupled with a, usually undetected, but significant decline in lexico-semantic writing abilities, particularly affecting vocabulary. Given the nature of an individual's available lexicon, as a resource reliant upon intact semantic retrieval, the results of this study may be interpreted in terms of Didic *et al*.'s theory as evidence of disruption to the semantic anterior MTL network thought to occur in the very first stages of AD.

Further evidence of a disease related decline in lexical abilities in Murdoch's work comes from a study by Le *et al*., (2011). In their retrospective study, these authors not only analysed the works of Murdoch, but also the work of two further prominent authors: P.D. James, and Agatha Christie. As a prolific writer thought to show no evidence of cognitive decline, the work of P.D. James in this case was considered a linguistic model of healthy ageing, while Agatha Christie's work was included in light of the consensus that Christie likely suffered from undiagnosed dementia. Using a wider range of Murdoch's novels than the three analysed by Garrard *et al*., (2005), Le *et al*., (2011) were able to replicate the previous findings, confirming a significant decline in lexical ability and use of vocabulary towards the end of Murdoch's career. Furthermore, analysis of the novels of P. D. James, who also continued to write into later life, revealed no declines of significance in the breadth of vocabulary, lexical repetition or verb specificity across her novels, with any slight changes being attributable to the normal changes in vocabulary for healthy ageing.

2.1.2.2. Evidence of the Semantic Deficit Among Prodromal and Preclinical Patients

Additional evidence for a semantic memory deficit in the earliest stages of AD comes from prospective studies utilising patient groups thought to represent the very initial stages of AD pathology. This has included MCI patients, individuals with subjective cognitive decline (SCD), at risk individuals (e.g. those with a copy of the Apolipoprotein-E ε4 allele [ApoE - ε4]) and even pre-symptomatic individuals followed longitudinally through to diagnosis. One of the first prospective studies aiming to characterise the semantic deficit in the early stages of AD came from Hodges and Patterson (1995). This study revealed that even patients considered as having minimal AD (Mini Mental State Examination [MMSE] score > 23) were significantly impaired relative to controls on a range of tests assessing semantic processing, including category fluency, naming, answering questions related to semantic features and the picture-picture matching task: Pyramids and Palm Trees (Howard and Patterson, 1992). The results of this study suggested that such impairment of the semantic system was not universal across patients however, with some patients in the minimal AD group showing little to no deficits on specific tests or even any at all. This led to the conclusion that, although a semantic memory impairment may occur even in the mild disease stages, damage to the discrete subhippocampal areas of the anterior MTLs (aMTLs) is not sufficient to cause significant semantic memory impairment, upholding the widely held view that such disruption of the semantic system is likely to occur only when pathology has spread significantly throughout the temporal neocortex (Hodges and Patterson, 1995).

However, recent work with MCI patients has since challenged this view. MCI patients have been found by a number of studies to present with significant deficits in a wide range of semantic processing tasks, including language tasks such as object naming, semantic fluency and spontaneous speech, as well as semantic knowledge of famous people and culture (Barbeau *et al*., 2012; Gardini *et al*., 2013). Object knowledge was first assessed in MCI patients by Adlam *et al*., (2006), following the finding that tests of this nature were more sensitive to semantic dysfunction than classic measures of semantic processing in patients with semantic dementia (Bozeat *et al*., 2002). Using a non-verbal test of object use knowledge, requiring participants to match objects to recipients, functions and actions, Adlam *et al*., (2006) showed that MCI patients were not only impaired on all three of these measures but also on classic tests of semantic function such as category fluency and a difficult object-naming test. Although the results of this study appeared to indicate that

measures of object knowledge may be more sensitive to a breakdown of the semantic system than classic measures of semantic processing, the finding that MCI patients were also significantly impaired on measures of category fluency provides evidence to support previous work that suggests that this relatively simple neuropsychological test provides an accurate measure of semantic memory function.

Many authors had previously interpreted a deficit in category fluency, a test that requires participants to recall as many exemplars belonging to a particular category as they can in one minute, as an indication of degradation of semantic memory function (Albert *et al*., 2001; Hodges and Patterson, 1995). Use of a similar verbal fluency test known as letter or phonemic fluency, requiring participants to recall words beginning with a certain letter, further allows for isolation of the semantic component of the category fluency test. Researchers have since demonstrated a significant reduction in the semantic advantage apparent in healthy controls during this task in AD as well as MCI (Henry, Crawford & Phillips, 2004; Murphy, Rich & Troyer, 2006), a phenomenon reflected in the lack of impairments found in the MCI group on the letter fluency task in Adlam *et al*.'s (2006) study, despite significant impairment in the semantic version of the same task. Verbal fluency tasks have been found to not only provide sensitive and specific measures for differentiating participants with dementia from healthy controls (Canning *et al*., 2004), but have also been found to be a useful predictor for conversion to dementia among 'pre-dementia' AD patients (Vogel *et al*., 2005).

Joubert *et al*., (2008) aimed to provide a better understanding of how a semantic memory deficit may present among different domains in early AD by studying a group of amnestic MCI (aMCI) patients. Contrary to Hodges and Patterson (1995), the authors demonstrated in this study that aMCI patients were significantly impaired on all measures of semantic processing, relative to controls, including knowledge of famous people and events as well as knowledge of objects. Despite earlier studies using object knowledge alone to assess semantic deficits in MCI patients (Adlam *et al*., 2006), Joubert *et al*. found greater impairments in their aMCI cohort in famous person and event knowledge. In one of the first studies assessing semantic deficits in MCI across multiple domains, these findings suggest that different domains of semantic knowledge may be differentially affected by AD pathology in its earliest stages. Given the nuanced and unique nature of knowledge of famous people and events, these types of semantic knowledge are likely to be affected to a greater extent by discrete pathology. Where object knowledge and recognition may be facilitated by more generic and shared properties, famous events and people are separated by their own

individual idiosyncrasies. Retrieval of such specific semantic details are likely to rely on higher order processing sustained by discrete areas of cortex more vulnerable to disease. This interpretation has since been supported by recent imaging studies that suggest that anterior areas of the MTL, first affected by AD pathology, such as medial PRC, may play a significant role in the naming of living relative to non-living items (Kivisaari *et al*., 2012). Furthermore, recognition of famous faces has also been shown to be a useful predictive measure for AD conversion in patients presenting with SCD. In a study by Estévez-González *et al*. (2004), of a cohort of 116 patients admitted to a memory clinic with SCD, who were followed longitudinally over a period of 2 years, 17 did not go on to develop objective cognitive impairment (i.e., controls), 26 developed MCI without progression and 27, who developed MCI, had progressed to AD dementia by 2 years. Patients who went on to develop AD dementia performed significantly worse at baseline than those with MCI who had not progressed, as well as performing worse than controls. Patients with MCI who had not developed dementia performed at an intermediate level between controls and those who progressed to dementia. These findings suggest that the severity of a semantic memory deficit may indicate the duration of an underlying disease process and provide a useful indicator of incipient AD progression.

A very recent meta-analysis by Joubert and colleagues (2020) was able to confirm, using data from 476 healthy controls and 476 MCI patients, across 22 studies, that aMCI patients systematically present with significant impairments in semantic memory relative to controls, with the average effect size across studies being large to very large. Despite the fact that the results of this analysis concern cross-sectional studies only, the robustness of the findings across studies led authors to conclude, as suggested by previous findings, that semantic memory decline is likely to represent a significant and consistent aspect of AD related cognitive impairment in this prodromal stage of disease. As such, it is recommended by the authors that tests specifically assessing semantic functioning should be routinely applied in clinical practise for the identification of early AD.

Further evidence supporting this hypothesis comes from Amieva *et al*., (2008). This study utilised the longitudinal data from the PAQUID epidemiological study (Dartigues *et al*., 1992) that used a population-based cohort, recruited in southern France, made up of 3,777 community dwelling adults aged 65 or over. Participants were visited at home by psychologists every two years, with the final follow-up, at the time of Amieva *et al*.'s analysis, 15 years after initial recruitment. At each home visit, participants underwent neuropsychological evaluation, and a criteria checklist was completed by a psychologist to

assess for signs of dementia. Participants who met criteria for dementia were then assessed by a neurologist who confirmed diagnosis and the underlying cause of dementia was determined by a specialist panel. A diagnosis of AD was confirmed according to the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD (McKhann *et al*., 1984). Of the 3,777 participants recruited from the initial study, 350 developed Alzheimer type dementia over the 14 years of follow up following the first follow up visit. Scores for measures of cognitive, functional and depressive symptoms were taken from these 350 participants from the first to the final follow up along with the same scores from a matched control group. The semantic memory measures used in this study consisted of a verbal fluency measure and the similarities subset of the Wechsler Adult Intelligence Scale, as a measure of conceptual knowledge. At baseline, (i.e., 14 years prior to diagnosis) pre-dementia participants and controls did not differ significantly on any of the cognitive, functional or psychological measures used. Semantic memory function, measured by verbal fluency, was the first area to show evidence of significant decline in the pre-dementia group relative to controls at 12 years prior to AD diagnosis, followed by a decline in concept knowledge measured by the similarities test 2 years later (10 years prior to diagnosis). Although this study has certain limitations regarding the lack of objective measure for episodic memory, which may offer a more informative view of the pre-dementia stages of AD, it does demonstrate the presence of a measurable semantic memory decline more than a decade prior to patients reaching clinically definable dementia of the Alzheimer's type. Acting as a descriptive investigation of the pre-dementia phase of AD development, the findings of this study help to elucidate the clinical signs accompanying the initial pathological moments of AD. As described by the authors, the memory deficits demonstrated in this study may represent the neuropsychological correlates of the insidious accumulation of histopathological material within subhippocampal regions of the MTLs, 12 years prior to the hippocampal stage resulting in clinically defined AD. Papp *et al*., (2016; 2017) have since demonstrated that measures of category fluency show significantly greater declines in healthy ageing participants who test positive for amyloid beta (Aβ) accumulation than those who test negatively and that such category fluency tasks could account for unique variances in cognitive decline relating to Aβ accumulation. These results, therefore, support Amieva's conclusion that the semantic memory deficits demonstrated in their preclinical cohort may occur as a result of the significant accumulation of AD related histopathological material.

2.1.3. Neural Correlates of Semantic Memory

2.1.3.1. Pathological and Lesion Studies

A considerable amount of the knowledge we have pertaining to the neural basis of semantic memory function has been derived from studies on brain damaged or neurodegenerative patients and lesion studies using animals or transcranial magnetic stimulation (TMS). The most widely explored neurodegeneration known to disrupt semantic processing is the specific form of frontotemporal lobar degeneration underlying semantic dementia. Characterised by severe degradation of semantic memory function, including deprivation of conceptual knowledge and language ability, despite relatively intact episodic memory function, semantic dementia is classically associated with progressive bilateral but asymmetric atrophy and hypometabolism of the ventrolateral and polar temporal lobes, most severely affecting left hemisphere structures (Snowden, Goulding & Neary, 1989; Hodges *et al*., 1992; Mummery *et al*., 2000; Chan *et al*., 2001; Gorno-Tempini *et al*., 2004; Desgranges *et al*., 2007). Research into this condition has led to the conclusion that the temporal lobes, especially anterior structures, likely sustain the neural circuitry responsible for the retrieval and particularly, the storage of semantic knowledge (Mummery *et al*., 2000). In a review looking at semantic deficits resulting from a range of neuropathologies, Patterson, Nestor and Rogers (2007) outlined their 'semantic hub' model, citing the anterior temporal lobes (ATLs) as a pivotal node supporting the storage of amodal semantic information. This 'hub-and-spoke' model postulates that the ATLs act as a site of consolidation for multi-modal information, from a wide range of cortical areas, to be bound into conceptual representations for retrieval (***Fig. 2.1***).

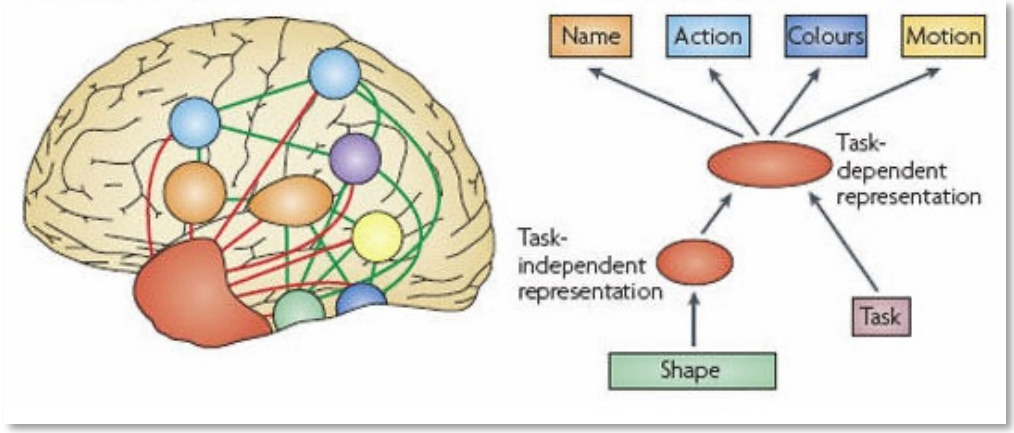


Figure. 2.1. *Taken from Patterson, Nestor and Rogers (2007), this figure depicts the 'hub-and-spoke' model hypothesised in their review that sites the anterior temporal lobes as an amodal hub for the binding of multi-modal information from a wide-range of cortical areas. Permissions to reuse this figure can be found in Appendix C.*

Lesion studies utilising TMS have since provided further support for this model. A study by Pobric, Jefferies and Lambon Ralph (2010) tested the 'semantic hub' model using low-frequency, repetitive TMS (rTMS) in order to disrupt transiently, the neural functioning of the left and right temporal poles. rTMS produced significant reductions in semantic processing efficiency in healthy participants, despite intact perceptual ability measured by a task of comparable difficulty. In this case, disruption to either the right or left temporal pole produced similar deficits for both semantic processing of words and pictures, while rTMS over a control region had no effect. These findings support the theory that neural circuitry within the ATLs sustain a hub responsible, at least in part, for the successful processing of semantic information regardless of modality.

2.1.3.2. Neuroimaging Studies

Further to studies examining patterns of brain damage in patients with semantic deficits, neuroimaging studies in healthy participants have contributed greatly to cortical mapping of semantic memory processing. A meta-analysis by Binder *et al*., (2009) aimed to combine the results of 120 articles utilizing functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to study the neural correlates of semantic processing in healthy adults. Articles included in this study were subject to strict inclusion and exclusion criteria to ensure the results were based purely on a semantic contrast. Examples of semantic contrasts may include the presentation of juxtaposing words against pseudowords, meaningful sentences against meaningless strings of words or nonsensical sentences or contrasting a semantic task (e.g., describing the word meaning) against a phonological task (e.g., giving an example of another word that rhymes with a given word). Reliability of the sites of activation reported in each of the studies was analysed using a volume-based technique known as activation likelihood estimation (Turkeltaub *et al*., 2002). The findings of this study, like previous work in brain damaged patients, point to the existence of a widely distributed network involved in the storage and retrieval of semantic information, with many activation sites in the left lateral temporal and parietal regions, overlapping with the locations of semantic dementia pathology, as well as the origin of semantic deficits in other pathological conditions (Mummery *et al*., 2000; Patterson, Nestor & Rogers, 2007). Broadly, Binder *et al*., (2009) grouped the regions of activation involved into three categories: posterior multimodal regions and heteromodal association cortex, heteromodal prefrontal cortex, and medial paralimbic regions with pervasive connections to

the hippocampal complex. Contrasting with Patterson *et al*.'s hub and spoke model, which argues for the existence of a single point of convergence in the temporal poles, the results from Binder *et al*. highlight the existence of multiple areas of convergence in a left lateralised network, including the lateral temporal, inferior parietal and ventral temporal cortices that are involved in general, multimodal semantic processing.

In a later paper, Binder and Desai (2011) outlined a neuroanatomical model of the semantic system based on a range of available data from pathological and neuroimaging studies. In this model, the authors describe a theory of semantic processing they term 'embodied abstraction'. At the core of this theory is the proposal that perceptual systems sustaining modality-specific sensory information are not also responsible for conceptual processing but rather that this higher level semantic-type processing is sustained within an amodal system of cortical areas not directly related to primary sensory cortices. Briefly, Binder and Desai suggest that conceptual representations are developed through a hierarchical structure formed of many layers of increasing abstraction from sensory, motor and affective inputs. Rather than each level being automatically active under any given circumstance, access to each level is subject to a number of task factors including context, familiarity and cognitive demands. The highest level of this system sustains schema-like conceptualisations that may be retrieved as concepts without detailed consideration of simple perceptual properties. In familiar contexts, these schematic concepts are sufficient to facilitate fast semantic processing. In contexts that are novel or less familiar, or during demanding tasks requiring deeper processing, the lower level sensory-motor-affective system provide more contributions to processing by providing detailed perceptual information for subsequent recognition or categorisation.

The neuroanatomical model proposed by Binder and Desai (2011) to underlie this psychological model of a hierarchical semantic memory system is outlined in ***Fig. 2.2***. According to this model, areas of cortex close in proximity to motor and affective networks as well as primary sensory areas (shown in yellow in ***Fig. 2.2***) provide input comprised of modality-specific perceptual representations of entities in the environment, serving to inform more complex conceptual representations of such entities within amodal semantic processing regions located in temporal and inferior parietal areas (highlighted in red in ***Fig. 2.2***). It is these high-level convergence zones that Binder and Desai (2011) cite as the areas involved in the binding of representations across modalities to form the basis of semantic knowledge, allowing for conceptual entities that may be meaningfully categorised or segregated based on a range of perceptual, emotional and action-based attributes. Unlike Patterson, Nestor and

Rogers (2007), Binder and Desai (2011) do not identify the temporal poles as being among the important convergence zones for the highest order semantic processing.

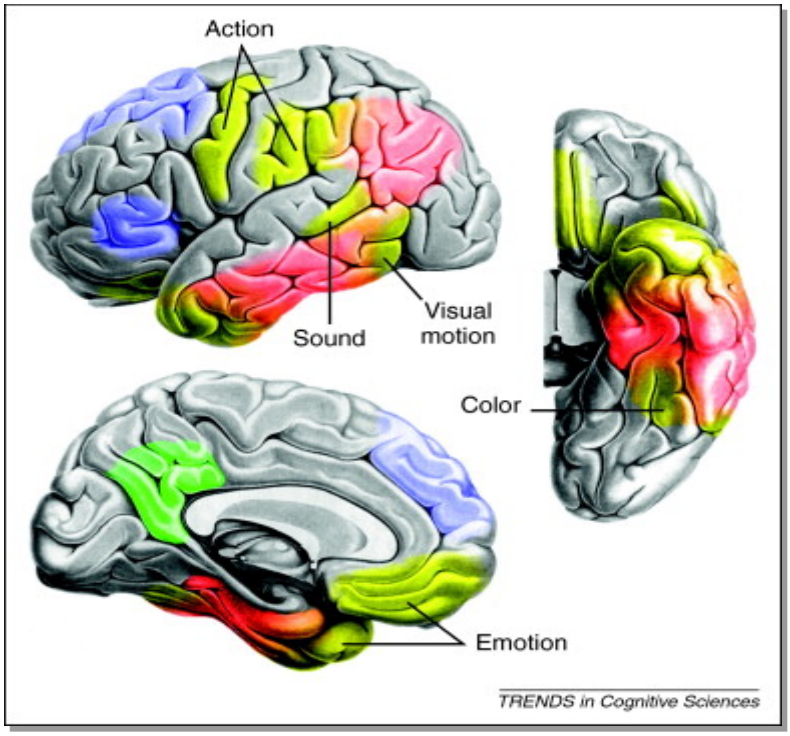


Figure 2.2. *Taken from Binder & Desai (2011): Neuroanatomical model of the semantic memory processing system. Based on a wide range of functional and pathological neuroimaging studies the model outlines modality-specific sensory, action and emotions systems (shown in yellow) which provide input to high-level convergence areas within the temporal and inferior parietal cortex (in red) that serve to sustain increasingly abstract conceptual knowledge. Dorsomedial and inferior prefrontal regions (highlighted in blue) sustain the activation and selection of temporoparietally stored semantic information and the posterior cingulate gyrus along with the precuneus (in green) appear to function as a relay between this semantic memory system and the episodic memory system sustained within the hippocampus, allowing for the binding of semantic knowledge to autobiographical memory. Permissions to reuse this figure can be found in Appendix D.*

These contrasting results reflect the degree of ambiguity in the literature concerning the role of the ATLs in amodal semantic memory processing. Despite many neuropsychological studies indicating a significant role of this area for this type of memory function (Mummery *et al*., 2001; Patterson, Nestor & Rogers, 2007; Pobric, Jefferies & Lambon Ralph, 2010), neuroimaging studies have produced conflicting results leading to the conclusion by Binder *et al*., (2009; 2011) that the temporal poles do not have the significance outlined in previous models (Patterson, Nestor & Rogers, 2007). Visser, Jefferies and Lambon Ralph (2010) aimed to address this ambiguity in the literature by conducting a meta-analysis of 164 fMRI and PET studies looking at semantic memory in healthy individuals. Their analyses indicated that a number of factors concerning experimental design and

analysis could influence the likelihood of finding activation within the ATLs during semantic retrieval. Firstly, the use of PET versus fMRI can have a significant impact on the pattern of activations observed, particularly in regard to the ATLs, an area well known for being subject to distortion artefacts caused by the large variations in magnetic susceptibility in brain areas in close proximity to large air-filled cavities such as the sinuses. This distortion often leads to a lack of observed activation in the ATLs in fMRI studies, despite evidence for such activation in studies utilizing PET, a finding best highlighted in a study by Devlin *et al*., (2000) who were able to obtain evidence of activation in this area during a semantic task using PET, despite finding no activation using the same task with fMRI. Furthermore, having a higher field of view, allowing for whole-brain coverage (e.g., above 15cm), and using the ATLs as a region of interest (ROI), also made it far more likely for studies to report activation in this area. Visser and colleagues also confirmed that modality of the semantic tasks used in each of the imaging studies did not appear to have any effect on the likelihood of recording activation within the ATLs, supporting the theory of the existence of a semantic 'hub' located in this area that supports amodal retrieval and consolidation of semantic information. Informed by this meta-analysis, Visser *et al*., (2010) went on to conduct a study using distortion corrected fMRI to reveal distinct correlations between semantic memory performance and bilateral temporal activations along the inferior temporal lobes extending from posterior regions of the fusiform gyrus to anterior regions including the ERC, PRC and posterior regions of the temporal pole.

Taken together, neuropsychological and neuroimaging studies have established a semantic system that is likely to employ a hierarchical structure in which cortical association areas, involved in perceptual processing, input into higher order convergence zones for the amodal binding of information into semantically related concepts. Although there has been some dispute between pathological studies and neuroimaging studies of healthy individuals as to the location of semantic convergence within the cortex, the evidence suggests that levels of this processing are likely to occur within the temporal lobes, with important nodes located in polar ATL structures (Patterson, Nestor & Rogers, 2007; Visser, Jefferies & Lambon Ralph, 2010; Visser *et al*., 2010), as well as more posterior ventral temporal areas, inferior parietal lobules and medial parietal areas such as the posterior cingulate and precuneus (Binder *et al*., 2009; Binder & Desai, 2011).

2.1.4. Neural Correlates of the Semantic Deficit in Alzheimer's Disease

Although the majority of pathological studies into the neural basis of semantic memory deficits have focussed on the overt semantic memory dysfunction in conditions such as semantic dementia and herpes simplex virus encephalitis (Patterson, Nestor & Rogers, 2007), there is now also a considerable body of literature aiming to understand the neural correlates of a semantic memory deficit in AD.

For many years, the semantic memory decline in AD was thought to be a secondary cognitive deficit to the prominent episodic memory deficit that defines this disease, occurring at a late stage when pathology has begun to affect the neocortex significantly (Hodges & Patterson, 1995; Graham & Hodges, 1997). Several studies however, as previously discussed, have now shown that there is a considerable semantic deficit present in AD patients in the earliest stages of disease, even prior to any other observable cognitive decline (Snowdon *et al*., 1996; Garrard *et al*., 2005; Vogel *et al*., 2005; Joubert *et al*., 2008; Ameiva *et al*., 2008; Le *et al*., 2011; Joubert *et al*., 2020). In line with these findings, recent evidence from neuroimaging studies into the neural basis of semantic dysfunction in AD and MCI patients has highlighted a central role of aMTL degradation, occurring early in the AD pathological cascade. Specifically, studies in this area have, in accordance with neuroanatomical theories of semantic processing systems (Mishkin *et al*., 1997; Didic *et al*., 2011), found that semantic memory processing in AD patients, unlike episodic memory, appears to correlate most strongly with structures of the aMTLs such as the transentorhinal cortex, PRC and ERC, affected prior to significant hippocampal involvement.

2.2. The Neural Correlates of Semantic Memory Processing Throughout the Course of Disease Progression in Alzheimer's Disease: A Systematic Review

2.2.1. Aim of Current Review

In light of previously discussed findings, the current review aims to summarise the evidence from existing literature that may answer the question of which neuropathological changes in preclinical, prodromal and early AD dementia contribute to the well documented semantic deficit in these groups. The scope of the current review, therefore, includes studies assessing the neural correlates of semantic memory function, reflected by neuroimaging in

functional, structural or molecular modalities, among populations at varying stages of AD from preclinical/genetically predisposed through to the dementia stages.

2.2.2. Review Question

1. What are the neural correlates of semantic memory processing deficits in Alzheimer's disease?
2. How do these proposed neural correlates change between disease stages?

2.2.3. Methods

2.2.3.1. Search Strategy

An initial literature search was conducted on the 15th December 2017. Databases searched were Web of Science, Scopus and PubMed. Initial searches identified 1417 records, 1075 following removal of duplicates. The search terms used were Alzheimer OR MCI OR "mild cognitive impairment" AND Semantic in titles, abstracts and key words. Only full length, English language, empirical studies were included for review and so a further 119 were discounted on account of being foreign language (32), meeting abstracts (60), reviews (17) or non-studies such as editorials, book chapters, commentaries etc. (10). Follow-up searches were conducted on 28th May 2019 using the same websites and search terms while limiting the results to the years 2017, 2018 and 2019. A further 940 studies were identified that were reduced to 533 following removal of duplicates. Again, following this search, another 21 papers were removed due to the previously listed exclusion criteria. As outlined in ***Fig. 2.3***, the full texts of 421 studies were retrieved for assessment.

2.2.3.2. Study selection, inclusion and exclusion criteria

All studies were subject to eligibility assessment conducted by a single individual researcher performed in an unblinded manner and recorded in an excel sheet with corresponding study ID numbers. Studies were initially screened based on the title and abstract and then full texts were further screened according to inclusion and exclusion criteria. Following screening, data from each study were extracted and entered into a table in excel. Information about exclusion and inclusion criteria can be found in **Table 2.1.**

Table 2.1

Table showing inclusion and exclusion criteria for study identification

Criteria	Included	Excluded
Participants	Adults diagnosed with MCI or mild AD as per standardised diagnostic criteria. Adults considered preclinical or 'at-risk' due to family history, genetics, amyloid load or cognitive profile. Cognitively normal controls (MMSE >24 or CDR 0)	MMSE < 18 CDR ≥2 GDS ≥3 MDRS <115
Neuropsychological Tests	Appropriate tasks accepted as reliable tests of semantic memory or processing e.g. Face/Item Recognition Verbal Fluency Semantic Priming Semantic Interference Naming Lexical Discrimination Word Definition Matching	Any tests not directly testing semantic memory or likely to be heavily confounded by other cognitive processes.
Neuroimaging	T1/T2 Weighted Structural or Functional MRI PET DTI Regionally defined Tau PET and Amyloid PET	Electrophysiology methods without MRI validated regional specificity Biomarker imaging without regional specificity
Pre-processing	Standardised pre-processing procedures should have been followed.	
Analysis/Outcome Measures	Differences between patient groups in measures of semantic memory function, brain structure or function or the relationship between the two variables Relationship between semantic memory function and brain structure or function within individual patient groups T-Tests ANOVA ANCOVA Linear Regression Multiple Regression (correlation between semantic test and brain structure/function) Non-parametric alternatives to the above in the case of non-normally distributed data.	

MMSE, Mini Mental State Examination (Folstein, Folstein and McHugh 1975) CDR, Clinical Dementia Rating Scale (Morris 1997), GDS, Global Deterioration Scale (Reisberg, Ferris, de Leon and Crook 1982), MDRS, Mattis Dementia Rating Scale (Mattis 1976,1988), PET, positron emission tomography, DTI, diffusion tensor imaging, ANOVA, analysis of variance, ANCOVA, analysis of covariance

2.2.3.3. Data Extraction

Data from the studies included in this review were recorded in a data extraction excel sheet. This included: Study ID no., Authors, Year, Title, no. of participants (ApoE-ε4, SCD, MCI, AD and controls), disease severity of patients (mean MMSE, Clinical Dementia Rating [CDR] or Mattis Dementia Rating Scale [MDRS] scores), type of neuroimaging used, semantic memory tasks of significance and proposed neural correlates.

2.2.4. Results

2.2.4.1. Details of Excluded and Included Studies

During the initial screening phase, 988 studies were removed based on the title and abstract. Following initial screening, full texts were assessed for their compliance to exclusion and inclusion criteria. A further 378 studies were excluded based on their methods, participants and background discussions. During this phase, an additional seven texts were included that had been found in the reference lists of studies found through initial literature searching or discovered post initial search. Following screening phases, 50 publications passed all criteria and were retained for data extraction. Details of the process of study inclusion and exclusion can be found in ***Fig. 2.3***. Details of each of the studies included for review can be found in **Tables 2.2-2.5**.

Of the fifty publications identified for further consideration, the majority were focussed on semantic memory in MCI cohorts (19/50), while the least commonly studied experimental group was those described here as 'preclinical' (which would have emerged in the search results thanks to the term 'Alzheimer' as *'preclinical Alzheimer's'* or *'presymptomatic Alzheimer's'* etc.). Studies involving these individuals made up only seven of the final 50 (***Fig. 2.4***). Furthermore, more than half of studies identified within the literature used structural imaging techniques as opposed to functional, with a small percentage employing the use of both and only four studies utilising biomarker imaging either alone or in conjunction with further structural analysis (***Fig. 2.4***).

Almost all studies included were case-control studies, including a control group, with only six considering the patient groups alone either in isolation (Apostolova *et al*., 2008; Frings *et al*., 2011; Meyer *et al*., 2013; Loewenstein *et al*., 2017b; Curiel *et al*., 2018) or categorised into sub-groups according to amyloid positivity (Loewenstein *et al*., 2018a) or performance (Frings *et al*., 2011). In the case of Frings *et al*. (2011), the need for a control

group was eliminated by the use of standardised norms to categorise patients into normal and pathological performers for analysis (Berres *et al*., 2000). As a replication study, Loewenstein *et al*. (2017b) aimed to determine the extent to which they could replicate the results of their original study (Loewenstein *et al*. 2017a) in an independent patient group. The original study included a control group. The remaining studies could be described as cohort studies, although the participants were not followed up in time. The mean number of controls in each group was 31 with a median of 19 and a range of four to 183. The mean number of patients in each separate experimental group was 28 with a median of 20 and a range of six to 145.

All studies were cross-sectional, with the exception of two that utilised longitudinal imaging data (McDonald *et al*., 2012; Hirni *et al*., 2016).

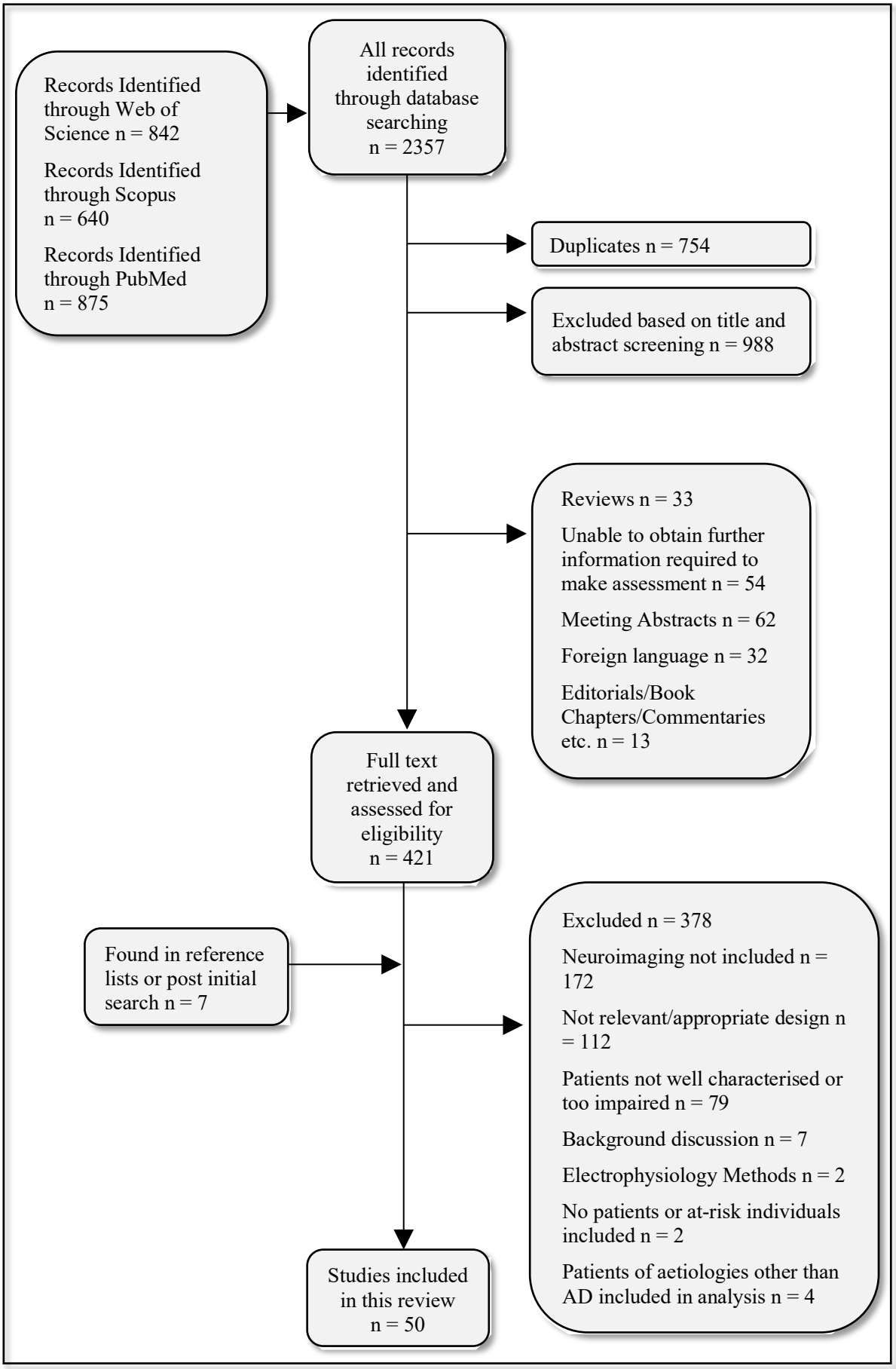


Figure 2.3. *Flowchart depicting the process of study inclusion and exclusion*

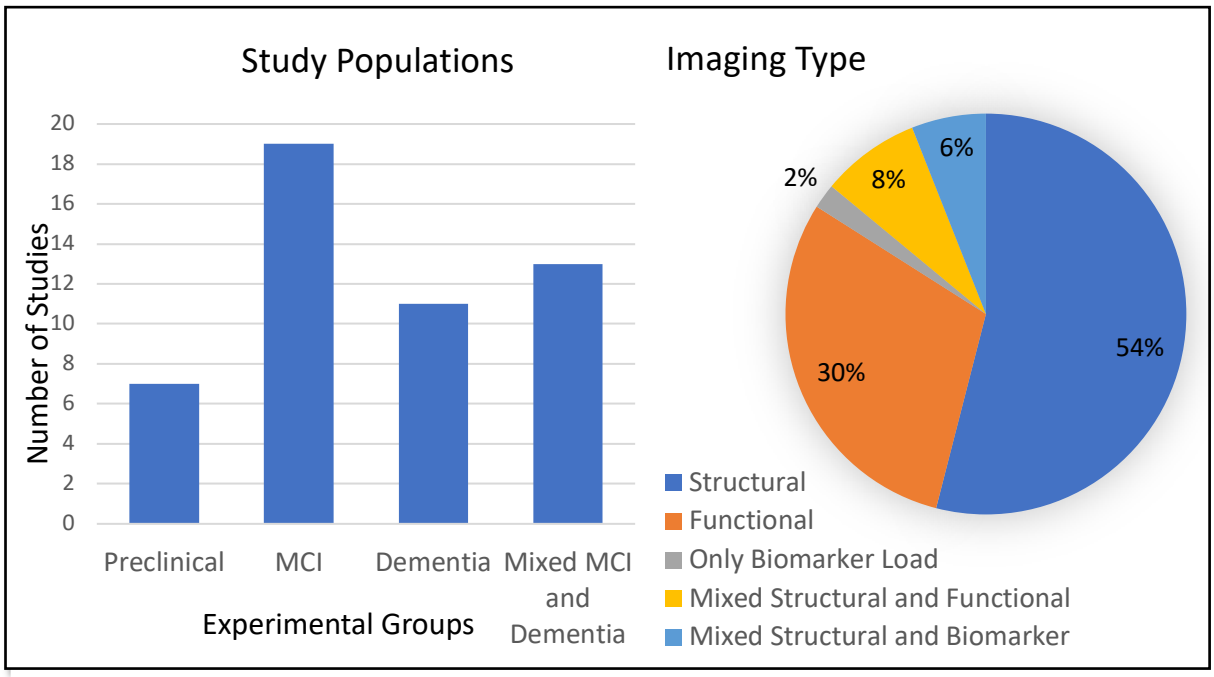


Figure 2.4. *Left: bar chart showing the different classes of disease severity and the number of studies that included experimental groups belonging to each class. Right: pie chart showing the percentage of studies utilising each imaging technique as the primary measure of interest.*

Table 2.2 *Table showing characteristics of imaging studies in preclinial populations. (number of participants included in imaging analysis).*

Preclinical Populations

Study	Participants (N)						Neuroimaging	Semantic Memory Test of Significance	Behavioural Findings	Neural Correlates
	SCD	O-LOAD	ApoE-ε4 Carriers	MCI	AD	HC				
Seidenberg *et al*., 2009		23	23 (Plus FH)			23	Event-related fMRI	Famous name discrimination	• No differences found between groups on any neuropsychological tests including fMRI task.	• FH+ε4 and FH groups: Increased MR signal in multiple regions for famous vs unfamiliar names. • HC: Increased signal present only for unfamiliar relative to famous names. • 11 fROIs exhibited greater activity for famous than unfamiliar names. • FH+ε4 and FH groups: significantly greater MR signal intensity than HC in bilateral precuneus/PCC, bilateral MFC, left AG and right MTG. • FH+ε4 group: Significantly greater activity than FH and HC in right middle frontal region.
Woodard *et al*., 2009			19 (Plus FH)	19		19	Event-related fMRI	Famous name discrimination	• No difference between groups on discrimination performance	• At-risk and MCI: Significantly greater percent signal change than HC in 8 of 14 ROIs including MTL, TPJ, PCC/precuneus. • MCI: Greater activation than HC in frontal regions • At risk and MCI: Increased activity in H (when atrophy controlled).
Hirni *et al*., 2016					28	28	MRI	German CVLT (EM) and CF	• Estimated mPRC and ERC functioning (using CF/CVLT) • Significantly different in HC who converted to AD12 years preceding diagnosis.	• Both CF and CVLT significantly predict mPRC thickness. • CVLT only significant predictor of ERC volume.
Loewenstein *et al*., 2016	33: 18 SCD (11), 15 PreMCI (3)			29 (10)		31 (7)	Florbetapir PET	LASSI-L	• MCI, PreMCI and SCD: Significant deficits in recovery/compensation for PSI (Recall B2) compared with HC	• At-Risk: Recovery from PSI (B2 Recall) most highly associated with total amyloid and regional amyloid in ACC, PCC, precuneus and frontal lobes (not <.01). Initial learning also associated with these areas to similar or lesser extent. • MCI patients included: All measures (not including cued A3 measures) associated with total amyloid load. B2 most strongly correlated with regional loads in all areas (least significant [not <.01] in frontal lobes) Initial learning: Significant associations with amyloid in ACC and precuneus. Cued A3 associated with ACC.

Table 2.2 Cont.

Sánchez et al., 2017	21	20	fMRI	LASSI-L	• O-LOAD: Lower scores on delayed recall of List A targets on the LASSI-L and greater intrusion errors during 1B Cued Recall and 2B Cued Recall suggesting difficulties in PSI and frPSI. • 10/21 O-LOAD had more than 1 intrusion error on List 2B recall 0/20 HC had more than 1 intrusion error.	• O-LOAD: Lower connectivity between ERC and OFC, ACC, and ATL than HC. B2 cued recall negatively correlated with connectivity between anterodorsal thalamus and contralateral PCC. B2 cued intrusions negatively correlated with connectivity of H, insular, PCC, DLPFC, precunei and anterior thalamus. • HC: B2 cued recall negatively correlated with connectivity between right ERC and insula.
Crocco *et al*., 2018	49 (23)	117 (53)	MRI	LASSI-L	• PreMCI participants evidenced greater LASSI- L deficits, particularly with regards to frPSI and delayed recall, relative to the CN group.	• Combined HC and preMCI group: frPSI uniquely related to increased dilatation of inferior lateral ventricle and decreased volume in the H, precuneus, superior parietal region, superior frontal, superior temporal, ERC, rostral middle frontal, PCC and SMG.
Abulafia *et al*., 2018	27	18	MRI, PET-PiB	LASSI-L	• O-LOAD: Performed worse in delayed RAVLT, as well as frPSI measures compared with HC. • After controlling for FDR only RAVLT delayed recall and LASSI-L B2 cued intrusions remained significantly different between groups.	• O-LOAD: frPSI measures related to greater cortical thickness in left medial occipital cortex and right SFG, precentral and postcentral gyrus. B2 cued intrusions (indicative of frPSI) negatively correlated with cortical thickness at level of left medial posterior parietal cortex, left temporo-occipital cortex, and right SFG. • HC: frPSI measures associated with greater cortical thickness in right OFC and left precentral and MFG. B2 cued intrusions not correlated with cortical thickness. • Recovery from retroactive semantic interference positively correlated with amyloid load in left temporal lobe in O-LOAD but not HC.

Note: ACC, anterior cingulate cortex; AD; Alzheimer's Disease; AG, Angular Gyrus; ATL, anterior temporal lobe; CF, Category Fluency; CVLT, California Verbal Learning Test; EM; episodic memory; ERC, entorhinal cortex; FDR, false discovery rate; FH, family history; fMRI, functional magnetic resonance imaging; fROI, functional region of interest; frPSI, failure to recover from proactive semantic intrusions; H, hippocampus; HC, healthy controls; LASSI-L, Loewenstein-Acevedo Scales for Semantic Interference and Learning; MCI, mild cognitive impairment; MFC, medial frontal cortex; MFG, middle frontal gyrus; mPRC, medial perirhinal cortex; MRI, magnetic resonance imaging; MTG, middle temporal gyrus; MTL, medial temporal lobe; OFC, orbitofrontal cortex; O-LOAD, offspring of late ons*et al*zheimer's disease; PCC, posterior cingulate cortex; PET, positron emission tomography; PRC, perirhinal cortex; PSI, proactive semantic intrusions; RAVLT, Rey Auditory Verbal Learning Test; ROI, region of interest; SFG, superior frontal gyrus; SI, semantic intrusions; SCD, subjective cognitive decline; SMG, supramarginal gyrus; TPJ, temporo-parietal junction; VF, verbal fluency

Table 2.3 *Table showing characteristics of imaging studies in MCI patients (number of participants used in imaging analysis).*

MCI Populations

Study	Participants (N)			Neuroimaging	Semantic Memory Test of Significance	Behavioural Findings	Neural Correlates
	MCI	AD	HC				
Venneri *et al*., 2011	14 (ApoE) 14 (non)		11	MRI	Lexical-Semantic Assessment, CF	• Significant differences seen in CF (P<0.01) between MCI e4 -carriers and noncarriers and HC. • Age of acquisition values of both MCI subgroups significantly different from HC.	• MCI e4 carriers: Tendency to retrieve earlier acquired words in CF task related to reduced volumes in left H, bilateral regions of uncus, and PCC • MCI noncarriers: Poor semantic performance related to reduced volumes in left uncus, bilateral regions of the PHG and H as well as a large number of neocortical regions.
Frings *et al*., 2011 (only MCI group imaging considered)	115	77		MRI	BNT	• Dementia group performed significantly worse than MCI on BNT	• MCI: Normal > Pathological performers in BNT: GMV in left ATL (anterior ITG)
Atienza *et al*., 2011	32		29	MRI	Biographical matching and conceptual priming of famous faces	• MCI: Performed similarly to HC in biographical matching task but accuracy on conceptual priming significantly less improved by semantically congruent cues.	• Semantic priming across groups correlated (at an uncorrected significance level) with volumes in the right ERC. • In MCI patients semantic priming positively correlated with ERC and negatively correlated with CA hippocampal volume reduction.
McDonald *et al*., 2012	103		90	MRI	BNT and CF	N/A	• MCI: BNT decline associated with 2-year atrophy rates within left ITG, left TP, left FG, and left PHG. • CF decline associated with atrophy rates within left lateral temporal, right lateral temporal, left ACC and left prefrontal lobar regions. • Left temporal lobe atrophy rates associated with naming decline, whereas bilateral temporal, left frontal, and left ACC atrophy rates associated with CF decline.
Barbeau *et al*., 2012	29		29	MRI/SPECT	Famous face naming, Info WAIS, Didactic Acquisition Questionnaire, Short EVE, Semantic Memory Composite Z score	MCI patients were impaired on all measures of semantic memory.	• MCI: Composite SM Z score correlated with reduced volume (compared to HC) in bilateral PRC, ERC and anterior H as well as left ACC and bilateral STG • Composite Z score correlated with SPECT perfusion in H, ERC and PRC.

Table 2.3 Cont.

van der Meulen *et al*., 2012	13	15	fMRI	Picture-pair memory task	• MCI: significantly lower accuracy and higher reactions times than HC. Significantly worse than HC when target picture paired with old foil relative to trials with new foil. (Deficit in both familiarity and recollection but recollection more severely impaired.) HC: significantly more errors in recognition of semantically related than unrelated pairs. No such difference in MCI.	• MCI: Network activity in bilateral middle/IFG, anteriorand PCC, superior MFC, insula, caudate, and precuneus, significantly less active in patients compared with HC during associative recognition. • During encoding of unrelated versus related picture pairs, HC showed differential activation in left-hemisphere network including PHG, inferior frontal cortex, and inferior temporal cortex. MCI showed much less activation.
Meyer *et al*., 2013	25		MRI	BNT and CF	N/A	• Performance on BNT and CF significantly correlated with reduced WMV in PRC, PHG and ERC regions.
Gardini *et al*., 2013	14	16	MRI	CF, visual naming, naming from definition of objects, actions and famous people, word-association for early and late acquired words and reading task	MCI: Scored more poorly in all tasks of naming, overall reading and reading of famous names, had fewer correct immediate recalls and more correct responses with cue in famous people naming, made more errors in naming and in naming from definition task for famous people.	• CF and Word Association: More extensive involvement of subcortical regions • Visual Naming: more contribution of frontal than temporo-parietal areas
Catricalà *et al*., 2015	8	16	fMRI	Picture Naming, Word Reading	Only main effect of task significant with naming less accurate than reading	• Picture Naming: Increased activity in MCI relative to HC in left postcentral gyrus, IPL, SMG, right SPL, postcentral and precentral gyri and Heschl gyrus (naming picture in heterogenous sets) • Word Reading: Increased activity in MCI relative to controls in right precuneus and precentral gyrus
Gardini *et al*., 2015	21 (16)	21 (20)	fMRI	CF, visual naming, naming from definition of objects, actions and famous people, word-association for early and late acquired words and reading task	MCI: Significantly impaired relative to HC on CF, visual naming, naming from definition, word association and reading	• MCI: Increased DMN connectivity between medial prefrontal regions and PCC and between PCC and PHG and anterior H relative to HC. A significant negative correlation was present between visual naming performance and mPFC connectivity between PHG and posterior H.

Table 2.3 Cont.

Peter *et al*., 2016	20		30	MRI	CF	MCI: Significantly impaired on CF compared with HC both on number of words produced and use of clustering and switching	• MCI: CF related to GMV in SFG and IFG. Switching related to bilateral SFG and right IFG. • HC: CF related to IFG only. Switching related to GMV in left IFG.
Chen and Chang, 2016	22		25	MRI	Word Association Task	MCI: significantly impaired on CF relative to HC. Also demonstrated lower associative discriminability on word association task and increased false alarm rate.	• Combined group: Discriminability of associative memory correlated with grey matter integrity of H and an aggregate MTL ROI (including H, PHG and ERC) • Semantically related false alarms across groups significantly correlated with integrity of lateral prefrontal regions and H.
Hirjak *et al*., 2017	38	38	31	MRI	Semi-Structured Interview	• Significant difference in semantic AM (SAM) observed for each life-time period. • MCI: Significantly impaired in SAM from childhood compared to HC. Similar increase in SAM from adulthood as HC. AD: Significantly impaired in SAM from adulthood compared to HC. SAM from last five years significantly impaired compared to MCI and HC.	• Semantic and episodic AM deficits associated with bilateral H atrophy in CA1, CA2-3, presubiculum, and subiculum. • Episodic, but not semantic AM loss associated with reduced cortical thickness in bilateral PHG and ERC. • In MCI, episodic, but not semantic AM deficits associated with alterations of CA1, presubiculum and subiculum.
Loewenstein *et al*., 2017a	29		38	MRI	LASSI-L, CF	MCI: Significant failure to recover from PSI and significantly impaired on a CF task compared with HC	• CF scores: positively correlate with ITL volume. • frPSI: Related to reduced volumes in H, precuneus, inferior temporal lobe, SPL, rostral middle frontal and temporal pole and with increased inferior lateral ventricle dilatation in MCI patients. • HC: only increased inferior lateral ventricle size associated with frPSI
Loewenstein *et al*., 2017b	45			MRI	LASSI-L	N/A	• frPSI: Related to reduced volumes in H, ERC, precuneus, TP, SPL and inferior temporal lobe and with increased dilatation of inferior lateral ventricle • Association with cortical thickness in ERC, precuneus and TP also observed.

Table 2.3 Cont.

Pineault *et al*., 2018	14	14	MEG/MRI	Famous Face Occupation Matching Task	MCI: significantly slower and less accurate on SM task	• MCI patients: Significant hyperactivation (and some hypoactivation) relative to controls in a number of regions of semantic network. Correlations between functional hyper/hypoactivation and cortical thickness suggest functional changes precede atrophy in this group.
Curiel *et al*., 2018	33		MRI/ Florbetaben PET/CT	LASSI-L	N/A	• frPSI: Related to greater total amyloid load and lower overall cortical thickness. • SI: Highly associated with reduced cortical thickness in left ERC and left mOFC
Loewenstein *et al*., 2018a	88: Aβ+ 34, Aβ-(SNAP) 29, Aβ-Non-AD 25		MRI/ Florbetaben PET/CT	LASSI-L	N/A	• SI on measures of PSI and frPSI, distinguished Aβ+ AD versus SNAP and non-AD cases. • SI: Negatively associated with reduced GMV in ERC, SMG and superior temporal regions. No such associations observed in SNAP or non-AD cases.
Venneri *et al*., 2019	50	50	MRI	CF, Prose Memory	MCI: Significantly worse than HC prose memory test and CF	• CF: Accounted for independent portions of volumetric variability in bilateral H and left PRC in addition to predictive strength of Rey-Osterrieth Figure. Also accounted for independent portion of volumetric variability in left H in addition to prose memory. • Prose memory: Accounted for independent portions of volumetric variability within almost all regions.

Note: ACC, anterior cingulate cortex; AD; Alzheimer's Disease; AM, autobiographical memory; ATL, anterior temporal lobe; BNT, Boston Naming Test; CF, Category Fluency; CT, computerised tomography; CVLT, California Verbal Learning Test; DMN, default mode network; ERC, entorhinal cortex; FG, fusiform gyrus; fMRI, functional magnetic resonance imaging; frPSI, failure to recover from proactive semantic intrusions; GMV, grey matter volume; H, hippocampus; HC, healthy controls; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LASSI-L, Loewenstein-Acevedo Scales for Semantic Interference and Learning; MCI, mild cognitive impairment; MEG, magnetoencephalography; MFC, medial frontal cortex; MFG, middle frontal gyrus; mOFC, medial orbitofrontal cortex; mPFC, medial prefrontal cortex; mPRC, medial perirhinal cortex; MRI, magnetic resonance imaging; MTG, middle temporal gyrus; MTL, medial temporal lobe; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PET, positron emission tomography; PRC, perirhinal cortex; PSI, proactive semantic intrusions; RAVLT, Rey Auditory Verbal Learning Test; ROI, region of interest; SFG, superior frontal gyrus; SI, semantic intrusions; SM, semantic memory; SMG, supramarginal gyrus; SNAP, suspected non-Alzheimer pathology; SPECT, single-photon emission computed tomography; SPL, superior parietal lobule; TP, temporal pole; WAIS, Wechsler Adult Intelligence Scale; WMV, white matter volume.

Table 2.4 *Table showing characteristics of imaging studies in AD patients*

AD Dementia Populations

Study	Participants (N)		Neuroimaging	Semantic Memory Test of Significance	Behavioural Findings	Neural Correlates
	AD	HC				
Saykin *et al*., 1999	9	6	fMRI	Semantic Decision Tasks	• AD: Impaired on *category-exemplar* task but not on *category-function* relative to HC. Also impaired relative to HC on BNT and CF.	• AD: Category-function task - Additional activation foci in left DLPFC and bilateral cingulate relative to HC. Category-exemplar task – Additional foci in bilateral mPFC, left postcentral gyrus and putamen relative to HC, positively correlated to performance.
Lekeu *et al*., 2003	31	31	FDG-PET	FCRT	• AD: Significantly impaired on FCRT measures compared to HC	• AD: Impaired performance on cued recall significantly correlated with reduced glucose uptake in bilateral PHG
Rinne *et al*., 2003	9	8	H2(15)O-PET	Category-specific word-matching task	• AD: Significantly longer RTs than HC	• AD: Increased activation compared with HC in left frontal lobe, right occipital cortex, midbrain and cerebellum bilaterally in response to the semantic task compared with non-semantic baseline
Grossman *et al*., 2003	11	16	fMRI	Word Pleasantness Judgement	• AD: Impaired on CF, confrontation naming and semantic judgement compared to HC. Performed same as HC on pleasantness judgement.	• AD: Less recruitment compared with HC in left posterolateral temporal, lateral frontal and occipital regions and right temporal and caudate regions during pleasantness judgement for both categories. • AD showed greater recruitment compared with HC in left inferior temporal lobe
Zahn *et al*., 2004	11	11	FDG-PET	Naming, PPT	• AD: All patients significantly impaired on CF. 8/11 impaired on naming. 4/11 impaired on PPT.	• Combined group: Metabolism in left ATL, posterior inferior temporal lobe, inferior parietal and medial occipital areas positively correlated with both verbal and nonverbal semantic performance • AD: Single cases revealed significant association between naming impairment and left hemispheric asymmetry of hypometabolism.
Giffard *et al*., 2008	17	15	FDG-PET	Lexical Decision Task	• No significant difference in semantic priming between groups but longitudinal data revealed reductions in semantic priming in AD in second session. • AD patients: Significantly impaired on CF compared with HC.	• AD: Semantic priming associated with reduced metabolism of bilateral STG, especially right side (p .001). CF positively correlated with metabolism in left ITG and MTG, encroaching upon left STG at .01 threshold.

Table 2.4 Cont.

Venneri *et al*., 2008	25	25	MRI	CF	• AD: Produced significantly fewer words, more typical and acquired earlier in life than HC.	• AD: Linguistic production deficits positively correlated with GMD in variety of areas, especially areas of PRC and PHG.
McGeown *et al*., 2009	29	19	fMRI	Word version of PPT	• AD: Significantly lower accuracy and longer RTs than both young and old HC groups. • No differences between young and old HC groups.	• AD whole group: Activated only left PFC and cingulate cortex in response to semantic task. Deactivation pattern similar to older HC. Less activation in left MFG and bilateral IFG compared with older HC. Older HC showed greater deactivation of bilateral MFG. • AD High performers: Significant activation only in left PFC. Significantly deactivated anterior midline frontal structures. • AD Low performers: Significant activation in wider PFC than high performers and left MFG. Failed to deactivate anterior midline structures.
Domoto-Reilly *et al*., 2012	145	183	MRI	BNT	• AD: Performed worse on BNT than HC but considerable range in naming ability with 59% of AD patients scoring within normal range.	• ROI Analysis: Specific correlation between cortical thinning of left ATL and impaired naming performance.
Rodríguez-Aranda *et al*., 2016	18	24	MRI/DTI	VF	• AD: Greater semantic intervals and less semantic and phonemic accuracy than HC.	• Combined MRI: VF accuracy positively correlated with GMV in left IFG (Broca's area), left insular and bilateral H and PHG. Semantic accuracy also associated with GMV in ACC and PCC, bilateral caudate and cerebellar crus II region. • Semantic accuracy in AD group: Correlated with GMV more strongly than HC in left amygdala, bilateral putamen and tectum • Combined DTI: Semantic accuracy uniquely correlated with FA in right IFOF and right SLF. Semantic accuracy uniquely correlated with MD in right cingulum.
Mascali *et al*., 2018	38	19	fMRI	Object Naming	• AD significantly worse on object naming than HC	• AD: Altered functional connectivity in pars opercularis and in posterior MTG (reduced connections to areas of semantic network). • HC: pMTG demonstrated connectivity with bilateral frontal and temporal regions as well as left parietal cortex related to naming while AD only showed connections with temporal regions.

Note: ACC, anterior cingulate cortex; AD; Alzheimer's Disease; ATL, anterior temporal lobe; BNT, Boston Naming Test; CF, Category Fluency; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; ERC, entorhinal cortex; FA, fractional anisotropy; FCRT, free and cued recall test; FDG-PET, fluorodeoxyglucose positron emission tomography; fMRI, functional magnetic resonance imaging; GMD, grey matter density; GMV, grey matter volume; H, hippocampus; HC, healthy controls; IFG, inferior frontal gyrus; IFOF, inferior fronto-occipital fasciculus; ITG, inferior temporal gyrus; MCI, mild cognitive impairment; MD, membrane density; MFG, middle frontal gyrus; mPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PPT, Pyramids and Palm Trees; PRC, perirhinal cortex; ROI, region of interest; RT, reaction time; SLF, superior longitudinal fasciculus; STG, superior temporal gyrus; VF, verbal fluency.

Table 2.5 *Table showing characteristics of imaging studies in combined AD dementia and MCI patient groups. (number of participants used in imaging analysis).*

Combined Dementia and MCI Populations

Study	Participants (N)			Neuroimaging	Semantic Memory Test of Significance	Behavioural Findings	Neural Correlates
	MCI	AD	HC				
Apostolova *et al*., 2008	5 (converters)	19		MRI	CF, BNT	N/A	• BNT: Positive correlations with GMV in posterior MTG and ITG, temporo-occipital and parieto-occipital association cortices, bilateral posterior MFG and SFG, right BA 46, 10 and 44 as well as left sensorimotor strips, posterior IFG, FG and right TP. Strong correlations also seen in bilateral ERC, ACC, and mesial OFC • CF: Also showed positive correlations with posterior SFG and MFG, somatomotor cortex, ACC and left posterior temporal association regions. No correlation in right TP. More strongly correlated with parietal association cortices than BNT. Visual association cortices more strongly correlated with BNT.
Joubert *et al*., 2010	15	16	16	MRI	Naming Objects and Famous People	• AD and MCI: Significantly impaired relative to HC on CF and naming of both objects and famous people	• AD and MCI: SM positively correlated with GMV in left ATL and left inferior PFC • MCI alone: Correlation in ATL and inferior PFC persisted
Balthazar *et al*., 2010	17	15	16	MRI	BNT	• AD: Worse than both aMCI and HC on total BNT score and spontaneous naming. • MCI: Only worse than HC on spontaneous answers.	• Combined group: Significant positive correlations between circumlocutory errors and GMD of TP, right ITG and left MTG. Significant positive correlation between coordinate errors and bilateral TPs.
Gigi *et al*., 2010	6	6	4	MRI/fMRI	General information (WAIS), CF, Object Naming (fMRI analysis)	• AD: Significantly impaired relative to MCI and HC in all tests. • MCI: Performed similarly to HC in all semantic tests	• MCI: Normal semantic performance associated with over activity in DLPFC and right H but reduced activity in parietal lobes compared with HC. • AD: SM elicited reduced brain activation in all ROIs (BA 7 and 40, DLPFC, H formation and FG) compared with HC.
Santos *et al*., 2011	60	34	32	MRI	CF, BNT	• AD and MCI: Significantly impaired on both CF and BNT compared with HC	• Combined group: CF positively correlated with GMD in left DLPFC, STG and right thalamus, while naming positively correlted with bilateral temporal cortex, including H.

Table 2.5 Cont.

Balthazar *et al*., 2011	17	15	16	MRI	BNT	• AD: Worse than both MCI and HC on total BNT score and spontaneous naming. • MCI: Only worse than HC on spontaneous answers.	• BNT scores: Positively correlated with GMD in right thalamic LDN, left thalamic MDN, pulvinar, bilateral H, bilateral PHG, left STG, left IFG, bilateral SFG, left MFG, and left precuneus. • Semantic errors: Negatively correlated with bilateral ATL, (inc STG; MTG and left ITG) bilateral H and right PHG, bilateral thalamic LDN and MDN and regions of basal ganglia.
Rodríguez-Ferreiro *et al*., 2012	13	14	13	MRI	CF, Picture Naming, Word-Picture Matching, Picture-Word Matching	• AD: Significantly impaired compared with HC on both retrieval and association batteries using objects and faces • MCI: Significantly impaired with HC on retrieval of objects but no impairment on either face-based battery	• HC: SM positively correlated with widely distributed bilateral network primarily including temporal, parietal and frontal lobes. • MCI: Objects battery showed similar widespread positive correlation as in HC but face battery correlations restricted to regions of fronto-temporal cortex (MFG, STG, MTG) • AD: Both face and object association tasks positively correlated only with GMV in right MTG. Face based retrieval positively correlated with right TTG, FG, STG, MTG and ACC.
Kivisaari *et al*., 2012	11	15	14	MRI	Picture Naming	• AD and MCI: Significantly impaired on naming task compared to HC.	• Combined group: Overall naming only significantly positively correlated with GMV of H. • Reduced volume in mPRC associated with poorer naming of living than non-living things.
Hirni *et al*., 2013	32	10	130	MRI/DTI	BNT and CF	• MCI and AD: Significantly impaired, relative to HC, on CF and BNT	• VBM: SM performance across combined cohort positively correlated with GMV in bilateral mPRC, ERC and H head when controlling for EM. • FA analysis: SM performance across cohort positively correlated with WMV in aILF.
Grossman *et al*., 2013	18 (4 for DTI)	15 (6 for DTI)	18	fMRI/DTI	Shared Feature Judgment	• Patients (AD and MCI combined): Significantly impaired on feature judgement for natural objects and to a lesser extent manufactured objects (p=.051) compared with HC	• Patients: Performance positively correlated with GMD in multiple regions of temporal, frontal and parietal cortex with significant overlaps between areas of GMD involved in natural kinds feature judgement and activation in HC (i.e. in PFC and TOC). Little correspondence found between patients GMD correlations with manufactured feature judgement and activations in HC. Performance associated with reduced connection between PFC and TOC compared with HC. • fMRI in HC: Both natural and manufactured conditions positively correlated with activations in bilateral PFC and TOC and left parietal cortex. Significantly greater activation for manufactured objects in left MTG and IFG and greater activation for natural kinds in left AG.

Table 2.5 Cont.

Eastman *et al*., 2013	40	10	9	MRI	CF	• AD: Significantly impaired on both fluency tasks compared with HC and MCI • MCI: Only significantly impaired on animal fluency task compared with HC	• Animal CF: Positive correlation with GMV in bilateral IPL, STG, premotor cortex and DLPFC. More diffuse correlations in left lateral and medial frontal cortex and right temporo-occipital cortex. (In combined group) • Vegetable CF: More diffuse correlations than animal fluency. Positive correlations with GMV in bilateral IPL, premotor and DLPFC. More diffuse correlations in left lateral frontal, medial frontal, lateral temporal, medial parietal and peristriate cortices as well as right temporoparietal and lateral visual association cortex.
Carter *et al*., 2014	12	8	13	MRI/DTI/FDG-PET	CF	• AD and MCI: Significantly impaired on CF compared with HC • AD also significantly impaired on naming	Across combined group: • CF positively correlated with FDG-uptake in temporoparietal cortex and left cuneus/PCC (more extensively correlated than EM measures) • CF positively correlated with GMV in ATL and medial frontal regions. • CF positively correlated with glucose metabolism in posterior temporal and inferolateral parietal cortices
Yap *et al*., 2017	12	18	31	fNIRS	CF	• AD: Significantly impaired on all CF tasks compared to HC. • MCI: Impaired on all but animal CF tasks.	• No results statistically significant when controlling for multiple comparison • HC: Shorter time to achieve target activation level in left PFC during CF compared with MCI and AD. • MCI: Greater mean activation in PFC than HC. Shorter time to achieve target activation level in right PFC than HC and AD. • AD: Least mean activation in PFC. Shorter time to achieve target activation level in left PFC than MCI but longer time in right PFC than both MCI and HC

Note: ACC, anterior cingulate cortex; AD; Alzheimer's Disease; AG, angular gyrus; aILF, anterior inferior longitudinal fasciculus; ATL, anterior temporal lobe; BNT, Boston Naming Test; CF, Category Fluency; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; EM, episodic memory; ERC, entorhinal cortex; FA, fractional anisotropy; FDG-PET, fluorodeoxyglucose positron emission tomography; FG, fusiform gyrus; fMRI, functional magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; GMV, grey matter volume; H, hippocampus; HC, healthy controls; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LDN, lateral dorsal nucleus; MCI, mild cognitive impairment; MDN, medial dorsal nucleus; MEG, magnetoencephalography; MFG, middle frontal gyrus; mPRC, medial perirhinal cortex; MRI, magnetic resonance imaging; MTG, middle temporal gyrus; MTL, medial temporal lobe; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PRC, perirhinal cortex; SFG, superior frontal gyrus; SI, semantic intrusions; SM, semantic memory; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG; superior temporal gyrus; TOC, temporo-occipital cortex; TP, temporal pole; TTG, transverse temporal gyrus; VBM, voxel based morphometry; WAIS, Wechsler Adult Intelligence Scale; WMV, white matter volume.

2.2.5. Discussion

2.2.5.1. Preclinical Cohorts

The least represented groups, in studies of this nature within the literature, were those considered to be pre-clinical or at-risk based on family history of disease, SCD, or genetic predisposition. This is likely due to the ambiguity of such classifications, and the lack of apparent cognitive decline among these individuals. Seven of the 50 studies included for review, however, did investigate how underlying changes in brain structure or function may mediate the sustained or already impaired semantic memory processes, even in these very early disease stages. Among these, there was an even split in imaging techniques between structural and functional MRI methods, with three studies utilising each and 1 using biomarker imaging alone. In four of 7 (Loewenstein *et al*., 2016; Sánchez *et al*., 2017; Crocco *et al*., 2018; Abulafia *et al*., 2018), the Loewenstein-Acevedo Scale for Semantic Interference and Learning (LASSI-L; Loewenstein *et al*., 2016; Loewenstein *et al*., 2017), a cognitive "stress test" assessing the effects of semantic interference on memory performance, was the chosen behavioural measure. A full description of the LASSI-L and its administration procedures are presented in Appendix E. As tests such as this focus on automatic semantic priming processes, as opposed to effortful semantic retrieval, it seems an appropriate measure for assessing subtle cognitive changes unlikely to be detectable in preclinical cohorts on more commonly used semantic memory tasks. Two earlier studies included (Seidenberg *et al*., 2009; Woodard *et al*., 2009) used a famous name discrimination task. Although successful performance on this task is more reflective of explicit semantic memory function, likely to be intact in these cohorts, it represents a more difficult and specific task for probing memory function when compared with the Category Fluency task (Newcombe, 1969) or Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001), more frequently used among disease populations. In contrast with the findings of all studies using the LASSI-L, however, neither study using a famous name discrimination task was able to demonstrate differences between the preclinical cohort and the control group at this behavioural level. This is in line with previous evaluations of the LASSI-L that have demonstrated that this more sensitive test paradigm is often superior to more commonly used diagnostic tasks, previously presumed to be most accurate in diagnosing AD pathology, such as the Free and Cued Selective Reminding Test (Buschke, 1984; Matias-Guiu *et al*., 2018), suggesting that cognitive stress

paradigms such as this represent valuable advancements in the instruments for early diagnosis (Crocco *et al*., 2014; Loewenstein *et al*., 2016; Matias-Guiu *et al*., 2018). One final study by Hirni *et al*., (2016) applied more commonly used tasks in their study, including the California Verbal Learning Test (Delis, 1994), to evaluate episodic memory function and the Category Fluency test, to evaluate semantic memory. As this longitudinal study had a fixed *a priori* hypothesis, it was focussed specifically on the function of the medial PRC and ERC, estimated through cortical thickness and age, along with the two behavioural measures, as a predictor of subsequent conversion to AD. For this reason, it may be argued that, though a useful study in predictive measures of disease, it may be less relevant to the localisation of semantic memory neural correlates among preclinical AD populations. Nonetheless, the results of this study do demonstrate the neurally dissociable nature of declarative memory function, as described by Mishkin *et al*. (1997) and Didic *et al*. (2011), as semantic memory in this case significantly predicted the cortical thickness of only medial PRC not ERC. Episodic memory, however, was predictive of both. This finding is likely due to the verbal nature of the episodic memory task selected by Hirni and colleagues. As a task dependant on language function, successful performance on the California Verbal Learning Test inherently requires a level of semantic involvement and so it is unsurprising to see that this task was predictive of the variance in both areas. These findings are therefore reflective of the theory that semantic memory is more heavily supported by discrete anterior MTL regions, particularly the PRC, as evidenced by its role in visual recognition memory (Meunier *et al*., 1993; Mumby & Pinel, 1994; Brown & Aggleton, 2001; Barker *et al*., 2007; Kivisaari *et al*., 2012), than the more posterior regions such as the ERC and hippocampus. Episodic memory however, which is thought to be largely reliant on the consolidation of semantic knowledge (Reder, Park, & Kieffaber, 2009; Greenberg & Verfaellie, 2010), is likely to correlate with more widespread regions of the MTLs, including the hippocampus but also the ERC. According to a review by Lavenx and Amaral (2000), the ERC may be considered a relay between the PRC (an amodal consolidation hub receiving semantic information from association cortices) and the hippocampus proper, for episodic memory formation. Furthermore, Hirni *et al*. were able to demonstrate that the function of the medial PRC and ERC, as predicted by both semantic and episodic memory tasks, differs significantly in cases of incipient AD, when compared with healthy ageing. According to these findings, significant differences between converters and non-converters may be apparent up to twelve years prior to a dementia diagnosis. At four years pre dementia development, the function of these areas seems to drop dramatically in preclinical AD compared with healthy ageing.

Aside from those focussing on limited ROIs (Hirni *et al*., 2016; Sánchez *et al*., 2017), the majority of studies in this group described a wide range of areas in addition to MTL structures that were differentially involved with semantic memory processing among preclinical patients, when compared with controls. The two studies using the famous name discrimination task, both of which utilised fMRI measures, noted increases in activity in response to famous names relative to non-famous names in preclinical participants. This finding was not apparent within control populations however, with Seidenberg *et al*., (2009) actually demonstrating the opposite in their control group, where greater activations were apparent in response to unfamiliar names relative to familiar names. Between-group analysis in both studies revealed that such increases in activation were significantly greater among preclinical populations relative to controls in a number of AD related areas including, but not limited to, precuneus/posterior cingulate cortex (PCC) temporoparietal junction and MTLs. Furthermore, in Woodard *et al*.'s (2009) study, which included MCI patients, they found that increases in activity were greatest among this patient group, with preclinical participants representing an intermediate group between MCI and controls. This finding is in line with studies discussed later in this review that have also demonstrated significant increases in brain activity, measured by fMRI, among MCI, and even dementia patients, in response to semantic memory tasks when compared with controls (Saykin *et al*., 1999; Rinne *et al*., 2003; Grossman *et al*., 2003; McGeown *et al*., 2009; Gigi *et al*., 2010; Catricalà *et al*., 2015; Gardini *et al*., 2015; Mascali *et al*., 2018). One explanation for such increases would be the presence of compensatory activity in response to reduced efficiencies within areas of the semantic network affected by incipient AD. This interpretation is in line with the functional recruitment hypothesis that describes the nature of age-related changes in fMRI activation as the presence of compensatory recruitment, serving to maintain cognitive function in ageing, particularly in at-risk populations representing preclinical AD, prior to the rapid decline observed in clinical populations (Twamley *et al*., 2006; Nielson *et al*., 2006; Seidenberg *et al*., 2009).

In contrast to the studies utilising famous name discrimination, all studies using the more sensitive LASSI-L task were able to demonstrate significant behavioural differences between healthy controls and the preclinical groups, in particular on measures of semantic interference. It appears then, that the LASSI-L task, in comparison with famous name discrimination, may be more sensitive to detecting declines in automatic processes that are less likely to be mediated by compensatory cortical recruitment in at-risk individuals. It is, therefore, reasonable to suggest that the neural correlates of LASSI-L measures described in

these studies are more accurately reflective of those areas involved in a failure or impairment of semantic processing, whereas the famous name discrimination task, among preclinical populations at least, appears to reflect a measure of sustained semantic processing. For this reason, the results of these studies demonstrate positive correlations between semantic interference and grey matter volume, cortical thickness, fMRI connectivity and even regional amyloid load, across a number of AD related areas, including a number of semantic memory-related regions. In preclinical populations, a failure to recover from proactive semantic interference (frPSI), considered to be the most valuable measure of the LASSI-L for discriminating between patients and healthy populations (Loewenstein *et al*., 2016; Lowenstein *et al*., 2017; Sánchez *et al*., 2017; Crocco *et al*., 2018; Abulafia *et al*., 2018), was associated with decreased connectivity of the PCC, an area widely known to be affected by the very earliest stages of AD. Number of intrusions on the task were further correlated to connectivity within a network of areas including the hippocampus, PCC, precunei and insulae, as well as dorsolateral prefrontal cortices and anterior thalamus (Sánchez *et al*., 2017). This widespread pattern of connectivity associated with frPSI related intrusions, is highly reminiscent of those areas involved in the semantic network in healthy individuals (Binder *et al*., 2009; Binder & Desai, 2011). Similar areas were highlighted in the results of Crocco *et al*.'s (2018) structural imaging study, looking at the relationship between brain volume and frPSI, which found correlations within the hippocampus, precuneus and PCC, as well as Abulafia *et al*.'s (2018) study, measuring cortical thickness, which reported correlations in areas of frontal cortex, medial posterior parietal cortex and temporo-occipital cortex. Amyloid load has also been associated with frPSI in terms of total load, as well as regional loads within areas of the anterior and posterior cingulate cortex, the precuneus and to a lesser extent, the frontal lobes (Loewenstein *et al*., 2016) and left temporal lobe (Abulafia *et al*., 2018). These findings, taken together, suggest that there is an imminent and significant breakdown of the semantic system at extremely early stages of disease development, possibly related to the accumulation of amyloid, which are detectable through the use of semantic memory tests, in particular in the form of cognitive stress tasks such as the LASSI-L.

2.2.5.2. Mild Cognitive Impairment Cohorts

Nineteen of the studies included in the current review focused primarily on the relationship between brain imaging measures and semantic memory decline in patients with MCI. Two of the studies included in this category also included an AD dementia group,

however, the reported mean MMSE for these patients suggested that some may have fallen below the mild status of dementia (i.e., MMSE < 18) and therefore were not taken into consideration for this review. The majority of the studies focussing on this prodromal stage of disease tended to favour structural imaging techniques over functional imaging, with only five of the 19 studies in this group analysing brain function measures. Unlike the preclinical groups, all the studies in this category that compared patient and control behavioural performance found that MCI patients demonstrated significant impairments in semantic memory, when compared with controls, in line with the now well-established understanding that semantic memory impairments, along with declines in episodic memory, are a prominent and common part of the earliest stages of AD (Amieva *et al*., 2008; Joubert *et al*., 2008; Didic *et al*., 2011; Joubert *et al*., 2020). Similarly, in contrast with the preclinical populations, disease progression is evident among MCI populations, with the majority of studies evidencing associations between semantic memory and imaging measures within anterior and MTL structures associated with early disease related dysfunction and atrophy. Specifically, of the fourteen structural studies in this disease group, only 2 did not specifically identify a relationship between semantic memory function and grey matter integrity within hippocampal or extra hippocampal regions of the parahippocampal gyrus, ERC and PRC.

One study that did not highlight a role of the MTLs was conducted by Peter *et al*. (2016) who used the Category Fluency test as the primary measure of semantic processing. This study followed an ROI approach measuring the volumes from two areas of the frontal lobe, namely the superior and inferior frontal gyri, implicated in control of semantic retrieval (Wagner *et al*., 2001), as well as volumes of the temporal pole, thought to be related to semantic knowledge storage (Patterson, Nestor & Rogers, 2007). They found that performance on semantic fluency in aMCI patients was related to volumes in both the superior and inferior frontal gyrus, whereas performance in controls was strongly related only to the superior frontal gyrus. Furthermore, aMCI participants were significantly impaired not only in their performance but also their use of effective strategies, namely clustering and switching, for improving semantic fluency. In healthy controls, switching between sub-categories was associated with left inferior frontal gyrus volumes, whereas in aMCI switching was associated with bilateral superior frontal gyrus and right inferior frontal gyrus. These findings are consistent with the theory that the left inferior prefrontal cortex is integral to the executive control of semantic retrieval (Thompson-Schill *et al*., 1997; Wagner *et al*., 2001) and further demonstrates the presence of compensatory cortical recruitment within frontal structures, highlighted by functional studies of preclinical cohorts (Seidenberg *et al*.,

2009; Woodard *et al*., 2009), among MCI patients. The presence of significant semantic memory decline in the MCI patients, compared with the healthy controls in this study, suggests that such mechanisms may shift to decompensation at the clinical stages of disease, suggesting that maladaptive functional recruitment of the frontal lobes may explain the semantic deficit in these individuals. However, the restriction of the ROI analyses to include only the temporal pole as a site of semantic memory consolidation likely limited the results in this investigation. Unlike semantic dementia patients, whose deficits are thought to relate directly to degradation of the ATLs (Snowden, Goulding & Neary, 1989; Hodges *et al*., 1992; Mummery *et al*., 2000; Chan *et al*., 2001; Gorno-Tempini *et al*., 2004; Desgranges *et al*., 2007; Patterson, Nester & Rogers, 2007), patients with AD type pathology are likely to sustain relatively little damage within this region in the earliest stages. Given previous findings that early damage to MTL structures may significantly contribute to semantic memory dysfunction in MCI patients, independently of the ATLs and temporal poles (Atenzia *et al*., 2011; Venneri *et al*., 2011; Meyer *et al*., 2013; Barbeau *et al*., 2012), the authors might have considered including these areas in their analysis to scrutinise further structural changes mediating semantic memory impairment in their patient cohort.

Gardini *et al*., (2013) also demonstrated correlations between semantic memory measures and grey matter volumes within MCI patients that were primarily focused in cortical areas other than the temporal lobes. This included sub-cortical, frontal and cerebellar regions. It is not clear why semantic memory measures in this cohort did not exhibit associations within MTL structures, as per the other investigations of MCI populations included for review. However, in this study it is not made apparent at what stage of cognitive decline the MCI patients were in (i.e., MMSE, CDR etc.), so it is therefore possible that a number of the fourteen individuals included in the MCI group may have reached a stage of pathological decline in which MTL structures have degraded to the point where greater reliance on less diseased areas, such as the cerebellum and sub-cortical regions, may have led to an increase in the amount of semantic memory variance accounted for by the integrity of these structures. The authors explain these findings as a possible restructuring of semantic memory mechanisms among patient groups to rely more heavily on control mechanisms, mediated by subcortical and cerebellar structures, to support a loss of automatic functions mediated by cortical areas.

As in the preclinical cohort, functional studies among MCI patients primarily demonstrate an increase in activation in response to semantic memory tasks, particularly within frontal and parietal regions, when compared with controls (Catricala *et al*., 2015;

Gardini *et al*., 2015). In contrast however, all MCI patient groups, in the studies included for review, demonstrated significant impairments when compared with controls on measures of semantic memory. It is possible therefore, as suggested by Peter *et al*.'s structural imaging study (2016), that these increases in activation, seen at the clinical stage, have shifted from successful compensatory mechanisms to decompensatory and potentially maladaptive processes, meaning patients are no longer able to sustain normal cognition. The literature in this area remains inconclusive however, as studies have also demonstrated significant reductions in fMRI activation in a widespread network during semantic processing, in comparison with controls (van der Meulen *et al*., 2012). Van der Meulen *et al*. (2012) used fMRI and a picture-pair memory task to assess semantic deficits in MCI. In contrast to the majority of studies included in this review, this study assessed semantic function by investigating the neural correlates of semantic encoding as well as retrieval. Patients not only showed reduced brain activation during encoding and recognition compared with controls, but the results of the picture-pair memory task revealed a significantly greater impairment in MCI on associative recollection, thought to be more heavily reliant on the encoding of semantic information, than recognition based on familiarity; reliant on contextual, episodic encoding. Deficient encoding of semantically related picture pairs in MCI was associated with reduced activation in a left-hemisphere network comprising of the parahippocampal gyrus, inferior frontal gyrus and inferior temporal cortex, relative to controls, and network activity within a number of frontal and parietal regions was also found to be significantly reduced in these patients during associative recognition. Similar temporal regions as highlighted by the encoding task have previously been implicated in the binding, maintenance and organisation of semantic information (Murray & Richmond, 2001) and the inferior frontal gyrus has been similarly suggested to be highly involved in these semantic encoding processes (Martin & Chao, 2001). The results of this study, therefore, suggest that the semantic network may be disrupted not only at the level of retrieval, but also at the level of encoding in MCI and that this disruption may reveal important changes in cognitive and neuroimaging measures that could distinguish normal and pathological ageing.

Inconsistencies in the literature regarding hyper/hypoactivation in MCI patients in response to semantic memory tasks may be due to the differences in the nature of the semantic tasks used. Differing tasks are likely to scrutinise different aspects of the semantic network, therefore revealing elements of dysfunction including both hyperactivity in response to semantic tasks (Catricalà *et al*., 2015) and in resting state networks (Gardini *et al*., 2015), as well as some hypoactivation under event-related conditions (van der Meulen *et al*., 2012;

Pineault *et al*., 2018). Regardless, the patterns of hyper/hypoactivation among MCI patients in relation to semantic tasks demonstrate a significant alteration in functioning of the semantic network that has been suggested to precede the emergence of structural changes (Pineault *et al*., 2018) and therefore is an important indicator of incipient pathological decline.

2.2.5.3. Dementia Cohorts

Only eleven of the studies included focused only on populations with a dementia diagnosis. Many studies were discounted during the selection process for including patients at a too severe stage of disease. These eleven studies, therefore, represent only early AD dementia patients. A surprising aspect of this group of studies is that only three use purely structural imaging techniques, with the rest using functional methods. Unlike the investigations in MCI or preclinical cohorts, which almost exclusively utilised MRI techniques, aside from some biomarker imaging using PET, a number of the studies in this group used PET imaging techniques to measure cerebral blood flow or glucose metabolism in relation to semantic processing. This absence of structural imaging techniques may be reflective of the research questions addressed by these investigations. Structural differences between controls and those with established dementia are already well understood and documented (McKhann *et al*., 2011; Dubois *et al*., 2007) and the robust relationship between such structural differences and the declines in episodic memory relied upon for diagnosis (Eichenbaum, 2001; Dubois *et al*., 2007; Albert *et al*., 2011) means that structural neural correlates of semantic memory decline at this stage are unlikely to provide any additional clinical benefit. It is well established however, that changes in glucose metabolism and cerebral perfusion, particularly in precuneus and PCC, occur in AD at a very early stage of disease progression (Minoshima *et al*., 1997; Bradley *et al*., 2002). Therefore, establishing the relationship between semantic memory decline and these functional indices in a well-characterised cohort, with established dementia of the Alzheimer's type, may prove informative in the search for a marker of incipient disease, prior to significant structural change. Each of the studies using 18 fluorodeoxyglucose-PET revealed significant correlations between semantic memory decline and a reduction in glucose metabolism. Primarily, areas of reduced metabolism associated with semantic processing impairment were located within areas of the temporal lobe, including anterior and medial structures (Lekeu *et al*., 2003; Zahn *et al*., 2004), but also inferior posterior, as well as superior regions (Zahn *et*

al., 2004; Giffard *et al*., 2008). The range of temporal areas highlighted across these studies reflects the range of areas involved in the semantic network (Binder *et al*., 2009; Binder & Desai, 2011) that may be highlighted by different tasks. This is especially evident in the extended correlations within medial occipital and inferior parietal structures identified in Zahn *et al*.'s study that implemented a range of verbal as well as non-verbal semantic tasks (Zahn *et al*., 2004). Interestingly however, Rinne *et al*.'s study (2003) was the only PET study measuring cerebral blood flow, as opposed to glucose metabolism, and they reported a more widespread increase in blood flow elicited by lexical-semantic decision-making, when compared with controls, among their AD dementia group. This extensive recruitment of brain areas included areas of the left frontal lobe, right occipital cortex, midbrain and bilateral cerebellum, compared with recruitment of only left frontal and right cerebellar regions in the controls. Semantic memory performance is thought to rely heavily on the integrity of two distinct cognitive processes: storage of semantic information and control of semantic retrieval (Wagner *et al*., 2001; Patterson *et al*., 2007; Venneri *et al*., 2018). The activation of frontal regions elicited by the lexical-semantic decision-making task is, therefore, in line with previous models outlining the presence of a semantic control network within frontal lobe structures (Gabrieli *et al*., 1996; Thompson-Schill *et al*., 1997; Wagner *et al*., 2001). Moreover, subcortical and cerebellar inputs in controlled retrieval processes have also been demonstrated by the previously discussed study by Gardini *et al*. (2013) who found structural substrates of semantic processing in MCI patients within similar regions. The lack of behavioural differences between the AD and control groups in Rinne *et al*.'s study (aside from time taken to answer) further supports the authors' conclusion that this additional cortical and subcortical recruitment in the dementia group likely indicates the presence of compensatory recruitment of areas involved in cognitive control in response to a decline in automatic semantic memory processes, due to progressive neurodegenerative disease. As with the conclusion drawn from studies focused on MCI patients, the ambiguity in the literature regarding increases/decreases in brain functional responses to semantic memory tasks needs to be interpreted very carefully, taking into consideration the nature of the neuropsychological task, as well as the structural or functional proxy employed for assessing neuronal substrates. Semantic processing is a unique and highly convoluted cognitive process that spans a diverse range of cognitive domains (Patterson *et al*., 2007; Wagner *et al*., 2001) and an equally diverse range of cortical regions involved in differing aspects of the consolidation and retrieval of semantic information (Patterson *et al*., 2007; Binder *et al*., 2009; Binder & Desai, 2011; Gabrieli *et al*., 1996; Thompson-Schill *et al*., 1997; Wagner *et*

al., 2001). For this reason, in the pursuit of neuropsychological makers of early pathological changes in AD, researchers need to be aware of the effects of task, taking into account a number of confounding factors including, but not limited to, semantic control, lexical or linguistic processing and associative or recognition memory processes, and how the differences between semantic tasks, in terms of these cognitive domain profiles, may affect correlations seen at the neural level. Differences in neural responses to cognitive tasks, in particular among patients, can further be explained by inter-individual variance in cognitive and neural reserve. It is well documented that patients with higher cognitive reserve are able to sustain normal cognitive functioning in the presence of greater levels of neurodegeneration, than those with low cognitive reserve (Stern, 2012). It is thought that the maintenance of normal cognition may reflect both an ability to utilise adaptable cognitive strategies during neuropsychological testing but also effective implementation of the neural networks underlying task performance (Stern, 2009). It is possible, therefore, that variance in the levels of cognitive reserve among the patient groups of individual studies may account for the presence or absence of compensatory activity in response to semantic tasks.

Corresponding with the findings among MCI patients, as well as the mixed results of the PET studies in the dementia patients, fMRI experiments in these cohorts also demonstrated a mix of hyper- and hypoactivation, among dementia patients, in response to semantic processing tasks. Saykin and colleagues (1999) used fMRI to measure the activity differences between mild AD patients and healthy controls when performing a lexical-semantic decision task. In the *category-function* condition, which required patients to decide whether verbally presented word pairs were matched in their function (e.g., *beverage – sip*), AD patients performed at a comparable level and showed significant increases in the spread of activation within areas of the left precentral gyrus compared to controls. In contrast however, in the *category-exemplar* condition, where participants had to decide whether a given word represented an exemplar of the paired subordinate category (e.g., *beverage-milk*), AD patients were significantly impaired compared with controls. Although AD patients still demonstrated significantly higher activation levels in large areas of bilateral precentral gyrus, extending into the left postcentral gyrus and putamen, compared to controls, subsequent covariance analyses indicated that performance in this *category-exemplar* condition showed a strong positive correlation to signal increase in bilateral medial prefrontal cortex, suggesting that impairments in this task may be explained by inadequate activation of compensatory mechanisms within frontal lobe regions mediating controlled retrieval (Wagner *et al*., 2001; Henry, Crawford and Philips, 2004). It is possible that retrieval of a relatively simple *noun-*

function relationship may be more easily achieved through such compensatory recruitment, whereas, although similar over-activation is elicited in AD groups during the more demanding *category-exemplar* task, it is not sufficient, in this case, to overcome the effects of disease. However, given that the healthy controls in this study performed better on the *category-exemplar* than the *category-function* task, it is not accurate to say that the former is inherently more demanding than the latter. Rather, the greater impairment seen in the AD group on this task may reflect a greater demand on retrieval mechanisms in relation to accessing semantic knowledge at differing levels. In 1969, Collins and Quillian proposed, according to the hierarchical model of semantic memory posited by Quillian (1967; 1969), that it takes more time for an individual to recall items from the semantic store that require moving between levels than it does to simply access a semantic feature of a given item at the same level. For example, accessing 'Labrador' as an exemplar of 'dog' would take more time, and presumably, therefore, somewhat more effort, than simply recalling 'barks' as a feature of 'dog' that may be accessed as the same semantic level. In a healthy individual, this extra level of processing is unlikely to have an effect on task performance, despite possibly slower reaction times. However, in the presence of neurodegenerative disease, in which the connectivity of the semantic network is likely to be compromised, greater levels of compensatory activation may be needed to fulfil an increased processing requirement. Therefore, not only do patients show impairments compared with controls on this task, but those patients unable to achieve the further increase in compensatory activation demanded during this more difficult condition perform poorly compared to those with relatively less compromised semantic networks.

Again however, there is ambiguity in the literature, with contrasting findings by McGeown *et al*., (2009) demonstrating that the Pyramids and Palm Trees task, requiring participants to identify the item most semantically related to a target item in a series of cards depicting three objects (Howard & Patterson, 1992), elicited activation in the left prefrontal and cingulate cortex only. However, in this cohort, deactivation in anterior midline structures was associated with higher performance in the AD group while comparatively, more widespread activation, and a failure to deactivate midline structures, characterised the low performance group. The lack of deactivation in these areas is of particular interest given the role of these areas in the well-established default mode network (DMN, Raichle *et al*., 2001), suggesting dysfunctional activation in this network may play an important role in the semantic memory deficit present in AD. This ambiguity in the literature may again be a reflection of the differences in task demands present between the lexical-semantic decision

task used by Saykin *et al*. (1999), which is likely to scrutinise more heavily frontally mediated strategic semantic retrieval and inhibitory processes, and the Pyramids and Palm Trees task used by McGeown *et al*. (2009) that, given the automatic nature of picture recognition, may be more likely to scrutinise automatic semantic priming effects (Gold *et al*., 2006). Greater frontal activation in AD patients may, therefore, be beneficial for successful completion of lexical-semantic decision tasks in a way that is actually maladaptive for more automatic semantic association processes.

Structural studies in AD dementia patients revealed largely similar results to those in MCI patients, revealing a significant relationship between semantic memory measures and grey matter integrity within areas of the temporal lobes, including MTL structures such as the hippocampus (Rodríguez-Aranda *et al*., 2016), PRC and parahippocampal gyrus (Venneri *et al*., 2008) as well as the ATLs (Domoto-Reilly *et al*., 2012). These findings further support the hypothesis that aMTL structures play a significant role in semantic memory processing (Didic *et al*., 2011) and that, despite widespread involvement of a number of cortical regions in this cognitive process (Binder *et al*., 2009; Binder & Desai 2011), degradation of these areas is likely the most significant factor in the decline of this memory function in the earliest stages of AD and, therefore, should be considered a promising candidate for earlier diagnostic testing.

2.2.5.4. Combined MCI and Dementia Cohorts

The second largest group of studies (13 out of 50) looked at multiple and, in some cases, combined cohorts including both MCI and dementia patients, compared with controls. Unlike studies looking at dementia alone, investigations of this kind tended to favour structural techniques such as MRI and diffusion tensor imaging (DTI) over functional imaging techniques, with only three studies in this group using some form of functional imaging and only 1 using a functional technique in isolation without any structural analysis. These studies, therefore, more closely resemble those seen in MCI cohorts. This may be due to the fact that the added variance elicited by the inclusion of less impaired/atrophic MCI patients, along with the more severely affected dementia patients, in a combined patient group, allows for more valid interpretations of the relationship between brain structure and semantic memory performance, counteracting the dilution of variance that may be seen within a dementia-only group, caused by confounding structural and cognitive deficits. The functional imaging studies that do exist for these cohorts tended to show complementary

results. Yap *et al*., (2017) and Gigi *et al*., (2010) used semantic verbal fluency and object naming tasks, respectively, during task-based functional near-infrared spectroscopy and fMRI to assess activation differences between patients and controls during semantic processing. Both studies included patient cohorts of both MCI and mild AD, allowing for comparisons to be made at incremental disease stages. Both studies noted decreased activation in the prefrontal cortex in mild AD patients, compared to controls, but over-activity of this region in MCI. Both attribute the relatively preserved semantic memory performance in MCI patients, compared with the AD groups, to this over-activity, potentially acting as a compensatory mechanism for a compromised semantic system. Particularly, Gigi *et al*., (2010) found no difference in performance on semantic memory tasks between MCI and controls despite significantly different activation patterns demonstrated by fMRI. Specifically, in response to an object task, MCI patients showed a significantly lower number of activated voxels in parietal and fusiform areas, thought to be of particular importance to object recognition tasks, but a significant increase in signal change and the number of activated voxels in the dorsolateral prefrontal cortex. As mentioned previously, it has been well established that, even in the earliest stages of AD and MCI, significant functional changes, such as reduced glucose metabolism and brain perfusion, are detectable within areas of the medial parietal lobes (Minoshima *et al*., 1997; Bradley *et al*., 2002). The results of this study, therefore, suggest that, in response to the disruption of the semantic system serving object recognition, MCI patients show compensatory increases in activation in the frontal areas serving control of semantic retrieval. This extra reliance on the semantic control network may explain why MCI patients, in comparison to mild AD, who in this study showed reduced activation in all ROIs compared to controls, can maintain normal semantic performance in spite of underlying pathology. Carter *et al*. (2014) also demonstrated significant reductions in glucose metabolism within posterior temporal and inferolateral parietal cortices within their combined dementia and MCI patient group that strongly correlated with semantic cognition. In this study the researchers also found significant relationships between grey matter volume and semantic cognition within MTLs, ATLs, as well as medial frontal regions; areas that are known to form part of the distributed semantic memory system (Patterson, Nestor & Rogers 2007; Binder *et al*., 2009; Binder & Desai, 2011). In light of the current review, the results of these functional studies can now be understood as representative of a pattern of semantic network alteration and ultimately dysfunction that occurs early on as a result of Alzheimer's pathology.

When including both MCI and dementia patients in a single patient group, many of the whole-brain structural imaging studies included for review found relationships between brain structure and semantic memory performance across widely distributed brain areas (Apostolova *et al*., 2008; Balthazar *et al*., 2011; Dos Santos *et al* 2011; Rodriguez-Ferreiro *et al*., 2012; Eastman *et al*., 2013). Given that the structural studies in MCI cohorts alone tend to show more focused patterns of correlations in AD related regions within the temporal lobes, with only some further involvement of frontal and parietal structures (Venneri *et al*., 2011; Frings *et al*., 2012; McDonald et a., 2012; Barbeau *et al*., 2012; Loewenstein *et al*., 2017a; Loewenstein *et al*., 2017b; Loewenstein *et al*., 2018a; Curiel *et al*., 2018), the widespread findings within the combined cohorts likely reflect the effects of increased variance across wider areas of cortex caused by the presence of more significant atrophy among dementia patients.

Despite this, ROI analyses among combined patient cohorts reveal similar results as those studies that included MCI patients alone, with significant correlations found to be present between indices of semantic memory and structural integrity of the anterior temporal and MTL regions (Balthazar *et al*., 2010; Kivisaari *et al*., 2012; Hirni *et al*., 2013). A study directly exploring the hierarchical organisation of declarative memory function within the MTL was conducted by Hirni *et al*., (2013). Using ROI analysis of grey matter volumes, measured by structural MRI, as well as whole brain fractional anisotropy measurements, determined by DTI, the researchers measured the association between volumes of the left and right ERC, medial PRC and hippocampal head, along with their white matter connections, and scores on the Boston Naming Test and a category verbal fluency task, while controlling for episodic memory performance. In accordance with Mishkin (1997) and Didic *et al*., (2011), Hirni *et al*. found that, when controlling for episodic memory, semantic memory performance was significantly related to volumes within the medial PRC, ERC and hippocampal head. In contrast however, when controlling for semantic memory, episodic memory performance was significantly related only to bilateral ERC and hippocampal head without any involvement of medial PRC. Similar results from Kivisaari *et al*. (2012) found that, although overall naming scores correlated significantly only with volumes of the hippocampus proper, volumes of the medial PRC alone (with no involvement of lateral PRC, ERC or hippocampus) predicted poorer performance on naming of living relative to non-living things. Furthermore, the authors were able to show an interaction with measures of global atrophy so that minimal global atrophy in the presence of reduced PRC volume predicted poorer performance on naming of living things compared to non-living, whereas

moderate global atrophy in the presence of reduced PRC volume showed the opposite effect with poorer performance on non-living items vs. living ones. The authors explained this effect in terms of the proposed hierarchical structure of perceptual and semantic representations of objects within the temporal lobes (Murray & Richmond, 2001). According to this hypothesis, caudal areas of the inferior temporal lobes are thought to consolidate simple differentiating features while more rostral portions represent increasingly complex, overlapping features, with the PRC serving to disambiguate perceptually similar items through binding of more nuanced perceptual features with semantic associations (Murray & Richmond, 2001). Therefore, PRC atrophy in the presence of intact caudal temporal lobes would be more likely to disturb disambiguation of perceptually and semantically similar living items such as 'cat' and 'dog' with the relative preservation of naming inanimate items such as 'boat' and 'telephone' that can be more simply distinguished by functional or visual attributes. Atrophy of the PRC in the presence of a disruption to the semantic system more globally however, indexed here by global atrophy, could lead to the differential pattern of impairment seen in this study, given that simpler associations require less processing power and therefore may be more easily compensated for in the presence of more pervasive neural loss. The results of this study therefore suggest that the earliest stages of AD pathology within the anterior MTL, preceding significant hippocampal involvement, may be sufficient to disrupt the processing of semantically complex visual stimuli through disturbing the function of the binding site for semantic and perceptual information. The findings of these ROI studies are, therefore, in accordance with those conducted in MCI patients that also demonstrated significant associations between semantic memory decline and the structural integrity of the MTLs, particularly within the anterior extrahippocampal regions (Atenzia *et al*., 2011; Barbeau *et al*., 2012; Meyer *et al*., 2013; Chen & Chang, 2016; Hirjack *et al*., 2017; Venneri *et al*., 2019).

2.2.5.5. Limitations

The limitations of the present review lie primarily in the method of retrieval of relevant literature. Retrieval and quality assessment for the current review were carried out by a single individual, therefore potentially biasing the study inclusion. However, strict adherence to study inclusion and exclusion criteria and systematic data extraction should have mitigated any potential bias.

2.2.5.6. Conclusions

The aim of the present review was to outline the neural correlates of the semantic memory deficit in AD and describe, using the findings of the current literature in this area, how these correlations alter throughout disease progression. The results of this review reveal a traceable pattern of structural and functional changes related to semantic memory processing from the preclinical through to the dementia phase of AD. Results from preclinical and at-risk cohorts suggest that significant alterations in the semantic memory network may occur many years prior to a dementia diagnosis. It is likely that these alterations stem from the earliest known changes within aMTL structures (Braak & Braak, 1991; Hirni *et al*., 2016) that lead to significant disconnections between a number of integral nodes in the network (Sánchez *et al*., 2017). In these asymptomatic stages, it has been suggested that overt semantic memory functioning may be sustained through compensatory increases in the volume of activation in response to semantically related material that would usually only be present in response to unfamiliar stimuli within healthy populations (Seidenberg *et al*., 2009; Woodard *et al*., 2009). As disease progresses to the MCI stages, this compensatory recruitment in response to semantic tasks remains apparent, particularly within frontally and subcortically mediated semantic control networks (Gardini *et al*., 2013; Catricalà *et al*., 2015; Gardini *et al*., 2015; Pineault *et al*., 2018). Although, as in preclinical cohorts, the direction of activity compared with controls is highly task dependant (van der Meulen *et al*., 2012). At this stage of disease an apparent relationship between the structural integrity of anterior and medial temporal structures and semantic memory performance is clear (Atenzia *et al*., 2011; Barbeau *et al*., 2012; Meyer *et al*., 2013; Chen & Chang, 2016; Hirjack *et al*., 2017; Venneri *et al*., 2019). The results of this review are therefore in line with theory that discrete structural changes associated with Braak stages I and II (Maass *et al*., 2018; Xie *et al*., 2018) may be the predominant contributor to the breakdown of the semantic memory network in AD (Didic *et al*., 2011). This is further supported by structural studies among mild dementia patients (Venneri *et al*., 2008; Domoto-Reilly *et al*., 2012; Rodríguez-Aranda *et al*., 2016). Functional changes among this more severe patient group, reported by experimental studies, suggest that at these stages compensatory increases in activation are likely to be also accompanied by disease related decreases in activation in a number of regions (Grossman *et al*., 2003, Mascali *et al*., 2018). Furthermore, the presence of additional activation foci during semantic memory tasks among this patient population has been suggested to impede performance, suggesting that, with increased disease severity, such compensation becomes maladaptive as the network

is no longer able to cope with the exacerbated pathological burden (Saykin, 1999; McGeown *et al*., 2009).

The progressive course of neural involvement in AD related semantic impairment, outlined by this review, again demonstrates the potential of such impairments to inform the diagnosis and prognosis of disease that has been highlighted by previous reviews in this area (Venneri *et al*., 2018). These findings indicate a clearly definable breakdown of the semantic network, likely instigated by the earliest depositions of pathological material, which, with continued research and refinement of neuropsychological methods, may provide a sensitive and informative measure of incipient disease, informing preclinical imaging protocols and providing reliable tests for earlier diagnosis, unconfounded by the processes of normal ageing (Rönnlund *et al*., 2005).

2.2.5.7. Recommendations for Future Research

This review has highlighted two main considerations for future investigations in this area. Firstly, increasing the data variance through the inclusion of both MCI and AD dementia patients in neuroimaging analyses may not have the desired effect of enhancing the correlation between cortical regions and semantic memory measures. The studies included in this review demonstrated that, among segregated MCI or AD dementia groups, it was possible to demonstrate more focused correlations between semantic processing and the structural integrity of brain regions than when using a combined group. It is likely that the vast differences between the two disease stages, in terms of cortical atrophy as well as cognitive decline, may introduce a greater number of confounding factors contributing to the spread of variance associated with the experimental task. Given the conclusion that changes in neural structure and functioning differentially contribute to semantic memory declines in a progressive manner throughout disease, it would, therefore, be recommended that patients at differing disease stages be segregated for analysis to improve homogeneity within the groups.

Along these lines, it would also be recommended that researchers take great care when selecting the task used to assess semantic processing in AD patient groups. As described previously, semantic memory is a complex function that relies on the successful implementation of a range of cognitive processes, mediated by a range of cortical regions, in order to be sustained (Binder *et al*., 2009; Binder & Desai 2011). For this reason, any experimental semantic memory task used in neuroimaging analysis needs to be well described, with a clear demonstration that the investigators understand the cognitive functions

contributing to its successful completion, and with appropriate steps being taken to account for these extraneous variables. Any contribution from cognitive processes that cannot be directly controlled for need to be taken into careful consideration when interpreting the results.

Chapter 3 | Aims and Objectives

Overwhelmingly, research suggests that the preclinical stages of Alzheimer's disease (AD) can begin years, even decades prior to a dementia diagnosis (Jack *et al*., 2013). Given what we know about the initial depositions of hyperphosphorylated Tau within discrete areas of the medial temporal lobes (MTLs) (Braak and Braak, 1991), it is imperative that, in the interest of earlier diagnosis, we focus our attention on sensitive neuropsychological markers of transentorhinal dysfunction, in a shift away from the traditional measures of later stage hippocampal damage that we currently rely upon in clinical diagnostic practise (Dubois *et al*., 2007; McKhann *et al*., 2011). One such neuropsychological measure found to show decline, even at the preclinical stages of disease, is semantic memory processing (Ameiva *et al*., 2008). As outlined in *Chapter 2*, this type of memory processing has not only been found to show decline early on in pathologically confirmed cases of AD (Snowdon *et al*., 1996; Garrard *et al*., 2005; Le *et al*., 2011), but such decline has also been confirmed to be related to underlying changes in the structure and function of discrete anterior MTL structures known to be affected in the nascent stages of the AD pathological cascade (Venneri *et al*., 2008; Barbeau *et al*., 2012; Kivisaari *et al*., 2012; Hirni *et al*., 2013). Previous hypotheses have suggested, based on the evidence within the literature, that a semantic memory deficit may precede episodic memory impairment, in the pre-hippocampal stages of disease (Didic *et al*., 2011).

The use of semantic memory decline as a marker for prehippocampal AD, however, is currently limited by the neuropsychological tools available with which semantic memory may be tested. Studies have suggested that anterior temporal regions may have a significant role to play as a hub of amodal consolidation of semantic information coming from the wider semantic system (Patterson, Nestor & Rogers, 2007; Visser *et al*., 2010). However, it is likely that damage to the discrete transentorhinal/perirhinal areas in very early AD would produce reasonably subtle changes in semantic processing, due to the highly specific functions these areas are thought to contribute to semantic cognition (Kivisaari *et al*., 2012), in contrast with the more severe semantic declines caused by the widespread anterior temporal atrophy associated with semantic dementia (Mummery *et al*., 2000; Chan *et al*., 2001; Gorno-Tempini *et al*., 2004; Desgranges *et al*., 2007). As such, despite the overwhelming evidence for the existence of such declines in prodromal and preclinical stages of disease, efforts are required

to develop highly sensitive techniques to detect cognitive alterations in these stages for use in a clinical setting.

In light of this, the primary aim of the present research is to establish novel neuropsychological markers of brain structural alterations in early AD patients, with a particular focus on semantic memory measures. In detail, the specific objectives of this project are:

1.) To assess the utility of verbal fluency decline discrepancies in the identification of cognitive dysfunction in AD.

In line with the development of novel cognitive markers of AD semantic dysfunction, the neuropsychological component of *Experiment 1* investigates the hypothesis that AD pathology may disproportionately impact semantic verbal fluency performance to a greater extent than phonemic verbal fluency performance as a result of deficits in semantic memory function. A phenomenon that has been well documented within the literature (Monsch, 1992; Henry, Crawford & Phillips, 2004; Murphy, Rich & Troyer 2006; Clark *et al*., 2009; Vaughan *et al*., 2018; Casles *et al*., 2019), this experiment aims to replicate the findings of previous studies and establish the benefit of such discrepancies as a means to detect subtle semantic processing declines in the absence of poor raw performance scores on a semantic fluency task alone. The results of this investigation are presented in *Chapter 4, Experiment 1*.

2.) To establish the relationships between grey matter integrity and semantic memory function in patients at differing disease stages from very early prodromal disease through to moderate dementia.

Following on from the results of the systematic review, which assessed the current state of the literature in reference to what previous neuroimaging studies have already established about functional and structural changes associated with semantic memory dysfunction at incremental disease stages, the first experiment focusses on neural change and semantic processing across the AD spectrum. Using both whole brain voxel-based morphometry analysis and a region of interest approach, this structural experiment evaluates how the relationship between brain structure and semantic memory may shift from a focal relationship with discrete anterior MTL structures in the earliest stages, to further involvement of posterior MTL and lateral temporal lobes with further disease progression. The findings of this experiment are presented in *Chapter 4, Experiment 1*.

3.) To identify the neural correlates of the semantic/phonemic verbal fluency discrepancy in AD.

Despite considerable evidence for the existence of the semantic/phonemic verbal fluency decline discrepancy in even the earliest stages of AD, at the time of writing, literature searches reveal no studies that had actively investigated the neural underpinnings of such discrepancies. The present structural imaging study (*Chapter 4, Experiment 1*) therefore further aims to establish the cortical signature of the phenomenon in both prodromal patients and those with AD dementia.

4.) To determine the existence of distinct relationships between semantic functioning and cortical structure among patients with mild cognitive impairment (MCI) of differing subtypes.

Results obtained in *Experiment 1* indicate that the neuropsychological subtype of MCI may have a substantial influence on neuroimaging findings reflective of cortical involvement associated with semantic memory function. *Experiment 2,* therefore, aims to test the hypothesis that patients with a multi-domain cognitive profile may present with distinctly weaker correlations between semantic processing and grey matter integrity than those with a single-domain profile and furthermore, the hypothesis that patients of an amnestic profile would be more likely to demonstrate relationships with AD related brain regions than those with a non-amnestic profile. The findings of this investigation can be seen in *Chapter 4, Experiment 2*.

5.) To evaluate the utility of graph theoretical techniques in identifying differences in the structure of cognitive networks between the stages of healthy ageing and in neurodegenerative disease.

To investigate further novel techniques for the identification of abnormal cognitive decline, *Experiment 3* applies the methods of graph theory to cognitive networks in an effort to evaluate network-level characteristics of neuropsychological profiles that are indicative of healthy vs pathological ageing. Looking at cognition from a non-reductionist approach, by evaluating the topology of the cognitive network and the shifting relationships between cognitive domains, may provide a novel approach to the assessment of abnormal cognition in the early stages of AD. The present investigation, outlined in *Experiment 3, Chapter 5,* represents the first study to apply graph theoretical methods to analyse cognitive networks in neurodegenerative disease.

6.) To assess differences in the topology of brain structural networks throughout the stages of healthy ageing and in neurodegenerative disease.

The final experiment, *Experiment 4,* applies the same graph theoretical methods as used in the previous study to brain networks derived from regional grey matter volumes. To determine whether the results of *Experiment 3* may be explained by alterations in brain structure, *Experiment 4* assesses the structural network topology of cortical regions in young, middle aged and older healthy adults, as well as three groups of patients including those with an amnestic MCI profile, a non-amnestic profile and AD dementia, as per the previous experiment. The results of this experiment can be found in *Experiment 4, Chapter 5*.

Chapter 4 | Structural Correlates of Semantic Fluency Performance in MCI and Alzheimer's Type Dementia

As previously outlined in *Chapter 2*, a large number of studies to date have utilised verbal fluency tasks as a measure of semantic memory when investigating declines in this function among Alzheimer's disease (AD) patients. Verbal fluency refers to a neuropsychological measure in which participants are required to list as many words as possible beginning with a certain letter (e.g., F), as in phonemic, or letter fluency (Benton, 1968), or belonging to a given category (e.g., Animals), as in semantic, or category fluency (Newcombe, 1969), in a specific time constraint.

It is well documented that semantic memory performance relies heavily on the presence of two cognitive processes: storage of semantic information and control of semantic retrieval (Henry & Crawford, 2004a, 2004b; Wagner *et al*., 2001; Patterson, Nestor & Rogers, 2007). During both types of verbal fluency task, significant engagement of controlled retrieval processes, mediated by intact executive functioning, thought to be reliant on frontal lobes structures, is required for successful performance. In category fluency however, this retrieval process relies further on the integrity of semantic associations contained within the semantic memory store, thought to be sustained by the temporal lobes (Henry & Crawford, 2004a, 2004b; Vonk *et al*., 2019). This neuropsychological test, therefore, provides an easily administered task that draws upon both these broadly defined cognitive functions and is often administered when testing AD patients in clinic (Morris *et al*., 1989). Importantly, perhaps the most beneficial aspect of using tasks such as this, is that the concurrent use of both category and letter fluency measures allows for the isolation of the multiple cognitive processes involved in each, to ascertain the presence of a controlled retrieval deficit vs semantic access impairment (Reverberi *et al*., 2014). It is surprising then, that, to date, only a handful of studies have focussed on the difference in performance declines between these two tasks, as a more highly controlled measure of semantic memory performance, than simply the category fluency task alone. Moreover, what research there is in this area has largely been focussed on the behavioural phenotype of disease and has not yet explored the underlying changes in brain structure and function that may explain this discrepancy phenomenon. Given the prevalence of such discrepancies in AD and even mild cognitive impairment (MCI)

(Henry, Crawford & Phillips, 2004; Murphey, Rich & Troyer, 2006), it follows that this phenomenon may represent an appropriate behavioural measure for the severity of underlying disease processes and could feasibly highlight discrete structural changes within medial temporal regions thought to result in early semantic memory declines (Braak & Braak, 1991; Ameiva *et al*., 2008). However, this hypothesis has yet to be tested within the literature.

4.1. Experiment 1 – Associations between grey matter volume and discrepancy in category/letter fluency decline across the clinical stages of Alzheimer's disease.

4.1.1. Introduction

Considerable research has investigated the impact of AD related cortical degradation on measures of verbal fluency. It is now well documented that, although both types of verbal fluency are susceptible to AD type neurodegeneration, even in the earliest stages (Mueller *et al*., 2015), category fluency appears to be consistently impaired to a greater extent, suggesting that degradation of the semantic system, due to temporal lobe damage in this cohort, significantly outweighs disruption of executive functions (Henry, Crawford & Phillips, 2004). This has been reflected by both lesion studies and those comparing AD patients with patients diagnosed with neurological conditions primarily affecting frontal structures, who tend to show either an opposite pattern of discrepancy, with greater declines in letter fluency, or similar declines in both verbal fluency measures (Rascovsky *et al*., 2007; Capitani *et al*., 2009). One of the first studies to outline such a discrepancy in AD patients was carried out by Monsch and colleagues (1992) who found that category fluency was best able to differentiate AD patients from healthy older controls, with a sensitivity of 100% and specificity of 92.5%, in contrast with letter fluency that discriminated patients and controls with only 89% sensitivity and 85% specificity. Since this seminal paper, a number of studies have recorded a similar discrepancy between the relative deficits in each of these forms of verbal fluency task in AD patients. In a meta-analysis conducted by Henry, Crawford and Phillips (2004), it was concluded, when considering studies using verbal fluency tasks as well as a number of other neuropsychological measures, that AD patients present with significantly more impairment on category fluency tasks, as well as other tasks of semantic memory, such as the Boston Naming Test, compared to tasks of letter fluency. Furthermore, category fluency impairments, and not letter fluency impairments, were considered a

standalone deficit independent of declines in verbal intelligence or psychomotor speed. Taken together, these findings suggest that the category fluency deficit present in AD is likely to reflect considerable damage to the semantic memory store rather than a disruption of controlled retrieval. Finally, the authors report that category fluency was generally impaired to a greater extent than the Boston Naming Test, suggesting that the added demands of effortful retrieval in this task makes it a more sensitive marker of semantic memory decline than a simple naming task.

Further evidence from research in MCI patients has since described a similar pattern of verbal fluency task impairment in this prodromal cohort. Murphy, Rich and Troyer (2006) administered letter and category fluency trials on three participant groups consisting of amnestic MCI (aMCI), AD and healthy control participants. Using a cross sectional design, this study was able to demonstrate the change in verbal fluency task performance patterns from healthy ageing through to AD type dementia. In accordance with normative data (Vaughan *et al*., 2016), healthy older adults demonstrated a significant advantage in the semantic condition relative to the phonemic condition. However, in the patient groups, this advantage disappeared, with MCI patients showing only a marginal, non-significant semantic advantage and the dementia group showing a reverse pattern, with a significant phonemic advantage. More recent evidence from Chasles *et al*., (2020) has similarly demonstrated this pattern in one-to-one matched groups of aMCI patients, patients with dementia and healthy controls. Again, a significant semantic advantage was evidenced in the control group that fell below significance in the aMCI group and was virtually non-existent in patients with dementia. Furthermore, aMCI patients also performed similarly to controls on the measure of phonemic fluency in this study, despite showing significant impairment relative to controls on semantic fluency. Further research by Clark *et al*., (2009), using longitudinal data, has additionally been able to document this decline in category fluency, demonstrating that both preclinical patients who developed dementia during follow up and patients who presented with dementia at baseline showed a significantly greater rate of decline in category relative to letter fluency. Furthermore, at baseline both groups were significantly more impaired in category fluency than letter fluency than a group of cognitively normal controls who remained healthy throughout follow up, with the preclinical group performing comparatively with the cognitively normal group in letter fluency, and the cognitively normal group replicating the semantic advantage (in the animal condition) found in Murphy, Rich and Troyer's previous work (2006). Although in this study greater semantic decline was also evident among the cognitively normal group, despite the relative preservation of semantic

memory in ageing (Hedden & Gabrieli, 2004), this effect was significantly exacerbated in the preclinical AD group. In the AD dementia group both verbal fluency tasks showed significant decline, but the degradation of category fluency continued to decline at a much faster rate. These findings indicate that although declines in category fluency may be present in normal ageing, this is significantly accelerated by AD pathology and such acceleration may be observable several years prior to diagnosis. Clark and colleagues further comment that given the known presence of AD pathology even decades prior to the dementia stages (Jack *et al*., 2010), there is a possibility that members of the control group used in this study may have already been experiencing the initial stages of AD pathology, despite appearing cognitively normal on neuropsychological testing. As semantic memory function is thought to be relatively well preserved in healthy ageing populations (Hedden & Gabrielli, 2004), this may indicate that category fluency could be a sensitive measure to the very earliest stages of pathological decline. More recently, evidence from Vaughan *et al*., (2016) has demonstrated that specifically, discrepancies in verbal fluency performance reflecting a reduction in semantic advantage (semantic fluency score - phonemic fluency score), may provide a potential predictive indicator for progression to dementia among MCI patients. Patients in this longitudinal study who progressed to dementia were found to have a significantly reduced semantic advantage when compared with both controls and MCI patients who remained stable during the study. A further longitudinal study of individuals without dementia, conducted by Vonk and colleagues (2020), was similarly able to demonstrate lower baseline semantic fluency performance and faster declines in semantic performance among individuals at-risk for AD, when compared with those considered low risk. Specifically, those with incident dementia and aMCI at follow-up had significantly lower baseline semantic fluency scores and faster rates of semantic fluency decline than those with no MCI or non-amnestic MCI (MCI-na). Furthermore, similar differences were seen at baseline, and in the rate of semantic decline, among Apolipoprotein-E ε4 allele (ApoE-ε4) carriers compared with non-carriers and those with a score on the Clinical Dementia Rating Scale (CDR) of 0.5, compared with a CDR of 0. Importantly, despite evident declines in semantic fluency among groups at-risk for AD (i.e., ApoE-ε4 carries, participants with a CDR of 0.5, aMCI and incident dementia groups), only the group evidencing dementia at follow-up demonstrated declines in letter fluency and even this was to a lesser extent than category fluency declines. Neurodegenerative measures relating to AD including lower hippocampal volumes, increased white matter hyperintensities and overall cortical thinning, as well as reduced metabolic functioning within a number of AD related areas, including the entorhinal cortex (ERC),

inferior parietal lobule and posterior cingulate gyrus (PCC)/precuneus, were all correlated with lower semantic fluency performance at baseline and similar findings were seen in relation to faster rates of semantic fluency decline. Conversely, no such relationships were found between baseline letter fluency scores and cortical signatures of AD and, although overall indices of neurodegeneration were correlated with the rate of letter fluency decline, this showed no specificity for AD-type alterations. Taken together, these findings therefore suggest, as per the conclusion of previous studies, that declines in semantic fluency, particularly in the absence of letter fluency decline, represent a distinct marker for AD degeneration early on in the course of disease that may predict subsequent development of aMCI or dementia.

Previous cross-sectional research into the diagnostic utility of such discrepancies, using sensitivity and specificity calculations, however, has not necessarily demonstrated the same predictive power (Cerhan *et al*., 2002). Similarly, a meta-analysis re-addressing the phenomenon of the well-described semantic-phonemic fluency discrepancy in AD, concluded that, in the fifty studies chosen for analysis, the effect size for the discrepancy scores did not differ between the 2167 controls and 1771 AD patients included (Laws, Duncan & Gale, 2010). In light of the previous conclusions from Henry and colleagues' (2004) similar meta-analyses, these findings reflect considerable conflict in the literature. Such conflict may be potentially explained by a simple limitation in the methodology of the majority of studies exploring verbal fluency discrepancy; the calculation of discrepancy based on the number of words produced, alone. The use of raw fluency scores to calculate discrepancy does not provide any information as to how far patients have declined on each test, relative to controls. A raw score of twelve on letter fluency and 11 on category fluency would provide a relatively small discrepancy score, however, if control participants scored a mean of 22 on letter fluency but 42 on category fluency then the difference in the amount of decline, relative to controls, would be far greater and would provide a more accurate measure of verbal fluency decline discrepancy. This could, therefore, explain why the AD patients in Cerhan *et al*., (2002) were found to differ significantly from controls in terms of discrepancy, but that this discrepancy was not useful in terms of predicting group membership. This would also explain why the results of Laws and colleagues (2010) demonstrated significantly greater effect sizes for semantic fluency when compared with phonemic fluency across the entire 135 studies, despite showing no difference in effect sizes for discrepancy between patients and controls in the smaller 50 study sample. Furthermore, evidence from longitudinal studies looking at rates of decline, rather than static differences in raw fluency scores, have consistently shown

significantly greater rates of decline in semantic fluency compared with phonemic fluency (Salmon, Heindel & Lange, 1999; Clark *et al*., 2009; Vaughan *et al*., 2016; Vonk *et al*., 2020), suggesting that verbal fluency discrepancy measures are most accurate when reflecting differences between the relative distance from a control mean.

Evidence from studies utilising at-risk groups, such as carriers of ApoE-ε4 and those testing positive for Aβ accumulation, has since supported this, suggesting that differences in category fluency performance are detectable even in cognitively healthy individuals who do not yet show any additional signs of neurodegeneration (Rosen *et al*., 2005; Papp *et al*., 2016; Papp *et al*., 2017; Vonk *et al*., 2019). In particular, a study from Papp *et al*., (2016), demonstrated that clinically normal older adults who tested as Aβ positive (Aβ+) declined to a significantly greater extent longitudinally, than Aβ negative (Aβ-) participants, on a measure of category fluency. Furthermore, this difference remained significant even when covarying for letter fluency. In contrast, however, although Aβ+ participants also showed similarly greater declines in letter fluency relative to the Aβ- group, this difference did not retain significance when category fluency was added as a covariate. Furthermore, Papp and colleagues went on to suggest, in a later study, that category fluency tasks could explain unique variances in cognitive declines related to Aβ accumulation, with Aβ+ individuals demonstrating continued significant decline relative to Aβ- in category fluency even when controlling for the overall decline measured by the preclinical Alzheimer's cognitive composite (PACC) (Papp *et al*., 2017). Moreover, the removal of category fluency from the PACC in this study resulted in a longitudinal reduction in amyloid-related decline of 20% at 3 years of follow-up, making category fluency one of the greatest contributors to the PACC found in this study. Interestingly, further research looking at the relationship between verbal fluency and total tau levels have also demonstrated significant correlations between this cerebrospinal fluid biomarker and category fluency performance among MCI patients (Mirandez *et al*., 2017), suggesting that this measure is indicative of both preclinical and prodromal accumulations of AD related protein aggregates.

Given the interest surrounding verbal fluency task deficits as part of the AD presentation, there has now been a substantial body of work aiming to uncover the neural correlates of such changes. Studies using AD patients have found a variety of regions associated with a category fluency deficit, including temporal areas such as superior and middle temporal gyri (Venneri *et al*., 2008), as well as anterior cingulate (Apostolova *et al*., 2008; Venneri *et al*., 2008) and frontal and parietal regions, including posterior superior and middle frontal gyri and parietal association cortices (Grossman *et al*., 2003; Apostolova *et al*.,

2008). Similar regions have since been implicated in the category fluency decline seen in MCI patients (McDonald *et al*., 2012) and further research has even demonstrated that category fluency declines in this population can highlight variance within medial temporal regions, despite patients presenting with no significant decreases in grey or white matter volumes relative to controls (Meyer *et al*., 2013). Moreover, performance on semantic memory tests such as this in MCI patients has been related specifically to grey and white matter volumes within the perirhinal cortex (PRC) and ERC, the first areas affected by AD pathology (Hirni *et al*., 2013; Meyer *et al*., 2013).

Verbal fluency discrepancies, however, have rarely been utilised in imaging studies, perhaps due to the conflicting evidence of their diagnostic efficacy within the literature (Cerhan *et al*., 2002; Henry, Crawford & Phillips, 2004; Laws, Duncan & Gale, 2010; Vaughan *et al*., 2016). One study by Keilp *et al*., (1999) however, did explore the neural correlates of this measure, among AD patients and controls, through the use of a resting, Xenon-inhalation, regional cerebral blood flow measurement (^{133}Xe-rCBF). The advantage of this study was that, unlike previously mentioned research, the verbal fluency discrepancies in this case were calculated using measures of category and letter fluency performance that had been standardised to *z* scores using norms stratified by age, sex (only in letter fluency) and education levels. As in previous research, this study demonstrated that AD patients performed significantly worse on measures of category fluency, relative to letter fluency, in this case an entire standard deviation (SD) below the letter fluency scores. When correlated with rCBF indices, calculated for parietal and frontal regions across the whole sample, both the standardised category and letter fluency scores were associated only with the standard AD measures within the parietal cortex as well as a measure of diffuse cortical perfusion reductions (mean flow). Discrepancy scores within the AD group were strongly, negatively correlated with the frontal index bilaterally, such that the greater the blood flow within these areas, the less discrepancy in the amount of decline between the two fluency measures. In line with previous research, this study simply serves to reiterate the notion that more frontally focussed cortical damage is likely to be associated with comparable decline in verbal fluency measures (Kitabayashi *et al*., 2001; Mummery *et al*., 1996; Henry & Crawford 2004a, 2004b; Rascovsky *et al*., 2007; Capitani *et al*., 2009) and provides little information about the disease mechanisms underlying a decline discrepancy.

4.1.1.1. Aims and Hypotheses

Given the findings of previous research, the present study aimed to assess the relationship between verbal fluency decline discrepancy and AD pathology, as assessed by structural magnetic resonance imaging (MRI). Three groups of patients, stratified by disease severity, underwent extensive neuropsychological testing, including measures of letter and category fluency. Further behavioural analysis was conducted using normative data from a matched control group to investigate the presence of an accelerated and more severe decline of category relative to letter fluency in the presence of AD pathology. A measure of discrepancy was further analysed in conjunction with grey matter volumetric data in order to ascertain the anatomical basis of disease mechanisms associated with this well documented phenomenon (Henry, Crawford & Phillips, 2004).

It was hypothesised, in light of previous work, that discrepancies in mild MCI patients would correlate most strongly with anterior medial temporal areas, reflecting the limited spread of pathology in this group. As disease severity increased however, it was expected that increased involvement of posterior medial temporal lobe (MTL) structures including the hippocampus would become apparent and further include wider areas of neocortex in the AD dementia group, in accordance with the greater spread of pathology in these patients. Behaviourally, it was expected that all groups, even those only mildly affected by AD pathology would likely present with a significant discrepancy in the severity of the decline on measures of verbal fluency, such that category fluency would show significantly greater decline relative to letter fluency. Between groups it was expected that category fluency scores would differ significantly, showing a linear relationship with disease severity, whereas letter fluency would show little change in the amount of decline despite disease progression.

4.1.2. Materials and Methods

4.1.2.1. Participants

Three groups took part in this study, consisting of a total of 202 participants, recruited into the EU funded Virtual Physiological Human: DementiA Research Enabled by IT (VPH-DARE@IT) study at two sites, the Royal Hallamshire Hospital, Sheffield, United Kingdom and the IRCCS Fondazione Ospedale San Camillo, Venice Lido, Italy. For the purposes of this project, participants were stratified into groups according to disease severity. In the first instance, two groups were formed of AD patients at the dementia stage (40 males, 33

females) and at the MCI stage (54 males, 75 females). Both AD dementia and MCI patients were recruited through a memory clinic after receiving a medical diagnosis from a neurologist, following referral from their GP. All the participants underwent extensive clinical assessment, including completion of comprehensive neuropsychological assessment, as well as structural brain imaging, prior to a diagnosis. A probable AD diagnosis was confirmed adhering to the NINCDS-ADRDA clinical criteria (McKhann *et al*., 2011) and MCI patients of the AD aetiology were diagnosed following the criteria outlined in Albert *et al*. (2011). All participants were fluent in English, in the case of the Sheffield cohort, or Italian in the case of the Venice cohort. All procedures were carried out according to the Declaration of Helsinki. Ethical approval for this study was granted by the Yorkshire and Humber Regional Ethics Committee (Ref No: 12/YH/0474) for the Sheffield cohort and the joint ethics committee of the Health Authority Venice 12 and San Camillo IRCCS (Protocol number 2014.08) for the Venice cohort.

I. MCI Classification

MCI patients were then further stratified into mild and moderate disease severity groups, as defined by a median split of their performance on the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). The use of the MMSE to distinguish disease stages is reflective of evidence that MMSE scores strongly correlate with histopathological measures of AD pathology, including the density of plaques and tangles in a range of cortical regions, as well as the Braak stages (Sabbagh *et al*., 2010). Furthermore, MMSE score segregation has shown substantial agreement with widely recognised measures of disease staging in dementia such as the CDR (Hughes *et al*., 1982; Perneczky *et al*., 2006). In accordance with studies that have found a cut-off of 27 on the MMSE to be a sensitive marker of cognitive decline (O-Bryant et al., 2009; Creavin et al., 2016), participants were categorised as mild (n = 74) if they achieved the median score of 27 or more on this measure of cognition and as moderate (n = 55) if they achieved less than the median score of 27. To characterise the sample further and identify sub-types, classification of MCIs was carried out according to the neuropsychological test battery utilised in this study. Sample-based norms for cognitive test scores were created using two cohorts of healthy controls consisting of 30 participants from Sheffield and 60 from Venice that were matched with the MCI patients for age, education, gender and nationality. All controls underwent a clinical interview to ensure they had no history of neurological diseases, or any other afflictions that may affect their

cognition. Furthermore, all underwent laboratory, MRI and neuropsychological assessment to confirm the absence of any abnormalities. Sample-based normative data, taken as the mean raw score from each of these control samples, were established for each neuropsychological test, and a cut-off of 1.5 SDs below the normal mean was determined for each (1.5 SDs above the mean for Stroop measures) (See **Table 4.1**). This is in accordance with clinical diagnostic protocols, which recommend that a test score 1.5 SDs below the average score for a given person's age or education level, in the context of their clinical history, may be considered indicative of cognitive impairment (Petersen, 2004; Albert et al., 2011). In the case of missing data, fifty-nine controls were used to create *z* scores for the Token test and each Stroop measure. MCI patients were then categorised based on the tests for which they scored at or below cut-off (or above in the case of Stroop measures), revealing sixty-nine patients as multi-domain amnestic MCI (aMCI-md), 11 as single-domain amnestic MCI (aMCI-sd), 10 as single-domain non-amnestic MCI (sd-MCI-na) and 21 as multi domain non-amnestic MCI (md-MCI-na) (see ***Fig. 4.1***). Eighteen participants were excluded from the study at this point, as they performed within a healthy range on all tests and therefore could not be classified. This left fifty-three participants in the moderate MCI group and 58 in the mild MCI group.

Table 4.1

Table showing normative data acquired using the mean scores of two control samples, gathered from Venice and Sheffield, on each test within the neuropsychological test battery used for this study, along with the standard deviations (SD). The cut-offs in this case were calculated by subtracting 1.5 SD from the mean. In the case of the two Stroop measures the cut-off was calculated as 1.5 standard deviations above the mean.

Neuropsychological Test	Venice (n = 60)			Sheffield (n = 30)		
	Mean	SD	Cut off	Mean	SD	Cut off
MMSE	28.62	1.55	26.29	28.00	1.49	25.77
Raven Matrices	28.52	4.43	21.87	31.83	4.25	25.43
Letter fluency	33.48	11.63	16.04	49.60	15.14	26.89
Category fluency	38.07	9.94	23.15	56.13	12.05	38.06
Digit Cancellation	51.13	6.81	40.91	52.20	6.92	41.82
Similarities	20.00	4.74	12.88	24.60	3.92	18.72
Token Test	33.92	2.14	30.71	34.92	1.10	33.27
Rey Figure Copy	32.28	3.40	27.18	31.50	3.29	26.56
Rey Figure Recall *	14.04	5.56	5.70	14.42	4.02	8.39
Stroop Time Interference	27.76	10.26	43.15	23.92	15.46	47.11
Stroop Error Interference	1.09	1.81	3.81	0.28	1.11	1.95
Digit Span Forward	5.90	0.97	4.45	6.13	1.20	4.34
Digit Span Back	4.17	0.78	2.99	5.27	1.31	3.30
Prose Memory Immediate *	9.28	3.41	4.18	14.93	3.10	10.29
Prose Memory Delayed *	12.72	4.73	5.63	18.73	2.39	15.14
Paired Associates *	11.63	3.47	6.43	16.23	3.18	11.46
Confrontation Naming	18.80	1.75	16.17	18.97	1.13	17.28

* Scores on these tests were used as measures of memory function. Therefore, a score below cut-off in these tests would automatically classify a patient as amnestic variant MCI.

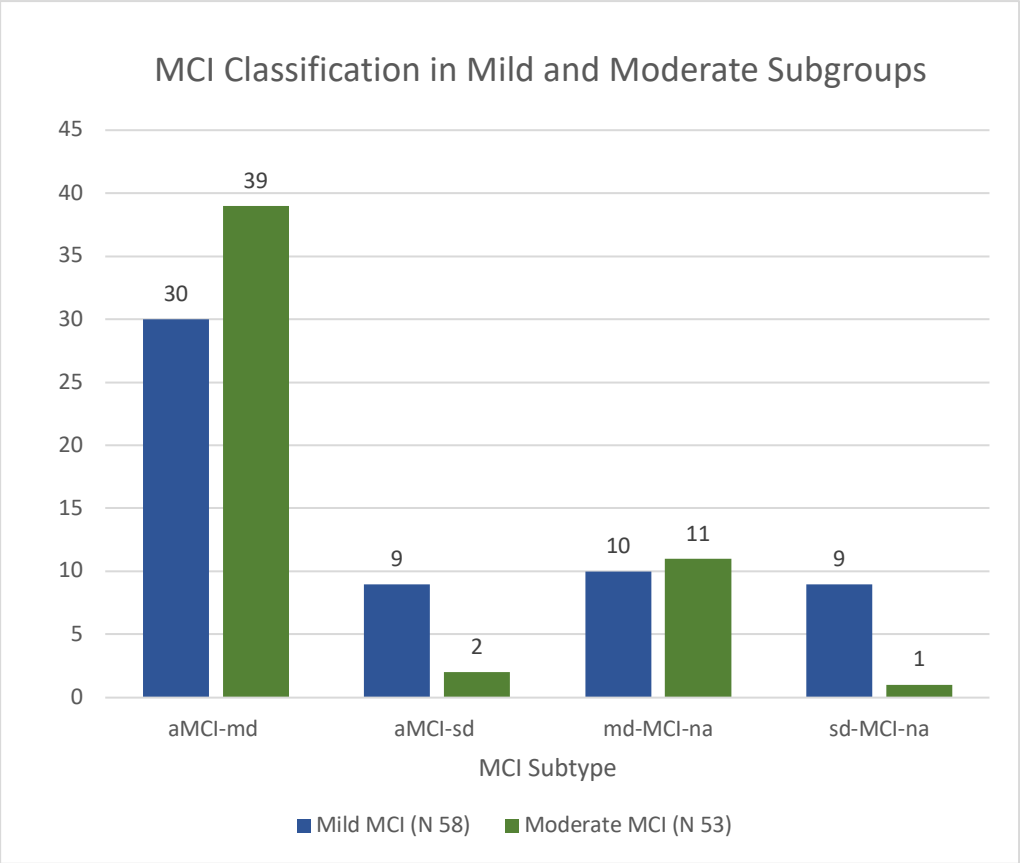


Figure 4.1. *Bar chart showing the number of MCI patients assigned to each of the MCI sub-types according to the neuropsychological test score cut-offs defined as 1.5 standard deviations below the mean score of age, education and nationality matched control groups.*

4.1.2.2. Demographic Data

The demographic data and MMSE (Folstein, Folstein, & McHugh, 1975) scores of all participants can be seen in **Table 4.2**. A Pearson Chi Square revealed no significant difference in the proportion of female and male participants between the dementia, mild MCI and moderate MCI groups, X^2 (2, N = 184) = 5.73, p = .057. Unlike MCI patients however, the dementia group did include a higher number of male than female participants. Given participants were selected retrospectively, one-to-one matching was not possible in this case. As such, selecting patients who were more closely matched in age and education took precedent over gender, given these factors would likely have a greater impact on results. Kruskal-Wallis H test revealed no significant differences between groups in terms of age at scan, $X^2(2) = 1.49$, $p = .47$, with mean ranks of 96.66 for mild MCI, 96.08 for moderate MCI and 86.60 for dementia. The same test revealed no difference in years of education between groups, $X^2(2) = .61$, $p = .736$, with mean ranks of 96.82 for mild MCI, 91.68 for moderate MCI and 89.66 for dementia. The medians and interquartile ranges for each group are outlined in **Table 4.2**.

Table 4.2

Gender ratios, medians (and interquartile range) for age, years of education and Mini Mental State Examination (MMSE) are presented for Alzheimer's disease (AD) and mild cognitive impairment (MCI) patient groups. Between-group differences assessed with a Kruskall-Wallis H test. Gender-ratio differences were calculated with a chi-square test.

	Mild MCI (*n* = 58)	**Moderate MCI (*n* = 53)**	**AD (*n* = 73)**
Age (Years)	75.00 (9.00)	74.00 (14.00)	74.00 (19.00)
Years of Education	10.00 (5.00)	10.00 (5.00)	11.00 (7.00)
Gender (M/F)	21/37	20/33	40/33
MMSE	28.00 (2.00)	25.00 (1.00) [a]	21.00 (5.00) [ab]

[a] Significantly lower than mild MCI [p<0.05], [b] Significantly lower than Moderate MCI [p <0.05]

4.1.2.3. Neuropsychological Assessment

In order to ensure that none of the participants violated the prerequisites for study inclusion, all received neurological screening by a senior clinical neurologist. Exclusion criteria in the present study encompassed any diagnostic entity, medical profile, significant psychiatric condition or significant pharmacological treatment involving psychotropic medicines that could explain or affect the study outcome. Following clinical assessment all participants were then required to complete a neuropsychological test battery, including a range of tests measuring semantic memory, episodic memory, speed of processing and executive function. An exhaustive list of this battery can be seen in **Table 4.1**.

I. Semantic Memory Function

Semantic memory function was assessed using semantic verbal fluency, otherwise known as category fluency (Newcombe, 1969). Category fluency, in its standard form, requires participants to recall as many words as they can, belonging to a certain category, in one minute. For the purposes of this study, the categories chosen for the Sheffield cohort were presented in this order: cities, animals, fruits. The categories for the Venice cohort differed slightly with car brands replacing the 'cities' category in the following order: car brands, fruits, animals. Participants' scores amounted to the total number of unique words produced within one minute for each category. This type of verbal fluency is often administered in conjunction with a further verbal fluency test known as phonemic, or letter, fluency (Benton, 1968). This type of verbal fluency tests differs from category fluency in that it requires participants to produce words beginning with a certain letter. In this case, the letters used for Venice and Sheffield were the same for each cohort: F, P and L. Controlling for letter fluency allows for the isolation of the cognitive process of semantic retrieval, only

required during category fluency, while controlling for extraneous cognitive processing, such as the executive functions, elicited during both tasks. Given the differences between the two centres in terms of language used and category choice, patients' scores were all standardised according to the means and SDs of matched control groups, as described below in section *4.1.2.4. II.*

4.1.2.4. MRI Protocol

Three-dimensional T1-weighted scans were collected from all participants recruited in Sheffield and a subset of participants collected in Venice, using an identical MRI protocol with a Philips Ingenia 3.0 T scanner. The parameters used were as follows: voxel dimension .94 × .94 × 1.0 mm, field of view 256 mm, matrix size 256 × 256 × 124, repetition time 8.2 msec, echo time: 3.8 msec, and flip angle 8°. One-hundred and five of the participants collected in Venice however, underwent an MRI protocol acquired using a 1.5 T Philips Achieva scanner with parameters as follows: Turbo Field Echo 3D sequence, voxel dimension 1.1 × 1.1 × 0.6 mm, field of view 250 mm, matrix size 256 × 256 × 124, repetition time: 7.4 ms, echo delay time: 3.4 ms and flip angle: 8°.

I. Pre-processing Procedures

Using SPM12 software run in a Matlab environment (version R2011b; Mathworks Inc., UK), Voxel Based Morphometry (VBM) preprocessing procedures were applied to 202 anatomical scans (Ashburner & Friston, 2000). Firstly, images were individually reoriented in accordance with six rigid body transformations. In this procedure the origin of the cross hair was set to the anterior commissure and was further aligned on the sagittal plane with the posterior commissure and on the coronal and axial planes along the longitudinal fissure. Reorientation acts as a contributory step allowing for more accurate execution of later pre-processing stages when scans are normalised to adhere to a homogenous space. Secondly, the segmentation of images separated them into maps pertaining to the tissue classes of grey matter, white matter and cerebrospinal fluid. This process is carried out by calculating the Bayesian probability for each voxel that it will belong to each tissue class based on *a priori* information (Ashburner & Friston, 2000). Finally, normalisation was carried out on the warped, segmented grey matter maps in order that each one adhered to a common space based on the data of the Montreal Neurological Institute (MNI). The normalised grey matter maps were further smoothed with an 8-mm full width at half-maximum Gaussian filter

Global volumes for all tissue classes taken from each scan in the native space were acquired using the "get totals" script (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) (**Table 4.3**). Tissue volumes from each group were compared, revealing the dementia group to differ significantly, in relation to both the mild and moderate MCI groups, on a number of tissues class measures listed in **Table 4.3**. However, no differences were apparent between this group and the other two groups on white matter volume (mild MCI p = .20, moderate MCI p = .28) or overall head size, as measured by total intracranial volume (mild MCI p = 0.34, moderate MCI p = .31). Results are outlined in the **Table 4.3**.

Table 4.3

Mean tissues class volumes and standard deviations (SDs) for AD and MCI. Also includes mean tissue class fractions for each group. Independent samples t tests along with Mann-Whitney U tests were used to calculate between-group differences. ([a] Significantly lower than mild MCI [p<0.05], [b] Significantly lower than Moderate MCI [p <0.05], [c] Significantly lower than dementia [p<0.05]), Significant results defined by Mann-Whitney presented as [a, b, c])

	Mild MCI (*n* = 58)		**Moderate MCI (*n* = 53)**		**AD (*n* = 73)**	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Total Intracranial Volume (ml)	1396.58	152.75	1395.70	139.33	1422.54	152.37
Grey-matter volume (ml)	550.82	63.90	554.55	67.22	523.40 [a, b]	68.67
White-matter volume (ml)	411.14	54.63	409.47	53.61	399.05	52.70
Cerebrospinal-fluid volume (ml)	434.62 [c]	97.3	431.69 [c]	114.06	500.09	113.90
Grey-matter fraction	0.40	0.04	0.40	0.05	0.37 [a, b]	0.04
White-matter fraction	0.29	0.03	0.29	0.03	0.28 [a, b]	0.03
Brain parenchymal fraction	0.69	0.05	0.69	0.06	0.65 [a, b]	0.06

Note: Tissue class fractions were calculated as tissue volume (in ml) (acquired using get_toals) divided by the total intracranial volume i.e. the value of all tissue classes combined.

II. Neuropsychological Analytical Procedures

In order to ascertain the relative declines in letter and category fluency in each of the patient groups, fluency scores were taken from two healthy control groups, selected to match with all patient groups for age, education, gender and nationality, made up of 60 participants from the UK and 53 from Italy. The data from these healthy groups were used to create sample-based normative data for both of the fluency scores. To characterise decline, the means and SDs taken from the controls for each of the verbal fluency measures were used to obtain standardised z scores for the patient data. In order to control for the effects of shared cognitive processes associated with both verbal fluency measures, the category fluency z scores were subtracted from the letter fluency z scores to obtain a discrepancy score for each

participant, reflecting the relative difference in the amount of decline on each verbal fluency task. Control data are presented in **Table 4.4**.

Table 4.4

Mean scores and standard deviations on the category and letter fluency tasks taken from British and Italian control groups.

	Venice Controls (*n* = 53)	**Sheffield Controls (*n* = 60)**
Letter Fluency	32.08 (9.84)	46.65 (13.81)
Category Fluency	37.09 (9.16)	56.55 (12.03)

III. Whole Brain VBM Analytical Procedures

The relationship between grey matter volumes and measures of verbal fluency were assessed separately for each group using whole brain regression analyses carried out in SPM12. Two patients from the dementia group were removed from the model as they did not have verbal fluency scores available. The final numbers of participants included in each group for VBM analysis were therefore, seventy-one in the dementia group, 58 in the mild MCI group and 53 in the moderate MCI group. Analyses were run using the discrepancy scores, calculated as described previously, as the independent variable. The dependant variable in all cases was the grey matter volumes determined by VBM and all multiple regression paradigms included age at scan, years of education, MMSE scores and total intracranial volume (ml) as covariates, to account for the variability explained by these variables. The threshold of significance chosen in this study was an uncorrected set-level *p* value equal to .005. Clusters surviving a cluster-level Family-Wise Error-corrected (FWE) $p < .05$ were the only observed clusters considered for interpretation. Peak coordinates of clusters surviving the FWE ($p < .05$) were converted into Talairach space using a non-linear transform (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m) and were interpreted using the Talairach Daemon client (http://www.talairach.org/client.html), selecting the "Nearest Grey Matter" search option (Lancaster *et al*., 2000).

IV. Region of Interest Procedure

Twelve regions of interest were selected using the cytoarchitecturally defined Brodmann's areas (BAs) that encompassed the majority of the temporal lobe (**Table 4.9**). Included were the hippocampus, as well as anterior medial temporal regions of the PRC and ERC. The PRC was defined here as BA 35 and 36 (Ding & Van Hoesen, 2010), while the ERC was defined as BA 28 and 34 (Fischl *et al*., 2009). The WFU_PickAtlas toolbox

(Maldjian *et al*., 2003) was used within SPM12 to generate separate right and left hemisphere region of interest (ROI) masks for each of these BAs. The created BA masks were then co-registered to a smoothed grey matter map taken from a control participant. These co-registered masks were then entered in to the "get_totals ([],[],[])" script, along with the smoothed grey matter maps from each of the participants, giving the grey matter volumes of each ROI in millilitres. As well as the ROIs, the grey matter volumes of the temporal lobes in each hemisphere were calculated using the same method. The volumes taken from each ROI were divided by the volumes of the temporal lobe of that hemisphere to create temporal lobe ratios. These temporal lobe ratios were then entered into partial correlation models to test the association between semantic memory measures, including either category fluency z scores or discrepancy scores, and the grey matter volumes of interest. Either Pearson's r or Spearman's Rho correlations were run between each semantic memory measure and each regional fraction depending on the normality of the variables. Again, each partial correlation model further included the control variables age, MMSE score and years of education. As in the whole brain analysis, age was controlled for given its known effect on cognitive ability and brain volume (Tarroun *et al*., 2007), education levels controlled for the effects of cognitive reserve (Stern, 2009) and finally, MMSE scores served to control for variability in extraneous cognitive performance due to differences in disease severity that may contribute to the findings. Partial correlations including category fluency *z* scores also included letter fluency z scores as a further covariate.

V. White Matter Lesion Analysis

Given the differences in cognitive profile between the two MCI groups, analysis into the vascular burden of the present MCI participants was conducted using white matter lesions as a proxy for vascular damage. This was to ensure further that the two groups did not significantly differ from each other in terms of aetiology. Where available, fluid-attenuated inversion recovery (FLAIR) images taken from each participant were reoriented along with the T1 images taken on the same day. Due to the unavailability of FLAIR images for some participants, one mild MCI and 3 moderate MCI patients were excluded from this analysis. Lesion segmentation was conducted using the lesion growth algorithm implemented by the Lesion Segmentation Tool toolbox version 2.0.1 (www.statistical-modelling.de/lst.html) within SPM12. A pre-chosen initial threshold of 0.3 was chosen by visual inspection of the FLAIR images. FLAIR images were inputted along with the reoriented T1 images.

The algorithm first segments the T1 images into the three main tissue classes (cerebrospinal fluid [CSF], grey matter and white matter). This information is then combined with the coregistered FLAIR intensities in order to calculate lesion belief maps. By thresholding these maps with a pre-chosen initial threshold (0.3) an initial binary lesion map is obtained that is subsequently grown along voxels that appear hyperintense in the FLAIR image. The result is a lesion probability map. The volume (in ml) and number of lesions for each participant can then be extracted from this output map and used for statistical analysis.

4.1.3. Results

4.1.3.1. Neuropsychological Results

All participants completed the same neuropsychological test battery as listed in **Table 4.1**. Normality checks were carried out for each of the variables to reveal that the majority of the behavioural data for each participant group was not normally distributed. For this reason, a non-parametric Kruskal-Wallis H test was first used to determine significant differences between the group mean ranks. This excluded the scores on the Raven matrices (Raven, 1947) as these were normally distributed in all three groups. The statistical findings of the Kruskal-Wallis are reported in **Table 4.5**. In some cases, there were missing data, due to patients being unable to complete testing, that is reflected in the number of participants listed along with each test in **Table 4.5**. A one-way ANOVA revealed significant differences between groups for the scores on the Raven matrices ($F(2, 175) = 24.52$, $p < .001$. Post-hoc analyses, using a Bonferroni correction, revealed that dementia patients ($N = 67$, $m = 19.36$) scored significantly lower than both mild ($m = 26.78$, $p < .001$) and moderate MCI groups ($m = 24.02$, $p < .001$).

Table 4.5

Table containing the results of a Kruskal-Wallis H test to determine which neuropsychological tests scores differed significantly between the three groups according to disease severity (e.g. Mild MCI, Moderate MCI and Dementia). Post-hoc Dunn tests were further carried out between each pair. A Bonferroni correction was applied to adjust the p value for multiple comparisons. Significant differences between group pairs are highlighted. ([a] Significantly lower than mild MCI [p<0.05], [b] Significantly lower than Moderate MCI [p <0.05]). Differences determined by independent-samples t-tests are denoted as [a] [b]) WAIS, Wechsler Adult Intelligence Scale

Neuropsychological Test	Patient Group	*n*	Mean (SD)	Median (IQR)	Mean Rank	Chi-Square	df	p value
Letter fluency (Raw Scores) (Benton, 1968)	Mild MCI	58	31.00 (11.20)	31.00 (17.00)	114.69	18.28	2	<.001
	Moderate MCI	53	25.30 (10.39) **a**	23.00 (15.00)	87.92			
	Dementia	71	22.61 (11.29) a	20.00 (16.00)	75.23			
Letter Fluency *Z* Scores	Mild MCI	58	-0.26 (1.17)	-0.38 (1.45)	119.40	28.25	2	<.001
	Moderate MCI	53	-.95 (1.0) **a**	-1.13 (1.53)	89.91			
	Dementia	71	-1.35 (0.97) a	-1.35 (1.22)	69.90			
Category fluency (Raw Scores) (Newcombe, 1969)	Mild MCI	58	31.22 (9.50)	29.50 (10.00)	119.50	38.42	2	<.001
	Moderate MCI	53	27.09 (9.32)	26.00 (15.00)	99.12			
	Dementia	71	20.83 (9.40) ab	19.00 (13.00)	62.94			
Category Fluency *Z* Scores	Mild MCI	58	-.90 (.87)	-1.03 (1.04)	130.34	66.36	2	<.001
	Moderate MCI	53	-1.54 (.87) a	-1.54 (1.20)	97.86			
	Dementia	71	-2.35 (0.81) **ab**	-2.37 (1.09)	55.02			
Discrepancy Scores	Mild MCI	58	.64 (1.25)	0.35 (1.51)	82.69	6.47	2	.04
	Moderate MCI	53	.58 (.97)	0.67 (1.31)	84.55			
	Dementia	71	1.01 (0.92) ab	0.94 (0.97)	103.89			
Digit Cancellation (Spinnler & Tognoni, 1987)	Mild MCI	58	47.31 (7.37)	49.00 (12.00)	123.10	45.64	2	<.001
	Moderate MCI	53	42.66 (8.93) a	42.00 (10.00)	97.90			
	Dementia	71	33.11 (13.06) **ab**	35.00 (19.00)	60.91			
WAIS Similarities (Wechsler, 1997)	Mild MCI	58	18.59 (4.36)	19.00 (5.00)	118.31	40.02	2	<.001
	Moderate MCI	53	16.26 (4.33) **a**	16.00 (6.00)	96.58			
	Dementia	68	12.38 (6.06) ab	11.50 (9.00)	60.72			
Token (De Renzi & Vignolo, 1962)	Mild MCI	57	33.34 (2.14)	33.00 (3.00)	123.71	51.29	2	<.001
	Moderate MCI	53	31.86 (2.58) a	32.00 (2.75)	97.38			
	Dementia	70	29.04 (3.96) ab	30.00 (5.00)	58.25			
Rey Figure Copy (Osterreith, 1944)	Mild MCI	58	29.82 (5.73)	31.25 (7.00)	118.22	38.63	2	<.001
	Moderate MCI	52	26.62 (6.96) a	28.00 (8.60)	94.13			
	Dementia	68	20.03 (9.93) ab	21.50 (16.60)	61.46			
Rey Figure Recall (Osterreith, 1944)	Mild MCI	58	8.66 (5.17)	7.25 (8.40)	111.31	29.10	2	<.001
	Moderate MCI	52	7.02 (4.43)	6.75 (5.40)	98.79			
	Dementia	68	4.11 (4.27) ab	3.00 (6.40)	63.79			
Stroop Time (Venneri *et al*., 1992)	Mild MCI	58	32.23 (15.79)	31.50 (25.60)	75.66	5.29	2	.071
	Moderate MCI	52	42.23 (26.68)	34.50 (32.60)	92.10			
	Dementia	65	50.25 (48.53)	40.00 (47.80)	95.73			
Stroop Errors (Venneri *et al*., 1992)	Mild MCI	58	3.03 (5.71)	0.50 (25.00)	61.84	29.20	2	<.001
	Moderate MCI	52	5.85 (7.77) a	2.50 (7.50)	88.68			
	Dementia	65	10.16 (9.25) a	7.00 (15.50)	110.79			

Table 4.5 cont.

Neuropsychological Test	Patient Group	*n*	Mean (SD)	Median (IQR)	Mean Rank	Chi-Square	df	p value
Digit Span Forward (Wechsler, 1997)	Mild MCI	58	5.74 (1.05)	6.00 (1.00)	113.66	21.12	2	<.001
	Moderate MCI	53	5.30 (0.82)	5.00 (1.00)	94.21			
	Dementia	72	4.96 (0.94) [a]	5.00 (1.00)	72.92			
Digit Span Backward (Wechsler, 1997)	Mild MCI	58	3.98 (0.1)	4.00 (2.00)	112.14	21.75	2	<.001
	Moderate MCI	53	3.58 (0.97)	4.00 (1.00)	97.77			
	Dementia	72	3.13 (0.99) [ab]	3.00 (2.00)	71.53			
Prose Memory Immediate (Wechsler, 1997)	Mild MCI	58	7.78 (3.29)	8.00 (4.30)	119.03	43.26	2	<.001
	Moderate MCI	53	6.66 (3.79)	7.00 (5.00)	102.93			
	Dementia	71	3.68 (2.92) [ab]	3.00 (5.00)	60.47			
Prose Memory Delayed (Wechsler, 1997)	Mild MCI	58	8.22 (4.67)	8.00 (7.00)	114.89	41.96	2	<.001
	Moderate MCI	53	7.75 (5.44)	7.00) (9.00)	107.85			
	Dementia	71	3.23 (3.87) [ab]	2.00 (5.00)	60.19			
Paired Associates (Wechsler, 1997)	Mild MCI	58	9.51 (3.01)	9.25 (3.60)	118.32	58.59	2	<.001
	Moderate MCI	52	8.68 (3.50)	8.25 (4.80)	105.78			
	Dementia	68	5.15 (3.18) [ab]	4.50 (3.00)	52.47			
Naming	Mild MCI	57	18.37 (1.64)	19.00 (6.00)	109.02	21.65	2	<.001
	Moderate MCI	53	17.79 (2.35)	18.00 (2.00)	97.89			
	Dementia	69	15.43 (4.10) [ab]	16.00 (6.00)	68.23			

Further *post-hoc* analyses were performed between group pairs for the cognitive tests scores that were found to be normally distributed in two of the three groups. Significant group differences as determined by *post-hoc* independent-samples *t*-tests are outlined in **Table 4.5.**

I. Verbal Fluency Z Scores

As outlined in **Table 4.5**, significant differences between groups were observed in both letter and category fluency *z* scores as well as discrepancy scores. As demonstrated by the results of a Kruskall Wallis *H* test, including *post-hoc* Dunn tests, with Bonferroni correction, the dementia group tended to perform significantly further below the control mean than the mild MCI group on both the letter fluency (p <.001) and category fluency (p <.001) tests, represented in the above table by their respective *z* scores. An independent-samples *t*-test further confirmed that the dementia group also demonstrated significantly lower *z* scores (m = -2.35) for the category fluency test when compared with the moderate MCI group (m = -1.54) $t(122) = 5.38$, $p < .001$ and a *post-hoc* Mann-Whitney *U* test also suggested that, despite not surviving a Bonferroni correction, there was a modest but significant difference between the moderate MCI and dementia group on letter fluency *z* scores, with dementia

patients (mdn = -1.35) tending to perform significantly further below the control mean than the moderate MCI group (mdn = -1.13) ($U = 1455$, $p = .03$).

An independent-samples *t*-test similarly revealed that the moderate MCI group also demonstrated declines on the letter fluency task, as represented by *z* scores (m = -.95), that were significantly further from the control mean than the mild MCI group (m -.26) $t(109) = 3.34$, $p = .001$. Likewise, a Mann-Whitney *U* test demonstrated similar differences between the groups on category fluency *z* scores (mild MCI: mdn = -1.03, moderate MCI: mdn = -1.54) $U = 927$, $p < .001$.

Within-group analysis was also carried out in order to assess the difference in the relative declines on each type of verbal fluency at each stage of disease progression. Based on the normality checks already performed for each variable, the non-normality found in category fluency *z* scores within the mild MCI group and letter fluency *z* scores in the dementia group meant that within group differences for these groups were assessed using non-parametric Wilcoxon Signed Rank tests. The within group differences between verbal fluency *z* score means in the moderate MCI, however, were assessed using a paired-samples *t*-test. The mild MCI group demonstrated significantly greater declines in category fluency relative to letter fluency (mdn = -.38) as evidenced by significantly lower category fluency *z* scores ([mdn = -1.03] $z = -3.79$, $p < .001$). The moderate MCI group also showed significantly greater declines in category fluency relative to letter fluency $t(52) = 4.41$, $p < .001$. Finally, the dementia group again demonstrated the same pattern with significantly lower category fluency *z* scores (mdn = -2.37) relative to letter fluency *z* scores (mdn = -1.35) $z = -6.66$, $p < .001$. A summary of these findings is outlined in ***Fig. 4.2***.

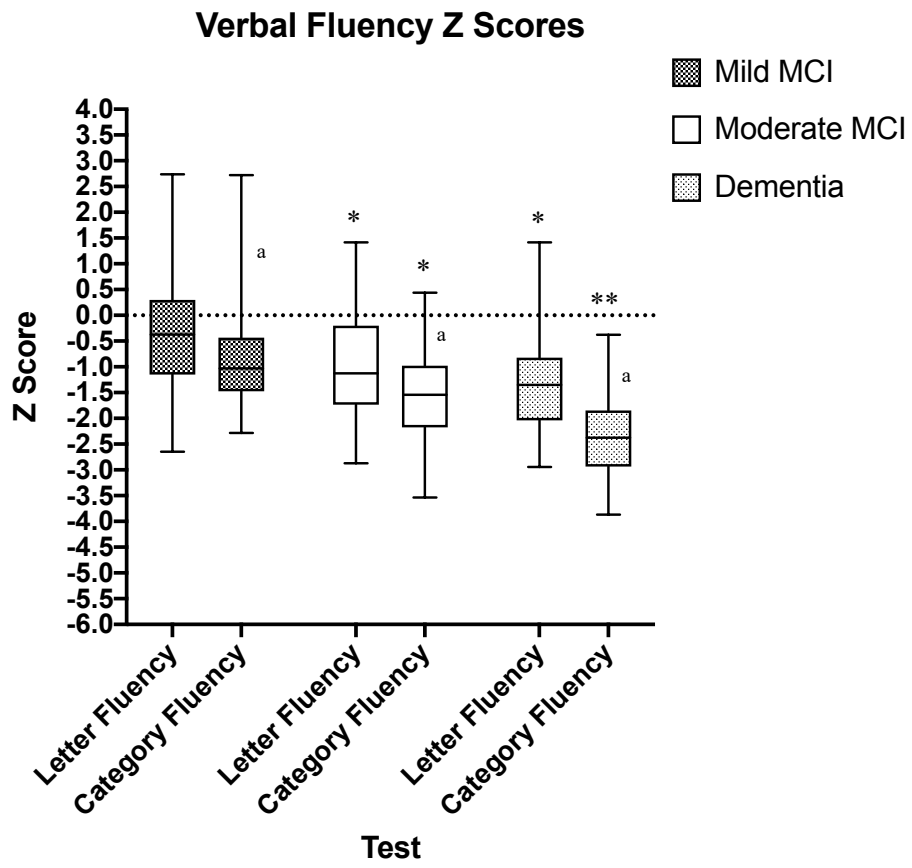


Figure 4.2. *Box plot depicting the median of verbal fluency z scores, calculated using the means and standard deviations of a group of matched controls, in each of the patient groups. Boxes represent interquartile range and error bars represent the range. Significant differences are highlighted as * significantly lower than mild MCI ** significantly lower than mild and moderate MCI. [a] significantly lower than letter fluency.*

Discrepancy scores were calculated as the letter fluency *z* score minus the category fluency *z* score for each participant. Differences in mean discrepancy scores between the mild (m = .64, sd = 1.25) and moderate MCI (m = .58, sd = .97) groups were calculated using an independent-samples *t*-test, revealing no difference in the discrepancy scores between these two groups $t(109) = .25$, $p = .80$. Given the non-normality of discrepancy in the dementia patient group, *post-hoc* Mann-Whitney *U* tests were carried out to assess the difference between the dementia group and the two MCI groups in terms of discrepancy scores. These indicated that the dementia group had significantly higher discrepancies in verbal fluency decline (m = 1.01, mdn = .94) when compared to both the mild MCI ([m = .64 mdn = .35] U = 1570 $p = .021$) and moderate MCI groups ([m = .58, mdn = .66] $U = 1491$ $p = .049$). These findings are shown in ***Fig. 4.3***.

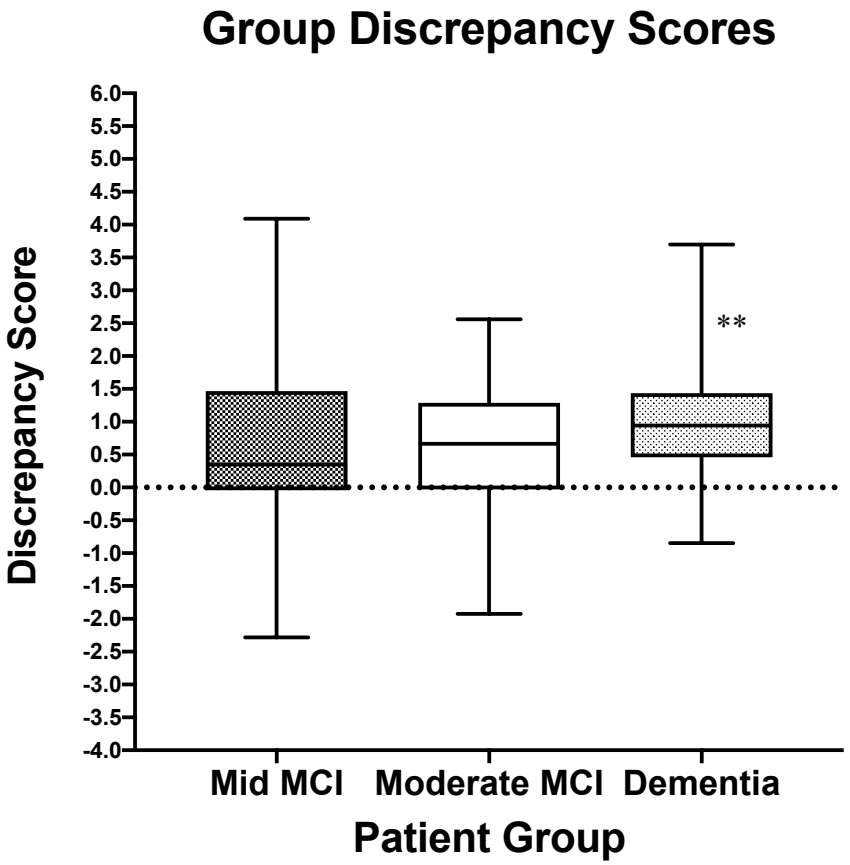


Figure 4.3. *Box plot depicting the median discrepancies between the verbal fluency z scores, calculated using the means and standard deviations of a group of matched controls, in each of the patient groups. Boxes represent interquartile range and error bars represent the range. Significant differences are highlighted as ** significantly higher than mild and moderate MCI.*

4.1.3.2. Whole Brain Imaging Results

I. Mild MCI

In the mild MCI group, verbal fluency discrepancy scores (**Table 4.6** and ***Fig. 4.4***) correlated significantly with regions of the right anterior temporal lobes (ATLs). This included involvement from areas of the right uncus, anterior parahippocampal gyrus (PRC: BA 36, 35), hippocampus and more lateral involvement in areas of temporal neocortex (BA 20, 21).

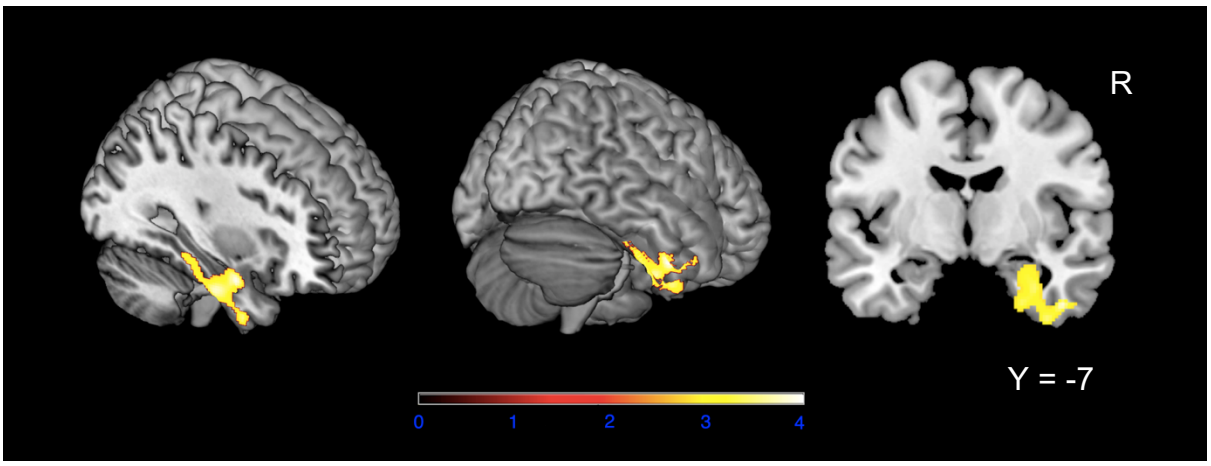


Figure 4.4. *Areas of significant negative correlation between grey matter volumes and verbal fluency discrepancy scores in the mild MCI group (n = 58) in the right temporal lobes. Coordinate corresponds to MNI space.*

Table 4.6

Areas of significant negative correlation between grey matter volumes and verbal fluency discrepancy scores in the mild MCI group (n = 58). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc, Uncorrected; BA, Brodmann's Area. Thresholded p = .005

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level p unc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Inferior Temporal Gyrus (20)	R	.004	<.001	1976	3.6	44	-5	-32	44	-4	-38
Amygdala	R				3.51	30	-3	-18	30	-2	-22
Uncus (36)	R				3.49	26	0	-34	26	2	-40
Uncus (20)	R				3.38	32	-15	-24	32	-14	-30
Middle Temporal Gyrus (21)	R				3.37	42	2	-32	42	4	-38
Inferior Temporal Gyrus (20)	R				3.33	38	-12	-36	38	-10	-44
Middle Temporal Gyrus (21)	R				3.16	34	1	-38	34	3	-45
Hippocampus	R				3.05	33	-28	-12	33	-28	-16
Middle Temporal Gyrus (21)	R				3	48	6	-31	48	8	-36
Parahippocampal Gyrus (35)	R				2.91	33	-24	-19	33	-24	-24
Uncus (20)	R				2.84	34	-7	-32	34	-6	-38

II. Moderate MCI

No significant clusters were found in the moderate MCI group when controlling for the FWE. However, a trend of correlation between discrepancy scores and grey matter volume was revealed at the uncorrected level (thresholded $p < .05$) in areas of the temporal lobe including anterior medial temporal areas such as perirhinal regions of anterior parahippocampal gyrus (BA 36) and temporal pole (BA 38) as well as more lateral areas such as the inferior and middle temporal and fusiform gyri (BA 20 and 21). These areas are highlighted in ***Fig. 4.5***.

Despite not being significant at the cluster level, when scrutinised using a 3-millimetre sphere small volume correction a number of peak coordinates were confirmed to be significant at the FWE rate. The significant peaks are listed in **Table 4.7**.

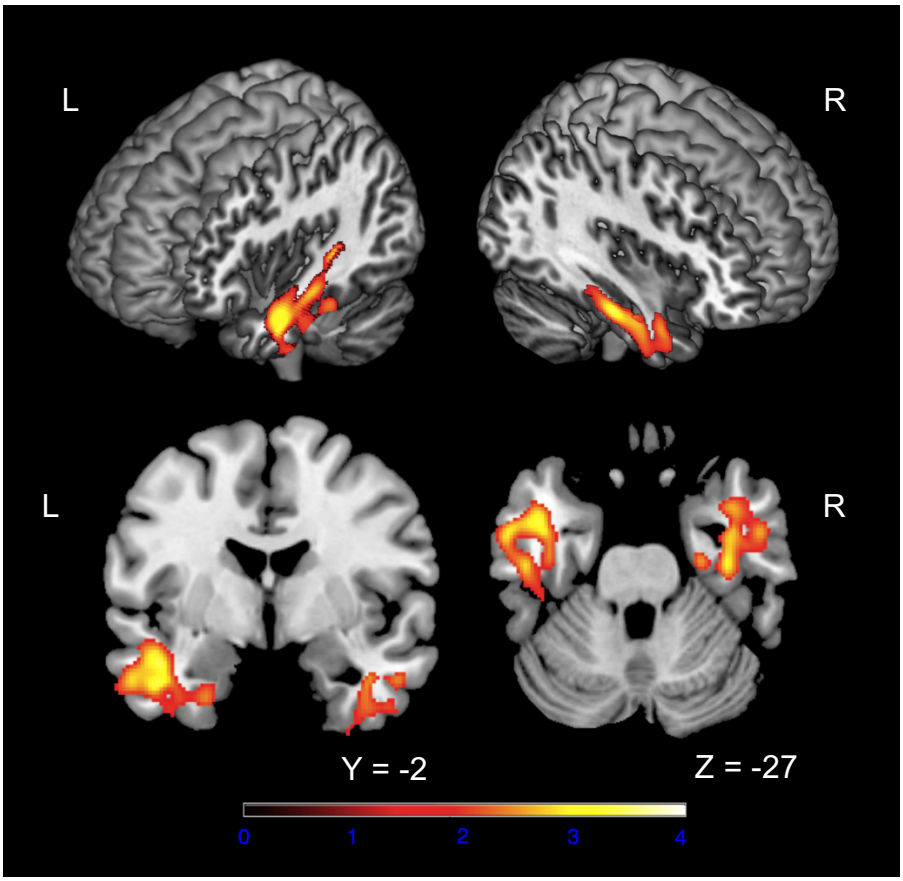


Figure 4.5. *Areas of non-significant but trending negative correlation between grey matter volumes and verbal fluency discrepancy scores in the moderate MCI group (n = 53) in bilateral temporal lobes. Coordinates refer to MNI space.*

Table 4.7

Peaks of significant negative correlation between grey matter volume and verbal fluency discrepancy scores in the moderate MCI group (n = 53). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc, Uncorrected; BA, Brodmann's Area. Thresholded p = .05

Brain Region (BA)	Hemisphere	Cluster Level pUnc	Peak Level pFWE	3mm Sphere pFWE	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
							X	Y	Z	X	Y	Z
Middle Temporal Gyrus (21)	L	.007	0.9	0.001	4567	3.63	-45	1	-25	-45	2	-30
Inferior Temporal Gyrus (21)	L		0.961	0.002		3.52	-56	-15	-16	-57	-15	-20
Middle Temporal Gyrus (21)	L		1	0.004		3.2	-44	-1	-18	-44	0	-22
Inferior Temporal Gyrus (20)	L		1	0.012		2.81	-48	-30	-15	-48	-30	-20
Fusiform Gyrus (20)	L		1	0.013		2.79	-56	-5	-23	-57	-4	-28
Fusiform Gyrus (20)	L		1	0.017		2.68	-50	-19	-22	-50	-18	-27
Parahippocampal Gyrus (36)	L		1	0.019		2.63	-40	-20	-12	-40	-20	-16
Superior Temporal Gyrus (41)	L		1	0.021		2.6	-42	-32	3	-42	-33	2
Sub-Gyral (20)	L		1	0.025		2.53	-39	-15	-17	-39	-15	-21
Uncus (36)	L		1	0.031		2.43	-26	0	-30	-26	2	-36
Superior Temporal Gyrus (22)	L		1	0.03		2.34	-45	-37	2	-45	-38	0
Sub-Gyral (20)	R	.05	1	0.004	2121	3.19	38	-20	-19	38	-20	-24
Sub-Gyral (20)	R		1	0.02		2.62	39	-9	-21	39	-8	-26
Middle Temporal Gyrus (38)	R		1	0.23		2.56	42	5	-22	42	6	-26
Middle Temporal Gyrus (21)	R		1	0.034		2.39	50	-5	-22	51	-4	-27
Parahippocampal Gyrus (36)	R		1	0.041		2.3	27	-17	-22	27	-16	-27

III. Dementia

In the dementia patient group, a variety of areas were found to be correlated with the verbal fluency discrepancy scores (**Table 4.8** and ***Fig. 4.6***). These included bilateral regions of the occipital cortex, including lingual and middle occipital gyri, as well as the cuneus (BA 18), but also extended further to include right hemisphere posterior temporal regions such as areas of parahippocampal (BA 19) and superior temporal gyri (BA 22). Further correlations with areas surrounding the central sulcus were also observed bilaterally (BA 3, 5 and 6).

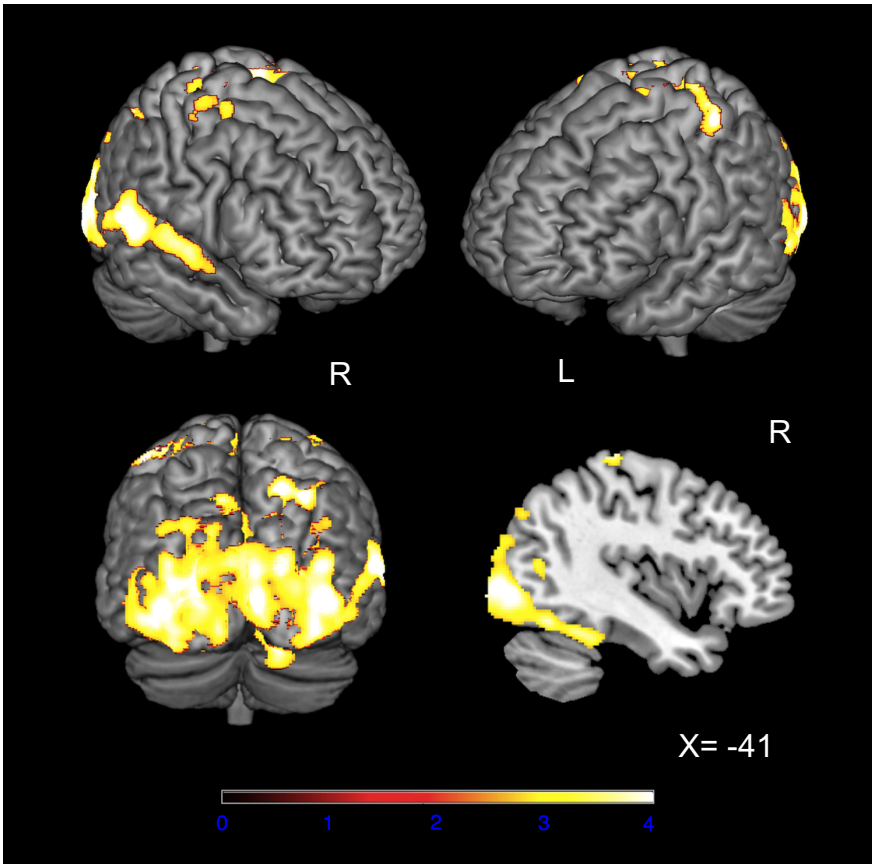


Figure 4.6. *Areas of significant negative correlation between grey matter volumes and verbal fluency discrepancy scores in the dementia group (n =71). Coordinates refer to MNI space.*

Table 4.8

Areas of significant negative correlation between grey matter volume and verbal fluency discrepancy scores in the dementia group (n = 71). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc: Uncorrected; BA: Brodmann's Area. Thresholded p = .005

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Middle Occipital Gyrus (18)	L	<.001	0	38924	4.78	-21	-84	12	-21	-87	9
Lingual Gyrus (18)	L				4.73	-21	-76	-6	-21	-78	-12
Lingual Gyrus (18)	L				4.71	-18	-79	-6	-18	-81	-12
Superior Temporal Gyrus (22)	R				4.51	65	-42	13	66	-44	12
Middle Occipital Gyrus (19)	R				4.51	44	-81	8	44	-84	4
Parahippocampal Gyrus (19)	R				4.46	24	-56	0	24	-58	-3
Superior Parietal Lobule (7)	R				4.44	20	-61	55	20	-66	56
Cuneus (18)	R				4.41	26	-78	18	26	-81	15
Cuneus (18)	R				4.29	20	-82	24	20	-86	22
Lingual Gyrus (19)	L				4.28	-20	-60	-2	-20	-62	-6
Parahippocampal Gyrus (19)	R				4.25	36	-45	-1	36	-46	-4
Cuneus (17)	R				4.25	8	-90	10	8	-93	6

Table 4.8 Cont.

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level p unc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Precuneus (7)	L				4.23	-10	-67	50	-10	-72	51
Parahippocampal Gyrus (19)	R				4.19	34	-44	-6	34	-45	-10
Lingual Gyrus (18)	R				4.19	14	-73	-1	14	-75	-6
Superior Temporal Gyrus	R				4.16	67	-33	9	68	-34	8
Superior Frontal Gyrus (6)	L	.029	0.001	1685	4.16	-14	-14	69	-14	-18	74
Postcentral Gyrus (1)	L				4.14	-48	-23	59	-48	-27	63
Postcentral Gyrus (3)	L				3.65	-39	-26	64	-39	-30	68
Paracentral Lobule (5)	L				3.65	-15	-30	48	-15	-33	50
Postcentral Gyrus (3)	L				3.45	-26	-29	70	-26	-33	74
Postcentral Gyrus (3)	L				3.28	-10	-34	61	-10	-38	64
Cingulate Gyrus (24)	L				2.6	-8	-19	43	-8	-22	46
Precentral Gyrus (6)	R	.042	0.002	1540	3.78	9	-20	70	9	-24	75
Precentral Gyrus (6)	R				3.63	14	-18	69	14	-22	74
Paracentral Lobule (5)	R				3.57	14	-29	49	14	-32	52
Paracentral Lobule (6)	R				3.2	10	-34	72	10	-39	76
Middle Frontal Gyrus (6)	R				3.2	33	-1	63	33	-4	68
Postcentral Gyrus (3)	R				3.11	24	-29	68	24	-33	72
Postcentral Gyrus (3)	R				3.06	24	-30	64	24	-34	68
Precentral Gyrus (6)	R				3.06	36	-12	65	36	-16	70
Precentral Gyrus (6)	R				3.04	26	-17	62	26	-21	66
Paracentral Lobule (5)	R				3.04	20	-37	44	20	-40	46
Sub-Gyral (40)	R				2.7	26	-40	57	26	-44	60
Precentral Gyrus (6)	R				2.69	44	-15	59	44	-18	63

4.1.3.3. Region of Interest Analysis

Results of the partial correlations between semantic memory measures and grey matter volumes from twelve ROIs are outlined in **Table 4.9**. Among the moderate MCI group, significant negative correlations between regional temporal lobe fractions and discrepancy scores included medial and inferior temporal regions such as right BA 36 and 20. Furthermore, a positive correlation was also seen in this group between category fluency *z* scores and right BA 36. Conversely however, a negative correlation was found in this group between category fluency *z* scores and the temporal lobe fraction of the left fusiform gyrus (BA 37), which was further reflected by a significant positive correlation between this area and discrepancy scores. In the dementia group, significant positive correlations were seen between category fluency *z* scores and bilateral superior temporal gyrus (BA 22), a significant negative correlation was seen between discrepancy scores and the right superior temporal gyrus (BA 22) and a significant positive correlation was seen between discrepancy scores and left BA 20.

Table 4.9

*Coefficients of partial correlation between regional temporal volumes and measures of sematic memory. Age, Years of Education and MMSE scores were used as control variables. Letter Fluency z Scores were an additional control for Category Fluency Z Score correlations. [a] Spearman's Rho correlation coefficients used as data not normally distributed. Significant ($p < 0.05$) coefficients of correlations indicated in bold. BA: Brodmann's Area; *: $p < 0.05$; **: $p < 0.01$ Correlations surviving a Bonferroni correction for multiple comparisons are underlined.*

Brain Region	Mild MCI (*n* = 58)				Moderate MCI (*n* = 53)				Dementia (*n* = 71)			
	Category Fluency *z* Scores [a]		Discrepancy Scores		Category Fluency *z* Scores		Discrepancy Scores		Category Fluency *z* Scores		Discrepancy Scores [a]	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Hippocampal Fraction	.132	.118 [a]	-.058	-.086 [a]	-.167 [a]	.043 [a]	.081 [a]	-.029 [a]	-.107	-.203	-.040	-.025
Perirhinal Fraction	.026 [a]	.210	-.071 [a]	-.049	-.021	.037	-.009	-.011	-.126	-.055	.040	-.067
Entorhinal Fraction	-.093 [a]	.148 [a]	.040 [a]	-.065 [a]	.043	.085 [a]	-.043	-.135 [a]	.073	.016	.048	.037
BA 36 Fraction	-.025	.044	-.056	-.193	.099	**.287***	-.157	**-.319***	-.168	-.175	.114	.086
BA 34 Fraction	.065	.041	.022	.106	-.007	.102 [a]	-.040	-.241 [a]	-.162	-.185	.140	.162
BA 27 Fraction	-.094	.135	.040	-.091	-.220	-.083	.089	-.054	-.016	.003	-.024	-.035
Amygdala Fraction	.101	.152	-.073	-.141	.027	.070	-.061	-.191	-.183	-.233	.044	.112
BA 20 Fraction	-.024	.083	-.063	-.150	.276	.269	-.222	**-.290***	-.086	-.179	**.245***	.188
BA 38 Fraction	.005	.131 [a]	.022	.015 [a]	.168	.090 [a]	.007	.005 [a]	.048 [a]	.100 [a]	.127 [a]	.125 [a]
BA 22 Fraction	-.077	-.094	-.002	.067	-.128	-.162	.162	.271	**.309***	**<u>.357**</u>**	-.170	**-.246***
BA 21 Fraction	.088	.123	-.175	-.212	.168	.134	-.087	-.113	-.033	.010	.206	.112
BA 37 Fraction	-.078	-.083	.082	.152	**-.299***	.053	**.310***	.052	.175	-.104	-.098	.071

4.1.3.4. White Matter Lesion Analysis

A Mann-Whitney *U* test between mild and moderate MCI groups was used to compare the distribution of lesion volume and number between the two groups. No differences were observed between mild (mean rank = 55, mdn = 3.67) and moderate MCI groups (mean rank = 52.86, mdn = 3.15) in terms of lesion volume (U = 1368 *p=.72*) or lesion number (mild MCI mean rank 50.96, mdn = 12) (moderate MCI mean rank = 57.46, mdn = 13.5) U = 1252 *p=.28*.

4.1.3.5. Post Hoc Analyses

In light of the results among the moderate MCI group, further analyses were carried out on the dementia group and the MCI group as a whole. For this, the dementia group, like

the MCI group, were split according to their MMSE scores with patients scoring 21 or above considered as 'early dementia' and those scoring below 21 considered as 'late dementia'. Regression models were also applied to the MCI group taken as a whole, thereby increasing the potential variability among patients, to further scrutinise the findings from the mild MCI group.

I. Whole MCI Group

A regression model assessing the correlation between grey matter volumes and verbal fluency discrepancy, including scans from the entire MCI group (n = 111), revealed a very similar pattern as was observed in the mild group alone (**Table 4.6**, ***Fig. 4.4***). This included significant negative correlations with grey matter in regions of the right anterior parahippocampal gyrus in both perirhinal (BA 36) and entorhinal (BA 28) regions as well as inferior and middle temporal gyri (BA 20, 21) and temporal pole (**Table 4.10**, ***Fig 4.7***).

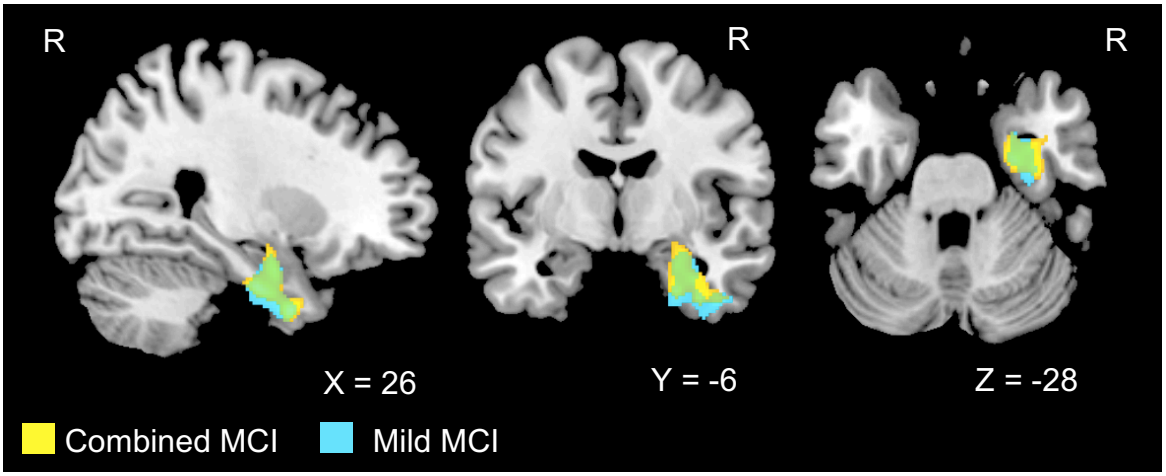


Figure 4.7. *Overlapping areas of significant negative correlation between grey matter volumes and verbal fluency discrepancy scores in the combined MCI group and mild MCI group in anterior temporal regions. Coordinates refer to MNI space.*

Table 4.10

Areas of significant negative correlation between grey matter volume and verbal fluency discrepancy scores in the combined MCI group (n = 111). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc, Uncorrected; BA, Brodmann's Area. Thresholded p = .005

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Middle Temporal Gyrus (21)	R	0.018	0.001	1573	3.45	39	-4	-28	39	-3	-34
Uncus (36)	R				3.25	24	2	-34	24	4	-40
Amygdala	R				3.25	30	-3	-18	30	-2	-21
Uncus (28)	R				3.18	27	-11	-26	27	-10	-32
Parahippocampal Gyrus (36)	R				3.12	34	-26	-16	34	-26	-20
Uncus (20)	R				3.07	36	-13	-25	36	-12	-30
Sub-Gyral (20)	R				3.02	36	-21	-19	36	-21	-24
Middle Temporal Gyrus (20)	R				3.01	34	1	-39	34	3	-46
Inferior Temporal Gyrus (20)	R				2.73	46	-10	-28	46	-9	-34
Superior Temporal Gyrus	R				2.69	39	5	-19	39	6	-22

II. Early Dementia

A regression model including only patients with AD dementia with an MMSE score of 21 or above (n = 41), revealed significant negative correlations between verbal fluency discrepancy scores and grey matter volumes predominantly within restricted areas of the left occipital cortex and posterior temporal cortex, including lingual gyrus (BA 18), middle occipital gyrus and cuneus (BA 18 and 19), as well as the fusiform and middle temporal gyri (BA 37 and 19) (**Table 4.11**, ***Fig. 4.8***).

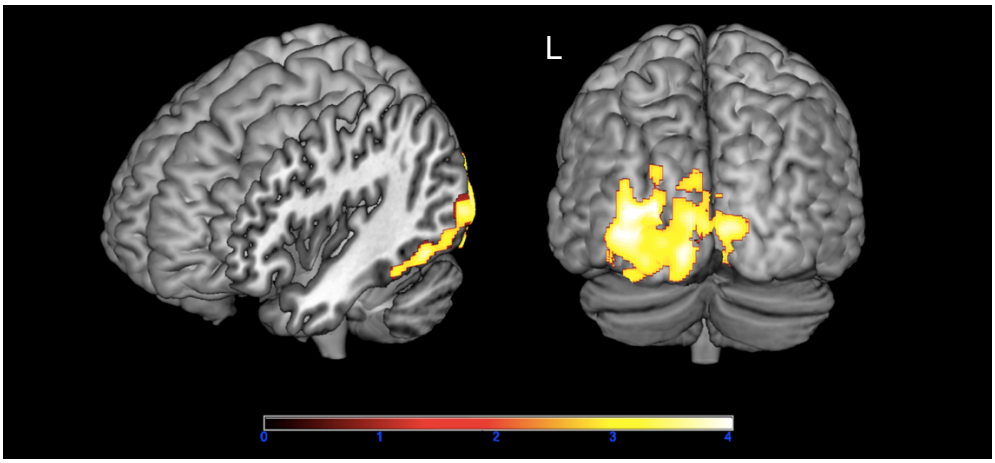


Figure 4.8. *Areas of significant negative correlation between grey matter volumes and verbal fluency discrepancy scores in the early dementia group (n = 41) in occipital and posterior temporal regions.*

Table 4.11

Areas of significant negative correlation between grey matter volume and verbal fluency discrepancy scores in the early dementia group (n = 41). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc, Uncorrected; BA, Brodmann's Area. Thresholded p = .005

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Cuneus (17)	L	<.001	<.001	5677	4.18	-21	-83	13	-21	-86	10
Fusiform Gyrus (37)	L				3.81	-40	-61	-10	-40	-62	-15
Middle Occipital Gyrus (19)	L				3.74	-39	-79	6	-39	-82	2
Middle Occipital Gyrus (19)	L				3.73	-34	-84	15	-34	-87	12
Lingual Gyrus (17)	L				3.62	-10	-95	2	-10	-98	-3
Middle Occipital Gyrus (19)	L				3.55	-32	-85	7	-32	-88	3
Middle Occipital Gyrus (18)	L				3.43	-8	-95	16	-8	-99	12
Cuneus (17)	R				3.41	8	-89	10	8	-92	6
Lingual Gyrus (18)	L				3.36	-21	-76	-5	-21	-78	-10
Lingual Gyrus (18)	L				3.29	-15	-84	-6	-15	-86	-12
Inferior Occipital Gyrus (18)	L				3.21	-28	-93	-2	-28	-96	-8
Cuneus (18)	L				3.19	-2	-93	14	-2	-96	10
Middle Occipital Gyrus (18)	L				3.12	-21	-95	7	-21	-98	2
Cuneus (18)	L				3.12	-9	-99	10	-9	-102	6
Middle Temporal Gyrus (19)	L				3.11	-38	-80	24	-38	-84	22
Cuneus (18)	L				2.94	-4	-83	15	-4	-86	12

III. Late Dementia

A regression model including only patients with AD dementia with an MMSE score of 20 or below (n = 30), revealed significant correlations between grey matter volume and verbal fluency discrepancy scores in widespread areas (**Table 4.12**, ***Fig. 4.9***), largely restricted to the right hemisphere, within a number of regions in the temporal and occipital cortices including inferior, middle and superior temporal gyri (BA 20, 21 and 22) and lingual, middle and inferior occipital gyri (BA 18 and 19). Correlations also extended to restricted portions of the cerebellum.

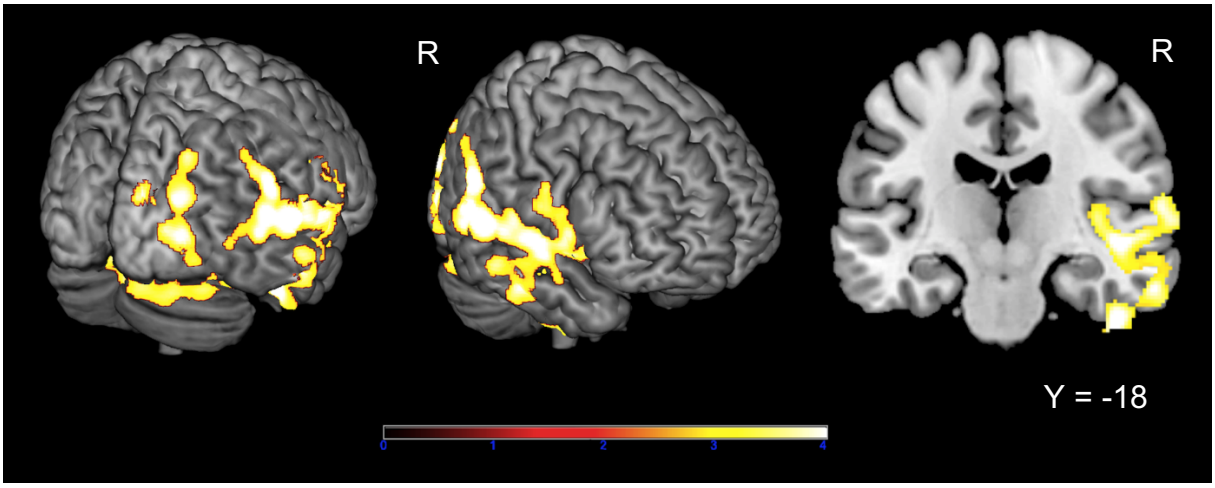


Figure 4.9. *Areas of significant negative correlation between grey matter volumes and verbal fluency discrepancy scores in the late dementia group (n = 30) in occipital and temporal regions. Coordinates refer to MNI space.*

Table 4.12

Areas of significant negative correlation between grey matter volume and verbal fluency discrepancy scores in the late dementia group (n = 30). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc, Uncorrected; BA, Brodmann's Area. Thresholded p = .005

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Superior Temporal Gyrus (22)	R	<.001	<.001	8364	4.83	67	-32	9	68	-33	8
Superior Temporal Gyrus (22)	R				4.2	46	-14	-4	46	-14	-6
Inferior Parietal Lobule (40)	R				4.1	61	-41	26	62	-44	26
Superior Temporal Gyrus (22)	R				4.07	62	-6	3	63	-6	3
Superior Temporal Gyrus (22)	R				4.06	62	-43	11	63	-45	10
Inferior Temporal Gyrus (20)	R				3.96	45	-17	-31	45	-16	-38
Inferior Temporal Gyrus (20)	R				3.85	48	-22	-29	48	-21	-36
Superior Temporal Gyrus (22)	R				3.6	50	-38	4	51	-39	2
Middle Temporal Gyrus (21)	R				3.59	62	-49	5	63	-51	3
Inferior Temporal Gyrus (20)	R				3.54	61	-16	-18	62	-16	-22
Superior Temporal Gyrus (42)	R				3.48	67	-20	7	68	-21	6
Precentral Gyrus (6)	R				3.47	44	-6	31	44	-8	33
Transverse Temporal Gyrus (41)	R				3.43	51	-26	14	52	-27	14
Transverse Temporal Gyrus (42)	R				3.41	63	-17	9	64	-18	9
Superior Temporal Gyrus (22)	R				3.39	56	-16	-1	57	-16	-2
Superior Temporal Gyrus (22)	R				3.38	55	8	3	56	8	4
Parahippocampal Gyrus (30)	R	<.001	<.001	10819	4.62	16	-37	6	16	-38	4
Parahippocampal Gyrus (36)	R				4	32	-30	-20	32	-30	-26
Lingual Gyrus	R				3.78	15	-66	1	15	-68	-3
Parahippocampal Gyrus (19)	R				3.77	36	-43	-5	36	-44	-8
Culmen (Anterior Lobe of Cerebellum)	R				3.69	8	-56	0	8	-58	-3
Lingual Gyrus (19)	R				3.67	26	-60	0	26	-62	-4
*	L				3.64	0	-70	-8	0	-72	-14
Lingual Gyrus (18)	L				3.64	-20	-79	-6	-20	-81	-12

Table 4.12 Cont.

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Culmen (Anterior Lobe of Cerebellum)	R				3.6	4	-64	-4	4	-66	-9
Declive (Posterior Lobe of Cerebellum)	R				3.58	24	-68	-12	24	-69	-18
Declive of Vermis (Posterior Lobe of Cerebellum)	R				3.57	0	-71	-20	0	-72	-28
Lingual Gyrus (18)	L				3.55	-10	-70	2	-10	-72	-2
Posterior Cingulate (31)	L				3.46	-3	-66	17	-3	-69	15
Culmen (Anterior Lobe of Cerebellum)	L				3.44	0	-56	3	0	-58	0
Pulvinar at Thalamus	L				3.42	-15	-33	4	-15	-34	3
Lingual Gyrus (19)	L				3.41	-20	-60	0	-20	-62	-4
Cuneus (18)	R	0.004	<.001	1960	4.25	20	-80	22	20	-84	20
Middle Temporal Gyrus (19)	R				3.7	39	-80	24	39	-84	22
Middle Occipital Gyrus (19)	R				3.67	42	-81	8	42	-84	4
Precuneus (31)	R				3.59	24	-71	23	24	-74	21
Cuneus (18)	R				3.41	15	-74	29	15	-78	27
Middle Occipital Gyrus (19)	R				3.35	34	-83	10	34	-86	6
Precuneus (19)	R				3.28	39	-72	42	39	-76	42
Precuneus (19)	R				3.2	36	-68	39	36	-72	39
Inferior Occipital Gyrus (19)	R				2.98	46	-79	-3	46	-81	-8
Cuneus (18)	R				2.76	9	-83	23	9	-87	20

4.1.4. Discussion

The aims of this study were principally to elucidate the progressive change in brain regions involved in category/letter fluency decline discrepancies at varying stages of AD pathological progression. It was hypothesised that, in the early stages of disease, limited pathology would be reflected by the discrete involvement of subhippocampal anterior MTL (aMTL) structures in this measure of semantic memory function. Later in the course of disease progression however, it was posited that the structural neural correlates of verbal fluency discrepancies would expand to include more posterior temporal cortical areas involved in the semantic system, reflecting the more severe pathology in this group. Behaviourally, it was expected that all groups would show significant discrepancies in the relative declines on each of the verbal fluency measures, with a significantly greater decline in category fluency, and that this discrepancy would be exacerbated by disease progression.

4.1.4.1. Neuropsychological Findings

As expected, declines in verbal fluency in the present study, as measured using *z* scores indicating the distance from a control mean, increased linearly across the disease

spectrum with mild MCI patients presenting with the least amount of decline and dementia patients presenting with the most, with moderate MCI reflecting an intermediate stage of decline. Interestingly however, where the differences in mean category fluency decline were significant between all groups, the moderate MCI group, although being significantly more impaired than the mild MCI group, did not differ significantly, when corrected for multiple comparisons, from the dementia group on measures of letter fluency decline. This finding could, therefore, suggest that, although in the initial stages of cognitive decline both types of fluency are compromised as a result of the impact of neuropathological damage on overall effortful retrieval, in the early stages of disease progression, category fluency continues to decline in a linear fashion whereas letter fluency decline reaches a plateau between the later MCI and early dementia stage. This finding is supported by a meta-analytic review of lesion studies by Henry and Crawford (2004b), aiming to elucidate the neural correlates of verbal fluency tasks, that demonstrated that in the presence of focal frontal cortical lesions both phonemic and semantic fluency tasks are impaired to large and comparable extents. However, declines in phonemic fluency tasks, requiring little input from the semantic system, are subject to limited levels of decline in the presence of temporal lobe damage when compared with semantic fluency. In terms of the pathological cascade associated with AD, these findings suggest that in the initial stages in which tau pathology and subsequent cortical atrophy is localised to the temporal lobes (Braak & Braak, 1991) there would be a significantly greater effect of neuropathology on category fluency performance relative to letter fluency. As the disease progresses to involve frontal structures however, both types of fluency would show significant decline compared with earlier stages. The results of the present study cannot confirm whether this pattern would emerge in later stages of AD, as all the patients were in the early stages of dementia, but the pattern described between the prodromal and early dementia stages is certainly indicative of early degradation of the semantic store, despite intact controlled retrieval processes (Henry, Crawford & Phillips, 2004; Henry & Crawford, 2004a; 2004b).

The present study successfully replicated findings of previous work that has demonstrated that declines in verbal fluency in MCI and AD cohorts is often characterised by a significantly greater impairment in category fluency relative to letter fluency (Henry, Crawford & Phillips, 2004; Murphy, Rich & Troyer, 2006; Clark *et al*., 2009; Chasles *et al*., 2020; Vonk *et al*., 2020). This is observable particularly in the mild MCI group, as the mean *z* score for letter fluency performance in this group was well within a normal range, at around 0.3 SDs from the control mean. The mean category fluency *z* score however, although still

within the normal range (i.e. less than 1.5 SDs from the control mean), approached the clinical cut-off with a mean *z* score around 0.9 SDs from the control mean. As disease severity increased, category fluency *z* scores decreased to below clinical cut off in both the moderate MCI and dementia groups. Letter fluency *z* scores however, remained above the cut-off suggesting that, although there was some decline in this type of fluency, patients, even in the later stages of disease, were performing within the normal range in this non-semantic verbal fluency task. Furthermore, the results suggest that raw verbal fluency scores offer little value in determining disease severity in the early stages of disease progression, as demonstrated by the lack of statistically significant differences between each of the fluency raw scores between mildly and moderately affected MCI groups. The relative decline in verbal fluency reflected by the *z* scores, however, was found to be far more representative of disease severity, particularly in category fluency, which showed significantly greater declines in groups at a later stage of pathological decline.

Another interesting finding highlighted by the neuropsychological data, concerns the ability of standard cognitive testing in differentiating the mild MCI patients from the moderately affected group. The present research was unable to demonstrate statistically significant differences between the mild and moderate MCI groups on any of the standard memory tests, including recall of the Rey Figure (Osterreith, 1944), immediate or delayed prose recall, or the paired associates test (Wechsler, 1997). The only memory test that revealed a statistically significant difference between the two MCI groups was the similarities subset of the Wechsler Adult Intelligence Scale. In line with the findings of Amieva *et al*., (2008) and the hypothesis of Didic *et al*., (2011), these findings suggest that in the earliest stages of disease progression semantic memory and concept formation are among the most susceptible cognitive functions to underlying cortical damage, resulting in significant progressive declines in the early stages, even between comparable disease severity groups. The lack of differences between the MCI groups in episodic memory function, as measured by the other cognitive tests mentioned above, suggests that this type of memory function may remain relatively stable in the level of impairment until disease progression reaches the dementia stages. This again, is in line with the theory put forward by Didic *et al*., (2011) that suggests that semantic memory decline in AD would likely occur as a result of the initial progressive degradation of subhippocampal cortical structures, whereas episodic memory decline would be only exacerbated once pathology reaches the hippocampus at the time of dementia onset and diagnosis. Although there were also no significant differences found in the raw category fluency scores between the two MCI groups, significant differences in both

verbal fluency tasks were found when these scores were standardised into *z* scores representing the amount of decline in each task, relative to a group of matched controls, revealing significantly greater decline of both types of verbal fluency in the moderate MCI group relative to the mild MCI group. These findings, taken together, suggest that, in the earliest stages of disease, the currently relied upon tests of episodic memory are not sufficient to separate early from late-stage cognitive impairment in a prodromal group. Tests of semantic memory however, such as the similarities test and relative declines on category fluency, could prove more informative in identifying the subtle progressions in underlying pathology in the early stages, and potentially be good prognostic indicators for further decline.

The use of standardised fluency scores, created in accordance with norms derived from healthy controls matched according to the patients' nationality, should have diminished any effect of language on the present findings. However, it should be noted that when comparing the healthy control groups from Italy and the UK, the group from Sheffield tended to produce substantially more words on both the letter and category fluency tasks than the group from Venice. Given that these controls were chosen to match with their respective patient groups and not each other, it is likely that substantial differences in demographics between the two, in terms of age and education, are the primary explanation for this difference in performance, given the known effects that these factors can have on verbal fluency tasks (Kempler *et al*., 1998; Tombaugh, Kozak & Rees, 1999; Troyer, 2000; Zarino *et al*., 2014). However, if verbal fluency tasks are to be implemented as a screening tool for cognition across the world then language and cultural background are factors that ought to be taken into consideration.

Early research into the effects of language and culture on verbal fluency tasks has indicated that both can have an impact, to some extent, on both the quantitative and qualitative aspects of fluency performance. Performance on category fluency tasks in particular has shown to be significantly affected by cultural differences. Acevedo and colleagues (2000) for example, found that when comparing performances on semantic fluency tasks between English speakers and Spanish speaking immigrants living in Florida, English speakers tended to produce more words in the category of vegetables while Spanish speakers tended to produce more animal words, despite both producing a similar number of words in the fruit category. Such differences were thought by the authors to reflect a difference in the early lives of individuals growing up in either Latin America or the United States, in terms of their exposure to differing types of animals and vegetables. However, this

finding may also be partially explained by language differences, given that the English word 'vegetables' represents an inherently more restrictive category than the closest translation in Spanish, 'vegetales', which, unlike its English equivalent, refers to all plants (Real Academia Española, 2014) and not only "a plant or part of a plant that is eaten as food" (Oxford Dictionary of English, 2010). A similar study by Kempler *et al*. (1998) used an animal fluency task to assess the quantitative and qualitative differences in verbal fluency performance between speakers of Vietnamese, Chinese, Spanish, and English, from both White and African American backgrounds, living in southern California. The results of this study demonstrated that although the words produced with the highest frequency were similar regardless of cultural background (i.e., 'dog', 'cat' and 'horse'), different exemplars were produced in each group. While words like 'ox' and 'bison' were produced with a high frequency among Vietnamese participants, 'rat' and 'donkey' were found to have higher frequencies among Chinese and Spanish speaking groups respectively. Such differences in category exemplars are thought to reflect the differences between groups in terms of the culture and environment of their upbringing and have even been demonstrated between native speakers living in the same country in urban vs rural areas (Brucki & Rocha, 2004). What Kempler and colleagues were also able to demonstrate was a significant discrepancy in the number of words produced overall between groups, with Spanish speakers producing the fewest words and Vietnamese speakers the most, even when controlling for the effects of age and education. This discrepancy was thought to relate to the average word length of animal names in the respective languages, as Vietnamese animal words tend to be one syllable, while Spanish animal words are mostly two or more. However, more recent research comparing English and Finnish speakers found no differences in the number of words produced on either a clothing or animal fluency task, despite finding a significant difference in the mean length of words produced (Pekkala *et al*., 2009). Research using bilingual participants has similarly demonstrated limited effects of language on overall semantic fluency scores when comparing bilingual's performance in English with their performances in French or Spanish (Roberts & Le Dorze, 1997; Rosselli *et al*., 2002). Despite limited evidence regarding language effects on the quantity of words produced on category fluency tasks, cultural effects on the types of category exemplars produced, similar to those demonstrated by Kempler's study, have also been reported, although to a lesser extent, by more recent investigations (Rosselli *et al*., 2002; Pekkala *et al*., 2009).

Language effects on letter fluency tasks have also proved minimal, with bilinguals and monolinguals producing a similar number of words when given an alphabetical cue,

regardless of language (Snodgrass & Tsivkin, 1995; Rosselli *et al*., 2002). Despite the potential for contrasting languages to have differing population sizes, in terms of frequency of dictionary entries, for words beginning with particular letters, previous research has demonstrated that phonemic fluency tasks, which allow for retrieval of any word type, in contrast with category fluency tasks, which rely on only concrete nouns, are far less influenced by population size and as such are relatively unaffected by language differences (Snodgrass & Tsivkin, 1995). There is, however, evidence to suggest that as in category fluency, the types of exemplars produced during letter fluency may differ depending on language (Rosselli *et al*., 2002).

Limited evidence regarding a quantitative effect of language and culture on verbal fluency performance supports the conclusion that, in this case, the differences seen between the British and Italian control groups in this study are likely a reflection of a disparity in age and levels of education between the groups. However, despite uncertainty as to the impact of these factors on the total number of words produced, it is important that such factors be taken into account when developing the normative data required for discrepancy scores to be translated into clinical use. In particular, the translation of verbal fluency into languages with different writing systems such as Chinese, where the cognitive processes and retrieval strategies tested by such tasks may differ substantially from alphabetic Latin languages (Eng *et al*., 2019) will be essential if this approach is to have an impact on diagnosis worldwide.

4.1.4.2. VBM Findings

I. Mild MCI

In line with the initial hypothesis, discrepancy scores correlated predominately with areas of the medial temporal lobes in the mild MCI group, specifically, with areas of the right parahippocampal gyrus described by Braak and Braak (1991) as perirhinal regions (BA 35 and 36) as well as the right amygdala and uncus (BA 20). Discrepancy scores in this cohort, therefore, appear to reflect the integrity of semantic memory function, highlighting inferior and medial regions of the ATLs, thought to be integral to semantic memory processing (Patterson, Nestor & Rogers, 2007; Venneri *et al*., 2008; Visser *et al*., 2010). The right lateralisation of the correlation in this group could be thought of as surprising, given the left lateralised nature of language functions (Vigneau *et al*., 2006), however, the nature of the discrepancy score as a way to isolate semantic retrieval processes, likely omits any variance

explained by differences in language production ability. According to Didic's (2011) theory and the present hypothesis, it is thought that variance in the integrity of the MTL regions, highlighted here, may explain the variance in the patients' ability to retrieve information from the semantic store successfully. It is well known that AD pathology tends to affect the brain in an asymmetric pattern in the early stages, with the left hemisphere showing an initial acceleration in degradation before atrophy evens out bilaterally towards the later stages (Thompson *et al*., 2003; Shi *et al*., 2009). This would suggest a need for greater reliance on right hemisphere structures in the presence of early left sided degradation in the mild MCI patients, therefore explaining the right-side lateralisation demonstrated in this group.

Didic *et al*., (2011) outline in their model how degradation to subhippocampal areas, such as the PRC (BA 35 and 36), highlighted in this group, may be detrimental to semantic memory functioning in the early stages of AD. In accordance with this model, the findings of the present study demonstrate how the semantic component of a verbal fluency task, isolated through controlling for phonemic task features, can accurately illustrate the degradation of discrete areas of MTL associated with the very earliest moments of AD pathology. The finding that semantic memory deficits may be related to PRC damage has been repeatedly demonstrated by animal lesion studies utilising visual recognition tasks (Meunier *et al*., 1993; Mumby & Pinel, 1994; Brown & Aggleton, 2001; Barker *et al*., 2007). Such research has demonstrated that ablations to the rhinal cortices (e.g., PRC and ERC) can cause significant impairments on recognition memory tasks in both rats and rhesus monkeys, without involvement of hippocampal formation. Furthermore, in an early study, Meunier *et al*., (1993) found that even when such lesions were limited to the PRC, impairments of the same severity were observed, a finding that was not replicated when ablations were restricted to the ERC. These findings suggest that the PRC in particular, plays a significant role in context-free semantic memory processing. Brown and Aggleton (2001) posit that, given the nature of the visual recognition tasks, disruption of this task in the presence of PRC damage demonstrates the role of this area in the recognition of individual (i.e., context independent) stimuli, reflecting the importance of this area in supporting this form of context-free, semantic memory processing. Unlike hippocampal regions, which Brown and Aggleton (2001) suggest only become relevant to recognition memory in the presence of contextual associations, the PRC, while less intrinsic to the retrieval of autobiographical information, represents an essential component of a familiarity and recency discrimination system, of particular significance to semantic memory function. Further to animal studies, subsequent research in human participants with frontotemporal neurodegeneration have similarly

demonstrated that the extent of degradation within the PRC directly correlates with the severity of a semantic memory deficit (Davies *et al*., 2004). Furthermore, evidence from studies examining medial temporal amnestic patients with discrete damage to the hippocampus, but relative sparing of the PRC, demonstrates that patients of this description retain the ability to acquire new semantic knowledge despite significant damage to the hippocampal formation (Corkin *et al*., 1997; Mishkin, Vargha-Khadem, & Gadian, 1998; Vargha-Khadem *et al*., 1997).

As the focus of AD research has shifted towards the earliest stages of disease, results from these early animal and focal lesion studies have informed subsequent research in AD and MCI cohorts. Given the involvement of the PRC in the earliest known stages of temporal neurodegeneration in these patient groups (Braak & Braak, 1991), it is unsurprising that a large body of research now exists aiming to investigate AD related semantic memory decline and its relationship with the integrity of this subhippocampal structure. Kivisaari *et al*., (2012) were able to replicate the findings of animal lesion studies, demonstrating that cortical damage within the medial PRC, in patients with mild AD and MCI, related to impairments in the naming of semantically confusable objects and similar research by Hirni *et al*., (2013) and Barbeau *et al*., (2012) has replicated these findings in the PRC in early and prodromal AD patients, using semantic memory tasks in modalities other than that of visual recognition.

Category fluency in particular, has proved to be a useful tool for detecting degenerative changes within PRC and aMTL regions in AD patients. A study by Venneri and colleagues (2008) examining the lexical attributes of words produced in a semantic fluency task were able to detect significant correlations between the conjunct effect of the age of acquisition and typicality of words produced by an early AD cohort and discrete regions of the aMTL (Venneri *et al*, 2008). Lexical attributes of the category fluency task were significantly correlated with areas of the cortex centred around the most anterior regions of the parahippocampal gyrus, including the PRC (BA 35, 36 and 28). The present study was able to replicate these findings through utilisation of the verbal fluency discrepancy measure. Taken together with previous findings, therefore, the results of the present research suggest that discrete damage to aMTL structures, such as the PRC, could be sufficient in causing significant disruption to the semantic memory system.

Further areas of the MTL including the uncus (BA 20) and amygdala were also highlighted by discrepancy scores in the mild MCI group. Anterior temporal structures have consistently been implicated in semantic memory functions in neurodegenerative as well as healthy individuals (Mummery *et al*., 2000; Patterson, Nestor & Rogers, 2007; Pobric,

Jefferies & Lambon Ralph, 2010; Visser *et al*., 2010). It is unsurprising therefore, that correlations in this study extended to include regions of ATL outside the PRC. Importantly, these VBM findings support previous research informed by semantic dementia patients, as well as repetitive transcranial magnetic stimulation (rTMS) studies, and more recently, functional neuroimaging that has distinctly related ATL structures with semantic memory processing (Mummery *et al*., 2000; Patterson, Nestor & Rogers, 2007; Pobric, Jefferies & Lambon Ralph, 2010; Visser *et al*., 2010).

The discrepancy between the levels of impairment on verbal fluency tasks is well documented in AD with significantly greater impairment occurring in semantic relative to phonemic fluency in even prodromal and preclinical stages of the disease (Henry, Crawford & Philips, 2004; Murphy, Rich & Troyer, 2006; Clark *et al*., 2009, Papp *et al*., 2016; Vonk et al., 2020). A novel finding of this study, however, is the relationship demonstrated between this verbal fluency discrepancy and cortical areas known to be involved in semantic memory processing in a group of mildly affected MCI patients. Although previous research has successfully identified this phenomenon in MCI groups (Murphy, Rich & Troyer, 2006; Lonie *et al*., 2009; Teng *et al*., 2013), this study is among the first to demonstrate, using neuroimaging, that a verbal fluency discrepancy in such cohorts is likely to be attributable to structural changes within aMTL regions in the earliest stages of AD pathology that are associated with semantic memory function. This finding is of particular importance in light of the behavioural results of this study. As expected, given the findings of previous studies (Murphy, Rich & Troyer, 2006), mild MCI patients produced a comparable number of words in both category and letter fluency tasks, demonstrating an absence of the semantic advantage often seen in healthy individuals given the same tasks (Murphy, Rich & Troyer, 2006; Lonie *et al*., 2009; Vaughan *et al*., 2016). When scores were standardised according to a control mean however, there was a significantly greater decline in category fluency in comparison with letter fluency, to an extent that matched those in the more severely affected MCI patient group. Given that decline in category fluency in this mildly affected group, despite approaching the clinical cut-off, remained below 1.5 SDs, and therefore within a normal range of functioning, a discrepancy in the relative levels of decline between the two types of verbal fluency may be more informative clinically, in highlighting possible underlying disease processes, as demonstrated in previous studies through the significantly exacerbated presence of verbal fluency decline discrepancies in preclinical patients relative to controls (Clark *et al*., 2009; Papp *et al*., 2016). Relating this phenomenon to underlying pathological mechanisms associated with the earliest stages of AD is, therefore, extremely beneficial for

subsequent neuropsychological research utilising fluency measures, as it evidences an attribute of verbal fluency that may be more accurate in detecting semantic memory decline than raw scores alone. The results of the present study confirm previous hypotheses relating fluency discrepancies to damage within the temporal lobes (Henry & Crawford, 2004a, 2004b; Henry, Crawford & Philips, 2004) and, in accordance with previous studies (Venneri *et al*., 2008; Barbeau *et al*., 2012; Kivisaari *et al*., 2012; Hirni *et al*., 2013), further identify such discrepancies as an appropriate measure of semantic memory that can detect discrete structural changes within areas of subhippocamapal aMTL in even mildly affected prodromal AD patients.

II. Moderate MCI

The limited findings yielded by VBM in the moderate MCI group may be a result of the heterogeneous nature of this particular patient group. Compared with the mild MCI group, the moderate group had substantially more patients classified as multi-domain. Where fifty of the 53 moderate MCI patients had a multi-domain presentation, only 40 out of 58 were classified as multi-domain in the mildly affected group. Having so many patients classified as multi-domain from a behavioural perspective, suggests a degree of underlying heterogeneity in the disease process among the moderate MCI group that could have led to a dilution of the amount of variance within hypothesised regions of involvement but also a dilution in the amount of variance in the discrepancy scores that directly pertained to a semantic memory deficit. In contrast, the mild MCI group had nine patients classified as aMCI-sd, compared with only 2 in the moderate group, making it more likely that the variance in discrepancy scores in this group was more strongly related to differences in semantic memory function and therefore more strongly related to the expected areas of ATL. Furthermore, the moderate MCI group presented with a slightly higher proportion of patients with a non-amnestic multi-domain profile than the mild group. Although the overall number of non-amnestic patients was higher in the mild group, almost half were of a single-domain non-amnestic profile, which, along with a mild presentation, does not rule out prodromal AD as a possible cause. Reaching a moderate stage of cognitive decline without the development of a significant deficit in memory function, however, may indicate the presence of a pathological aetiology other than AD (Busse *et al*., 2006) and so dilution of the variance within the moderate MCI patients may be attributable to the presence of MCI patients who represent the prodromal stage of some other neurodegenerative disease.

Another possible explanation for the dilution of variance among the moderate MCI group may relate to heterogeneity concerning the progression of pathological damage and the emergence of neuropsychological decline among AD patients. The concept of cognitive reserve can explain why individuals with a similar level of AD related cortical damage can show distinct variability in their cognitive performance (Stern, 2009; 2012). The results presented here indicate that the measure of verbal fluency discrepancy loses its anatomical specificity towards the later stages of disease. The possibility, therefore, that a number of patients in the moderate MCI group may represent a later stage of the AD pathological cascade, despite maintaining cognitive function, possibly owing to higher levels of cognitive reserve, may further explain why the imaging results of this patient group were diluted compared with the mild patients, despite showing similar areas of correlation within the MTLs.

Interestingly, although yielding no significant results at the cluster-level FWE rate in the moderate group, the discrepancy scores did reveal a distinct trend of significant correlations, at the uncorrected significance level, with grey matter in bilateral temporal regions. When the peak coordinates from these clusters were further scrutinised using a small-volume correction, this revealed significant peaks ($pFWE < .05$) in anterior areas such as the PRC (BA 36) and temporal pole (BA 38), as well as more lateral areas such as the inferior, middle and superior temporal and fusiform gyri (BA 20, 21 and 22). The involvement of bilateral, but more apparent left-sided association in this group, in contrast with the right-side involvement in the mild MCI group, is again reflective of the pattern of atrophy associated with AD (Thompson *et al*., 2003; Shi *et al*., 2009). Although the mild MCI group are likely to have demonstrated right-side dominance in the presence of initial asymmetries in MTL atrophy, the moderate group may represent a stage in which atrophy begins to even out bilaterally and therefore the left-hemisphere dominance in language functions would remain apparent (Vigneau *et al*., 2006). This finding is suggestive that even in a heterogeneous group such as this, verbal fluency discrepancies are relatable to the degradation of structures sustaining semantic memory functions to a degree that may be more sensitive than simply the number of words produced during category fluency. Furthermore, as predicted by Didic's model and the present hypothesis, medial temporal lobe regions of significance in this group encompassed not only anterior structures including the PRC and inferior temporal cortex, involved heavily in the milder MCI group, but also more widespread posterior medial and lateral temporal structures. This finding, therefore, supports the model by Didic *et al*., (2011) that suggests that, in accordance with the Braak stages (1991), the

earliest involvement of anterior subhippocampal MTL regions would relate to a semantic memory deficit and as pathology spreads to further regions of the temporal lobes, so would the relationship between grey matter atrophy and semantic memory performance.

III. Dementia

Discrepancy scores in the dementia group correlated bilaterally with a variety of cortical regions. In contrast with the MCI groups, correlations in this group were not confined to the temporal lobes. Significant findings in this group were instead, largely focussed within occipital and posterior temporal regions but also included bilateral areas clustered around the paracentral lobule. Finding clusters of significance in the mild MCI and dementia groups, despite not identifying any among the moderately affected MCI subgroup, could suggest that as disease progresses, the heterogeneity displayed at MCI stages first increases before decreasing again in later stages in favour of a more homogenised presentation. As MCI is thought of as a transitionary phase between healthy ageing and dementia, known to be a particularly heterogeneous diagnosis (Petersen *et al*., 2001; Petersen, 2004; Albert *et al*., 2011), this finding is in line with a progression of disease beginning with discrete areas of pathology, associated with limited cognitive decline, through a heterogeneous period of differential rates of progression, to a homogenous dementia presentation associated with the accumulation of more widespread pathology. The finding of significant clusters in bilateral hemispheres in this group reflects a greater reliance on a wide distribution of semantic representations, thought to occur bilaterally (Gold & Kertesz, 2000; Castano, 2003; Hickok & Poeppel, 2007). The widespread involvement of cortical structures other than that of the temporal lobes is in accordance with the hypothesis that in later disease stages semantic memory processing will be associated with extended cortical areas in the presence of significant MTL damage (Venneri *et al*., 2008).

The temporal regions identified in this group were limited to posterior regions of superior temporal gyrus (BA 22) and parahippocampal gyrus (BA 19). This finding is again in line with the hypothesis that as disease progresses, more posterior regions of MTL will be recruited during semantic memory processing, as pathology spreads throughout anterior structures. Where the findings within the moderate MCI group demonstrate a slight posterior shift in semantic memory correlates relative to the mild group, these findings within the dementia group demonstrate yet a further posterior shift relative to both MCI groups, recruiting only very restricted posterior medial and lateral temporal areas with no

involvement of anterior or even inferior temporal lobe. In line with previous imaging studies (Binder *et al*., 2009; Visser *et al*., 2010), models of the semantic system (Patterson, Nestor & Rogers, 2007; Binder & Desai, 2011) and models describing visual object recognition (Saksida & Bussey, 2010) that, taken together, point to a hierarchical organisation of semantic processing within the temporal lobes, this shift in grey matter correlation can be thought of as representative of increased reliance on posterolateral temporal structures to facilitate semantic retrieval in the presence of significant MTL atrophy. Despite finding no evidence for significant involvement of ATL structures, Binder *et al*., (2009, 2011) specifically identified lateral temporal and medial paralimbic regions, such as the areas highlighted by discrepancy scores in the dementia group, as sites of importance for the amodal consolidation of semantic information. Furthermore, Visser *et al*., (2010) were able, using distortion corrected functional MRI (fMRI), to identify a pattern of cortical involvement in semantic processing that encompassed posterior regions, including the fusiform gyrus, and extended to inferior anterior temporal regions including the ERC, PRC and temporal poles. The results of each of these studies indicate that extensive regions of the temporal lobes may be implicated in semantic memory processing and, in accordance with the hierarchical organisation of the temporal lobes in relation to increasingly semantically confusable objects (Lavenex & Amaral, 2000; Saksida & Bussey, 2010; Kivisaari *et al*., 2012), damage to anterior structures at the top level of the hierarchy would likely result in a shift towards the recruitment of lower level posterior temporal cortices.

Extensive regions of occipital cortex were also associated with increased declines on category fluency compared with letter fluency in this patient group. Areas of significant correlation included bilateral extrastriate regions of the middle occipital gyrus (BA 18 and 19), as well as medial regions of the cuneus (BA 17 and 18) and lingual gyrus (BA 18 and 19) extending into the temporal lobe. Finding significant correlations in the occipital lobes in these dementia patients is unsurprising given the relative sparing of this area in AD. Moreover, these so-called 'visual' areas are known to be highly plastic, as demonstrated in blind individuals, facilitating language tasks such as sentence processing, semantic associations and even verbal memory function (Röder *et al*., 2002; Burton, Diamond & McDermott, 2003; Amedi *et al*., 2003). It is possible therefore, that the association with the occipital lobes in dementia patients reflects a reorganisation of the functions underlying semantic fluency to areas of limited atrophy, in the presence of significant degradation of the semantic store within the temporal lobes. Neural reorganisation in relation to semantic memory retrieval, such as this, has previously been demonstrated in MCI patients, in whom a

significant alteration in the functional architecture of both default mode and semantic networks has been found to be negatively associated with semantic memory function, potentially reflecting maladaptive compensatory cortical recruitment in this patient group (Gardini *et al*., 2015; Pineault *et al*., 2018). Similarly, alterations in cortical recruitment during semantic memory tasks have been shown to occur between disease stages, with MCI patients demonstrating evidence of widespread cortical involvement, in alignment with Gardini *et al*., (2015), in contrast with limited temporal involvement in AD dementia patients (Rodríguez-Ferreiro *et al*., 2012). Such evidence suggests that the neural organisation of semantic retrieval mechanisms can be altered by progressive pathology.

The cortical organisation of speech processing is thought to exist within a dorsal stream, for mapping acoustic speech sound to articulatory processing in frontal lobes, and a ventral stream, for mapping speech sounds to meaning (Hickok & Poeppel, 2007; Kümmerer *et al*., 2013). A recent multilevel-lesion study by Almairac *et al*. (2015) demonstrated a significant relationship between a semantic verbal fluency task and areas of white matter overlapping with the inferior fronto-occipital fasciculus (IFOF). Recently described in dissection and diffusion tensor imaging (DTI) studies, the IFOF has been implicated in connecting well-known semantically related cortical structures, including posterior prefrontal cortex, posterior temporal regions and occipital structures (Martino *et al*., 2010; Sarubbo *et al*., 2013), making it a likely candidate for an associative pathway sub-serving semantic memory processing. In support of this suggestion, intraoperative electrical stimulation of the IFOF along the entire bundle has been found to produce semantic paraphasias (Duffau *et al*., 2005; Duffau *et al*., 2008). The connections of the IFOF suggest that the occipital lobes play a significant role in semantic memory processing, even if primarily for visual input. Areas in which the IFOF terminates, including inferior and middle occipital gyri and posterior basal temporal regions (Martino *et al*., 2010), are therefore likely to be relied upon further in AD patients in support of a dysfunctional fronto-temporal semantic network.

Finally, as the origin of the ventral visual object recognition pathway (Mishkin *et al*., 1983), the extrastriatal occipital lobes function as the lowest level of this pathway, integral to semantic processing of visual stimuli. It is again possible, therefore, that degradation of automatic semantic retrieval processing sustained by the ATLs (Troyer *et al*., 1998; Henry & Crawford, 2004a, 2004b) causes a cognitive shift in AD patients, in which reliance upon more posterior temporal and occipital areas reflects retrieval strategies utilising concrete visual features to identify appropriate responses on a task of category fluency, in the absence of spontaneous categorical associations. Early fMRI studies have implicated the lingual gyrus

(BA 19), highlighted in the AD patients by discrepancy scores, and posterior fusiform gyrus (BA 19 and 37), in sustaining the neural correlates of visual imagery in the absence of perceptual stimuli (D'Esposito *et al*., 1997). A review by Slotnick (2004) suggests that in a similar mechanism, human visual memory is sufficient to induce activity in the same modality, domain and feature-specific processing regions that are associated with visual perception. Similarly, more recent imaging studies have indicated a role of extrastriatal occipital regions in facilitating visual imagery processes relating to visual memory retrieval (Huijbers *et al*., 2011; Leshikar, Duarte & Hertzog, 2012). Furthermore, fMRI has revealed significant associations between temporo-occipital areas including Brodmann areas 18, 19 and 37 and confrontation naming of visually presented line drawings (Abrahams *et al*., 2003), demonstrating the role of these areas in semantic processing of visual information. These findings could suggest, therefore, that as the semantic store is compromised by AD pathology in anterior temporal regions (Braak & Braak, 1991; Troyer *et al*., 1998; Henry & Crawford, 2004a, 2004b; Patterson, Nestor & Rogers, 2007), retrieval of semantically related items may become more reliant on processes sustaining visual semantic representations located in posterior inferior temporo-occipital cortex. However, this interpretation cannot be confirmed in the present study as retrieval strategies were not scrutinised in these participants.

Dementia patients also demonstrated significant correlations between discrepancy scores and areas of paracentral lobule, pre- and postcentral gyri (BA 1,3, 5 and 6), as well as superior and middle frontal gyri. Similarly to the correlations found within the occipital lobes, it is likely that the variance within these regions in the dementia group is largely driven by a lack of pathological spread within primary motor and sensory regions and therefore a relative sparing of their function (Braak & Braak 1991; Braak, Braak & Bohl, 1993). Lesion studies however, as well as functional imaging in healthy participants, have consistently demonstrated significant involvement of frontal areas during fluency tasks, including frontal isocortex as well as the anterior cingulate cortex (ACC), also highlighted by discrepancy scores in this patient group (Frith *et al*., 1991; Henry & Crawford, 2004a, 2004b; Birn *et al*., 2010). Such involvement of these structures is thought to relate to the executive functions of cognitive control and attention involved in word retrieval (Henry & Crawford, 2004a, 2004b) or, in the case of precentral gyri, simple motor function during speech production (Birn *et al*., 2010). However, a specific region of the supplementary motor area (SMA, BA 6), known as the pre-SMA, has been demonstrated to show activation in response to a semantic judgement task seemingly unrelated to word production (Chee *et al*., 1999) and present with similar activation when listeners are simply required to attend to the affective meaning of words

without any overt speech (Hinojosa *et al*., 2014). The pre-SMA has also been shown to display significant semantic priming effects in fMRI studies, suggesting some involvement in automatic semantic processing responses (Ulrich *et al*., 2013). Based on findings such as these, a review by Hertrich, Dietrich and Ackermann (2016) surmised that the pre-SMA may act as a key node within a cortico-subcortical circuit engaged in semantic retrieval. Furthermore, increased frontal activation during semantic memory tasks has been evidenced in functional imaging studies in both MCI and AD patients (Saykin *et al*., 1999; Rinne *et al*., 2003; Gigi *et al*., 2010; Yap *et al*., 2017), potentially reflecting the presence of compensatory executive retrieval mechanisms. Such increases in the spread of frontal involvement during semantic memory tasks in MCI patients has been associated with the maintenance of semantic memory function despite significant disruptions in parietal and fusiform areas thought to be of particular importance during these tasks (Gigi *et al*., 2010). These findings suggest a shift of reliance in AD to the semantic control network of the frontal lobes (Wagner *et al*., 2001) in response to significant early pathological changes within temporoparietal areas (Braak & Braak, 1991; Minoshima *et al*., 1997; Bradley *et al*., 2002). In dementia patients however, Yap *et al*., (2017) and Gigi *et al*., (2010) indicate a reduction in frontal activations relative to controls in their respective studies, likely reflecting an underlying structural change in line with the results of the present study. Grossman *et al*., (2013) demonstrated that impaired performance on a shared feature judgement task, using printed noun words, correlated most strongly with reduced volumes of the prefrontal cortex and temporo-occipital cortex, and their white matter connections, in a mixed group of MCI and AD dementia patients. These areas of reduced grey matter volume were found to overlap with the areas of activation highlighted in a healthy control group on blood-oxygen-level dependant (BOLD) fMRI, therefore suggesting that the semantic memory deficit in AD related cognitive decline could be, in part, rooted in the continued reliance on a similar network of brain areas, involved in semantic memory retrieval, as in healthy individuals, despite significant structural damage. This evidence may, therefore, explain the findings of previous functional imaging studies. Increases in frontal activations have also been evidenced in AD dementia patients however, with some discrepancies in the literature relating to the assumed beneficial or detrimental nature of this supposed compensatory cortical recruitment (Saykin *et al*., 1999; Rinne *et al*., 2003; McGeown *et al*., 2009). One study in particular, by McGeown *et al*., (2009), found that the Pyramids and Palm Trees (Howard & Patterson, 1992) task only elicited activation among AD patients in the left prefrontal and cingulate cortex. However, deactivation in anterior midline structures among patients was associated

with high performance in the AD group, while low performers tended to show more widespread activation and a failure to deactivate midline structures. As described in *Chapter 2*, the association of these areas with the default mode network (DMN, Raichle *et al*., 2001), known to be significantly deregulated in AD (Greicius *et al*., 2004), is indicative of a role for dysfunctional activation within this network in the semantic memory deficit present in this disease (Gardini *et al*., 2015).

Together, the results of these studies indicate that increased reliance upon frontal areas involved in controlled semantic retrieval (Troyer *et al*., 1998; Thompson-Schill *et al*., 1997; Wagner *et al*., 2001) may occur in AD patients from an early stage of disease (Gigi *et al*., 2010; Yap *et al*., 2017), reflecting a compensatory mechanism that may become increasingly detrimental as structural changes progress (McGeown *et al*., 2009; Grossman *et al*., 2013). The present study particularly highlighted correlations in the precentral, middle and superior frontal gyri (BA 6) as well as regions of anterior cingulate cortex (BA 24). Damage to these regions have been suggested by Binder *et al*., (2009) to contribute to linguistic impairments through disruption to the cognitive control and attention networks, mediated by these areas (Fan *et al*., 2005), that facilitate semantic retrieval. Finding significant correlations between verbal fluency and these frontal areas, despite having controlled for executive control functions through the use of discrepancy scores in the statistical model, is in line with previous studies evidencing the widespread involvement of neocortex with category fluency in AD patients (Venneri *et al*., 2008). Furthermore, this finding emphasises that observable, significant recruitment of widespread semantic systems is present in response to significant pathological damage, even when controlling for variances explained by executive functions not specific to semantic memory processing.

4.1.4.3. Region of Interest Analyses

ROI analyses were further included in this study, in addition to whole-brain VBM, in order to confirm the observed posterior shift between patient groups, in relation to the correlation between verbal fluency discrepancy scores and grey matter volumes within regions of the temporal lobes. Category fluency *z* scores were also included as an independent variable in this portion of the study, adding letter fluency *z* scores as an extra control variable. In these analyses none of the regions of interest were significantly correlated with either category fluency *z* scores or discrepancy scores in the mild MCI group. This finding may be attributed to the limited amount of pathology present within these patients in

the very early disease stages (Braak & Braak 1991; Sabbagh *et al*., 2010). As evidenced in the whole brain analysis, correlations between the discrepancy measure and grey matter volumes are clearly present within the temporal lobes, however, when normalised to represent atrophy relative to temporal lobe volume, such limited atrophy would likely be undetectable as part of a large ROI, delineated by Brodmann's areas. In the moderate MCI group however, in accordance with the initial hypothesis, significant correlations were present between discrepancy scores and category fluency *z* scores and temporal lobe fractions of right BA 36. Significant correlations between discrepancy scores were also apparent within right BA 20. These findings suggest that, unlike the milder patients who likely have limited anterior atrophy, as evidenced through whole brain analysis, patients in the moderate stage of disease have developed significant levels of atrophy within parahippocampal regions that have reached great enough levels to show significant correlations with semantic memory measures. Furthermore, correlations within BA 20 are suggestive of a shift in correlation towards areas outside of the MTL. A further posterior shift was seen within the dementia group, who demonstrated significant correlations between category fluency *z* scores and bilateral BA 22, but also between discrepancy scores and right-side BA 22, without any involvement of medial temporal or anterior temporal structures. These results are, therefore, in line with the hypothesis that, as disease progresses, a shift will be seen in correlations between semantic memory function and grey matter volume, from aMTL structures towards increasingly posterior, neocortical structures. It must also be noted that the correlation between right BA 22 and category fluency *z* scores was the only finding of the ROI analyses surviving a Bonferroni correction for multiple comparisons. However, given the findings of the whole-brain VBM analysis, indicating a significant relationship between semantic memory and grey matter volumes within varying temporal lobe regions across all disease groups, along with significant background evidence to support the hypothesis that semantic memory decline is associated with temporal lobe changes in AD (See *Chapter 2* for a full review), it may be concluded that, in this case, use of the highly strict Bonferroni correction may be inappropriate and could potentially lead to Type II statistical errors (Perneger, 1998).

A notable negative correlation was also present between category fluency *z* scores and the temporal lobe fraction of left BA 37 within the moderate MCI group, as well as a positive correlation between the same area and discrepancy scores. In the dementia group however, positive correlations between discrepancy scores were present between this measure and temporal lobe fractions of left BA 20. Seemingly counterintuitive, these correlations may reflect maladaptive recruitment of different brain regions during semantic memory tasks in

the presence of disease. As mentioned in section *4.1.4.2. III*, such maladaptive compensatory mechanisms have previously been described in functional imaging studies (Gardini *et al*., 2015; Pineault *et al*., 2018) in relation to semantic memory tasks. In accordance with the hierarchical shift hypothesis, the results within the fusiform gyrus (BA 37) among the moderate MCI patients may be reflective of an, as yet detrimental reliance on less specialised regions, upstream of the MTL in the 'ventral visual-perirhinal-hippocampal processing stream' described by Saksida and Bussey (2010) in their 'representational-hierarchical view' model. This view posits, as discussed previously, that semantic representations are formed in a hierarchical manner along the ventral visual stream, passing from posterior occipital cortex, through ventral temporal structures, culminating within the MTL. It is possible, therefore, that the negative associations between semantic memory performance and BA 37 in the moderate group is reflective of an ineffective recruitment of lower order representations to facilitate semantic memory function. The left lateralised presentation of this association is particularly pertinent in light of the asymmetric nature of initial AD related atrophy (Thompson *et al*., 2003; Shi *et al*., 2009) and the left lateralisation of language function (Vigneau *et al*., 2006). Positive correlations between temporal lobe fractions of BA 36 and BA 20 in the right hemisphere suggest that in light of the limited atrophy within these areas, when compared with left hemisphere structures, involvement of these regions in semantic memory function remains a successful process in this group. Negative correlations within left BA 37 however, suggest that, during language-based tasks such as this, significant atrophy within left MTL structures has led to an unsuccessful reliance on more posterior left hemisphere temporal regions that might usually be involved in language processing. In the dementia group, negative correlations between semantic memory function and left BA 20 may suggest that in the presence of more global temporal lobe atrophy, continued reliance on heavily damaged anterior temporal structures to facilitate semantic retrieval is actually associated with poorer semantic memory performance and therefore greater discrepancies between category and letter fluency tasks.

4.1.4.4. Post-Hoc Analyses

Post-hoc whole-brain analyses examining the MCI group as a whole, confirmed that, despite the correlations within the moderate MCI group not reaching cluster level significance, when added to the mild group, patterns of correlation within the ATLs were detectable and were even highly overlapping with the findings in the mild group. This

therefore suggests that the trend towards these areas is present within more moderate MCI groups but may limited in significance due to the dilution of the variance relating to heterogeneous patterns of disease progression.

Analysis separating early and late dementia patients served to further elucidate progressive changes in correlations between grey matter volume and semantic memory in AD throughout disease stages. In this case, early dementia patients (MMSE > 20) demonstrated significant correlations that were restricted primarily to left-sided occipital and very posterior temporal regions including lingual gyrus (BA 19), fusiform gyrus (BA 37) and middle temporal gyrus (BA 19). Late dementia patients (MMSE ≤ 20) however, showed much more widespread correlations within multiple areas including similar, but mostly right-sided, occipital and posterior medial temporal regions (BA 18, 19, 30 and 36), but also further areas of right lateralised temporal regions, largely contained in superior areas, such as the superior and transverse temporal gyri (BA 22, 41 and 42), as well as spreading into the inferior parietal lobule (BA 40). Further correlations were also seen within middle (BA 21) and inferior (BA 20) temporal gyri and some cerebellar regions. Again, occipital involvement in both groups, and also cerebellar involvement in the late group, is unsurprising, given that the relative sparing in these areas would likely mean a greater level of variance and therefore stronger correlations, in addition to the possibility of altered retrieval strategies involving more visual areas, as previously described. The temporal lobe results however, reveal a pattern of discrepancy score correlation that spreads from discrete regions of posterior temporal lobes, in the early dementia group, to far more widespread involvement of lateral temporal neocortex among the late-stage dementia patients. This finding is, therefore, in line with the previously described theory that throughout the progression of AD there is a detectable shift in correlation between grey matter and semantic memory function from discrete, high-order semantic consolidation nodes within the ATLs, towards more posterior areas, that will eventually spread laterally to include superior temporal and temporoparietal areas, further upstream of this hierarchical system (Patterson, Nestor & Rogers, 2007; Binder *et al*., 2009; Saksida & Bussey, 2010; Binder & Desai, 2011; Kivisaari *et al*., 2012).

4.1.4.5. Conclusions

The current findings have confirmed and extended the results of previous research indicating that a significant decline in semantic memory is present even in early AD (Vogel *et al*., 2005; Adlam *et al*., 2006; Joubert *et al*., 2008; Barbeau *et al*., 2012; Gardini *et al*.,

2013; Joubert *et al*., 2020), that such a decline is apparent on measures of verbal fluency (Vogel *et al*., 2005; Adlam *et al*., 2006; Gardini *et al*., 2013) and that there is a significant discrepancy in the rate of decline on semantic and phonemic fluency tasks throughout the course of disease, even in its earliest prodromal stages (Henry, Crawford & Phillips, 2004; Murphy, Rich & Troyer, 2006; Clark *et al*., 2009; Chasles *et al*., 2020; Vonk *et al*., 2020). Furthermore, imaging analyses have confirmed previous findings that the semantic deficit in prodromal AD is likely underpinned by pathological changes within the aMTL occurring in the initial stages of disease (Barbeau *et al*., 2012; Hirni *et al*., 2013) and further demonstrated a pattern of pathological progression, across the disease spectrum, that is traceable through the utilisation of semantic memory measures. As demonstrated by the findings of the systematic review in *Chapter 2*, the present study similarly confirmed that semantic memory decline, as measured by the semantic/phonemic verbal fluency discrepancy, is most indicative of aMTL damage in the earliest stages of disease. As disease progresses, the specificity of the marker to changes in these areas is lost, instead demonstrating correlations within more widespread, posterior cortical areas. As such, the power of this cognitive marker to AD specific cortical degradation appears to be greatest in the earliest stages of disease.

4.2. Experiment 2 – Associations between semantic memory and grey matter volume among differing MCI profiles.

4.2.1. Introduction

As outlined in section *4.1.4* of this chapter, the previous experiment provides compelling evidence for a relationship between semantic memory decline and aMTL structures involved in the earliest stages of AD. Furthermore, evidence from patients in the dementia stages indicates a pattern of semantic memory related cortical involvement that appears to progress from anterior structures in the earliest manifestations of disease through to more posterior temporal and occipital regions in later stages. A limitation of the previous experiment, however, is the lack of adequate explanation for the absence of significant findings within patients at a moderate stage of cognitive impairment. One interpretation given is that greater levels of heterogeneity among this group, in terms of cognitive profile, which may be reflective of similar heterogeneity in underlying disease processes (Edmonds *et al*., 2016), could have been responsible for the dilution of variance in discrepancy scores and grey matter volumes that directly pertained to semantic memory dysfunction in this group.

Previous research has shown that MCI patients of differing cognitive subtypes present both structurally and functionally with notably distinctive cortical deficits (Bell-McGinty *et al*., 2005; Whitwell *et al*., 2007b; Caffarra *et al*., 2008; Zhang *et al*., 2012; Li *et al*., 2013a; Li *et al*., 2013b; Li *et al*., 2014; López *et al*., 2014; Li & Zhang, 2015; Csukly *et al*., 2016) and that such differences may not only be related to variations in aetiology (Petersen *et al*., 2001; Petersen, 2004; Petersen & Negash, 2008), but also to disease severity (Edmonds *et al*., 2016). In order to test the hypothesis that such heterogeneity may influence the neural correlates of semantic memory in MCI, the present experiment was conducted in which MCI patients of differing cognitive profiles were separated according to subtype.

4.2.1.1. Aims and Hypotheses

The aim of the present experiment was to determine the pattern of cortical involvement associated with semantic memory function in differing MCI subtypes and identify any potential differences in semantic memory neural correlates between MCI patients with differing cognitive profiles and disease severities. It was hypothesised, given the previous work, that patients presenting with impairments within multiple domains of cognition would likely demonstrate weaker correlations between semantic memory function and cortical grey matter volumes than those with a profile of single domain impairment. In accordance with previous research demonstrating higher conversion to AD dementia in patients with an amnestic profile than in those with a non-amnestic profile (Busse *et al*., 2006) and the lack of disproportionate semantic fluency declines in non-amnestic groups (Rinehardt *et al*., 2014; Vonk *et al*., 2020), it was also hypothesised that those with aMCI would be more likely to present with neural correlates relating to verbal fluency discrepancy within areas involved in the progression of AD than those with non-amnestic MCI (MCI-na).

4.2.2. Materials and Methods

4.2.2.1. Participants

A total of 111 participants fitting the criteria for mild cognitive impairment (MCI) were included in this experiment. Details of patient recruitment and diagnosis can be found in section *4.1.2.1.* As in the previous experiment, MCI patients were stratified according to disease severity (see section *4.1.2.1. I*) and were further stratified according to their cognitive profiles into the subtypes outlined by Petersen (2004): aMCI-sd, aMCI-md, sd-MCI-na and

md-MCI-na (see section *4.1.2.1. I*). The distributions of each MCI subtype within the mild and moderate groups, and therefore the number of participants in each group, can be seen in section *4.1.2.1 I.* in ***Fig. 4.1***. Ethical approval for this study was as detailed in *Experiment 1* (See section *4.1.2.1.*).

4.2.2.2. Neuropsychological Analysis

Neuropsychological analysis was conducted using the same neuropsychological test battery as was applied in the previous experiment (See section *4.1.2.3*.). Similarly, semantic memory function was assessed using verbal fluency scores standardised into *z* scores using the means and SDs of a group of matched controls, as per section *4.1.2.4. II*. In order to maximise the number of participants in each group, the analysis of neuropsychological test data was carried out between MCI subtypes considering the MCI group as a whole, without stratifying them by disease severity. Post-hoc analyses were also run on a group of 82 controls matched with each MCI sub-group in terms of age and gender. All patient groups were similarly matched with each other. Controls were further matched with most groups in terms of education levels, however, because of unusually high levels of education among the patients with aMCI-sd, all other groups including controls were significantly less educated than that particular group. Demographic data for each group can be found in **Table 4.13** and a complete list of all neuropsychological tests can be seen in **Table 4.14**.

4.2.2.3. VBM Imaging Analysis

As in the previous experiment, three-dimensional T1-weighted scans were used for all participants collected by either a Philips Ingenia 3.0 T scanner (n = 34) or, for the majority of participants from the Venice cohort, a 1.5 T Philips Achieva scanner (n = 77) (see section *4.1.2.4*. for protocols). Voxel-based morphometry was used to assess the relationship between grey matter volumes and verbal fluency discrepancies. The same pre-processing steps and whole-brain imaging analyses were applied in this experiment as outlined in section *4.1.2.4*. Regression analyses between grey matter volumes and verbal fluency discrepancy scores, calculated as per the methods outlined in section *4.1.2.4. II,* were applied separately to each MCI subtype, split according to disease severity. This included four groups of mild MCI patients stratified by subtype and 2 moderate MCI groups split into aMCI-md and md-MCI-na. Given that only two moderate MCI patients had a single domain amnestic profile and only 1 a single domain non-amnestic profile, subsequent analysis in this group was first run only

on the multi-domain groups. The single-domain participants were then added to the multiple-domain amnestic and non-amnestic groups respectively to assess any effects this may have had on the variance. As in the previous experiment, regression models included the covariates of age, education, MMSE and total intracranial volume (ml).

4.2.2.4. Post-Hoc Analysis

Post-hoc analyses were also run on a group of matched controls. The control group consisted of 82 individuals with available MRI scans, taken as a subsample of the larger control group used to calculate the verbal fluency *z* scores for the patients (See section *4.1.2.4. II* **Table 4.4**). Discrepancy scores for this group were calculated using the same data used for calculating patients' *z* scores from the original larger control sample.

4.2.3. Results

4.2.3.1. Demographic Data

Demographic data for each MCI subgroup, not stratified according to disease severity can be found in **Table 4.13**. The results of individual independent-samples *t*-tests and Mann-Whitney *U* tests are outlined in this table, showing significant differences between the aMCI-sd group and all other groups in terms of education, as well as significant differences between both the multi-domain groups and the control group in terms of MMSE score. Neither single domain group differed significantly from controls on the MMSE.

Table 4.13

Gender ratios and means (and standard deviations) for age and years of education are presented for MCI subtypes and control group. Significant differences were calculated using independent-samples t-tests. MMSE scores were non-normally distributed, therefore the median and interquartile range is given and significant differences were calculated using Mann-Whitney U tests. Significant differences are indicated as: [a] Significantly lower than controls ($p < 0.05$), [b] Significantly higher than all other groups ($p < 0.05$)

	aMCI-sd (*n* = 11)	**aMCI-md (*n* = 69)**	**md-MCI-na (*n* = 21)**	**sd-MCI-na (*n* = 10)**	**Controls (*n* = 82)**
Age (Years)	72.27 (8.20)	73.04 (9.28)	72.93 (9.34)	75.30 (4.45)	72.71 (8.06)
Years of Education	14.73 (3.20) [b]	10.43 (4.35)	10.20 (4.05)	10.40 (3.98)	10.89 (3.67)
Gender (M/F)	7/4	24/45	6/15	4/6	31/51
MMSE (Mdn/IQR)	28.00 (2.00)	26.00 (3.00) [a]	26.00 (1.00) [a]	27.50 (2.00)	29.00 (3.00)

4.2.3.2. Neuropsychological Results

The results of a non-parametric Kruskall-Wallis *H* test between groups on each of the cognitive test scores are outlined in **Table 4.14**. Significant differences on cognitive tests, as determined by *post-hoc* Dunn tests with a Bonferroni correction, were particularly apparent between controls and MCI patients with a multi-domain profile. Single domain patients demonstrated far more restricted impairments, with the aMCI-sd group only significantly differing from controls on the category fluency test, the delayed Prose Memory measure and verbal fluency discrepancy scores, and the sd-MCI-na group performing at a similar level to controls on all tests. Only the amnestic patients demonstrated significantly greater verbal fluency discrepancy scores than controls and both the aMCI-md and md-MCI-na groups had significantly lower category fluency *z* scores than controls. Although the aMCI-sd group did not demonstrate significantly lower category fluency *z* scores than controls, their raw scores were significantly lower, along with both multi-domain groups.

Within group analysis was further carried out to assess differences in performance and decline on category and letter fluency tests within each participant group. Paired comparisons between the raw category and letter fluency scores as well as the standardised category and letter fluency scores revealed significant differences in performance and relative levels of decline on each test in a number of the groups. Wilcoxon signed rank tests were used to assess differences in raw test scores between each of the fluencies in both amnestic MCI groups and the controls. Controls scored significantly higher on measures of category fluency (mdn = 41) than letter fluency (mdn = 37.5) $Z = -4.19$, $p < .001$. No significant differences were found between category and letter fluency raw scores in either the aMCI-sd group ($Z = -1.68$, $p = .09$) or the aMCI-md group ($Z = -1.31$, $p = 1.9$) (medians and interquartile ranges are outlined in **Table 4.14**). Paired samples *t*-tests were used to assess differences in category and letter fluency raw scores in each of the non-amnestic groups. No significant differences were found between the measures in either the md-MCI-na group ($t[20] = -.77$, $p = .45$) or the sd-MCI-na group ($t[9] = -.48$, $p = .64$) (medians and interquartile ranges are outlined in **Table 4.14**).

Further paired-samples *t*-tests were used to assess differences in category and letter fluency *z* scores within both the non-amnestic groups and the controls. No significant differences were found between each of the standardised measures in either the md-MCI-na group ($t[20] = 1.65$, $p = .12$) the sd-MCI-na group ($t[9] = .649$, $p = .53$) or the control group ($t[81] = 0.77$, $p = .44$) (means and SDs are reported in **Table 4.14)**. Wilcoxon signed rank

tests were used to assess differences in category and letter fluency *z* scores within each of the amnestic MCI groups. Patients with an aMCI-sd profile presented with significantly lower category fluency *z* scores (mdn = -1.09) than letter fluency *z* scores (mdn = .30) $Z = -2.49$, $p = .01$. Similarly, patients with an aMCI-md profile also had significantly lower category fluency *z* scores (mdn = -1.52) than letter fluency *z* scores (mdn = -1.13) $Z = -4.67$, $p < .001$.

Table 4.14

Table containing the results of a Kruskal-Wallis H test to determine which neuropsychological tests scores differed significantly between the five groups according to MCI subtype. Post-hoc Dunn tests were further carried out between each pair. A Bonferroni correction was applied to adjust the p value for multiple comparisons. Significant differences between group pairs are highlighted. ([a] Significantly lower than aMCI-sd [p<0.05], [b] Significantly lower than aMCI-md [p <0.05], [c] Significantly lower than md-MCI-na [p <0.05], [d] Significantly lower than sd-MCI-na [p <0.05], [e] Significantly lower than healthy controls [p <0.05])

Neuropsychological Test	Patient Group	*n*	Mean (SD)	Median (IQR)	Mean Rank	Chi-Square	df	p value
Letter Fluency Z Scores	aMCI-sd	11	0.55 (0.91)	0.30 (1.22)	138.45	36.90	4	< .001
	aMCI-md	69	-0.88 (1.03)	-1.13 (1.51) [ae]	68.01			
	mdMCI-na	21	-0.55 (1.19)	-0.62 (1.73)	84.95			
	sdMCI-na	10	0.04 (1.04)	0.14 (1.10)	113.85			
	Controls	82	0.08 (1.04)	0.06 (1.53)	116.86			
Category Fluency Z Scores	aMCI-sd	11	-0.77 (1.26)	-1.09 (1.09)	84.68	72.32	4	< .001
	aMCI-md	69	-1.48 (0.81)	-1.52 (1.17) [de]	56.64			
	mdMCI-na	21	-0.95 (0.67)	-0.98 (0.92) [e]	86.00			
	sdMCI-na	10	-0.29 (0.90)	-0.00 (1.48)	121.75			
	Controls	82	0.00 (1.00)	-0.12 (1.37)	132.41			
Discrepancy Score	aMCI-sd	11	1.32 (1.40)	1.69 (1.58)	141.45	18.17	4	< .001
	aMCI-md	69	0.60 (0.95)	0.53 (1.18)	109.77			
	mdMCI-na	21	0.41 (1.13)	0.18 (1.41)	101.43			
	sdMCI-na	10	0.33 (1.62)	-0.10 (1.27)	82.65			
	Controls	82	0.09 (1.03)	0.01 (1.27) [ab]	80.91			
Raven	aMCI-sd	11	31.18 (4.00)	33.00 (8.00)	139.32	43.21	4	<. 001
	aMCI-md	69	24.58 (5.25)	25.00 (9.00) [ae]	71.29			
	mdMCI-na	21	24.43 (4.41)	24.00 (6.00) [ae]	65.60			
	sdMCI-na	10	27.40 (4.12)	27.00 (9.00)	94.80			
	Controls	82	29.55 (4.65)	30.50 (8.00)	121.27			
Letter Fluency	aMCI-sd	11	38.64 (8.19)	38.00 (12.00)	129.95	37.78	4	< .001
	aMCI-md	69	26.33 (10.72)	24.00 (12.00) [ae]	69.88			
	mdMCI-na	21	26.90 (11.35)	26.00 (17.00) [e]	74.36			
	sdMCI-na	10	33.60 (9.73)	34.00 (9.00)	106.85			
	Controls	82	38.54 (14.68)	37.50 (20.00)	119.99			
Category Fluency	aMCI-sd	11	31.45 (12.55)	27.00 (12.00) [e]	74.82	64.34	4	< .001
	aMCI-md	69	28.06 (9.92)	27.00 (12.00) [e]	64.46			
	mdMCI-na	21	28.81 (5.28)	28.00 (8.00) [e]	69.60			
	sdMCI-na	10	36.00 (8.82)	39.50 (11.00)	110.90			
	Controls	82	44.06 (13.81)	41.00 (18.00)	132.68			
Digit Cancellation	aMCI-sd	11	51.55 (5.11)	53.00 (9.00)	120.82	46.29	4	< .001
	aMCI-md	69	44.10 (8.46)	44.00 (12.00) [e]	71.20			
	mdMCI-na	21	41.90 (8.46)	42.00 (11.00) [ade]	57.81			
	sdMCI-na	10	51.50 (3.87)	52.00 (6.00)	119.76			
	Controls	82	51.46 (6.84)	53.00 (9.00)	122.78			
Similarities	aMCI-sd	11	21.36 (4.50)	21.00 (7.00)	121.91	45.55	4	<. 001
	aMCI-md	69	17.29 (4.41)	17.00 (7.00) [e]	76.14			
	mdMCI-na	21	14.86 (3.20)	15.00 (5.00) [ae]	47.93			
	sdMCI-na	10	20.00 (3.37)	20.00 (5.00)	108.05			
	Controls	82	21.51 (5.04)	22.00 (9.00)	122.43			
Token	aMCI-sd	11	34.95 (1.15)	35.00 (2.00)	135.91	42.29	4	< .001
	aMCI-md	68	32.55 (2.62)	33.00 (3.38) [ae]	78.45			
	mdMCI-na	21	31.45 (2.16)	31.00 (2.25) [ae]	51.07			
	sdMCI-na	10	33.05 (0.86)	33.00 (1.63)	78.85			
	Controls	82	34.27 (1.90)	35.00 (3.00)	119.08			

Table 4.14 Cont.

Neuropsychological Test	Patient Group	*n*	Mean (SD)	Median (IQR)	Mean Rank	Chi-Square	df	p value
Rey Copy	aMCI-sd	11	33.64 (2.20)	34.00 (4.00)	141.18	31.58	4	< .001
	aMCI-md	68	27.45 (6.58)	29.25 (6.90) [ae]	73.05			
	mdMCI-na	21	27.88 (5.90)	28.00 (7.80) [ae]	75.33			
	sdMCI-na	10	29.15 (8.20)	31.25 (9.80)	99.45			
	Controls	82	31.83 (3.40)	32.50 (4.00)	115.01			
Rey Recall	aMCI-sd	11	9.41 (4.36)	10.00 (6.00)	85.86	68.43	4	< .001
	aMCI-md	68	6.46 (4.74)	5.00 (5.40) [ce]	56.09			
	mdMCI-na	21	10.29 (3.60)	9.00 (6.30)	96.40			
	sdMCI-na	10	10.80 (5.49)	8.50 (9.40)	98.65			
	Controls	82	14.23 (5.00)	14.75 (7.10)	131.20			
Stroop Time	aMCI-sd	11	20.86 (7.37)	19.50 (13.00) [b]	57.18	25.02	4	< .001
	aMCI-md	68	41.32 (24.57)	36.75 (26.80)	117.79			
	mdMCI-na	21	35.45 (16.66)	40.50 (18.80)	112.62			
	sdMCI-na	10	28.20 (13.98)	22.75 (18.10)	84.15			
	Controls	82	26.71 (12.64)	24.00 (17.00) [b]	80.14			
Stroop Error	aMCI-sd	11	0.14 (0.32)	0.00 (0.00) [bc]	57.23	49.38	4	< .001
	aMCI-md	68	5.43 (7.52)	2.00 (6.40)	125.69			
	mdMCI-na	21	4.88 (6.81)	3.00 (7.50)	118.29			
	sdMCI-na	10	0.65 (1.42)	0.00 (1.00) [b]	70.50			
	Controls	82	0.84 (1.71)	0.00 (1.00) [bc]	73.71			
Digit Span Forward	aMCI-sd	11	6.18 (1.08)	6.00 (2.00)	117.82	12.26		0.016
	aMCI-md	69	5.45 (0.90)	6.00 (1.00)	85.03			
	mdMCI-na	21	5.33 (0.73)	5.00 (1.00)	78.12			
	sdMCI-na	10	5.80 (1.48)	6.00 (2.00)	96.95			
	Controls	82	5.95 (1.08)	6.00 (2.00)	109.12			
Digit Span Backward	aMCI-sd	11	4.36 (0.81)	4.00 (1.00)	113.50	28.33	4	0.014
	aMCI-md	69	3.64 (1.00)	4.00 (1.00) [e]	75.37			
	mdMCI-na	21	3.76 (0.94)	4.00 (1.00) [e]	75.76			
	sdMCI-na	10	4.30 (1.06)	4.00 (2.00)	117.39			
	Controls	82	4.55 (1.14)	4.00 (1.00)	105.50			
Prose Memory Immediate	aMCI-sd	11	7.73 (3.32)	8.00 (6.00)	81.18	53.09	4	< .001
	aMCI-md	69	6.19 (3.55)	6.00 (4.50) [ce]	60.97			
	mdMCI-na	21	9.24 (2.47)	9.00 (4.00)	103.52			
	sdMCI-na	10	9.80 (3.05)	8.50 (7.00)	109.90			
	Controls	82	11.35 (4.33)	11.00 (6.00)	126.20			
Prose Memory Delayed	aMCI-sd	11	6.00 (3.72)	5.00 (3.00) [e]	50.95	74.69	4	< .001
	aMCI-md	69	6.72 (5.11)	5.00 (8.00) [ce]	58.60			
	mdMCI-na	21	11.19 (2.84)	11.00 (4.00)	101.12			
	sdMCI-na	10	12.30 (4.22)	11.00 (8.00)	110.00			
	Controls	82	14.82 (5.00)	15.00 (8.00)	132.85			
Paired Associates	aMCI-sd	11	10.27 (3.20)	10.00 (3.50)	88.82	51.87	4	< .001
	aMCI-md	68	8.57 (3.46)	8.00 (4.90) [e]	64.47			
	mdMCI-na	21	9.81 (2.37)	9.50 (4.00) [e]	83.36			
	sdMCI-na	10	10.15 (3.06)	9.50 (4.30)	86.65			
	Controls	82	13.35 (4.01)	13.25 (5.50)	128.66			
Naming	aMCI-sd	11	18.91 (1.64)	20.00 (2.00)	115.09	13.89	4	0.008
	aMCI-md	68	17.99 (2.26)	19.00 (3.00)	86.43			
	mdMCI-na	21	17.71 (1.52)	18.00 (3.00) [e]	68.36			
	sdMCI-na	10	18.70 (1.42)	19.00 (2.00)	102.60			
	Controls	82	18.77 (1.61)	19.00 (2.00)	108.82			

4.2.3.3. Imaging Results

I. Mild MCI

A whole-brain multiple regression model run only including patients with a non-amnestic profile in the mild MCI group revealed no significant correlations between grey matter and discrepancy scores at the FWE rate. The amnestic multi-domain group also did not demonstrate any correlations that were significant at the FWE rate however two clusters retained significance at the false discovery rate (FDR).

Ia. Amnestic Single-Domain

A whole brain multiple regression analysis within the mild single domain aMCI patients revealed significant negative correlations between discrepancy scores and grey matter volumes within multiple regions across the cortex with particular involvement of the frontal and temporal lobes (***Fig. 4.10***). A full list of coordinates can be found in **Table 4.15**.

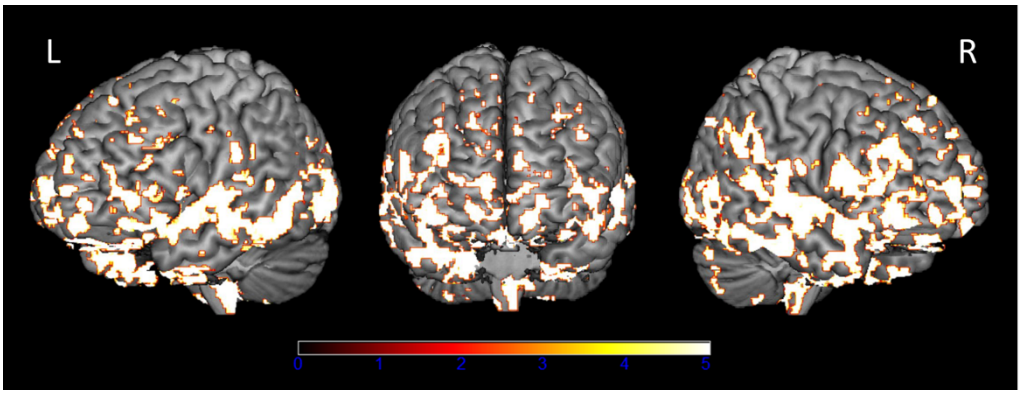


Figure 4.10. *Areas of significant negative correlation between grey matter volumes and verbal fluency discrepancy scores in the amnestic single domain mild MCI group (n = 9) in extensive cortical regions largely in frontal and temporal lobes.*

Table 4.15

*Areas of significant negative correlation between grey matter volume and verbal fluency discrepancy scores in the mild aMCI-sd (n = 9). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc, Uncorrected; BA, Brodmann's Area; FWE, Family Wise Error. *no given Brodmann area. Thresholded p = .005*

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Superior Temporal Gyrus (38)	R	0	0	6770	4.09	45	18	-19	45	20	-22
Uncus (36)	R				4.01	26	-9	-33	26	-8	-40
Uncus (36)	R				4	20	-8	-35	20	-6	-42
Inferior Temporal Gyrus (20)	R				3.93	59	-13	-21	60	-12	-26
Superior Temporal Gyrus (38)	R				3.87	50	21	-14	50	22	-15
Middle Temporal Gyrus (21)	R				3.87	55	-3	-10	56	-3	-12
Superior Temporal Gyrus (22)	R				3.84	56	3	-3	57	3	-3
Middle Temporal Gyrus (21)	R				3.84	61	-8	-6	62	-8	-8
Middle Temporal Gyrus (21)	R				3.83	55	-9	-15	56	-8	-18
Middle Temporal Gyrus (20)	R				3.82	63	-42	-15	64	-42	-20
Inferior Temporal Gyrus (20)	R				3.79	57	-24	-22	58	-24	-28
Inferior Parietal Lobule (40)	R				3.76	53	-26	23	54	-28	24
Inferior Parietal Lobule (40)	R				3.74	57	-35	38	58	-38	39
Superior Temporal Gyrus (21)	R				3.74	63	-14	-2	64	-14	-3
Uncus (38)	R				3.73	28	8	-29	28	10	-34
Superior Temporal Gyrus (38)	R				3.73	33	13	-28	33	15	-33
Inferior Frontal Gyrus (45)	R	0	0	1292	4.07	56	26	13	57	26	15
Inferior Frontal Gyrus (46)	R				3.86	44	34	11	44	34	14
Middle Frontal Gyrus (10)	R				3.82	36	40	24	36	40	28
Inferior Frontal Gyrus (44)	R				3.76	56	18	13	57	18	15
Inferior Frontal Gyrus (45)	R				3.75	56	25	1	57	26	3
Middle Frontal Gyrus (46)	R				3.72	44	34	22	44	34	26
Middle Frontal Gyrus (10)	R				3.71	42	44	12	42	45	15
Middle Frontal Gyrus (46)	R				3.67	42	42	27	42	42	32
Inferior Frontal Gyrus (45)	R				3.67	55	21	16	56	21	18
Inferior Frontal Gyrus (47)	R				3.62	53	29	0	54	30	2
Inferior Frontal Gyrus (46)	R				3.56	57	30	10	58	30	12
Inferior Frontal Gyrus (47)	R				3.54	55	29	-4	56	30	-3
Middle Frontal Gyrus (46)	R				3.54	40	32	18	40	32	21
Middle Frontal Gyrus (9)	R				3.52	27	39	26	27	39	30
Middle Frontal Gyrus (9)	R				3.49	30	38	23	30	38	27
Inferior Frontal Gyrus (46)	R				3.46	48	37	4	48	38	6
Middle Temporal Gyrus (37)	R	0	0	1790	4.05	57	-61	5	58	-63	2
Middle Temporal Gyrus (39)	R				3.92	53	-61	9	54	-63	6
Inferior Occipital Gyrus (19)	R				3.89	40	-73	-8	40	-75	-14
Inferior Temporal Gyrus (20)	R				3.75	50	-55	-12	51	-56	-18
Inferior Occipital Gyrus (18)	R				3.75	24	-88	-7	24	-90	-14
Fusiform Gyrus (37)	R				3.71	56	-56	-16	57	-57	-22
Inferior Temporal Gyrus (19)	R				3.69	50	-66	-3	51	-68	-8
Inferior Occipital Gyrus (19)	R				3.66	45	-80	-3	45	-82	-8
Middle Occipital Gyrus (19)	R				3.65	56	-64	-4	57	-66	-8
Sub-Gyral (37)	R				3.64	51	-49	-4	52	-50	-8
Fusiform Gyrus (19)	R				3.64	36	-69	-12	36	-70	-18
Middle Occipital Gyrus (18)	R				3.63	30	-82	-9	30	-84	-16
Fusiform Gyrus (19)	R				3.62	40	-67	-9	40	-69	-15
Middle Temporal Gyrus (21)	R				3.61	61	-56	6	62	-58	3
Inferior Occipital Gyrus (18)	R				3.57	40	-84	1	40	-87	-4
Middle Occipital Gyrus (37)	R				3.54	50	-65	-9	50	-66	-14

Table 4.15 Cont.

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Medial Frontal Gyrus (38)	R	0	0	874	4.03	12	64	2	12	66	6
Medial Frontal Gyrus (10)	R				3.83	12	51	3	12	52	6
Superior Frontal Gyrus (11)	R				3.63	18	56	-15	18	58	-14
Medial Frontal Gyrus (11)	R				3.5	6	60	-13	6	62	-12
Medial Frontal Gyrus (10)	R				3.49	12	67	-6	12	69	-3
Superior Frontal Gyrus (10)	R				3.47	14	68	5	14	70	9
Medial Frontal Gyrus (10)	L				3.46	-2	58	-5	-2	60	-3
Superior Frontal Gyrus (11)	R				3.45	18	58	-10	18	60	-9
Superior Frontal Gyrus *	R				3.38	20	64	2	20	66	6
Medial Frontal Gyrus (10)	R				3.34	2	55	-5	2	57	-3
Medial Frontal Gyrus *	L				3.31	-10	64	0	-10	66	4
Superior Frontal Gyrus (11)	R				3.3	2	65	-12	2	68	-10
Medial Frontal Gyrus (10)	L				3.24	-10	60	0	-10	62	3
Medial Frontal Gyrus (10)	R				3.19	9	55	6	9	56	10
Superior Frontal Gyrus (10)	R				3.09	28	61	4	28	63	8
Medial Frontal Gyrus (10)	R				3.03	18	49	3	18	50	6
Inferior Temporal Gyrus (19)	L	0	0	1186	4	-50	-58	0	-50	-60	-4
Inferior Occipital Gyrus (19)	L				3.91	-45	-78	-3	-45	-80	-8
Middle Occipital Gyrus (37)	L				3.55	-51	-68	3	-52	-70	0
Middle Occipital Gyrus (19)	L				3.54	-42	-81	12	-42	-84	9
Middle Occipital Gyrus (19)	L				3.54	-50	-73	-4	-51	-75	-9
Middle Temporal Gyrus (39)	L				3.44	-50	-66	17	-51	-69	15
Middle Occipital Gyrus (19)	L				3.4	-50	-79	8	-50	-82	4
Middle Temporal Gyrus (19)	L				3.37	-51	-60	14	-52	-62	12
Middle Occipital Gyrus (19)	L				3.37	-42	-85	7	-42	-88	3
Middle Temporal Gyrus (39)	L				3.3	-40	-75	13	-40	-78	10
Middle Temporal Gyrus (39)	L				3.27	-50	-71	16	-51	-74	14
Inferior Occipital Gyrus (18)	L				3.27	-40	-84	1	-40	-87	-4
Middle Temporal Gyrus (37)	L				3.19	-55	-56	0	-56	-58	-3
Middle Temporal Gyrus (39)	L				3.19	-50	-61	11	-50	-63	9
Middle Occipital Gyrus (18)	L				3.15	-32	-82	-8	-32	-84	-14
Middle Temporal Gyrus (19)	L				3.12	-46	-78	18	-46	-81	15
Inferior Temporal Gyrus (20)	L	0	0	922	3.97	-61	-34	-15	-62	-34	-20
Middle Temporal Gyrus *	L				3.89	-62	-45	1	-63	-46	-2
Middle Temporal Gyrus (20)	L				3.77	-57	-41	-13	-58	-42	-18
Middle Temporal Gyrus (21)	L				3.64	-67	-41	-11	-68	-42	-15
Middle Temporal Gyrus (21)	L				3.59	-65	-48	4	-66	-50	2
Middle Temporal Gyrus (21)	L				3.35	-61	-33	-10	-62	-33	-14
Inferior Temporal Gyrus (20)	L				3.34	-53	-24	-22	-54	-24	-28
Inferior Temporal Gyrus (20)	L				3.31	-59	-28	-16	-60	-28	-21
Middle Temporal Gyrus (21)	L				3.24	-61	-27	-11	-62	-27	-15
Fusiform Gyrus (20)	L				3.22	-55	-33	-19	-56	-33	-24
Middle Temporal Gyrus (21)	L				3.08	-61	-50	6	-62	-52	4
Fusiform Gyrus (20)	L				3.08	-51	-32	-21	-52	-32	-27
Middle Temporal Gyrus (21)	L				2.83	-46	-29	-1	-46	-30	-3
Superior Temporal Gyrus (22)	L				2.8	-48	-32	2	-48	-33	0
Middle Temporal Gyrus (22)	L				2.75	-51	-39	5	-52	-40	3
Inferior Frontal Gyrus (10)	L	0.047	0	288	3.93	-45	44	-4	-45	46	-2
Inferior Frontal Gyrus (10)	L				3.79	-42	49	-1	-42	50	2
Middle Frontal Gyrus (10)	L				3.66	-36	51	10	-36	52	14
Superior Frontal Gyrus (10)	L				3.32	-36	56	12	-36	57	16
Middle Frontal Gyrus (10)	L				2.79	-39	53	6	-39	54	9

Table 4.15 Cont.

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Anterior Cingulate (32)	L	0.015	0	349	3.92	-8	36	17	-8	36	20
Medial Frontal Gyrus (9)	L				3.91	-10	38	20	-10	38	24
Anterior Cingulate (24)	L				3.85	-8	32	18	-8	32	21
Anterior Cingulate (32)	L				3.63	-9	39	7	-9	40	10
Anterior Cingulate (32)	L				3.51	-8	43	0	-8	44	2
Anterior Cingulate (33)	L				3.34	-6	22	19	-6	22	22
Medial Frontal Gyrus (10)	L				3.03	-10	50	0	-10	51	3
Anterior Cingulate (32)	L				2.94	-6	44	9	-6	45	12
Anterior Cingulate (32)	L				2.85	-9	33	9	-9	34	12
Inferior Frontal Gyrus (47)	L	0	0	1882	3.85	-48	27	-13	-48	28	-14
Inferior Temporal Gyrus (21)	L				3.8	-57	-9	-16	-58	-8	-20
Superior Temporal Gyrus (38)	L				3.71	-50	14	-13	-50	15	-15
Inferior Frontal Gyrus (47)	L				3.69	-46	38	-17	-46	40	-18
Middle Frontal Gyrus (11)	L				3.68	-38	42	-15	-38	44	-15
Insula (13)	L				3.67	-32	15	10	-32	15	12
Middle Temporal Gyrus (21)	L				3.67	-61	-4	-12	-62	-4	-14
Superior Temporal Gyrus (22)	L				3.66	-59	2	3	-60	2	3
Inferior Frontal Gyrus (47)	L				3.6	-51	26	-11	-52	27	-12
Superior Temporal Gyrus (22)	L				3.58	-56	6	-3	-57	6	-3
Middle Temporal Gyrus (21)	L				3.56	-59	-12	-8	-60	-12	-10
Inferior Frontal Gyrus *	L				3.41	-48	16	1	-48	16	2
Middle Temporal Gyrus (21)	L				3.33	-62	-15	-6	-63	-15	-8
Insula (13)	L				3.31	-42	12	1	-42	12	2
Superior Temporal Gyrus (22)	L				3.27	-53	8	-5	-54	9	-6
Superior Temporal Gyrus *	L				3.26	-61	-6	0	-62	-6	0
Middle Frontal Gyrus (11)	R	0.006	0	400	3.85	44	44	-7	44	46	-6
Inferior Frontal Gyrus (10)	R				3.83	40	45	-2	40	46	0
Middle Frontal Gyrus (11)	R				3.65	44	44	-15	44	46	-15
Middle Frontal Gyrus (11)	R				3.55	46	42	-14	46	44	-14
Inferior Frontal Gyrus *	R				3.51	36	44	1	36	45	3
Middle Frontal Gyrus (10)	R				3.4	38	52	-1	38	54	2
Middle Frontal Gyrus (11)	R				3.36	38	50	-15	38	52	-15
Superior Frontal Gyrus (10)	R				3.29	38	61	-5	38	63	-2
Inferior Frontal Gyrus (47)	R				2.76	51	43	-10	52	45	-9
Inferior Frontal Gyrus (47)	R				2.67	53	38	-9	54	40	-9
Uncus (38)	L	0	0	722	3.83	-20	8	-36	-20	10	-42
Middle Temporal Gyrus (20)	L				3.83	-34	0	-39	-34	2	-46
Superior Temporal Gyrus (38)	L				3.75	-24	10	-39	-24	12	-46
Superior Temporal Gyrus (38)	L				3.6	-33	8	-34	-33	10	-40
Middle Temporal Gyrus (38)	L				3.57	-40	4	-37	-40	6	-44
Uncus (20)	L				3.49	-22	-10	-40	-22	-8	-48
Uncus (28)	L				3.46	-24	-10	-30	-24	-9	-36
Inferior Temporal Gyrus (20)	L				3.44	-42	-2	-37	-42	0	-44
Uncus (38)	L				3.42	-28	2	-38	-28	4	-45
Inferior Temporal Gyrus (20)	L				3.4	-36	-6	-38	-36	-4	-45
Uncus (20)	L				3.19	-34	-11	-33	-34	-10	-40
Parahippocampal Gyrus (35)	L				3.18	-27	-15	-26	-27	-14	-32
Inferior Temporal Gyrus (20)	L				3.13	-44	-9	-33	-44	-8	-40
Inferior Temporal Gyrus (20)	L				2.86	-42	-11	-28	-42	-10	-34
Uncus (28)	L				2.75	-16	4	-32	-16	6	-38
Rectal Gyrus (11)	L	0	0	939	3.79	0	28	-20	0	30	-22
Orbital Gyrus (47)	L				3.61	-14	26	-24	-14	28	-27
Rectal Gyrus (11)	L				3.58	-2	32	-24	-2	34	-27
Orbital Gyrus (11)	L				3.53	-6	30	-28	-6	32	-32
Orbital Gyrus (11)	R				3.52	6	44	-21	6	46	-22
Rectal Gyrus (11)	L				3.34	0	38	-25	0	40	-27
Rectal Gyrus (11)	L				2.86	0	48	-28	0	51	-30
Middle Frontal Gyrus (11)	R				2.85	15	42	-20	15	44	-21
Rectal Gyrus (11)	R				2.85	6	26	-28	6	28	-32

Table 4.15 Cont.

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Cuneus (18)	L	0.003	0	437	3.77	0	-80	29	0	-84	27
Cuneus (18)	L				3.5	-2	-80	24	-2	-84	22
Cuneus (18)	L				3.47	-2	-78	20	-2	-81	18
Cuneus (18)	L				3.4	-3	-76	24	-3	-80	22
Cuneus (19)	R				3.37	6	-77	31	6	-81	30
Precuneus (7)	R				3.36	3	-77	40	3	-81	39
Precuneus (31)	R				3.33	4	-73	24	4	-76	22
Precuneus (19)	R				3.14	8	-82	37	8	-86	36
Cuneus (18)	R				3.01	4	-77	24	4	-81	22
Posterior Cingulate (30)	R	0.005	0	413	3.69	21	-54	17	21	-56	16
Posterior Cingulate (23)	R				3.37	4	-57	19	4	-60	18
Posterior Cingulate (30)	R				3.29	8	-66	11	8	-68	8
Precuneus (31)	R				3.19	8	-63	20	8	-66	18
Posterior Cingulate (30)	R				3.16	9	-56	6	9	-58	4
Posterior Cingulate (31)	R				3.14	4	-60	17	4	-63	15
Cingulate Gyrus (31)	R				3.08	9	-53	30	9	-56	30
Posterior Cingulate (31)	R				2.91	10	-51	21	10	-54	20
Cerebellar Tonsil	L	0	0	829	3.49	-4	-51	-45	-4	-50	-56
Cerebellar Tonsil	L				3.47	0	-47	-41	0	-46	-51
					3.4	4	-49	-50	4	-48	-62
Inferior Semi-Lunar Lobule (Cerebellum)	L				3.25	-14	-60	-42	-14	-60	-54
Cerebellar Tonsil	L				3.24	-12	-45	-41	-12	-44	-51
	No grey matter				3.18	-4	-41	-40	-4	-40	-50
	No grey matter				3	-2	-40	-45	-2	-39	-56
Cerebellar Tonsil	L				2.99	-20	-58	-46	-20	-57	-58
	No grey matter				2.86	2	-37	-39	2	-36	-48
	No grey matter				2.8	-4	-46	-50	-4	-45	-62
Cerebellar Tonsil	L				2.72	-12	-48	-35	-12	-48	-45
Transverse Temporal Gyrus (42)	L	0.013	0	360	3.41	-61	-15	12	-62	-16	12
Postcentral Gyrus (43)	L				3.39	-57	-14	20	-58	-15	21
Insula (13)	L				3.33	-44	-18	20	-44	-20	21
Precentral Gyrus (3)	L				3.21	-56	-13	26	-57	-15	28
Insula (13)	L				3.13	-38	-14	17	-38	-15	18
Insula (13)	L				3.09	-45	-13	10	-45	-14	10
Postcentral Gyrus (43)	L				3.08	-50	-14	17	-51	-15	18
Superior Temporal Gyrus (42)	L				3.01	-67	-19	9	-68	-20	9

Ib. Amnestic Multi-Domain

A whole brain regression analysis revealed no significant correlation between grey matter volumes and discrepancy scores at the FWE rate within mild MCI patients with a multi-domain amnestic profile. However, two clusters reported here, retained significance when controlling for the FDR with a lenient p threshold of .05. These clusters encompass areas of bilateral temporal lobe, particularly left medial temporal structures such as the hippocampus, uncus and areas of parahippocampal gyrus as well as right sided middle and superior temporal gyrus. Although not considered significant, these results have been

included here for the purposes of later discussion (***Fig. 4.11***). A full list of coordinates can be found in Appendix G (**Table G1**).

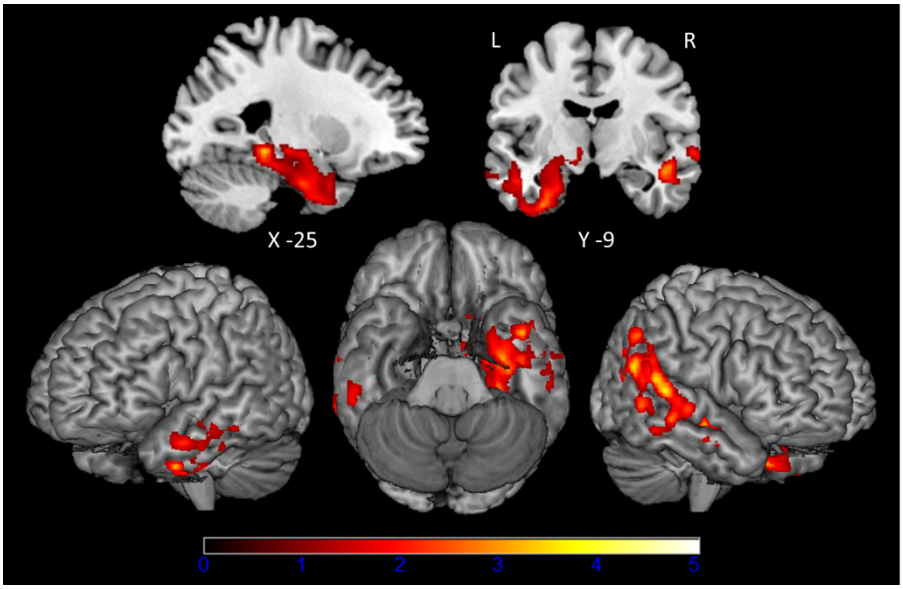


Figure 4.11. *Areas of non-significant but trending negative correlation between grey matter volumes and verbal fluency discrepancy scores in the amnestic multi-domain mild MCI group (n = 30) in temporal and parietal cortex. Coordinates refer to MNI space.*

Ic. Amnestic Single and Multi-Domain

Considering the mild amnestic group as a whole, including both multi-domain and single domain patients, a significant negative correlation was found between grey matter volume and verbal fluency discrepancy within a distinct area of right sided temporoparietal cortex including areas of supramarginal and middle temporal gyri (BA 40 and 22) (**Table 4.16**, ***Fig. 4.12***).

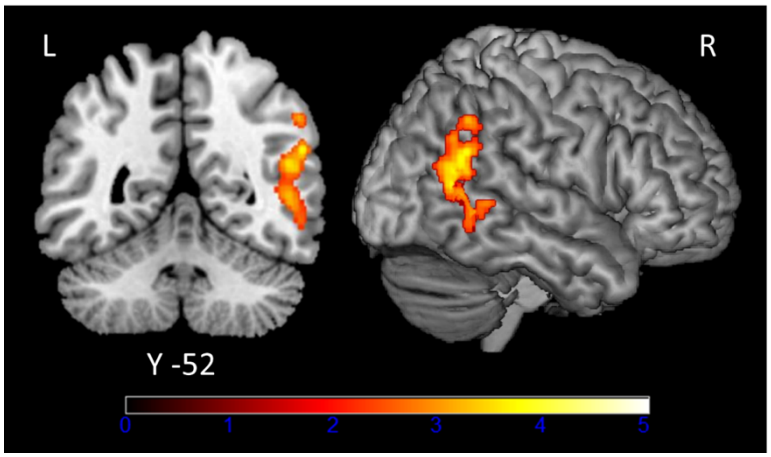


Figure 4.12. *Areas of significant negative correlation between grey matter volumes and verbal fluency discrepancy scores in the single and multi-domain amnestic mild MCI group (n = 39) in right sided temporal and parietal cortex. Coordinates refer to MNI space.*

Table 4.16

Areas of significant negative correlation between grey matter volume and verbal fluency discrepancy scores in the mild aMCI (single and multi-domain) (n = 39). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc, Uncorrected; BA, Brodmann's Area; FWE, Family Wise Error. Thresholded p = .005.

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Middle Temporal Gyrus (39)	R	0.035	0.001	1285	3.78	48	-56	11	48	-58	9
Supramarginal Gyrus (40)	R				3.63	55	-49	26	56	-52	26
Superior Temporal Gyrus (22)	R				3.6	50	-54	19	50	-57	18
Superior Temporal Gyrus (39)	R				3.6	51	-53	23	52	-56	22
Middle Temporal Gyrus (22)	R				3.45	50	-49	1	50	-50	-2
Inferior Parietal Lobule (40)	R				3.26	55	-48	38	56	-51	39
Supramarginal Gyrus (40)	R				3.11	50	-55	32	50	-58	32
Middle Temporal Gyrus (22)	R				3.02	65	-42	5	66	-44	3

II. Moderate MCI

As in the mild group, no significant correlations were found between grey matter volume and verbal fluency discrepancy when considering only non-amnestic patients within the moderate MCI group. Similarly, a regression model including only moderate aMCI-md patients also did not reveal any correlations significant at the FWE rate. The inclusion of the two aMCI-sd patients in this group however, revealed a trend of correlation within the left temporal lobe.

A regression analysis assessing the relationship between discrepancy scores and grey matter volume within all amnestic type moderate MCI patients, including both multi and single domain, revealed no significant correlations at the FWE when adhering to a thresholded p of .005. However, a more lenient p threshold of .05 revealed a significant negative correlation within widespread areas of the left temporal lobe including a number of anterior structures such as the temporal pole (BA 38) and perirhinal cortex (BA 36) as well as extending into more posterior regions including fusiform (BA 37) and posterior parahippocampal gyrus (BA 19) (See ***Fig. 4.13***). Again, these results will not be considered significant in the current experiment but have been included for the purposes of discussion. A full list of coordinates is available in Appendix G (**Table G2**).

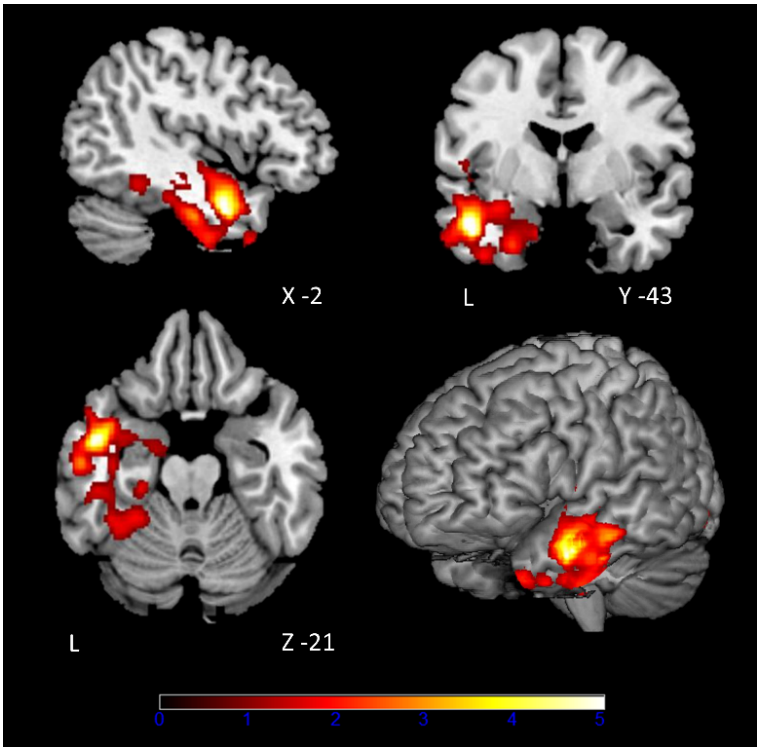


Figure 4.13. *Areas of non-significant but trending negative correlation between grey matter volume and verbal fluency discrepancy scores among moderate aMCI, including single and multi-domain patients (n = 41), within areas of the left sided temporal lobe. Coordinates refer to MNI space.*

III. Post-Hoc Analyses on Controls

In response to the findings among the mild aMCI-sd group, some further *post-hoc* analyses were run using data from a group of matched controls.

A whole-brain multiple regression analysis revealed no significant regions of correlation between grey matter and verbal fluency discrepancy among the control group. A trend in the frontal lobes was found at a threshold of .05, revealing a pattern of correlation within largely right sided orbitofrontal regions along with areas of superior frontal gyrus. These results can be seen in ***Fig. 4.14*** and a table of coordinates will be included in Appendix G (**Table G3**). Given the lenient threshold, once again these are not considered significant in this investigation.

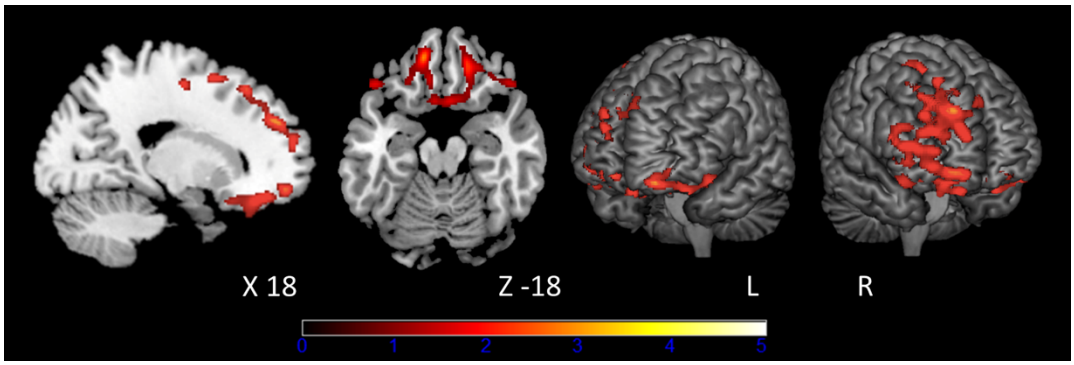


Figure 4.14. *Areas of trending negative correlation (p threshold .05) between grey matter volume and discrepancy scores in the control group (n = 82) within areas of the orbitofrontal lobes and superior frontal gyrus.*

4.2.4. Discussion

The aim of the present experiment was to interrogate the influence of differing cognitive profiles in MCI on the observable neural correlates of semantic memory performance. Experiment one demonstrated, along with the findings of previous studies (see *Chapter 2* for a systematic review), that throughout the course of disease progression in AD, differing patterns of cortical involvement emerge in relation to performance on tests of semantic memory. In particular, the findings of the first experiment showed that in MCI patients at a more severe stage of disease, correlations between semantic memory and grey matter volume were much weaker than those seen in patients in the mildest stages, failing to reach the significance level defined by this study, despite demonstrating a trend within structures of the temporal lobes. Given the heterogeneous nature of MCI, particularly in terms of progression to dementia (Petersen, 2004; Busse *et al*., 2006), it was surmised that the lack of significant results among moderate MCI patients may be indicative of a dilution in variance mediated by substantial heterogeneity in the development of both cognitive and physiological changes associated with this stage of disease (Bell-McGinty *et al*., 2005; Caffarra *et al*., 2008; Zhang *et al*., 2012; Li *et al*., 2014; Li & Zhang, 2015; Edmonds *et al*., 2016). This conclusion was supported by the fact that MCI patients within the moderate group were more likely than those in the mild group to present with a multi-domain cognitive profile. The rationale behind the present experiment, therefore, was to determine the neural correlates of semantic memory function, using verbal fluency discrepancy scores, at both mild and moderate stages of MCI, taking into account their cognitive subtype.

4.2.4.1. Neuropsychological Findings

In accordance with their diagnoses, MCI patients with a multi-domain profile tended to perform significantly worse on a range of cognitive tests when compared with patients with a single-domain profile. In particular, aMCI-md patients performed significantly worse than aMCI-sd on a number of tests measuring visuoconstructive ability, abstract reasoning, language comprehension and executive functioning. Similarly, patients in the md-MCI-na group tended to perform significantly worse than aMCI-sd in these functions, as well as having a lower attentional capacity, as measured by the Digit Span test. Further to these direct comparisons, comparisons with the healthy control group revealed no significant differences between patients with sd-MCI-na and healthy individuals in cognitive test performance and only minimal differences between controls and the aMCI-sd group on limited tests of memory. Specifically, the aMCI-sd group performed significantly worse than controls on two measures of semantic memory function: the category fluency test and the verbal fluency discrepancy scores, and one measure of delayed verbal episodic recall from the Prose Memory test. In contrast, both multi-domain groups demonstrated significantly impaired performance, compared with controls, on a number of cognitive tests spanning a wide range of cognitive domains. These results are in line with the findings of previous studies suggesting that multi-domain profiles of MCI are likely representative of a more moderate phase of disease (Alexopoulos *et al*., 2006; Tabert *et al*., 2006; Whitwell *et al*., 2007b; Nordlund *et al*., 2010; Zhang *et al*., 2012; Li *et al*., 2014; Raamana *et al*., 2014; Li & Zhang, 2015). Moreover, of the limited deficits found among aMCI-sd patients, two of the tests showing significant impairment were indicative of some dysfunction in semantic memory. As patients with a single-domain profile may be considered representative of the earliest clinical manifestation of disease (Edmonds *et al*., 2016), the finding that semantic memory changes were the most prominent differences found between this group and controls is indicative of earlier hypotheses that declines in semantic memory function may be one of the earliest neuropsychological changes observable in the initial stages of AD (Amieva *et al*., 2008; Didic *et al*., 2011). Patients with aMCI-md however, not only performed significantly worse than controls on all memory measures but also on a number of tests assessing a variety of cognitive functions. This is suggestive therefore, as in Didic's model (Didic *et al*., 2011), that as disease progresses from the very earliest stages, the spread of pathological material from anterior to posterior regions of MTLs and the wider temporal lobes, leads to worsening

in semantic and verbal memory function and further gives rise to declines in episodic memory, as well as a broadening range of deficits in wider cognitive domains.

Within-group analyses assessing differences on category and letter fluency performance found that no significant differences were apparent between the raw test scores in any of the patient groups. Healthy controls however, tended to perform significantly better on measures of category fluency when compared with letter fluency. Again, no significant differences were seen between the relative levels of decline (as determined by *z* scores derived from the data of a matched control group) on each of the fluency measures in either of the non-amnestic patient groups or in the healthy control group. Despite there being no difference in raw scores however, significant differences in the relative levels of decline on each test were found among both aMCI-sd and aMCI-md patients with both performing significantly worse relative to controls on measures of category fluency when compared with measures of letter fluency. These findings are in line therefore, with the findings of previous studies suggesting that, even in the earlier stages of AD, patients tend to show greater declines on measures of category fluency than letter fluency, most likely due to the degradation of structures sustaining semantic memory stores within the ATLs (Henry, Crawford & Phillips, 2004; Henry & Crawford, 2004a, 2004b; Murphy, Rich and Troyer, 2006; Clark *et al*., 2009; Chasles *et al*., 2020; Vonk *et al*., 2020). The selectivity of this finding within amnestic patients is further supported by the results of previous studies (Vonk *et al*., 2020) and is indicative that such discrepancy scores are likely a feature which is specifically symptomatic of early AD related neurodegeneration. The lack of findings within non-amnestic patients may, therefore, be reflective of the decreased likelihood of this cohort to represent a true case of prodromal AD (Busse *et al*., 2006).

4.2.4.2. Mild MCI Imaging

For imaging analysis, the MCI patients were split not only by subtype but further stratified by disease severity. The mild MCI group was, therefore, again split into the four clinical subtypes. No significant correlations were found between verbal fluency discrepancy scores and grey matter volumes in either non-amnestic group. As an entity, non-amnestic MCI is inherently heterogenous. Having no uniting domain of impairment, such as the memory deficits that underlie aMCI, MCI-na may describe a range of cognitive profiles that differ significantly in terms of the most prominent impairments. Furthermore, given that the earliest stages of tau deposition and subsequent structural change in AD occur within medial

temporal regions responsible for memory function (Braak and Braak, 1991; Thompson *et al*., 2003; Apostolova *et al*., 2010), aMCI is usually considered a prodromal stage of AD (Morris *et al*., 2001; Petersen, 2004; Dubois and Albert, 2004), with patients with an amnestic profile being more likely to convert to later AD dementia than those with MCI-na (Busse *et al*., 2006) who may represent the prodromal stages of a number of differing non-AD dementia aetiologies (Petersen *et al*., 2001; Petersen, 2004; Petersen & Negash, 2008; Ferman *et al*., 2013). For this reason, it is plausible that the lack of findings within the non-amnestic groups is reflective of the heterogeneity within this patient cohort in terms of both the cognitive deficits contributing to differences in verbal fluency performance as well as the potential underlying variation in neurodegenerative aetiology.

I. Amnestic MCI

Only nine of the mild MCI patients presented with a profile of aMCI-sd, with the remaining 30 aMCI patients presenting with impairments in multiple domains. Correlations between grey matter volume and discrepancy scores within the aMCI-sd group revealed widespread involvement from a multitude of regions bilaterally across the cerebral cortex and some small areas of cerebellum. Both bilateral frontal and temporal lobes demonstrated the greatest involvement in a variety of areas. Much of the involvement within the frontal lobes was centred around orbitofrontal regions including BA 10, 11 and 47, while the correlations seen in the temporal lobes, despite showing a high level of involvement within anterior regions such as the temporal poles (BA 38) and uncus (BA 28, 36), also showed significant involvement from all areas of bilateral temporal lobes including posterior regions such as the fusiform gyrus (BA 37), stretching into both occipital and parietal cortices (BA 19 and 39) as well as many areas of the inferior, middle and superior temporal gyri (BA 20, 21 and 22).

As in the previous experiment, significant involvement of temporal regions among aMCI-sd patients likely reflects the role of such regions, particularly anterior structures such as the temporal pole, in semantic memory processing (Mummery *et al*., 2000; Patterson, Nestor & Rogers, 2007; Pobric, Jefferies & Lambon Ralph, 2010; Visser *et al*., 2010). Further involvement of more posterior temporal lobe structures, as well as parietal regions surrounding the temporoparietal junction, is also indicative of the involvement of high level amodal convergence zones within the semantic memory system that have been found to be associated with these areas in studies of healthy individuals (Binder *et al*., 2009; Binder & Desai, 2011). Significant involvement from a range of frontal regions among this group is

further indicative of the recruitment of multiple areas of the semantic system, including areas sustaining controlled retrieval processes in regions such as the inferior prefrontal cortex (Wagner *et al*., 2001; Devlin *et al*., 2003; Henry & Crawford, 2004a, 2004b; Costafreda *et al*., 2006; Binder & Desai, 2011). As aMCI-sd patients were found to be the least impaired of the MCI subtypes in a number of domains, despite their impairments in memory function, it is highly likely that the results shown here are indicative of widespread recruitment of the semantic memory system helping to sustain semantic processing in response to initial changes within medial temporal structures. Furthermore, given the limited number of participants in this mild MCI group, the finding of widespread results throughout the semantic system may be due to limited disease-related variance in grey matter volume leading to a pattern of variation more usually associated with healthy individuals.

Post-hoc analyses in the control group, although not significant, demonstrated a similar pattern of involvement within structures of the orbitofrontal cortex. Although no significant differences were found between category and letter fluency *z* scores in the control group, subsequent analysis revealed that controls tended to score significantly better on tests of category fluency compared with tests of letter fluency. This is in line with previous research demonstrating that in healthy individuals letter fluency is often associated with greater task difficulty, due to the lack of a semantic component, where category fluency is generally more easily completed given the facilitation of retrieval via semantic associations (Murphy, Rich and Troyer, 2006; Vaughan *et al*., 2016; Chasles *et al*., 2020). Discrepancy scores in the control group, therefore, were not only very low compared with the patient groups, but also were more likely to reflect differences in controlled retrieval abilities rather than variance in semantic memory function. This was further reflected by the finding that, on average, letter fluency *z* scores in this group were much further from the mean than those of category fluency. As healthy individuals do not have a significant impairment in either fluency test, the lack of significant findings is likely due to a lack of variance in verbal fluency discrepancy scores among this group. The trend seen within frontal regions among this participant group, however, is likely to reflect the involvement of frontally mediated controlled retrieval processes, on verbal fluency performance among healthy controls (Binder *et al*., 2009; Binder & Desai, 2011).

The overlap seen between the areas of correlation highlighted among mild aMCI-sd patients and the healthy controls supports the assumption that patients with such a mild form of disease likely present with a pattern of cortical involvement, in relation to verbal fluency performance, that is similar to that seen in normal individuals. However, verbal fluency

discrepancy in this group, unlike the controls, was reflective of significantly greater levels of decline in semantic fluency than phonemic fluency. The extensive involvement from other brain regions among these patients, including particularly high levels of correlation within the temporal lobes, may therefore support the conclusion that, in contrast with the frontally mediated verbal fluency discrepancy seen in controls, even in this very mild stage of disease, AD related alterations to areas sustaining the brain's semantic memory store (Henry, Crawford & Philips, 2004; Henry & Crawford, 2004a, 2004b; Binder *et al*., 2009; Binder & Desai, 2011) likely contribute to a semantic memory deficit, causing significant discrepancies in verbal fluency performance. Despite some variance in discrepancy scores being attributable to regions involved in executive retrieval processes, the involvement from regions more heavily related to semantic memory storage and processing, such as the temporal pole and temporoparietal junction (Patterson, Nestor & Rogers, 2007; Binder *et al*., 2009; Binder & Desai, 2011), suggests that in mild cases of aMCI-sd, verbal fluency discrepancy is associated not only with executive functioning differences, as in healthy controls, but is further heavily influenced by semantic dysfunction, a finding that may not be applicable to healthy ageing. As semantic memory is known to show declines from even the preclinical stages of disease (Amieva *et al*., 2008), these findings suggest that verbal fluency discrepancy scores may be particularly valuable in differentiating insidious pathological decline from healthy age-related cognitive change by highlighting alterations in the functioning of the semantic memory system, possibly mediated by early dysfunction within the aMTLs (Braak & Braak, 1991, Didic *et al*., 2011).

In contrast with single-domain participants, no significant results were found among mild MCI patients with a profile of aMCI-md. The areas that showed a trending correlation at the FDR, however, were highly similar to those found in the moderate MCI group in the first experiment, with overlapping areas of correlation within right-sided middle temporal gyrus (BA 21) and left-sided inferior temporal and parahippocampal gyrus (BA 20 and 36). The lack of significant results in this group, as well as the areas of overlapping correlation between these findings and the areas highlighted among moderate MCI patients, supports the explanation outlined in the former experiment that increased heterogeneity among the moderate MCI group, in the form of greater numbers of multi-domain patients, likely contributed to a dilution of the variance in verbal fluency discrepancy that could be attributable to a purely semantic deficit and therefore led to a weakened correlation with grey matter volume. A multi-domain presentation does not, alone, indicate a more severe stage of disease. However, impairments in multiple areas of cognition have been associated with

greater risks of subsequent conversion to dementia than single domain impairments (Alexopoulos *et al*., 2006; Tabert *et al*., 2006; Nordlund *et al*., 2010), and multi-domain patients have been shown to present with greater and more widespread atrophy than single domain patients in a number of regions (Whitwell *et al*., 2007b; Zhang *et al*., 2012; Li *et al*., 2014). The limited findings here and among moderate MCI patients, may suggest therefore, that as disease advances from the mildest single-domain stages through to a more moderate phase of cortical degradation, a level of heterogeneity occurs in the progression of both pathological deposition and cognitive presentation that subsequently weakens the observable relationship between semantic memory performance and grey matter integrity (Edmonds *et al*., 2016). Despite this, observable trends within areas of the anterior and medial temporal lobes within both groups, as well as areas of inferior posterior parietal cortex in mild aMCI-md patients, demonstrates the presence of a relationship between verbal fluency discrepancy scores and widespread areas involved in both semantic memory and AD related cortical degradation (Braak & Braak, 1991; Binder *et al*., 2009; Binder & Desai, 2011). Furthermore, greater involvement of hippocampal and anterior parahippocampal regions in the mild aMCI-md group compared with the moderate MCI group, who presented with involvement from more lateral temporal structures, is in line with the conclusion of the previous study, as well as many earlier investigations (See *Chapter 2* for a systematic review), that found that cortical changes associated with semantic memory decline in AD demonstrate a progression of involvement that shifts from the very earliest changes in discrete regions of the aMTLs, in mildly affected patients, through to more posterior areas of the temporal lobes in later stages. In accordance with the hierarchical organisation of semantic processing within the temporal lobes (Patterson, Nestor & Rogers, 2007; Binder *et al*., 2009; Visser *et al*., 2010; Saksida & Bussey, 2010; Binder & Desai, 2011), the finding that patients identified as having a mild form of disease presented with grey matter correlations within more medial temporal structures while moderate patients did not, is in line with the hypothesis that with the spread of pathology throughout the MTLs, there is an increased reliance on posterolateral temporal structures for the facilitation of semantic memory retrieval.

Including the aMCI-sd patients in the regression model along with the aMCI-md group, revealed an area of significant correlation within temporoparietal regions including the superior and middle temporal gyri (BA 22 and 39) and areas of the supramarginal gyrus and inferior parietal lobule (BA 40). A possible explanation for this is that the degree of overlap in correlation within these areas among both groups, led to a high degree of variance in these regions driven by the much larger aMCI-md group in combination with some significant

involvement of these areas within the aMCI-sd group. Unlike medial temporal structures that were differentially involved in each group, with aMCI-sd patients showing correlations in more anterior regions than the aMCI-md group, the degree of variance within these temporoparietal regions showed a high level of convergence between both groups, therefore leading to the significant results in this area. In both groups, it is likely that involvement of these regions may reflect a greater reliance on areas sustaining the consolidation of semantic memory, outside of the MTLs (Binder & Desai, 2011), in response to dysfunction of the ATLs and hippocampal complex. Substantial differences between patterns of significant correlation between the groups, however, supports the conclusion of the systematic review outlined in *Chapter 2* that, when investigating the neural correlates of semantic memory function in AD, it is important to stratify patients according to disease severity in order to facilitate a clearer understanding of the progression of disease related changes and their relationship with subsequent semantic dysfunction.

4.2.4.3. Moderate MCI

As in the mild group, no significant correlations were found between verbal fluency discrepancy scores and grey matter volumes in the non-amnestic moderate MCI group. Similarly, no significant correlations between discrepancy scores and grey matter were found when considering the aMCI-md moderate MCI group alone. However, a trend was revealed within left sided temporal structures when including the aMCI-sd patients in the analysis. Regions of the parahippocampal (BA 36) and fusiform (BA 20, 37) as well as middle and inferior temporal gyri (BA 20, 21) that were highlighted within this group, at a lenient threshold ($p < .05$), overlapped with previous results seen among the entire moderate MCI group (see section *4.1.3.2. II.*). These results therefore support the interpretation that high levels of heterogeneity within the moderate MCI patients were likely responsible for the lack of significant findings among this group. The overlap in trending correlations within the temporal lobes suggests that the results seen within the moderate MCI group as a whole were primarily driven by patients with an amnestic profile, while the inclusion of non-amnestic patients would likely have diluted the variance related to semantic memory seen within these regions. Furthermore, the lack of significant or trending correlations found when excluding aMCI-sd patients demonstrates how greater levels of heterogeneity among individuals, implied by multiple impairments within varying cognitive domains, can serve to weaken the association between semantic memory function and grey matter volume. Unlike the aMCI-sd

patients within the mild MCI group, the inclusion of aMCI-sd patients here, whose discrepancy scores were more likely to be purely reflective of a semantic memory decline and whose status as moderate MCI suggests a greater degree of disease related degradation within temporal lobe structures, served to focus the variance within these areas, therefore leading to stronger correlations despite the high levels of heterogeneity among the rest of the group. This suggests therefore, as discussed in relation to the previous experiment (see section *4.1.4.2. II.*), that a greater number of aMCI-sd patients among the mild MCI group could explain why significant correlations within anterior temporal structures were found within this group as a whole, despite finding no significant areas of correlation within the moderately affected group.

4.2.4.4. Conclusion

Taken together, these findings suggest that even in the earliest manifestations of AD, as represented by those with a profile of aMCI-sd (Edmonds *et al*., 2016), significant changes that occur within structures of the aMTLs (Braak & Braak, 1991) likely mediate declines in semantic memory function (Didic *et al*., 2011) that may be highlighted by disproportional deficits on measures of category and letter fluency performance. In accordance with conversion rates to AD type dementia, the findings here further support the hypothesis that non-amnestic profiles of MCI tend to reflect a highly heterogeneous group, less likely to represent a true form of prodromal AD (Busse *et al*., 2006), therefore leading to both a lack of significant discrepancy between each fluency score, as well as a lack of consistent correlation between these scores and grey matter volume.

As demonstrated by the results of the first experiment in this chapter, and outlined by the systematic review in *Chapter 2*, the results shown here indicate a degree of progressive shift in the neural correlates of semantic memory function in AD from the most anterior portions of the MTLs and temporal lobes in the mildest stages, through to more posterior regions of the MTLs and wider temporoparietal cortex in more moderate stages of disease. In the present experiment, aMCI-sd patients in the mildest group presented with patterns of cortical involvement related to verbal fluency discrepancy that, while partially overlapping with areas involved in healthy participants, included significant portions of the aMTLs and ATLs. In the aMCI-md group however, a relationship was seen between multiple areas of more posterior MTLs including the hippocampus, while also spreading to posterior areas of the temporal neocortex. Further to that, aMCI patients within the moderately affected group

demonstrated a relationship between discrepancy scores and grey matter within areas that no longer included the hippocampus and instead involved large areas of parahippocampal gyrus as well as, primarily, regions of lateral temporal cortex. Given the suggestion that a multi-domain profile is indicative of a more severe stage of disease (Alexopoulos *et al*., 2006; Tabert *et al*., 2006; Nordlund *et al*., 2010; Whitwell *et al*., 2007b; Zhang *et al*., 2012; Li *et al*., 2014), the results presented here could be interpreted as demonstrating incremental shifts in the neural correlates of semantic memory from the most anterior structures of the MTLs in mildly affected aMCI-sd patients, to more posterior MTL structures in mildly affected aMCI-md patients and finally wider regions of the temporal neocortex in moderately affected aMCI patients. It is also clear that this highly focal neuropsychological measure loses its topographical specificity as pathology progresses, to include a wider range of cortical structures, as demonstrated here by the multi-domain and moderate MCI patients, as well as by the dementia group in the previous experiment. This is therefore in accordance with Didic's (2011) model and demonstrates, as the previous experiment suggests, progressively greater reliance on posterior temporal structures, involved in increasingly upstream processes within the hierarchical semantic memory system, in order to sustain semantic memory function in the presence of mounting pathological degradation of the higher-order convergence zones within the aMTLs (Binder *et al*., 2009; Binder & Desai, 2011; Patterson, Nestor & Rogers, 2007; Saksida & Bussey, 2010; Kivisaari *et al*., 2012).

Chapter 5 | A Graph Theoretical Approach to Clarifying Ageing and Disease Related Changes in Cognitive Functioning and Structural Brain Networks

While the previous chapter focussed on the efficacy of semantic memory decline, as indicated by verbal fluency discrepancies, as a potential diagnostic proxy for the earliest manifestations of Alzheimer's disease (AD) neurodegeneration, the present chapter outlines an investigation into the dynamics of the cognitive network, to explore the role of semantic memory in cognitive profiles representative of both normal ageing and neurodegenerative disease. While previous studies, including those presented in *Chapter 4*, have provided compelling evidence to support the use of semantic memory impairment as an early diagnostic marker for AD (see *Chapter 2* for an overview), evidence for how these impairments may characterise cognitive profiles associated with neurodegeneration, thereby differentiating disease processes from healthy age-related cognitive change, is relatively limited. As the focus of the present research concerns the development and refinement of novel, sensitive neuropsychological markers for the nascent stages of AD, the following chapter explores the utility of innovative graph theoretical techniques in the identification of subtle, network-level alterations to cognition, in normal ageing and disease groups, and the structural brain changes which may underlie them. By exploring differences in cognition and brain structure from a network level perspective, across differing age groups and disease severities, including the influence of semantic cognition on wider cognitive functioning, the studies presented in the current chapter provide evidence and theoretical rationale as to why semantic processing, in particular, may provide a good neuropsychological marker of AD related cognitive impairment which is distinct and different from age-related changes.

As the performance of individual cognitive tasks may be influenced by diverse neuropsychological processes, task specific impairments that can occur as a result of both the normal ageing process (Harada *et al*, 2013), as well as within a range of neurodegenerative diseases, may relate to a variety of underlying functional deficits. Semantic verbal fluency declines, for example, can occur as a result of either disruption to the semantic store or an impairment of executively mediated controlled retrieval processes (Henry & Crawford, 2004a, 2004b), as explored in the previous chapter. A challenge of cognitive neuroscience,

therefore, is the identification of specific processes that may underlie similarly presenting cognitive change within a diverse population of individuals, representing both the healthy elderly and distinct age-related neurodegenerative disease aetiologies. Previous research has demonstrated the potential of cognitive profiles, characterised by methods of graph theory, to examine cognitive change in patients with epilepsy, as well as describe symptom interaction within psychiatric cohorts (Kellerman *et al.,* 2015; Garcia-Ramos *et al.,* 2015; Kellerman *et al.,* 2016; Garcia-Ramos *et al.,* 2016; Beard *et al*., 2016). To date however, no studies have yet utilised graph theoretical techniques in the quantification of cognitive profiles relating to neurodegenerative disease. The present investigation, therefore, aimed to address network-level differences that may underlie aspects of age and AD related cognitive dysfunction through the assessment of topological relationships between differing cognitive domains.

Network approaches in neuroimaging have previously demonstrated the existence of significant differences in structural networks measured by cortical volumes, thickness and white matter integrity, between healthy controls and AD patients in a range of graph theory parameters (He, Chen & Evans, 2008; Yao *et al*., 2010; Lo *et al*., 2010; Bai *et al*., 2012; Li *et al*., 2012; Tijms *et al*., 2013a, 2013b; Phillips *et al*., 2015; Fischer *et al*., 2015). Considerable ambiguity exists within the literature however, as to the exact nature and direction of such differences, likely owing to substantial variations in network formation methods between studies (Tijms *et al*., 2013a; Phillips *et al*., 2015). Further to the evaluation of neuropsychological profiles, the same network techniques were, therefore, applied to structural magnetic resonance imaging (MRI) data within a similar cohort, to address the hypothesis that changes in structural brain networks may underlie similar alterations in cognitive networks.

5.1. Experiment 3 – Differences in cognitive networks across the stages of ageing and Alzheimer's Disease assessed using methods of graph theory.

5.1.1. Introduction

The integrity of our cognitive functions is heavily influenced by a number of factors including, but not limited to, our educational background (Katzman, 1993), age (Glisky, 2007; Harada *et al.,* 2013), and the structure and function of the physiological systems that underlie them. In the face of rapidly rising life expectancies and the subsequent growth of the ageing population, cognitive research has particularly focussed on the diverse effects this

universal process can have on cognition. An increase in life expectancies has furthermore brought about an increase in the number of people currently living with age-related neurodegenerative dementias (Prince *et al*., 2013). Although more heavily exacerbated in disease, declines in cognitive function are inherent to the healthy ageing process (Salthouse *et al.,* 2003). Trajectories of decline in this population can be highly heterogeneous (Hayden *et al.,* 2011) and a high proportion of rapid decline cannot be attributed to underlying neurodegenerative conditions (Boyle *et al.,* 2013). Of particular importance, therefore, is the distinction of normal age-related cognitive change from impairments suggestive of incipient pathological degeneration.

A well-established characteristic of age-related cognitive decline is the tendency for impairment to occur in skills reflecting fluid cognition that determines one's general ability to react and respond to new situations (Cattell, 1971; Harada *et al.,* 2013). Impairments in executive functioning, attention, visuospatial skills, certain types of memory function and a general slowing of processing speed can all occur, to a greater or lesser extent, as a result of normal ageing (Harada *et al.,* 2013). Crystallised abilities however, such as vocabulary, general knowledge and semantic memory, have been shown to remain relatively stable throughout the lifespan, showing markedly low levels of decline in old-age, compared with functions such as episodic memory (Nyberg *et al.,* 1996; Rönnlund *et al.,* 2005), with some tests even being found to show gradual improvement rates between the decades of life until around the age of 60 (Nilsson *et al.,* 2003; Rönnlund *et al.,* 2005; Salthouse, 2009; Verhaeghen, 2003).

Of equal importance to the quantification of cognitive profiles in healthy ageing, is the identification of cognitive profiles suggestive of some underlying neurodegenerative condition. Despite recent advances in biomarker identification (Olsson *et al.,* 2016; Jack *et al.,* 2018), clinical diagnosis of many neurodegenerative diseases continues to rely on the detection of distinct cognitive or behavioural changes (National Institute for Health and Care Excellence, 2018). As ageing itself is a major risk-factor associated with the development of dementia due to a number of aetiologies, it is imperative that clear distinctions may be drawn between what can be determined age-related and pathology-related cognitive decline. Currently, diagnostic criteria routinely applied in clinical settings rely heavily on the presence of domain specific impairments in cognitive or, more generally, psychological function to characterise a given disease. Dementia due to AD, for example, requires a measurable decline in episodic memory function (McKhann *et al.,* 2011), while the behavioural variant of frontotemporal dementia, due to frontotemporal lobar degeneration, may be recognised

through high levels of apathy or disinhibition (Rascovsky *et al.,* 2011). Due to the heterogenous nature of neurodegenerative conditions, particularly in the prodromal stages of disease (Petersen, 2004; Ismail *et al.,* 2016), evaluations of individual cognitive functions in this manner tend to be limited in their ability to differentiate accurately between aetiologies and predict future progression to dementia (Loewenstein *et al.,* 2006; Fischer *et al.,* 2007).

Although the traditional reductionist approach towards the study of cognitive functioning is clinically helpful and provides a valuable theoretical avenue for the formulation of inter-disciplinary research hypotheses (Barendregt & van Rappard, 2004), a more global, non-reductionist view is of help to characterise cognitive profiles in psychopathology, in a way that is more attentive to the intertwined nature of symptoms (Borsboom *et al*., 2019). This would be particularly valuable in clinical neuropsychological practice, where diagnoses are formulated as a function of profiles of test scores that are the result of inter-connected, rather than isolated functions.

In line with a non-reductionist view of cognitive profiles along the ageing trajectory, one concept of senescent change that has recently received increasing interest is that of "neural dedifferentiation". Rather than referring to individual declines in distinct domains, neural dedifferentiation refers to the robust finding that the neural underpinnings of cognitive functioning become less specific and selective with increasing stages of ageing (Koen & Rugg, 2019; Koen, Hauck & Rugg, 2019; Koen, Srokova & Rugg, 2020). In their computational model of the phenomenon, Li and colleagues hypothesised that dedifferentiation, mediated by disruptions to neuromodulatory systems, may result in compromises to the precise and efficient allocation of neural resources and processing, particularly in response to novel tasks requiring fluid cognitive abilities (Li & Lindenberger, 1999; Li *et al.,* 2001; Li, Lindenberger & Sikström, 2002; Li & Reikman, 2014). This, therefore, led authors to suggest that such dedifferentiation in the neural response to stimuli may contribute to the particular declines in cognition associated with age (Li *et al.,* 2001; Li & Sikström, 2002), a hypothesis that has since been confirmed in a small number of empirical investigations (Park *et al.,* 2010; Koen, Srokova & Rugg, 2020). Using multivariate pattern analysis with fMRI, to characterise neural activations, Park *et al*., (2010) measured the distinctiveness of neural responses to the presentation of two differing categories of visual stimuli (faces vs houses), during a same/different visual stimulation task, among two groups of young and older healthy adults. Compared with younger adults, older adults demonstrated significantly lower levels of neural specificity, as defined by how accurate the trained classifier was in predicting the stimulus category based on neural activation patterns.

Variations in neural specificity were subsequently found to be significantly associated with performance on a number of cognitive tasks assessing fluid intelligence processes, including a letter fluency task, the trail making task, the dot-matching task and the digit symbol task from the Wechsler Adult Intelligence Scale (WAIS). Such findings provide compelling evidence to support the notion that age-related dedifferentiation of the neural response may contribute to cognitive declines, particularly in fluid cognition, that are typically associated with healthy ageing (Harada *et al*., 2013). Similarly, network analyses using resting-state fMRI have demonstrated significant age-related alterations in the segregation of brain systems, with older adults presenting with greater between-network connectivity and reduced within-network connectivity that has been found to relate to performance on tests of long-term memory functioning, processing speed, fluid intelligence and motor function (Chan *et al*., 2014; Geerlings *et al*., 2014; Geerlings *et al*., 2015; King *et al*., 2018; Varangis *et al*., 2019). Whether modulation of the relationship between neural differentiation and cognition occurs directly as a result of increasing age remains unclear however, with many studies failing to assess the influence of age on their findings (Varangis *et al*., 2019; Koen, Srokova & Rugg, 2020). Current evidence even suggests that the predictive power of neural specificity for cognitive performance, measured either by network segregation or selectivity of the BOLD response, may be independent of age (Chan *et al*., 2014; Koen, Hauck & Rugg, 2019; Koen, Srokova & Rugg, 2020). It is likely that dedifferentiation in ageing is reflective of both maladaptive broadening of the neural response, as well as effective compensatory mechanisms (Carp, Gmeindl & Reuter-Lorenz, 2010). As such, this area of research requires continued exploration in regard to how age-dependant and age-independent factors may mediate the effects of neural dedifferentiation on cognitive processing (Koen & Rugg, 2019; Koen, Srokova & Rugg, 2020).

The concept of neural dedifferentiation, however, was preceded and influenced by psychometric research demonstrating evidence for age-related cognitive dedifferentiation. The so-called *differentiation-dedifferentiation hypothesis* first arose from the findings of early developmental research by Garret (1946) who found evidence for stronger correlations between intellectual domains among children, when compared with adolescents. Such findings led to the hypothesis of developmental *differentiation,* proposing that while intellect in young children may reflect some general aptitude factor, maturation into adolescence and early adulthood results in a separation of cognitive functions into more distinct domains, reflective of independent abilities. Later, this hypothesis was further extended to reflect the findings of studies evaluating the inter-relatedness of cognitive abilities across the lifespan, in

the *differentiation-dedifferentiation hypothesis*. This hypothesis states that while the transition from childhood to adulthood will result in a disconnection of our cognitive functions into a structure of independent, dissociable domains, the subsequent transition into old age will be characterised by a distinct loss of domain differentiation and an increase in inter-domain correlations, similar to those seen in childhood (Reinert, 1970; Baltes *et al*., 1980). Having been proposed to result from biological constraints associated with age-related alterations to neurotransmission, such as those outlined by Li and colleagues (Li & Lindenberger, 1999; Li *et al.,* 2001; Li, Lindenberger & Sikström, 2002; Li & Reikman, 2014), resulting in broad cognitive declines and increased performance variability, evidence in support of the cognitive dedifferentiation hypothesis of ageing has primarily been derived from the results of factor or principal component analyses utilising both cross-sectional and longitudinal designs (Baltes *et al*., 1980; Schultz, Kaye, & Hoyer, 1980; Cunningham & Birren, 1980; Schaie *et al*., 1989; Schaie et al., 1998; Baltes & Lindenberger, 1997; Nyberg *et al*., 2003; Li *et al*., 2004; Deary *et al*,. 2004; de Frias *et al*., 2007; Androver-Roig *et al*., 2012; Hülür *et al*., 2015; La Fleur, Meyer & Dodson, 2018; Tucker-Drob, Brandmaier, & Lindenberger, 2019). Such studies have assessed a broad range of cognitive and sensory domains and have frequently demonstrated age related increases in inter-domain correlations and a higher proportion of variance accounted for by limited components or factors of cognitive processing among older adults, when compared with younger adults. As such, the cognitive dedifferentiation hypothesis remains a central concept within the study of ageing and cognition, due largely to the assumption that the well-established dedifferentiation in neural function and response to cognitive tasks in older individuals is likely to result in greater correlations between subsequent task performance in tasks of differing domains. However, considerable conflicting evidence in the literature has led to debate concerning the existence of the dedifferentiation phenomenon. Many studies have, in fact, failed to demonstrate a consistent age-related pattern of dedifferentiation in cognitive function, both longitudinally and using cross-sectional data (Anstey, Hofer, & Luszcz, 2003; Zelinski & Lewis, 2003; Tucker-Drob & Salthouse, 2008; Tucker-Drob, 2009; Batterham, Christensen & Mackinnon, 2011; La Fleur, Meyer & Dodson, 2018). The inconsistency of these findings has been theorised to reflect the inconsistency within the literature regarding the differing types of cognitive abilities tested and the differing age ranges of participants included (La Fleur, Meyer & Dodson, 2018). Indeed, some cognitive functions may show greater levels of dedifferentiation than others. In particular, processing speed, a function which can have significant influence on a number of cognitive abilities, has been suggested to represent a

central factor mediating cognitive decline in old age (Hertzog, 1989; Verhaeghen & Salthouse, 1997). As such, studies have suggested that age-related alterations in processing speed may largely contribute to increased covariance between task performances, due to the shared constraints that such declines would place on a number of domains (Hertzog & Bleckley, 2001; La Fleur, Meyer & Dodson, 2018). Other studies have suggested that cognitive dedifferentiation may be non-linear in nature, occurring only at a certain point in old age rather than gradually developing throughout adulthood (de Frias et al., 2007). To this end, some researchers have suggested that dedifferentiation is altogether unrelated to ageing and instead represents a factor of abnormal cognitive impairment relating to underlying disease processes (Batterham, Christensen & Mackinnon, 2011). More recently, issues regarding the contrasting findings of cross-sectional and longitudinal studies have been discussed by Tucker-Drob, Brandmaier and Lindenberger (2019) who highlight a critical need to differentiate the concepts of *dynamic* (*i.e.,* an age-related increase in the covariance of change in differing cognitive abilities over time) vs *static dedifferentiation* (*i.e.,* higher covariance between tests themselves as a function of age). The results of their meta-analysis found that shared variation in cognitive change among differing domains did appear to increase as a result of ageing, suggesting that *dynamic dedifferentiation* may provide evidence for a general factor underlying cognitive ageing that strengthens in influence into advanced age.

Despite conflicting evidence in the literature regarding the existence of this phenomenon (de Frias *et al.,* 2007; Tucker-Drob, 2009; Fleur *et al.* 2018; Tucker-Drob, Brandmaier & Lindenberger, 2019), the concept of dedifferentiation remains a valuable alternative way to consider cognitive ageing. In line with *common factor* hypotheses of ageing, which have sought to identify some general psychological factor underlying the widespread effects of age on our cognitive abilities (Salthouse, 1991; Verhaeghen & Salthouse, 1997; Harada et al., 2013; Salthouse, 2016), the dedifferentiation hypothesis allows for a non-reductionist approach to ageing effects on the global cognitive system, considering changes to the overall structure and dynamics of cognition as a mediator of decline, rather than seeking an explanation for age effects in individual domains. As such, this hypothesis may be thought of as one example of how a system-level approach may be beneficial to elucidate subtle changes to cognition, beyond the level of individual abilities or behaviours. Alterations in the structure and function of neural networks, which have been established in a range of neurodegenerative aetiologies (Seeley *et al.,* 2009), provide a rationale for the exploration of this phenomenon, and other system-level changes, as they

may occur in disease, beyond the range of healthy ageing. The controversy that currently surrounds the concept of cognitive dedifferentiation, therefore, leaves a gap in the literature that has inspired, in the present work, a new approach to cognitive modelling through the application of methods of graph theory.

Graph theory is a mathematical tool that allows for the topological quantification of any system that could reasonably be described as a network. In this case, a network comprises a set of entities, referred to as nodes, joined by a series of connections referred to as edges (Bondy & Murty, 1976). Although adhering to distinct domains, cognitive functions themselves do not exist in isolation from one another. Rather, successful performance of most tasks relies on the interdependence of a number of cognitive functions. The characteristic separation and dynamic interplay of cognitive abilities, therefore, allows for the conceptualisation of a cognitive network in which performance on each cognitive task corresponds to a node and the interrelatedness or correlation between them, an edge (Garcia-Ramos *et al.,* 2016). Despite the abundance of research using graph theory methods to explore brain network connectivity (Sporns, 2018; Farahani, Karwowski & Lighthall, 2019), such techniques have rarely been applied to interrogate the nature of our cognitive systems. A number of studies by Hermann and colleagues probing the nature of cognition in epilepsy (Kellerman *et al.,* 2015; Garcia-Ramos *et al.,* 2015; Kellerman *et al.,* 2016; Garcia-Ramos *et al.,* 2016) have, however, exploited graph theory methods in this area to some effect, demonstrating the utility of the technique in identifying measurable differences in neuropsychological profiles between distinct groups.

5.1.1.1. Aims and Hypotheses

In the present study, methods of graph theory were applied to describe the structure of cognitive networks in different age groups and in patients with various types and severity of cognitive impairment. In this context, the concept of network connectivity is used to describe the correlational structure of the network, thereby representing statistical similarities between cognitive tests. In accordance with the cognitive dedifferentiation hypothesis (Baltes *et al*., 1980; Baltes & Lindenberger, 1997), in the present study it was expected that the cognitive performance of older healthy adults would lead to graphs considerably richer in the number of edges than those of younger groups and that the cognitive networks of young adults, older adults and patients with cognitive impairment, would present with substantial qualitative and

quantitative differences in graph properties, in relation to their underlying differences in cognitive functioning and cortical integrity.

5.1.2. Materials and Methods

5.1.2.1. Participants

The participant sample (N = 415 datasets) included in this study were identified retrospectively from a large database coordinated by the University of Sheffield's Department of Neuroscience. Healthy adults (n = 220) were approached using multiple recruitment strategies, with a proportion being carers of patients and a proportion obtained via word of mouth in the manner of opportunity sampling. All patients included in the study were recruited through a memory clinic after neurological examination. Of the 195 patients, 60 had a clinical diagnosis of dementia with "probable Alzheimer's disease", in adherence to the NINCDS-ADRDA criteria (McKhann *et al*., 2011) and 135 received a diagnosis of mild cognitive impairment (MCI), following the criteria outlined in Albert *et al*. (2011). All procedures were carried out according to the Declaration of Helsinki. This study received ethical approval from the West of Scotland Regional Ethics Committee 5, Ref No: 19/WS/0177. Written informed consent was obtained from all participants.

Participants were segregated into six groups. Healthy adults were assigned to one of three groups according to their age; a younger group aged 18-39 (n = 75), a middle-aged group aged 40-64 (n = 75) and an older group aged 65+ (n = 70). Patients were split according to clinical diagnosis into those with an amnestic MCI profile (aMCI, n = 75), those with non-amnestic MCI (MCI-na, n = 60) and those with AD dementia (n = 60) (see section *4.1.2.1. 1* for MCI group classification procedures).

Demographic data for all participant groups can be found in **Table 5.1**. There was no significant difference between the oldest group of healthy controls and any of the patient groups in terms of age and all the patient groups were matched with one another in terms of age and education. All the healthy control groups were also matched with each other in terms of education. Education levels differed significantly between patients and controls however, with all patient groups reporting significantly fewer years of education than each of the control groups. There were no significant differences across any of the six groups in terms of gender ratios.

Table 5.1

Medians (and interquartile range) of demographics for participant groups.

	Young (*n* = 75)	Middle Aged (*n* = 75)	Older (*n* = 70)	aMCI (*n* = 75)	MCI-na (*n* = 60)	Dementia (*n* = 60)
Age (years)	23.00 (10.00) [e]	53.00 (8.00) [b c]	72.00 (7.00)	75.00 (12.00)	71.00 (12.00)	74.50 (17.00)
Education (years)	15.00 (3.00)	14.50 (5.00)	14.00 (4.00)	10.00 (5.00) [d]	12.00 (6.00) [d]	11.00 (5.00) [d]
Gender (M/F)	31/44	37/38	31/39	29/46	27/33	33/27
MMSE	29.00 (2.00) [a]	30.00 (1.00)	29.00 (2.00) [a]	26.00 (3.00) [c]	27.00 (2.00) [c]	21.00 (4.00) [d]

Individual Mann-Whitney U tests were applied between all groups to assess differences between Age, Education and Mini Mental State Examination (MMSE) scores. Gender-ratio differences were calculated with a chi-square test. Significant differences ($p < .05$) are highlighted as: [a] Significantly lower than middle-aged controls, [b] Significantly lower than older controls, [c] Significantly lower than all patient groups [d] Significantly lower than all control groups, [e] Significantly lower than all other groups.

5.1.2.2. Neuropsychological Assessment

All participants completed an extensive neuropsychological test battery assessing a range of cognitive domains, including language (Token Test, Confrontation Naming Test), immediate and delayed verbal and visual memory (Rey-Osterrieth Complex Figure - Recall, Prose Memory Test, Verbal Paired Associates Learning subtest of the Wechsler Memory Scale), executive function (Letter Fluency, Digit Span, Stroop Test) attention (Digit Cancellation), visuospatial skills (Rey-Osterrieth Complex Figure - Copy) semantic processing (Category Fluency, Confrontation Naming) and abstract reasoning (Similarities subset of the WAIS, Raven's Progressive Matrices). A comprehensive list of included cognitive tests can be seen in **Table 5.2** and a list of citations corresponding with each can be found in **Table 4.5**. A detailed description of these well-known neuropsychological tests can be found in Neuropsychological Assessment, 5th Edition (Lezak *et al*., 2012). For between group comparison of test scores, the scores taken from the healthy adult groups were converted to a *z*-score based on the means and standard deviations (SDs) of the overall healthy reference sample. In the case of patients, standardisation of scores was based on sample-based norms created using the means and SDs of a group of 198 age, gender, education and nationality matched controls. This harmonisation served to standardise data variability according to each group's age range and assess variability in test scores in relation to normal functioning. The medians and interquartile ranges of the standardised cognitive test scores for each group can be found in **Table 5.2**.

Table 5.2

Median (and interquartile range) cognitive test Z-scores for each participant group with results of a Kruskal-Wallis H-test.

Neuropsychological Test	Patient Group	N	Median (IQR)	Mean Rank	Kruskal-Wallis H	df	p value
Raven's Progressive Matrices Z Scores	Young	75	0.36 (1.03)	281.03	135.628	5	<.001
	Middle Aged	75	0.36 (1.12)	286.66			
	Older	70	-0.24 (1.96) [ab]	216.69			
	aMCI	75	-0.62 (1.80) [ab]	180.89			
	MCI-na	60	-0.86 (1.59) [ab]	165.88			
	Dementia	60	-2.19 (2.55) [f]	84.27			
Letter Fluency Z Scores	Young	75	-0.15 (0.98)	240.81	80.104	5	<.001
	Middle Aged	75	0.29 (1.20)	279.09			
	Older	70	-0.04 (1.33)	235.15			
	aMCI	75	-0.59 (1.51) [b]	186.12			
	MCI-na	60	-0.92 (1.40) [abc]	164.13			
	Dementia	60	-1.28 (1.11) [abcd]	117.67			
Category Fluency Z Scores	Young	75	-0.22 (1.28)	266.61	198.682	5	<.001
	Middle Aged	75	0.16 (1.07)	307.12			
	Older	70	-0.21 (1.75)	264.36			
	aMCI	75	-1.52 (1.08) [abc]	137.93			
	MCI-na	60	-1.08 (1.45) [abc]	174.4			
	Dementia	60	-2.36 (1.10) [f]	66.27			
Digit Cancellation Z Scores	Young	75	0.53 (1.04)	290.05	139.272	5	<.001
	Middle Aged	75	0.40 (0.97)	279.47			
	Older	70	-0.16 (1.62) [a]	226.39			
	aMCI	75	-0.77 (1.76) [ab]	175.67			
	MCI-na	60	-1.09 (1.60) [abc]	152.57			
	Dementia	60	-2.06 (2.65) [abcd]	90.49			
Similarities Z Scores	Young	75	-0.53 (1.29) [b]	220.28	118.952	5	<.001
	Middle Aged	75	0.32 (1.44)	279.77			
	Older	70	0.32 (1.50)	276.88			
	aMCI	75	-0.52 (1.65) [ab]	195.93			
	MCI-na	60	-1.00 (1.64) [abc]	151.65			
	Dementia	60	-1.98 (1.90) [abcd]	94.02			
Token Test Z Scores	Young	75	0.19 (1.25)	257.77	131.499	5	<.001
	Middle Aged	75	0.73 (0.54)	286.02			
	Older	70	0.19 (1.62)	237.98			
	aMCI	75	-0.31 (2.25) [b]	201.64			
	MCI-na	60	-1.04 (2.54) [abc]	147.64			
	Dementia	60	-2.63 (3.28) [f]	81.59			
Rey-Osterrieth Complex Figure - Copy Z Scores	Young	75	0.48 (0.76)	296.23	108.129	5	<.001
	Middle Aged	75	0.10 (1.29)	242.95			
	Older	70	0.06 (1.46) [a]	224.16			
	aMCI	75	-0.51 (1.94) [ab]	184.13			
	MCI-na	60	-0.81 (2.05) [ab]	177.59			
	Dementia	60	-2.80 (4.32) [f]	95.43			
Rey-Osterrieth Complex Figure - Recall Z Scores	Young	75	0.65 (1.19)	316.13	191.69	5	<.001
	Middle Aged	75	-0.09 (1.19)	269.83			
	Older	70	-0.30 (1.23) [a]	231.45			
	aMCI	75	-1.54 (1.33) [abc]	136.79			
	MCI-na	60	-0.89 (1.21) [ab]	196.67			
	Dementia	60	-2.37 (0.73) [f]	68.53			

Table 5.2 Cont.

Neuropsychological Test	Patient Group	N	Median (IQR)	Mean Rank	Kruskal-Wallis H	df	p value
Stroop Test - Time Interference Z Scores	Young	75	0.50 (0.80)	301.58	87.65	5	<.001
	Middle Aged	75	0.10 (0.84)	251.50			
	Older	70	-0.38 (1.53) [ab]	188.64			
	aMCI	75	-0.88 (2.14) [ab]	172.43			
	MCI-na	60	-1.15 (1.98) [ab]	166.93			
	Dementia	60	-1.26 (3.92) [ab]	144.77			
Stroop Test - Error Interference Z Scores	Young	75	0.23 (0)	238.92	116.16	5	<.001
	Middle Aged	75	0.23 (0.05)	273.84			
	Older	70	0.28 (0.05)	270.27			
	aMCI	75	-0.13 (2.08) [abc]	174.59			
	MCI-na	60	0.19 (2.49) [abc]	171.90			
	Dementia	60	-4.98 (6.70) [f]	92.27			
Digit Span Forward Z Scores	Young	75	0.12 (1.00)	254.13	40.01	5	<.001
	Middle Aged	75	-0.11 (1.55)	233.52			
	Older	70	-0.11 (2.10)	213.01			
	aMCI	75	-0.20 (1.07)	202.99			
	MCI-na	60	-0.49 (1.36)	195.18			
	Dementia	60	-1.07 (1.51) [abcd]	131.68			
Digit Span Backward Z Scores	Young	75	-0.29 (2.25)	245.01	55.16	5	<.001
	Middle Aged	75	-0.29 (0.93)	237.67			
	Older	70	-0.29 (1.09)	242.48			
	aMCI	75	-0.11 (1.23)	196.00			
	MCI-na	60	-0.83 (1.23)	191.66			
	Dementia	60	-1.14 (0.72) [f]	115.78			
Prose Memory Test - Immediate Recall Z Scores	Middle Aged	75	0.02 (1.24)	242.00	151.84	4	<.001
	Older	70	-0.25 (1.36)	216.46			
	aMCI	75	-1.22 (1.55) [bce]	128.01			
	MCI-na	60	-0.50 (1.28) [b]	193.7			
	Dementia	60	-2.33 (1.48) [f]	57.43			
Prose Memory Test - Delayed Recall Z Scores	Middle Aged	75	-0.06 (1.66)	248.77	183.10	4	<.001
	Older	70	-0.28 (1.50)	237.2			
	aMCI	75	-1.84 (1.24) [bce]	117.54			
	MCI-na	60	-0.70 (1.97) [ab]	175.45			
	Dementia	60	-2.66 (3.84) [f]	56.09			
Verbal Paired Associates Learning Test Z Scores	Young	75	0.42 (1.50)	303.03	174.14	5	<.001
	Middle Aged	75	-0.04 (1.34)	272.09			
	Older	70	-0.50 (1.24) [a]	231.76			
	aMCI	75	-1.06 (1.16) [abc]	153.50			
	MCI-na	60	-0.67 (1.19) [ab]	193.52			
	Dementia	60	-2.09 (1.54) [f]	63.99			
Confrontation Naming Test Z Scores	Young	75	-0.02 (1.78)	230.97	40.11	5	<.001
	Middle Aged	75	0.64 (1.01)	252.21			
	Older	70	-0.02 (1.56)	207.92			
	aMCI	75	-0.19 (1.63)	203.51			
	MCI-na	60	-0.19 (1.63)	209.83			
	Dementia	60	-1.42 (3.41) [f]	127.90			

To allow for between-group comparisons, z-scores were recalculated for the control groups based on the mean and standard deviation of the three groups' combined test scores. [a] Significantly lower than young controls [p<.05], [b] Significantly lower than middle aged controls [p <.05], [c] Significantly lower than older controls [p<.05], [d] Significantly lower than aMCI [p<.05], [e] Significantly lower than MCI-na [p<.05], [f] Significantly lower than all other groups [p<.05].

5.1.2.3. Network Formation

For network formation, standardised test scores for each of the healthy control groups were recalculated based on the means and SDs of their own group (i.e., *z* scores for young adults were created using the mean and SD of the young adult group for each test). For patient groups, the same standardised scores were used, as in the between group neuropsychological test comparisons, based on sample-based norms taken from matched controls. Within-group correlations were run between standardised test scores of each of the 16 cognitive measures. In the youngest control group, the number of measures was reduced to 14 because data for the Prose Memory test was not part of the original testing protocol available for the younger age segment of the healthy controls. All cognitive test scores were adjusted (i.e., multiplying scores by -1, where needed) so that a higher score was indicative of better performance and age and years of education were included as control variables in all correlational analyses. Non-parametric correlation coefficients with a *p*-value less than .05 were considered significant. From the correlation matrix, a binary adjacency matrix was then created for each group in which a one was given for a significant correlation and a zero for a non-significant correlation (***Fig. 5.1***). As in previous work in this area, four negative correlation coefficients were removed at this point, 1 from each control group and 1 from the MCI-na group, in adherence with the validation of graph theory measures on positively connected networks (Kaiser, 2011; Kellermann *et al*., 2016). For each group, therefore, a cognitive network was created that was comprised of 16 nodes representing each cognitive test (14 in the case of the youngest controls) and a number of binary links, or edges, between the nodes that represented significant positive correlations. Due to the use of the absolute threshold of $p < .05$, the number of edges differed between groups. A proportional threshold was avoided in this case due to the known potential of such thresholds to include spurious, non-significant correlation coefficients as edges (van den Heuvel *et al*., 2017). As one objective of the present study was to explore the concept of cognitive dedifferentiation in ageing, the use of an absolute threshold in this case was also considered more appropriate to highlight differences in network density between groups.

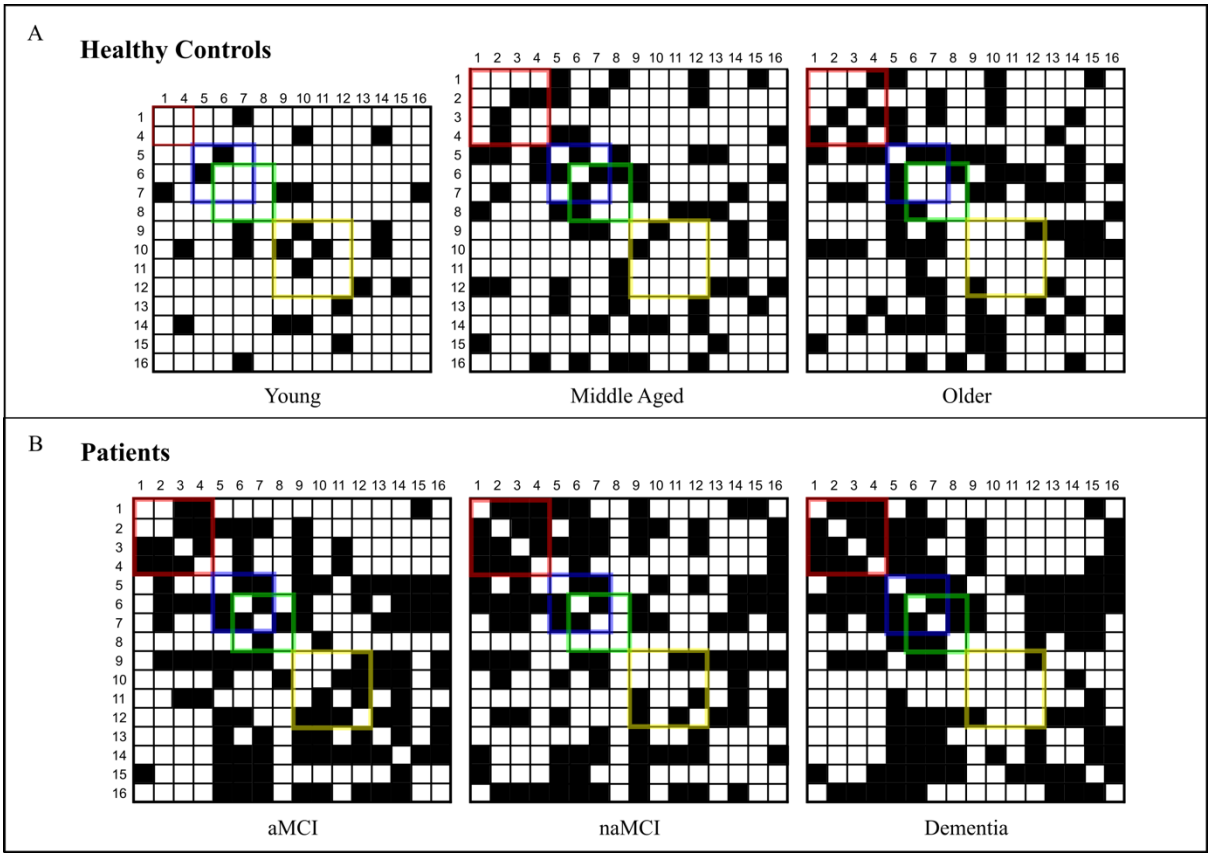


Figure 5.1. *Binary adjacency matrices for each participant group. A grid square filled in black represents a significant positive correlation (an edge) between two cognitive tests (nodes). Correlations between memory tests are enclosed by the red square, abstract reasoning by the blue square, semantic processing by the green square and executive functions by the yellow square. For ease, cognitive tests have been converted to numbers so that: 1 = Rey-Osterrieth Complex Figure - Recall, 2 = Prose Memory Test - Immediate Recall, 3 = Prose Memory Test - Delayed Recall, 4 = Verbal Paired Associated Learning Test (WMS), 5 = Raven's Progressive Matrices, 6 = Similarities (WAIS), 7 = Category Fluency Test, 8 = Confrontation Naming Test, 9 = Letter Fluency Test, 10 = Stroop Test - Time Interference, 11 = Stroop Test – Error Interference, 12 = Digit Span Test - Backward, 13 = Digit Span Test - Forward, 14 = Digit Cancellation Test, 15 = Rey-Osterrieth Complex Figure - Copy, 16 = Token Test*

5.1.2.4. Network Structure Visualisation

In order to visualise the structure of each cognitive network, the binary adjacency matrices for each group were exported to the Gephi software (http://gephi.github.io/), where the data were transformed into two-dimensional graphs. These were then displayed applying the Force Atlas algorithm (scaling = 1000, gravity = 100 with 'prevent overlap' selected) (ForceAtlas2, Jacomy *et al*., 2014). The algorithm forces poorly connected nodes apart while pulling well connected nodes together, improving the structural visualisation of each graph.

To quantify network structure further, the community conformation of each graph was calculated using the Louvain community detection algorithm applied to each node using the Brain Connectivity Toolbox within MATLAB (Rubinov & Sporns, 2010). Nodes with high interconnectivity are grouped within modules, while nodes with low levels of connectivity

are segregated from one another. This allows for the detection of sub-network communities that were colour-coded accordingly in the graphs.

5.1.2.5. Network Analysis

Quantification of node-level network parameters was then performed on each adjacency matrix using the Brain Connectivity Toolbox run in a MATLAB environment. The specific parameters assessed included clustering coefficient, betweenness centrality and both the global and local efficiency of each individual node. Whole network connection density was also computed for each graph. Together, these parameters function to quantify the local interactions of each node as well the importance of each node within the wider connectivity of the network. Specifically, betweenness centrality represents a measure of how integral a node is to the efficient communication of the overall network, i.e., the fraction of shortest paths between any two nodes that include the given node. Clustering coefficient and local efficiency, however, are measures of network segregation that assess the interconnectivity of the nodes neighbouring the node of interest. Clustering coefficient is a metric that gives the fraction of a node's neighbours (i.e., other nodes it is connected to by an edge) that are also connected to each other. The local efficiency of a given node also depends on the interconnectivity of its neighbours and is highly related to the clustering coefficient, though in this case, it is an inverse measure of the average path length between a given node and the nodes surrounding it. Efficiency is an inverse measure because the shorter the shortest path length between nodes is the more efficient the connection between them. Global efficiency, therefore, is this measure calculated per node, in relation to the rest of the nodes across the entire network and can be averaged as a measure of overall efficiency. Finally, connection density, sometimes referred to as *wiring cost*, simply refers to the fraction of edges that are present in the graph in relation to the number of possible edges that may be available, given the number of nodes (Bullmore & Sporns, 2009). Please refer to Bullmore and Sporns (2009) for a succinct description of network parameters and Rubinov and Sporns (2010) for an overview of the mathematical formulas used to calculate the network metrics included in this study.

Further assessment of how network parameters differed between cognitive domains was conducted through the use of mean network metrics derived from select nodes. Metrics relating to memory function were calculated using a mean score derived from the nodes corresponding to recall of the Rey Figure, both Prose Memory measures and the Verbal

Paired Associates Learning Test of the Wechsler Memory Scale. Mean metrics for semantic processing were calculated using data derived from the Similarities sub-set of the WAIS, the Category Fluency Test and the Confrontation Naming Test. Similarly, mean abstract reasoning metrics were calculated again using the Similarities and Category Fluency Test but including Raven's Progressive Matrices in place of the Confrontation Naming Test. Finally, metrics relating to executive functioning were calculated using data derived from each of the Stroop Test interference measures, the Letter Fluency Test and the backwards version of the Digit Span Test.

5.1.2.6. Statistical Procedures

The majority of demographic and neuropsychological characteristics were non-normally distributed. Between-group differences in test performance were, therefore, assessed using the non-parametric *Kruskall-Wallis H*-test with *post-hoc Dunn* tests and a *Bonferroni* correction, applied to adjust the *p*-value for multiple comparisons, with significance set at $p < .05$ (**Table 5.2**). Between-group differences in age, education and Mini Mental State Examination (MMSE) scores were assessed using individual *Mann-Whitney U*-tests between groups, and gender ratios were compared using individual *Chi-Square* tests between group pairs (**Table 5.1**). Standardised cognitive tests scores were again, in the majority of cases, non-normally distributed. As such, within-group correlations between cognitive tests were computed using a non-parametric version of the Partial Correlation procedure based on *Spearman's ρ* correlations. These partial correlations were run controlling for age and education to account for any variability attributable to these factors in each group.

Statistical analyses between groups to assess differences in network parameters were performed using individual *Mann-Whitney U-tests*. Connection density, in this case, was measured using the mean network degree. The degree of a node is the number of edges it shares with surrounding nodes and the mean network degree (i.e., the cumulative degree of all nodes divided by the number of nodes) is commonly used as a measure of density (Rubinov & Sporns, 2010). Between-group comparison of density was again conducted using *Mann-Whitney U*-tests.

5.1.3. Results

5.1.3.1. Cognitive Task Performance

The results of a *Kruskall-Wallis H*-test comparing task performances between groups can be seen in **Table 5.2**. Dementia patients performed significantly worse than controls and MCI patients on the majority of cognitive tests. Similarly, both MCI groups performed significantly worse than young and middle-aged control groups on the majority of tests. Amnestic MCI patients performed significantly worse than older controls on all memory measures and again significantly worse than MCI-na on both the immediate and delayed recall of the Prose Memory Test. Non-amnestic MCI patients however, performed significantly worse than healthy older controls on tasks spanning differing cognitive domains while showing no deficits on any of the memory tests.

5.1.3.2. Visualisation of Network Structure

Fig. 5.1 shows the binary adjacency matrices that were created for each of the six participant groups. The number of correlations between each of the cognitive tests, which is represented here in the connection density of each graph, demonstrated differences between groups that showed a linear trend from the youngest to oldest control groups and then again between controls and patients, with the greatest graph density being apparent in the graph of the dementia group (***Fig. 5.2***). As expected, the majority of groups demonstrated correlations between highly related tests in a practical sense (e.g., Digit Span Forward and Backwards) as well as highly related tests corresponding to particular domains such as the Prose Memory measures and the Verbal Paired Associates Learning Test, that both assess the domain of memory.

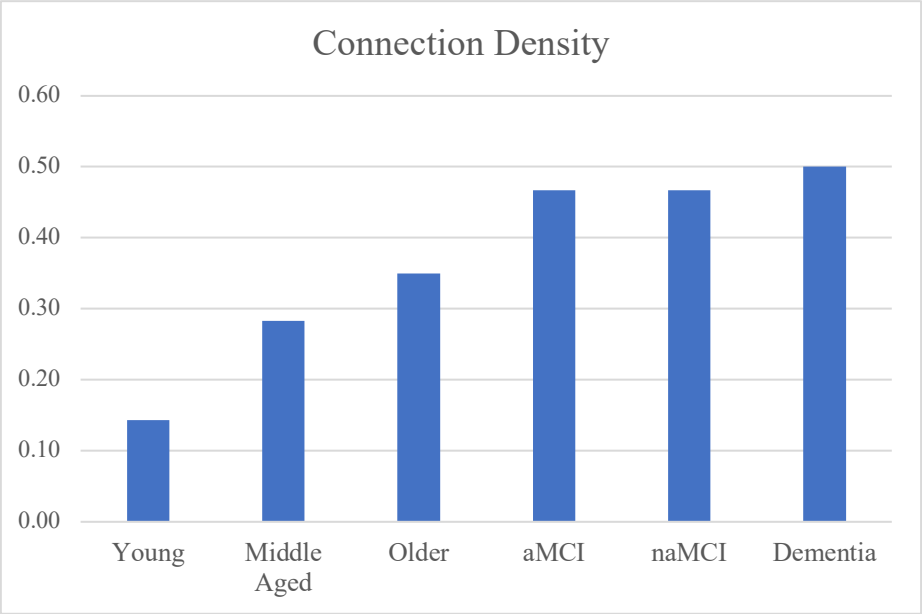


Figure 5.2. *Bar chart showing levels of connection density in each participant group. Y axis represents fraction of present edges to possible edges.*

Notable qualitative differences were apparent between groups in terms of the organisation of the networks. Two-dimensional representations of each graph can be seen in ***Fig. 5.3***. Among the control groups, there was an apparent difference in edge density (or degree) between the younger and older adults, with the youngest group having the least number of edges and the oldest the greatest number, with the middle-aged adults in between. There were also substantial differences in community structure across the healthy adults. The younger group presented with a sparse network, including many nodes with no network connections, thereby creating many individual modules, whereas both older groups showed more interconnected networks with definable community structures. Where modularity class calculated in the middle-aged groups revealed four sub-network communities, in the older group this was reduced to three. Modularity was also a factor that differed in disease, with both the aMCI and MCI-na groups producing highly interconnected networks with three subnetwork communities and the graph of the dementia group only having 2 definable sub-network communities.

Among the youngest healthy controls, network organisation was less determined by cognitive domain than the networks produced by middle-aged and healthy older adults and those with aMCI or dementia. Among healthy older adults the three modules present could be described as corresponding to episodic memory and visuoconstructive ability (coloured blue in ***Fig. 5.3Aiii***), language comprehension and semantic processing (coloured green in ***Fig.***

5.3Aiii) and verbal memory and executive functioning (coloured pink in ***Fig. 5.3Aiii***). Among the middle-aged group, the four module classes delineated adhered to a similar categorisation including both language comprehension and semantic processing (coloured green in ***Fig. 5.3Aii***) and verbal memory and executive functioning (coloured orange in ***Fig. 5.3Aii***). The final modules apparent in this group were split into recollective memory function (coloured blue in ***Fig. 5.3Aii***) and finally, a less clearly defined module corresponding to multiple domains including memory, language functioning and abstract reasoning (coloured pink in ***Fig. 5.3Aii***). Similarly, the network modules defined within the MCI-na group appeared to again correspond to cognitive domains, with sub-networks of nodes corresponding to episodic memory and visuoconstructive ability (coloured pink in ***Fig. 5.3Bi***), verbal memory and executive function (coloured green in ***Fig. 5.3Bi***) and attention and abstract reasoning (coloured blue in ***Fig. 5.3Bi***). These modules were less clearly delineated than in the control groups however, particularly in relation to tests of language and semantic processing, that were more evenly spread between modules in this group than in either the middle aged or older control groups.

Among the aMCI and dementia patients, module class was heavily related to a given nodes' relation to memory functioning. In the aMCI group, module class was similar to the MCI-na patients, with three discernible sub-communities corresponding to memory function (coloured pink in ***Fig. 5.3Bii***), semantic processing and visuoconstrucutive ability (coloured blue in ***Fig. 5.3Bii*)** and a heterogenous module including tests of language, abstract reasoning, verbal memory and executive function (coloured green in ***Fig. 5.3Bii*).** Unlike the MCI-na group however, nodes within the aMCI network were less evenly spread between modules. Despite having a well-defined module for memory function, the remaining two modules were less distinct, including both a very large module comprising of nodes related to multiple domains and a very small three-node module including two tests of semantic function and one un-related task of visuoconstructive ability. In this sense, the cognitive network of the aMCI group was more similar to the dementia patients, in which only two modules were present. In this case, sub-networks were clearly delineated into one module consisting only of tests of language and memory function (coloured green in ***Fig. 5.3Biii***) and another consisting of tests corresponding to any other cognitive domain (coloured red in ***Fig. 5.3Biii***). In both groups, the module relating to memory function included the same six cognitive tests.

Overall, there was distinctly less differentiation of cognitive tests among healthy older individuals when compared with the younger groups. This was clearly exacerbated in disease groups, particularly among the aMCI and dementia groups.

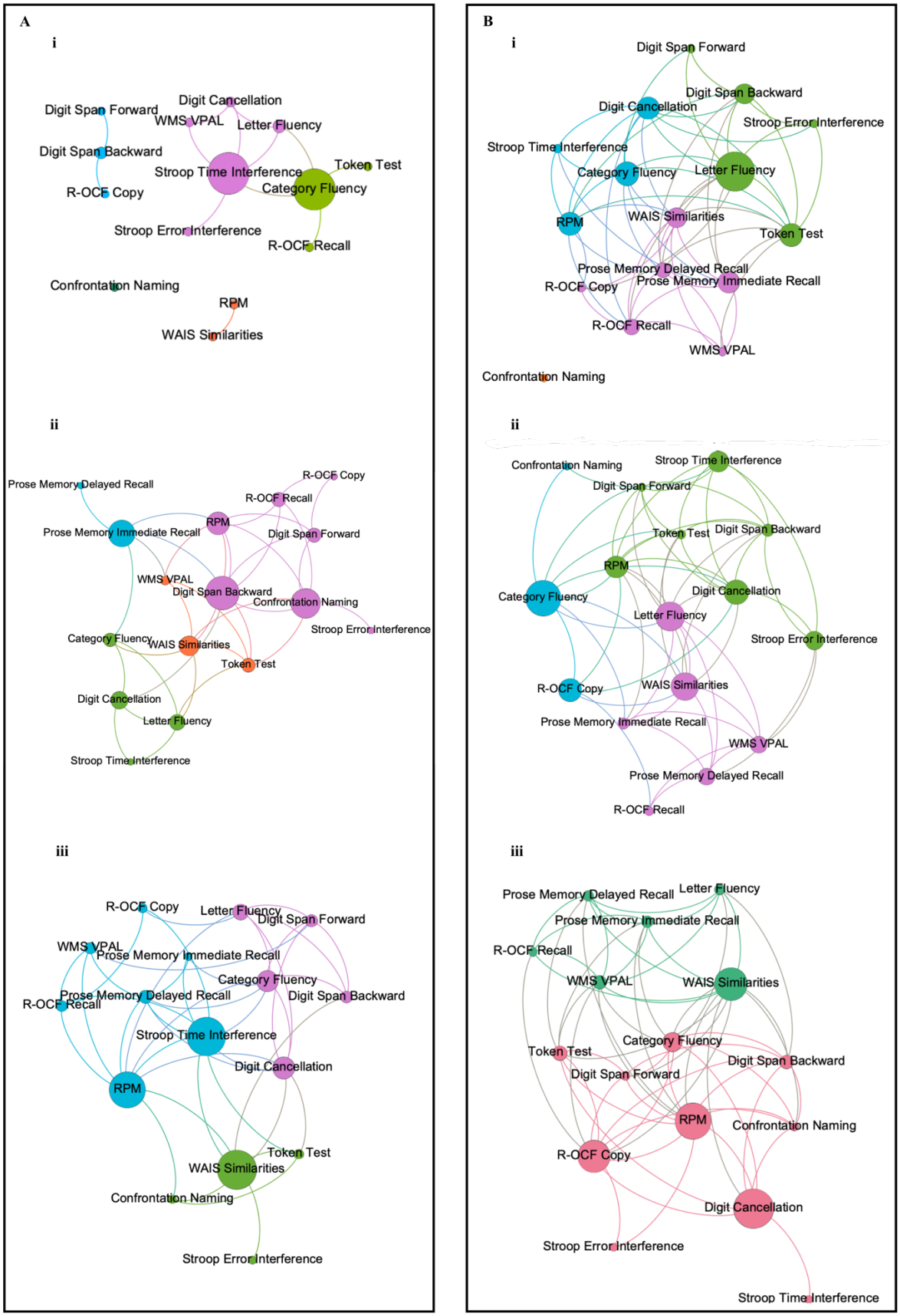


Figure 5.3. *Two dimensional graphs representing the structure of each participant groups' cognitive network. Figures Ai, Aii and Aiii represent the graphs of Young, Middle Aged and Older controls, respectively. Figures Bi, Bii and Biii represent the graphs of MCI-na, aMCI and AD dementia groups, respectively. Each node corresponds to a cognitive test and each edge represents a significant correlation between tests. Colour is reflective of modularity class, identified using the Louvain community detection algorithm, and node size is representative of betweenness centrality relative to the individual graph. RPM, Raven's Progressive Matrices; R-OCF, Rey- Osterrieth Complex Figure; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale, VPAL, Verbal Paired Associates Learning*

5.1.3.3. Network Metrics

Each of the network parameters included were calculated on a node-by-node basis. Both average global and local efficiency measures, as well as clustering coefficients, showed linear differences across the healthy control groups, with the youngest controls having the lowest average and the older controls the highest. This difference was further exacerbated within patient groups, with each patient group showing higher averages in all three measures when compared with all control groups. Betweenness centrality however, demonstrated a different pattern. This measure was lowest among the youngest healthy controls and highest in the middle-aged group. The older controls demonstrated notably a lower average betweenness centrality when compared to the middle-aged group and again this reduction was exacerbated within all disease groups, with both the aMCI and dementia groups showing lower betweenness centrality than older controls and the MCI-na patients showing the lowest overall (***Fig. 5.4***). Significant differences, calculated by *Mann-Whitney U-tests,* between groups on each network parameter are outlined in ***Fig 5.4***. Differences in connection density are also presented, with values for each node calculated as the number of edges belonging to a node divided by the number of possible edges if the node was connected by an edge to all other nodes in the network. See ***Fig. 5.5*** for an overview of the network metrics for each node in each participant group.

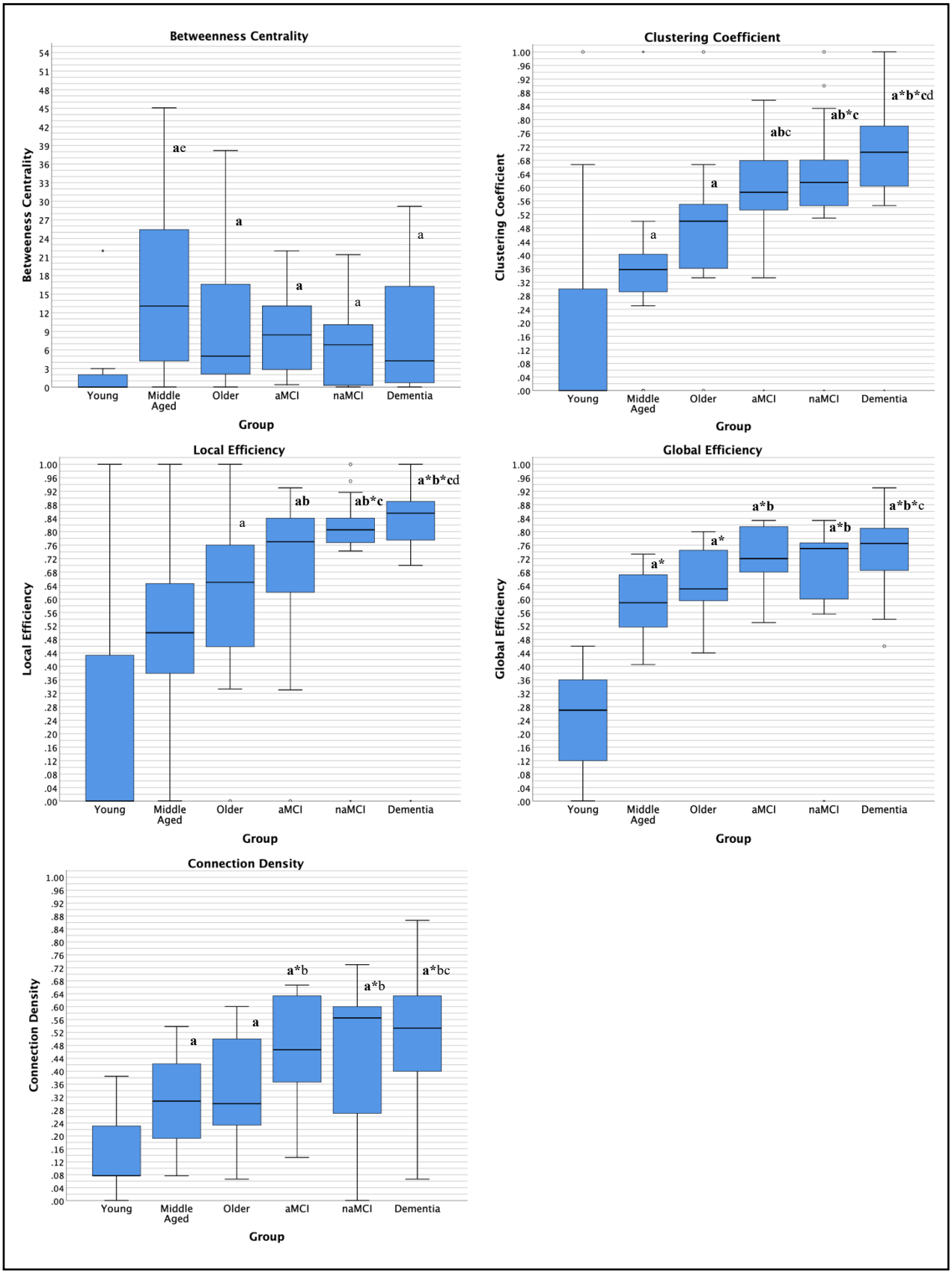


Figure 5.4. *Box plots showing the median and interquartile range of network metrics for the graphs of each participant group with significant differences calculated using independent Mann-Whitney U tests. Significant differences are indicated as:* [a] *Significantly greater than young controls,* [b] *Significantly greater than middle aged controls,* [c] *Significantly greater than older controls,* [d] *Significantly greater than aMCI.* [e] *Significantly greater than naMCI. Significance considered as p <.05. Bold letters indicate p < .01. *significant with Bonferroni correction for multiple comparisons (p < .001).*

Figure 5.5. *Line graphs showing network parameter values for each cognitive test across all participant groups. RPM, Raven's Progressive Matrices; R-OCF, Rey-Osterreith Complex Figure; WAIS, Wechsler Adult Intelligence Scale; WMS; Wechsler Memory Scale, VPAL, Verbal Paired Associates; Imm, immediate; Del, delayed*

5.1.3.4. Cognitive Domains

Statistical analysis between groups in terms of network parameters for each cognitive domain was impossible due to the restricted number of node parameter values constituting the mean values for each domain. As such, the results presented below are purely

observational and allow for the discussion of qualitative differences between groups, relating to cognitive domains, in graph theoretically derived neuropsychological profiles.

I. Global Efficiency

As with the network average, global efficiency measures in all cognitive domains showed a linear trend of difference between the control groups, with the youngest group having the lowest efficiency scores and the oldest group the highest (***Fig. 5.6***). Global efficiencies relating to all domains tended to be higher in aMCI patients than older controls and were higher once again in dementia patients, relative to aMCI, in all domains but executive functioning. The average global efficiency in each domain was slightly more variable within MCI-na patients. In this group, global efficiency was slightly higher than older controls in all domains apart from semantic processing, in which global efficiency was lower than both middle-aged and older controls. In contrast, global efficiency in this group was lower than aMCI in all domains apart from memory and lower than dementia patients in all domains, apart from executive functioning (***Fig. 5.6***).

II. Local Efficiency and Clustering Coefficient

Again, reflecting the global network averages, local efficiency and clustering coefficient showed a tendency to be higher within the patient groups when compared with controls. This was particularly apparent in the domains of executive functioning and abstract reasoning, where all patient groups demonstrated greater levels of both measures when compared with all three control groups. For the dementia group this was again the case in the domains of semantic processing and memory. However, in the case of each of these domains, the aMCI group presented with lower local efficiency and clustering coefficients than the healthy older adults and in the semantic processing domain also presented with lower averages for each measure than the middle-aged group. In the case of MCI-na, both measures were higher than all the controls groups in all domains apart from semantic processing, in which, similarly to aMCI, this group demonstrated lower levels of each network parameter than older controls and similar levels to middle-aged controls (***Fig. 5.6***).

In the domains of abstract reasoning and semantic processing the control groups again presented with a pattern of local efficiency and clustering coefficients that ranged from lowest in the youngest group and highest in the older group with the middle-aged group in between the two. In the case of memory and executive functioning however, this pattern

differed slightly with the middle-aged group having the lowest measures of local efficiency and clustering coefficient in the memory domain and the highest measures of each parameter in the domain of executive functioning when compared with the other healthy groups (***Fig. 5.6***).

III. Betweenness Centrality

Betweenness centrality was lowest in the youngest control group in all cognitive domains, aside from executive function where the dementia group presented with a lower average. The highest betweenness centrality in the domains of memory, semantic processing and executive function was seen in the middle-aged group. In abstract reasoning however, the highest betweenness centrality was seen among older healthy adults.

All patient groups, the MCI-na group in particular, showed considerably lower average betweenness centrality than older controls in the domains of semantic processing and abstract reasoning. This was also true in the domain of executive functioning, although here the difference between the healthy older group and the aMCI patients was much less pronounced. In contrast, the average betweenness centrality in the memory domain was very similar between patient groups and the healthy older adults. Both patients and healthy older adults however, demonstrated substantially lower betweenness centrality in this domain when compared with the middle-aged healthy controls.

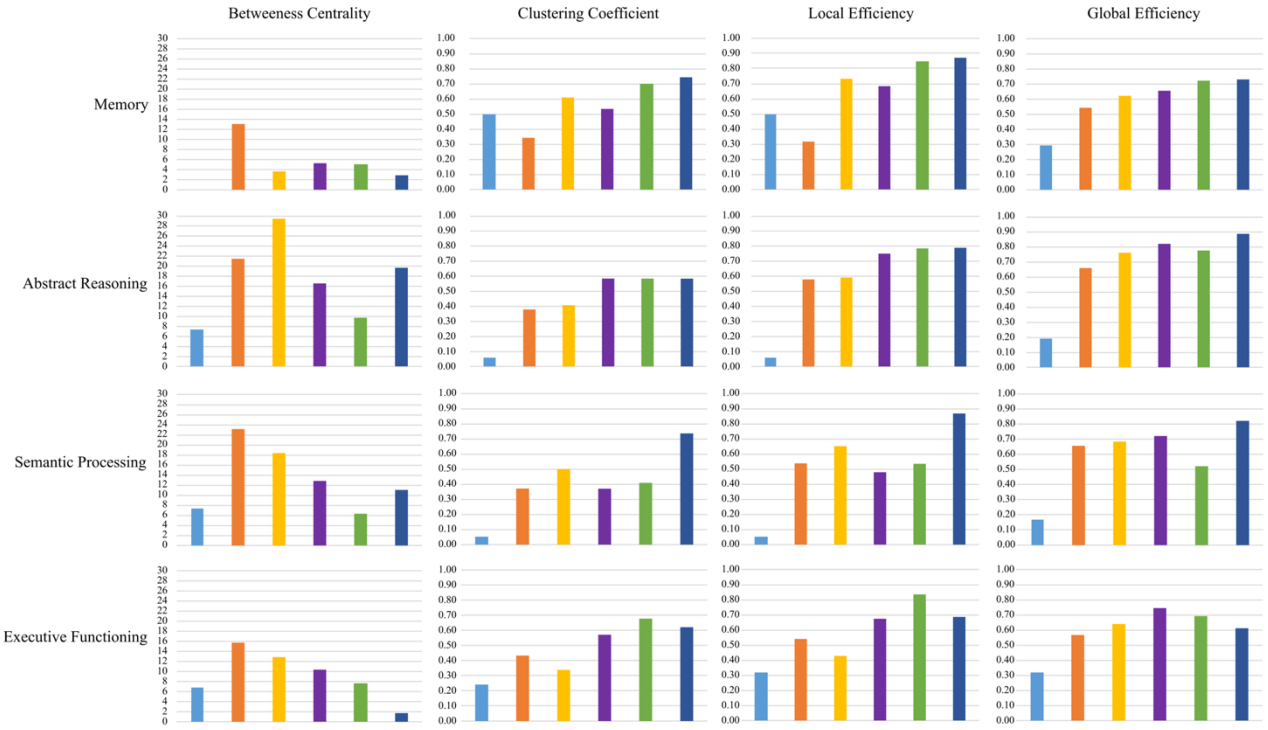


Figure 5.6. *Bar charts showing the average network metrics for each cognitive domain across participant groups*

5.1.4. Discussion

Both the processes of normal ageing and neurodegenerative disease are associated with significant changes in cognitive functioning. Until now, such changes have primarily been characterised through the use of individual or composite test scores investigating a range of cognitive domains. Given these changes have frequently been reported to coincide with underlying variations in neural network functioning in ageing and differentially, in disease (Seeley *et al.,* 2009; Koen & Rugg, 2019), the present study aimed to implement a new approach to the characterisation of cognitive profiles in cognitively impaired or unimpaired adults through the quantification of cognitive networks.

5.1.4.1. Neuropsychological Findings

Although the focus of this research was not on group differences in individual cognitive test scores, cross-sectional analyses were carried out to determine which domains were most severely affected by ageing and disease and how this may inform the interpretation of subsequent network analysis. As expected, patients with dementia performed significantly worse than all other groups on the majority of cognitive tests, while aMCI patients tended to show poor performance mainly on tests of memory, when compared with controls. As expected, MCI-na patients showed no differences in memory function when compared with the older control group but did, however, demonstrate poor performance when compared with this group in tasks of language and executive function, indicating the presence of deficits more frequently associated with this MCI subtype (Petersen, 2004).

Amongst the healthy control groups, older adults tended to perform poorly when compared with younger controls only in domains previously established as vulnerable to the ageing process (Harada *et al.,* 2013), performing significantly worse than both younger and middle-aged participants on measures of fluid intelligence including Raven's Progressive Matrices and taking significantly more time when completing the executive functioning measure: the Stroop Test. Despite also performing worse than both younger groups in other domains including attention (Digit Cancellation), visuospatial skills (copying of the Rey-Osterrieth Complex Figure) and memory function (recall of the Rey-Osterrieth Complex Figure and the Paired Associates Learning Test), these impairments were only significant in healthy older adults when compared with the youngest group. No significant differences were found between the control groups on tasks relating to language or semantic memory function,

including both verbal fluency measures, the Token Test and the Confrontation Naming Test. The only significant finding between age groups in tasks of this nature was the better performance seen among the middle-aged controls when compared with the younger group on the Similarities sub-set of the Wechsler Adult Intelligence Scale. This, therefore, reflects the findings of previous research reporting the enhancement and subsequent maintenance of crystallised intelligence throughout the lifespan (Nyberg *et al.,* 1996; Salthouse, 2009; Harada *et al.,* 2013).

5.1.4.2. Connection Density

The aim of the present investigation, however, was to explore between-group cognitive differences in ageing and disease, at a network level. In ageing in particular, it has been suggested that a level of dedifferentiation occurs in cognition whereby task performances in differing cognitive domains become more highly correlated with one another (Baltes et al., 1980; Baltes & Lindenberger, 1997). Despite the propensity to affect certain domains more than others, a level of global decline is often apparent in the presence of neurodegeneration (Bäckman *et al*., 2005; Grober *et al*., 2008; Amieva *et al*., 2005, 2008), and as such it was expected in the present study that dedifferentiation would be likely to occur in a similar, if not exacerbated, manner among these populations as it does in healthy ageing. Here, methods of graph theory were applied to cognitive data derived from participant groups spanning multiple age ranges and types of impairment. Significant differences in the connection density of cognitive networks were found between the youngest healthy controls and both older control groups, with the youngest group presenting with a network much sparser than the other two. Although not a significant difference, greater connection density was also apparent among the oldest control group when compared with the middle-aged group. This measure, therefore, demonstrates definable differences between the stages of healthy ageing in the independent function of separate cognitive domains and provides supporting evidence for the existence of age-related cognitive dedifferentiation, particularly in the transition between early life (< 40 years old) and middle age.

Differences in network density between the disease groups and healthy older adults indicated an even greater level of dedifferentiation. All patient groups presented with significantly greater connection densities when compared with both the young and middle-aged healthy control groups. Furthermore, the group of dementia patients also demonstrated significantly greater connection density than the healthy older group. Greater density was

also apparent among both the MCI-na and aMCI patients when compared with healthy older adults, although this was not significant. Higher connection densities among disease populations in this case reflect higher numbers of significant correlations between tests scores in these groups, therefore suggesting a greater tendency for individuals in these cohorts to demonstrate a concordance in their dysfunction across a range of disparate cognitive tests. In accordance with the suggestion that age related cognitive dedifferentiation may reflect the effects of undiagnosed disease processes (Batterham, Christensen & Mackinnon, 2011), it is likely that the impact of neuropathological damage on overall effortful cognitive processing may result in shared variances in task performance across a number of domains. This finding is, therefore, indicative of the presence of a global impairment that may influence the variance of test performance across multiple domains to a similar degree, supporting the use of graph theory measures to highlight system-wide differences in cognitive functioning among disease populations (Garcia-Ramos *et al.,* 2016; Kellermann *et al.,* 2016). Cognitive covariance networks such as this may, furthermore, provide a means to partial out the effect of such global declines when assessing neuropsychological functioning among cognitively impaired patient groups. The suggestion that performances on individual cognitive tests are influenced not only by deficits in a specific domain but furthermore, by some general disease related constraint on cognition, may be somewhat problematic in the pursuit of early differential diagnosis of neurodegenerative aetiologies. The quantification of cognitive profiles, using graph theoretical techniques, eliminates the potential for global impairments to impact on the identification of disease specific cognitive change. By evaluating the topology of the cognitive network and the inter-relatedness of its various domains, the underlying neuropsychological mechanisms influencing individual task performances can be more readily examined. As such, this technique may provide a clearer indication of the specific alterations driving cognitive impairments and therefore be beneficial for differential diagnosis.

5.1.4.3. Modularity

Further to the connection density of the graphs, another indication of dedifferentiation among the older healthy participants and the patient groups was the reduction in the number of modules that were classified in the graphs of these groups when compared with the younger controls. As in previous studies reporting similar age-related decreases in network modularity within brain systems (Cao *et al.,* 2014; Chan *et al.,* 2014; Han *et al*., 2018; Chong

et al., 2019), the number of modules delineated in each graph reduced by one between each stage of healthy ageing, with the graph of the youngest group being separated into five sub-network communities and the oldest group only three. While both the aMCI and MCI-na retained three definable modules, the graph of the dementia patients included only 2 module classes. Given that the nature of module identification serves to maximise the number of within-module edges while minimising the number of between-module edges (Rubinov and Sporns, 2010), a low number of definable modules indicates a globally well-connected graph with relatively low distinction between separable node groups of higher interrelatedness. This characteristic by definition, therefore, can be applied as a measure of domain differentiation in the cognitive network, and the results presented here demonstrate that such differentiation may show a decrease between the stages of healthy ageing, in a similar manner to age-related dedifferentiation of the neural response (Koen & Rugg, 2019), which is further solidified by the presence of disease, particularly in the case of Alzheimer's type dementia. To some extent, the calculation of community modules is comparable to factor analysis, reducing a larger number of variables to fewer number of influential factors that, in the present study, may be best described in terms of cognitive domain (Park *et al*., 2012; Agelink van Rentergem *et al*., 2020). Modularity in this case, however, is calculated as part of a complex set of metrics that refer to a different theoretical framework and therefore functions as a contributing factor to the thorough description of the entire cognitive scaffold.

Of particular interest was the finding that the discernible modules in the graphs of the amnestic and dementia patient groups were clearly separated by their relation to language and memory function, a characteristic that was not apparent among the healthy older participants or the MCI-na patients. As both these domains are significantly affected in AD (McKhann *et al*., 2011), the graphs presented here appear to reflect an accurate neuropsychological profile that is characteristic of this type of neurodegeneration and can be clearly differentiated from the profile of healthy older individuals as well as patients with a non-amnestic profile who may be more likely to represent the prodromal stages of a differing neurodegenerative disease (Petersen *et al*., 2001; Petersen, 2004; Busse *et al*., 2006; Petersen and Negash, 2008; Ferman *et al*., 2013). This finding, therefore, supports the utility of graph theory in characterising differential cognitive profiles between disparate populations (Garcia-Ramos *et al.,* 2016; Kellermann *et al.,* 2016). Future work in this area will endeavour to include a wider range of aetiologies to determine applicability of these methods in the distinction of divergent presentations of cognitive decline.

5.1.4.4. Network Parameters

As evidenced by differences in network density and modularity, the use of graph theory techniques in the present study allowed for the novel quantification of a dynamic cognitive network that appears to evolve with increases in age and is heavily impacted in the presence of cognitive impairment. In particular, measures of clustering and network efficiency were shown to present with a trend of differences coherently aligned along the age-impairment continuum. Both older control groups demonstrated significantly greater levels of global efficiency when compared with the younger group and all patient groups demonstrated significantly higher levels when compared with both younger and middle-aged healthy adults. The dementia group, furthermore, showed significantly greater levels of this measure when compared with the healthy older group. Similarly, measures of clustering coefficient were found to be significantly higher among both middle-aged and older healthy adults, compared with the youngest group, and the oldest control group was also found to have significantly higher levels of local efficiency when compared with this group. Again, however, both of these measures were found to be greatest among patients. In the case of clustering coefficients, all patient groups demonstrated significantly higher levels than all healthy control groups. Differences in local efficiency followed the same pattern, with only the aMCI patients failing to demonstrate a significant difference when compared with healthy older adults, despite still presenting with markedly higher levels of this network parameter.

As measures of network segregation, both the differences in clustering coefficient and local efficiency that were found to be present between the stages of healthy ageing, and between healthy individuals and patient groups, indicate a difference in the local interconnectivity between neighbouring nodes, suggesting higher levels of cognitive network segregation in older adults and furthermore, in disease. Conversely, as a measure of network integration, higher levels of global efficiency are an indication of greater network-wide interconnectivity, depending on the average path length between any two nodes (Rubinov and Sporns, 2010). A network that demonstrates high levels of network segregation in combination with high levels of network integration can be described as presenting with the property of ‘small-worldness’ (Watts & Strogatz, 1998). Previously, neuroimaging studies assessing the topology of both structural and functional neural networks, have demonstrated significant alterations in the small-world properties of such networks in AD patients at varying disease stages, including patients with both prodromal and even preclinical manifestations of disease (He, Chen & Evans, 2008; Yao *et al*., 2010; Bai *et al*., 2012; Zhao

et al., 2012; Zhou & Lui, 2013; Tijms *et al*., 2013a; Wang *et al*., 2013; Brier *et al*., 2014; Fischer *et al*., 2015; Tijms *et al*., 2016; Pereira *et al*., 2016; Pereira *et al*., 2018; Franciotti *et al*., 2019; Dai *et al*., 2019). Despite such alterations indicating a breakdown in the small-worldness of brain networks among AD patients, the results presented here suggest that, at the cognitive level, functional domains may show greater levels of network integration and segregation, in terms of their statistical correlation, among patient groups, compared with controls and, to a lesser extent, healthy older adults compared with younger age groups. Given that this is the first investigation to use graph theoretical methods to model neuropsychological profiles within a cognitively impaired, neurodegenerative population, it remains unclear what the relationship may be between underlying alterations of physiological network topology and the differences seen at a cognitive level. However, in line with the findings previously outlined, relating to connection density, and the demonstration by previous studies of a significant relationship between brain network graph theory parameters and measures of cognition (Shu *et al*., 2012; Tijms *et al*., 2013b; Tijms *et al*., 2014; Dicks *et al*., 2018; Verfaillie *et al*., 2018), it may be plausible that the results presented here could be explained as reflecting greater cognitive dedifferentiation among patient groups, caused by a breakdown in neural network functioning that may influence the variance in task performance in a similar manner across domains.

Betweenness centrality however, showed a differing pattern, with the highest level of this metric being apparent among the middle-aged group, differing significantly from both the youngest control group and the MCI-na patients. Although not a direct measure of interconnectivity, betweenness centrality may be influenced by the density of the network. As a fractional value, dependant on the number of shortest paths between any two nodes to which a given node belongs, lower betweenness centrality values may be influenced by the average shortest path length of the graph. If each node is connected to each other node by a single edge, for example, then no particular node is going to present with a higher fraction of shortest paths to which it belongs. A graph containing a higher number of binary, undirected edges will inherently present with a shorter average path length, as was demonstrated by the linear increase in connection density and global efficiency outlined between participant groups. This, therefore, may reduce the fraction of shortest paths to which a given node belongs, thereby reducing that node's betweenness centrality (See Rubinov and Sporns, 2010 for exact arithmetical formula). It could be argued, therefore, that a potential limitation of this study was the use of an absolute threshold to identify edges within the graphs of each participant group, leading to differences in network density between the groups. As outlined

previously however, an absolute threshold was chosen to avoid the inclusion of non-significant correlations in the networks (van den Heuvel *et al.,* 2017), particularly where significant correlations were highly sparse, as in the youngest control group. Use of an absolute threshold in this case, instead provided an arguably more accurate visualisation of how the structure of cognitive networks changes throughout ageing and disease, with network density itself proving an integral alteration that likely reflects the breakdown of highly segregated domain-specific functioning (Chan *et al.,* 2014; Chong *et al*., 2019), and provides compelling evidence for the existence of cognitive dedifferentiation in ageing and disease.

5.1.4.5. Analysis of Cognitive Domains

Averages of network parameters for particular cognitive domains allowed for more nuanced insight into domain-specific differences between the groups. In general, network parameters in each domain revealed a similar pattern of differences between the various age groups that was exacerbated in the groups of patients with cognitive impairment. However, measures of betweenness centrality indicated substantial differences between groups in how integral differing domains were to the efficient communication of the network. In particular, in the domain of memory, both the older healthy adults as well as each patient group similarly demonstrated a considerably low level of betweenness centrality, when compared with the middle-aged group. In contrast, however, betweenness centrality in the domain of abstract reasoning was highest among the older healthy controls, while showing substantially lower levels in patients, particularly in the MCI-na group, again below the levels seen in the middle-aged group. This measure, in the domains of semantic processing and executive functioning, was also much lower in patients than in both the middle-aged group, who, as in the memory domain, showed the greatest levels of betweenness centrality in these areas, and the healthy older group. Despite the healthy older adults also demonstrating lower levels of betweenness centrality in these domains, when compared with the middle-aged group, this difference was much less pronounced than that seen between middle-aged controls and patients. Overall, executive functioning and memory produced the lowest levels of betweenness centrality regardless of group, with abstract reasoning and semantic processing the highest. High betweenness centrality in semantic processing and abstract reasoning in both the middle-aged and older groups suggests an increased reliance on this type of crystallised intelligence, which is developed throughout the lifetime (Cattell, 1971), to support healthy cognitive function across multiple domains, as we age and our fluid abilities

decline (Harada *et al.,* 2013). This is in accordance with the lack of age-related differences between groups on measures of semantic function shown in the present study, as well as with previous studies demonstrating the relative maintenance of semantic processing and language functions in normal ageing, despite notable declines in other areas such as episodic memory and processing speed (Nyberg *et al.,* 1996; Salthouse, 2009). Particularly low levels of memory-related betweenness centrality in both the older healthy groups and patients, when compared with the middle-aged group is, therefore, likely to be reflective of the tendency for this cognitive function to decline in both normal ageing and disease and, as such, play a diminishing role in the connectivity of the wider cognitive network. Similarly, comparable levels of clustering coefficient, as well as local and global efficiency, between the healthy older group and patients in tests of memory function likely reflects greater connectivity between tests corresponding to this domain, due to similar declines in performance, leading to higher correlations in this local area of the network.

Low levels of betweenness centrality in semantic and abstract reasoning domains among the patient groups when compared with controls, however, may reflect a disease related decrease in the reliance on such functions to facilitate cognition. This is further supported by studies finding that significant declines in semantic processing tend to occur in concomitance with early pathology-related change in AD (Joubert *et al*., 2010; Barbeau *et al*., 2012; Venneri *et al*., 2019; Joubert *et al*., 2020). The novel findings presented here, therefore, support the utility of graph theoretical methods to highlight differences in neuropsychological profiles in normal ageing and disease, particularly through the assertion that age-related reliance on crystallised semantic ability, or knowledge, to facilitate cognitive function is greatly diminished in the presence of pathology. Evidence from longitudinal studies has implicated semantic memory impairment as one of the earliest markers of cognitive decline in individuals who go on to develop AD dementia (Amieva *et al*., 2008; Vonk *et al*., 2020) and as such, neuropsychological profiling in this manner may have significant implications in the identification of incipient disease processes.

5.1.4.6. Conclusion

In conclusion, through the novel application of graph theory, the present study provides a new approach to the modelling of age-related and disease-related cognitive decline. Quantification of the structure of cognitive networks within both patients and healthy controls revealed compelling evidence for the existence of measurable alterations in

neuropsychological profiles throughout healthy ageing that are distinct from alterations associated with underlying pathological change. Furthermore, topological distinctions between the cognitive graphs of differing diagnostic groups suggests some potential for the further exploitation of graph theory methods for the differentiation of cognitive profiles associated with varying disease aetiologies. In accordance with previous theories of cognitive dedifferentiation (Baltes *et al*., 1980; Baltes & Lindenberger, 1997), the results presented here demonstrate the utility of graph theory to elucidate topological differences in network-wide connectivity related to the varying stages of the ageing process, and further suggest that underlying neural network dysfunction and global cognitive impairment may contribute to similar and more exacerbated dedifferentiation in disease groups. Furthermore, examinations of network parameters in specific cognitive domains provide clearly definable distinctions between the structural changes of cognitive networks associated with age and those associated with neurodegenerative disease. In particular, the prominent role of crystallised abilities, such as semantic processing, in the network connectivity of healthy older adults was greatly diminished in the patient groups, a defining feature that may serve to inform future investigations into novel diagnostic approaches.

5.2. Experiment 4 – Differences in structural brain networks across the stages of ageing and Alzheimer's Disease assessed using methods of graph theory.

5.2.1. Introduction

Experiment 3 provides compelling evidence that a potentially predictable relationship exists between the stages of ageing and the characteristics of cognitive networks, that may be measurably altered by the presence of neurodegenerative disease. Changes in both the structural and functional integrity of brain systems are a prominent feature of both early AD and the normal ageing process (Minoshima *et al*., 1997; Kogure *et al*., 2000; Bradley *et al*., 2002; Greicius *et al*., 2004; Raz *et al*., 2005; Fjell *et al*., 2009; Frisoni *et al*., 2010; Nyberg *et al*., 2010; Walhovd *et al*., 2011; Grady, 2012; Song *et al*., 2014; Cabeza *et al*., 2018) and the characterisation of such changes, particularly in terms of their relationship to cognitive decline, are of vital importance to neurodegenerative research. In the pursuit of a novel cognitive marker for incipient disease, it is imperative that we are able to clarify the specific mechanism by which AD related physiological alterations may result in subtle characteristic neuropsychological disturbance at the nascent stages of pathological progression. Despite

providing an adequate diagnostic marker for AD (Frisoni *et al*., 2010), gross markers of change, such as accelerated atrophy within the hippocampus, which correlate best with episodic memory deficits, are insufficient to explain very early cognitive changes that may occur at a stage prior to significant hippocampal involvement. Given that structural change, as measured by atrophy, is considered one of the best neural correlates for cognitive impairment in AD (Jack *et al*., 2009; Sluimer *et al*., 2010; Serrano-Pozo *et al*., 2011), differences in the topology of brain structural networks may provide a means to identify AD specific, network-level degradation, that is distinct from that of healthy ageing, prior to significant cortical damage.

Human brain connectomics has undergone a period of significant development in recent years, with many studies adopting graph theoretical methods to explore brain network topology measured via a range of neuroimaging techniques (Sporns, 2013a). Cumulatively, the results of these investigations have demonstrated significant differences in network characteristics across modalities in not only a wide range of pathological cohorts, but further between the normal developmental stages of the human lifespan, suggesting that alterations in brain network topology identified by graph theory parameters, may have significant consequences for both cognition and behaviour (Guye *et al*., 2010; Zhu *et al*., 2012; Xie & He, 2012; Agosta *et al*., 2013; Wu *et al*., 2013; Zhao *et al*., 2015; Zhou *et al*., 2016; Karwowski *et al*., 2019).

There are several aspects of network topology that can be interrogated via the methods of graph theory (Rubinov & Sporns, 2010). However, in terms of the human brain connectome, a few particular characteristics have been identified that are thought to describe best a healthy brain network. Topologically, the human brain network may best be characterised by high levels of segregation within a modularly organised network that is densely and efficiently connected and integrated via the presence of highly centralised nodal hubs (Basset & Bullmore, 2006; He, Chen & Evans, 2007; Bullmore & Sporns, 2009; He & Evans, 2010; Meunier, Lambiotte & Bullmore, 2010; Bullmore & Sporns, 2012; Sporns, 2013b; van den Heuvel & Sporns, 2013; Liao *et al.,* 2017). In terms of graph theoretical measures, these characteristics manifest as high levels of modularity, global efficiency, clustering coefficient and centrality (Bullmore & Sporns, 2009). In particular, high clustering and global efficiency (otherwise measured by a low characteristic path length) are defined as a property of brain networks known as ‘small-worldness’. First described by Watts and Strogatz (1998), a network that displays the property of small-worldness is said to present with a high level of clustering, while having a short characteristic path length, meaning that

despite having highly segregated node clusters, inter-cluster connections, even between distal areas of the graph, remain short. As such, a 'small-world' network is highly efficient in the propagation of information, having the low wiring costs required for the uniquely complex dynamics of the human brain connectome (Basset & Bullmore, 2006; Bullmore & Sporns, 2012). Disruptions to the optimal small-world organisation of brain networks are, therefore, often considered indicative of significant network degradation, which may be detrimental to healthy cognition, given the support that such organisation provides to the efficient transmission of information within both densely connected anatomically proximal regions as well as between distal functionally related areas, properties that are integral to successful human brain function (Liao *et al.,* 2017).

Many studies have demonstrated significant AD related alterations to the small-worldness of brain networks, even in prodromal disease, particularly characterised by an increase in characteristic path length and decrease in local clustering measures that indicate both a reduction in the overall efficient connectivity of the network and a disruption to the segregation of densely connected clusters (He, Chen & Evans, 2008; Yao *et al*., 2010; Bai *et al*., 2012; Zhao *et al*., 2012; Tijms *et al*., 2013a; Wang *et al*., 2013; Zhou & Lui, 2013; Franciotti *et al*., 2019; Dai *et al*., 2019). As a disease that, even in the earliest stages, is heavily characterised by neurological disconnection both structurally and functionally (Greicius *et al*., 2004; Chua *et al*., 2008; Sexton *et al*., 2011; Filippi & Agosta, 2011) (see *Chapter 1, sections 1.4.3.1 and 1.4.3.2)*, alterations in small-worldness in AD, as identified by graph theoretical measures, are thought to reflect these underlying physiological changes, therefore supporting a disconnection hypothesis of AD related cognitive decline (Delbeuck, Van der Linden, & Collette, 2003; Pievani *et al*., 2011). A number of studies have already successfully identified a prominent relationship between graph theoretical parameters indicative of network disruption and measures of cognition (Shu *et al*., 2012; Tijms *et al*., 2013b; Tijms *et al*., 2014; Dicks *et al*., 2018; Verfaillie *et al*., 2018), revealing the potential existence of an AD type disconnection syndrome, similar to those first outlined by Geschwind in 1965 (Delbeuck, Van der Linden, & Collette, 2003).

In healthy ageing, it is thought that small-world properties of brain networks are generally preserved (Zhu *et al*., 2012; Wu *et al*., 2013; Cao *et al.,* 2014; Liao *et al.,* 2017), and instead an area of network analysis that has gained considerable attention, in terms of lifespan alterations, is network modular organisation (Cao *et al.,* 2014; Chan *et al.,* 2014; Han *et al*., 2018; Chong *et al*., 2019). As described in the previous experiment, modularity defines how optimally a network may be divided into sub-network modules. Previous studies have

demonstrated age-related decreases in network modularity, with older individuals presenting with lower within module connectivity in favour of higher between module connectivity when compared with younger adults (Cao *et al.,* 2014; Chan *et al.,* 2014; Han *et al*., 2018; Chong *et al*., 2019). Differences between the stages of ageing in the number of definable sub-network modules is a finding that was reflected in the neuropsychological study presented earlier within this chapter, and as such, one aim of the present experiment was to ascertain the replicability of these results in structural brain networks, in relation to the present cohort, as a means to explain similar age-related differences at the cognitive level.

Network analysis has proved particularly beneficial in the detection of AD, not only having a high diagnostic and predictive accuracy for both AD dementia patients and those with MCI likely to progress (Li *et al*., 2012; Khazaee, Ebrahimzadeh, & Babajani-Feremi, 2015; Khazaee, Ebrahimzadeh, & Babajani-Feremi, 2016; Pereira *et al*., 2016; Khazaee, Ebrahimzadeh, & Babajani-Feremi, 2017; Hojjati *et al*., 2017; Tijms *et al*., 2018), but further demonstrating utility in the identification of subtle functional and structural alterations in prodromal groups (Li *et al*., 2012; Wang *et al*., 2013; Franciotti *et al*., 2019), and even preclinical cohorts (Brier *et al*., 2014; Fischer *et al*., 2015; Tijms *et al*., 2016; Pereira *et al*., 2018; Verfaillie *et al*., 2018). Although a significant portion of the literature in this area has focussed primarily on functional imaging modalities, a number of previous studies have investigated structural alterations in brain networks across the stages of AD, through the use of structural MRI, assessing both cortical thickness and regional cortical volumes, as well as white matter integrity (He, Chen & Evans, 2008; Yao *et al*., 2010; Lo *et al*., 2010; Bai *et al*., 2012; Shu *et al*., 2012; Li *et al*., 2012; Tijms *et al*., 2013a, 2013b; Phillips *et al*., 2015; Fischer *et al*., 2015; Pereira *et al*., 2018; Rashidi-Ranjbar *et al*., 2020). The results of these investigations have proved somewhat unclear however, with variabilities in imaging modality, node selection and network formation procedure all demonstrating significant impacts on the study outcome and direction of group differences (Tijms *et al*., 2013a; Phillips *et al*., 2015).

5.2.1.1. Aims and Hypotheses

Given the evidence supporting a significant association between disruptions in structural brain network topology and cognitive decline (Shu *et al*., 2012; Tijms *et al*., 2013b; Tijms *et al*., 2014; Dicks *et al*., 2018; Verfaillie *et al*., 2018), the aims of the present study were to evaluate differences in structural brain network topology between the stages of

healthy ageing and in neurodegenerative disease, and to assess how the findings of the previous study in cognitive function may relate to measurable alterations in network topology at the structural level. It was expected, in light of the current literature, that AD patients with either dementia or an amnestic MCI profile would likely present with significant alterations in small-world properties relating to clustering and global efficiency, while differences observed between the stages of healthy ageing would more likely correspond to changes in network modularity.

5.2.2. Methods

5.2.2.1. Participants

As in the previous experiment (see section *5.1.2.1.*), the participant sample (N = 230) in this study were identified retrospectively from a large database coordinated by the University of Sheffield's Department of Neuroscience. Many of the participants were taken as a subsample of those included in the previous experiment, however, where MRI images were unavailable participants with matching demographics and available scans were chosen as replacements. Healthy adults (n = 120) were again approached using multiple recruitment strategies, with a proportion being carers of patients and a proportion obtained via word of mouth in the manner of opportunity sampling. All patients included in the study were recruited through a memory clinic after neurological examination. Of the 110 patients, 40 of those included had a clinical diagnosis of dementia with "probable Alzheimer's disease", in adherence to the NINCDS-ADRDA criteria (McKhann *et al*., 2011) and 70 had received a diagnosis of MCI, following the criteria outlined in Albert *et al*. (2011). All procedures were carried out according to the Declaration of Helsinki. This study received ethical approval from the Yorkshire and Humber Regional Ethics Committee, Ref No: 12/YH/0474 and from the West of Scotland Regional Ethics Committee 5, Ref No: 19/WS/0177. Written informed consent was obtained from all participants.

Participants were again segregated into six groups, as per the previous experiment, with healthy adults being assigned to one of three groups according to their age; a younger group who in this case were aged 21-39 (n = 40), a middle-aged group aged 40-64 (n = 40) and an older group aged 65+ (n = 40). Patients were also again split according to clinical diagnosis into those with an amnestic MCI profile (aMCI, n = 40), those with non-amnestic MCI (MCI-na, n = 30) and those with AD dementia (n = 40) (see section *4.1.2.1. I*).

Healthy controls all had an MMSE score above 24. All MCI patients had an MMSE score of 24 or above and were impaired compared to a group of matched controls in at least one cognitive domain. Dementia patients all had an MMSE score below 24, with 35 fulfilling criteria for mild dementia (MMSE > 18) and only 5 fulfilling criteria for moderate dementia (MMSE 14-18). Demographic data for all participant groups can be found in **Table 5.3**. The oldest groups of healthy controls and all the patient groups were matched with each other in terms of both age and levels of education. Education levels differed significantly between patients and younger controls however, with all patient groups reporting significantly fewer years of education than each of the younger control groups. There were no significant differences across any of the six groups in terms of gender ratios.

Table 5.3

Medians (and interquartile range) of age, years of education and MMSE scores as well as gender ratios for each group.

	Young (*n* = 40)	Middle Aged (*n* = 40)	Older (*n* = 40)	aMCI (*n* = 40)	MCI-na (*n* = 30)	Dementia (*n* = 40)
Age (years)	30.00 (12.00) [f]	55.00 (9.00) [cd]	76.00 (8.00)	77.00 (7.00)	74.50 (10.00)	77.00 (8.00)
Education (years)	16.00 (3.50)	13.00 (8.80) [a]	8.00 (6.80) [ab]	8.00 (2.80) [ab]	9.50 (5.30) [ab]	8.00 (7.80) [ab]
Gender (M/F)	20/20	18/22	17/23	15/25	10/20	18/22
MMSE	29.00 (2.00)	30.00 (1.00)	29.00 (3.00)	27.00 (4.00) [e]	27.00 (2.00) [e]	21.00 (4.00) [f]

Individual Mann-Whitney U tests were applied between all groups to assess differences in Age, Education and MMSE scores. Gender-ratio differences were calculated with a chi-square test. Significant differences ($p < .05$) are highlighted as: [a] Significantly lower than young controls, [b] Significantly lower than middle-aged controls, [c] Significantly lower than older controls, [d] Significantly lower than all patient groups, [e] Significantly lower than all control groups, [f] Significantly lower than all other groups

5.2.2.2. Network Formation

Structural brain networks were quantified using areas defined by the Brainnetome Atlas as described by Fan *et al*., (2016). This atlas includes 246 regions of the bilateral cerebral cortex, omitting both the cerebellum and brainstem, as presented in ***Fig 5.7***. For each participant a smoothed T1 weighted MRI scan was obtained following the pre-processing procedures outlined in section *4.1.2.4. I.* Parameters and protocols for each can be found in section *4.1.2.4.* Region of interest (ROI) masks were created for the Brainnetome regions using the MarsBaR toolbox (Brett *et al*., 2002) in SPM, run in a Matlab environment and were then co-registered to a smoothed grey matter map taken from a control participant. Using the "get_totals ([],[],[])" script (http://www0.cs.ucl.ac.uk/staff/g.ridgway/

vbm/get_totals.m), the volumes of each ROI were then extracted from each participant's smoothed grey matter map. Each volume was then converted to a fraction of the individual's total intracranial volume calculated as the combined volumes of grey matter, white matter and cerebrospinal fluid, extracted as per section *4.1.2.4. I.* Each ROI corresponded to a node in the graphs created for each participant group. As in the previous experiment, the edges of each group's graph were defined by using non-parametric partial correlations, controlling for age, levels of education and MMSE scores, between regional volumes to determine the relationships between each of the nodes. Binary adjacency matrices were then created for each group (see section *5.1.2.3*.). The application of a Bonferroni correction revealed substantial differences in graph sparsity (calculated as the percentage of edges present out of the number of possible edges in a fully connected graph) between groups when applying an absolute threshold. Sparsity ranged from 8.07% in the MCI-na group to 33.99% among healthy middle-aged controls. In order to account for group differences in network parameters that may occur due to differences in edge density, therefore, a range of six relative edge defining thresholds were applied to the results of the correlation analysis to produce 6 different binary adjacency matrices for each participant group. The six binary adjacency matrices created for each participant group included the top 5, 10, 15, 20, 25 and 30% of significant correlations as edges to reflect the range of sparsity across participant groups. Where there were negative correlations, of which only one was found among the MCI-na group at the 30% threshold, the next most significant positive correlation coefficient was included in the graph as a replacement. This was due to the uncertainty surrounding the biological underpinnings of a negatively directional correlation between areas of grey matter (Gong *et al*., 2012). *Post-hoc* analysis was further conducted between groups using a single relative threshold of 8% sparsity to include only Bonferroni corrected significant correlations as the edges for all groups.

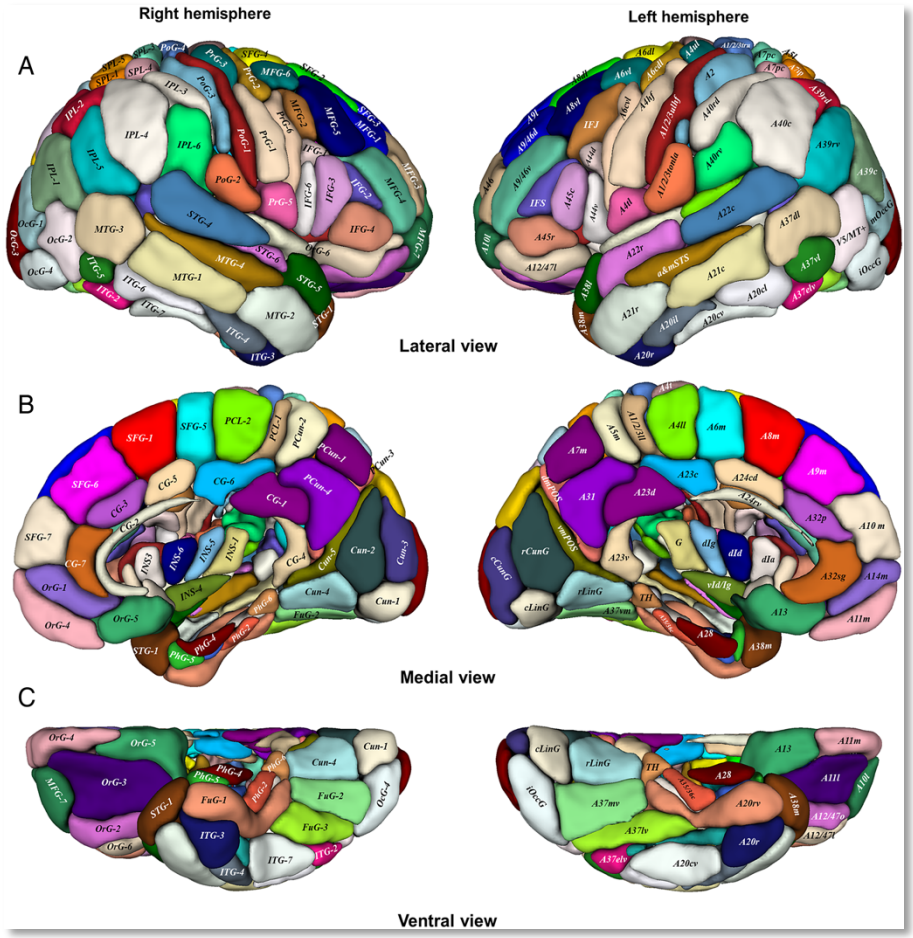


Figure 5.7. *Figure taken from Fan et al., (2016)(accessed at: https://academic.oup.com/cercor/article/26/8/3508/2429104) showing parcellation of 246 brain regions of the Brainnetome Atlas. Reused with permissions under the Creative Commons Licence (http://creativecommons.org/licenses/by-nc/4.0/).*

5.2.2.3. Network Analysis

As per the previous experiment, network analysis was carried out on each adjacency matrix using the Brain Connectivity Toolbox run in MATLAB (Rubinov & Sporns, 2010). The same network parameters were examined in the present study as were used in *Experiment 3*, namely, betweenness centrality, global and local efficiency, clustering coefficient and modularity, as described in section *5.1.2.5.* To determine group differences, mean network parameters were calculated for each node from the values taken for that node across each edge defining threshold. The number of nodes was kept constant for the graphs of each threshold. The presence of disconnected nodes at lower thresholds had no effect on network parameter calculations of the wider graph and mean values for such nodes were calculated including zeros for thresholds at which they were not connected. For the youngest group one node remained disconnected even at the highest threshold meaning that the value

of all network parameters for the ventrolateral inferior temporal gyrus (Brodmann Area 37) was zero across all thresholds. The mean values for each node were then used to determine statistical differences between groups in each network parameter. *Post-hoc* analyses run using an 8% sparsity for all groups was conducted only on fully connected clusters. As such, any disconnected nodes were discounted from the analysis resulting in 236 nodes within the graph of the youngest control group, 241 in the middle-aged group, 245 in older controls, 243 in aMCI patients, 243 in MCI-na and 246 in the dementia group. Further *post-hoc* analysis looking at differences in network parameters were additionally carried out between groups separately for each lobe. These analyses included nodes corresponding to the bilateral frontal lobes, temporal lobes, parietal lobes, occipital lobes, limbic lobes, insula lobes and subcortical areas. A list of brain areas included for each lobe can be found in **Table 5.4** and an exhaustive description of the nodes (ROIs) that each of the areas are comprised of can be found in Fan *et al*., (2016). As a further means to assess regional network alterations, nodes reflecting hub-like properties were defined in each group. A network hub may be defined as a node that exerts significant effects on the connectivity of the wider network through either a high number of connections or a high centrality (van den Heuvel & Sporns, 2013). As per the recommendations of previous research highlighting the importance of including both local and global measures of network integration in hub definition (Sporns, Honey & Kötter, 2007; Zuo *et al*., 2012; van den Heuvel & Sporns, 2013), the present study included multiple parameters to assess hub-like characteristics and as such hubs were defined as nodes that had both a betweenness centrality and degree more than 1.5 SDs above the group mean.

Table 5.4

Table showing list of brain areas included in each lobe with associated regions.

Lobe	Areas	Associated Regions
Frontal Lobe	Superior Frontal Gyrus	
	Middle Frontal Gyrus	
	Inferior Frontal Gyrus	Pars Opercularis, Pars Triangularis
	Orbital Gyrus	Pars Orbitalis, Lateral and Medial Divisions of Orbital Gyrus, Frontal Pole
	Precentral Gyrus	
	Paracentral Lobule	
Temporal Lobe	Superior Temporal Gyrus	Superior Temporal Gyrus, Temporal Pole, Transverse Temporal Cortex
	Middle Temporal Gyrus	
	Inferior Temporal Gyrus	
	Fusiform Gyrus	
	Parahippocampal Gyrus	Entorhinal Area, Parahippocampal Gyrus
	Posterior Superior Temporal Sulcus	Banks of the Superior Temporal Sulcus
Parietal Lobe	Superior Parietal Lobule	
	Inferior Parietal Lobule	Inferior Parietal Lobule, Supramarginal Gyrus
	Precuneus	
	Postcentral Gyrus	
Occipital Lobe	Medioventral Occipital Cortex	Cuneus, Lingual Gyrus, Ventromedial Parietooccipital Sulcus
	Lateral Occipital Cortex	Superior Occipital Gyrus, Middle Occipital Gyrus, Inferior Occipital Gyrus, Area V5/MT, Occipital Pole
Insula	Insula Gyrus	
Limbic Lobe	Cingulate Gyrus	Anterior Cingulate Gyrus, Posterior Cingulate Gyrus, Caudal Cingulate Gyrus
	Amygdala	Medial and Lateral Divisions
	Hippocampus	Rostral and Caudal Divisions
Subcortical	Basal Ganglia	Caudate Nucleus, Putamen, Globus Pallidus, Nucleus Accumbens
	Thalamus	Medial/Lateral Prefrontal Thalamus, Medial Premotor Thalamus, Sensory Thalamus, Rostral/Caudal Temporal Thalamus, Posterior Parietal Thalamus, Occipital Thalamus

5.2.2.4. Statistical Procedures

The majority of demographic characteristics were non-normally distributed. Between-group differences in age, education and MMSE scores were therefore assessed using individual *Mann-Whitney U*-tests between groups; gender ratios were compared using individual *Chi-Square* tests between group pairs (**Table 5.3**). Standardised regional volumes were again, in many cases, non-normally distributed. As such, within-group correlations between regional volumes were computed using a non-parametric version of the Partial Correlation procedure based on *Spearman's ρ* correlations. These partial correlations were run controlling for age, education and MMSE.

As described in section *5.1.2.6*, statistical analyses between groups to assess differences in network parameters were performed using individual *Mann-Whitney U-tests*. Connection density for lobes were measured, in addition to the network parameters calculated on the whole graphs, using the degrees of each node within the lobe. Between-group comparison of connection density was again carried out using *Mann-Whitney U*-tests.

5.2.3. Results

5.2.3.1. Whole Graph Network Metrics

Fig. 5.8 shows the mean network parameters for the whole graphs of each group across each of the six edge defining thresholds. Some trends, such as low global efficiencies in young adults and low clustering coefficients in aMCI patients, were clear across thresholds; however, differences in the results obtained at each threshold resulted in further analysis carried out only on mean values for each node, taking into account all thresholds, as a way to ameliorate the effects of edge density. The results of this analysis can be seen in ***Fig. 5.9.*** Significant differences calculated by individual *Mann-Whitney U-tests* revealed significantly higher levels of global efficiency overall in aMCI patients than both young (p = .016) and older (p = .02) healthy controls as well as the MCI-na group (p = .04). Similarly, the dementia patients also showed significantly higher global efficiencies than young (p = .034) and older (p = .031) controls. The only significant differences between groups in terms of both clustering coefficient and local efficiency were seen in relation to the aMCI group. Amnestic MCI patients demonstrated significantly lower levels of local efficiency than the MCI-na group (p = .004), dementia group (p = .034) and the young controls (p = .002) as measured by individual *Mann-Whitney U-tests* and had significantly lower levels of clustering coefficient than all other groups (middle-aged: p = .006; dementia: p = .035). Differences between groups that retained significance when applying a Bonferroni correction for multiple comparisons ($p \leq .002$) were between the aMCI group and the youngest control group in terms of local efficiency and between the aMCI group and both the youngest and oldest controls as well as the MCI-na group in terms of clustering coefficient. Betweenness centrality was highest in the oldest control group and the dementia patients with *Mann-Whitney U-tests* revealing significantly higher betweenness centralities in older controls than both the young (p = .004) and middle-aged control groups (p = .006) as well as aMCI patients (p = .035) and dementia patients presenting with significantly higher betweenness

centralities when compared with the youngest (p = .038) and middle aged control (p = .045) groups. These results along with the medians and interquartile ranges of network parameters in each group can be seen in ***Fig. 5.9***.

As in the previous study, the Louvain community detection algorithm was applied using the Brain Connectivity Toolbox to assess how the graphs may be segregated into sub-network modules in a way that maximises the number of within-module edges and minimises the number of between-modules edges (Rubinov & Sporns, 2010). The number of sub-network modules in the graphs of each group across edge defining thresholds can be seen in ***Fig. 5.10a***. ***Fig. 5.10b*** shows the median and range of the number of modules present in the graphs of each group across thresholds. The youngest control group tended to have the highest number of sub-network modules regardless of threshold and a *Mann-Whitney U-test* revealed a significant difference between the variance in the number of modules delineated for the graphs of this group when compared with the variance in the dementia patients (p = .29, see ***Fig. 5.10b***).

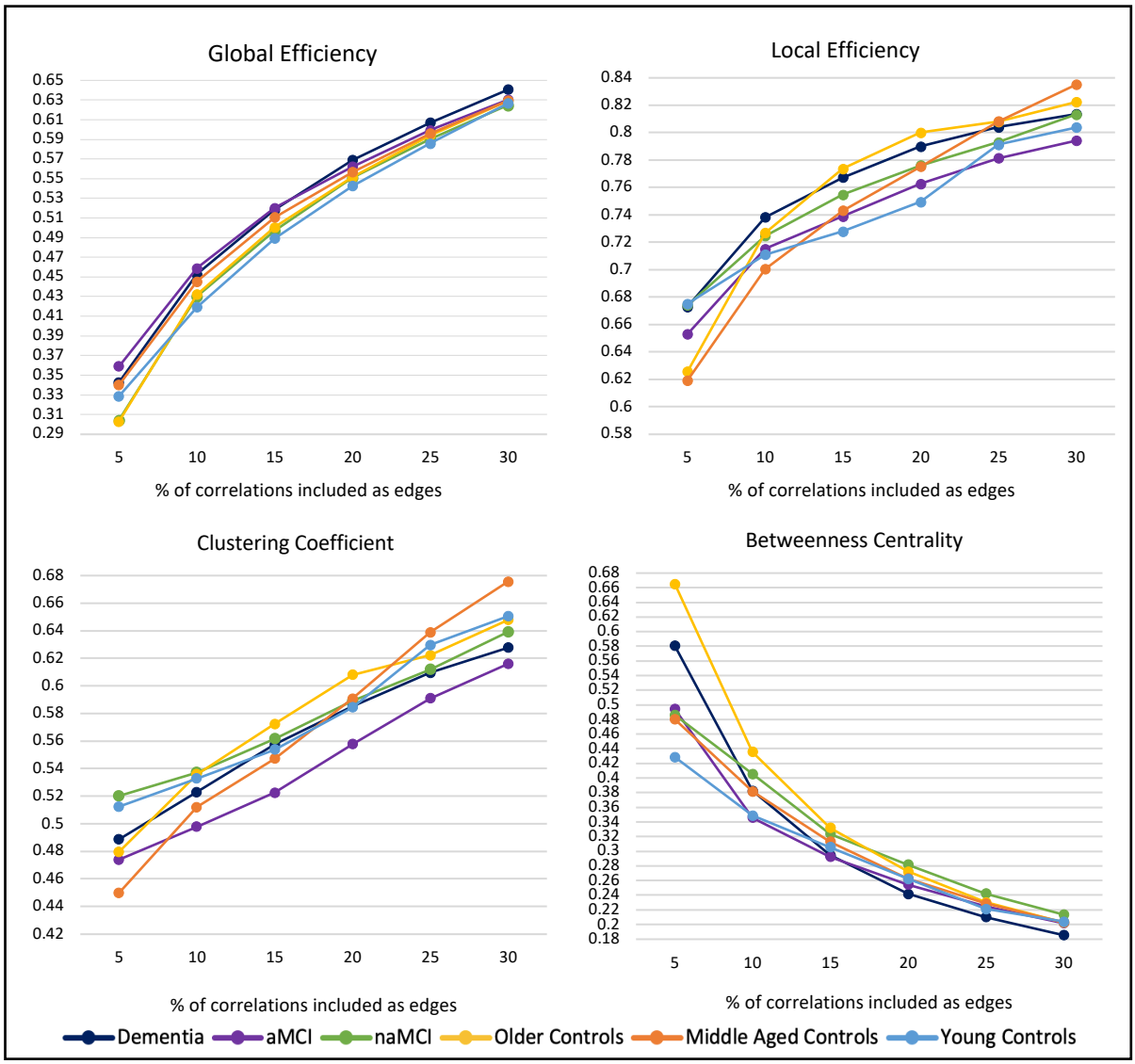


Figure 5.8. *Line graphs showing mean whole graph network parameters for each group across edge defining thresholds. Differing scales were applied to the y-axes according to the data range for each parameter.*

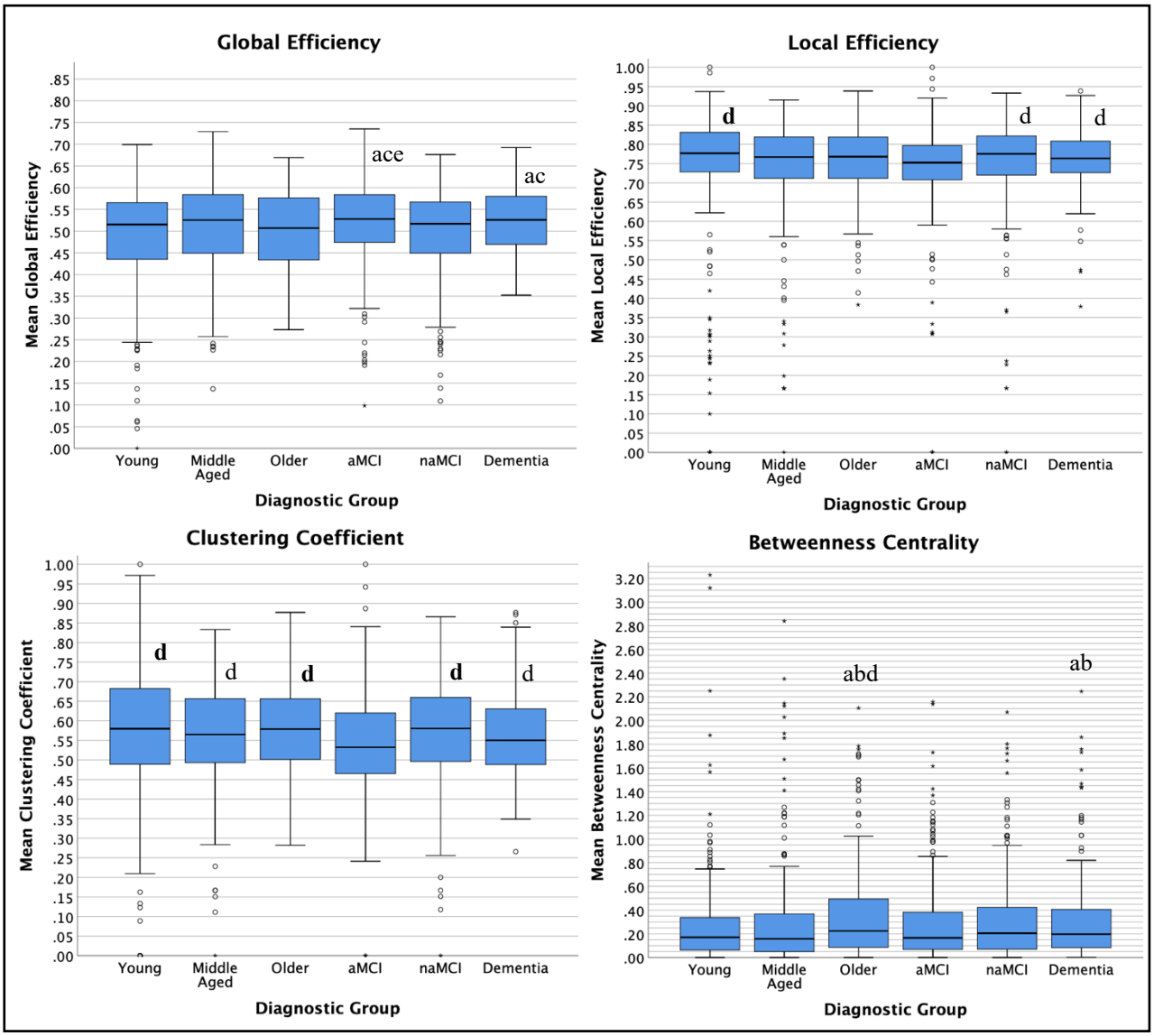


Figure 5.9. *Box plots showing the median and interquartile range of network metrics for the graphs of each participant group with significant differences calculated using independent Mann-Whitney U tests. Significant differences ($p < .05$) are indicated as: [a] Significantly greater than young controls, [b] Significantly greater than middle aged controls, [c] Significantly greater than older controls, [d] Significantly greater than aMCI, [e] Significantly greater than MCI-na. Bold letters indicate significance when controlling for multiple comparisons using a Bonferroni correction ($p \leq .002$)*

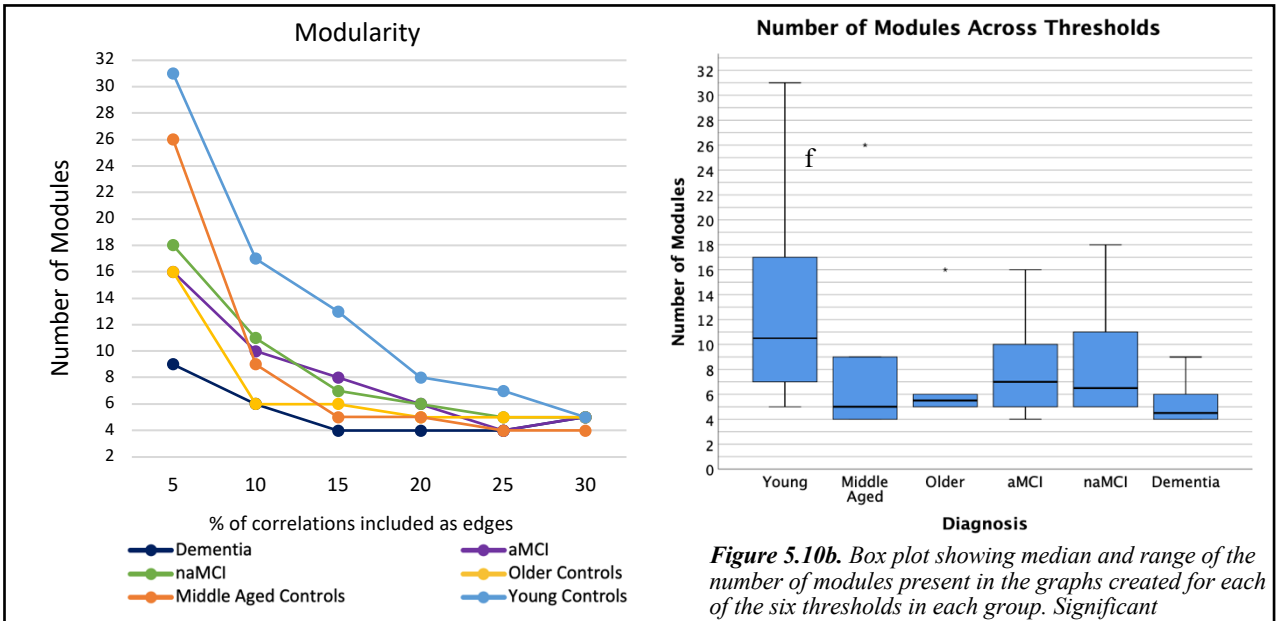


Figure 5.10a. *Line graph showing the number of modules in the graphs of each participant group across edge defining thresholds.*

Figure 5.10b. *Box plot showing median and range of the number of modules present in the graphs created for each of the six thresholds in each group. Significant differences were calculated using Mann-Whitney U tests. [f] Significantly greater than dementia patients $p < .05$.*

5.2.3.2. Post-Hoc Analysis

Post-hoc analyses on a single 8% threshold, which represented the highest sparsity level possible for all groups in which only correlations significant when corrected for multiple comparisons would be included, found similar results to those presented for the mean network parameters across thresholds. ***Fig. 5.11.*** shows box plots presenting the medians and interquartile ranges for the network parameters measured within each group at this more restrictive threshold. As in the previous analysis, dementia patients and aMCI patients demonstrated the highest levels of global efficiency. Individual *Mann-Whitney U-tests* found that dementia patients had significantly higher global efficiencies than both the older (p = .005) and younger (p = .012) control groups, whereas the aMCI patients had significantly higher global efficiencies than all the other groups. When compared with the youngest and oldest controls, as well as the MCI-na patients, higher global efficiencies in the aMCI group were all significant at the Bonferroni corrected level ($p \leq .002$), while differences between this group and middle-aged controls (p = .029) and dementia patients (p = .018) were only significant at the uncorrected level. Furthermore, this analysis revealed significantly higher global efficiency levels in the middle-aged control group when compared with the youngest group (p = .028).

As in the previous results, the group with the lowest local efficiency and clustering coefficient was the aMCI group. However, in this instance, only the youngest control group demonstrated significantly higher local efficiencies than the aMCI group (p = .005) with no significant differences being identified between the aMCI group and any other group. When analysing clustering coefficients, *Mann-Whitney U-tests* again revealed significant differences only between the aMCI group and other groups, with this group presenting with significantly lower clustering coefficients than the youngest controls (p = .004), oldest controls (p = .002), MCI-na (p = .008) and dementia groups (p = .045).

Finally, betweenness centrality again showed a very similar pattern of results to those presented above. However, despite both the older group and dementia group presenting again with the highest levels of betweenness centralities compared with other groups, in this instance significant differences were only found in relation to the youngest control group, with all other groups demonstrating significantly higher betweenness centralities. In the case of the oldest controls, MCI-na and dementia groups, this difference was significant even when correcting for multiple comparisons ($p \leq .002$), whereas differences in betweenness

centrality between the youngest group and the middle-aged (p = .042) and aMCI (p = .038) groups were only significant at the uncorrected level.

Finally, differences in modularity were again apparent between groups in a similar manner to the previous findings, with the youngest group having the greatest number of definable modules (11) and the AD dementia group the lowest (6). In the case of the aMCI and older control groups, each had seven definable modules while the MCI-na and middle-aged groups had 8 each.

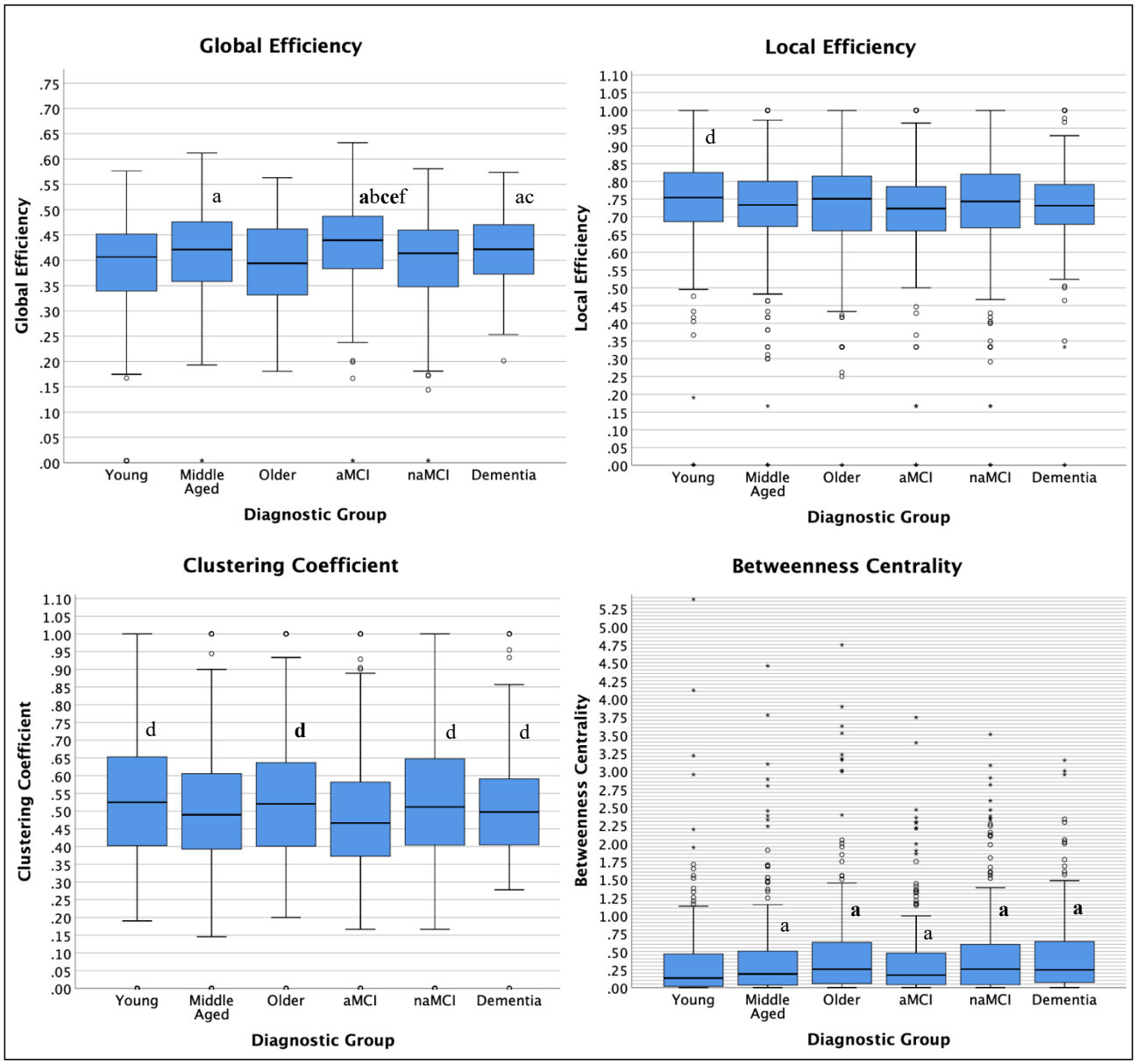


Figure 5.11. *Box plots showing the median and interquartile range of network metrics for the graphs of each participant group at an 8% sparsity, with significant differences calculated using independent Mann-Whitney U tests. Significant differences ($p < .05$) are indicated as:*
[a] Significantly greater than young controls, [b] Significantly greater than middle aged controls, [c] Significantly greater than older controls, [d] Significantly greater than aMCI, [e] Significantly greater than MCI-na. Bold letters indicate significance when controlling for multiple comparisons using a Bonferroni correction ($p \leq .002$)

5.2.3.3. Network Metrics of Individual Lobes

Differences between groups in network metrics relating to individual lobes are presented in **Table 5.5** and ***Fig. 5.12a-e***. A number of significant differences between groups were established using individual Mann-Whitney U-tests and are outlined in **Table 5.5** along with the median and interquartile range for each measure. Significant results that survived a Bonferroni correction for multiple comparisons are outlined in ***Fig. 5.12a-e.***

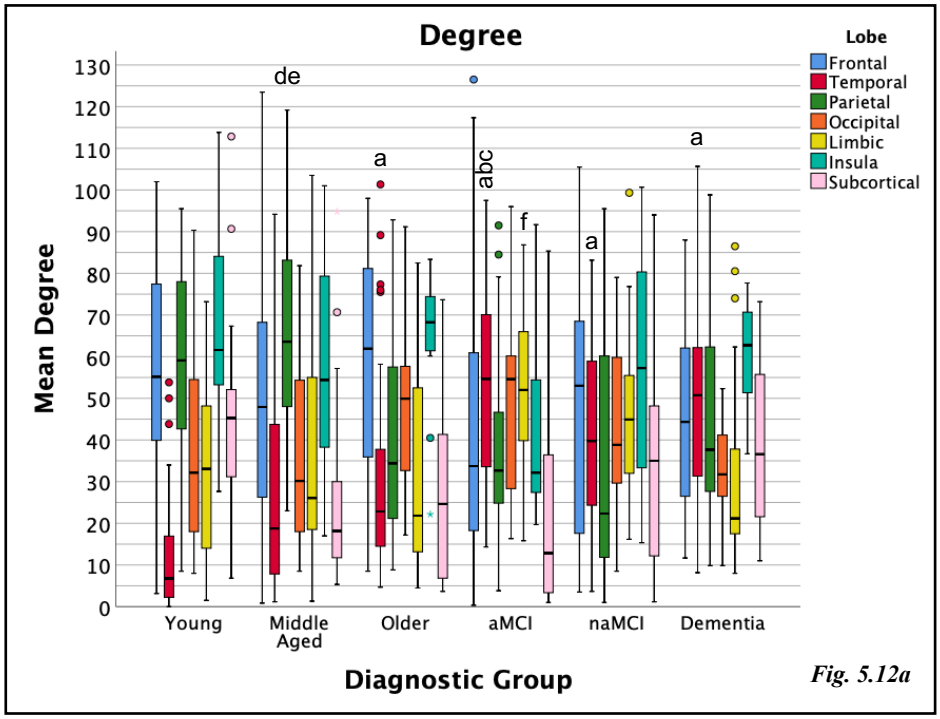


Fig. 5.12a

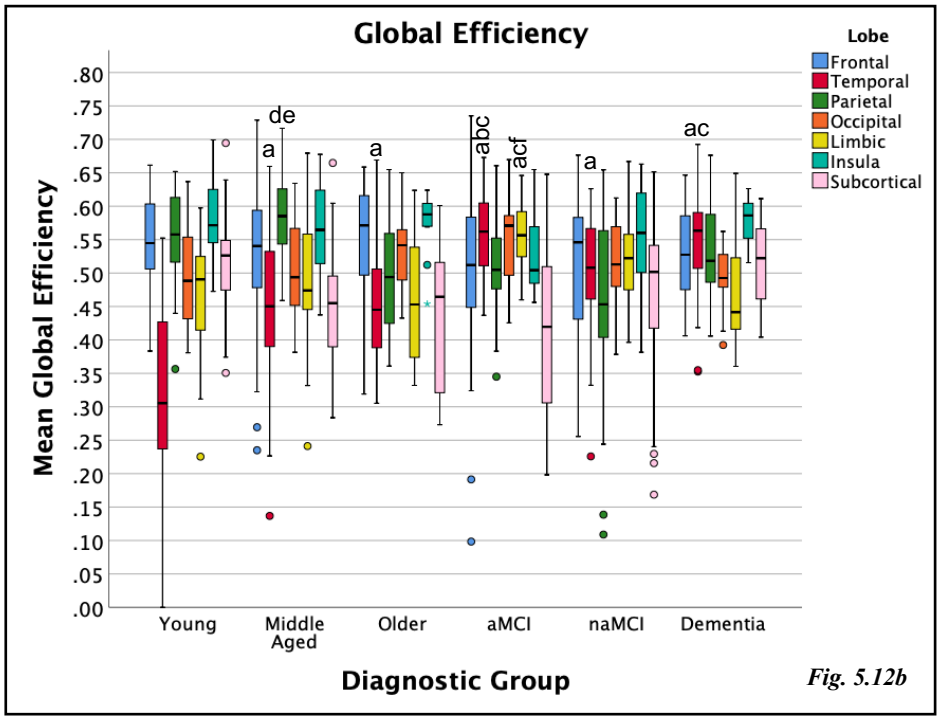


Fig. 5.12b

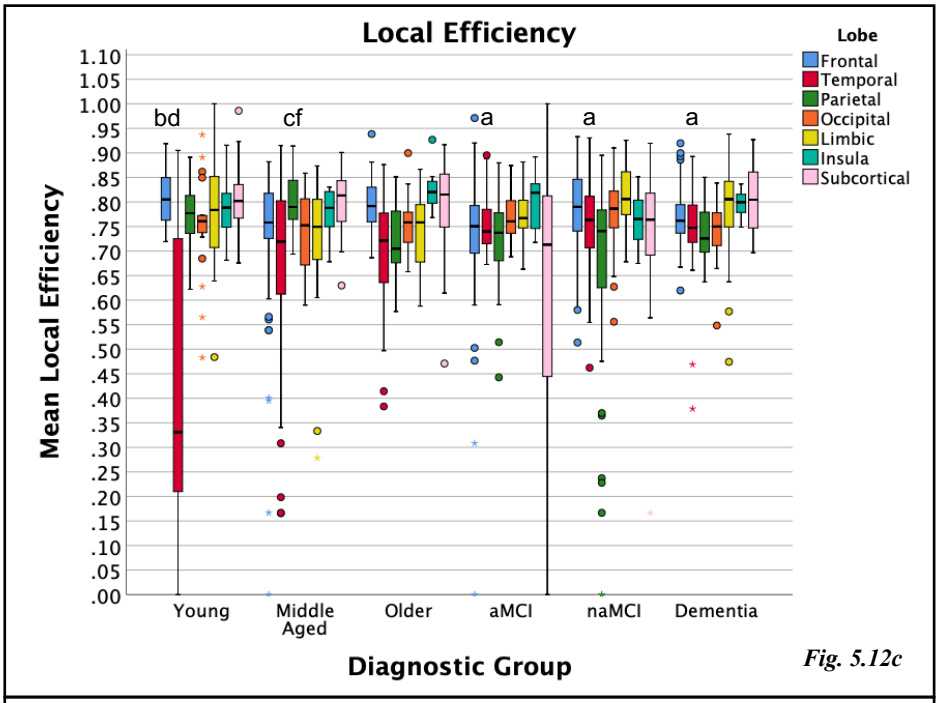


Fig. 5.12c

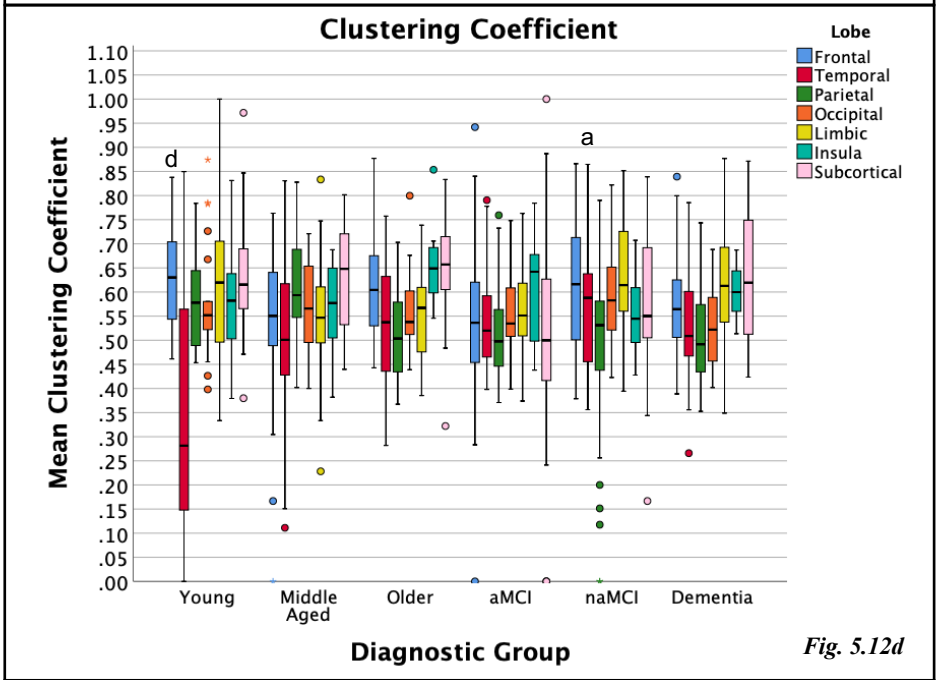


Fig. 5.12d

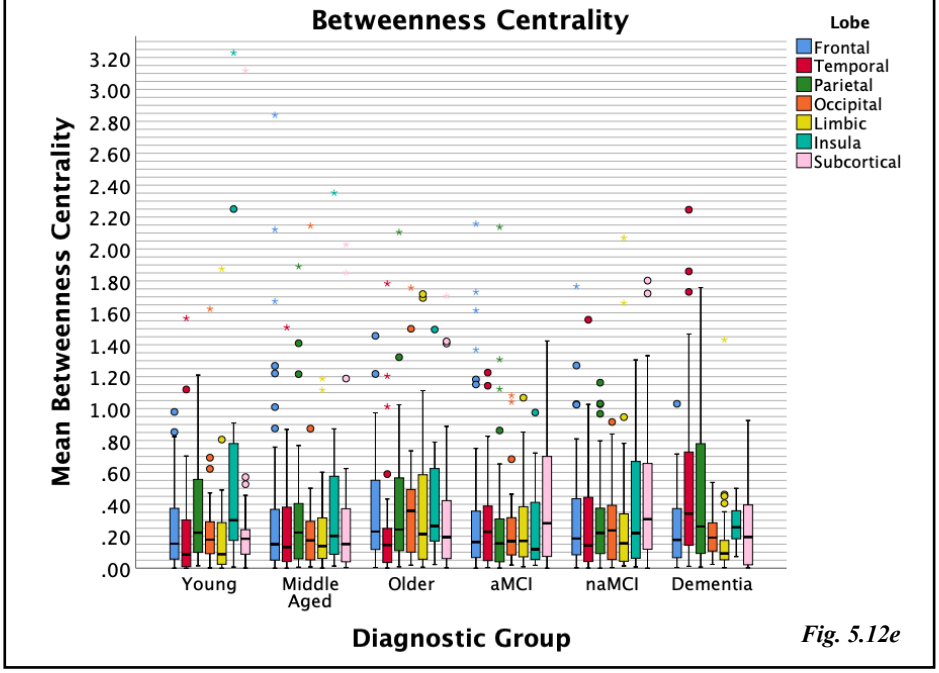


Fig. 5.12e

Figure 5.12. *Box plots showing medians and interquartile ranges of the network parameters calculate for each cortical lobe across groups. Significant differences corrected for multiple comparisons using a Bonferroni correction ($p < .000033$) are highlighted as:*

[a] Significantly greater than young controls

[b] Significantly greater than middle aged controls

[c] Significantly greater than older controls

[d] Significantly greater than aMCI

[e] Significantly greater than MCI-na

[f] Significantly greater than dementia

Table 5.5

Table showing the median and interquartile range of network parameters for the brain regions in each participant group with significant differences calculated using non-parametric Mann Whitney U tests.

Lobe	Parameter	Young	Middle Aged	Older	aMCI	MCI-na	Dementia
Frontal Lobe	Degree	55.17 (38.33) *df*	47.92 (42.50)	61.92 (45.63) *bdef*	33.75 (43.17)	53.00 (51.63)	44.33 (36.13)
	Betweenness Centrality	0.15 (0.32)	0.15 (0.32)	0.23 (0.43) *abdf*	0.16 (0.3)	0.19 (0.35)	0.18 (0.32)
	Clustering Coefficient	0.63 (0.16) ***bdf***	0.55 (0.16)	0.60 (0.15) *bdf*	0.54 (0.17)	0.62 (0.21) *bd*	0.56 (0.12)
	Local Efficiency	0.81 (0.09) ***bdf***	0.76 (0.09)	0.79 (0.07) *bdf*	0.75 (0.1)	0.79 (0.11) *bd*	0.76 (0.06)
	Global Efficiency	0.54 (0.1)	0.54 (0.12)	0.57 (0.12) *def*	0.51 (0.14)	0.55 (0.15)	0.53 (0.11)
Temporal Lobe	Degree	6.75 (15.25)	18.75 (37.04) *a*	22.83 (23.88) ***a***	54.67 (37.08) ***abce***	39.75 (35.13) ***a****bc*	50.75 (31.00) ***a****bc*
	Betweenness Centrality	0.09 (0.3)	0.13 (0.35)	0.15 (0.21)	0.23 (0.35)	0.14 (0.42)	0.34 (0.60) *abcde*
	Clustering Coefficient	0.28 (0.43)	0.50 (0.19) *a*	0.54 (0.20) *a*	0.52 (0.13) *a*	0.59 (0.19) ***a***	0.51 (0.14) *a*
	Local Efficiency	0.33 (0.53)	0.72 (0.19) *a*	0.72 (0.15) *a*	0.74 (0.07) ***a****c*	0.76 (0.11) ***a****bc*	0.75 (0.08) ***a***
	Global Efficiency	0.31 (0.19)	0.45 (0.15) ***a***	0.45 (0.12) ***a***	0.56 (0.10) ***abce***	0.51 (0.11) ***a****bc*	0.56 (0.08) ***a****bce*
Parietal Lobe	Degree	59.08 (35.96) *cdef*	63.58 (36.63) *ac****d****ef*	34.42 (38.17)	32.67 (22.50)	22.33 (48.63)	37.67 (36.83) *e*
	Betweenness Centrality	0.22 (0.48)	0.22 (0.36)	0.24 (0.48)	0.16 (0.27)	0.22 (0.29)	0.26 (0.70) *d*
	Clustering Coefficient	0.58 (0.16) *cdef*	0.59 (0.15) *cdef*	0.50 (0.15)	0.50 (0.12)	0.53 (0.15)	0.49 (0.14)
	Local Efficiency	0.78 (0.08) *cdef*	0.79 (0.08) ***c****d****e****f***	0.70 (0.11)	0.74 (0.10)	0.74 (0.17)	0.73 (0.09)
	Global Efficiency	0.56 (0.10) *cde*	0.59 (0.09) ***c****d****e****f***	0.49 (0.14)	0.50 (0.08) *e*	0.45 (0.16)	0.52 (0.11) *e*
Occipital Lobe	Degree	32.17 (38.54)	30.17 (38.00)	49.92 (25.75) *bf*	54.58 (32.29) *f*	38.83 (31.58)	31.75 (16.75)
	Betweenness Centrality	0.18 (0.22)	0.17 (0.25)	0.36 (0.41)	0.17 (0.25)	0.24 (0.35)	0.19 (0.19)
	Clustering Coefficient	0.55 (0.09)	0.57 (0.16)	0.54 (0.10)	0.53 (0.11)	0.58 (0.14)	0.52 (0.14)
	Local Efficiency	0.76 (0.04)	0.75 (0.14)	0.76 (0.06)	0.76 (0.07)	0.79 (0.08) *f*	0.75 (0.07)
	Global Efficiency	0.49 (0.13)	0.49 (0.12)	0.54 (0.08) *af*	0.57 (0.09) *abf*	0.51 (0.09)	0.49 (0.06)
Limbic Lobe	Degree	33.08 (34.92)	26.08 (38.67)	21.83 (40.08)	52.00 (26.38) *abc****f***	44.92 (24.25) *abcf*	21.17 (20.58)
	Betweenness Centrality	0.09 (0.26)	0.14 (0.26)	0.21 (0.54) *af*	0.17 (0.32)	0.16 (0.31)	0.09 (0.13)
	Clustering Coefficient	0.62 (0.21)	0.55 (0.12)	0.57 (0.14)	0.55 (0.11) *f*	0.61 (0.17) *bcd*	0.61 (0.16) *bc*
	Local Efficiency	0.78 (0.15)	0.75 (0.13)	0.76 (0.12)	0.77 (0.06)	0.81 (0.09) *bcd*	0.81 (0.10) *bc*
	Global Efficiency	0.49 (0.11)	0.47 (0.12)	0.45 (0.17)	0.56 (0.07) ***abcef***	0.52 (0.08) *acf*	0.44 (0.11)

Table 5.5 Cont.

Lobe	Parameter	Young	Middle Aged	Older	aMCI	MCI-na	Dementia
Insula Lobe	**Degree**	61.58 (36.67) *d*	54.42 (45.04)	68.25 (14.08) *d*	32.17 (32.17)	57.25 (50.75)	62.75 (21.08) *d*
	Betweenness Centrality	0.30 (0.67)	0.20 (0.63)	0.26 (0.48)	0.12 (0.46)	0.22 (0.74)	0.26 (0.19)
	Clustering Coefficient	0.58 (0.15)	0.58 (0.17)	0.65 (0.10) *be*	0.64 (0.19)	0.54 (0.13)	0.60 (0.09)
	Local Efficiency	0.79 (0.07)	0.79 (0.08)	0.82 (0.05) *be*	0.82 (0.10)	0.77 (0.09)	0.80 (0.04)
	Global Efficiency	0.57 (0.09) d	0.56 (0.13)	0.59 (0.04)	0.50 (0.10)	0.56 (0.13)	0.59 (0.06) *d*
Subcortical Regions	**Degree**	45.25 (24.29) *bcd*	18.17 (19.04)	24.67 (35.08)	12.83 (38.04)	35.00 (36.58) *d*	36.58 (36.50) *bcd*
	Betweenness Centrality	0.18 (0.16)	0.15 (0.34)	0.19 (0.37)	0.28 (0.65)	0.31 (0.56)	0.20 (0.38)
	Clustering Coefficient	0.62 (0.14) *de*	0.65 (0.20) *d*	0.66 (0.11) *de*	0.50 (0.23)	0.55 (0.19)	0.62 (0.24) *d*
	Local Efficiency	0.80 (0.07) *de*	0.81 (0.09) *de*	0.82 (0.12) *d*	0.71 (0.40)	0.76 (0.13)	0.80 (0.12) *de*
	Global Efficiency	0.53 (0.09) *bcd*	0.46 (0.11)	0.46 (0.20)	0.42 (0.22)	0.50 (0.13)	0.52 (0.11) *bcd*

Significant differences (p <.05) are indicated as: [a] Significantly greater than young controls, [b] Significantly greater than middle aged controls, [c] Significantly greater than older controls, [d] Significantly greater than aMCI, [e] Significantly greater than MCI-na, [f] Significantly greater than dementia. Letters in bold indicate significance when corrected for multiple comparisons using a Bonferroni correction (p < .000033)

5.2.3.4. Network Metrics of Individual Brain Regions and Hubs

Finally, network metrics from individual brain regions were assessed to determine the specific areas driving differences between groups in terms of lobe related network parameters. In this case, statistical testing was impossible in many cases due to the low number of nodes that comprised individual areas and so the results presented in ***Figures 5.13-5.17*** are purely observational and included only for the purposes of discussion in light of the findings presented in section *5.2.3.2*. ***Figures 5.13-5.17*** show the mean network parameters of a range of brain areas listed in **Table 5.4**.

The number and location of hub regions identified varied substantially between groups. Young controls had the lowest number of network hubs while aMCI patients had the highest. A full list of hub regions for each group can be found in **Table 5.6**.

Table 5.6

Table showing hub regions identified in each participant group reflecting nodes with a degree and betweenness centrality more than 1.5 standard deviations above the group mean.

	Region	Position of Node	Brodmann Area	Hemisphere
Dementia	Superior Temporal Gyrus	Rostral	22	L
	Superior Temporal Gyrus	Primary Auditory Cortex	41	L
	Inferior Temporal Gyrus	Caudoventral	20	R
	Inferior Parietal Lobule	Caudal	40	L
	Inferior Parietal Lobule	Rostroventral	39	L
	Inferior Parietal Lobule	Rostroventral	40	L
	Inferior Parietal Lobule	Rostroventral	40	R
	Precuneus	Dorsomedial Parietooccipital Sulcus	7	L
	Precuneus	Dorsomedial Parietooccipital Sulcus	7	R
	Cingulate Gyrus	Caudal Posterior	23	L
aMCI	Middle Frontal Gyrus	Ventral	9/46	L
	Orbitofrontal Gyrus	Lateral	11	R
	Orbitofrontal Gyrus	Medial	11	L
	Orbitofrontal Gyrus	Ventromedial	13	L
	Orbitofrontal Gyrus	Ventromedial	13	R
	Precentral Gyrus	Caudal Ventrolateral	6	L
	Superior Temporal Gyrus	Lateral	38	R
	Middle Temporal Gyrus	Dorsolateral	37	R
	Inferior Parietal Lobule	Caudal	39	L
	Inferior Parietal Lobule	Caudal	40	R
	Cuneus	Caudal	17	R
	Middle Occipital Gyrus	Lateral	19	L
	Nucleus Accumbens			R
MCI-na	Middle Frontal Gyrus	Dorsal	9/46	L
	Inferior Frontal Gyrus	Rostral	45	L
	Precentral Gyrus		4	L
	Superior Temporal Gyrus	Rostral	22	L
	Middle Temporal Gyrus	Caudal	21	R
	Postcentral Gyrus		1/2/3	R
	Insula	Dorsal Agranular Insula	13	R
	Insula	Dorsal Granular Insula	13	L
	Insula	Dorsal Dysgranular Insula	13	R
	Cingulate Gyrus	Caudal Posterior	23	R
	Caudate	Ventral		L
	Thalamus	Occipital Thalamus		R
Older	Superior Frontal Gyrus	Medial	10	L
	Middle Frontal Gyrus	Dorsal	9/46	R
	Orbitofrontal Gyrus	Lateral	11	R
	Orbitofrontal Gyrus	Ventromedial	13	R
	Superior Temporal Gyrus	Caudal	22	L
	Middle Temporal Gyrus	Anterior Superior Temporal Sulcus	21	R
	Inferior Parietal Lobule	Rostroventral	39	R
	Precuneus	Dorsomedial Parietooccipital Sulcus	7	R
	Cuneus	Ventromedial Parietooccipital Sulcus	17	R
Middle Aged	Inferior Frontal Gyrus	Ventral	44	R
	Orbitofrontal Gyrus	Orbital	12/47	L
	Orbitofrontal Gyrus	Lateral	11	L
	Orbitofrontal Gyrus	Lateral	12	R
	Precentral Gyrus		4	R
	Precentral Gyrus	Caudal Ventrolateral	6	R
	Inferior Parietal Lobule	Caudal	40	L
	Inferior Parietal Lobule	Caudal	41	R
	Inferior Parietal Lobule	Rostroventral	39	L
	Insula	Dorsal Dysgranular Insula	13	L
	Thalamus	Rostral Temporal Thalamus		R
Young	Superior Frontal Gyrus	Medial	9	L
	Superior Parietal Lobule	Rostral	7	L
	Postcentral Gyrus		2	R
	Insula	Hypergranular Insula		L
	Insula	Dorsal Granular Insula		L
	Insula	Dorsal Granular Insula		R
	Occipital Gyrus	Middle Temporal Visual Area (V5)	19	L
	Putamen	Dorsolateral		L

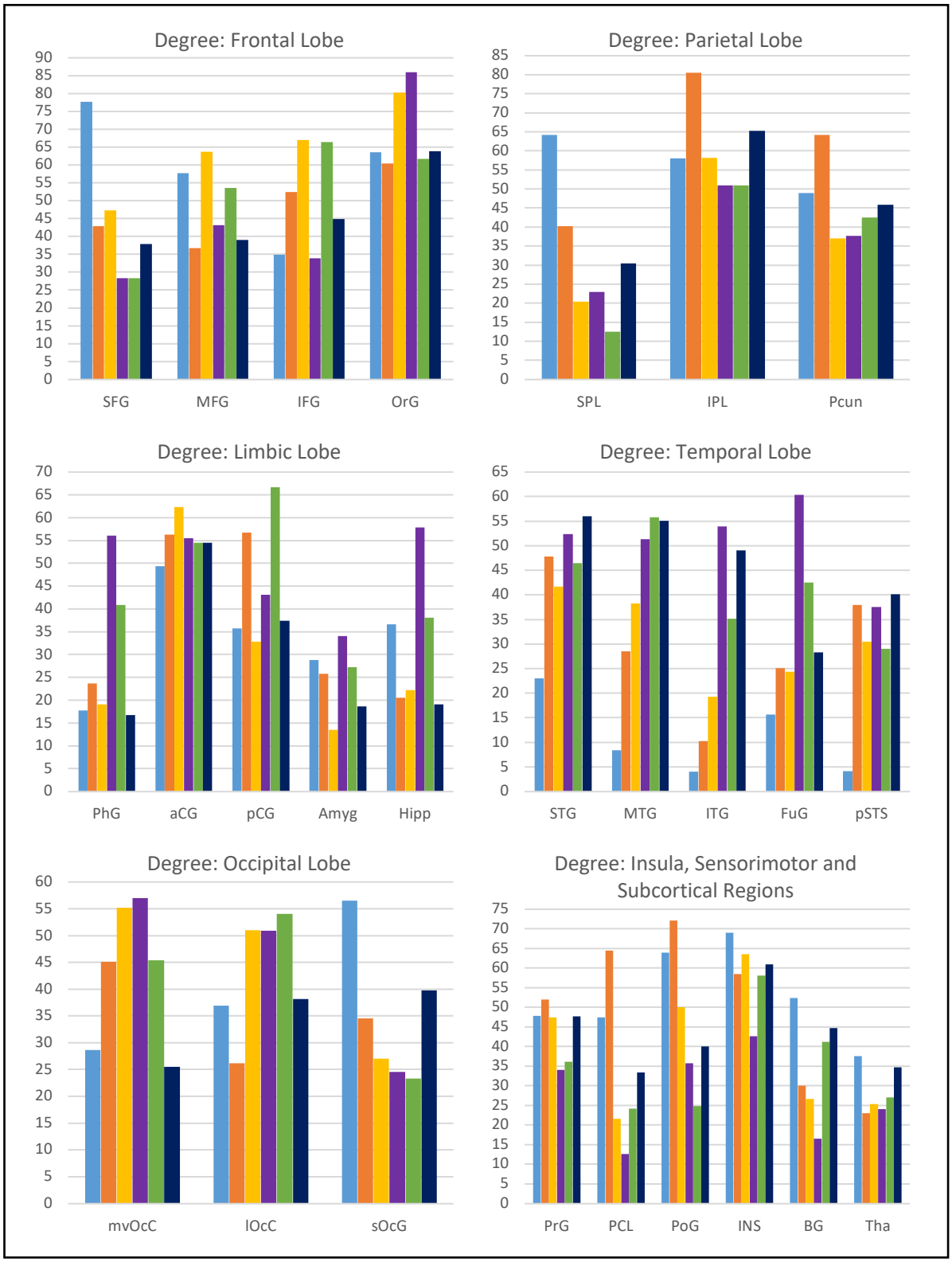


Figure 5.13. *Bar charts showing mean degree for nodes in a range of brain areas labelled as: SFG, superior frontal gyrus; MFG, medial frontal gyrus; IFG, inferior frontal gyrus; OrG, orbital gyrus; SPL, superior parietal lobule; IPL inferior parietal lobule; Pcun, precuneus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; FuG, fusiform gyrus; pSTS, posterior superior temporal sulcus; PhG, parahippocampal gyrus; aCG, anterior cingulate gyrus; pCG, posterior cingulate gyrus; Amyg, amygdala; Hipp, hippocampus; mvOcC, medioventral occipital cortex; lOcC, lateral occipital cortex; sOcG, superior occipital gyrus; PrG, precentral gyrus; PCL, paracentral lobule, PoG, postcentral gyrus; INS, insula cortex; BG, basal ganglia, Tha, thalamus*

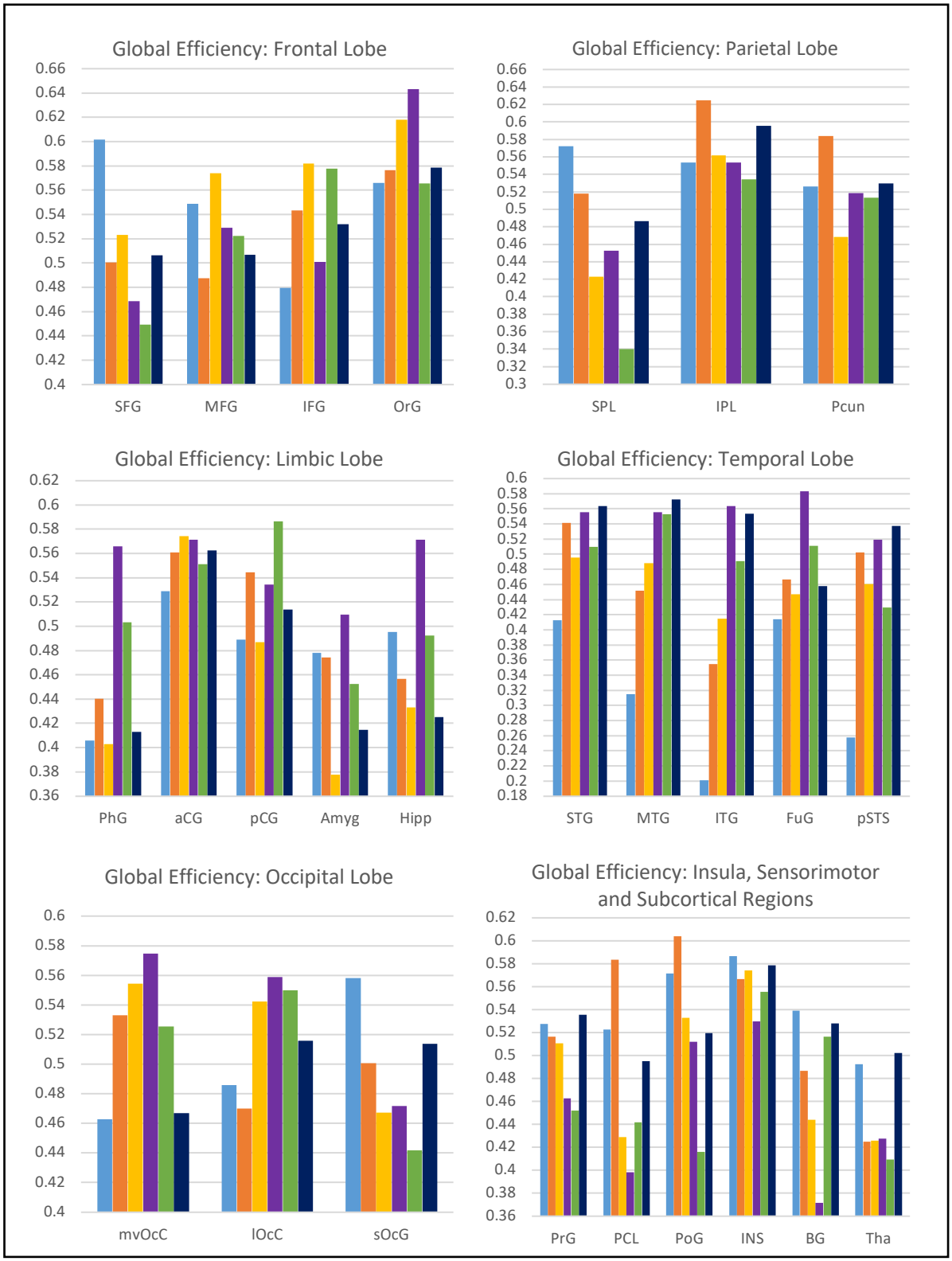


Figure 5.14. *Bar charts showing mean global efficiency for nodes in a range of brain areas labelled as: SFG, superior frontal gyrus; MFG, medial frontal gyrus; IFG, inferior frontal gyrus; OrG, orbital gyrus; SPL, superior parietal lobule; IPL inferior parietal lobule; Pcun, precuneus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; FuG, fusiform gyrus; pSTS, posterior superior temporal sulcus; PhG, parahippocampal gyrus; aCG, anterior cingulate gyrus; pCG, posterior cingulate gyrus; Amyg, amygdala; Hipp, hippocampus; mvOcC, medioventral occipital cortex; lOcC, lateral occipital cortex; sOcG, superior occipital gyrus; PrG, precentral gyrus; PCL, paracentral lobule, PoG, postcentral gyrus; INS, insula cortex; BG, basal ganglia, Tha, thalamus*

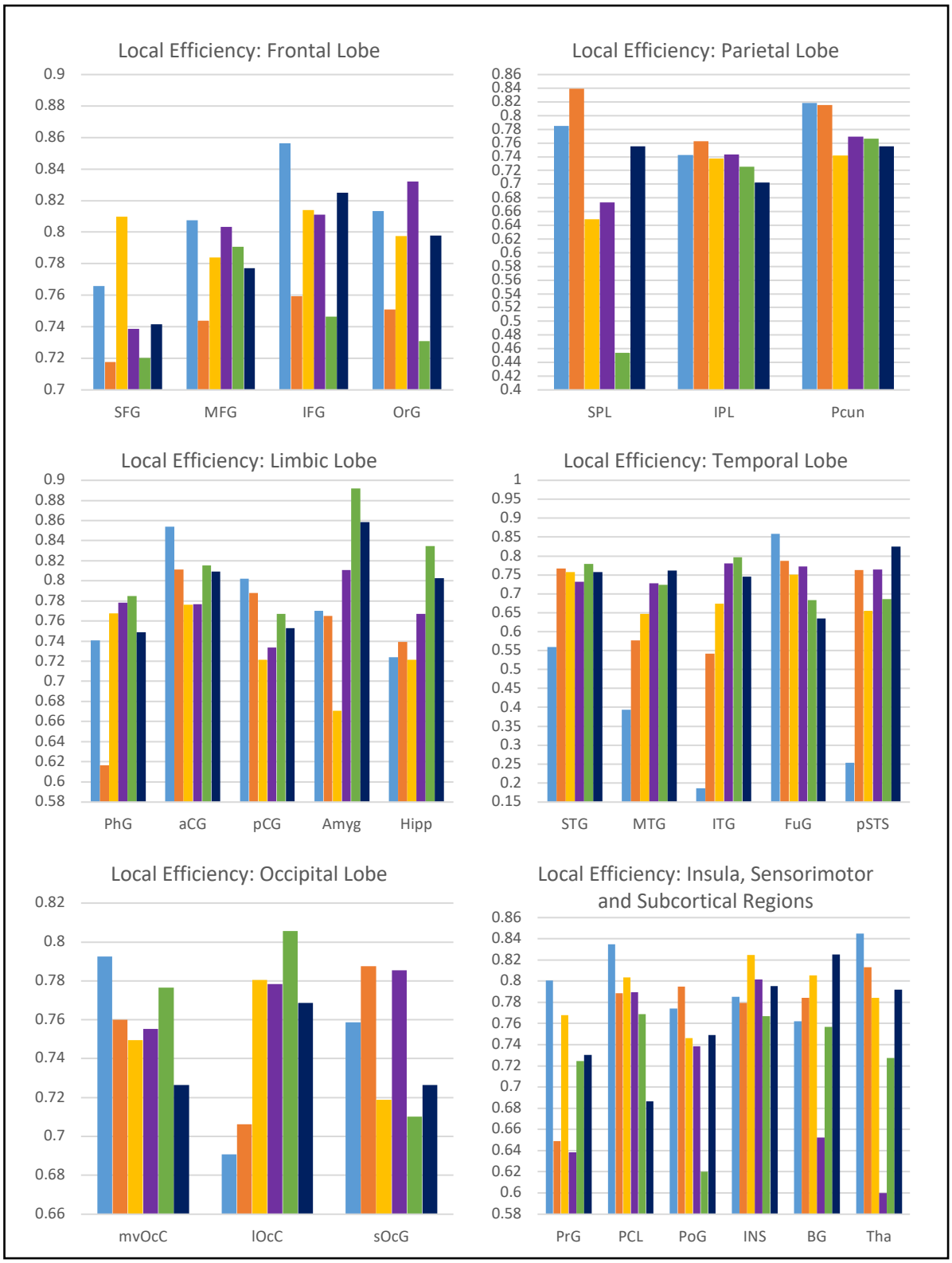


Figure 5.15. *Bar charts showing mean local efficiency for nodes in a range of brain areas labelled as: SFG, superior frontal gyrus; MFG, medial frontal gyrus; IFG, inferior frontal gyrus; OrG, orbital gyrus; SPL, superior parietal lobule; IPL inferior parietal lobule; Pcun, precuneus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; FuG, fusiform gyrus; pSTS, posterior superior temporal sulcus; PhG, parahippocampal gyrus; aCG, anterior cingulate gyrus; pCG, posterior cingulate gyrus; Amyg, amygdala; Hipp, hippocampus; mvOcC, medioventral occipital cortex; lOcC, lateral occipital cortex; sOcG, superior occipital gyrus; PrG, precentral gyrus; PCL, paracentral lobule, PoG, postcentral gyrus; INS, insula cortex; BG, basal ganglia, Tha, thalamus*

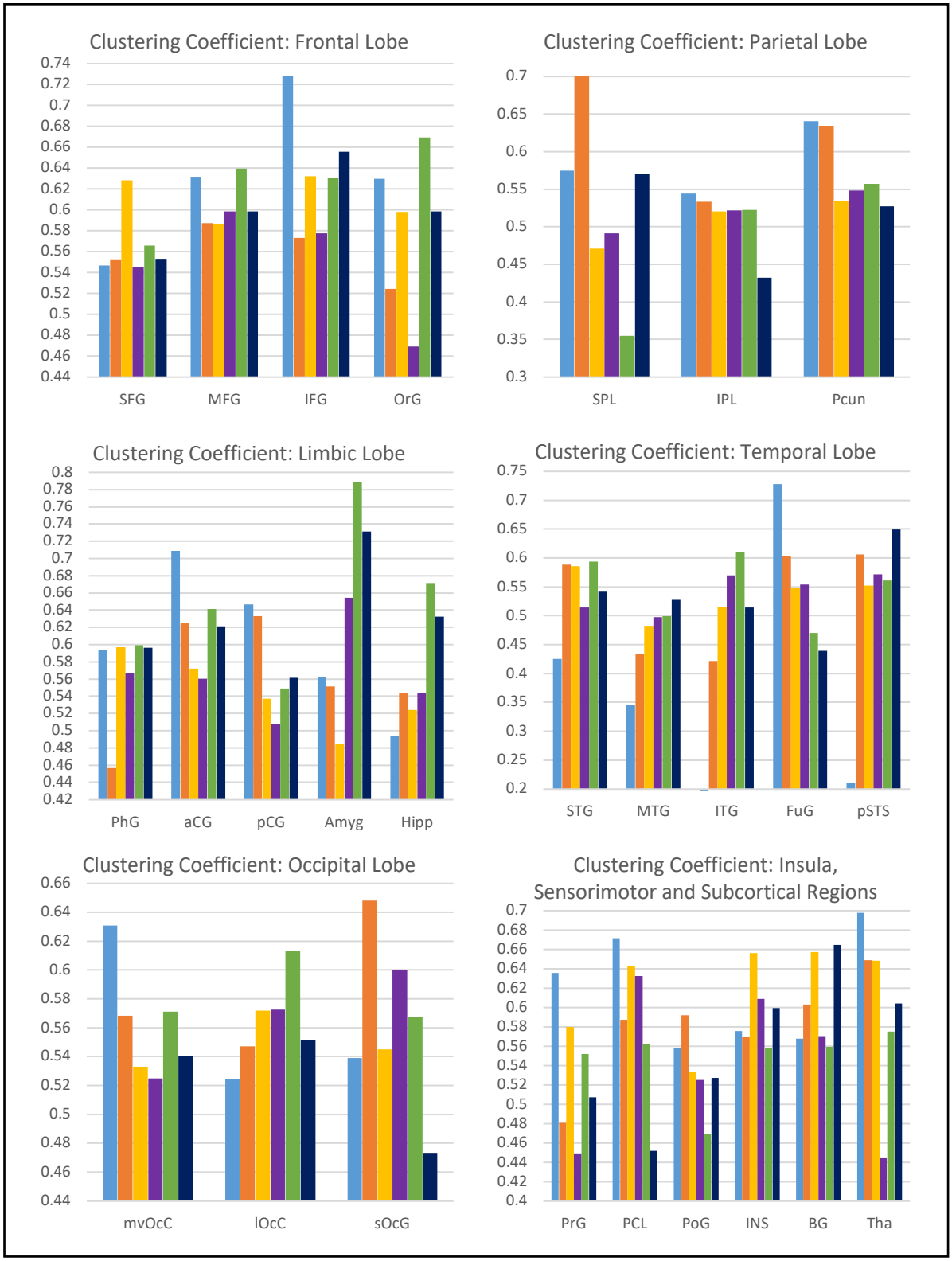


Figure 5.16. *Bar charts showing mean clustering coefficient for nodes in a range of brain areas labelled as: SFG, superior frontal gyrus; MFG, medial frontal gyrus; IFG, inferior frontal gyrus; OrG, orbital gyrus; SPL, superior parietal lobule; IPL inferior parietal lobule; Pcun, precuneus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; FuG, fusiform gyrus; pSTS, posterior superior temporal sulcus; PhG, parahippocampal gyrus; aCG, anterior cingulate gyrus; pCG, posterior cingulate gyrus; Amyg, amygdala; Hipp, hippocampus; mvOcC, medioventral occipital cortex; lOcC, lateral occipital cortex; sOcG, superior occipital gyrus; PrG, precentral gyrus; PCL, paracentral lobule, PoG, postcentral gyrus; INS, insula cortex; BG, basal ganglia, Tha, thalamus*

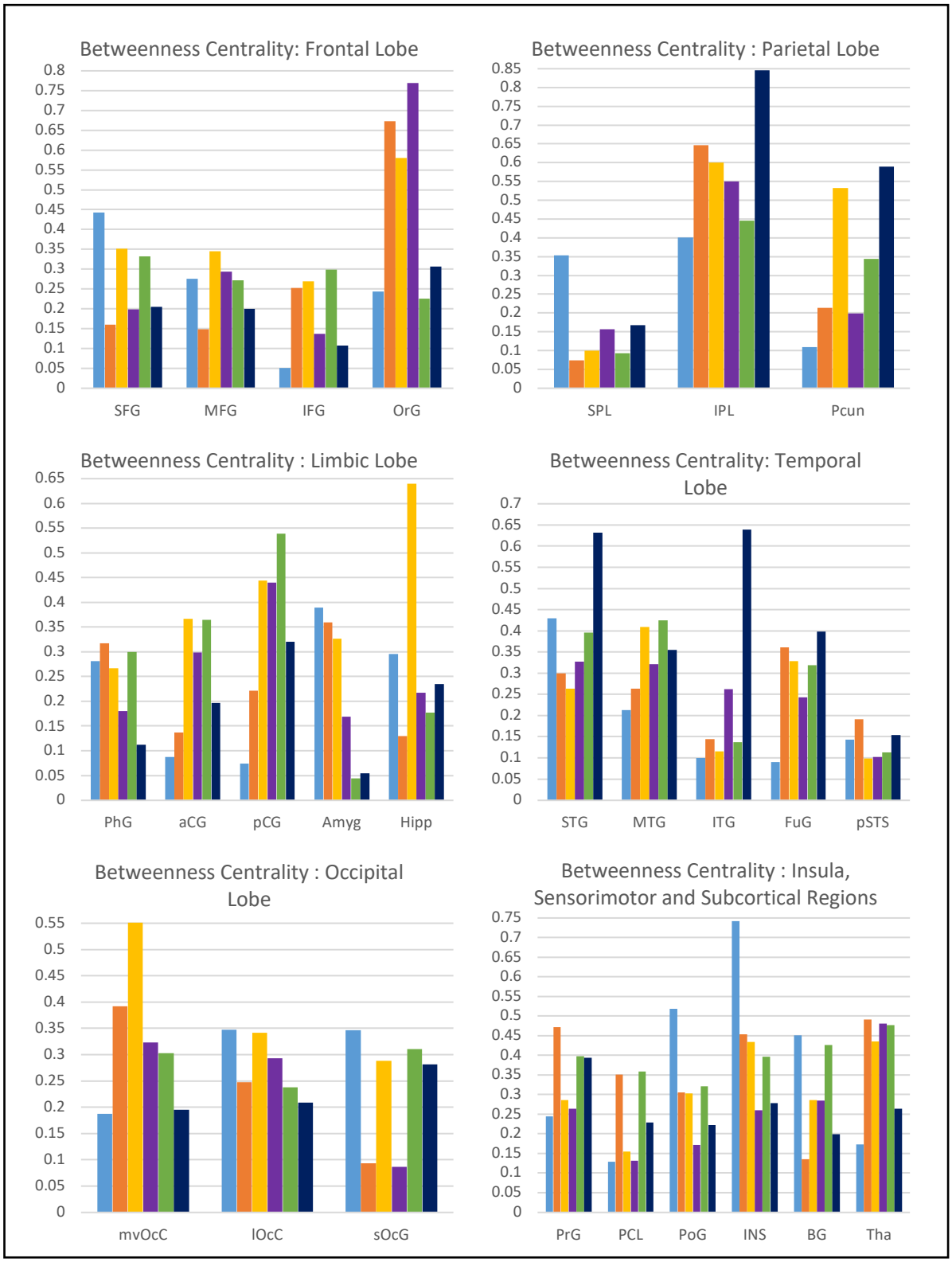


Figure 5.17. *Bar charts showing mean betweenness centrality for nodes in a range of brain areas labelled as: SFG, superior frontal gyrus; MFG, medial frontal gyrus; IFG, inferior frontal gyrus; OrG, orbital gyrus; SPL, superior parietal lobule; IPL inferior parietal lobule; Pcun, precuneus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; FuG, fusiform gyrus; pSTS, posterior superior temporal sulcus; PhG, parahippocampal gyrus; aCG, anterior cingulate gyrus; pCG, posterior cingulate gyrus; Amyg, amygdala; Hipp, hippocampus; mvOcC, medioventral occipital cortex; lOcC, lateral occipital cortex; sOcG, superior occipital gyrus; PrG, precentral gyrus; PCL, paracentral lobule, PoG, postcentral gyrus; INS, insula cortex; BG, basal ganglia, Tha, thalamus*

5.2.4. Discussion

In light of previous research demonstrating significant alterations in structural network composition among AD patients in varying disease stages (He, Chen & Evans, 2008; Yao *et al*., 2010; Lo *et al*., 2010; Bai *et al*., 2012; Li *et al*., 2012; Tijms *et al*., 2013a, 2013b; Phillips *et al*., 2015; Fischer *et al*., 2015; Pereira *et al*., 2018), the present study sought to investigate the topology of structural brain networks across the stages of ageing and AD to elucidate potential neural correlates underlying cognitive network differences revealed by the previous experiment.

Significant differences were demonstrated between groups, particularly when comparing patients and controls, in a number of network parameters both calculated on whole-brain networks and when segregated by lobe. These findings and their relation to the current literature on the subject, as well as how they map on to the results of the previous cognitive study, will be discussed in the following sections.

5.2.4.1. AD Related Alterations in Network Segregation

Firstly, the results of the present experiment, in terms of whole-brain network parameters, are in line with previous studies that have demonstrated significant alterations to the small-world properties of structural brain networks in even the earliest stages of AD (Li *et al*., 2012; Tijms *et al*., 2013b; Zhou & Lui, 2013; Tijms *et al*., 2014; Phillips *et al*., 2015; Pereira *et al*., 2016). Specifically, the results presented here, revealed significantly lower clustering coefficients, a measure of network segregation, among aMCI patients when compared with both younger and older controls. Such a finding has been reflected by earlier structural studies demonstrating similar differences in network segregation among MCI patients, relative to controls, in terms of both clustering coefficients and other similar segregation measures such as local efficiency (Li *et al*., 2012; Zhou & Lui, 2013; Pereira *et al*., 2016). These findings were demonstrated not only in the primary analysis but were further validated by *post-hoc* analysis that took into account only those edges that remained when applying a Bonferroni correction and were reflected, although to a much lesser extent, by differences in local efficiency. Furthermore, these results are in line with previous studies of AD dementia patients showing similarly low clustering coefficients compared with controls (Li *et al*., 2012; Tijms *et al*., 2013b; Tijms *et al*., 2014; Phillips *et al*., 2015; Pereira *et al*., 2016). Such negative alterations in the clustering of structural networks have even been

shown to have predictive value for further cognitive decline in MCI and the progression of prodromal disease to AD dementia (Li *et al*., 2012; Pereira *et al*., 2016; Tjims *et al*., 2018; Dicks *et al*., 2018). They have further been found to relate to preclinical manifestations of AD including lower levels of cerebrospinal fluid Aβ42 (Tijms *et al*., 2016), higher positron emission tomography (PET) amyloid burden (Ten Kate *et al*., 2018) and steeper rates of change among individuals with subjective cognitive decline (SCD, Verfaillie *et al*., 2018). The findings presented here, therefore, support the notion that AD type network dysfunction may not only be identifiable via methods of graph theory at a very early stage of disease, but may provide further means to assess the likelihood of future declines.

It should be noted however, that the direction of alterations in graph theory parameters observed among AD patients, when compared with controls, has proved somewhat inconsistent, with some studies reporting increased clustering in structural networks among AD dementia and preclinical cohorts (He, Chen & Evans, 2008; Yao *et al*., 2010; Pereira *et al*., 2018). It is unclear as to the exact causes underlying these discrepancies in the literature, however, some studies have indicated that certain methodological differences in network formation, node selection and imaging modality between studies, as well as the impact of sample size and patient characteristics pertinent to any neuroimaging analysis, may have significant impacts on the study outcome (Wang *et al*., 2009; Zalesky *et al*., 2010; Fornito, Zalesky & Breakspear, 2013; Tijms *et al*., 2013a; Phillips *et al*., 2015). Despite this uncertainty, findings of studies indicating longitudinal declines in clustering coefficients in MCI patients and the utility of such declines in predicting progression to dementia (Li *et al*., 2012; Pereira *et al*., 2016; Tjims *et al*., 2018; Dicks *et al*., 2018) suggest that decreases in clustering coefficients are likely indicative of AD related network disruption characteristic of, at least, this prodromal stage of disease. Evidence from functional studies has further suggested that network alterations in AD may not progress between disease stages in a linear manner but rather show initial substantial decreases in network segregation, in prodromal disease, before showing a gradual re-increase in segregation measures as disease progresses to dementia (Seo *et al*., 2013). These findings were reflected in the present study, with dementia patients having significantly higher local efficiencies and clustering coefficients than the aMCI group, while showing no differences in these parameters when compared with the healthy controls. Seo *et al*., (2013) explained these non-linear findings in their functional study as a reflection of the more discrete, localised hypometabolisms in MCI that contrast with the more diffuse, widespread patterns of hypometabolism present in the dementia stage of disease. Given the particular dependence of structural network segregation

on significant correlations between anatomically proximal regions or clusters, lower clustering coefficients in the structural networks of aMCI patients, compared with both healthy controls and the dementia group in this experiment, may similarly reflect early patterns of focal atrophy within discrete brain regions, resulting in reduced regional correlation and subsequent disruption to the connectivity of sub-network clusters. In later disease stages, where atrophy may be more diffuse and regional volumes more homogenous across individuals than in the more heterogenous stage of MCI, where patients may be at significantly variable stages of cortical degradation, correlations between anatomically proximal regions are likely to show a gradual increase.

Modularity among AD patients also showed significant alterations. As in the previous cognitive study, young controls demonstrated the highest levels of network modularity, with the graphs of this group, across thresholds and within *post-hoc* analyses, revealing a high number of sub-network modules, indicating a low number of between module connections with high numbers of within-module connections. Dementia patients, however, across thresholds, tended to show the lowest number of sub-network modules, being significantly lower than young controls, in line with the findings of both the cognitive study and previous functional and structural brain network studies, suggesting that reductions in modularity and network segregation are a feature typical of AD pathology (de Haan *et al*., 2012; Brier *et al*., 2014; Jalili, 2017; Contreras *et al*., 2019). However, no significant differences between older controls and either MCI or dementia patients were present in terms of modularity, a finding that will be discussed in relation to age related network alterations in a later section.

5.2.4.2. AD Related Alterations in Network Integration

A further robust finding that was validated by both the primary and *post-hoc* analyses, was the finding of significantly higher levels of global efficiency in both the aMCI and dementia groups when compared with controls. As in the case of decreased clustering coefficients, increases in global efficiency in AD patients, which may also be measured by a decrease in characteristic path length, have previously been demonstrated by both structural and functional imaging studies (Stam *et al*., 2009; Sanz-Arigita *et al*., 2010; Tijms *et al*., 2013b; Tijms *et al*., 2014). In correspondence with differences in network segregation however, such differences between AD patients and controls in terms of this measure of network integration has proved to be a contentious issue, with many studies demonstrating significant increases in characteristic path length and therefore decreases in global efficiency

in AD and MCI (He, Chen & Evans, 2008; Yao *et al*., 2010; Bai *et al*., 2012; Zhao *et al*., 2012; Daianu *et al*., 2013; Wang *et al*., 2013; Pereira *et al*., 2016; Franciotti *et al*., 2019; Dai *et al*., 2019). As with network segregation, such discrepancies in the literature in terms of global efficiency are unlikely to have a simple explanation. However, methodological differences in network formation resulting in differing graph densities, have been found to alter significantly the directionality of results in both clustering coefficients and path length when comparing AD patients with controls (Phillips *et al*., 2015). Studies have suggested that higher global efficiencies in structural networks among MCI patients compared with both controls and dementia patients, as was demonstrated in the present study, may reflect a compensatory response in the prodromal stages of disease that is gradually lost with increasing disease severity (Zhou & Lui, 2013). In line with the results relating to clustering coefficient, significantly higher global efficiencies in the aMCI group were apparent in comparison to both younger and older controls as well as the MCI-na group. Similarly, dementia patients also demonstrated higher global efficiencies than younger and older controls, but these were slightly lower than in the aMCI group and so did not reach significance when compared with MCI-na patients. *Post-hoc* analyses using a single 8% sparsity revealed that, at this edge density, aMCI patients also presented with significantly higher global efficiencies than even the AD dementia group. These findings are, therefore, in line with previous suggestions that alterations in the small-world properties of neural networks in AD do not follow a linear progression throughout the disease spectrum, but rather present with more extreme changes in the initial stages, possibly relating to more focal alterations in network connectivity, individual heterogeneity and compensatory mechanisms, all of which may be gradually ameliorated by the later stages of disease (Seo *et al*., 2013; Zhou & Lui, 2013).

Similarly, alterations in betweenness centrality between disease stages in relation to healthy controls were non-linear, with aMCI patients demonstrating significantly lower levels of betweenness centrality than the older control group in the primary analysis and dementia patients instead demonstrating similar levels to older controls. Furthermore, primary analyses revealed that both the dementia patients and the older control group had significantly higher levels of betweenness centrality than both the younger control groups. Although *post-hoc* analyses only demonstrated significant differences in relation to the youngest control group, the original pattern of results remained the same. The lack of differences between older controls and dementia patients in terms of this measure, may reflect the previously demonstrated lack of discriminative power that this parameter has shown in identifying AD

when applied to both functional and structural neural networks (Peraza *et al*., 2019; Zhao *et al*., 2019). Despite studies indicating a reduction in the betweenness centrality in certain brain regions in AD (Seo *et al*., 2013), overall betweenness centrality may be unlikely to show disease related effects, particularly when edge density is kept constant across groups. This is particularly likely in the present study, where high global efficiencies in the dementia group, compared with healthy controls, suggest that disease related correlations between regional volumes can result in a well-integrated structural network. Instead, differences in this type of network integration are likely be reflected by alterations in regional hubs. Network hubs can be defined via a number of measures of centrality and are generally considered to represent nodes that provide highly strong contributions to the global network connectivity through the wealth or centrality of their connections to the wider network (van den Heuvel & Sporns, 2013). Studies have indicated that pathological change may disproportionately affect hub regions of the human connectome, due to the high metabolic demands and long-distance connections associated with these regions that are implied by their topological centrality (Buckner *et al*., 2009; Crossley *et al*., 2014). As such, findings from structural network analyses in AD and MCI, have revealed decreases in betweenness centrality among certain areas and increases in others, resulting in a shift in the location of network hubs in relation to healthy controls, as well as a loss in the overall number of hub regions in AD (He, Chen & Evans, 2008; Yao *et al*., 2010; Tijms *et al*., 2013a; Li *et al*., 2016b). In the present study, assessment of betweenness centrality showed that both aMCI and dementia patients demonstrated significantly lower levels of betweenness centralities in the frontal lobe than older healthy adults, although only at the uncorrected level, and dementia patients further demonstrated significantly lower betweenness centralities than healthy controls in limbic regions. In contrast, however, the dementia patients in this study presented with significantly higher betweenness centralities in temporal lobe regions than all other groups, again at the uncorrected level. Such findings are, therefore, in line with the notion that AD pathology may have a significant impact on the centrality of select hubs within frontal and MTL regions present in healthy structural networks (Buckner *et al*., 2009; van den Heuvel & Sporns, 2013), causing a shift in betweenness centrality to new regions within wider temporal lobes, not necessarily present in healthy controls. Furthermore, these findings suggest that the breakdown of betweenness centralities associated with healthy ageing, within areas such as the frontal lobes, may be an early effect of disease, while decline in betweenness centrality of AD related limbic regions may occur more gradually as disease progresses, being accompanied by gradual increases in lateral temporal lobe centrality. The loss of betweenness

centrality within frontal regions, particularly among AD dementia patients, is further reflective of similar losses in the betweenness centrality of executive functions, highlighted in these patients by the previous study.

Interestingly, despite showing intermediate betweenness centralities between healthy controls and AD dementia patients, global efficiency and average nodal degrees within the temporal and limbic lobes were highest in the aMCI group, with both parameters in these regions being significantly greater than those of all control groups, even when corrected for multiple comparisons in the case of the temporal lobes. Furthermore, each of these parameters within limbic regions were also significantly higher in aMCI than dementia patients, even with correction for multiple comparisons. Such alterations among aMCI patients in nodal degree, without the presence of significant alterations in betweenness centrality, may, in the case of limbic regions, reflect initially exacerbated correlations between areas of limbic cortex and the wider brain network that simply occur as a result of the relationship of these areas with disease severity in AD (Braak & Braak, 1991; Frisoni *et al*., 2010). As the biological nature of structural networks that are based upon covariance of regional cortical volumes remains a topic of debate (Phillips *et al*., 2015), it may be plausible that the results presented here demonstrate gradual AD related degradation of structural network hubs present within limbic regions (van den Heuvel & Sporns, 2013), evidenced by low betweenness centralities, while simultaneously demonstrating the propensity for these regions to exhibit high numbers of superficial connections in early AD, mediated by volumetric variance. Conversely, high nodal degrees within lateral temporal lobes among aMCI patients, in the presence of increasing betweenness centrality, two measures heavily related to hub formation (Hagmann *et al*., 2008; van den Heuvel & Sporns, 2013), may reflect the initial stages of hub alteration, from the frontal areas showing high betweenness centrality in healthy older adults, to the temporal regions demonstrating high betweenness centralities in the dementia stages of disease. Despite previous studies finding a decrease in betweenness centrality within temporal regions among AD patients (He, Chen & Evans, 2008; Yao *et al*., 2010), more recent studies have shown similar increases in betweenness centrality within temporal areas among MCI patients (Li *et al*., 2016b). Furthermore, the propensity for disease to affect central hubs (Buckner *et al*., 2009; Tijms *et al*., 2013a; Crossley *et al*., 2014), particularly within limbic regions in the case of AD, as demonstrated here and within earlier studies (Tijms *et al*., 2013b), could plausibly result in increased importance of less damaged areas of temporal lobe in the presence of significant limbic degradation.

In accordance with previously discussed findings in clustering coefficient and global efficiency, findings relating to centrality among AD patients remain a topic of contention. However, recent studies have demonstrated a utility of centrality measures in discriminating AD patients from controls and identifying the earliest signs of pathological alteration in this patient group, although betweenness centrality itself may be somewhat limited in this regard (Peraza *et al*., 2019; Zhao *et al*., 2019). Furthermore, the finding of the primary analysis that found significantly lower betweenness centrality among aMCI patients, compared with controls, while finding similarly high levels as controls within dementia patients, is supportive of a model of structural network alteration in AD that follows a U-shaped trajectory between the stages of disease severity, in which clustering coefficient, characteristic path length and betweenness centrality all decline in the early stages of disease, before being re-established in later stages, albeit with a significantly altered configuration than that of healthy older adults (Seo *et al*., 2013; Zhou & Lui, 2013).

In scrutinising the hub-like regions evident in each group, defined in this case as nodes presenting with a betweenness centrality and degree more than 1.5 SDs above the group mean, the results of the present study reflected those of previous studies finding a shift in the location of hub regions among dementia patients, compared with healthy older controls, despite both groups in this study showing a similar number of hubs overall (He, Chen & Evans, 2008; Yao *et al*., 2010; Tijms *et al*., 2013a; Li *et al*., 2016b). In particular, there was a total lack of hubs within frontal regions among dementia patients. In contrast with the healthy older group, who presented with hubs regions within the superior and middle frontal gyrus, as well as orbitofrontal areas, hubs identified among dementia patients were restricted to AD related areas such as the superior and inferior temporal gyri, as well as bilateral inferior parietal lobules, and medial parietal regions including the precuneus and posterior cingulate cortex (PCC). Previous studies of brain networks within healthy individuals, using both structural and functional imaging methods, including those based on volumetric covariance as in the present study, have consistently identified distinct hub regions within association cortices that largely correspond with the components of the default mode network (DMN) (Hagmann *et al*., 2008; Buckner *et al*., 2009; Gong *et al*., 2009; Zhu *et al*., 2012; van den Heuvel & Sporns, 2013; Cao *et al*., 2014). Accordingly, the network of the healthy older controls in the current study not only included hubs within medial areas of the prefrontal cortex, but also within the precuneus, inferior parietal lobules and lateral temporal regions, all regions associated with the anatomy of the DMN (Raichle *et al*., 2001; Buckner *et al*., 2008; Buckner & DiNicola, 2019). Similarly, the hub regions identified within the

dementia group are representative of the posterior DMN (Buckner *et al*., 2008), known to be particularly affected by AD type pathology, even in the earliest stages of disease (Minoshima *et al*., 1997; Kogure *et al*., 2000; Bradley *et al*., 2002; Greicius *et al*., 2004; Bai *et al*., 2011; Damoiseaux *et al*., 2012). Alterations to DMN function are known to represent a core aspect of neurological change in both healthy ageing and disease (Greicius *et al*., 2004; Damoiseaux *et al*., 2008; Damoiseaux, 2017). The finding that hub regions relating to volumetric covariance are largely located within the regions of this network in both groups, therefore, suggests that, in both healthy ageing and AD, the functional alterations seen within the DMN may reflect underlying anatomical network alterations that are highly influential on the integrity of the wider cortical structure. This interpretation is supported by the findings of previous functional MRI (fMRI) and diffusion tensor imaging (DTI) studies that have shown significant overlap between functional and structural alterations in DMN connectivity, among both healthy ageing and AD populations (Greicius *et al*., 2004; Andrews-Hanna *et al*., 2007; Zhang *et al*., 2007; Bai *et al*., 2008; Zhou *et al*., 2008; Villain *et al*., 2008; Villain *et al*., 2010; Damoiseaux, 2017; Filippi *et al*., 2020). The high number of hub regions within posterior DMN and further temporal regions in dementia patients, in spite of a lack of frontal lobe hubs, may therefore reflect a pattern of cortical change associated with AD distinct from that seen within healthy ageing. In the absence of disease, healthy ageing has often been associated with significant alterations of structure and function disproportionately affecting frontal, anterior portions of the DMN (O'Sullivan *et al*., 2001; Cabeza, 2002; Cabeza *et al*., 2002; Salat *et al*., 2005; Pfefferbaum, Adalsteinsson & Sullivan, 2005; Bennett *et al*., 2010; Cabeza & Dennis, 2012), while AD is considered to affect primarily the regions of the posterior DMN, in particular within midline parietal areas (Minoshima *et al*., 1997; Kogure *et al*., 2000; Bradley *et al*., 2002; Greicius *et al*., 2004; Bai *et al*., 2011; Damoiseaux *et al*., 2012). The lack of hub regions within frontal lobes among AD dementia patients in favour of hubs within temporoparietal areas, a finding that has been identified in previous network studies assessing volumetric covariance (Rashidi-Ranjbar *et al*., 2020), is therefore likely to reflect an AD specific pattern of structural network alterations within posterior as opposed to anterior DMN regions.

In contrast with dementia patients, aMCI patients presented with the highest number of hub regions, including areas of bilateral orbitofrontal gyrus and middle frontal gyrus, as well as superior and middle temporal gyri, bilateral inferior parietal lobules and areas of the occipital cortex.

Despite having a lower overall betweenness centrality within the frontal lobes, when compared with healthy older adults, the presence of multiple hub regions within the orbitofrontal gyrus/medial prefrontal cortex in aMCI patients suggests that these areas, at least at this early stage of disease, retain their hub-like properties in the transition from healthy ageing. Examination of network parameters at a regional level however, revealed substantially lower clustering coefficients in this region, as a non-statistical observation, among aMCI patients compared with all other groups, suggesting that disease related disruption to this hub region, in terms of the structural brain network, may first occur as a decline in local connectivity. Given that previous studies have identified a distinct loss of frontal lobe hubs among aMCI patients, in a similar manner to AD dementia patients (Rashidi-Ranjbar *et al*., 2020), it seems a possibility that the aMCI patients included in this study were representative of an earlier stage of disease in which local connectivity of these regions is affected prior to measures of global integration. Furthermore, in accordance with findings relating to global and local efficiency, as well as clustering coefficient, it may be reasonable to suggest that the results presented here reflect changes in degree and betweenness centrality within orbitofrontal regions that occur in a non-linear manner between the stages of AD (Seo *et al*., 2013; Zhou & Lui, 2013). aMCI patients showed the highest degree and betweenness centrality in this area, even when compared with healthy controls, with AD dementia patients presenting with substantially lower levels of each parameter in this area, compared with both aMCI and healthy older adults. Although not statistically significant, this finding has further implications for the identification of non-linear changes in the topology of structural networks throughout the stages of AD and suggests that prior to degradation of frontal cortical hubs, structural network alterations may initially result in the exacerbation of hub-like characteristics in these regions in aMCI.

Decreases in anterior DMN functional network centrality, in favour of posterior DMN network centrality, have been confirmed recently within individuals presenting with SCD, a stage thought to represent potentially a preclinical manifestation of AD (Xie *et al*., 2019). Despite finding contrasting results among aMCI patients in the present study, it is a possibility that changes in centrality and hub regions, such as those identified among the dementia group, may be identifiable at a very early stage of disease, albeit through differing methods of network analysis.

5.2.4.3. Network Alterations in Between the Stages of Healthy Ageing

Despite primary analyses revealing very limited differences between healthy control groups in terms of network-level alterations in graph theory parameters, significant differences were seen between the older group and both younger groups in relation to betweenness centrality. Although some functional studies have demonstrated a significant decrease in centrality associated with ageing (Tomasi & Volkow, 2012; Cao *et al*., 2014), research has further suggested that the relationship between network centrality and ageing may be significantly affected by the centrality measure of choice, likely as a result of diverse changes to short and long-distance connections within the human brain connectome across the lifespan and individual node relationships to specific network modules (Meunier *et al*., 2009; Zuo *et al*., 2012). Zuo and colleagues (2012), for example, demonstrated significant decreases in functional network degree centrality, a measure of local integration, associated with increasing age within precuneus and posterior cingulate regions, whereas they found no such association with age when considering eigenvector centrality, a more global measure of integrity that takes into account a node's connection with other highly central nodes throughout the network. The high betweenness centralities demonstrated by the older group in the present study, therefore, support the notion put forward by Zuo *et al*., that although local or direct measures of centrality may be affected by increasing age, the connectivity of hub-like regions with the wider network may be maintained. Furthermore, as with the high betweenness centralities presented by dementia patients in the temporal lobes, reductions in connectivity that may lead to low centralities in functional networks may have the reverse effect in volumetric covariance networks. As mentioned previously, structural connectivity studies assessing the integrity of white matter, have revealed similar patterns of change as those revealed by functional imaging, suggesting a correlation between structural alteration and functional disruption (Greicius *et al*., 2004; Andrews-Hanna *et al*., 2007; Zhang *et al*., 2007; Bai *et al*., 2008; Zhou *et al*., 2008; Villain *et al*., 2008; Villain *et al*., 2010; Damoiseaux, 2017). Such findings suggest that structural alterations within areas that are functionally well connected throughout the network are, therefore, likely to demonstrate high levels of covariance between a wide range of cortical regions, therefore presenting with high centrality measures in anatomical networks.

No significant differences were found between the healthy age groups in terms of any other network parameters in the primary analysis. The *post-hoc* analysis looking at the results of the Bonferroni corrected sparsity threshold revealed significantly higher levels of global

efficiency in the middle-aged group, compared with the younger group, that were also slightly, although not significantly, higher than the older group. This inverted U shape of change across the stages of ageing, which was present also in the primary analysis, although not statistically relevant, has previously been demonstrated by fMRI studies in measures of local efficiency (Cao *et al*., 2014). Despite finding no differences between healthy groups in terms of local efficiency, the similar findings in global efficiency support the existence of some form of non-linear development of cortical networks throughout the lifespan.

Findings from individual lobes revealed that age-related alterations in network topology may best be appreciated at a regional level. Specifically, within the temporal lobes, all network measures, with the exception of betweenness centrality, showed differences between the stages of ageing that increased in a linear manner, with older adults showing significantly higher measures of each parameter when compared with the youngest group. In contrast, network measures in the parietal lobe appeared lower as a function of age, with both the younger groups presenting significantly higher network parameters than older controls in this area, excluding betweenness centrality. Finally, as described in an earlier section, older adults presented with significantly greater betweenness centralities than both younger groups in the frontal lobes and further demonstrated significantly higher levels of both clustering coefficient and local efficiency, as well as a higher average degree, in this lobe when compared with the middle-aged group. Interestingly, differences in this region again appeared in a U shape, with the younger group also demonstrating higher network segregation measures, of clustering coefficient and local efficiency, than the middle-aged group in frontal lobes as well as a higher average degree, although this was not significant. This heterogeneity in age-related alterations across brain regions has been similarly identified by functional imaging studies (Cao *et al*., 2014).

In terms of the present structural cortical networks, formed by volumetric correlations between brain regions, graph theoretical measures at differing stages of ageing may have diverse biological underpinnings. In the present study, overall betweenness centrality was very low within the youngest group, with the highest average betweenness centrality in this group being present within the insula. It is likely, given the lack of disease or age-related structural change in these individuals, that no particular group of cortical regions formed a high number of correlational connections with the wider network and, as such, betweenness centrality, as well as the number of identified hub regions in this group, tended to be very low. Instead, in contrast with the functional connections between distant brain regions that may drive alterations in network parameters in the presence of age or AD related change, in

this case, volumetric covariance between areas of anatomical proximity are likely to have a greater effect on network topology. This interpretation is in line with previous work that has indicated the existence of a "local to distributed" shift in brain network organisation throughout development (Fair *et al*., 2009) and is evidenced by the extremely high levels of centrality within the insula cortex seen in the younger group, in contrast with very low betweenness centralities elsewhere. Given its anatomical proximity with the frontal, temporal and parietal lobes (Uddin *et al*., 2017), the insula represents an area that is likely to present with a high convergence of volumetric correlations with nodes from multiple cortical structures that may be not otherwise connected, thereby creating a high level of betweenness centrality. Similarly, a high average degree within subcortical structures among this group suggests that the intrinsic structural and functional connectivity present between these areas and a multitude of cortical regions (Behrens *et al*., 2003; Hwang *et al*., 2017; Greene *et al*., 2020) is likely to result in a high level of local network centrality, although this may not be necessarily translatable to global network measures.

In contrast with this theory, it is possible that high levels of network segregation within frontal regions among young adults reflects an aspect of network topology that may be explained as a result of functional specificity rather than simple anatomical characteristics. It is known that as we age our cognitive processes are significantly altered, presumably as a consequence of functional and structural changes within the brain and the human connectome (Harada *et al*, 2013; Koen & Rugg, 2019; Koen, Hauck & Rugg, 2019; Koen, Srokova & Rugg, 2020). A particular aspect of such change that has gained considerable attention is the observation of the tendency for younger adults to demonstrate greater reliance on top-down processes to facilitate cognitive performance, in the form of fluid intelligence mediated by executive control, while older individuals tend to use approaches to cognitive tasks that rely more heavily on learned knowledge and processes represented by crystallised cognition (Cattell, 1971; Harada *et al.,* 2013). Given that aspects of cognition including memory, learning and life experience have been implicated as mediating factors in the development and maintenance of cortical structure and function (Maguire *et al*., 2000; Als *et al*., 2004; Zatorre, Fields & Johansen-Berg, 2012; Schlegel *et al*., 2015), it is possible that the findings presented here demonstrate the effect of this type of executively mediated cognition in contributing to densely connected, highly segregated clustering within frontal lobe structures in the earlier stages of adulthood. The differences in network parameters within the temporal lobes, which showed a linear increase between age groups, therefore, further support the notion that anatomical network topology may show changes as a function of altered cognitive

processing in ageing, with temporal structures mediating learning and memory gaining higher importance within the network in later life. A U-shaped trajectory of these network parameters throughout ageing may, therefore, reflect the transition away from frontally mediated processing in middle-age, with the re-emergence of higher levels of all parameters in the frontal lobes of older controls, likely reflecting the involvement of these areas in age-related cortical degradation (O'Sullivan *et al*., 2001; Cabeza, 2002; Cabeza *et al*., 2002; Salat *et al*., 2005; Pfefferbaum, Adalsteinsson & Sullivan, 2005; Bennett *et al*., 2010; Cabeza & Dennis, 2012). This theory is supported by the fact that betweenness centralities in the frontal lobes of older individuals were significantly higher than both younger groups, suggesting that high network segregation in young age may be mediated solely by local connections and anatomically proximal correlations, whereas high network parameters in old age appear to be further influenced by the global importance of these regions within the wider network, in the presence of age-related structural alterations.

The results of this study further suggest that network parameters within the parietal lobes, particularly relating to the property of small-worldness, are significantly altered by the ageing process. Specifically, both the older healthy controls and all patient groups presented with significantly lower average degrees, clustering coefficients and local efficiencies within parietal lobes compared with both the young and middle-aged groups. Furthermore, global efficiencies were also significantly lower in older controls and both MCI groups, when compared with both younger and middle-aged controls, and further significantly lower in dementia patients when compared with the middle-aged group. The lack of differences in this lobe identified between the healthy older group and the patients, along with the consistency of the differences seen between the two younger groups and each of the others, suggests that such declines in small-world properties, including reduced global efficiency and clustering coefficient, are a consequence of healthy ageing that is relatively unaltered by the presence of disease. When assessing regional alterations, non-statistical observations found that older groups, including both patients and healthy adults, tended to show lower levels of clustering coefficient and local and global efficiency in all areas of the parietal lobes including superior, and inferior parietal lobules, precuneus and even the post-central gyrus, when compared with younger controls, and in particular, in comparison with the middle-aged group. The age-related breakdown of small-worldness within these regions may reflect the findings of previous studies of white matter integrity that have contributed to a disconnection hypothesis of ageing (Bennett & Madden, 2014). Despite evidence for age-related white matter changes throughout the cortex (Bennett & Madden, 2014), a particularly prominent anterior-posterior

gradient of change has been identified in ageing that suggests that frontal regions may be disproportionately affected while posterior areas, although also showing evidence of change, may be better preserved over time (O'Sullivan *et al*., 2001; Pfefferbaum, Adalsteinsson & Sullivan, 2005; Bennett *et al*., 2010). In the present study, frontal regions within older adults showed the highest levels of small-world characteristics, while also demonstrating high betweenness centralities. As with the low clustering coefficients within the orbitofrontal regions seen among aMCI patients, the breakdown of small-world characteristics within parietal regions among older individuals, without significant changes in betweenness centrality, may be reflective of earlier, less severe changes within parietal regions associated with age. Such an interpretation is supported by the differential age-related alterations within anterior vs posterior cortical areas, in particular within regions of the DMN, that have been evidenced by previous studies (Davis *et al*., 2008).

As mentioned within an earlier section, hub regions identified among healthy older controls were largely representative of structures pertinent to the DMN. Despite both the middle aged and younger groups demonstrating the presence of hub regions within medial prefrontal areas, and the middle-aged group further presenting with hubs within the inferior parietal lobules, any other indications of DMN involvement in the younger groups was lacking, with neither group indicating hub-like nodes within temporal or medial parietal areas. A possible interpretation for the lack of hub regions within these areas, despite finding medial parietal hubs in all older groups, with the exception of aMCI patients, may relate to the development of structural network hubs throughout the stages of healthy ageing. Previous investigations have demonstrated a significant effect of age on the functional connectivity of areas of the DMN, with older adults often showing a reduction in connectivity between these regions compared with younger adults (Damoiseaux, 2017). Research has also demonstrated a breakdown in network segregation relating to older age, in which older adults demonstrate lower within-network connectivity of the DMN and other well-described functional networks, while conversely showing an increase in between-network connectivity (Chan *et al*., 2014; Grady *et al*., 2016; Spreng *et al*., 2016; Ng *et al*., 2016). As described previously, earlier studies have demonstrated a significant overlap in structural and functional network alterations in the DMN (Andrews-Hanna *et al*., 2007; Damoiseaux, 2017) and, as such, one explanation for the findings presented here is that age-related structural alterations within regions of the DMN may exacerbate the importance of these areas in a volumetric co-variance network. Conversely, younger adults tended to retain hub regions within areas of cortex that are anatomically proximal to a high number of surrounding structures or tend to

be well structurally connected to diverse areas of cortex such as the insula and subcortical regions as well as primary sensorimotor areas.

Finally, observational differences in modularity were once again apparent between the stages of ageing, in a similar manner to those identified within the cognitive study. As in the previous experiment, the number of modules identified in each of the control groups decreased linearly between the stages of ageing, with the youngest group having the highest number of modules across thresholds and the oldest group the lowest, with middle-aged adults demonstrating intermediate numbers. In accordance with previous studies showing similar age-related decreases in modularity within brain systems (Cao *et al.,* 2014; Chan *et al.,* 2014; Han *et al*., 2018; Chong *et al*., 2019), the results presented here support the theory put forward by the previous experiment that cognitive dedifferentiation in ageing may occur as a result of similar dedifferentiation in neural systems.

5.2.4.4. Network Alterations in Non-Amnestic Patients

When assessing whole-network parameters in either the primary or *post-hoc* analyses, none of the aforementioned differences in aMCI and AD dementia patients were found to be present within the non-amnestic group. In all measures, MCI-na patients were found to be similar to healthy controls and only demonstrated significant differences when compared with aMCI patients on measures of global and local efficiency and clustering coefficient, a pattern that was similarly reflected by the healthy groups. At the time of writing, only one other study found during a literature search had included both MCI-na and amnestic patients in a study of structural brain networks. In accordance with the present findings in the dementia group, the study by Rashidi-Ranjbar and colleagues (2020) revealed a similar loss of network hubs within frontal regions within aMCI and dementia patients, while demonstrating a high number of temporoparietal hub regions; alterations that were distinctly lacking within MCI-na patients. In the current study, MCI-na patients similarly retained a number of hub regions within the frontal lobes while showing no particular pattern of hub regions within DMN associated temporoparietal areas, as were seen in the aMCI and dementia groups. Instead, MCI-na patients presented with a number of hub regions within the insula, in a similar manner to healthy younger adults, suggesting that the pattern of hub-forming connections in this group may be similarly driven by anatomical proximity as in the younger group, rather than a specific correlations relating to disease mediated structural change.

The results of the present study, along with those of Rashidi-Ranjbar *et al*., (2020), therefore, suggest that graph theory techniques have utility in identifying AD specific alterations within aMCI patients, the MCI subtype most likely to represent the prodromal stage of AD, that are distinct from alterations within groups such as MCI-na who may represent the prodromal stage of a number of differing aetiologies (Petersen *et al*., 2001; Petersen, 2004; Busse *et al*., 2006; Petersen & Negash, 2008; Ferman *et al*., 2013).

5.2.4.5. Conclusion

In line with previous functional imaging studies demonstrating inverted U shaped trajectories of functional alterations throughout the AD continuum, as a result of compensatory processes in the early stages (Dickerson & Sperling, 2009; Catricala *et al*., 2015; Gardini *et al*., 2015; Corriveau-Lecavalier *et al*., 2019), the results presented here suggest a similar pattern of progressive change in the topology of structural networks in AD. Significant network alterations in relation to those of healthy older adults, therefore, appear to have the greatest discriminatory power in the earlier stages of pathology, represented here by aMCI patients, in which disruptions to small world-topology are most exacerbated before being resolved by the dementia stages, albeit in a significantly altered network configuration. Furthermore, as in the cognitive study, network alterations within MCI-na patients were found to be inconsistent with those seen among the other two patient groups suggesting, in line with the previous work and the findings of previous studies (Rashidi-Ranjbar *et al*., 2020), that the topological changes identified among aMCI and dementia patients are specific to AD pathology. In addition to these findings, age-related decreases in modularity, along with diverging cortical hub regions across the stages of ageing and in disease, suggest that the findings presented by the current study may provide a neural basis for the cognitive dedifferentiation and domain specific alterations identified by *Experiment 3*.
Despite the uncertainty surrounding the biological underpinnings of volumetric covariance within the brain, the results presented here, in agreement with previous cortical thickness and regional volumetric studies, have demonstrated a utility of structural covariance networks in identifying AD specific changes in the structure of cortical networks (He, Chen & Evans, 2008; Yao *et al*., 2010; Lo *et al*., 2010; Li *et al*., 2012; Tijms *et al*., 2013a, 2013b; Phillips *et al*., 2015; Fischer *et al*., 2015; Rashidi-Ranjbar *et al*., 2020). Such findings may be particularly pertinent to early diagnostic protocols, given the suggestion by earlier studies that

topological changes in structural networks may precede changes to functional networks among MCI patients who later convert to AD dementia (Filippi *et al*., 2020).

Chapter 6 | General Discussion

In any degenerative disease, early diagnosis is imperative for the effective implementation of treatment, appropriate intervention, and prolonged quality of life. In Alzheimer's disease (AD), despite there being limited treatment options, both pharmacological and alternative therapeutic interventions have proved beneficial in slowing the rates of neurodegeneration and cognitive decline, reducing caregiver burden, and retaining patients' daily functioning, particularly when administered in the early stages (Dubois *et al*., 2015; Cavedo *et al*., 2016; Cavedo *et al*., 2017; Hampel *et al*., 2018; Zucchella *et al*., 2018). Furthermore, in the pursuit of disease modifying therapies, researchers have suggested that the repeat failures of clinical trials lie in the late administration of compounds at a stage in which pathophysiological development can no longer be reversed (Selkoe, 2019). In light of this information, one can appreciate the necessity for research that aims to develop reliable, cost effective methods for early AD diagnosis. Current biomarkers that rely on either neuroimaging or cerebrospinal fluid (CSF) samples to measure the pathological hallmarks of disease, remain limited in their availability in a clinical setting, owing to the high costs associated with imaging and the invasive and time-consuming nature of the lumbar punctures required for CSF analysis. Recent developments in blood-based biomarkers for AD are still in the early stages and as such, despite their potential to provide a routine screening tool, are, at present, unable to fulfil the requirement for a quick and inexpensive diagnostic marker (Blennow, 2017). Neuropsychological testing, however, not only provides a means to assess individuals at a low cost and in a relatively time effective manner, but it has also been found to differentiate successfully individuals with prodromal and even preclinical disease from healthy controls, at a stage of pathological development where intervention may prove most effective (Amieva *et al*., 2008).

The present research aimed, primarily, to explore aspects of cognitive change throughout the spectrum of AD that may provide accurate measures of underlying neurodegeneration and therefore contribute to diagnosis at an early stage of disease. A particular focus was concentrated on the alterations in semantic processing that have been established as an extremely early indicator of cognitive decline in AD (Garrard *et al*., 2005; Amieva *et al*., 2008; Le *et al*., 2011; Joubert *et al*., 2020) and have been correlated with the earliest known manifestations of structural and functional degradation in the AD brain (Atienza *et al*., 2011; Barbeau *et al*., 2012; Hirni *et al*., 2013; Meyer *et al*., 2013; Gardini *et*

al., 2015; Chen & Chang, 2016; Hirni *et al*., 2016; Sánchez *et al*., 2017; Hirjack *et al*., 2017; Pineault *et al*., 2018; Venneri *et al*., 2019; Vonk *et al*., 2020) (See *Chapter 2* for an overview). As semantic cognition is considered to be relatively robust to the normal ageing process (Levine *et al*., 2002; Rönnlund *et al*., 2005; Spreng *et al*., 2018), tests of semantic memory ought to provide a sensitive technique for identifying subtle changes in cognitive function, relating to AD, that are divergent from healthy age-related memory decline. However, current screening tools for AD are relatively limited in their ability to detect early manifestations of semantic decline, likely due, in part, to the more easily compensated for nature of a semantic memory deficit and the compensatory cortical recruitment associated with the preclinical and prodromal stages of disease (Saykin *et al*., 1999; Rinne *et al*., 2003; Grossman *et al*., 2003; McGeown *et al*., 2009; Seidenberg *et al*., 2009; Woodard *et al*., 2009; Gigi *et al*., 2010; Didic *et al*., 2011; Catricalà *et al*., 2015; Gardini *et al*., 2015; Mascali *et al*., 2018). In an effort to overcome the issue of insensitivity relating to raw semantic test scores in the mildest stages of AD, the studies presented here focussed the neural correlates of more subtle and specific aspects of semantic decline associated with AD degeneration. Furthermore, novel analytical techniques for the identification of network-level cognitive alterations allowed for the exploration of the role of semantic cognition in cognitive profiles, associated with healthy ageing and disease, providing compelling evidence in favour of semantic memory deficits as a marker of abnormal cognitive decline.

Experiment 1 was designed in two parts: a neuropsychological study aiming to confirm the existence of a semantic/phonemic verbal fluency discrepancy within AD dementia and mild cognitive impairment (MCI) patients, and a neuroimaging study aiming to identify the neurological substrates of such discrepancies across the stages of disease. It was hypothesised in this case, that patients along the AD spectrum would all demonstrate significantly greater declines in semantic fluency performance, when compared with controls, than phonemic fluency performance and that such discrepancies would provide a measure of semantic memory function that would show correlations with anterior medial temporal lobe (aMTL) structures associated with the earliest stages of disease (Didic *et al*., 2011).

In line with a wealth of previous research (Henry, Crawford & Phillips, 2004; Murphy, Rich & Troyer, 2006; Clark *et al*., 2009; Chasles *et al*., 2020; Vonk *et al*., 2020), the findings presented here did indeed indicate the presence of significantly greater declines in semantic fluency performance relative to controls, compared with phonemic fluency, in all stages of disease severity. The results of the neuroimaging study further confirmed our hypotheses, finding in the mild MCI group a significant relationship between the grey matter

volume of the aMTLs and verbal fluency discrepancy scores. Despite previous research assessing the neural substrates of semantic and phonemic fluency in healthy older adults (Vonk *et al*., 2019), and the established differences in semantic/phonemic fluency performances between AD patients and patients presenting with lesions or pathology localised to frontal areas (Rascovsky *et al*., 2007; Capitani *et al*., 2009), there has been limited research assessing the direct neural correlates of the verbal fluency discrepancy in AD. The first experiment in the current work is therefore novel in its identification of a significant relationship between semantically mediated verbal fluency discrepancies and areas of the aMTLs in the mildest stages of prodromal disease. This study further demonstrated how verbal fluency discrepancies may lose their specificity in highlighting cortical change within these very early affected regions as disease progresses. Instead, in more moderate MCI and dementia patients, discrepancy scores highlighted the progression of cortical degradation throughout the temporal lobes and wider neocortex, as has been found by previous research looking at the neural correlates of semantic memory in the varying stages of AD (See the conclusions of *Chapter 2*).

Due to the apparent issue of heterogeneity among the moderate MCI group in the first experiment, *Experiment 2* aimed to elucidate the neural correlates of semantic memory performance, as measured by verbal fluency discrepancies, across the MCI neuropsychological subtypes and stages of severity. It was hypothesised, given the findings of the previous experiment, that MCI patients at a more moderate stage of disease, indicated by cognitive impairments within multiple domains, would likely present with weaker grey matter correlations, relating to semantic memory function, that would be less specified to the aMTLs. Given the findings of previous verbal fluency studies showing no evidence of verbal fluency decline discrepancies in non-amnestic MCI (MCI-na) patients (Rinehardt *et al*., 2014; Vonk *et al*., 2020) and those indicating a lower incidence of AD conversion among MCI-na patients when compared with amnestic MCI (aMCI) patients (Busse *et al*., 2006), it was further hypothesised that patients with an amnestic profile would be far more likely to demonstrate patterns of correlation within AD related MTL regions than those with a non-amnestic profile.

As expected, in line with the findings of the first experiment and the studies reviewed in *Chapter 2*, this study was able to demonstrate an anterior-posterior shift in semantic memory cortical correlations within the temporal lobes from the mildest to the more moderate stages of disease. Furthermore, as expected, only the aMCI patients demonstrated any correlation between grey matter volumes and verbal fluency discrepancy. The lack of

significant neuroimaging correlations within the non-amnestic patients was reflective of the finding that, unlike the amnestic groups, patients in these groups demonstrated no evidence of a significantly disproportionate decline in semantic fluency relative to phonemic fluency when compared with controls, a finding that is supported by the results of earlier studies (Rinehardt *et al*., 2014; Vonk *et al*., 2020) and may be explained by the fact that such patients are far less likely to represent the prodromal stages of AD (Busse *et al*., 2006).

Taken together, these first two experiments outline a marker for AD neurodegeneration that is not only sensitive to the earliest stages of cortical degradation but can further be said to be specific to AD type cognitive decline. Although verbal fluency discrepancy may lose its specificity for aMTL regions in the later stages of disease, the relationship between semantic memory decline and AD pathological progression, demonstrated both in the present studies and in earlier research, suggests that tests of semantic processing may not only provide a means for early diagnosis in AD, but also provide a supportive evaluation for disease staging and prognosis.

Despite the promising findings of the two voxel-based morphometry (VBM) studies presented in *Chapter 4*, overt structural alteration within the MTLs represents a relatively late stage of pathophysiological development in AD, following significant build-up of proteinopathies (Jack *et al*., 2010). As such, research is continually exploring alternative methods to measure subtle but definable alterations in brain structure and function that potentially relate to such build-ups prior to this stage of disease. One method that has received considerable attention in recent years, is that of network analysis or graph theory (Sporns, 2018; Farahani, Karwowski & Lighthall, 2019). The strength of graph theoretical measures lies in the non-reductionist appraisal of network topology in either functional, structural or even cognitive systems. A method that assesses not the integrity of AD related brain structures alone, but rather the relationships between these structures and the rest of the human brain connectome, and the role they play in network topology, has the potential to identify alterations in network-level systems that may occur prior to significant degradation of a single area. Given the well-established relationship between cortical networks and cognition, graph theoretical analysis of the structure of cognitive networks in healthy ageing and AD, as conducted in *Experiment 3*, was thought to be a compelling tool for identifying possible network-level cognitive alterations that may correspond to early underlying physiological change. Although semantic memory declines have proved valuable in the very early detection of AD (Garrard *et al*., 2005; Amieva *et al*., 2008; Le *et al*., 2011; Joubert *et al*., 2020), cognitive tests assessing individual domains remain limited in their ability to

differentiate accurately between diverse neurodegenerative diseases (Loewenstein *et al.,* 2006; Fischer *et al.,* 2007). In particular, early impairments in semantic memory may easily be confused with the semantic variant of frontotemporal dementia (FTD) and, in the absence of further AD related declines in episodic memory, may prove somewhat inadequate as a differential diagnostic tool. In line with the cognitive profiling that represents a core aspect of diagnosis in neurodegenerative diseases (National Institute for Health and Care Excellence, 2018), *Experiment 3,* therefore, aimed to define a neuropsychological profile indicative of AD type decline, according to network topology and interrelatedness of patient performance in differing neuropsychological domains, as a means to overcome the limitations of domain-specific markers and establish how semantic cognition, and its relationship to the wider network, may be specifically altered in this disease. With the inclusion of multiple healthy controls groups at differing stages of ageing, this experiment expected to find alterations in the structure of cognitive networks in disease that were distinct from those present throughout healthy ageing. Furthermore, the inclusion of a non-amnestic MCI group served to validate any findings within amnestic MCI and AD dementia patients, as relating to a specific pattern of change associated with AD pathology, rather than a function of general neurodegenerative insult. As expected, differences in cognitive profiles, identified via graph theory parameters, were identified not only between the stages of healthy ageing, but were furthermore identified in relation to the presence of disease. The segregation and integration of cognitive networks showed incremental differences between each of the healthy age groups, with measures of both appearing to increase as a function of age, in a manner reflecting the cognitive dedifferentiation hypothesis of ageing (Baltes *et al*., 1980; Baltes & Lindenberger, 1997). In all patient groups, these differences appeared to be exacerbated and furthermore, distinct alterations in the centrality of the domains of semantic cognition and abstract reasoning appeared to best differentiate these groups from healthy older adults. As crystallised cognition and semantic processing abilities are thought to be preserved and even improved throughout the ageing process, being relied upon more heavily in the face of decline in other areas of fluid intelligence (Cattell, 1971; Levine *et al*., 2002; Rönnlund *et al*., 2005; Harada *et al.,* 2013; Spreng *et al*., 2018), the results presented here suggest, as outlined by the first experiment, that semantic cognition may provide a sensitive marker for abnormal impairment in old age. Furthermore, these findings provide evidence that visualisation of the cognitive network in this manner may have a meaningful differential diagnostic utility in the future, particularly in light of the similarities between the aMCI and AD dementia networks that were found not to be present within the non-amnestic group.

In light of the results outlined within *Experiment 3*, the final experiment aimed to identify network alterations relating to ageing and AD pathology within structural brain networks reflecting grey matter covariance. Differences in cognitive profiles, seen within the previous study, are indicative of some underlying age and disease related changes to brain network topology, and as such it was hypothesised that *Experiment 4* would reveal significant alterations in graph theoretical parameters characterising the structural brain connectome between the stages of ageing and in disease. As reflected by a multitude of earlier experiments, significant differences were found to be apparent in structural brain networks between healthy adults and AD patients in terms of both network segregation and integration (He, Chen & Evans, 2008; Yao *et al*., 2010; Lo *et al*., 2010; Li *et al*., 2012; Tijms *et al*., 2013a, 2013b; Phillips *et al*., 2015; Fischer *et al*., 2015; Rashidi-Ranjbar *et al*., 2020). Specifically, these changes appeared to occur in a non-linear manner, with amnestic MCI patients showing exacerbated declines/increases in network parameters, relative to controls, a finding that was not apparent within the non-amnestic group, that appeared to be present but less apparent by the dementia stages of disease. In depth regional analysis of individual lobes and specific cortical structures revealed a pattern of network topology showing significant alteration in aMCI and AD groups that was heavily distinct from the topological alterations seen across the stages of healthy ageing. Furthermore, such regional alterations, in both ageing and disease, appeared, to an extent, to reflect the network changes within cognitive profiles presented by the previous experiment.

Given that graph theoretical measures have proved successful in identifying even preclinical subversions of network topology in AD (Brier *et al*., 2014; Fischer *et al*., 2015; Tijms *et al*., 2016; Pereira *et al*., 2018), the results presented here support the notion that such methods may prove beneficial in early diagnostic protocols. In particular, the novel findings relating to the changes seen in cognitive networks, in even the prodromal stages of disease, suggest that physiological network alterations may be identified via the cost-effective approach of neuropsychological evaluation. With the evidence for semantic memory decline as a particularly early marker of AD related cognitive decline (Garrard *et al*., 2005; Amieva *et al*., 2008; Le *et al*., 2011), the apparent network-level changes in this type of cognition, indicated by the current research, suggest that this method of cognitive profiling may represent an effective tool for the identification of early semantically mediated neuropsychological impairment in AD that may be otherwise missed or misdiagnosed via classic methods of cognitive testing.

Together, this body of work has not only contributed to the growing area of research supporting the implementation of semantic memory tasks in routine clinical assessment (Joubert et al., 2020), but has further provided a means to understand and quantify the role of semantic cognition in healthy ageing and AD, as it relates to the cognitive network. Evidence obtained in the two VBM studies provides a compelling argument to suggest that semantic declines are not only present in prodromal AD, as highlighted by verbal fluency discrepancies, but that the likely cause for such declines stems from early involvement of the aMTLs. Although this finding supports the use of semantic tasks as a proxy for AD-related structural change, an argument is to be made that the sensitivity of episodic memory tests, already utilised in clinics, to MTL degradation renders semantic impairments redundant (Grober *et al*., 1999; Eichenbaum, 2001; Petersen *et al*., 2000; Dubois *et al*., 2007; Albert *et al*., 2011; Dubois *et al*., 2014). The graph theoretical studies, therefore, compliment these findings by providing a rationale as to why semantic memory impairment, in particular, may represent a good early marker for abnormal cognitive decline in ageing. By quantifying differences in the topology of cognitive systems, as they occur in both healthy ageing and disease, *Experiment 3* demonstrates how, throughout normal ageing, multiple cognitive domains may become increasingly influenced by the accrual of crystallised intelligence or semantic knowledge. In disease groups however, the centrality of semantic processing in the cognitive network appeared weakened relative to healthy adults, while the role of functions such as episodic memory, which are known to be vulnerable in AD, was similarly altered in normal ageing. Such findings therefore support the use of semantic memory as a diagnostic marker by emphasising the possible superiority of this measure in differentiating normal ageing from disease, given the role it plays in supporting normal cognitive functioning in healthy ageing and the breakdown of this support in cognitive decline. Graph theoretical analysis in this context is in line with a growing area of research beginning to quantify neurodegenerative diseases in terms of their selective impact on neural networks (Buckner *et al*., 2009; Seeley *et al*., 2009; Zhou *et al*., 2012; Warren *et al*., 2013; Fornito, Zalesky & Breakspear, 2015; Ahmed *et al*., 2016; Sepulcre *et al*., 2017). The application of network analysis to measures of cognitive function has the potential to highlight not only areas of cognition most pertinent to diagnostic protocols, which can differentiate healthy ageing from abnormal disease processes, but to renew interest in dementia as a disconnection syndrome (Delbeuck, Van der Linden, & Collette, 2003; Pievani *et al*., 2011). Such an approach allows for the quantification of disease related disconnection that is characterised not only by breakdowns in neural connectivity (see discussion of *Experiment 4*) (Minoshima et al., 1997;

Kogure et al., 2000; Bradley et al., 2002; Greicius et al., 2004; Bai et al., 2008; Zhou et al., 2008), but furthermore by alterations in the interrelatedness of cognitive abilities.

Through a combination of hypothesis driven investigations into the neural correlates of semantic memory in AD and exploratory network analysis of the cognitive profiles associated with healthy ageing and disease, the experiments presented here, provide both a rationale for and a means to test semantic impairments in clinics. Verbal fluency tests are fast, easily administered and already in widespread use. As such, evidence of the relationship between discrepancy scores and aMTL volumes supports the viability of such tasks as a reliable screening tool for use in primary care settings. Graph theoretical analysis, despite requiring further experimentation and development, represents a mechanism for the quantitative appraisal of cognitive profiles. Given that dementia diagnosis already involves cognitive profiling in a similar manner by neuropsychologists, an objective means to evaluate an individual's likelihood to represent a given disease, based on the topology of their cognitive network, would have significant implications for future diagnostic protocols. These results can therefore be said to have significant relevance both in the development of accurate and early diagnostic protocols and also our understanding of the dementia syndrome and its manifestation in our wider cognitive systems.

6.1. Future Directions

The current work has the laid the foundation for many future directions of research. While experiments one and two provide compelling evidence for the use of verbal fluency discrepancy scores as a means to detect neurodegeneration in AD patients at an earlier stage of disease, subsequent research corroborating these findings in a prospective study, with an independent patient sample, is essential if the measure is to be taken forward into clinical application. Furthermore, given the recent longitudinal findings by Vonk and colleagues, demonstrating baseline discrepancies in verbal fluency performance in individuals at-risk for AD dementia (Vonk *et al*., 2020), a longitudinal investigation assessing fluency performance in patients with functional or subjective memory impairments, compared to those in a preclinical phase of AD, would be highly beneficial for the validation of this method as a primary care screening test for neurodegeneration, given the high referral rates of functional and psychiatric patients to memory clinics (Larner, 2014; Bell *et al*., 2015). Longitudinal studies would additionally benefit from the inclusion of patients who represent the preclinical or prodromal stages of other neurodegenerative aeitologies, particularly patients who go on to

develop the semantic variant of FTD. Despite some evidence suggesting a relative lack of verbal fluency discrepancies in FTD patients, when compared with AD groups (Rascovsky *et al*., 2007), it is likely that in the preclinical and even prodromal stages of disease, where in the semantic FTD variant structural damage is most apparent within polar temporal regions, patients will present with similarly exaggerated declines in semantic fluency compared with phonemic, prior to significant disruptions to word generation (Snowden, Goulding & Neary, 1989; Hodges *et al*., 1992; Hodges, Graham & Patterson, 1995; Mummery *et al*., 2000; Chan *et al*., 2001; Gorno-Tempini *et al*., 2004; Desgranges *et al*., 2007; Hodges & Patterson, 2007). As such, subsequent investigations will need to consider the utility of verbal fluency discrepancies in differentiating these two distinct diseases in their earliest manifestations.

Experiment three is one of the first investigations to date to have applied graph theoretical methods to determine differential alterations to cognitive profiles relating to healthy ageing and neurodegeneration. As such, the findings from this study can be thought of as an initial, exploratory step which may inspire a wealth of subsequent research. In the present studies, graph theory analysis was conducted, necessarily, using group level data. A potential direction for this research would, therefore, be to include longitudinal data, possibly correlating test scores of a single individual over multiple time points, to determine whether individual variations in cognitive test performance, in the presence of neurodegenerative disease, is similarly reflective of the topological alterations highlighted by the results presented here. Given the continued reliance on cognitive profiling to diagnose neurodegenerative disease in clinical settings (National Institute for Health and Care Excellence, 2018), a means to quantify profiles representative of a given disease, through graph theory analysis, would likely be extremely beneficial, particularly for early differentiation of underlying aetiologies in prodromal patients who may revisit clinics for several years before progressing to a dementia that can be formally diagnosed (Petersen, 2004). In order that such techniques be translatable into clinical practice, however, future research would not only need to explore methods for graph theoretical assessment at the level of the individual, but would further need to include investigations into cognitive profiles which are characteristic of a range of neurodegenerative aetiologies, other than that of AD. It is likely, given the findings of *Experiment 3*, which found marked similarities between cognitive profiles associated with aMCI and AD dementia, while finding limited similarities between these two groups and those with a non-amnestic profile, that dementias arising from differing aetiologies will present with highly distinct cognitive networks. Although in clinics neuropsychological evaluations already serve to provide an assessment of cognitive profiles

as they may relate to underlying disease, graph theoretical analysis could provide a means to evaluate such profiles in a quantitative manner, allowing for a more objective differential diagnostic protocol. Future studies should therefore endeavour to establish the topological characteristics of cognitive networks in a range of neurodegenerative disease populations.

Finally, experiment four contributed to an already well-developed, but somewhat controversial, area of research. As such, the inclusion of healthy groups of differing ages, as well as patient groups of differing disease severities and subtypes, in the same investigation, served to provide a degree of clarity to the question of how the topology of structural covariance networks may be altered by ageing and disease processes, and furthermore explore how the findings of the cognitive graph theory analysis may be explained by underlying differences in brain networks. Future directions for this research may include an investigation using functional MRI, to identify differences in functional network topology among the same participant groups, that may more clearly explain the results of the cognitive study. Ideally, similar analyses could be conducted using diffusion tensor imaging to assess structural connectivity, according to white matter integrity, allowing for a mechanistic interpretation of the structural covariance network analysis.

Recent findings evidencing a relationship between functional and structural network alterations in AD, which have suggested that structural alterations to white matter may precede functional changes in aMCI patients, support the use of structural covariance networks as a means to identify early patterns of neural degradation associated with this disease (Filippi *et al*., 2020). Typically, AD is characterised, primarily, by significant changes in grey matter integrity, given the distribution of pathological materials and associated pattern of neurodegeneration (Braak & Braak, 1991; Frisoni *et al*., 2010). As such, future research utilising structural covariance networks in this manner, may reveal, in line with Filippi et al.'s (2020) findings, that network alterations reflective of variance in grey matter integrity may provide a marker which is identifiable, not only before functional changes, but even prior to significant alterations to white matter connections. As in Filippi's study (2020), longitudinal datasets, involving preclinical populations who later progress to AD dementia, are required in order to test this hypothesis, proving another possible future avenue for this research.

In line with the graph theory analysis of cognitive profiles, a further possible direction for future research in this area would be to include groups representative of multiple disease aetiologies. Following contemporary research that has emphasised the selective degradation of neural networks in neurodegenerative disease (Buckner *et al*., 2009; Seeley *et al*., 2009;

Zhou *et al*., 2012; Warren *et al*., 2013; Fornito, Zalesky & Breakspear, 2015; Ahmed *et al*., 2016; Sepulcre *et al*., 2017; Filippi *et al*., 2020), graph theoretical evaluations of structural and functional network topologies across differing disease aetiologies will contribute to a growing area of brain connectomics seeking to develop quantitative MRI-based differential diagnostic markers for translation into clinical practice.

6.2. Conclusions

Taken together, the present work has outlined novel techniques for the identification of cognitive change and degradation of brain structure in the early stages of AD. In light of the significant negative impact this neurodegenerative disease has had in societies and on healthcare systems across the world (Prince *et al*., 2015), developing a means to recognise AD type degeneration, prior to the impairments of episodic memory that are currently relied upon in clinics (McKhann *et al*., 2011), is imperative to the pursuit of effective treatment and care. The studies presented within this thesis aimed to contribute to that development and the outcomes suggest that specific evaluations of semantic memory decline and the novel application of graph theoretical measures to cognitive profiles may provide meaningful avenues for earlier diagnostic protocols.

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APPENDIX E – Description of LASSI-L Procedure

The Loewenstein-Acevedo Scale of Semantic Interference and Learning (LASSI-L) has been described by Loewenstein and colleagues as a cognitive stress paradigm developed to test the effects of semantic interference on memory performance (Crocco et al., 2014; Loewenstein et al., 2016). Having been consistently shown to out-perform traditional list-learning tests in the detection of preclinical and prodromal AD (Loewenstein et al., 2017a; Matias-Guiu et al., 2018), the LASSI-L specifically addresses issues identified in earlier paradigms such as the lack of controlled learning, the failure to evaluate semantic interference effects and the failure to account for initial memory performance (Loewenstein et al., 2018b). The procedural sequence of the LASSI-L is outlined in ***Fig. E1***. As a test of semantic interference effects, the LASSI-L involves the presentation of two competing word lists that each include words belonging to one of three shared semantic categories. In the first instance, the participant is instructed to remember an initial list of fifteen words (List A) which belong to either the category of fruit, musical instruments or items of clothing (five words per category). Participants are required to read the words aloud as each one is presented, at a rate of one word every four seconds. Following this learning trial, the person is asked to recall freely as many of the fifteen words as they can. Next, a cued recall trial requires the person to remember the words that had belonged to each category, having been provided with their categorical semantic cues. After cued recall, List A targets are presented again in a secondary learning trial, before a second trial of cued retrieval is conducted to strengthen acquisition and recall of this initial word list. Encoding and retrieval procedures for the competing, semantically related word list, List B, are then conducted in an identical procedure, with an initial learning trial being followed by both free and cued retrieval, a secondary exposure to List B targets and finally a second cued retrieval trial. Free recall of List B assesses proactive interference effects, while retroactive interference is assessed by the two final steps of the protocol in which participants perform a delayed free and delayed cued recall of List A. With each target word presented for four seconds and the maximum allotted times for recall being 60 and 20 seconds for free recall and individual category cues respectively, the entire procedure can be carried out in around twelve minutes.

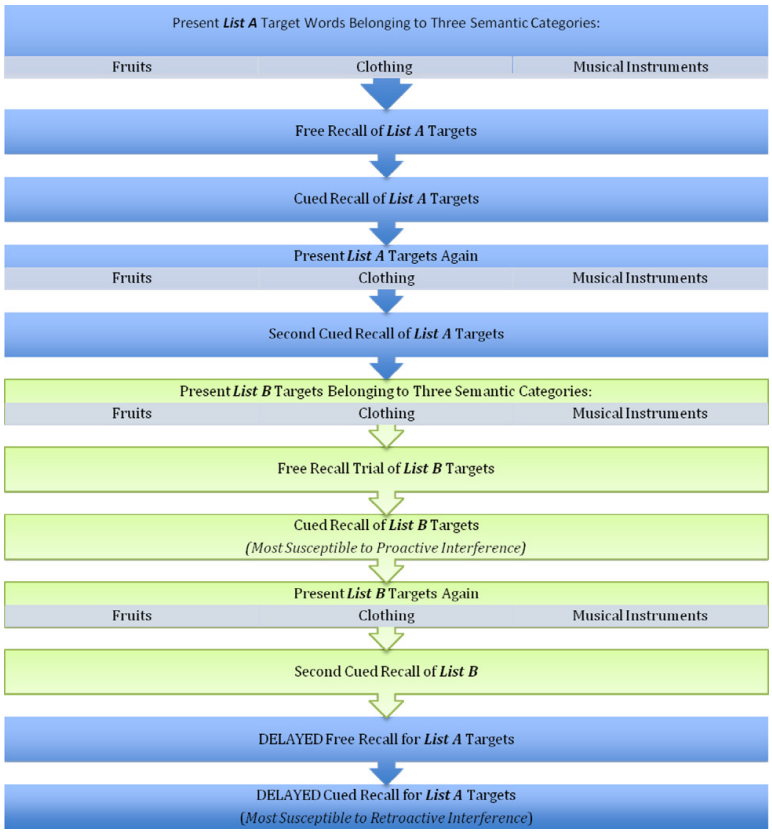

Figure E1. The sequence of the LASSI-L procedure. Permission to reuse this figure, taken from Crocco et al., (2014) is evidenced by the license included in Appendix F.

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GENERAL TERMS

APPENDIX G

Table G1

*Areas of non-significant but trending negative correlation between grey matter volume and verbal fluency discrepancy scores in mild aMCI-md (N 30). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc, Uncorrected; BA, Brodmann's Area; FWE, Family Wise Error. *no given Brodmann area. Thresholded p = .05*

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pFDR	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
							X	Y	Z	X	Y	Z
Superior Temporal Gyrus (21)	R	0.075	0.037	0.001	6265	3.45	62	-26	7	63	-27	6
Supramarginal Gyrus (40)	R					3.35	55	-51	22	56	-54	21
Superior Temporal Gyrus (22)	R					3.35	62	-32	15	63	-34	14
Superior Temporal Gyrus (39)	R					3.29	48	-59	20	48	-62	18
Superior Temporal Gyrus (13)	R					3.21	55	-40	21	56	-42	21
Sub-Gyral (21)	R					3.05	48	-9	-12	48	-9	-15
Middle Temporal Gyrus (21)	R					2.93	61	-24	-7	62	-24	-10
Middle Temporal Gyrus (39)	R					2.9	48	-58	12	48	-60	10
Middle Temporal Gyrus (39)	R					2.89	46	-56	6	46	-58	4
Superior Temporal Gyrus (22)	R					2.87	53	-18	-1	54	-18	-2
Inferior Parietal Lobule (40)	R					2.84	53	-50	39	54	-54	40
Middle Temporal Gyrus (21)	R					2.82	62	-44	1	63	-45	-2
Superior Temporal Gyrus (39)	R					2.73	50	-57	32	50	-60	32
Superior Temporal Gyrus (21)	R					2.67	63	-12	-2	64	-12	-3
Middle Temporal Gyrus (21)	R					2.59	50	-24	-7	50	-24	-10
Inferior Parietal Lobule (40)	R					2.51	65	-32	26	66	-34	26
Hippocampus	L	0.081	0.037	0.001	6159	3.26	-26	-35	-5	-26	-36	-8
Hippocampus	L					3.22	-30	-28	-11	-30	-28	-15
Middle Temporal Gyrus (21)	L					3.11	-42	2	-33	-42	4	-39
Hippocampus	L					3.09	-28	-32	-8	-28	-33	-12
Uncus (20)	L					3.05	-32	-13	-30	-32	-12	-36
Uncus (20)	L					2.98	-34	-19	-27	-34	-18	-33
Parahippocampal Gyrus (36)	L					2.96	-28	-15	-24	-28	-14	-30
Inferior Temporal Gyrus (20)	L					2.68	-42	-13	-32	-42	-12	-39
Parahippocampal Gyrus (35)	L					2.58	-22	-13	-22	-22	-12	-27
Middle Temporal Gyrus (21)	L					2.56	-50	2	-22	-50	3	-26
Inferior Temporal Gyrus (20)	L					2.54	-48	-9	-20	-48	-8	-24
Hippocampus	L					2.45	-27	-22	-6	-27	-22	-8
Middle Temporal Gyrus (21)	L					2.38	-53	-15	-13	-54	-15	-16
Hypothalamus	L					2.36	-10	-6	-7	-10	-6	-9
Lateral Globus Pallidus	L					2.33	-24	-14	-7	-24	-14	-9
Uncus (28)	L					2.17	-24	3	-27	-24	4	-32

Table G2

*Areas of non-significant but trending negative correlation between grey matter volume and verbal fluency discrepancy scores in moderate aMCI including both single and multi-domain (n = 41). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc, Uncorrected; BA, Brodmann's Area; FWE, Family Wise Error. *no given Brodmann area. Thresholded p = .05.*

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Middle Temporal	L	0.014	<.001	10464	4.6	-48	-3	-20	-48	-2	-24
Inferior Occipital	L				3.52	-33	-82	-3	-33	-84	-9
Fusiform Gyrus (20)	L				3.26	-46	-19	-24	-46	-18	-30
Inferior Temporal Gyrus (21)	L				3.21	-56	-15	-16	-57	-15	-20
Parahippocampal Gyrus (19)	L				3.03	-18	-43	-3	-18	-44	-6
Lingual Gyrus	L				2.89	-18	-76	-1	-18	-78	-6
Fusiform Gyrus (37)	L				2.84	-40	-44	-11	-40	-45	-16
Fusiform Gyrus (20)	L				2.82	-59	-7	-25	-60	-6	-30
Uncus (36)	L				2.74	-26	-2	-30	-26	0	-36
Superior Temporal Gyrus (38)	L				2.74	-28	13	-33	-28	15	-39
Fusiform Gyrus (37)	L				2.68	-36	-49	-13	-36	-50	-18
Inferior Temporal Gyrus (20)	L				2.61	-44	-11	-36	-44	-9	-44
Middle Temporal	L				2.54	-44	10	-38	-44	12	-45
Amygdala	L				2.49	-33	-4	-12	-33	-3	-15
Parahippocampal Gyrus (36)	L				2.45	-24	-37	-10	-24	-38	-14
Parahippocampal Gyrus (36)	L				2.45	-24	-33	-12	-24	-33	-16

Table G3

Areas of non-significant but trending negative correlation between grey matter volume and verbal fluency discrepancy scores in controls (N 82). Covariates: Age, Education, MMSE & Total Intracranial Volume. Unc, Uncorrected; BA, Brodmann's Area; FWE, Family Wise Error. Thresholded p = .05.

Brain Region (BA)	Hemisphere	Cluster Level pFWE	Cluster Level pUnc	Cluster Extent (voxels)	Peak level *Z* Score	Talairach Coordinates			MNI Coordinates		
						X	Y	Z	X	Y	Z
Insula (13)	R	0.01	<.001	9061	3.4	33	18	8	33	18	10
Superior Frontal Gyrus (9)	R				3.36	28	35	31	28	34	36
Inferior Frontal Gyrus (45)	R				3.3	48	21	7	48	21	9
Middle Frontal Gyrus (8)	R				3.25	28	15	38	28	14	42
Superior Frontal Gyrus (9)	R				3.19	18	50	25	18	50	30
Middle Frontal Gyrus (11)	L				3.16	-14	44	-17	-14	46	-18
Middle Frontal Gyrus (6)	R				3.05	24	-6	52	24	-9	56
Insula (13)	R				2.96	42	10	19	42	9	21
Superior Frontal Gyrus (11)	R				2.95	21	50	-13	21	52	-12
Superior Frontal Gyrus (11)	R				2.84	15	54	-14	15	56	-14
Inferior Frontal Gyrus (47)	R				2.83	36	27	-5	36	28	-4
Superior Frontal Gyrus (8)	R				2.82	18	31	45	18	30	51
Middle Frontal Gyrus (11)	R				2.78	16	40	-15	16	42	-16
Subcallosal Gyrus (25)	R				2.7	2	14	-12	2	15	-14
Inferior Frontal Gyrus (46)	R				2.65	48	37	4	48	38	6
Inferior Frontal Gyrus (47)	R				2.63	33	25	1	33	26	2

APPENDIX H

Original document of the ethical approval granted by the Regional Ethics Committee of Yorkshire and Humber.

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Dear Professor Venneri

Study title:	**Assessment of age and disease related cognitive impairment in normal volunteers and people with degenerative and vascular brain disease and assessment of the potential neuroplastic effect of non pharmacological treatment**
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We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Rachel Bell, nrescommittee.yorkandhumber-sheffield@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		18 September 2012
GP/Consultant Information Sheets	1.0	18 September 2012
Investigator CV		
Participant Consent Form: Patient 1	2	19 December 2012
Participant Consent Form: Patient 2	2	19 December 2012
Participant Consent Form: Volunteer 1	2	19 December 2012
Participant Consent Form: Volunteer 2	2	19 December 2012
Participant Information Sheet: Patient 1	2	19 December 2012

Participant Information Sheet: Patient 2	2	19 December 2012
Participant Information Sheet: Volunteer 1	2	19 December 2012
Participant Information Sheet: Volunteer 2	2	19 December 2012
Protocol		
REC application		
Response to Request for Further Information		19 December 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/YH/0474	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

Pp Professor Basil Sharrack
Chair

Email:nrescommittee.yorkandhumber-sheffield@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Ramila Patel, STH Research Department*

Amended ethical approval document: final version.

NHS
Health Research Authority

National Research Ethics Service

NRES Committee Yorkshire & The Humber - Sheffield

HRA NRES Centre Manchester
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Tel: 0161 625 7832
Fax: 0161 625 7299

20 November 2013

Ms Jodie Keyworth
Research Coordinator
Academic Directorate of Neurosciences
Sheffield Teaching Hospitals NHS Foundation Trust
N125d, N Floor
Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF

Dear Ms Keyworth

Study title:	**Assessment of age and disease related cognitive impairment in normal volunteers and people with degenerative and vascular brain disease and assessment of the potential neuroplastic effect of non pharmacological treatment**
REC reference:	**12/YH/0474**
Amendment number:	**Amendment 01**
Amendment date:	**03 October 2013**
IRAS project ID:	**84442**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

Approval was sought to add two additional patient groups. These would be patients with Multiple Sclerosis and Parkinson Disease. There would also be an additional three key collaborators.

The Committee specified that in paragraph four on page one of the Participant Information Sheets the sentence starting *'Your participant will be vital...'* should be revised as this wording is too persuasive.

The Committee also thought that the information given on page two about timings and visits could be clarified as it was not exactly clear how this would vary from four weeks to twelve weeks. Please could you revise the wording.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	Amendment 01	03 October 2013
Protocol	2.0	05 November 2013
Parkinson Disease Patient Information Sheet 2	1.0	05 November 2013
Parkinson Disease Consent Form 2	1.0	05 November 2013
Multiple Sclerosis Patient Information Sheet 2	1.0	05 November 2013
Multiple Sclerosis Consent Form 2	1.0	05 November 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

12/YH/0474:	**Please quote this number on all correspondence**

Yours sincerely

On behalf of
Mr Neil Sykes
Vice Chair

E-mail: nrescommittee.yorkandhumber-sheffield@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Professor Annalena Venneri
University of Sheffield

Dr Ramila Patel
Sheffield Teaching Hospitals NHS Foundation Trust

NRES Committee Yorkshire & The Humber - Sheffield

Attendance at Sub-Committee of the REC meeting on 20 November 2013

Name	*Profession*	*Capacity*
Mrs Yvonne Stephenson	Lead Technician in the Department of Infection and Immunity	Expert
Mr Neil Sykes	Retired Engineer/ Scientist	Lay Plus

APPENDIX I

Original document of the ethical approval granted by the Health Authority Venice and San Camillo IRCCS.

FONDAZIONE OSPEDALE SAN CAMILLO
OSPEDALE NEURORIABILITATIVO | ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO
SEDE LEGALE: 30126 | VENEZIA-LIDO | VIA ALBERONI, 70 | TEL. 041 22 07 111 | FAX 041 73 13 30
C.F. 94071440278 | P.I. 03953700279 | ISCRITTA PREFETTURA DI VENEZIA: REG. P.G. N. 409

Lido di Venezia, 23 dicembre 2015
Rif. CE: Protocollo 2014.08

Preg.ma signora
Dott.ssa Francesca Meneghello
IRCCS San Camillo

Oggetto: **Protocollo 2014.08 – Emendamento 01 VPH DARE**
Parere del Comitato etico

Gent.ma dott.ssa Meneghello,

ho il piacere di comunicarLe che il Comitato Etico per la Sperimentazione dell'ULSS12 e IRCCS San Camillo, nella seduta del 22 dicembre u.s., vista la documentazione presentata, ha espresso PARERE FAVOREVOLE all'applicazione dell'emendamento allo studio in oggetto.

Si allega alla presente un estratto del Verbale della seduta.

L'occasione è gradita per porgerLe cordiali saluti.

La Segreteria del Nucleo di Ricerca Clinica

Dott. Anesa Nicolò

COMITATO ETICO PER LA SPERIMENTAZIONE CLINICA DELLA PROVINCIA DI VENEZIA E IRCCS SAN CAMILLO(CESC)

SEDUTA del 22/12/2015

Verbale N° 37A/CESC

Il giorno 22/12/2015 alle ore 14.30 presso l'aula 512 – Azienda ULSS 12 VENEZIANA - si è riunito il Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS San Camillo, istituito in conformità alle disposizioni del DM 15/07/1997 e nominato con deliberazione del Direttore Generale ULSS12 n. 1803 del 25/09/2013 ai sensi del DM 8/2/2013 e della DGRV n°1066 del 28/6/2013 e che risulta così costituito:

	Componente	
P	Bon Dott. Giuseppe	Esperto in Bioetica
P	Boscolo Bariga Dott. Angelo	Clinico
G	Bova Prof. Sergio	Farmacologo
P	Burlon Dott.ssa Nerina	Farmacista
P	Carraro Dott. Daniele	Medico legale
P	Crovato Avv. Alberto	Esperto in materia giuridica e assicurativa
G	Della Bianca Dott.ssa Simona	Rappresentante del settore infermieristico
G	Ghi Dott.ssa Maria Grazia	Clinico
P	Gobbo Sig. Giorgio	Rappresentante del volontariato
P	Cavarzeran Dott. Fabiano	Biostatistico
P	Penzo Dott. Carlo	Clinico
P	Piccione Dott. Francesco	Clinico
P	Ponzetto Dott. Tiziana	Medico di Medicina Generale
P	Quatrale Dott. Rocco	Clinico
G	Righetti Dott. Andrea	Pediatra
G	Serino Dott. Francesco Saverio	Clinico
G	Barzan Dott.ssa Daniela	Esperto in dispositivi
P	Agostini Dott.ssa Michela	fisioterapista
P	Stradella Dott. Giovanni	Farmacista

A	Pianozza Dott.PierPaolo (sostituita dal Dott. Giovanni Mazzanti)	Direttore Sanitario ULSS 10
P	Dalla Barba Dott. Livio (sostituito dal Dott. Alvise Spolaor)	Direttore Sanitario ULSS 13
P	Finotto Dott.ssa Rita (sostituita dalla Dott.ssa Lisa Bertoncello)	Direttore Sanitario ULSS 12
NC	Malatesta Dott. Renzo	Direttore Sanitario P. S.Marco
NC	Cestrone Dott. Adriano	Direttore Sanitario casa di cura Rizzola
A	Sbrogiò Dott. Luca Gino(sostituito dal Dott. Paolo Venerucci)	Direttore Sanitario ULSS 14
NC	Sattin Dott. Guido	Direttore Sanitario Fatebenefratelli
P	Venneri Prof. Annalena	Direttore scientifico IRCCS San Camillo
NC	Giron Dott. Giampiero	Direttore Sanitario Villa Salus

G	Anglani Dott.ssa Franca	Esperta in genetica
NC	Semenzato Ing. Mara	Ingegnere clinico
NC	Spinella Prof. Paolo	Esperto in nutrizione
NC	Merenda Prof. Roberto	Esperto clinico per studi di nuove procedure tecniche, diagnostiche e terapeutiche invasive e semiinvasive

Legenda: P=presente A=assente G=assente giustificato NC=non convocato

La Dott.ssa Michela Zanutti, in qualità di Segretario Scientifico è presente alla seduta.

Riscontrato il numero legale dei componenti si procede alla visione e discussione degli argomenti stabiliti nell'ordine del giorno.

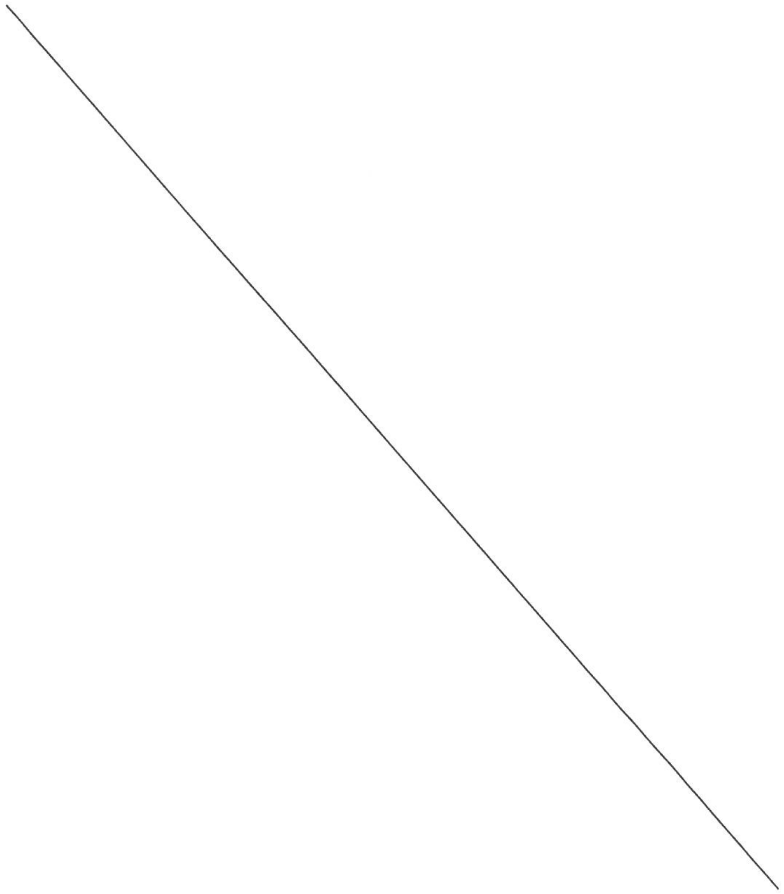
IL COMITATO

valutati tutti gli aspetti inerenti la validità scientifica e l'utilità clinica della ricerca, il protocollo e il disegno sperimentale, la correttezza etica, l'idoneità delle strutture coinvolte e le compensazioni finanziarie;

considerate con particolare attenzione tutte le condizioni di garanzia per i pazienti che partecipano agli studi clinici, dalle modalità di arruolamento alle forme di acquisizione del consenso ed all'eventuale indennizzo;

preso atto che tutti gli aspetti degli studi sono pienamente corrispondenti alle indicazioni contenute ai DGRV n. 1376 del 27/4/1999, DGRV n. 57 del 23/01/2004, n. 3456 del 11/01/2004, n. 4049 del 22/12/2004, n. 4430 del 28/12/2006; DGRV n. 2855 del 7.10.2008, DLgs n. 211 del 24/06/2003 e s.m., Decreto del Ministero della Salute del 12/05/2006 (G.U. n. 194 del 22/08/2006) e successive integrazioni normative, inerenti alla costituzione ed il funzionamento dei Comitati Etici per la sperimentazione clinica dei farmaci.

Procede ad esaminare la seguente documentazione:



[OMISSIS]

Chiarimenti Emendamento 1 allo Studio n. 585/IRCCS San Camillo
Studio osservazionale – no profit
Relatore *Dr.ssa Agostini*

Titolo Studio	VIRTUAL PHYSIOLOGY IN HUMAN DEMENTIA RESEARCH ENABLED BY IT	
Codice Protocollo	VHP-DARE@IT	**Eudract**
Promotore	IRCCS SAN CAMILLO	**CRO**
Principio Attivo		
Struttura	UOSD di Riabilitazione neuropsicologica, IRCSS San Camillo	
Sperimentatore	Dott.ssa Francesca Meneghello	

Documentazione esaminata

- **Lettera di intenti** *del 10/12/2015*
- **Protocollo di studio emendato v.2** *del 09/12/2015*
- **Sinossi del protocollo em. 01** *del 9/12/2015*
- **Foglio informativo per il paziente** *del 10/12/2015*
- **Lettera al medico curante** *del 10/12/2015*

Esaminata la documentazione, il Comitato esprime il seguente parere:

✓ *Approvata*

[OMISSIS]

VIENE RIBADITO

che questo Comitato Etico dovrà essere informato di ogni successivo emendamento ai protocolli, nonché degli eventi avversi o inattesi registrati nel corso degli studi tali da influire sulla sicurezza dei soggetti o sul completamento degli studi stessi e, a conclusione delle ricerche, dovrà acquisire i risultati finali;

che al responsabile della sperimentazione compete stabilire una procedura di gestione dei medicinali in studio, secondo il D.M. 15 luglio 1997 "Recepimento delle linee guida dell'Unione Europea di buona pratica clinica per la esecuzione delle sperimentazioni cliniche dei medicinali", la D.G.R. del Veneto n. 1376 del 27.4.1999 "Linee guida per la costituzione ed il funzionamento dei Comitati Etici per la sperimentazione clinica dei farmaci" e le successive integrazioni normative, nonchè ai sensi del DLgs n. 211 del 24/6/2003 e alle Linee Guida per gli studi osservazionali sui farmaci (determinazione AIFA-20 marzo 2008)

che il Servizio di Farmacia Ospedaliera/Servizio Farmaceutico Territoriale in ogni singola Azienda ULSS consegnerà, nei casi che lo prevedono, i farmaci in unica soluzione al

ricercatore il quale, alla chiusura dello studio, dovrà restituire i prodotti inutilizzati al medesimo Servizio per la successiva resa degli stessi allo sponsor;

che i costi della sperimentazione non dovranno gravare sul SSN come previsto art. 20 del D.Legislativo n. 211 del 24 giugno 2003 e al comma 1 art.6 D. M 12/5/2006 e per gli studi No Profit si applica il DM 17/12/2004;

che al responsabile della sperimentazione è demandato, inoltre, l'onere della conservazione degli atti relativi alle ricerche per il tempo e con le modalità previsti dalle disposizioni in vigore.

La seduta si conclude alle ore

IL RESPONSABILE DELLA
SEGRETERIA SCIENTIFICA
(Dr.ssa Michela Zanutti)

IL VICEPRESIDENTE DEL
COMITATO ETICO
(Dr.ssa Nerina Burlon)

APPENDIX J

Original document of the ethical approval granted by the West of Scotland Regional Ethics Committee.

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Annalena Venneri
The University of Sheffield
Department of Neuroscience
Sheffield
S10 2RX

Email: hra.approval@nhs.net
HCRW.approvals@wales.nhs.uk

21 November 2019

Dear Professor Venneri

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Optimising detection of cognitive decline and associated symptoms**
IRAS project ID:	**244064**
REC reference:	**19/WS/0177**
Sponsor	**Sheffield Teaching Hospitals NHS Foundation Trust**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **244064**. Please quote this on all correspondence.

Yours sincerely,
Rekha Keshvara

Approvals Manager

Email: hra.approval@nhs.net

Copy to:

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
GP/consultant information sheets or letters [General practitioner information sheet]	1	30 September 2019
IRAS Application Form [IRAS_Form_29102019]		29 October 2019
IRAS Application Form XML file [IRAS_Form_29102019]		29 October 2019
IRAS Checklist XML [Checklist_29102019]		29 October 2019
Letter from funder		04 January 2019
Participant consent form [Patient consent form]	1	23 October 2019
Participant information sheet (PIS) [Patient information sheet]	2	18 November 2019
Participant information sheet (PIS) [Patient information sheet - Highlighted]	2	18 November 2019
Research protocol or project proposal [Ethics protocol]	1	25 October 2019
Response to Additional Conditions Met [Email]		18 November 2019
Summary CV for Chief Investigator (CI) [Annalena Venneri - CV]	1	30 September 2019
Summary CV for student [Laura Wright - CV]	1	30 September 2019
Summary CV for student [Jose' Manuel Valera Bemejo - CV]	1	30 September 2019
Summary CV for student [Ronan O'Marley - CV]	1	30 September 2019
Summary CV for supervisor (student research) [Matteo De Marco - CV]	1	30 September 2019
Summary CV for supervisor (student research) [Daniel Blackburn - CV]	1	30 September 2019
Summary CV for supervisor (student research) [Ptolemaios Sarriggianis - CV]	1	30 September 2019
Summary CV for supervisor (student research) [Riccardo Manca - CV]	1	30 September 2019

IRAS project ID	244064

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is one participating NHS organisation taking part in the study in England. Therefore, there is one site type undertaking the research activities as detailed in the study protocol	This is a single site study sponsored by the participating NHS organisation. You should work with your sponsor R&D office to make arrangements to set up the study. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used	The study is funded by the Neurocare.	A Principal Investigator is expected to be in place at the participating NHS sites.	Where existing contractual or healthcare placement arrangements are not already in place it is expected that postgraduate students are supervised under close clinical supervision, when undertaking activities that may have a direct bearing on the quality of care, by a clinical supervisor who is an NHS employee or an HEI employee with an honorary clinical or research contract. Where a postgraduate student is undertaking research and clinical supervision is not available or not appropriate, the student should obtain an letter of access. Evidence of standard DBS and barred list checks with occupational health clearance would be expected to support a
					research passport application for letter of access where obtained.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.