Is Age-related Macular Degeneration related to Alzheimer's Disease? Evidence from neuroimaging and behavioural data.

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Abstract

Although age-related macular degeneration (AMD) is an eye disease and Alzheimer's disease (AD) is a dementia caused by neurodegeneration in the brain, both are common diseases affecting older people, and studies have suggested a link between them. Cognitive impairments in language and memory, and biological changes in the eye have been found in both AD and AMD. The first aims of this thesis were to compare atrophy patterns in brain structure in AMD, AD, and age-matched controls both cross-sectionally and longitudinally. Cross-sectional data revealed significantly thinner entorhinal cortex and angular gyrus in late AMD compared to controls, while longitudinal results found accelerated thinning in entorhinal cortex and decelerated thinning in the inferior frontal gyrus in early AMD (non-significant patterns). Both cross-sectional and longitudinal results suggest that there are shared patterns of neurodegeneration for AMD and mild AD. However, comparing participants with early and late-stage AMD found that entorhinal cortex is affected in early AMD, while the occipital pole is affected in late AMD, suggesting AMD has its own neurodegenerative pattern. Finally, the relationship between brain structure, physical activity levels (lifestyle and exercise), and cognitive function was assessed in AMD and control participants. A positive correlation was found between lifestyle and exercise physical activity and entorhinal cortex (non-significant medium-to-large effect), but only lifestyle was positively correlated with the hippocampus (non-significant medium effect). However, cortical measures were not positively associated with Montreal Cognitive Assessment scores measuring global cognitive function. Overall, this thesis reveals that AMD and AD have similar but diverging patterns of change in brain structures, and that changes in physical activity levels may modulate brain changes. Altogether, the findings suggest that AMD patients are at risk of experiencing atrophying brain structures involved in cognitive function beyond occipital visual regions that may increase the risk of developing AD.

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Author's Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Chapter 2 – study 1

This study used data from York Neuroimaging Centre after gaining permission from the researchers and obtaining ethics for its use (YNIC: late AMD and controls), and data from Alzheimer's Disease Neuroimaging Initiative that required ethical approval from University of York before access was granted to the data (ADNI: mild AD and controls). Here I recruited and collected data for nine YNiC controls prior to my PhD in 2016. All data was processed and analysed by me from MRI nifty data. Researchers are acknowledged by name on page 50.

Chapter 3 – study 2

This study used ADNI data for all participants groups (mild AD, early AMD, and controls). All data was processed and analysed by me from MRI downloaded as nifty files. Cognitive data was calculated based on ADNI scoring.

Chapter 4 – study 3

This study used AMD MRI cortical estimates from study 1 (YNiC: late AMD and controls) and study 2 (ADNI: early AMD and controls). All data was analysed by me based on my processing of the raw data. This includes data collected by the researcher's named on page 50.

Chapter 5 – study 4

This study used data I collected in YNiC in 2019 with help from MSc students to recruit twelve control participants (acknowledged by names on page 125). The behavioural data I collected independently, and the MRI data was collected with assistance from a Level 1 MRI operator provided by YNiC (two operators needed in the scanner room). I processed, scored, and analysed data independently.

As per Alzheimer's Disease Neuroimaging Initiative's (ADNI) data agreement, the below statement must be included in any published works using their data. Data used from the ADNI database are clearly stated in this thesis, as detailed above.

"Data used in the preparation of this article [thesis] were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in

2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org. Although ADNI data has been used in this report, ADNI have not reviewed this manuscript [thesis]."

Chapter 1: Introduction.

1.1 Background

1.1.1 Age-related macular degeneration

Age-related macular degeneration (AMD) is a retinal disease that affects the macula, a highly specialised region of the retina. It is centrally located at the back of the eye, and is important for central vision and the perception of fine details and colour (Gehrs, Anderson, Johnson, & Hageman, 2006). Its importance in vision is highlighted as it accounts for nearly 10% of the visual field (Gehrs et al., 2006). Damage to the macula has a major impact on vision because it contains the fovea which is the only region in the eye able to produce 20/20 vision (20/20 or 6/6 in the UK, is normal acuity). Consequently, patients with AMD find that their colour and fine detail vision is altered as a result of the disease (Gehrs et al., 2006; Kauppinen, Paterno, Blasiak, Salminen, & Kaarniranta, 2016; Ratnayaka, Serpell, & Lotery, 2015). AMD is a progressive disease, meaning minor-to-no disturbances in central vision at the start of disease could eventually result in noticeable visual impairments years later. About a third of all AMD patients were found to have severely impaired vision or were classified as legally blind in the World Health Organisation's global eye disease survey (Gehrs et al., 2006; Kaarniranta, Salminen, Haapasalo, Soininen, & Hiltunen, 2011).

The decline in central vision has been attributed to one of two characteristic pathologies that affect the macular. The formation of drusen in early stages, often considered a hallmark of disease, and neovascularisation in later stages (growth of new leaky blood vessels). Drusen are extracellular deposits that build between the basal lamina of the retinal pigment epithelium (RPE; the deepest layer of the retina) and Bruch's membrane, a membrane that separates the choriocapillaris (the capillaries in the choroid) from the retina (Rudolf et al., 2008; Williams, Craig, Passmore, & Silvestri, 2009). Drusen are clinically classified as soft or hard depending on their shape and size, and they are visible using a fundus examination where they appear as yellow dots located on the macula or in the periphery (Gehrs et al., 2006; Lynn et al., 2017; Nesterova & Ermilov, 2015; Williams et al., 2009). Hard drusen are usually classified as drusen that have a diameter of <63µm, or if they are <125µm in diameter with distinct edges but look flat; and soft drusen are classified as drusen that are >63µm in diameter, have indistinct edges, and substance (Crabb et al., 2002; Gehrs et al., 2006; Williams et al., 2009). Whereas sporadic hard drusen can be found in normal ageing eyes (Nesterova & Ermilov, 2015; Rozzini et al.,

2014; Williams et al., 2009), soft drusen is often clinically associated with AMD pathology and morphology (Crabb et al., 2002; Nesterova & Ermilov, 2015). However, having large amounts of hard drusen present in the retina increases the risk of developing soft drusen, owing to the possibility that these drusen may increase in size with advancing age (Williams et al., 2009).

AMD can be split in to two clinically accepted sub-types: wet AMD, and dry AMD (Gehrs et al., 2006; Nesterova & Ermilov, 2015; Zhao et al., 2015). The majority of AMD patients, around 85%, are diagnosed with the dry sub-type of AMD (Evans & Syed, 2013; Sivak, 2013; Zhao et al., 2015). Dry AMD is characterised by clinical signs of progressive drusen formation, pigment disruption, thickening of Bruch's membrane, and degradation of RPE and choroid cells (Evans & Syed, 2013; Gehrs et al., 2006; Kaarniranta, Tokarz, Koskela, Paterno, & Blasiak, 2017; Sivak, 2013). Approximately 15% of d-AMD cases will progress into the more damaging form of AMD called wet AMD, which in later stages is referred to as exudative AMD. In wet AMD, choroidal neovascularization (CNV) occurs (Evans & Syed, 2013; Gehrs et al., 2006; Kaarniranta & Salminen, 2009). Choroidal neovascularization is the process in which the RPE produces an increased amount of vascular endothelial growth factor that encourages the growth of new fragile blood vessels. Alongside this, the blood-retina barrier is weakened resulting in these new blood vessels expanding from the choroid in to the retina (Kauppinen et al., 2016). For patients who do not develop wet AMD, drusen in dry AMD can continue to grow in diameter with age, resulting in further destruction of the RPE and photoreceptors in the macula. When this destruction occurs, it is considered the later stage of dry AMD, called geographic atrophy, due to atrophy apparent in the fundus tissues (Ratnayaka et al., 2015; Sivak, 2013).

As a result of the progressive nature of AMD, the disease can be broken down into stages of decline, starting at early AMD, with no visual impairment, and ending in late-stage geographic atrophy or late-stage wet AMD, where vision is likely to be irreversibly impaired (Age-Related Eye Disease Study Research Group, 2001; Klein et al., 1991). Deterioration in AMD is linear in nature, meaning changes can be measured by the number and size of drusen, amount of geographic atrophy, and pigmentary changes in the macula (Gehrs et al., 2006). The stages of AMD were categorised by the Age-Related Eye Disease Study (AREDS) in 2001. They defined four stages of AMD progression from no AMD to advanced AMD. Category 1 (no AMD) includes individuals who have no macular abnormalities or have the presence of only a few small drusen (<63µm in diameter). Category 2 (early AMD) includes patients who have mild to borderline features of AMD, including the presence of multiple small drusen, or a few intermediate drusen (63µm - 124µm in diameter), or some pigment abnormalities. Category 3 (intermediate-AMD) includes patients who have extensive intermediate drusen, at least 1 large

drusen (>125μm in diameter), or noncentral geographic atrophy. Category 4 (advanced-AMD) contains patients with advanced AMD in at least one of their eyes (Age-Related Eye Disease Study Research Group, 2001; Clemons, Rankin, & McBee, 2006). Although there are several changes in the eye, it is the accumulation of drusen that increases a patient's risk of developing advanced AMD (Kauppinen et al., 2016).

The AREDS scale has been used in later AREDS studies (Clemons et al., 2006) and the stages of the disease have also been defined by AREDS's severity scale system (Davis et al., 2005). This scale consisted of 9 stages overall, dependant on the size of drusen (6 stages) and the amount of pigmentary abnormalities (5 stages) in different combinations to make the scale. The scale was later simplified (Ferris et al., 2005), and other studies have defined early to late AMD in other ways. Baker *et al*. (2009) described early AMD as the presence of one indicator of AMD (either RPE de-pigmentation, or presence of soft drusen), or a combination of soft drusen with increased RPE pigment. Alternatively, those with depigmentation that is not classified as late AMD were also in this group. Whereas late AMD was defined as retinas exhibiting later-stage wet AMD symptoms with detachment of the RPE, subretinal haemorrhage, and fibrous scarring evident; or the presence of pure geographic atrophy (late-stage dry AMD) (Baker et al., 2009). Regardless of which scale is used to indicate the stages of the disease, each stage represents a clear progression of clinical and damaging features associated with AMD, showing how the disease progresses in patients with time.

1.1.2 Alzheimer's disease

Dementia, including Alzheimer's disease (AD) is the leading cause of death in England according to the Office for National Statistics (Cornish, 2021). Alzheimer's disease is the most common form of dementia. It is a progressive neurodegenerative disease targeting the brain and is clinically characterised by a loss of memory, the inability to learn new information, and eventual cognitive decline (Götz, Schild, Hoerndli, & Pennanen, 2004; McKhann et al., 2011; Pini et al., 2016; Sivak, 2013). This is because AD causes damage to the brain starting in the medial temporal lobe (MTL), affecting regions such as the entorhinal cortex and hippocampus that are important for forming memories, before affecting additional areas of the brain resulting in widespread atrophy and cognitive impairment. The exact cause of AD is unknown but has been associated with the deleterious effects of amyloid beta plaques.

The hallmarks of AD includes progressive memory loss, hyperphosphorylated tau resulting in neurofibrillary tangles, and increased levels of extracellular deposits of amyloid beta peptides that form amyloid beta plaques in the brain (Dong, Duan, Hu, & Zhao, 2012). The amyloid

cascade hypothesis states that the accumulation of amyloid aggregates initiates a cascade of changes; including the hyperphosphorylation of tau causing tangles, loss of neurons and synaptic function resulting in brain atrophy and cognitive decline (Spangenberg & Green, 2017). Symptoms are believed to be the result of amyloid beta plaques and tau neurofibrillary tangles building up in the hippocampus and cortex (Ohno-Matsui, 2011).

The relationship between amyloid beta plaques, tau neurofibrillary tangles, and AD patient's clinical symptoms is not straightforward. Although amyloid beta is speculated to be a key pathological feature in the development of AD (Ingelsson et al., 2004) as suggested by the amyloid cascade hypothesis (Hardy & Higgins, 1992), it is not directly associated with cognitive scores. Only weak correlations have been found between amyloid beta plaques and cognitive impairment (Giannakopoulos et al., 2003; Hardy & Selkoe, 2002). Furthermore, amyloid beta has been found in the brain of older individuals who have not exhibited signs of AD. One argument explaining these findings stated that this type of amyloid beta is dispersed and "not associated with surrounding neuritic and glial pathology" (Hardy & Selkoe, 2002, p. 353), distinguishing it from AD pathology. Alternatively, a relationship was found between tau neurofibrillary tangles and cognition in other studies, and tau has been closely linked to early clinical symptoms of AD (Brier et al., 2016; Giannakopoulos et al., 2003). Brier et al. (2016) concluded that amyloid beta imaging may provide a good marker for identifying early stages of AD, whereas tau imaging is better at predicting AD progression, which helps to demonstrate the intricate relationship of the key hallmarks of AD.

An AD diagnosis can only be confirmed post-mortem (Hyman et al., 2012; Javaid, Brenton, Guo, & Cordeiro, 2016). However, there are two types of AD diagnosis a patient can be given based on their living clinical features: possible AD, and probable AD. Patients who are diagnosed with probable AD have clinical features that reflect an uncomplicated linear disease course, whereas those who are diagnosed with possible AD have comorbidities or they demonstrate atypical clinical features alongside typical AD features (Villareal et al., 2003). Based on a patient's cognitive impairment the criteria for a probable diagnosis are: that the onset is gradual; cognitive decline is evident from past clinical testing; and the initial or prominent cognitive declines are within amnestic and non-amnestic presentations. For amnestic presentation, a deficit should be evident in the learning and recall of new information, and for non-amnestic presentation a deficit in language, visuospatial, or executive function should be present. These deficits can include word-finding, spatial cognition, and impaired judgement as an example for each presentation respectively (McKhann et al., 2011). For possible AD, the onset of clinical symptoms may not be gradual, even though the

symptoms reflect the criteria outlined above for probable AD, and there may be a mixed presentation of aetiology. Their AD symptoms may be mixed with cardiovascular disease, the presence of infarcts, a history of stroke associated with their cognitive decline, or higher than expected white matter hyperintensity burden (white matter lesions with high signal on T2-weighted images (Arvanitakis et al., 2016; McKhann et al., 2011)) which indicate demyelination and axonal loss (Fazekas et al., 1993).

Alzheimer's disease is a progressive disease and can be split into clinical stages based on disease severity. The progression of AD can be attributed to the build-up of amyloid beta plaques and tau neurofibrillary tangles that have distinct pathological activity but are both closely related in AD (Brier et al., 2016). The build-up of amyloid beta outside neurons results in a disruption of neuronal communication at synapses; and tau tangles, that build inside the neurone, prevents the transport of essential molecules. The combined action of plaques and tangles causes neuronal damage and cell death (Alzheimer's Association Report, 2020). Damage to the brain is often found in the MTL in the beginning stages of the disease, before moving up and forward towards the parietal and frontal lobes, and then to the occipital lobe where cortical thinning is observed (Braak, Braak, & Bohl, 1993; Singh et al., 2006).

It is accepted that there are five stages of AD. In the first stage patients will not know they have AD as this stage of AD starts before any symptoms are apparent. This is called the preclinical AD stage and is only identified using imaging techniques that can identify amyloid beta. Preclinical AD is usually discovered during research rather than in clinical settings. Prodromal AD is discovered once minor problems with memory and thinking begins, and is defined as mild cognitive impairment (MCI) with the presence of a positive AD biomarker (Bertens et al., 2019). Not everyone with MCI will go on to develop AD, however. Once AD is established, AD progresses through three stages classed as mild, moderate, and then severe as the disease progresses over time (Alzheimer's Association Report, 2020). Depending on when a person with AD was diagnosed, life expectancy can be between an average of 3-11 years. Continual cognitive decline means the development of early amnesia and executive dysfunction exacerbate as the disease spreads to other cognitive domains. Alzheimer's disease is often diagnosed during the mild stage of disease and is associated with early memory problems, such as remembering places, names, and events, as well as difficulty expressing themselves, problem solving, and completing complex tasks. Moderate AD is characterised by an increase in confusion, with changes in personality, and the requirement for help with daily activities and self-care. Severe AD is where poor judgement and problems with communication arise (Alzheimer's Association Report, 2020). Disease progression eventually results in end-

stage AD where the patient is incapacitated, unable to perform basic bodily functions such as swallowing and bladder control (Ball et al., 1997; Kaarniranta et al., 2011; Alzheimer's Association Report, 2020).

1.1.3 Shared Risk Factors

Alzheimer's disease and AMD share one characteristic: they are both progressive age-related neurodegenerative diseases; otherwise, no similarities between their main clinical features are evident, resulting in the inference that the two diseases are distinct from each other. However, similarities have been found between AD and AMD in several domains. Risk factors for the diseases can be broadly linked to four categories; age, environmental, biological, and genetic; although some of these factors have overlapping qualities - for example age causes biological changes. Similarities between AD and AMD are found for age, environmental risk factors, and their biology or pathophysiology, but genetically the diseases are diverse and only share some genetic components. For example they share genes that help control the complement system (part of the innate immune system) however Apolipoprotein E (APOE) allele 4 increases AD risk but is protective against AMD, and allele 2 increases risk for AMD but is protective for AD (Kaarniranta et al., 2011; Williams et al., 2015; Williams, Silvestri, Craig, Passmore, & Silvestri, 2014). Genetic factors are not reviewed in this section because genes work in combination with each other as well as environmental factors and are beyond the scope of this thesis.

The main risk factor for AD and AMD is age, with an increase in number of cases emerging each year past the age of 65. In the US, it was found that in a group of women aged 65-69 the prevalence of having either wet AMD or geographic atrophy was 0.70%, which increased to more than 16.39 % at age 80+ (Friedman et al., 2004). In a population study investigating the prevalence of AD, US citizens aged 65-74 had a 3% prevalence of AD that increased to 32% in those aged 85+ (Hebert, Weuve, Scherr, & Evans, 2013). These features of the diseases highlight the importance of age in both diseases' development.

Environmental risk factors are wide ranging but includes factors such as smoking (Brown, Lockwood, & Sonawane, 2005; Ersoy et al., 2014). Research found that those who smoke cigarettes have an increased risk of developing AD and AMD (Christen, 1996; Klein, Klein, & Moss, 1998; Ott et al., 1998; Seddon, Willett, Speizer, & Hankinson, 1996). In AMD, it is expected that a major component in cigarette smoke called hydroquinone (a pro-oxidant) has a toxic effect on the retinal cells in the RPE. Smoking causes the accumulation of vascular endothelial growth factor (a pro-angiogenic: VEGF) as well as decreasing pigment epithelial derived factor (an anti-angiogenic: PEDF). Cigarette smoke is suspected to alter the VEGF/PEDF

ratio in favour of angiogenesis - the process of forming new blood vessels. It was concluded that this change in the VEGF/PEDF ratio in cigarette smokers may encourage drusen formation, and result in the development of CNV in patients with wet AMD (Pons & Marin-Castaño, 2011).

For AD, animal studies have revealed similar negative effects of cigarette smoke on biological processes. Increased levels of soluble amyloid beta precursor protein beta (sAPPb) were found in rat hippocampus and cortex when exposed to cigarette smoke (Ho et al., 2012). In human amyloid beta formation, the cleavage of an amyloid precursor molecule (APP) by the enzymes alpha-secretase (neuroprotective) and beta-secretase (neurotoxic) is altered, resulting in higher levels of sAPPb that causes AD amyloid beta peptides and eventually amyloid beta plaques (Zhang, Thompson, Zhang, & Xu, 2011). The same biological process that occurs in the development of human amyloid beta plaques was reflected in the rat model as the higher sAPPb levels were associated with amyloid beta levels in the cortex and hippocampus (Ho et al., 2012), demonstrating a link between cigarette smoking and amyloid beta development. The findings were supported by a mouse model, in which increased amyloid beta was found in the cortex and hippocampus of cigarette smoke-exposed mice. The authors concluded that smoke exposure likely promotes the formation and maturation of new amyloid beta deposits, which is the main neuropathological feature of AD (Moreno-Gonzalez, Estrada, Sanchez-Mejias, & Soto, 2013).

The biological role of oxidative stress and inflammation in the development of both diseases is also noted in the literature (Biscetti et al., 2017; Dentchev, Milam, Lee, Trojanowski, & Dunaief, 2003; Donoso, Kim, Frost, Callahan, & Hageman, 2006; Kaarniranta et al., 2011; Kauppinen et al., 2016; Wyss-Coray & Rogers, 2012). Oxidative stress is caused by an imbalance between the production of harmful material, and the body's ability to remove or counteract the effects of that material, with increasing levels of harmful material available to damage cells. Oxidative stress reduces metabolic activity, increases reactive oxidant species production, and damages mitochondrial DNA (Kaarniranta et al., 2013). Inflammation is a natural immune response that maintains the homeostasis of cells in response to foreign, and potentially harmful, materials. In the short-term this is a highly effective protective mechanism. Over a longer period of time the inflammatory response can be detrimental to the cells it was trying to protect (Kauppinen et al., 2016). It is suggested that activated RPE cells with the activity of macrophages in AMD, and activity of microglia cells in AD produce similar mediators of the inflammatory response (Kaarniranta et al., 2011).

In AMD, oxidative stress and inflammation results in the development and progression of symptoms (Kauppinen et al., 2016). Each cell in the RPE spends a lot of its metabolic energy on

maintaining 30-40 photoreceptors. This maintenance includes heterophagy, a process of cell digestion where the ends of the outer segments of the photoreceptors are broken down. Due to this high metabolic activity, amongst a couple of other factors, the RPE is sensitive to oxidative stress (Kaarniranta et al., 2013). As people age and AMD develops, the continued ingestion of the outer segments of photoreceptors by RPE cells, whose function is compromised due to compensating for the loss of RPE cells around them, causes lipofuscin to accumulate in lysosomes. This ultimately blocks lysosomal enzymes and inhibits autophagy (a cellular cleaning system that maintains homeostasis) (Ferrington, Sinha, & Kaarniranta, 2016; Kaarniranta et al., 2013, 2017). A change in metabolic function in favour of oxidative stress results in inflammation, as damage to the RPE results in the release of cytokines (inflammatory immune cells) in the retina (Kauppinen et al., 2016).

The progressive increase of oxidative stress and inflammation from normal ageing to AD is expected to play a key role in AD pathology. Immune-mediated actions then drive AD progression (Heppner, Ransohoff, & Becher, 2015; Kaarniranta et al., 2011). It is expected that oxidative stress results from the imbalance created between the production and clearance of amyloid beta peptides; with higher levels of amyloid beta peptides damaging cells causing the development of tau (Hardy & Selkoe, 2002). The presence of several grouped amyloid beta peptides in the brain causes microglia (cells that mediate the immune response in the central nervous system (CNS)), to become cytotoxic (Landa, Butovsky, Shoshani, Schwartz, & Pollack, 2008). This process is suggested to block neurogenesis, where new neurons are formed (Eriksson et al., 1998; Landa et al., 2008). Neurogenesis occurs in the hippocampus of adult humans and the newly formed neurones become functional, meaning their generation is important for maintaining hippocampal functions such as memory (Eriksson et al., 1998; Van Praag et al., 2002).

1.1.4 Prevalence rates and comorbidity

Age-related macular degeneration and AD share several underlying mechanisms, but it is not known whether the diseases are related. Several studies have explored the prevalence rates of AD after an AMD diagnosis and vice versa with varying results (Biscetti et al., 2017; Demırcı et al., 2015; Frost et al., 2016; Keenan, Goldacre, Goldacre, & Hyman, 2014).

In a longitudinal study where just under 5,000 Taiwanese patients with AMD were tracked over time, the prevalence of AD in AMD patients was significantly higher in the AMD cohort when compared to non-AMD controls. This shows a diagnosis of AMD was linked to an increased chance of developing AD in this sample (Tsai, Chen, Huang, Yuan, & Leu, 2015).

Another study found that the frequency of AD in patients exhibiting late-stage AMD was significantly higher than in age-matched controls, standing at 40.7% in AD patients and 20.4% in controls (Demırcı et al., 2015). This study supports earlier work where an increased prevalence of AD was found in AMD patients (Klaver et al., 1999).

This interaction was found in the opposite direction, where a significantly higher proportion of AD patients were found to have early AMD compared to controls. In this study, the highly significant relationship ($p<.001$) between AMD and AD was found using only 22 AD patients. Even after controlling for confounds such as smoking, age, and hypertension which play a role in both diseases (Frost et al., 2016). The results indicate that the diseases could be intrinsically related.

Despite some prevalence studies revealing a connection between AMD and AD, other research casts doubt on their relationship. In Keenan et al.'s (2014) study, hospital records from the National Health Service (NHS) in the UK were used to assess the likelihood of those diagnosed with AD being treated for AMD, and those who were diagnosed with AMD experiencing AD. The study examined a large sample of hospital records, consisting of over 65,000 people with AMD, and over 168,000 people with AD. They concluded that there was not an increased risk of AD or AMD once a patient had a diagnosis of the other disease. The odds ratio for AD after an AMD diagnosis was 0.86, and for AMD after a diagnosis of AD was 0.04. These results showed that the chances of being treated for one disease after a diagnosis of the other was not elevated or different from chance. However, the findings reveal that AD patients are significantly less likely to be seen for AMD (Keenan et al., 2014; Szumilas, 2010). It is possible AD patients with eye complaints are less likely to ask about their symptoms or have treatment for AMD, distorting this figure (Keenan et al., 2014). Similarly, AD symptoms such as forgetfulness and changes in personality in AMD patients could be attributed directly to AMD rather than patients seeking investigation for AD. A major limitation of this study was that it examined patients with the wet form of AMD and no patients with the dry form of AMD. The authors also acknowledge that the AD group could be confounded with different dementias.

1.1.5 Cross-over in clinical features

1.1.5.1 Eye

In addition to the previously addressed risk factors and comorbidity rates, new evidence has emerged linking drusen (the main feature of AMD) with AD. Conversely, amyloid beta (the main feature of AD) has also been linked to drusen in AMD (Shoda et al., 2018; Ukalovic et al.,

2018). The overlap of these features is important as it demonstrates that clinical features associated with one disease can be present within the other disease.

The notion that the brain and eye are connected is not new (Javaid et al., 2016) because they are both derived from neural tissue that make up the CNS, of which the retina is an integral part (Ohno-Matsui, 2011). During embryonic development, the cranial end of the neural tube splits into three enlargements (primary structure), one of which is called the forebrain; this is the first structure where the eye and brain share neural tube tissue (Chow & Lang, 2001). From here, five brain divisions (secondary structure) start to emerge as the forebrain splits into the telencephalon and diencephalon. The telencephalon continues to develop into structures such as the cerebral cortex including areas such as the hippocampus, whilst the eyes and optic nerve develop from the diencephalon (Wilcock & Njaa, 2015).

Naturally, as the brain and retina develop from the same neural tissue, this suggests the retina and brain may have further similarities (den Haan, Verbraak, Visser, & Bouwman, 2017). This is reflected in their physical features as the brain and retina both have blood-tissue barriers (Ohno-Matsui, 2011). Similarities in metabolic activity are also found, where metabolic demand is higher than any other organ and comparable between the retina and brain (Wong-Riley, 2010). As a consequence the brain and retina have similar cell signalling and organelle function during ageing (Kaarniranta et al., 2011), making it plausible that a neurodegenerative brain disease can affect the retina, and the retina can exhibit interactions with the brain (Javaid et al., 2016). It has already been suggested that the eye “offers a direct window to cerebral pathology” (Lim et al., 2016, p.1), showing the possibility that AD and AMD may share other clinical symptoms. However, it should be noted that although there are many similarities between the brain and retina, they are not homogeneous due to variations in their anatomy (MacCormick et al., 2014).

The discovery of amyloid beta within drusen of AMD patients supports the argument that AMD may be related to AD. In an early study, amyloid beta was first found in the drusen of four out of nine AMD patients’ retinas and not found in any retinas of controls (Dentchev et al., 2003; Ratnayaka et al., 2015; Shoda et al., 2018). The study discovered amyloid beta in areas most at risk of further degeneration, specifically the edges of atrophy in geographic atrophy eyes. The authors concluded that the presence of amyloid beta correlated with the location of damage to the RPE and photoreceptors. It was not clear from these initial findings whether amyloid beta contributed to, or resulted from, retinal degeneration (Dentchev et al., 2003). However, amyloid beta has since been implicated in the progression of AMD (Dentchev et al., 2003; Ratnayaka et al., 2015) showing that it is key to AMD pathology. Although both hard and soft

drusen can be present in AMD, soft drusen is most associated with AMD pathology and has been found to contain amyloid beta (Ratnayaka et al., 2015; Shoda et al., 2018). In a sample of non-demented elderly participants, those that had high levels of cerebral amyloid beta also had soft drusen with larger diameters than those with lower levels of cerebral amyloid beta (Shoda et al., 2018). These studies provide evidence of an amyloid beta-drusen relationship within the retina.

Studies have also found that the presence of hard drusen in the retina is associated with AD (Ukalovic et al., 2018). Hard drusen was more prominent and larger in the retinas of AD patients compared to age-matched controls. It was even suggested that the development and progression of hard drusen within the periphery of the retina may act as a valid biomarker for AD (Aslam et al., 2014; Ritchie et al., 2011), based on the finding that hard drusen significantly increased in diameter in AD patients over a 2 year period compared to controls (Aslam et al., 2014). Increased drusen size, as shown in AD participants in Aslam et al. (2014), is a risk factor for developing AMD. A significant association was discovered between the number of intermediate hard drusen in the periphery of the retina and cerebral amyloid angiopathy severity in AD participants (Ukalovic et al., 2018). The drusen-amyloid beta relationship in AD is further evidence that the two diseases may share some aspects of pathophysiology. If the interaction between the eye and brain is bi-directional then drusen formation that causes photoreceptor damage in the retina of AMD patients, may be reflected in the brain beyond that observed in the visual cortex (Hanson et al., 2019; Hernowo et al., 2014).

1.1.5.2 Cognition

Shared clinical features between AMD and AD are not exclusive to their pathophysiology and the eye. To enhance the argument that AD and AMD may be related, AMD patients would have to show cognitive decline too, a key clinical feature of AD. Indeed, several studies have demonstrated cognitive impairments characteristic of AD in AMD patients (Koen & Yonelinas, 2014; Zhou et al., 2016). This shared cognitive impairment was revealed using global cognition assessments that are commonly used in dementia research and in clinical settings on AD patients; including the Mini-Mental State Examination (MMSE; Folstein, Folstein, & Mchugh, 1975), mini-cog (Borson, 2000), and Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), in addition to more specific tasks measuring different cognitive domains.

1.1.5.2.1 Global cognition

The MMSE is a well-known cognitive assessment often used in clinical and dementia research settings to measure global cognition due to its short administration time (Arevalo-Rodriguez et

al., 2015) and high specificity in discriminating AD from MCI (Zhou et al., 2016). Patients with AD consistently perform poorer on the MMSE compared to cognitively normal aged-matched controls of a similar education level (Amieva et al., 2005; Rodríguez-Aranda et al., 2016). Lower scores on recall, and time and place orientation questions compared to questions assessing attention and calculation are associated with signs of AD. An impairment on these questions first with better functioning on the other questions is found in mild AD, showing that lower scores on recall and orientation are specific to this type of dementia (Ashford, Kolm, Colliver, Bekian, & Hsu, 1989; Henneges, Reed, Chen, Dell'Agnello, & Lebrec, 2016; Small, Viitanen, & Backman, 1997).

The MMSE has recently been used to assess the cognitive ability of those with AMD. Studies found that participants with AMD performed significantly poorer on the MMSE compared to age-matched controls (Clemons et al., 2006; Demırcı et al., 2015; Woo et al., 2012; Zhou et al., 2016). Participants exclusively with late-stage AMD were also found to have poorer cognitive function compared to controls (Harrabi et al., 2015; Rozzini et al., 2014). To highlight the relationship between AMD and cognitive decline further, a study assessing the cognition of an aged population found that those who had lower scores on the MMSE were nearly twice as likely to be diagnosed with AMD (Baker et al., 2009), indicating that cognitive decline associated with AMD is beyond that expected in normal ageing, and may be pathological. Based on these findings, it could be concluded that advanced disease progression in AMD is associated with reduced cognitive function proportionate with the cognitive decline evident during mild AD (Henneges et al., 2016).

Despite the support for cognitive impairment in AMD, it could be suggested that, although the MMSE is a heavily verbal task (Tombaugh & McIntyre, 1992), AMD patient scores are lower because participants were unable to complete vision-based questions due to their impaired vision. In Harrabi et al.'s (2015) study, the MMSE-blind was used to assess patients' global cognitive function. The MMSE-blind removes eight items that rely on vision directly or indirectly, and has been validated as an appropriate tool to use on visually impaired participants (Busse, Sonntag, Bischkopf, Matschinger, & Angermeyer, 2002). Still, compared to cognitively normal age-matched controls, AMD patients' scores were significantly lower when using the MMSE-blind (Harrabi et al., 2015). This finding shows that a decline in AMD participant's cognitive score is not the result of the patient's inability to see the stimulus or to perform vision-related tasks.

A meta-analysis revealed significantly lower MMSE scores in AMD patients compared to cognitively healthy controls, regardless of whether a patient was diagnosed with wet or dry

AMD (Zhou et al., 2016); this was also found with the mini-cog in a separate study (Al-Salem & Schaal, 2014). The mini-cog is shorter to administer than the MMSE, only using a clock-drawing and recall task to quickly assess cognitive function, aspects found to be impaired in early AD (Cecato, Martinelli, Izbicki, Yassuda, & Aprahamian, 2016; Henneges et al., 2016). Despite its minimal testing length, the mini-cog is a good screening tool for AD and its use in research and clinical settings is recommended (Yang et al., 2016), validating the findings in this study.

The MoCA is another variation of global cognition tasks and has also been used in AD research due to its ability to highlight cognitive impairments linked to AD (Cecato et al., 2016). The MoCA is commonly used in clinical settings to track the progression of dementia (Chang et al., 2012). Like the MMSE, lower scores on certain questions within the MoCA are characteristic of AD. Questions on delayed recall and orientation were identified as specific to AD (similar to the MMSE), as well as clock-drawing (similar to the mini-cog), and naming questions. The scores on these cognitive domains were able to significantly distinguish MCI from AD (Cecato et al., 2016).

In AMD research, studies using the MoCA revealed significantly lower scores in AMD patients compared to healthy controls (Rozzini et al., 2014). Although the MoCA is a more sensitive measure of MCI (Dag, Örnek, Örnek, Günay, & Türkel, 2014), it is not often used in AMD research, probably because it contains more vision-based tasks. However, a benefit of using the MoCA is that the likelihood of a ceiling effect (a score of 28-30 out of 30) for cognitively healthy controls and those with MCI is reduced compared to the MMSE. In one study it was found that 71.4% of cognitively normal controls and participants with MCI were in the 28-30 score range using the MMSE compared to 18.1% when using the MoCA (Trzepacz, Hochstetler, Wang, Walker, & Saykin, 2015). Rozzini et al. (2014) accounted for patients' visual loss when administering the MoCA by using a magnifying glass to enlarge all their neuropsychological assessments. They demonstrated that AMD patients' scores were significantly reduced due to their cognitive ability rather than their ability to see the assessment. This shows that the MoCA can be used to test AMD patients as the sensitivity of the test is unlikely to be affected by any visual impairment if stimuli are enlarged.

To discover whether AMD and AD continue to share cognitive traits beyond overall global cognition scores, it is pertinent to explore cognition in areas that are particularly affected by AD or show impairment earlier in disease. Several studies show that patients who progress from MCI to AD often have impairments in episodic memory and executive function (Baudic et al., 2006; Rozzini et al., 2014). For successful integration of visual rehabilitation techniques in AMD patients, contextual memory and executive function were highlighted as important

cognitive domains (Whitson et al., 2010). This shows the importance of investigating and accounting for AMD patients cognitive ability during visual rehabilitation (Woo et al., 2012); especially as AMD patients experience higher rates of cognitive impairment than non-AMD controls (Pham, Kifley, Mitchell, & Wang, 2006).

1.1.5.2.2 Memory

One of the first, widely accepted symptoms of AD is the presence of memory impairment. Alzheimer's disease affects a person's episodic-memory with naming or semantic problems evident (Jahn, 2013). Memory impairments are not thought to occur in those with AMD as the disease is often associated with visual impairment. However, research into AMD patients' cognition has revealed that memory may be affected as a result of the disease (Clemons et al., 2006; Demırcı et al., 2015; Lindekleiv et al., 2013; Rozzini et al., 2014; Whitson et al., 2010).

The Logical Memory tasks are subtests of the Wechsler Memory Scale-Revised where participants are told a story and asked to recall it either immediately - immediate recall - or after 30 minutes - delayed recall. In a study with over 100 participants being treated for macular disease, 25.7% of participant scores on Logical Memory part 1 (immediate recall) were at least 1 standard deviation below their demographic mean, and 5.9% of participants' scores were at least 2 standard deviations below the demographic mean. The results were similar for Logical Memory part 2 (delayed recall) where 26% of participants scored at least 1 standard deviation below the mean compared to the control group, and 6% of participant's scores were at least 2 standard deviations below (Whitson et al., 2010). The results from this study clearly demonstrate an impairment in some patients' ability to recall information immediately and after a delay. However, the participants in this study had a mixed diagnosis of macular diseases, making it difficult to apply these findings specifically to AMD.

Further support for memory impairment was found in a study using only AMD diagnosed patients (Clemons et al., 2006). Participants were categorised by severity of their disease, from no AMD (control) to advanced AMD (four categories). A significant difference in scores between the groups was found in Logical Memory part 1 (immediate recall) and in Logical Memory part 2 (delayed recall) (Clemons et al., 2006). Again, these results show a decline in cognitive performance with disease progression. Logical Memory task scores are regularly used to decide the inclusion of AD patients in AD clinical studies, showing the importance of Logical Memory scores within AD (Chapman et al., 2016) and AMD research.

Other tasks have been used to reveal memory impairments in AMD patients, indicating that the memory impairment is not specific to the type of task used. Using a delayed word recall

task, where 10 common nouns were presented and then recalled 5 minutes later, scores for participants with late AMD were significantly lower than scores for participants without late stage AMD, even after controlling for age, gender, education, and the research centre where data were collected (Demırcı et al., 2015). However, this was not true for participants with very early AMD. This study was conducted on participants that were in their mid-50s at baseline, which is younger than usual for an AMD cohort in most AD-AMD research. Very early AMD, in this case, may not be applicable to the AD-AMD link due to the preservation of cognition in early AMD, further confounded by participants' younger ages. In this study, late AMD was defined as having pure geographic atrophy or signs of wet AMD, and early AMD was defined as the "presence of either soft drusen alone, RPE depigmentation alone, or a combination of soft drusen with increased retinal pigment and/or depigmentation in the absence of late ARM" (Wong et al., 2002, p. 3) based on the Wisconsin grading system (Klein et al., 1991).

AMD patients were also found to have significantly reduced scores compared to cognitively normal controls for the following tasks: Short-story recall, Rey List Immediate, and Rey List Delayed (Rozzini et al., 2014). List tasks, in which a list of words is given and free recall is used to measure memory such as Rey List immediate and delayed in this study, are shown to have high levels of sensitivity and specificity to diseases causing memory impairments such as AD (Gavett et al., 2009). The significantly lower scores on the Rey List immediate and delayed recall tasks, given its high specificity, indicates that memory impairment in AMD patients should be investigated. Both wet and dry AMD patients showed significantly lower scores in the Rey List immediate and Rey List delayed tasks compared to controls (Rozzini et al., 2014).

Furthermore, patients diagnosed with AMD were found to have significantly lower scores on a 12-word immediate recall memory test, but the presence of drusen was not associated with these memory scores (Lindekleiv et al., 2013), similar to how cognitive scores are not correlated with amyloid in AD. These findings suggest it is the presence of AMD that caused their memory impairment rather than changes in their vision or retina, supporting the idea that cognitive impairment is a symptom of the disease itself and not a side effect of visual loss or drusen presence. Further evidence to support the claim that memory impairment is related to AMD but not necessarily to retinal changes is found in Clemons et al. (2006). They found that significantly different memory scores remained between groups of differing disease severity when participants with a visual acuity of 20/40 (6/12 in the UK) or better (20/20 or 6/6 in the UK, is normal acuity) were included. This further ties in to the idea that disease severity is positively correlated with memory performance in the Logical Memory tasks, even though

the categories of AMD are based on drusen and other physical symptoms of AMD being present (Clemons et al., 2006), because disease duration may relate to memory performance. These were not the only studies arriving at this conclusion as Demirci et al., (2015) also found no association between assessment scores and visual acuity.

1.1.5.2.3 Executive function

Executive function can be described as the collection of cognitive abilities that help to control or guide behaviour, such as planning, decision-making, inhibition, organisation, and initiating behaviours (Anderson & Tranel, 2002). Executive dysfunction is evident in the early stages of AD (Baudic et al., 2006; Henry, Crawford, & Phillips, 2004; Kirova, Bays, & Lagalwar, 2015; Monsch et al., 1997). Deficits in flexibility and self-monitoring ability, visuospatial and episodic memory, and reasoning and concept formation were found (Baudic et al., 2006), as well as weak selective and divided attention skills (Kirova et al., 2015) in individuals with very mild AD compared to cognitively normal controls. Poor executive function in MCI is often an indicator of a further decline into AD (Kirova et al., 2015), making this area of cognition equally as important to memory impairment in determining AD progression and prognosis.

Studies on AMD patients have also shown that executive functioning is impaired (Rozzini et al., 2014; Zhou et al., 2016). Visuospatial ability, and selective and divided attention were impaired in AMD patients compared to cognitively normal controls. However, unlike scores from global cognition and memory tasks, these impairments are AMD sub-type specific (Rozzini et al., 2014; Zhou et al., 2016). Dry AMD patients were found to perform significantly worse than controls on tasks relating to divided attention and visuospatial abilities measured by trail-making task B, where participants join dots containing letters or numbers in ascending order, and the clock test, but wet AMD did not. Despite this, there was no significant difference between wet and dry AMD participants' scores on these tasks, and overall AMD scores (wet and dry scores in the same group) were not significantly different compared to controls (Rozzini et al., 2014). Similarly, a meta-analysis on selective attention, measured via trail making task A where participants join dots containing numbers in numerical order, revealed a significant impairment in wet AMD participants compared to controls, but an impairment was not found in dry AMD (Zhou et al., 2016). Overall AMD scores for trail making task A was significantly different from controls' scores in this meta-analysis (Zhou et al., 2016), but narrowly missed significance in another study, $p = .09$ (Rozzini et al., 2014).

Verbal fluency is another measure of executive function that has revealed impairments in both AD and AMD patients (Gomez & White, 2006; Henry et al., 2004; Monsch et al., 1992; Whitson et al., 2015). Verbal fluency tasks require participants to say as many words they can think of in

60 seconds belonging to either the same category (e.g. 'fruit'), referred to as category fluency, or starting with the same letter (e.g., 'A'), referred to as letter fluency. Although verbal fluency declines with normal ageing, it does so to a lesser extent than the decline seen in MCI and especially in comparison to AD (Rodríguez-Aranda et al., 2016). Lower verbal fluency performance occurs in AD patients for both category (Diaz, Sailor, Cheung, & Kuslansky, 2004; Monsch et al., 1992; Rodríguez-Aranda et al., 2016; Salmon, Heindel, & Lange, 1999) and letter (Henry et al., 2004; Monsch et al., 1997; Rodríguez-Aranda et al., 2016) fluency tasks. Verbal fluency is particularly impaired in very early stages of AD, and arguably could be used to detect AD from MCI (Gomez & White, 2006). A lower than average score is a proven early indicator of disease as lower scores were found in AD patients 9 years prior to diagnosis (Amieva et al., 2005).

Similar to patients with AD, AMD patients have impairments in both category and letter fluency tasks (Clemons et al., 2006; Demırcı et al., 2015; Rozzini et al., 2014; Whitson et al., 2010; Wong et al., 2002; Zhou et al., 2016). In a population-based study, participants who were in the lowest 10th percentile of verbal fluency scores were 60% more likely to have AMD compared to controls (Wong et al., 2002). When measuring letter fluency of patients with macular disease, 46% of participants scored at least 1 standard deviation below their demographic mean, and 18% of participants scored at least 2 standard deviations below (Whitson et al., 2010). A higher percentage of participants scored below their demographic mean for letter fluency (64%) than in the global cognition assessment (46.5%). As in AD, these results show that letter fluency may be a more sensitive indicator of cognitive impairment in AMD patients compared to cognitively healthy controls. However, it is important to note that these findings were from patients aged 65 and over with a range of macular diseases. The results cannot be directly applied to those with just AMD (Whitson et al., 2010).

Although Rozzini et al. (2014) found no significant difference between wet and dry AMD for verbal fluency scores, for both letter and category fluency, a later study did find a significant difference between wet AMD and dry AMD for both letter and category fluency (Demirci et al., 2015). Participants with dry AMD produced significantly fewer words in verbal fluency tasks compared to age-matched controls, but this was not found in wet AMD (Demirci et al., 2015). In both studies, the ages of wet AMD and dry AMD participants was not significantly different, and overall AMD patients' ages were not significantly different from controls. It is not clear why these differing results were found when examining their methodology. It is important to note that when AMD scores were compared to controls without separating into wet and dry

sub-type, AMD participants consistently produced significantly fewer words than controls (Demirci et al., 2015; Rozzini et al., 2014).

1.2 This thesis

1.2.1 Introduction

The first half of this chapter covered shared features between AMD and AD (section 1.13 – 1.1.5). Based on these features some studies have postulated that the two diseases could be related to each other (Bogolepova, Makhnovich, & Zhuravleva, 2019; Keenan et al., 2014; Ohno-Matsui, 2011; Roca-Santiago, Lago-Bouza, Millán-Calenti, & Gómez-Ulla-Irazazábal, 2006; Rong et al., 2019; Schwaber et al., 2020; Smilnak et al., 2019). Evidence points towards AMD starting in moderate to severe AD, where involvement of changes in eyesight emerge later in the AD disease course (Kirby, Bandelow, & Hogervorst, 2010; Ukalovic et al., 2018). Concurrently, the same pattern is found in AMD where AD is expected to start in late AMD, as this is where cognitive impairments are commonly reported compared to earlier stages of the disease (Harrabi et al., 2015; Rozzini et al., 2014; Wong et al., 2002).

Currently studies are directed towards exploring the eye in AD for biomarkers (Ngolab, Honma, & Rissman, 2019; Ukalovic et al., 2018). However, the reverse is yet to be done with research exploring potential brain changes in AMD beyond the visual cortex using ROI analysis. This thesis will explore whether AMD has similarities to mild AD brain changes based on the cognitive profile AMD shares with mild AD.

1.2.2 Why AMD with mild AD?

The idea that AMD and AD are related was first proposed based on the discovery of amyloid beta in the pathophysiology of AMD (Dentchev et al., 2003; Giaccone, Orsi, Cupidi, & Tagliavini, 2011; Johnson et al., 2002). Further to this, as reviewed previously in section 1.1.5.2, evidence suggests memory and verbal fluency performance may be impaired in AMD participants compared to controls (Clemons et al., 2006; Lindekleiv et al., 2013; Rozzini et al., 2014; Whitson et al., 2010; Zhou et al., 2016). This is important in the context of AD. Memory and verbal fluency are significantly impaired in mild AD (Jahn, 2013; Monsch et al., 1997), and impairments in these cognitive domains are key in separating MCI (which includes a mixture of clinical outcomes: cognitive deterioration, stability, and reversion (Ganguli et al., 2011)), from those who progress to AD (Baudic et al., 2006; Rozzini et al., 2014). This may be because memory impairments represent an amnestic presentation, and verbal fluency represents a

non-amnestic presentation, meeting the cognitive diagnostic criteria for AD (McKhann et al., 2011). These findings indicate a direct relationship is likely between the two diseases.

Despite this, an alternative explanation is that patients with eye diseases are susceptible to developing AD due to reduced visual input itself (Davies-Kershaw et al., 2018), a phenomenon found with loss of sensory input from hearing (Lin et al., 2011; Zhou et al., 2016). This can be explained by the sensory deprivation hypothesis; where the natural decline in perception is said to cause a degradation of neurons that then impacts on cognitive ability (Lindenberger & Baltes, 1994). For example, a study found that wearing prescription glasses can improve cognitive ability (Spierer, Fischer, Barak, & Belkin, 2016). More specifically, studies have shown that those experiencing self-reported vision loss were 2.2 times more likely to show cognitive impairment compared to those who did not self-report visual loss (Crews & Campbell, 2004) and that cognitive decline was associated with visual impairment in the elderly (Reyes-Ortiz et al., 2005). This argument would align with studies that found AMD and AD are not related to each other, but rather a consequence of age (Williams et al., 2014). The appearance of amyloid beta in AMD could then be dismissed as evidence of a relationship between AMD and AD because the role of amyloid beta in AMD is not well understood, and may be the result of cellular damage rather than an initiator of it (Dentchev et al., 2003). Overall, the relationship between vision and cognition was found to be weaker than first reported in the literature (Anstey, Hofer, & Luszcz, 2003; Lindenberger & Ghisletta, 2009). In the case of AMD, studies found that AMD features and visual acuity were not directly related to level of cognitive impairment (Clemons et al., 2006; Lindekleiv et al., 2013) suggesting a weak association between vision and cognition.

Alternatively, the relationship between AMD and mild AD can be explained with the 'use-it-or-lose-it' hypothesis (Salthouse, 2006). Both hypotheses (sensory deprivation and 'use-it-or-lose-it') result in the same outcome where cognition is negatively affected, but the contributing factor to this decline differs. The 'use-it-or-lose-it' hypothesis states that when vision declines a person may stop engaging in activities they used to, resulting in loss of neurones and eventually reduced cognition. Participants with reduced visual acuity have lower activity scores for leisure activities such as reading, cooking, and driving (Marsiske, Klumb, & Baltes, 1997; Swanson, Bodner, Sawyer, & Allman, 2012) and this is related to reduced cognitive reserve (Harrabi et al., 2015). Although the relationship between activity and brain measures has not been explored in AMD, reduced activities caused by AMD-related visual loss is associated with an increased risk of cognitive decline (Rovner, Casten, Leiby, & Tasman, 2009) demonstrating the 'use-it-or-lose-it' hypothesis.

Compared to controls, white matter atrophy in the frontal lobe was found in AMD participants (Hernowo et al., 2014). This same atrophy has not been reported in blind participants or glaucoma patients (the next prominent eye disease identified as related to AD (Lee et al., 2019)), where atrophy reported is localised to visually related brain areas in these visually impaired populations (Bogorodzki et al., 2014; Maller et al., 2016; Schoth, Burgel, Dorsch, Reinges, & Krings, 2006; Shu, Li, Li, Yu, & Jiang, 2009; Voss, Pike, & Zatorre, 2014; Wang et al., 2013). Hernowo et al.'s (2014) finding demonstrates how AMD can exhibit brain changes beyond that associated with reduced visual input, and could reveal further clinical similarities to AD atrophy.

Based on this review of the literature, there are argumennts for and against a direct relationship between AMD and AD with areas of conflicting theories or gaps in the literature. Although the effect of the 'use-it-or-lose-it' hypothesis has not been discounted as a mediator in the AMD and AD relationship, the findings by Hernowo et al. (2014) point towards brain neurodegeneration separate to loss of visual input. Given other evidence for a cross-over in AMD and mild AD clinical features, it may be that there are other brain areas affected by having AMD itself, and that these may be similar to mild AD. By focusing on AMD and mild AD, this thesis will contribute to our understanding of the complex relationship between the two diseases.

1.2.3 Structural MRI analysis

Atrophy is often an outcome measure used in research because it is a widely recognised age-related brain change and considered clinically relevant in AD (Chandra, Dervenoulas, & Politis, 2019; Grajauskas et al., 2019). Atrophy occurs as a consequence of reduced tissue volume arising from a combination of factors including loss of myelinated nerve fibres (Pakkenberg et al., 2003), neuronal cell death (Anderton, 2002; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010), and a reduction in synapses and dendrites (Barnes, 2003; Flood, Buell, Horwitz, & Coleman, 1987; Hanks & Flood, 1991). All processes occur in normal ageing but the extent that each factor contributes to cerebral atrophy varies depending on different diseases (Oster et al., 1995; Regeur, Badsberg Jensen, Pakkenberg, Evans, & Pakkenberg, 1994; Wegner, Esiri, Chance, Palace, & Matthews, 2006). In AD an increased amount of neuronal loss occurs compared to normal ageing (Gómez-Isla et al., 1997). A strength of using atrophy as an outcome measure over other clinical measures is that it has a greater ability to detect AD, especially compared to measuring amyloid beta (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010; Jack et al., 2009; Johnson et al., 2012; Sluimer et al., 2010), and it is not affected by ceiling or practice effects, as found in, for example, the MMSE.

Traditionally volume has been used to measure atrophy in AD, but the role of cortical thickness has recently been noted. Not only is cortical thickness considered a more informative measure for age-related changes (Aycheh et al., 2018), but it is a more direct and reliable measure of AD grey matter atrophy (Lerch et al., 2005; Regeur, 2000; Singh et al., 2006). The benefit of using cortical thickness is shown in its sensitivity to detect cortical thinning years before conversion to AD and prior to the onset of symptoms (Dickerson et al., 2009; Johnson et al., 2012; Julkunen et al., 2010). Cortical thickness in regions affected early in the disease process have also been able to accurately separate controls, MCI, and AD participants from each other (Apostolova et al., 2007; Chandra et al., 2019; Lerch et al., 2005, 2008; Querbes et al., 2009; Singh et al., 2006). Another distinctive feature of cortical thickness is that it is appropriate for pooled data as cortical thickness is unaffected by analysis of data from multiple research sites (Dickerson et al., 2009; Mueller et al., 2005; Murphy et al., 2006).

Despite the obvious role for cortical thickness in this type of exploratory research, not all regions are available as a cortical thickness measure. The hippocampus is an example. Cortical thickness measures are not routinely available in this region due to problems with defining its anatomic shape or because of resolution constraints (Schwarz et al., 2016).

Using volume as a measure is also not straightforward. It is recommended that the total intracranial volume (TIV) is added as a regressor in the statistical model, or that the value produced after dividing the raw volume estimate by TIV is used. This is to help correct for different head sizes. The relationship between TIV and volume can be complex and the presence of disease with age reduces the correlation between TIV and volume estimates in older populations (Schwarz et al., 2016). Correcting for volume with TIV has its weaknesses as over- or under-correction of volume can hide true effects and because the strength of correlation between TIV and volume is not consistent across brain regions (Im et al., 2008; Schwarz et al., 2016). Volume is also a product of two genetically independent measures – thickness and area – that are affected by different neurobiological processes that could make interpretation of findings complex (Panizzon et al., 2009; Rakic, 2009; Rakic, Ayoub, Breunig, & Dominguez, 2009; White, Su, Schmidt, Kao, & Sapiro, 2010). Given the potential issues surrounding correction for volume across the brain, age, and disease, uncorrected volume estimates will be used in this exploratory research.

Automated processing streams using atlases with predefined regions of interest (ROIs) are now widely available, allowing the extraction of structural brain measures in specific brain regions. The benefit of using automated analysis streams is that large datasets can be processed in a short amount of time, and the same method can be used across labs and research centres to

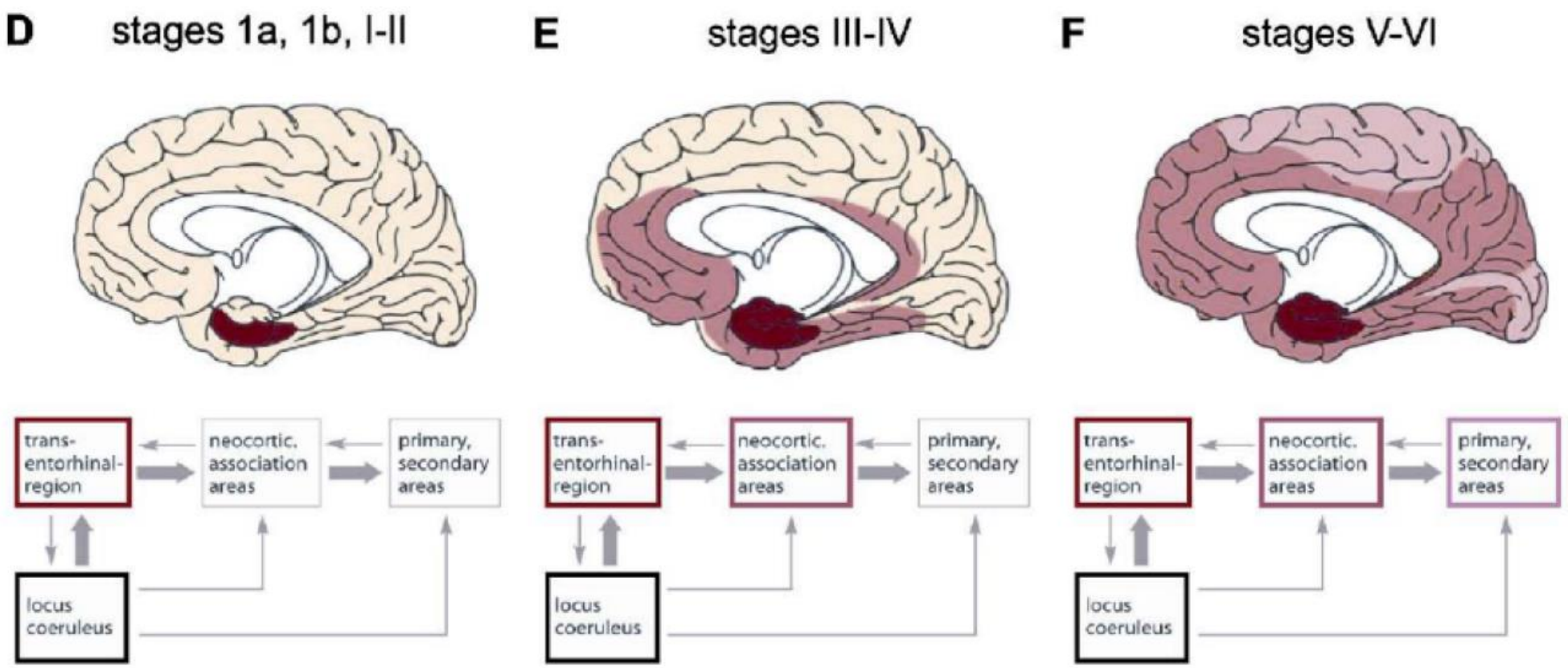
produce reproducible findings. The analysis software used in this thesis (Freesurfer) uses atlases with pre-defined ROIs ensuring ROIs are not reliant on researcher knowledge and reduces the chance of boundary differences when defining regions in different participants (Grajauskas et al., 2019; Keller & Roberts, 2009). Due to Freesurfer's automated process, manual editing is only required when soft errors (skull strip errors, segmentation errors, intensity normalization errors, pial surface misplacement, and topological defects) occur, and minimal research editing is recommended as stated under "Tips" in the Freesurfer troubleshooting guide (Freesurfer, n.d.). This is to further ensure reproducibility in the findings.

1.2.4 Structural brain changes

1.2.4.1 AD

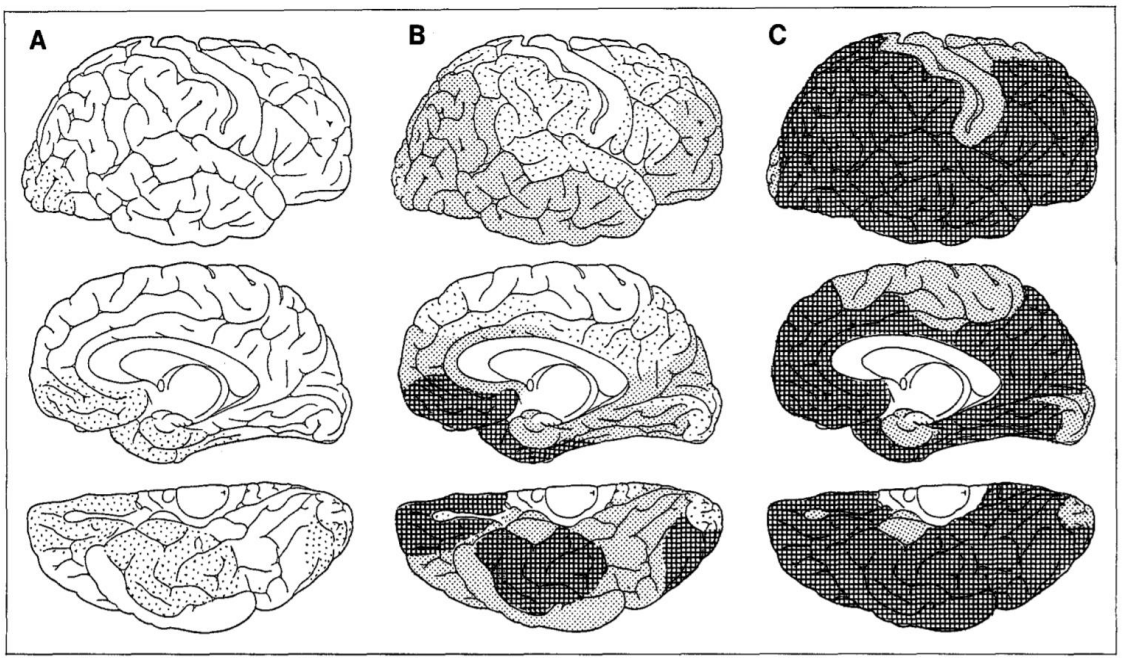
Based on autopsy observations, Braak and Braak (1991) devised a model to explain the pattern of pathological AD development in the brain covering 6 stages. Stages I and II are known as the transentorhinal stages, aptly named because neurofibrillary pathology is found in the entorhinal cortex in stage I and then the allocortical entorhinal region in stage II. Stages I and II are regarded as preclinical AD where patients will be asymptomatic despite the presence of AD pathology. Stages III and IV represent the limbic phase where AD pathology moves into the hippocampus followed by other medial temporal limbic regions. At this point, the clinical status of patients is said to represent prodromal AD. Finally, stages V and VI are called the isocortical stages where AD pathology spreads to isocortical association areas and primary neocortical fields. From stage V the patient will be classed as being in the clinical phase of AD based on measurable clinical features (Braak & Braak, 1991, 1995; Rüb et al., 2017). Put simply, Braak and Braak (1995) found that the distribution of neurofibrillary tangles and amyloid beta (see: Not for examination. Diagram 1a & 1b.) starts in the entorhinal cortex, spreading to other temporoparietal association cortices, before moving to the frontal regions and finally primary sensory and visual areas at the later stages of pathological development (Delacourte et al., 1999; Price & Morris, 1999).

Not for examination. Diagram 1a.



Tau pathology diagram taken from Braak *et al.* (2011), pg. 966.
Not for examination.

Not for examination. Diagram 1b.



Amyloid

Fig. 1. Distribution pattern of amyloid deposits. **Stage A** Initial deposits can be found in basal portions of the isocortex. **Stage B** The next stage shows amyloid in virtually all isocortical association areas. The hippocampal formation is only mildly involved. **Stage C** In the end-stage deposits can be seen in all areas of the isocortex including sensory and motor core fields. Increasing density of shading indicates increasing numbers of amyloid deposits

Amyloid beta diagram taken from Braak and Braak (1991), pg. 243.

Not for examination.

Braak staging focuses on how AD pathology develops across the brain, but structural brain changes closely follow this pattern (Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991; Buckner et al., 2005; Doherty et al., 2015; Smith, 2002). Areas with atrophy earlier in the disease course have a higher burden of pathologic accumulation (Arnold et al., 1991; Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Arriagada, Marzloff, & Hyman, 1992; Hyman, Van Hoesen, Damasio, & Barnes, 1984; Van Hoesen, Hyman, & Damasio, 1986). It is thought that atrophy occurs as a result of dendritic and neuronal loss, because neuronal counts were closely related to volume and cortical thickness of brain regions affected in AD at autopsy (for instance in the hippocampus) (Bobinski et al., 1999; Brun & Gustafson, 1976; Gosche, Mortimer, Smith, Markesbery, & Snowdon, 2002; Jack et al., 2002).

Structural brain changes associated with AD occur years before AD is first diagnosed, however, specific areas of brain changes are associated with atrophy during the prodromal, mild, moderate, and severe stages of disease (see: Not for examination. Diagram 2).

Not for examination. Diagram 2.

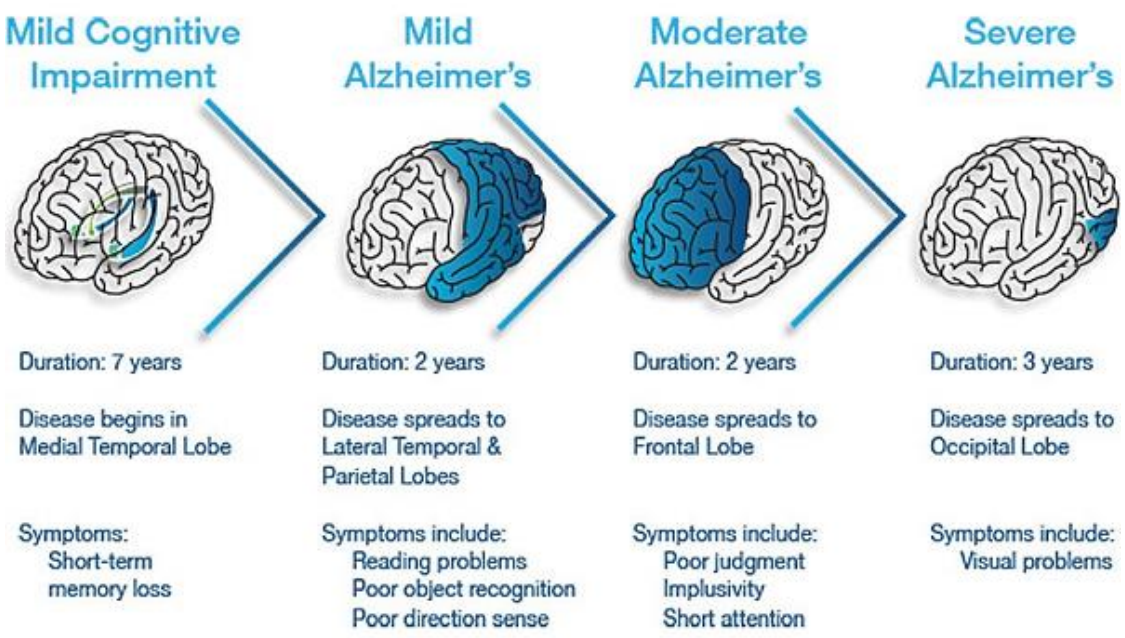


Diagram of structural brain changes taken from:

https://seniordirectory.com/articles/info/what-are-the-three-stages-of-alzheimers-disease

Last accessed 22/06/21

Not for examination.

Following Braak staging (Braak & Braak, 1991, 1995, 1996), cortical atrophy is first observed in the MTL. In mild AD the entorhinal cortex is affected first (Thompson et al., 2003) followed by the hippocampus at which point clinical memory impairment is evident. Volume for the entorhinal cortex was 38-40% smaller in mild AD compared to controls and the hippocampus was smaller by a slightly smaller margin at 26-27% compared to controls (Du et al., 2004). As AD progresses, it advances to other regions in the MTL such as the medial temporal gyrus, parahippocampus, parahippocampal and fusiform gyri, and temporal pole (Li, Coyle, Maguire, Watson, & McGinnity, 2011).

Moving from the temporal lobe, atrophy migrates towards the posterior temporoparietal region including the angular and supramarginal gyrus before moving towards the frontal lobes (Rabinovici et al., 2008). As moderate AD begins, there is minimal atrophy of the frontal lobe, primary visual cortex and sensorimotor cortex until later in the moderate stages of AD, where only the frontal lobe becomes severely affected (Thompson et al., 2003). There is a clear correlation between AD severity measured by MMSE and the degree of neurodegeneration.

After a drop in MMSE score from 18 to 13 most of the cortex is affected (Thompson et al., 2003). However, the sensorimotor regions are spared even when the cortex is significantly affected in the frontal, parietal, temporal, and occipital lobes (Du et al., 2007). Overall, the pattern of atrophy is said to follow a temporal – frontal – sensorimotor sequence (Thompson et al., 2003).

Referring to the structural brain changes above, it is evident that atrophy is unlikely to accelerate indefinitely in AD-affected brain regions (Frisoni, Prestia, Rasser, Bonetti, & Thompson, 2009). A sigmoidal shape of AD brain changes (see page 146) representing areas of accelerating and decelerating atrophy has been proposed and supported by various research since its proposal (Jack et al., 2013). Further research has shown that although this model fits for some brain areas, in others the acceleration period did not plateau supporting the suggestion that brain areas are affected in a staged fashion (Sabuncu et al., 2011; Schuff et al., 2012). This involves a severity-related pattern of acceleration and deceleration that maps onto the neural networks involved in each stage of AD (Frisoni et al., 2009). For example, during mild AD the reduction in cortical volume in regions affected by moderate and severe AD are lower than the reductions found in regions affected by mild AD. This would also be true when moving towards brain regions associated with moderate AD. The authors concluded this is evidence of waves of atrophy affecting different regions of the brain based on disease severity (Frisoni et al., 2009).

1.2.4.2 AMD

In AMD, structural brain changes occur because of long-standing central vision loss (Hanson et al., 2019; Hernowo et al., 2014). Occipital pole volume was significantly reduced in AMD patients compared to controls (Hernowo et al., 2014) and occipital pole cortical thinning was found between two timepoints of approximately five years in AMD patients (Hanson et al., 2019). Central vision is represented by primary visual areas where a loss of input has been found to cause significant thinning of V1 in AMD patients (Burge et al., 2016). Using surface-based analysis, another study found that cortical thinning only occurred in V2 of AMD patients (Prins, Plank, et al., 2016), however an earlier study with the same participants found decreased grey and white matter volumes in visual pathways and visual cortex when using voxel-based morphometry (VBM) (Hernowo et al., 2014). To date, no studies have shown grey matter changes beyond the visual cortex. Cortical thickness estimates are debatably more sensitive than voxel-based analyses that was used in Hernowo et al.'s (2014) study (Du et al., 2007) warranting further examination using ROI analysis.

1.2.5 Choosing regions of interest

Regions of interest (ROIs) were chosen via a mixture of methods:

1) Brain-behaviour relationships,
2) Brain areas characteristically impacted by mild AD or AMD (including brain-behaviour relationships).

1.2.5.1 Brain behaviour relationships

The basis for using some ROIs is that they are functionally or structurally related to verbal fluency or memory, measurable cognitive impairments found in both diseases.

1.2.5.1.1 Memory

A relationship between hippocampal volume and memory performance on cognitive tasks is often found in research because of the hippocampus' role in memory and more specifically recall (Banks, Jones-Gotman, Ladowski, & Sziklas, 2012; Kelley et al., 1998; Patai et al., 2015; Riedel & Micheau, 2001; Scott et al., 2016). Positive correlations between hippocampal volume and memory scores have been found in healthy populations of different ages. In young healthy participants, hippocampal volume was significantly correlated with participant's scores on the Four Mountains Task measuring topographical recognition memory (Hartley & Harlow, 2012) and with declarative memory (Pohlack et al., 2014). In an older adult population, hippocampal volume was found to correlate with episodic and semantic memory performance, with smaller volume associated with poorer performance; this pattern persisted across the age range of their participants (70 +/- 9) (Dong et al., 2015). In another study, it was found that episodic memory was positively associated with hippocampal volume in participants aged 65-80 (Gorbach et al., 2017). Not only is this positive correlation found across the lifespan in healthy populations (Dong et al., 2015; Hartley & Harlow, 2012; Pohlack et al., 2014; Raz, Daugherty, Bender, Dahle, & Land, 2015), it has been found for recall and recognition tasks in AD participants (Kramer et al., 2004; Teipel et al., 2010). This relationship has been found in MCI (Bonner-Jackson, Mahmoud, Miller, & Banks, 2015), Parkinson's Disease (Beyer et al., 2013), and depression (Videbech & Ravnkilde, 2004), indicating consistency in this relationship and ability to apply to other diseases.

Although there is strong evidence that a brain-behaviour relationship between hippocampal volume and memory exists, the relationship to functional changes in AD and AMD also give weight to the role of the hippocampus in both diseases. In an EEG study assessing the

functional connectivity of the hippocampus in AD, it was found that bilateral hippocampus activity in the alpha band was negatively related to verbal memory whereas only the left hippocampus in controls was positively related to verbal memory (Dickerson et al., 2004). It has been suggested that recruiting the contralateral side of the brain to help with tasks is a compensatory mechanism (Dickerson et al., 2004), that eventually becomes ineffective with disease progression (Toepper, 2017). It can be argued that initial bilateral recruitment of the hippocampus in the alpha band helped maintain memory function during early hippocampal atrophy, but has since become ineffective in these AD participants. This is further supported as hippocampal activity in the theta band was found to positively correlate with memory scores (Dickerson et al., 2004). Overall, it seems that loss of neurones in the hippocampus in AD reduces hippocampal volume and changes functional activity. This can also be seen in AMD, where resting-state was used to explore potential relationships between functional activity and memory. A stronger connectivity was found between a medial temporal network and episodic memory in AMD compared to controls. The authors concluded that stronger connectivity is a compensatory mechanism that may help support memory function, given memory impairment is found in this clinical group in other studies (Zuo et al., 2020). For this reason, the hippocampus was selected as a ROI for this thesis.

1.2.5.1.2 Verbal fluency

Verbal fluency is strongly associated with the inferior frontal gyrus (IFG; Robinson et al., 2012), which includes Broca's area (Brodmann area (BA)44 and BA45) and BA47, a newly discovered area important for language (Ardila, Bernal, & Rosselli, 2016; Wagner, Sebastian, Lieb, Tüscher, & Tadić, 2014). In a meta-analysis using likelihood estimation on peak brain activation during fluency tasks, BA47 was found to be associated to both category and letter fluency tasks, whereas BA44 was only involved in letter fluency (Wagner et al., 2014). In another study using repetitive transcranial magnetic stimulation (r-TMS), r-TMS to the left BA47 was found to significantly reduce letter fluency performance when compared to sham. However, the authors did not fMRI to identify regions for TMS and there could have been some involvement of BA44/45 aeas (Smirni et al., 2017). The IFG has been associated with language tasks that relate to semantic (category) and phonological (letter) processing similar to those used in verbal fluency tasks (De Carli et al., 2007), supporting IFG's role in verbal fluency scores. Cortical thickness atrophy in Broca's area was found to be related to category fluency scores in cognitively normal, MCI, and AD participants (Eastman et al., 2013) demonstrating a brain-structure relationship with fluency scores.

A decline in AD participants' verbal fluency performance was associated with altered functional connectivity in language areas of the brain (Kljajević, 2015). During a verbal fluency task there was increased functional connectivity between Broca's area and the right IFG in AD that was not found in cognitively normal controls. When using Broca's area as a seed region in the right IFG, an increase in alpha activity correlated with higher verbal fluency performance in AD, but no relationship was found for controls. The results suggest that AD patients are recruiting the right IFG to help them complete the verbal fluency task. The authors concluded that a decline in functional activity was found in areas that are most affected by atrophy (Kljajević, 2015). It can be speculated that the altered functional connectivity in the left and right IFG during verbal fluency tasks is a compensatory mechanism resulting from neuronal loss.

Altered connectivity patterns in AMD participants' brains have been discovered in relation to verbal fluency (Whitson et al., 2015; Zhuang et al., 2018), suggesting neurodegeneration may be present in the IFG. When correlating verbal fluency performance with connectivity in the right IFG, AMD participants with higher functional connectivity had higher verbal fluency performance (Whitson et al., 2015). This pattern was not shown in controls. The study highlights that AMD participants are recruiting the right IFG to help them complete the verbal fluency task. The authors conclude that this increased connectivity represents functional reorganisation or a functional advantage (Whitson et al., 2015), and is similar to other studies suggesting altered connectivity shows a compensatory mechanism to preserve cognitive ability (Dickerson, Feczko, et al., 2009; Dubovik et al., 2013; Kljajević, 2015). Additionally, a link between peak activation in AMD patients' prefrontal regions and increased accuracy and speed were found on language-based tasks, showing the role of frontal regions in language tasks in AMD (Szlyk & Little, 2009).

To summarise, increased connectivity was found for the right IFG during verbal fluency tasks in both AD and AMD but not in controls (Kljajević, 2015; Whitson et al., 2015). This increased connectivity is thought to represent a compensatory mechanism due to reduced neuronal integrity. For this reason, the IFG was chosen as an ROI in this thesis.

Category fluency was also found to be related to cortical atrophy in the inferior parietal lobule in a cognitively normal population (Eastman et al., 2013). A further study found that atrophy in the parietal region was associated with lower verbal fluency scores in AD. However, this relationship was stronger with category fluency (Apostolova et al., 2008). Using a three-letter or six-letter word-level recognition and language processing task in an fMRI study, AMD participants were found to have an increased level of activation in inferior parietal lobules

compared to their age-matched cognitively normal controls (Szlyk & Little, 2009). There is support for using an ROI from the inferior parietal lobe.

1.2.5.2 Brain areas characteristically affected

Areas of the brain found to be negatively affected in either AMD or mild AD were also included to assess similarities and differences between the two diseases. Previous literature has shown that primary visual regions are affected in AMD as a consequence of long-standing visual impairment (Burge et al., 2016; Hanson et al., 2019; Hernowo et al., 2014; Prins, Plank, et al., 2016) and arguably the only cortical brain region affected in AMD (based on the paucity of research in brain regions outside the visual cortex). Alternatively, the first brain area to be affected by AD is the entorhinal cortex (Braak et al., 1993; Chan et al., 2001; Dickerson et al., 2009; Killiany et al., 2002). Atrophy in the entorhinal cortex is also related to memory. Shrinkage in the entorhinal cortex in a normal ageing population was able to predict memory performance (Rodrigue & Raz, 2004), and reduced entorhinal volume was associated with subjective memory impairment (Jessen et al., 2006) and MoCA score (Ogawa et al., 2019; Zdanovskis, Platkājis, Kostiks, & Karelis, 2020)**.** Although the primary visual cortex has been found to represent changes in AMD, the occipital pole is more representative of the brain related to central vision loss, referred to as the lesion projection zone (Hanson et al., 2019). For this reason, the occipital pole and entorhinal cortex were chosen as ROIs in this thesis.

Lastly, when addressing the connection between AMD and AD, the pattern of brain changes across AD must be considered a base from which structural brain patterns are explored. As discussed in section 1.2.4.2 the MTL is typically affected in AD before changes move towards the temporoparietal area, but the frontal and occipital lobe are unaffected in mild AD. To gain a rounded representation of the pattern of brain changes in AD, for comparison to AMD, a ROI from the temporoparietal region was selected for completeness. The angular gyrus, that sits within the inferior parietal lobule, is an area of the brain that has been found to atrophy as a consequence of mild AD (Dickerson, Bakkour, et al., 2009; Du et al., 2007; Karas et al., 2004) and sits within the brain region associated with verbal fluency (De Carli et al., 2007; Eastman et al., 2013; Smirni et al., 2017; Whitson et al., 2015).

Using the ROIs selected for this research, the expected order of brain change found in AD is as follows: Entorhinal cortex, hippocampus, angular gyrus, IFG, and occipital pole. Where entorhinal cortex is expected to be the most affected ROI and occipital pole the least affected ROI in AD following the literature and Braak staging (Braak, Alafuzoff, Arzberger, Kretzschmar, & Tredici, 2006; Braak et al., 1993; Braak, Thal, Ghebremedhin, & Del Tredici, 2011; Braak &

Braak, 1991, 1995). The development of brain changes across the AMD course is to be established.

The final ROIs are 1) entorhinal cortex, 2) hippocampus, 3) angular gyrus, 4) inferior frontal gyrus, 5) occipital pole (Figure 1-1) where arrows indicate the pattern of changes expected to occur in mild AD.

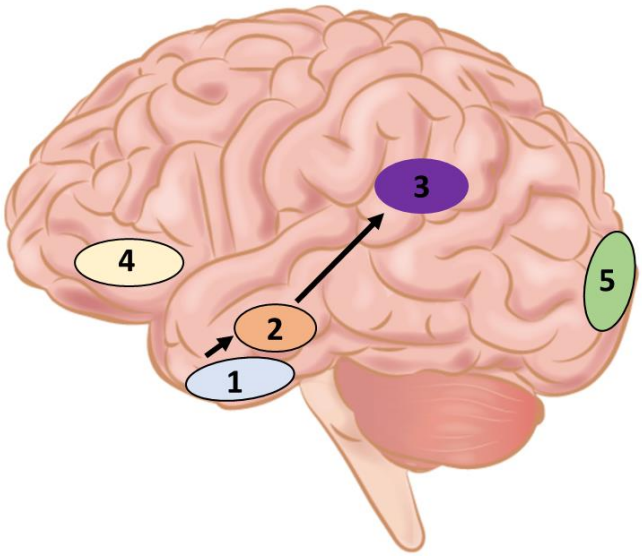


Figure 1-1. The regions of interest with the expected pattern of atrophy across the AD brain. Regions from 1 to 5 represent the regions of interest examined in this thesis. 1 represents the entorhinal cortex, the region expected to be affected first; 2 represents the hippocampus; 3 represents the angular gyrus; 4 represents the inferior frontal gyrus; 5 represents the occipital pole, the region expected to be affected last in AD. The arrows represent the direction of atrophy across the brain for mild AD. *Image source: human-memory.net, last accessed 19/04/2021*

1.3 Thesis Aims and outline

Structural ROI analysis is used in this thesis. The decision to use only structural analysis was based on the paper by Hernowo et al. (2016) that showed white matter volume reductions in the frontal lobes of AMD; the first AMD research to show brain changes outside the visual cortex. Combined with the shared cognitive profile of AMD with AD, and the previously discussed associated brain regions with these cognitive impairments, it is hypothesised that structural brain changes may also occur elsewhere in the AMD brain, with a focus on grey matter rather than white matter neurodegeneration. Although functional analysis in AMD is a small section of research, there is increasing awareness of the role functional alterations play

in AMD participant's cognitive impairment (Rosengarth et al., 2013; Whitson et al., 2015; Zuo et al., 2020). Research is yet to investigate the potential role brain structure atrophy has in AMD, and by extension whether there are further similarities between AMD and AD. While global atrophy is found in ageing, localised shrinkage is found in disease pathology (Grajauskas et al., 2019), a phenomenon that may occur in AMD and likely highlighted with ROI analysis. Due to the focus on shared cognitive impairment in AD and AMD and their associated brain regions, alongside specified neurodegeneration patterns of AD, a ROI analysis approach was taken in this thesis. Region of interest analysis is arguably more sensitive than whole brain voxel-based analysis (Du et al., 2007). A-priori regions and predictions can then be devised before analysis, allowing a direct comparison between the two diseases.

The overall aim of this thesis is to establish whether AMD is related to AD. Five empirical chapters explore the separate ways in which AMD could show a relationship to AD. The first aim of the thesis, addressed in chapters 2 (study 1) and 3 (study 2), assesses whether AMD shows signs of AD structural brain changes comparing AMD patterns with AD data. Chapter 2 (study 1) looks at specific brain patterns in AD and AMD separately using cross-sectional MRI data. Chapter 3 (study 2) extends this by looking at what changes occur across time in AMD that are characteristic of AD. The aim of chapter 4 (study 3) is to investigate the pattern of neurodegeneration in early AMD compared to late AMD. Lastly, chapter 5 (study 4) explores the relationship between behavioural measures and the brain to assess the contribution of potential mediators in the AMD-AD relationship.

Chapter 2: Study 1;

Is there evidence of grey matter neurodegeneration in late age-related macular degeneration, and is it similar to mild Alzheimer's disease? A cross-sectional study.

2.1 Introduction

In its simplest form, neurodegeneration refers to the pathological process in which neurones lose their structure, function, or both (Prins, Hanekamp, & Cornelissen, 2016). In most cases neurodegeneration is the progressive loss of neurones accompanied by a progressive loss of neuronal function (Jack et al., 2013). This process is demonstrated in AD where changes in brain structure precede cognitive impairment (Jack et al., 2010). In this study, the emphasis is placed on structural neurodegeneration where atrophy is considered an in vivo measure of neuronal loss (Johnson et al., 2012).

Alzheimer's Disease is characterised as having a medial temporal lobe (MTL) dominant form of neurodegeneration (Pettigrew et al., 2017; Scahill, Schott, Stevens, Rossor, & Fox, 2002) where the entorhinal cortex is the first region to be affected by AD pathology, from the presence of neurofibrillary tangles to neurodegeneration itself (Braak & Braak, 1991, 1996; Braak, Braak, & Bohl, 1993; Chan et al., 2001; Dickerson et al., 2009; Killiany et al., 2002). The relevance of measuring entorhinal cortex neurodegeneration in AD has been debated, but it has recently been proposed as a biomarker for indicating AD severity (Bakkour, Morris, & Dickerson, 2009; Dickerson et al., 2009; Fischl et al., 2009; Lerch & Evans, 2005; Schwarz et al., 2016). In favour of measuring entorhinal cortex neurodegeneration in AD research, some studies have found that it can offer the same or better discrimination of AD from normal ageing and other neurodegenerative diseases (Bobinski et al., 1999; Dickerson et al., 2001; Du et al., 2003; Killiany et al., 2002; Tapiola et al., 2008), and better indicate those who later convert to AD compared to hippocampal volume (Bobinski et al., 1999).

Regardless of the potential merits of measuring neurodegeneration of the entorhinal cortex in lieu of hippocampus, their combined use is useful for identifying AD-related brain changes (Blennow, de Leon, & Zetterberg, 2006; Chong & Sahadevan, 2005; Den Heijer et al., 2006; Holland, Desikan, Dale, & McEvoy, 2012; Holland, McEvoy, & Dale, 2012; Hua et al., 2008;

Schott, Kennedy, & Fox, 2006). Both the entorhinal cortex and hippocampus' annual atrophy rates reveal significant power to detect AD compared to other AD clinical measures (Holland, Desikan, et al., 2012; Holland, McEvoy, et al., 2012) and a further study showed that entorhinal cortex and hippocampus atrophy together can determine which MCI participants progress to AD (Blennow et al., 2006; Chong & Sahadevan, 2005; Den Heijer et al., 2006; Hua et al., 2008; Schott et al., 2006; Walker & Walker, 2005). This is because the presence of atrophy in the hippocampus is regarded as confirmation of typical AD, rather than MCI, because it is affected later in the disease course (Farrow et al., 2007; Whitwell et al., 2011). Overall, MTL atrophy can predict those who convert from MCI to AD with a sensitivity and specificity of 50-70% (DeCarli et al., 2007; Korf, Wahlund, Visser, & Scheltens, 2004).

The development of AD neurodegeneration through the brain follows the Braak staging of pathology (Braak & Braak, 1991). After MTL atrophy, the inferior parietal region including the angular gyrus is found to be affected early in the AD disease course (Dickerson et al., 2009; Du et al., 2007; Karas et al., 2004). Using participants from different databases, thinning in the inferior parietal cortex was found in two (very mild AD, and mild AD) out of three mild AD participant groups (incipient AD, very mild AD, and mild AD) compared to controls, indicating early involvement of this region. The lack of significance in one of the participant groups suggests that although this region is affected early in the disease course, there is a temporal delay between MTL atrophy and wider temporoparietal involvement, as expected (Dickerson et al., 2009). This temporal delay is supported by the finding of decreased grey matter in posterior temporoparietal regions in participants with established, but not early, mild AD in another study (Rabinovici et al., 2008).

Once temporoparietal atrophy is evident in mild AD, research has found variable findings in relation to the involvement of frontal regions (Baron et al., 2001; Bozzali et al., 2006; Karas et al., 2003; Whitwell et al., 2008). A potential reason for the mixed findings could be due to mild AD participants moving towards a more moderate stage of AD. Frontal region involvement is typically observed at the moderate stage of AD (Dickerson et al., 2009; Jack et al., 2010) when symptoms become more prominent (Buckner et al., 2005; Scahill et al., 2002). This idea of a shift from mild toward moderate AD accounting for the variable findings in frontal regions is plausible, as non-significant thinning of the IFG was found in mild AD (Singh et al., 2006) but significant IFG thinning was found in a study with mild and moderate AD participants, with a mean MMSE score of 20.7 (SD=3.1) (Busatto et al., 2003). During the moderate stage of AD there is wide-spread cortical atrophy, as shown in a sample of participants with a MMSE score

of 15.6 (SD=5.2). This study also showed that there was sparing of the occipital pole at this later stage of AD (Karas et al., 2003).

When it comes to comparing AD with other age-related diseases, the overall pattern of neurodegeneration should be considered. Although MTL regions are key to helping discriminate AD from normal ageing and MCI, MTL atrophy is not AD-specific (Barber, Ballard, McKeith, Gholkar, & O'Brien, 2000; Burton et al., 2009; Chan et al., 2001; Fjell & Walhovd, 2010; McKeith et al., 2005). Consequently, interpreting changes in the MTL in isolation may result in incorrect conclusions (Barber et al., 2000; Burton et al., 2009; Chan et al., 2001; Fjell & Walhovd, 2010; McKeith et al., 2005). An example of this can be found with hippocampal volume. Reduced hippocampal volumes are found in vascular dementia, Lewy body dementia, and frontotemporal dementia, however when matched for clinical severity this atrophy is greater in AD compared to these other dementias (Barber et al., 2000; Burton et al., 2009; Chan et al., 2001; McKeith et al., 2005). Based on these findings it suggests this difference between dementia type may not be immediately obvious in the prodromal stage of AD, when MTL atrophy is first starting. Due to the problem of interpreting findings from MTL regions in isolation, the overall pattern of brain changes relating to mild AD needs to be considered to conclude with certainty whether AD is likely (Johnson et al., 2012). This notion was supported by researchers after they reviewed AD neurodegeneration, where it was concluded that it was not possible to identify one area of atrophy that reflected AD, but the pattern of changes found in AD exhibited a medial temporoparietal circuitry (Fjell & Walhovd, 2010). This pattern of neurodegeneration is supported by the findings that atrophy within the inferior parietal lobes was representative of AD when compared with frontotemporal dementia, and was found in atypical AD (Rabinovici et al., 2008; Whitwell et al., 2011), highlighting the specificity of inferior parietal involvement to AD pathology.

Regarding the selected ROIs (see chapter 1, Figure 1-1), AD normally follows the progression from entorhinal cortex to hippocampus, angular gyrus, IFG, and occipital pole; without any distinction between volume and cortical thickness, as they have been found to be equally affected to reveal this pattern of neurodegeneration (Guo et al., 2009), with cortical thickness showing an increased sensitivity to emerging changes. For mild AD, atrophy will be represented in the entorhinal cortex, hippocampus, and sometimes in the angular gyrus depending on where patients are in the very mild to mild stage of AD (Chan et al., 2001; Dickerson et al., 2001; Fjell et al., 2010; Killiany et al., 2002).

Limited research is available on structural brain changes within AMD (Boucard et al., 2009; Burge et al., 2016; Hanson et al., 2019; Hernowo et al., 2014). What is known about grey

matter atrophy is that reduction in the primary visual cortex is reported as a consequence of AMD-related visual impairment (Boucard et al., 2009; Burge et al., 2016; Hanson et al., 2019; Hernowo et al., 2014). Beyond the visual cortex there are no previous findings of structural neurodegeneration in grey matter, although one previous study found frontal white matter reductions in AMD compared to controls (Hernowo et al., 2014). A couple of studies have found functional connectivity alterations in AMD participants during verbal fluency tasks related to inferior frontal gyrus and angular gyrus (Whitson et al., 2015; Zhuang et al., 2018), and memory related to parahippocampal regions (Zuo et al., 2020) where atrophy could be likely. In Whitson et al. (2015) a higher mean connectivity pattern in reference links including the IFG and angular gyrus was found in AMD participants that had reduced fluency scores compared to controls. The authors concluded that this was evidence of underlying brain changes relating to cognitive impairment. Secondly, Zuo et al. (2020) found that AMD participants showed a stronger relationship between memory scores and connectivity in the memory network hub, despite the absence of reduced memory performance or altered functional connectivity compared to controls. They concluded that a stronger brain-behaviour connection plays a role in supporting memory performance in AMD (Zuo et al., 2020). As memory impairments become evident in AMD (Clemons et al., 2006; Whitson et al., 2010) it is expected the results will reflect those found in Whitson et al. (2015) with altered connectivity emerging in the memory network hub.

Different patterns of atrophy between diseases are the consequence of disease specific neuronal vulnerability that results in characteristic regional disease expression (Johnson et al., 2012; Przedborski, Vila, & Jackson-Lewis, 2003). If AMD was related to AD, then the same pattern of changes within the brain should emerge based on this pattern of neuronal vulnerability. It is predicted that in mild AD the entorhinal cortex, hippocampus, and angular gyrus will be significantly affected with no significant difference from controls for inferior frontal gyrus and occipital pole. As atrophy of the entorhinal cortex, hippocampus, and angular gyrus (a mixture of cortical thickness and volume findings) is found in mild AD it is predicted that AMD will also show this pattern of change in these ROIs, with significant differences found in MTL regions that represent prodromal AD. However, if AMD is not related to AD, then AD pattern of changes will not be present. Alternatively, it is predicted that if any atrophy is evident in AMD (besides occipital pole), it will be found in the IFG and angular gyrus, where functional alterations in relation to poorer performance on a fluency task have previously been found (Whitson et al., 2015; Zhuang et al., 2018) alongside frontal white matter atrophy (Hernowo et al., 2014). Involvement of the hippocampus could be evident based on previously reported memory impairments in AMD (Clemons et al., 2006; Whitson et al., 2010). The

occipital pole is expected to be affected in either case due to the late AMD status of participants, in line with previous findings (Hanson et al., 2019; Hernowo et al., 2014).

2.2 Methods

Previously collected, anonymised data were used in this study. Alzheimer's Disease and associated healthy control data were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI; adni.loni.usc.edu; see acknowledgement of use on page 12-13).
Age-related macular degeneration data and associated healthy control data were used from York Neuroimaging Centre's (YNiC) MRI raw data folder after gaining permission from the researchers and obtaining ethics for its use:
- Six AMD participants came from the Fight for Sight project: 'Assessing the status of visual cortex in patients with macular disease', Brown et al., 2014-2017; (under review).
- Ten AMD participants came from the C2D2 Career Establishment Grant: 'Assessing visual cortex in candidates for retinal prosthetics', Hanson et al., 2015-17; (Hanson et al., 2019).
- Nine controls came from my MSc project 'Identifying the relationship between visual performance and myelin density', 2015.
- Seven controls came from Dr Fiona McNab's fMRI work on ageing, Charlotte Ashton, 2017.

With special thanks to all Master's students and research assistants who helped collect data for these projects: Farah Akthar, Charlotte Campbell, Lucy Evans, Ben Fosh, Buvneet Benning, Christina Martin, Sophie Waterson, Mason Wells, Aaron Wright, and Adele Wright.

2.2.1 AMD and control data:

2.2.1.1 Participants

YNiC data came from four different studies conducted in YNiC where AMD participants (N=16) had verified central vision loss as part of the inclusion criteria to their respective studies. For this reason, these AMD participants were defined as late AMD for the purpose of this thesis. Ten participants from YNiC's AMD group had bilateral dry AMD with acute onset of unilateral wet AMD (Hanson et al., 2019), the other six AMD participants experienced verified bilateral vision loss with either wet or dry features. Controls (N=16) were self-reported healthy (eight participants were screened using the MoCA to ensure normal cognitive function) with normal or corrected-to-normal vision. There were eight males and eight females with a mean age of 78.88 years (SD = 6.23) for AMD participants, and 10 males and six females with a mean age of 70.00 years (SD = 5.27) for controls (Table 2-1). Ethical approval was obtained from York Neuroimaging Ethics Committee for use of this anonymised data.

Table 2-1. AMD and control participants' demographics.

YNiC Participant	Participant Group	T1 Scan	Age	Sex
1	Control	GLASSER	73	M
2	Control	GLASSER	70	F
3	Control	GLASSER	70	M
4	Control	GLASSER	66	F
5	Control	GLASSER	82	M
6	Control	GLASSER	78	F
7	Control	GLASSER	71	M
8	Control	YNiCT1a	68	M
9	Control	YNiCT1a	63	M
10	Control	YNiCT1a	65	F
11	Control	YNiCT1a	64	F
12	Control	YNiCT1a	70	M
13	Control	YNiCT1a	75	M
14	Control	YNiCT1a	73	M
15	Control	YNiCT1a	67	M
16	Control	YNiCT1a	65	F
17	AMD	YNiCT1a	83	M
18	AMD	YNiCT1a	74	F
19	AMD	YNiCT1a	73	F
20	AMD	YNiCT1a	75	M
21	AMD	YNiCT1a	86	M
22	AMD	YNiCT1a	79	F
23	AMD	YNiCT1a	73	M
24	AMD	YNiCT1a	88	M
25	AMD	YNiCT1a	81	F
26	AMD	YNiCT1a	77	F
27	AMD	GLASSER	86	F
28	AMD	GLASSER	80	M
29	AMD	GLASSER	87	M
30	AMD	GLASSER	78	F
31	AMD	GLASSER	65	M
32	AMD	GLASSER	77	F

YNiC – York Neuroimaging Centre, AMD – age-related macular degeneration, YNiCT1a – T1 scan protocol used for some participants in this study, GLASSER T1 – T1 scan protocol used for some participant in this study, M- male, F - female.

2.2.1.2 Acquisition

Data were collected on the GE Excite 3T MRI scanner using an 8-channel radiofrequency coil. Two different T1-weighted scans were used during the four previous studies. T1-weighted scans based on the Human Connectome Project scan protocol (Glasser et al. 2013), known as "GlasserT1", used a 3D inversion recovery prepared fast spoiled gradient sequence with the

following parameters: repetition time (TR) 7.79 – 7.85ms, echo time (TE) 2.99ms, 10 flip angle, matrix 256 x 256 x 180, slice thickness 1mm, voxel size 1 x 1mm. Six AMD and seven controls were scanned using this protocol. T1-weighted scans using a protocol known as "YNiCT1a" used a 3D sagittal isotropic 3D fast spoiled gradient-recalled echo sequence with the following parameters: TR 7.8ms, TE minimum full (3ms), 20 flip angle, matrix 256 x 256 x 176, slice thickness 1mm, voxel size 1.13 x 1.13mm. Ten AMD participants and nine controls were scanned using this protocol.

2.2.1.3 Procedure

Sixteen anonymised AMD participants were identified on YNiC's MRI database using their participant ID. Their T1 images were checked in FSLView (version 4.0.1) to ensure the whole brain had been scanned and brain estimates could be collected from the regions of interest identified for this study; the same was done for 16 controls. The sex and age of YNiC AMD participants were then used to help find matched participants from the ADNI database as explained in 2.2.2.

2.2.2 AD and control data:

2.2.2.1 Participants

AD and control participants' data were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). There were eight males and eight females with a mean age of 78.63 years (SD = 5.80) for AD, and seven males and nine females with a mean age of 78.51 years (SD = 5.88) for controls. AD participants were clinically assessed to have probable mild AD with a mean MMSE score of 21.25 (SD = 1.00)**.** Mild AD was chosen as AMD is most likely to show mild AD at later stages of AMD, as explained in section 1.2.1. Controls were clinically assessed as cognitively healthy, all with MMSE scores of 30.

2.2.2.2 Acquisition

There are several scan parameters for ADNI data because ADNI is a multi-site study using different MRI scanners (GE Healthcare, Philips Medical Systems, and Siemens Medical Solutions). GE scanners used an inversion recovery-fast spoiled gradient recalled sequence, whereas Philips and Siemens used a magnetization-prepared rapid gradient echo sequence. The ADNI database optimised the sequences for the different scanners, and standardised their phantom-based monitoring, MRI protocol, and post-acquisition corrections to ensure comparability across research sites and scanners. This enabled the use of data collected from different sites and scanners within one dataset (Jack et al., 2015, 2008).

The target ADNI protocol for each MRI scanner were:
For Siemens scanners the following parameters were used: repetition time (TR) 2300ms, echo time (TE) 2.98ms, 9 flip angle, matrix 240 x 256 x 176, slice thickness 1.2mm, voxel size 1 x 1mm.
For Philips scanners the following parameters were used: repetition time (TR) 6.77ms, echo time (TE) 3.09ms, 9 flip angle, matrix 256 x 256 x 170, slice thickness 1.2mm, voxel size 1 x 1mm.
For GE scanners the following parameters were used: repetition time (TR) 6.98ms, echo time (TE) 2.85ms, 11 flip angle, matrix 256 x 256 x 196, slice thickness 1.2mm, voxel size 1 x 1mm.

This study used ADNI1 and ADNI2 data. Further details of individual protocols can be found on ADNI's website (http://adni.loni.usc.edu/methods/documents/mri-protocols/).

2.2.2.3 Procedure

To find all potential participants, an advanced search (beta) was done on ADNI's Image Data Archive (IDA, https://ida.loni.usc.edu/). This search allowed a tick-box selection of certain criteria. However, for this study participants were found using a previous version of the advanced search (beta) where AD and cognitively normal categories could not be directly selected. To help find AD participants, an MMSE range of 20-24 (out of 30, a score indicative of mild AD) was specified to help screen for mild AD. Other specified areas via the tick-box were: pre-processed MRI data (meaning images have been through ADNI's MRI Core quality control (Jack et al., 2015)), 3T scanner acquisition, and T1 images.

Alzheimer's Disease participants who matched YNiC's AMD participants for age and sex were highlighted. Additional checks were carried out to ensure participants had a probable diagnosis of AD (number 3 in DXCURRENT), and the professional's clinical severity was rated as mild (number 1 in DXAD) in ADNI's demographic document (DXSUM_PDXCONV_ADNIALL.csv). Participants were randomly selected from the list of potential participants to avoid bias in selection. Age and sex were matched as much as possible to the AMD participants.

To help find cognitively healthy participants from the ADNI database, an MMSE score of 30 (out of 30) was specified and participants were checked to make sure they were clinically confirmed cognitively normal (number 1 in DXCURRENT; DXSUM_PDXCONV_ADNIALL.csv). Participants were randomly selected following the same procedure as AD participants unless a direct match for age and sex could not be found. Otherwise, cognitively normal participants were matched for age as a priority (+/- 1 year to AD participants age) and then sex to ADNI AD

participants. One female AD participant aged 72 could not be matched with a direct control using the method explained above. The control participant used was a 71-year-old male.

After the ADNI participants had been matched (Table 2-2) and selected, one pre-processed MRI image was selected per participant. The 32 MRI images were downloaded from ADNI as NiFTI files and run through the same pre-processing and analysis as YNiC NiFTI data.

Table 2-2. AD and associated control participant's demographics.

ADNI Participant	Participant Group	Scanner	Age	Sex
1	Control	Philips	75	F
2	Control	Philips	84	F
3	Control	Siemens	89	M
4	Control	GE	83	M
5	Control	Philips	73	F
6	Control	Siemens	71	M
7	Control	GE	81	M
8	Control	GE	79	F
9	Control	GE	80	F
10	Control	Siemens	87	M
11	Control	Siemens	81	M
12	Control	Siemens	78	M
13	Control	Philip	78	F
14	Control	Siemens	77	F
15	Control	Siemens	75	F
16	Control	Siemens	66	F
17	AD	Siemens	81	F
18	AD	Siemens	78	F
19	AD	Siemens	72	F
20	AD	Philips	77	F
21	AD	Philips	75	F
22	AD	Siemens	79	F
23	AD	GE	66	M
24	AD	GE	89	M
25	AD	GE	73	M
26	AD	GE	83	M
27	AD	GE	81	F
28	AD	GE	84	M
29	AD	Siemens	80	M
30	AD	GE	78	F
31	AD	Siemens	87	M
32	AD	GE	75	M

AD – Alzheimer's Disease, Scanner – ADNI used different scanners to acquire data with differing protocols, M – male, F- female

2.2.3 MRI Pre-processing

2.2.3.1 Freesurfer recon-all

Freesurfer is a freely available analysis suite that performs cortical reconstruction and volumetric segmentation (http://surfer.nmr.mgh.harvard.edu/). All MRI data for YNiC (AMD and controls) and ADNI (AD and controls) were run through the 'recon-all' script using Freesurfer version 6.0. Recon-all is a fully automated process involving several stages and corrections to each image to produce cortical thickness, cortical volume, and subcortical volume estimates upon completion. As explained on Freesurfer's guide, recon-all involves brain extraction (Ségonne et al., 2004), Talairach transformation, segmentation of subcortical white matter and deep grey matter volumetric surfaces (including the hippocampus) (Fischl et al., 2002; Fischl, Salat, et al., 2004), intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the grey matter white matter boundary, topology correction (Fischl, Liu, & Dale, 2001; Ségonne, Pacheco, & Fischl, 2007), and surface deformation to optimally place the grey/white and grey/cerebrospinal fluid borders (Dale & Sereno, 1993; Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000). Once cortical reconstruction is complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl, Sereno, & Dale, 1999), registration to a spherical atlas (Fischl, Sereno, Tootell, & Dale, 1999), parcellation of the cerebral cortex (Desikan et al., 2006; Fischl, Van Der Kouwe, et al., 2004), and creation of surface based data including maps of curvature and sulcal depth.

This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness. Calculated as the closest distance from the grey/white boundary to the grey/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). The maps are created using spatial intensity gradients across tissue types and not reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data and are capable of detecting sub-millimetre differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). Freesurfer morphometric procedures show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006; Reuter, Schmansky, Rosas, & Fischl, 2012). For images that had a field of view larger than 256 (typically YNICT1a images), trilinear interpolation was used to re-slice the image to 256.

After recon-all finished, data were checked for soft errors (i.e skull strip errors, segmentation errors, intensity normalization errors, pial surface misplacement, and topological defects). If any errors were present, edits were made, and images were sent through the appropriate stage of recon-all to recalculate cortical thickness and volume estimates; data was re-examined upon completion. Following Freesurfer's guidance, images were not edited if there were no obvious errors, or a degree of uncertainty, to avoid over editing and to ensure reproducibility.

2.2.3.2 Data extraction

To gain cortical thickness and volume estimates of the IFG, occipital pole, and angular gyrus, the Destrieux atlas was used (Destrieux, Fischl, Dale, & Halgren, 2010) and for estimates of entorhinal cortex, the Desikan-Killiany atlas was used (Desikan et al., 2006). Predefined ROIs for left and right IFG (G_front_inf_Orbital, G_frontinf-Triangul, and G_front_inf-Opercular) were averaged to yield one value per participant. The same was done with the pre-defined Pole_occipital, pariet_inf-Angular, and entorhinal ROIs, where data from the left and right hemispheres were averaged to create one cortical thickness and one volume estimate per participant per ROI (Figure 2-1).

For the Hippocampus (Figure 2-2), estimates from the left and right hippocampal volumes from the aseg atlas (Fischl et al., 2002) were averaged to get one value for each participant.

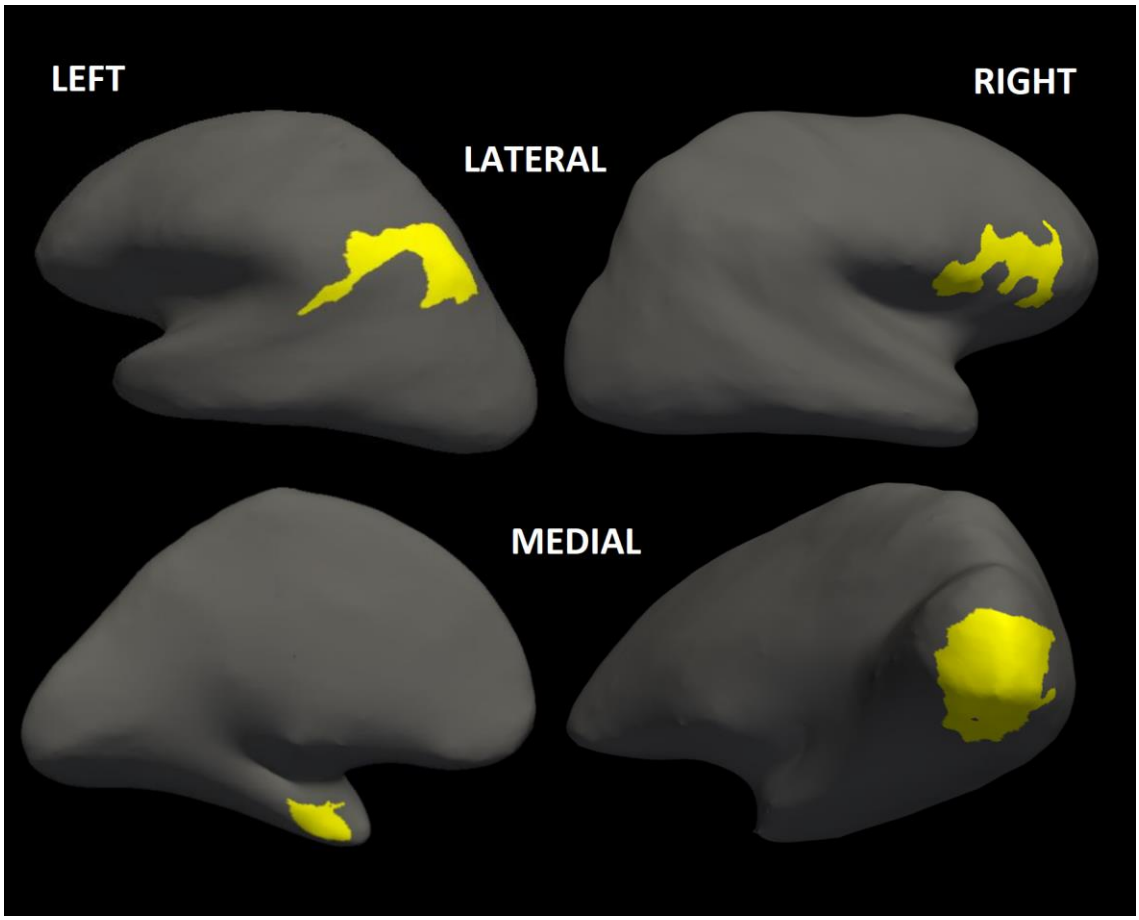


Figure 2-1. Angular gyrus, IFG, entorhinal cortex, and occipital pole regions of interest overlay on inflated hemisphere in yellow.
Top left lateral view: Angular gyrus (pariet_inf-Angular), bottom left medial: Entorhinal cortex (entorhinal); Top right lateral: Inferior frontal gyrus (G_front_inf_Orbital, G_frontinf-Triangul, and G_front_inf-Opercular); Bottom right medial (posterior angle): occipital pole (Pole_occipital).

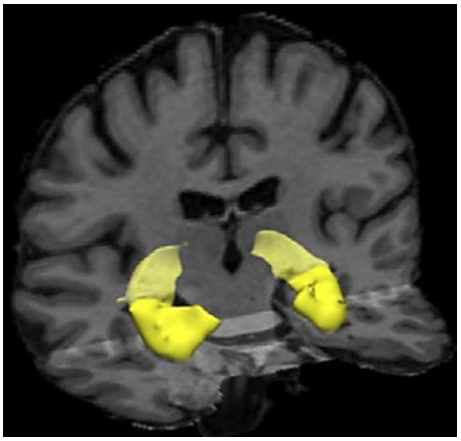


Figure 2-2. Hippocampus region of interest shown in yellow.
Coronal and sagittal slice of the brain showing the left (Left-Hippocampus) and right (Right-Hippocampus) hippocampus in yellow. *Image source: Google image search, last accessed 07/06/2018*

2.2.4 Data Analysis

Mean cortical thickness and volume estimates per participant were added to IBM SPSS statistics 25 to see if brain neurodegeneration patterns in these ROIs was shared across AD and AMD. All assumptions were met for the following models unless otherwise stated.

2.2.5 Data preparation

2.2.5.1 Effects of T1 scan protocol on YNIC data (AMD vs controls)

AMD participants and their controls' MRI scans were acquired using two different T1 protocols (GlasserT1 and YNICT1a). Controls required the same characteristics for enrolment, but AMD participants had bilateral vision loss in one study (GlasserT1) and unilateral vision loss in the other (YNICT1a). To see whether T1 protocol differences was reflected in their cortical thickness and volume estimates, a mixed ANOVA was run on the data. The controls' data will accurately reflect any differences whereas the ANOVA for AMD may detect differences in clinical features. Any difference between AMD participants is not of interest in this study, where the inclusion criteria only required a long-standing diagnosis of AMD. The data was split by participant group - controls and AMD - to explore the effect different T1 protocols had on cortical thickness and volume estimates, ensuring clinical features did not confound the results.

A mixed ANOVA (between subject variable T1 protocol with two levels: GlasserT1 and YNiCT1a; within subject variable ROI with four levels: entorhinal cortex, angular gyrus, IFG, and occipital pole) was conducted for cortical thickness and (between subject variable T1 protocol with two levels: GlasserT1 and YNiCT1a; within subject variable ROI with five levels: entorhinal cortex, hippocampus, angular gyrus, IFG, and occipital pole) volume on controls' (Figure 2-3) and AMD participants' estimates (Figure 2-4).

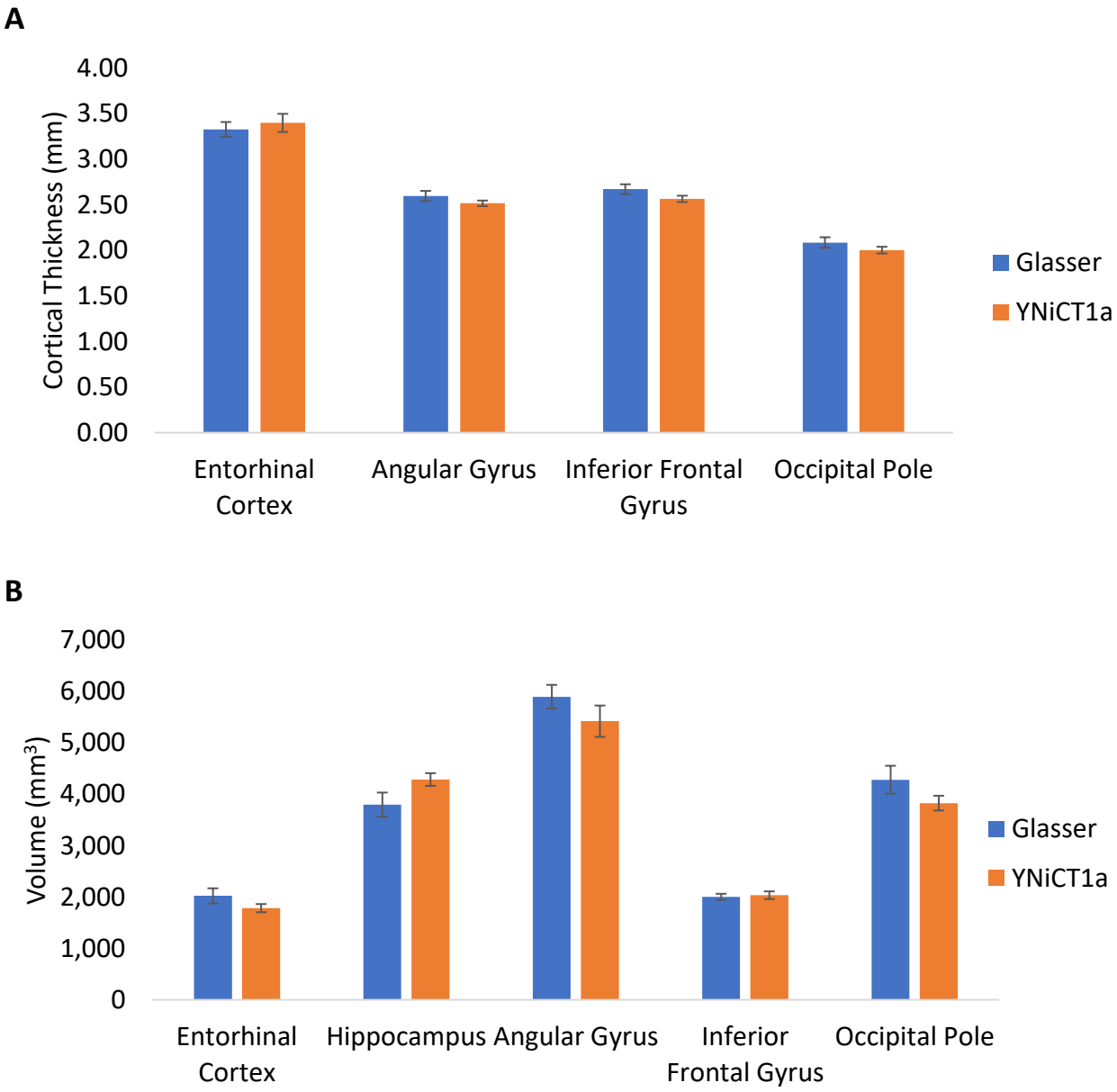


Figure 2-3. Control group's cortical thickness and volume means by ROI and T1 protocol. A shows cortical thickness means, B shows volume means. Glasser T1 (blue) has a different protocol to YNiCT1a (orange) – see section 2.2.1.2 for full T1 protocols. Error bars show standard error of the mean.

Results for controls cortical thickness revealed a significant difference between ROIs ($F(1.6, 22.39)=148.09$, $p<.001$, partial eta = 0.91), which was expected, but importantly no significant difference between T1 protocols ($F(1,14)=1.68$, $p=.216$, partial eta = 0.11). There was no significant interaction (Greenhouse-Geisser) between T1 protocol and ROIs ($F(1.60, 22.39)= 0.84$, $p=.422$, partial eta = 0.06) for cortical thickness estimates. The same result was shown for volume where there was an expected significant difference between ROIs ($F(1.88,26.30)=143.98$, $p<.001$, partial eta = 0.91) and no significant difference between T1

protocols (F(1,14)=1.32, p=.270, partial eta = 0.09). No significant interaction was found between T1 protocol and ROI for volume (F(1.88,26.30)=2.33, p=.120, partial eta = 0.14). Using only control data, the results from both mixed ANOVAs show that T1 protocol does not significantly affect the estimates Freesurfer produced for cortical thickness and volume.

For AMD (Figure 2-4), mixed ANOVA results for cortical thickness revealed an expected significant difference between ROIs (F(1.84,42)=66.58, p<.001, partial eta = 0.83) but an unexpected significant difference for T1 protocol (F(1,14)=7.73, p=.015, partial eta = 0.36) given no difference was found for controls. No significant interaction was found between T1 protocol and ROIs for cortical thickness (F(1.84, 42)=2.99, p=.072, partial eta =0.18). However this was not the same for volume, where a significant difference was found for ROI (F(2.03,56)=135.15, p<.001, partial eta = 0.91), but not for T1 protocols (F(1,14)=0.00, p=.978, partial eta = 0.00). No significant interaction was found between T1 protocol and ROIs for volume estimates (F(2.03,56)=1.59, p=.222, partial eta = 0.10). The significant difference for cortical thickness is anticipated to be due to the differences in clinical features rather than scan protocol. Especially as cortical thickness is more sensitive to clinical features than volume (Aycheh et al., 2018; Lerch et al., 2005; Regeur, 2000). Similarly, AMD volume and controls' thickness and volume findings showed no significant difference for T1 protocol on these brain estimates.

The two regions with a significant difference for cortical thickness between T1 protocol were IFG (Welch ANOVA p=.008) and entorhinal cortex (Welch ANOVA p=.016). Three participants were responsible for the thinnest cortex in IFG and entorhinal cortex (YNICT1a scan). After removing these participants and re-running the statistics, neither IFG (Welch ANOVA p=.101) or entorhinal cortex were significantly different for T1 protocol (Welch ANOVA p=.153). The three participants' scans were checked for soft errors and assessed to be valid datapoints. As scan protocol did not appear to affect the results after this exploration of data, data from all participants were combined across scan protocols in all subsequent analyses.

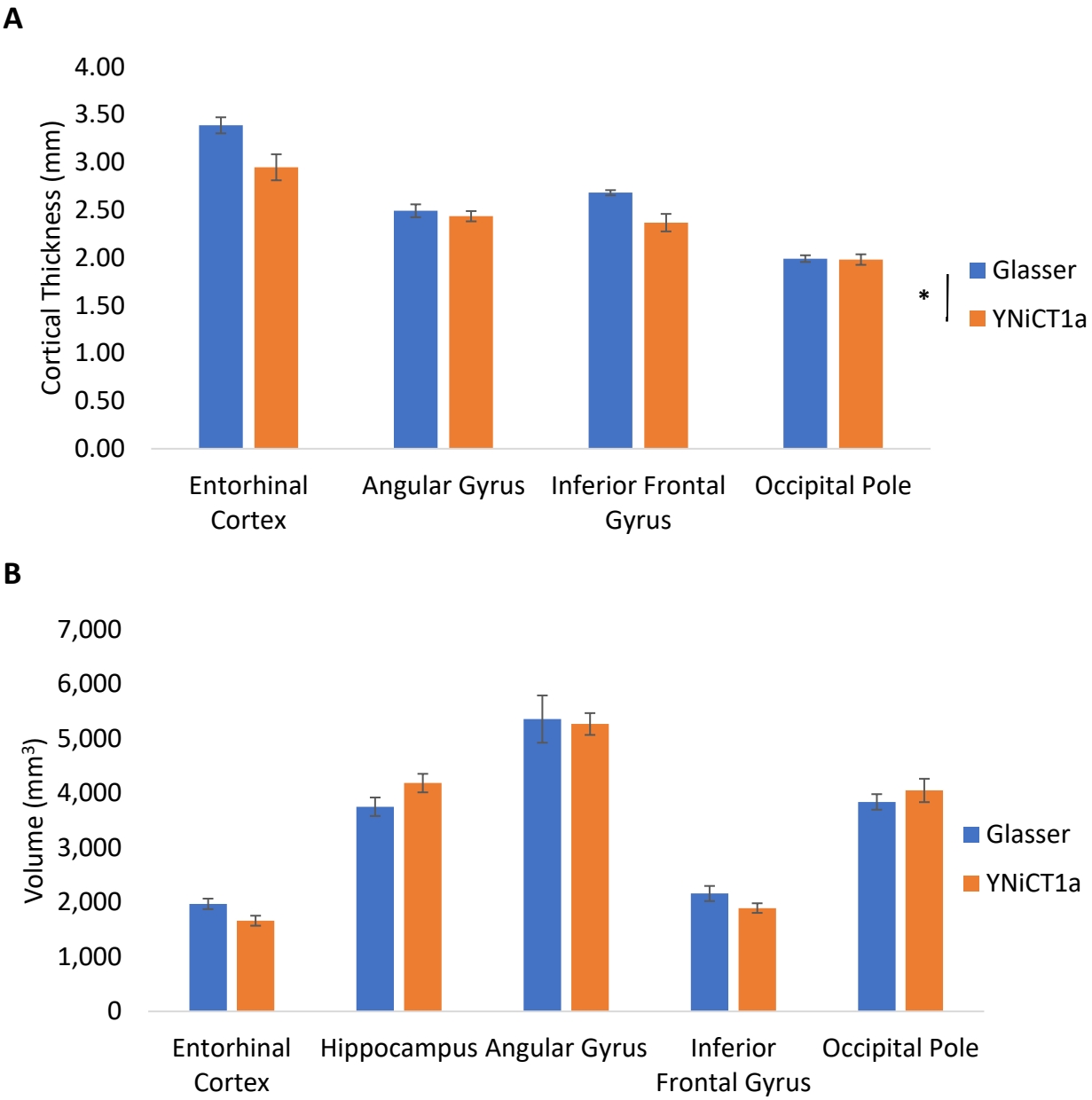


Figure 2-4. AMD group's cortical thickness and volume means by ROI and T1 protocol.
A shows cortical thickness means, B shows volume means. Glasser T1 (blue) has a different protocol to YNiCT1a (orange) – see section 2.2.1.2 for full T1 protocols. Error bars show standard error of the mean. *p<.05

2.2.5.2 Model selection

Alzheimer's Disease Neuroimaging Initiative (AD and controls) and YNiC (AMD and controls) data could not be compared to each other because YNiC estimates for controls were significantly thicker (repeated measures ANOVA, main effect of database; $F(1,30)=7.71$, $p=.009$) compared to ADNI data. The hypothesis was concerned with assessing the pattern of neurodegeneration across the brain for AMD, whilst ensuring the known AD patterns are revealed with this same method. For this reason, clinical groups were analysed separately (AD

compared to controls; AMD compared to controls), especially as AD results could drive differences in AD sensitive regions when comparing all clinical participants with controls.

Atrophy experienced in AMD is likely to be on a smaller scale compared to AD (otherwise both participant groups would have AD), showing that a non-significant interaction (participant group x region) in a mixed ANOVA would not appropriately address the hypothesis. Additionally, regions' volumes and thickness naturally vary, resulting in a naturally occurring significant difference between ROIs. The hypothesis is concerned with the pattern across the brain rather than a main effect of participant group. For these reasons, ROIs were assessed separately, using a t-test rather than a mixed ANOVA. With smaller sample sizes, effect sizes can help reveal trends in the data and are important measures to include in reporting findings. Given the small sample sizes, however, effect size estimates will be noiser compared to larger sample sizes and they should be interpreted with some caution because of this.

2.3 Results

2.3.1 Entorhinal Cortex

Entorhinal cortex is the first affected area in AD. Results comparing entorhinal cortical structure between AMD, AD and controls are shown in Figure 2-5. The results showed that the entorhinal cortex was significantly thinner ($t(30)=5.86$, $p<.001$, Cohen's $d = 2.09$) and smaller ($t(30)=4.96$, $p<.001$, Cohen's $d= 1.81$) in AD (thickness (mm): M=2.46, SD=0.48; volume (mm^3) M=1319.69, SD=295.43) compared to controls (thickness (mm): M=3.34, SD=0.36; volume (mm^3): M=2048.28, SD=508.00).

It is expected that if AMD shares similar patterns of changes in the brain to AD, then the entorhinal cortex will also be affected. An independent t-test revealed that the entorhinal cortex in AMD participants (M=3.11mm, SD=0.42) was significantly thinner ($t(30)=2.05$, $p=.049$, Cohen's $d = 0.74$) compared to controls (M=3.37mm, SD=0.26). Even though AMD had a smaller entorhinal volume (M=1777.50mm^3, SD=304.88) compared to controls (M=1887.47mm^3, SD=324.50) this difference was not significant ($t(30)=0.99$, $p=.331$, Cohen's $d = 0.41$).

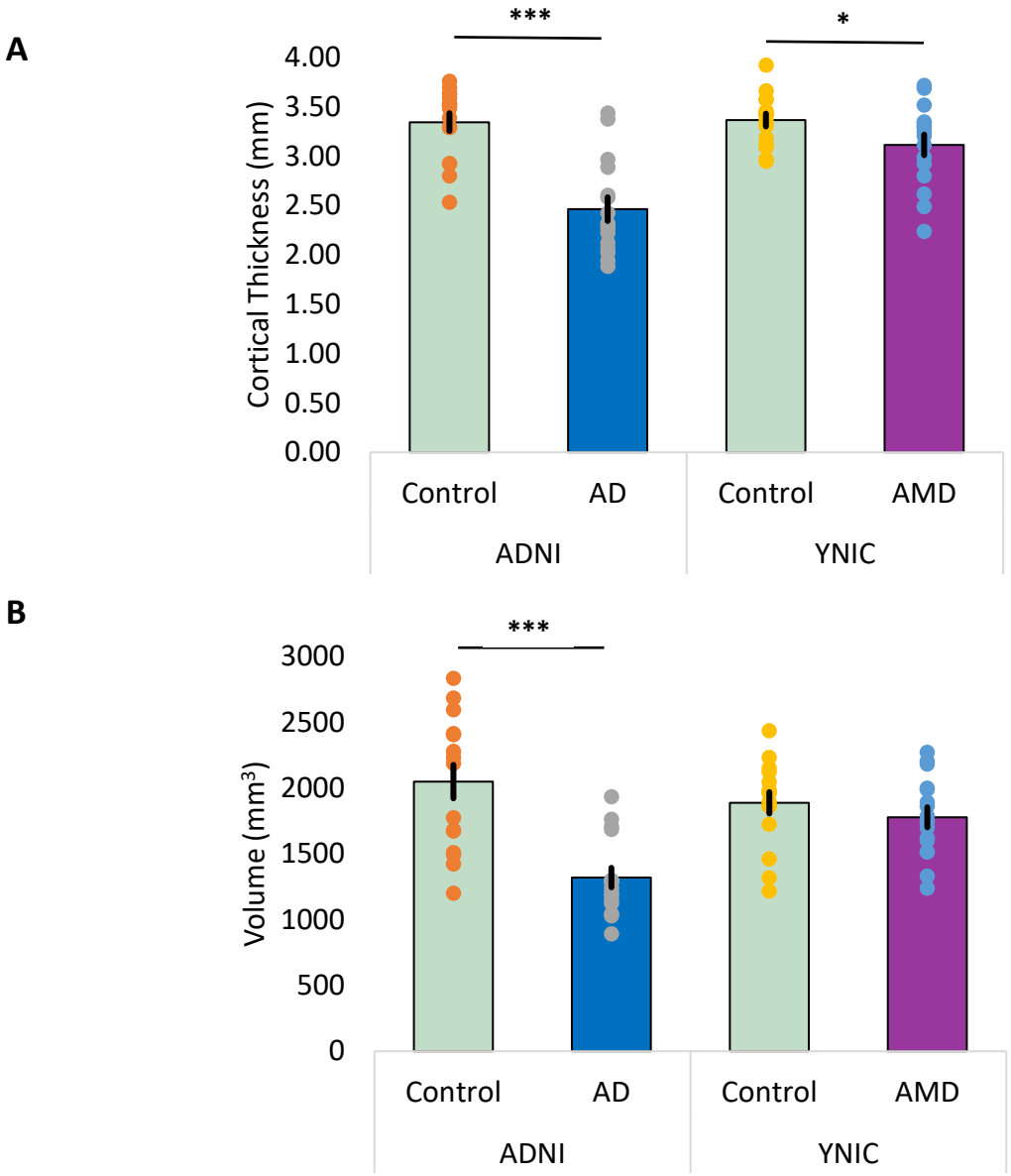


Figure 2-5. Mean entorhinal cortex results for AMD and AD compared to their respective controls. A shows cortical thickness results and B shows volume results. ADNI – Alzheimer's Disease Neuroimaging Initiative (left), YNiC – York Neuroimaging Centre (right), AD – Alzheimer's Disease (blue bar), AMD – Age-related macular degeneration (purple bar). Error bars show standard error of the mean. Dots show individual participant's cortical measure. ***p<.001 *p<.05

2.3.2 Hippocampus

Following the pattern of neurodegeneration in AD, the hippocampus is an area of the brain also commonly affected early in AD. Results for hippocampal volume are shown in Figure 2-6. A reduction in hippocampal volume in AD was confirmed with an independent t-test, indicating that the AD group (M=3002.17mm^3, SD=510.83) had significantly smaller hippocampal volume (t(30)=3.12, p=.004, Cohen's d=1.10) compared to controls (M=3546.83mm^3, SD=477.08).

The results for AMD showed that there was no significant difference (t(30)=0.27, p=.792, Cohen's d = 0.09) between AMD hippocampal volume (M=4020.37mm^3, SD=527.09) compared to controls (M=4070.52mm^3, SD=537.91). However, there was an outlier identified at 3SD below the mean for one of the controls. Removing this participant did not affect the overall conclusion (M=4178.96mm^3, SD=329.31, t(29)=1.00, p=.327, Cohen's d = 0.37).

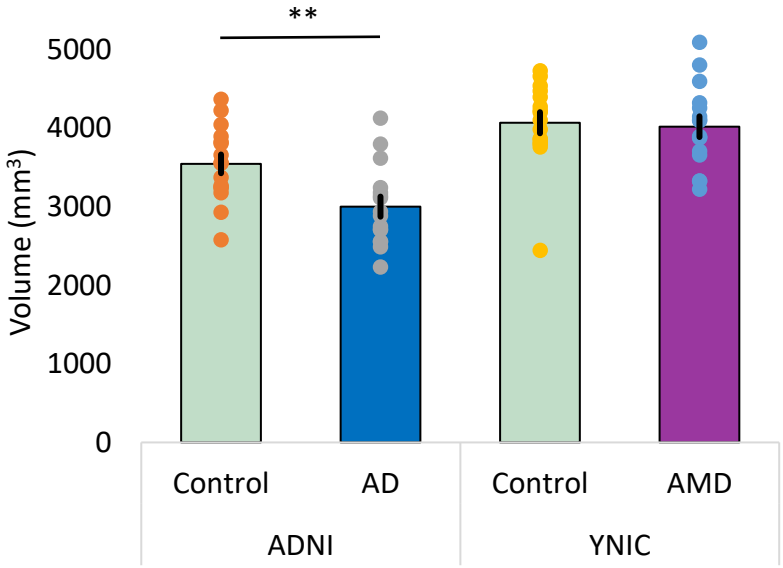


Figure 2-6. Mean hippocampal volume results for AMD and AD compared to their respective controls. ADNI – Alzheimer's Disease Neuroimaging Initiative (left), YNiC – York Neuroimaging Centre (right), AD – Alzheimer's Disease (blue bar), AMD – Age-related macular degeneration (purple bar). Error bars show standard error of the mean. Dots show individual participant's cortical measure. **p<.01

2.3.3 Angular Gyrus

As AD progresses, damage to the brain moves from the temporal lobe into the inferior parietal lobe. The results for angular gyrus are shown in Figure 2-7. AD group results shows the angular gyrus is significantly thinner (t(30)= 2.16, p=.039, Cohen's d = 0.76) and smaller (t(30)= 3.93, p<.001 Cohen's d = 1.40; thickness (mm): M=2.20, SD=0.23; volume (mm^3): M=4291.03, SD=736.51) compared to controls (thickness (mm): M=2.38, SD=0.26; volume (mm^3): M=5448.25, SD=919.40).

The angular gyrus is significantly thinner in the AMD group (M=2.38mm, SD=0.26) compared to controls (M=2.55mm, SD=0.12; t(30)=2.32, p=.027, Cohen's d = 0.89). After removing the two outliers in the AMD group (M=2.47mm, SD=0.13), the outcome was different where a near-significant p-value is found with a medium-to-large effect size (t(30)=1.78, p=.087, Cohen's d=0.65). A smaller volume was also found in AMD (M=5299.00mm^3, SD=785.25) compared to

controls (M=5626.50mm^3, SD=809.04) but again this difference was not significant (t(30)=1.16, p=.254, Cohen's d = 0.41).

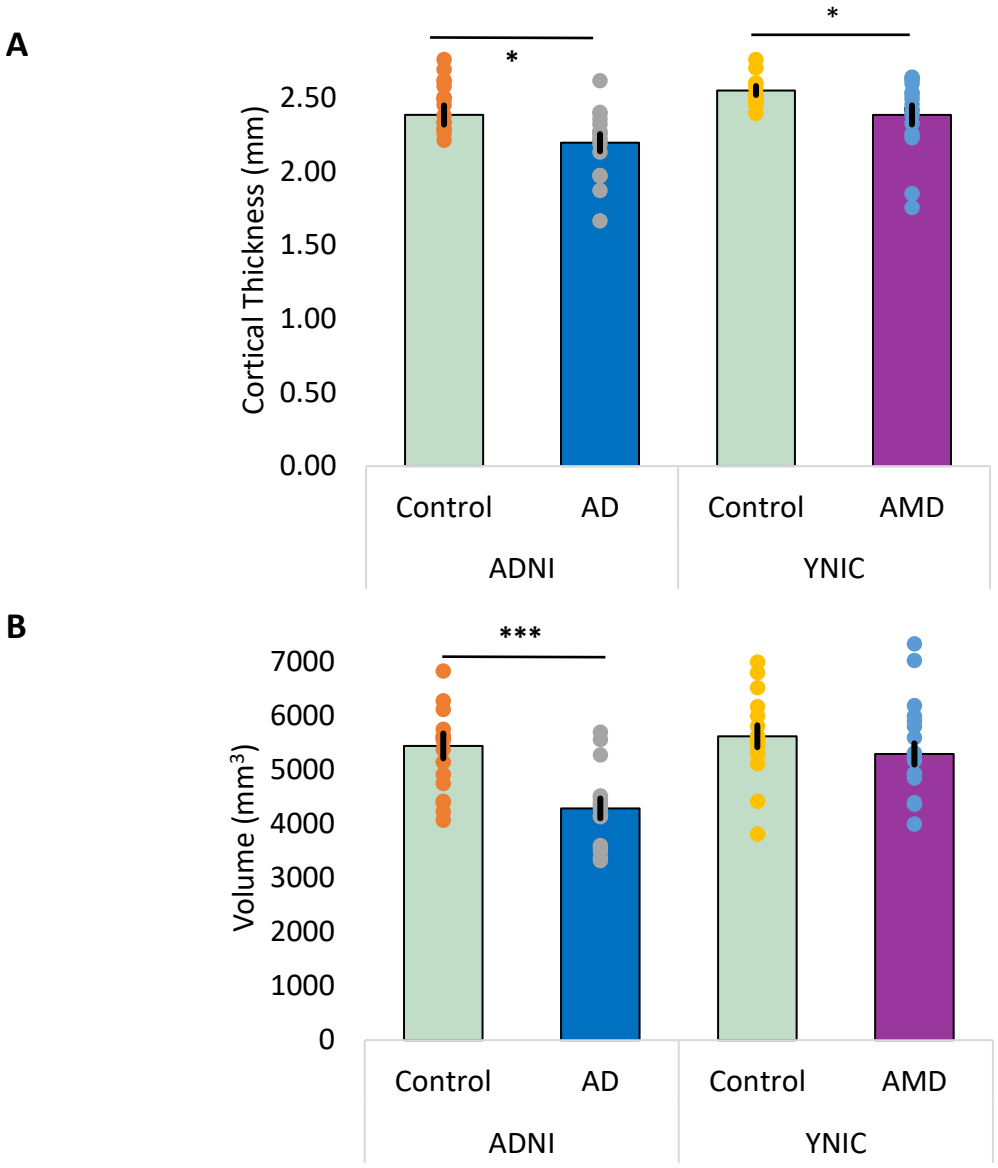


Figure 2-7. Mean angular Gyrus results for AMD and AD compared to their respective controls. A shows cortical thickness results and B shows volume results. ADNI – Alzheimer's Disease Neuroimaging Initiative (left), YNiC – York Neuroimaging Centre (left), AD – Alzheimer's Disease (blue bar), AMD – Age-related macular degeneration (purple bar). Error bars show standard error of the mean. Dots show individual participant's cortical measure. ***p<.001 *p<.05

2.3.4 Inferior Frontal Gyrus

In AD, damage in the brain moves towards the frontal lobes in moderate AD. As the participants selected for this study have mild AD it is expected that the IFG will not be affected in this participant group. The results, shown in Figure 2-8, indicate that AD participants do not have a significantly thinner or smaller IFG (thickness (mm): M=2.50, SD=0.12; volume (mm^3):

M=1947.30, SD=286.33) compared to controls (thickness: M=2.55, SD=0.13; volume: M=1908, SD=196.39) as expected (thickness (mm): t(30)=1.02, p=.317, Cohen's d = 0.36; volume (mm^3): t(30)=-0.44, p=.660, Cohen's d = -0.16).

The independent t-tests for AMD showed that there was also no significant difference between AMD (M=2.49mm, SD=0.28) and controls (M=2.61mm, SD=0.13) in IFG cortical thickness (t(30)=1.63, p=.114, Cohen's d = 0.61). IFG volume was also not significantly different (t(30)=0.29, p=.778, Cohen's d = 0.10) between AMD (M=1993.28mm^3, SD=320.85) and controls (M=2019.98mm^3, SD=193.88).

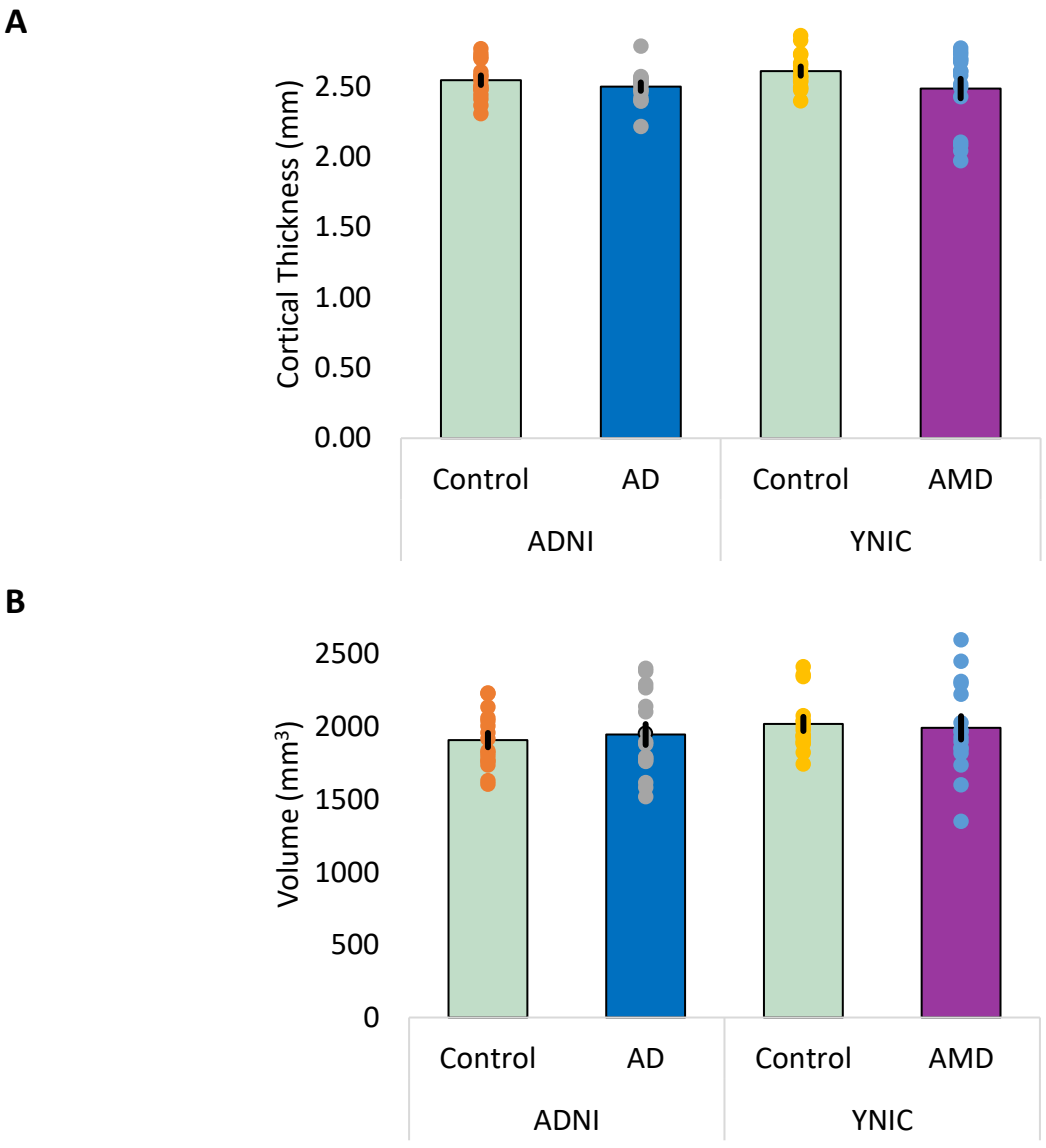


Figure 2-8. Mean inferior frontal gyrus results for AMD and AD compared to their respective controls. A shows cortical thickness results and B shows volume results. ADNI – Alzheimer's Disease Neuroimaging Initiative (left), YNiC – York Neuroimaging Centre (right), AD – Alzheimer's Disease (blue bar), AMD – Age-related macular degeneration (purple bar). Error bars show standard error of the mean. Dots show individual participant's cortical measure.

2.3.5 Occipital Pole

In AD, the occipital lobe is last to be affected by the disease. Results for the occipital pole are shown in Figure 2-9. Although the mean occipital pole was slightly thinner and smaller in the AD group, this difference was not significant either in thickness (t(30)=0.70, p=.489, Cohen's d = 0.25) or in volume (t(30)=1.62, p =.115, Cohen's d = 0.57; thickness: M=1.88, SD=0.13; volume: M=3568.50, SD=416.21) compared to controls (thickness (mm): M=2.55, SD=0.13, volume (mm^3): M=3815.97, SD=445.26).

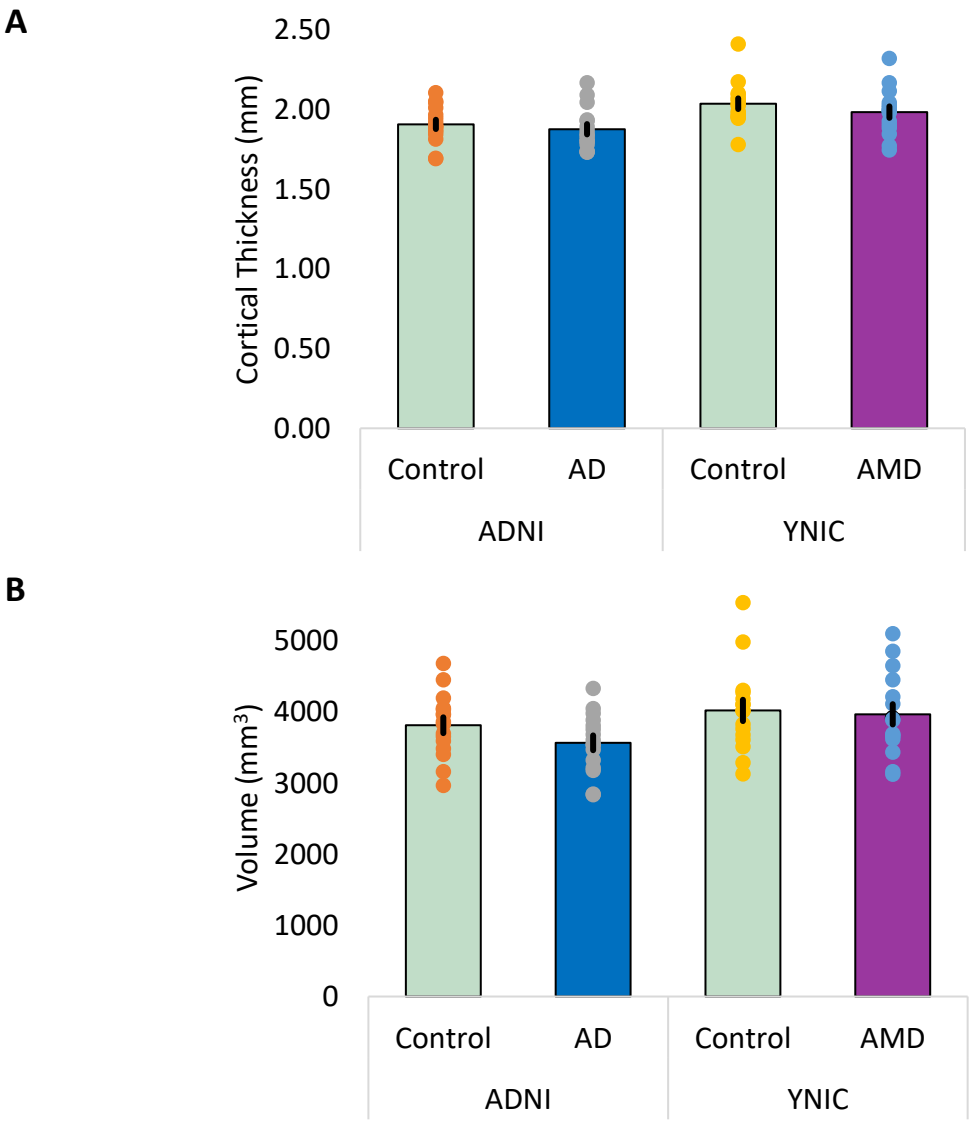


Figure 2-9. Mean occipital pole results for AMD and AD compared to their respective controls. A shows cortical thickness results and B shows volume results. ADNI – Alzheimer's Disease Neuroimaging Initiative (left), YNiC – York Neuroimaging Centre (left), AD – Alzheimer's Disease (blue bar), AMD – Age-related macular degeneration (purple bar). Error bars show standard error of the mean. Dots show individual participant's cortical measure.

Previous studies have reported structural reductions in the occipital pole in AMD. The results of the independent t-test revealed no significant difference (t(30)=1.08, p=.290, Cohen's d =

0.38) between occipital pole cortical thickness for AMD (M=1.99mm, SD=0.14) and controls (M=2.04mm, SD=0.13). There was also no significant difference between controls (M=4024.13mm^3, SD=599.74) and AMD (M=3969.31mm^3, SD=571.44) participants' occipital pole volume (t(30)=0.27, p=.793, Cohen's d = 0.09).

2.4 Discussion

The aim of this study was to establish whether AMD participants show evidence of brain neurodegeneration and if so, whether the pattern of degeneration was similar to that found in mild AD. The results for AD followed the expected pattern. The medial temporal lobe ROIs - entorhinal cortex and hippocampus - were found to be significantly affected, with both a smaller volume and a thinner cortex compared to controls. The angular gyrus was also found to be significantly affected with smaller volume and thinner cortex compared to controls. No significant differences were found between controls and AD for the IFG, or occipital pole as predicted. The results did not differ based on brain measures as cortical thickness and volume followed the same pattern.

For AMD, the different cortical measures (cortical thickness and volume) revealed different patterns. Addressing only cortical thickness the results showed that AMD brain changes follow a pattern of neurodegeneration representative of very mild AD. The entorhinal cortex is significantly thinner in AMD compared to controls, and the angular gyrus narrowly missed significance for thinner cortex in AMD when outliers were removed from analysis. However, volume estimates in medial temporal lobe ROIs and the angular gyrus were not significantly different from controls. This deviates from the pattern of results observed for AD. Consistent with AD, no significant difference was found for the IFG or occipital pole cortical thickness and volume estimates for AMD. Therefore, the results partially support the hypothesis that AMD will exhibit AD-related neurodegeneration patterns.

Structural changes in Alzheimer's disease.

The significant difference between controls and AD participants for the entorhinal cortex, hippocampus, and angular gyrus supports the predicted changes expected to occur in mild AD. The pattern of neurodegeneration in these ROIs is characteristic of AD in an established phase of mild AD demonstrating a temporoparietal pattern of neurodegeneration. This pattern supports previous studies suggesting this pattern of neurodegeneration specifically represents AD pathology (Fjell & Walhovd, 2010; Rabinovici et al., 2008; Whitwell et al., 2011). Beyond temporoparietal involvement, the non-significant finding for IFG thickness or volume was

predicted for this group of mild AD participants. The results align with previous studies that have found no frontal region involvement within mild AD (Singh et al., 2006) contrary to those that have in the moderate stage of disease (Dickerson et al., 2009; Jack et al., 2010). Cortical thickness results are consistent with Singh et al. (2006) where there is slight thinning of the IFG in mild AD, but this did not significantly differ from controls. The significant difference in angular gyrus for thickness and volume with no significant difference in IFG supports the notion that frontal region involvement occurs once symptoms become more prominent (Buckner et al., 2005; Scahill et al., 2002) nearer the beginning of moderate AD. In this study, AD participant's clinical severity was checked to ensure participants were rated as mild. This is unlike the participants in Busatto et al. (2003) where IFG involvement was found, but some of their participants were in the moderate stage of AD, potentially driving the difference found between AD and controls. In line with previous research showing that occipital lobes are last to be affected in AD (Karas et al., 2003), the occipital pole did not reveal any significant difference for cortical thickness or volume from controls.

Structural changes in age-related macular degeneration.

These results show, for the first time, a change in AMD grey matter outside of the occipital pole, where AMD brain changes are traditionally reported (Boucard et al., 2009; Hernowo et al., 2014). While cortical thickness results support the theory that AMD is related to AD (Baumritter et al., 2007; Bogolepova et al., 2019; Ohno-Matsui, 2011; Schwaber et al., 2020; Williams et al., 2014), the volume results do not. Cortical thickness results reveal the pattern of changes aligning with very mild AD as found in one of Dickerson et al.'s (2009) mild AD groups where no significant angular gyrus involvement was demonstrated. In this context, this result highlights the beneficial role of measuring entorhinal cortex in detecting prodromal AD (Bobinski et al., 1999; Dickerson et al., 2001; Du et al., 2003). Entorhinal cortex involvement without hippocampal involvement is characteristic of very mild AD (Dickerson et al., 2001; Schwarz et al., 2016), where AD memory problems may not be evident in these participants until the hippocampus is affected. Despite this, AMD entorhinal cortex volume revealed no significant difference or notable effect size compared to controls, a finding found in mild AD, suggesting a normal pattern of age-related brain changes. However, one study concluded that atrophy in cortical thickness and not volume was a feature of preclinical AD (Dickerson et al., 2009), which would support the use of cortical thickness over volume for research in AMD participants, who are more likely to sit within the preclinical to prodromal AD stage.

Changes in the occipital pole in AMD.

Although cortical thinning in AMD supports a prodromal AD pattern of neurodegeneration, previous literature states the prominent role of occipital pole in late-stage AMD. Consequently, a surprising result was the absence of occipital pole involvement in AMD. This finding is not consistent with previous findings where primary visual regions were found to be significantly affected (Boucard et al., 2009; Burge et al., 2016; Hanson et al., 2019; Hernowo et al., 2014). A potential reason for the lack of significant thinning could be due to the different AMD characteristics between the two AMD groups (being at different stages of the disease) or because of their controls (as they were not recruited alongside the AMD participants). Given AMD literature has previously reported primary visual region atrophy but not MTL atrophy, it was important to explore why no difference was found in this study.

One possible explanation that has already been hinted at, could be due to the differing clinical features and study aims between the AMD participants from the different studies. Ten participants were used from Hanson et al. (2019) where results show that there was no significant decline from timepoint 1 to timepoint 2 (3-4 months) from which participants' data is used in this study. Hence the lack of a significant difference could be due to participants' disease status. If participants later timepoints were used they may have shown AMD-related cortical thinning consistent with previous studies (Hanson et al., 2019; Hernowo et al., 2014).

The sensitivity of using clinical groups in potentially different stages of the disease course has already been revealed in AD, where participants in a very early stage of the disease may not show angular gyrus involvement (Dickerson et al., 2009) and the inclusion of some moderate AD participants with a mean MMSE score of 20.7 revealed frontal involvement (Busatto et al., 2003) whereas strictly mild AD with a mean MMSE score of 21.2 did not (this study). Likewise, no information was available for controls' visual status. Some control participants may have had visual complaints (such as unilateral visual impairment) that negatively affected their occipital pole estimates.

Volume verses cortical thickness.

The difficulties related to interpreting volume findings is highlighted with the AMD results. No significant differences were found from controls in this AMD group of participants, not even in the occipital pole, where volume reductions have been found in previous studies (Boucard et al., 2009). If cortical thickness is a more sensitive measure of direct neurodegeneration, as argued in previous studies (Hartikainen et al., 2012), and volume is affected by white matter surface area changes (Du et al., 2007), then it is plausible that AMD is exhibiting AD-related

neurodegeneration without volume reductions found in diagnosed mild AD participants. It may be that using uncorrected volume estimates, that could result in over or under estimations of real trends (section 1.2.3), has emphasised this phenomenon.

Limitations.

One of the weaknesses of this study is that the participants are from several different studies. Although potential differences between participant groups were investigated to account for or remove potential confounds (T1 scan protocol), this does not exclude the possibility that some may have remained.

Similarly, not having recruited the participants in a consistent way across the research studies from which this data is sourced, may have also resulted in subtle differences between the control and AMD participants that are hard to control for. Some controls were screened using the MoCA before enrolment to ensure optimal cognitive function. As ethics only allowed the use of anonymised brain data, no further information about the participants is accessible to help interpret the results.

Future directions and conclusions.

Future research could investigate the longitudinal pattern of changes in AMD; a within-subjects design could provide a more sensitive measure to determine whether the progression of AMD atrophy is similar to AD. AMD participants may exhibit accelerated declines in entorhinal cortex and hippocampal volume, even though the difference between AMD and controls is not detectable in a cross-sectional analysis.

In conclusion, AMD structural brain changes appears to replicate the pattern found in mild AD when considering only cortical thickness. There could be several reasons for the absence of significant results for volume, including not accounting for total intracranial volume (although no significant difference was found for TIV between participant groups), or because cortical thickness is a more sensitive measure of neurodegeneration. However, because entorhinal cortex thickness was significantly affected and a near-significantly thinner angular gyrus was evident, there is merit to believe that late AMD is following AD neurodegeneration patterns. Future studies following patients longitudinally may provide a more sensitive measure of atrophic changes.

Chapter 3: Study 2;

Is there evidence of grey matter neurodegeneration in early age-related macular degeneration, and is it similar to mild Alzheimer's disease across time?
A cross-sectional and longitudinal study.

3.1 Introduction

In the previous study, the main conclusion was that AMD participants exhibited preclinical AD neurodegeneration patterns based on significant thinning of the entorhinal cortex and a near-significantly thinner angular gyrus compared to controls; hinting at a pattern typically found in prodromal AD. However, studies have shown widespread atrophy in normal ageing that extends to MTL regions and the angular gyrus (Driscoll et al., 2009; Fjell, McEvoy, Holland, Dale, & Walhovd, 2013; Fjell, Walhovd, et al., 2009; Li et al., 2012; Pfefferbaum et al., 2013; Raz et al., 2010). Due to this vulnerability in normal ageing, studies have argued that AD is not pathological and just an accelerated process of normal ageing, particularly as the entorhinal cortex and hippocampus are significantly more affected by normal ageing from age 70 onwards (Fjell, McEvoy, Holland, Dale, & Walhovd, 2014; Fjell et al., 2012; Fjell, Westlye, et al., 2013; Raz et al., 2005; Scahill et al., 2003).

Without considering age effects, this shared pattern of vulnerability in AD-prone brain regions can cause a blurring of the distinction between normal age-related and prodromal AD-related patterns of atrophy. Although it is theorised that AD starts in late AMD (section 1.2.1), participants with impaired vision who decide to take part in MRI eye-related research (as in the previous chapter) could be cognitively healthier (and able to give informed consent) than those who decide not to take part. If this is true then the AMD participants in the previous study are likely to sit within the preclinical AD stage, highlighting the difficulty in identifying preclinical AD neurodegeneration from normal ageing using cross-sectional analysis. This is especially important if controls are not age-matched or when participants in each

experimental group sit above or below the age of 70, as seen in study 1. Overall, this highlights the complexity in deciphering pathological from normal age-related MTL neurodegeneration using cross-sectional analysis (Fjell et al., 2014; Raz et al., 2005).

Alzheimer's disease can be distinguished from normal ageing with longitudinal analysis, as MTL atrophy is to a lesser extent in normal ageing than observed in clinically recognised AD (Davatzikos, Xu, An, Fan, & Resnick, 2009; Fjell & Walhovd, 2010; Fjell, Walhovd, et al., 2009). Importantly, accelerated atrophy in these regions identifies prodromal AD. Cognitively normal individuals that progressed to MCI had greater rates of atrophy in AD-prone areas, including entorhinal cortex, compared to those who remained cognitively normal (Jack et al., 2004; Miller et al., 2013; Pacheco, Goh, Kraut, Ferrucci, & Resnick, 2015). These findings highlight the role of longitudinal MRI studies in confirming prodromal AD atrophy required for AMD research.

The importance of longitudinal studies is further demonstrated as cross-sectional and longitudinal studies can reveal different findings in the same participants. In normal ageing, a frontal region showing cortical thickening in cross-sectional analysis did not in longitudinal analysis (Yang et al., 2016). Alternatively, another study found hippocampal atrophy in cross-sectional analysis but no evidence of ongoing neurodegeneration in the same participants longitudinally (Wisse et al., 2018). One possible explanation for this difference is that cross-sectional analysis is affected by sampling bias and cohort effects whereas longitudinal analysis is not. This bias could be the result of several factors. Studies may attract participants who are interested in certain topics, such as the ADNI database; or exclude older adults based on lower cognitive scores, selecting higher functioning older adults at screening; and thirdly due to natural survivor bias in the oldest old (Fjell et al., 2014; Yang et al., 2016). Longitudinal studies have also been able to reveal trends that are not evident in cross-sectional studies (Du et al., 2006). These results suggest that cross-sectional analysis may underestimate the pattern of change in the brain. The large inter-variability in brain sizes may hide notable accelerating atrophy depending on participants recruited into the experimental group (Fjell, Westlye, et al., 2009).

Whilst cross-sectional studies reveal atrophy that has already taken place, where results can reflect age-differences rather than actual group differences, longitudinal studies are able to show ongoing atrophy patterns across time (Fjell & Walhovd, 2010; Wisse et al., 2018). The importance of the difference between the two measures is notable as thinner or smaller brain regions could be due to other reasons, such as inactivity or developmentally smaller brain sizes, that are reflected in cross-sectional analysis. Accelerated atrophy over time is likely to

reflect a pathological degenerative process (Wisse et al., 2018) and able to detect progression from normal ageing to prodromal AD (Fjell et al., 2014).

Longitudinal brain changes in mild AD are well defined. A pattern of accelerated temporoparietal atrophy compared to normal ageing is characteristic of AD, starting early in the AD disease course. Normal ageing, though, exhibits a frontotemporal pattern of atrophy (Chow et al., 2008). The differing longitudinal patterns between AD and normal ageing reveals a preservation of frontal lobes in mild AD relative to normal ageing (Busatto et al., 2003; Dickerson et al., 2009; Jack et al., 2010; Singh et al., 2006). This is another important indicator of prodromal AD as it was found that as older old (85+) participants started to exhibit MCI (considered prodromal AD) frontal cortex atrophy decelerated (Yang et al., 2016). These findings show that accelerating atrophy of frontal regions during normal ageing shifts into a state of preservation even when AD starts in those aged 85 and older. At this point, the IFG stops significantly atrophying across time, thinning at a non-significant rate (Singh et al., 2006). A double dissociation was proposed between the pattern of brain changes found in normal ageing compared to that found in AD. Mainly AD is characterised by the presence of MTL atrophy beyond that found in normal ageing; whereas normal ageing is characterised by a decline in the frontal lobes when AD initially shows sparing (Head, Snyder, Girton, Morris, & Buckner, 2005) despite no difference in the IFG detected in cross-sectional analysis (Singh et al., 2006).

This study extends on the first study by investigating longitudinal patterns of neurodegeneration within the three participant groups sourced from the same database. Participants were selected from ADNI, with more control over screening and wider access to participants' demographics and clinical information. Cross-sectional analysis was run on this new cohort to identify where participant groups may differ between studies (study 1 & 2) and for further interpretation of the longitudinal results. All participants were closely age-matched to remove any biases towards atrophy patterns reflecting differences in age, a weakness of the previous study.

As the entorhinal cortex and hippocampus are affected first in the AD course, and show higher rates of acceleration in AD compared to controls (Braak & Braak, 1996; Braak et al., 2011; Sluimer et al., 2009) it is predicted that both regions will show an accelerated rate of change in mild AD compared to controls. Mild AD then affects the angular gyrus that is predicted to show an accelerated rate of change compared to controls. With the frontal lobe unaffected in mild AD, and in contrast to the frontotemporal pattern of change in normal ageing, the IFG is predicted to show deceleration compared to controls. The occipital lobe is unaffected by mild

AD, and it is predicted that the occipital pole will show no significant difference in the rate of change compared to controls, as the occipital lobes are not susceptible to atrophy in either normal ageing or in AD.

If AMD follows an AD neurodegeneration pattern, then the entorhinal cortex will reveal an accelerated rate of change compared to controls. Given AMD participants in this study remained cognitively normal, it is unlikely there will be a significant increase in decline in the hippocampus' rate of change, as hippocampal involvement is usually found when AD cognitive impairments emerge. No difference in the rate of change for angular gyrus (reflecting a prodromal stage of AD) is expected. As found in AD, if the pattern of changes in AMD reflects an AD-like pattern of neurodegeneration, it is predicted that there will be preservation of the inferior frontal gyrus and no difference in the occipital pole. Although changes in AMD have been found with long-standing visual impairment, due to ADNI's exclusion criteria requiring good vision to complete the cognitive tasks, none of these participants fit into this category, and therefore, no changes are expected in the occipital pole.

3.2 Cross-sectional Methods

3.2.1 Participants

For cross-sectional analysis, 72 participants were included with 24 matched participants in each participant group (13 male) with a mean age of 79.66 years (SD = 5.48) for controls and AMD, and 79.63 years (SD=5.39) for AD. Participants were matched exactly for sex and age, except one participant aged 90 in the AD group that did not match the participants aged 91 in the other two participant groups. Participants were screened to ensure they did not have any neurological (stroke) or sensory (blindness, macular hole) cause for exclusion, and had the required clinical outcome to suggest they were either cognitively normal, had AMD and were cognitively normal, or had probable mild AD. All participants were required to have good enough vision to complete the cognitive tasks without assistance as set out by ADNI inclusion criteria, including those in the AMD group. For this reason, these AMD participants were presumed to be, and defined as, early AMD for the purpose of this thesis.

Not all participants from the cross-sectional analysis are used in longitudinal analysis. The longitudinal images were found around the cross-sectional images. For example, it may be that some scans were the first ones a participant had, aligning the longitudinal baseline scan with the cross-sectional scan. Alternatively, there may be times where the cross-sectional scan was the last scan the participant had in ADNI2 (up until the time this study was conducted)

meaning all images were at an earlier timepoint than the cross-sectional image. Primarily, cross-sectional data was chosen based on the required age for the study, the timepoint within ADNI was not important when participants were selected.

3.2.2 Acquisition and pre-processing

ADNI is a multi-site study using different MRI scanners (GE Healthcare, Philips Medical Systems, and Siemens Medical Solutions) with intentionally differing scan parameters (Table 3-1; see section 2.2.2.2 for acquisition details). Data were collected across the ADNI phases to increase sample size (ADNI1, ADNIGO, ADNI2); 1.5T images were more commonly acquired in ADNI1 than in ADNI2. There were 17 participants with 3T T1 images and seven participants with 1.5T T1 images in each participant group. Pre-processed MRI data were downloaded from ADNI as NiFTI files for further analysis using Freesurfer version 6.0 as explained in section 2.2.

Table 3-1. Number of participants scanned using the different MRI ADNI protocols in cross-sectional analysis.

	MRI Scanner		
Participant Group	Siemens	GE	Philips
Controls	9	11	4
AMD	9	10	5
AD	11	12	1

Participant Group: AMD = Age-related macular degeneration, AD = Alzheimer's Disease. MRI scanner: GE = GE Healthcare, Philips = Philips Medical Systems, Siemens = Siemens Medical Solutions.

3.2.3 Procedure

3.2.3.1 AMD

A search for "macular degeneration" was done on the recent medical history document (RECMHIST.csv) downloaded from ADNI. All participants that had "macular degeneration" listed in their medical history were highlighted and each person screened for their suitability for inclusion, to ensure they only had age-related macular degeneration. Those who had a history of stroke, TIA, or head injury were excluded. The same was done for those with glaucoma, macular holes, or any other listed eye conditions to make sure participants only had macular degeneration affecting their eyes at the time of the study**.** Corrected-to-normal eyesight was not a cause for exclusion. Eighty participants were found to be eligible after using this search and exclusion criteria.

Once participants fitted the inclusion and exclusion criteria, their participant ID was added into the MRI Advanced Search (beta) on the ADNI database to make sure participants had data

collected from them after enrolment. Participants with data were split into the cognitive group (cognitively normal, MCI, AD) they were placed in during enrolment. For example, those who were in the cognitively normal (CN) group at baseline were assigned to that same research group regardless of any change in cognitive status after their initial scan. After participants had been allocated to their enrolment group, there were only 61 participants from the initial screening that remained in the ADNI study long enough for there to be at least one datapoint on them. At enrolment, 25 participants had normal cognition, 28 had MCI, and eight had AD. The data from the 24 cognitively normal participants with AMD were used in this part of the study. Data used in this study was only selected after the AMD diagnosis had been confirmed in their recent medical history (RECMHIST; either at screening or at a later timepoint). One cognitively normal AMD participant's AMD diagnosis was first recorded in RECMHIST after they had converted to MCI and did not fit the criteria of the study. The age and sex of these participants were recorded for matching with the other participant groups.

Using conversion data (Table 3-2, 3-3), those who had converted to AD, at their last timepoint at the time this study was conducted, were slightly younger (M = 82.81, SD = 6.05) than those who did not (M = 85.09, SD = 6.14). From the age of 65, a person's risk of dementia increases from one in fourteen (7.14%) to one in six (16.67%) after the age of 80 (Alzheimer's Society, 2014). Using the Alzheimer's Society figures to cover the participants' ages, for the 80-84 age bracket the percentage of people who had Alzheimer's Disease was 11.1%, and in the 85-89 age bracket it was 18.3% (Alzheimer's Society, 2014). Using an average of the two values (15%) as the benchmark to assess the presence of AD in this sample, a binomial test was conducted on this AMD sample. The binomial test showed the proportion of those with AD after a diagnosis of AMD (.25) is significantly higher than expected in the general population (.15, p=.046 (1-sided)).

Table 3-2. Conversion information for cognitively normal AMD participants.

Cognitively normal	Mild cognitive Impairment	Alzheimer's Disease	Years after baseline M = 6.53 SD = 3.38
19			
3			
2			

Conversion data showing which cognitive group participants were in at their last timepoint. Nineteen participants remained cognitively normal, three converted to MCI and two to AD.

Table 3-3. Conversion information for mild cognitive impairment AMD participants.

Cognitively normal	Mild cognitive Impairment	Alzheimer's Disease	Years after baseline
1			M = 6.53
	17		SD = 3.38
	11		

Conversion data showing which cognitive group participants were in at their last timepoint. Nineteen participants remained cognitively normal, three converted to MCI and two to AD. One reverted back to cognitively normal.

3.2.3.2 AD

AD participants with pre-processed T1-weighted MRI images were found on Advanced Search (beta) using the tick box "AD". All AD participants who closely matched YNiC AMD participants for age and sex were highlighted and randomly selected before additional checks were carried out to ensure they did not have: any eye disease or neurological complication following the same exclusion as stated for AMD (MEDHIST.csv), that participants had a probable diagnosis of AD, and the professional's clinical severity was rated as mild (DXSUM_PDXCONV_ADNIALL.csv). Participants were also checked to make sure they did not have any congenital conditions or diseases that affected their other senses, for example, being congenitally deaf. A lot of participants from the list did not meet these criteria, but the search continued randomly selecting the next participant on the list until a participant was found. Participants that met these criteria were selected for this study, and the other AD participants that matched AMD participants for age and sex were discarded.

3.2.3.3 Controls

A second advanced MRI search (beta) for pre-processed T1-weighted images was conducted to find controls using the tick box "CN". Cognitively normal participants were matched for age and sex to ADNI AD participants. Participants were checked for eye diseases and neurological complications following the exclusion criteria stated for AMD (MEDHIST.csv) and to make sure they were clinically considered cognitively normal (DXSUM_PDXCONV_ADNIALL.csv; Table 3-4). Participants were also checked to make sure they did not have any congenital conditions or diseases that affected their other senses.

Table 3-4. Conversion information for cognitively normal control participants.

Cognitively normal	Mild cognitive Impairment	Alzheimer's Disease	Years after baseline
20			M = 6.23
3			SD = 3.05
1			

Conversion data showing which cognitive group participants were in at their last timepoint. Twenty participants remained cognitively normal, three converted to MCI and one to AD.

3.3 Longitudinal Methods

3.3.1 Participants

Sixty-six participants were included with 22 carefully matched participants (13 male) in each group with a mean age of 77.91 (SD=5.06) at baseline for controls, 78.27 (SD=5.93) for AMD, and 78.23 (SD=4.93) for AD. Both controls and AMD participants were cognitively normal at each timepoint used in the study.

3.3.2 Acquisition and Pre-processing

There were 11 participants with 3T images and 11 participants with 1.5T images (Table 3-5). There was no mixing between 1.5T and 3T images within participants' longitudinal images. Pre-processed MRI data were downloaded from ADNI as NiFTI files for further analysis.

Table 3-5. Number of participants scanned using the different MRI ADNI protocols in longitudinal analysis.

	MRI Scanner		
Participant Group	Siemens	GE	Philips
Controls	5	13	4
AMD	7	11	4
AD	6	15	1

Participant Group: AMD = Age-related macular degeneration, AD = Alzheimer's Disease. MRI scanner: GE = GE Healthcare, Philips = Philips Medical Systems, Siemens = Siemens Medical Solutions.

To extract reliable cortical thickness and volume estimates, images were automatically processed with the longitudinal stream (Reuter et al., 2012) in Freesurfer version 6. First, every image had been run through recon-all as described in section 2.2.3 before following the next steps of longitudinal processing (Cross). Second, an unbiased within-subject template space and image was created using robust inverse consistent registration (Reuter, Rosas, & Fischl, 2010: Template). Third, several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations were then initialised, with common information from the within-subject template used to significantly increase reliability and statistical power (Reuter et al., 2012). Brain estimate data was extracted from this last set of images (Long) (Figure 3-1).

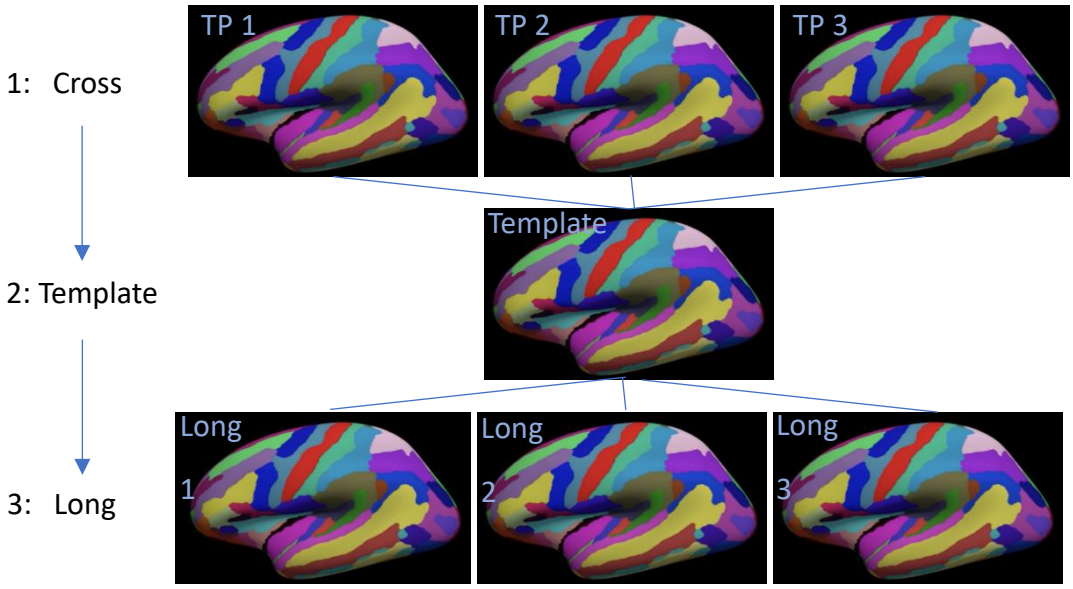


Figure 3-1. Schematic of Freesurfer's longitudinal processing stream.
The longitudinal analysis can be used with any number of initial images – this guide shows the process for three timepoints. Freesurfer's longitudinal processing stream includes three stages: Cross = Freesurfer's normal cross-sectional processing stream, Template = average of all cross-sectional runs using cross-sectional recon-all files, Long = the longitudinal data using the template image to ensure images are reliable and sensitive to changes across time. Image: TP N = timepoint followed by number of timepoints collected across time in chronological order i.e 1, 2, 3 for images in 2010, 2011, 2012; Long N = the final longitudinal image produced per timepoint. TP 1 will produce Long 1. *Image source for inflated brain: surfer.nmr.mgh.harvard.edu, last accessed 15/12/2019*

3.3.3 Procedure

To extract longitudinal data, an MRI search using the AMD participants' participant ID from the cross-sectional analysis was conducted, allowing all images in the ADNI database for each participant to be found. Two participants from the AMD group only had one MRI timepoint and were excluded from longitudinal analysis, leaving 22 participants. The two matched participants in the other participant groups (controls and AD) were also removed from further analysis, ensuring there were 22 participants in each group. Some AMD participants had longer follow-up timepoints in 1.5T than in 3T. For these participants, the 1.5T data was used to ensure maximum duration of time in the study. All MRI images, whilst AMD participants remained cognitively normal, were downloaded. Images for those who were in the control and AD groups from the cross-sectional analysis were also found and downloaded. Controls' clinical data were checked to ensure they remained cognitively normal for the duration of the study.

The same participants from the cross-sectional study were used, but participants' age ranges varied depending on where their cross-sectional scan was during their time in the study. Full details are shown in Table 3-6.

Table 3-6. Matched participant's longitudinal demographics.

Sex	Field Strength	Age range		
		Controls	AMD	AD
M	3.0T	89 - 93	90 - 91	89 - 90
M	3.0T	73 - 77	71 - 73	71 - 73
F	3.0T	75 - 79	74 - 78	78 - 79
M	3.0T	84 - 88	84 - 86	82 - 84
M	3.0T	73 - 77	72 - 73	74 - 76
M	3.0T	87 - 90	85 - 87	79 - 81
F	3.0T	75 - 79	71 - 76	72 - 74
M	3.0T	73 - 77	76 - 78	74 - 75
F	3.0T	75 - 77	75 - 78	77 - 79
M	3.0T	77 - 79	74 - 78	77 - 78
F	3.0T	73 - 75	70 - 72	72 - 73
F	1.5T	76 - 79	78 - 80	78 - 80
M	1.5T	76 - 79	85 - 89	84 - 86
M	1.5T	73 - 75	75 - 77	74 - 76
M	1.5T	77 - 78	80 - 82	78 - 80
M	1.5T	83 - 86	86 - 87	84 - 85
F	1.5T	84 - 86	86 - 88	86 - 88
F	1.5T	77 - 79	78 - 82	79 - 81
F	1.5T	78 - 80	78 - 79	78 - 79
M	1.5T	72 - 74	71 - 73	72 - 74
F	1.5T	80 - 82	80 - 83	80 - 82
M	1.5T	84 - 86	83 - 87	83 - 85

Sex: M = male, F = female; AMD = Age-related macular degeneration, AD = Alzheimer's Disease. Field Strength measured in Tesla.

3.3.4 Linear mixed effects models

3.3.4.1 Background

As part of the longitudinal process, Freesurfer recommends using a linear mixed-effects model to analyse the data. These models can handle missing timepoints and timepoints with different follow-up periods, as is the case in the ADNI dataset.

Linear mixed-effects models are an extension of linear models that consist of only fixed effects, by allowing the model to vary via random effects. Doing this reduces the error term of standard linear models. The linear mixed-effects model in this study consists of three participant groups (between subject difference: controls, AMD, AD) with time added as a linear regressor for longitudinal analysis. The group x time interaction was added to assess the slope between participant groups to measure difference in the rate of change. The mixed-effects model was designed pre-data collection to ensure data were analysed based on factors

deemed important to the hypotheses and research question using a decision tree. Time was added as a random effect because not every participant will have a similar pattern of change across time in each ROI (individual participant's slope, within subject changes), and participant was added as a random effect because of natural variance in participant's brain measure estimates at baseline (individual participant's intercept, between subject changes). Age was not added into the model to prevent model saturation and because groups were matched in age with no significant difference between the groups' baseline ages ($F(2,65)=0.03$, $p=.970$).

The final model (one per ROI) decided pre-analysis was (MATLAB syntax, revised by Dr Sam Berens):

ROI ~ 1 + AMD + AD + Time + AMD*Time + AD*Time + (1+Time|ParticipantID)

Two measures can be assessed with the mixed effects model: 1) Using modelled estimates, a paired-samples t-test is used to see whether ROIs are significantly declining across time; 2) the primary measure, rate of change (participant group and time interaction – the slope) with control data used as the reference group in the model. Clinical groups' rate of change was assessed against the control group's rate of change (slope) rather than against zero to directly assess whether any changes are significantly different from what is expected in normal ageing, to highlight pathological changes. Linear mixed-effects models were run in MATLAB R2018b.

3.3.4.2 Model Validation

Mixed-effects models have fewer assumptions than fixed-effects linear models. The data were checked to ensure they met the assumptions and could be analysed with mixed-effects linear models. This included ensuring linearity and normality of residuals, that homoscedasticity was present, and there was no multicollinearity. Fixed-effects and random-effects were examined in SPSS version 25 and all assumptions were met.

3.3.4.3 Timepoint data

When longitudinal data was selected the aim was to find three timepoints covering three years. The data differed from this number because of varying times between scans (between 3 months to a year). The AD group had the shortest time after the baseline scan ($M=1.74$ years $SD=0.55$) followed by AMD ($M=2.43$ years, $SD=0.98$) and then controls with the longest time after baseline ($M=2.65$ years, $SD=0.98$). A Welch ANOVA showed that there was a significant difference in the length of the timepoints used ($F(2,42.18)=9.92$, $p<.001$) with Games-Howell post-hoc tests showing that AD is significantly different from controls ($p=.001$) and AMD ($p=.013$). AMD and controls length of timepoints are not significantly different from each other

(p=.731). Despite this significant difference, time is added as a fixed and random effect in the model, and the model will account for this difference when predicting changes across time. Data was graphed prior to analysis to ensure the longitudinal data was linear.

This was also found in the number of MRI images downloaded for the study, 212 images were included in total with the aim of three images per participant. AD had the least MRI images per participant (M=2.79, SD=0.42), AMD had slightly more MRI images per participant (M=3.08, SD=0.72), and controls had the most images per participant (M=3.42, SD=0.50). A one-way ANOVA showed that there was a significant difference in the number of images at each timepoint used (F(2,69) =7.49,p=.001). Tukey post-hoc tests showed that AD was significantly different from controls (p=.001) but not AMD (p=.176). Controls did not have significantly different numbers of images compared to AMD (p=.105). The linear mixed effects model can handle varied numbers of images at each timepoint, so this will not impact on the results.

The main focus of this study is to explore the patterns in AMD, with AD data included to ensure the study methods were able to detect known neurodegenerative patterns of AD. Both AMD and controls have similar number of timepoints covering a similar amount of time, ensuring adequate data to reveal trends and patterns in the longitudinal analysis.

3.4 Cross-sectional Results

3.4.1 Entorhinal Cortex

Entorhinal cortex thickness results are displayed in Figure 3-2A. A one-way ANOVA was run on controls (M=3.39mm, SD=0.22), AMD (M=3.25mm, SD=0.34) and AD (M=2.50mm, SD=0.30) cortical thickness. Entorhinal cortical thickness revealed a significant difference between groups (F(2.69)=65.17, p<.001, η2= .65). AD had significantly thinner cortex compared to controls (p<.001, Cohen's d=3.41) and AMD (p<.001, Cohen's d= 2.35) but AMD was not different from controls (p=.238, Cohen's d=0.49) using Tukey post-hoc tests.

Entorhinal cortex volume results are displayed in Figure 3-2B. A further one-way ANOVA was run on controls (M=2065.00mm^3, SD=335.51), AMD (M=1903.73mm^3, SD=397.36) and AD (M=1329.13mm^3, SD=282.48) for volume. Entorhinal cortex volume revealed a significant difference between groups (F(2.69)=30.76, p<.001, η2 = .47). Tukey post-hoc test showed that AD had significantly smaller entorhinal cortex volume compared to controls (p<.001, Cohen's

d=2.38) and AMD (p<.001, Cohen's d= 1.69) but AMD was not significantly different from controls (p=.238, Cohen's d=0.44).

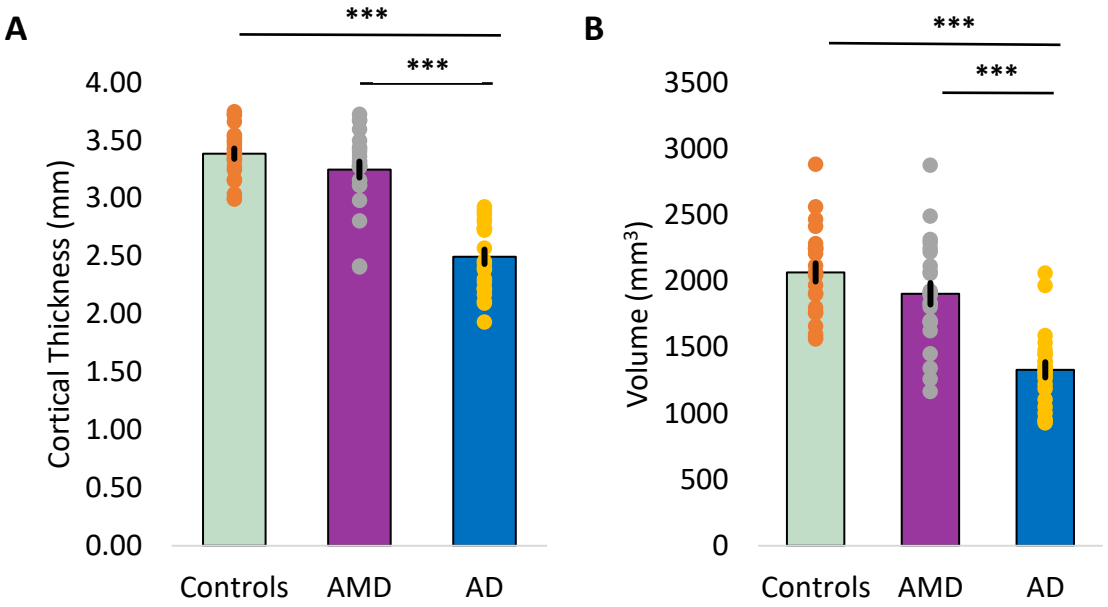


Figure 3-2: Mean entorhinal cortex cross-sectional results for controls, AMD, and AD. A shows cortical thickness, B shows volume, AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. Dots represent individual participant's cortical measure. *p<.05 ***p<.001

3.4.2 Hippocampus

The hippocampal volume results are shown in Figure 3-3. A one-way ANOVA run on controls (M=3543.61mm^3, SD=410.39), AMD (M=3282.69mm^3, SD=470.07) and AD (M=2949.40mm^3, SD=381.91) revealed that there was a significant difference between groups in hippocampal volume (F(2.69)=11.93, p<.001, η2 = .26). Tukey post hoc tests showed that AD was significantly smaller than both controls (p<.001, Cohen's d=1.50) and AMD (p=.021, Cohen's d= 0.78). AMD was not significantly different from controls (p=.089, Cohen's d=0.59) although this was nearing significance.

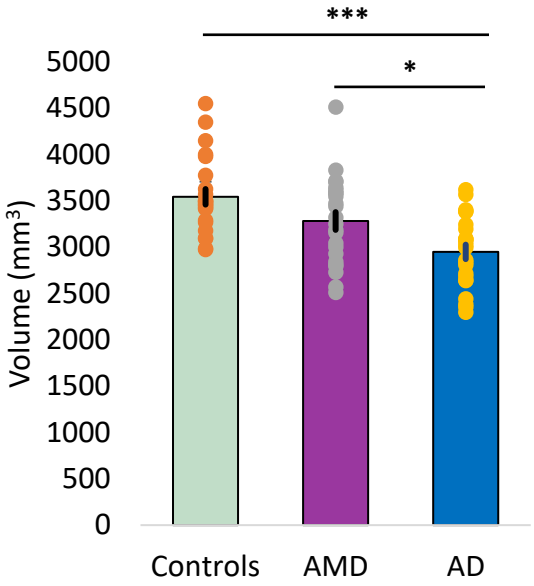


Figure 3-3. Mean hippocampal volume cross-sectional results for controls, AMD, and AD.
AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. Dots represent individual participants' cortical measure. *p<.05 ***p<.001

3.4.3 Angular Gyrus

The angular gyrus thickness results are shown in Figure 3-4A. One-way ANOVA ran on controls (M=2.35mm, SD=0.15), AMD (M=2.37mm, SD=0.16) and AD (M=2.23mm, SD=0.21) angular gyrus cortical thickness showed that there was a significant difference between participant groups (F(2,69)=4.30, p=.017, η2=.11). Tukey post hoc analysis showed that neither AMD (p=.921, Cohen's d = -0.13) nor AD was significantly different from controls, although AD just narrowly missed significance (p=.059, Cohen's d = 0.65). AMD was significantly thicker compared to AD (p=.023, Cohen's d = 0.74).

The volume results are shown in Figure 3-4B. One-way ANOVA for controls (M=5154.54mm^3, SD=688.87), AMD (M=5085.58mm^3, SD=1133.40) and AD (M=4659.98mm^3, SD=838.11) angular gyrus volume showed that there was no significant difference between participant group volumes (F(2,69)=2.10, p=.130, η2 = .06). Effect sizes calculated from the controls reflected this non-significant result for AMD (Cohen's d = 0.08) although the effect size for AD was larger (Cohen's d = 0.65).

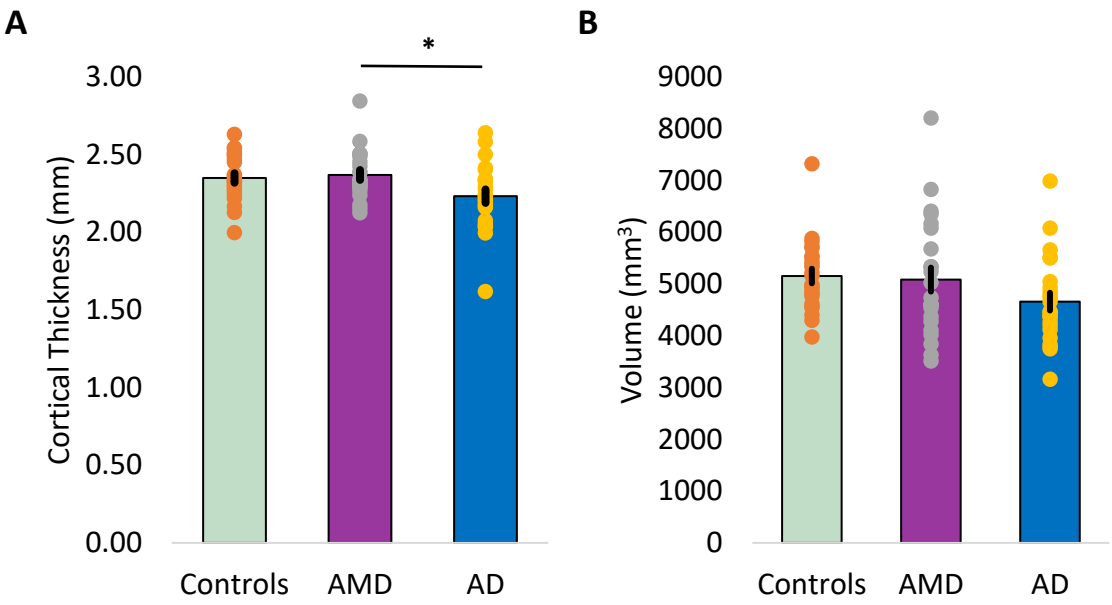


Figure 3-4: Mean angular gyrus cross-sectional results for controls, AMD, and AD.
A shows cortical thickness, B shows volume, AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. Dots represent individual participants' cortical measure. *p<.05

3.4.4 Inferior Frontal Gyrus

Inferior Frontal Gyrus thickness results are displayed in Figure 3-5A. One-way ANOVA for controls (M=2.50mm, SD=0.16), AMD (M=2.49mm, SD=0.13) and AD (M=2.41mm, SD=0.14) showed that the results narrowly missed significance revealing no significant difference between the groups for IFG thickness ($F(2,69)= 2.94$, $p=.060$, $\eta2= .08$), with a medium effect size. Comparing AD and AMD separately with controls, it was found that AMD had a small effect size (Cohen's d=0.11) whereas AD had a medium effect size (Cohen's d=0.63).

The same pattern was found in IFG volume (Figure 3-5B) where a one-way ANOVA showed that there was no significant difference between controls (M=1845.67mm^3, SD=273.71), AMD (M=1837.33mm^3, SD=288.65) and AD (M=1808.56mm^3, SD=242.09) IFG volumes ($F(2,69)=0.13$, $p=.882$, $\eta2= .00$). Effect sizes for AD (Cohen's d=0.14) and AMD (Cohen's d=0.03) remained small when compared to controls.

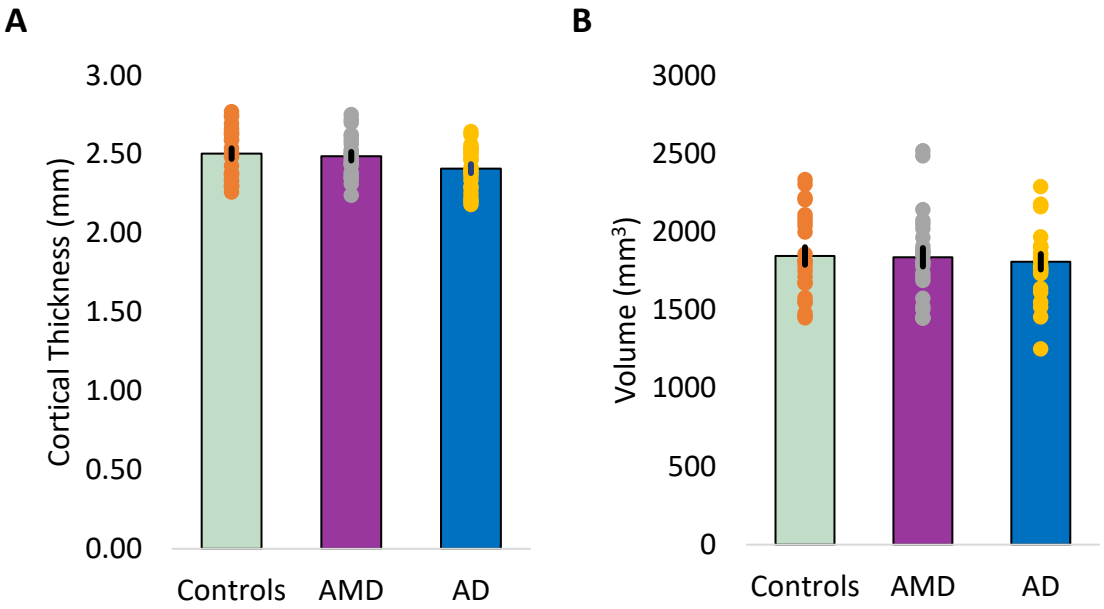


Figure 3-5. Mean inferior frontal gyrus cross-sectional results for controls, AMD, and AD. A shows cortical thickness, B shows volume, AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. Dots represent individual participants' cortical measure.

3.4.5 Occipital Pole

Occipital pole thickness is displayed in Figure 3-6A. A one-way ANOVA for controls (M=1.84mm, SD=0.11), AMD (M=1.82mm, SD=0.09) and AD (M=1.82mm, SD=0.11) cortical thickness revealed no significant difference between groups ($F(2.69)=0.21$, $p=.808$, $\eta 2= .01$).

Occipital pole volume results are displayed in Figure 3-6B. A one-way ANOVA on controls (M=3483.77mm^3, SD=483.54), AMD (M=3456.40mm^3, SD=416.58) and AD (M=3396.63mm^3, SD=504.93) volume showed that there was no significant difference between the participant groups ($F(2.69)=0.22$, $p=.806$, $\eta 2=.01$).

Effect sizes for AD and AMD calculated from the controls remained small for cortical thickness (Cohen's d=0.14, Cohen's d=0.18) and volume (Cohen's d=0.18, Cohen's d=0.06) respectively.

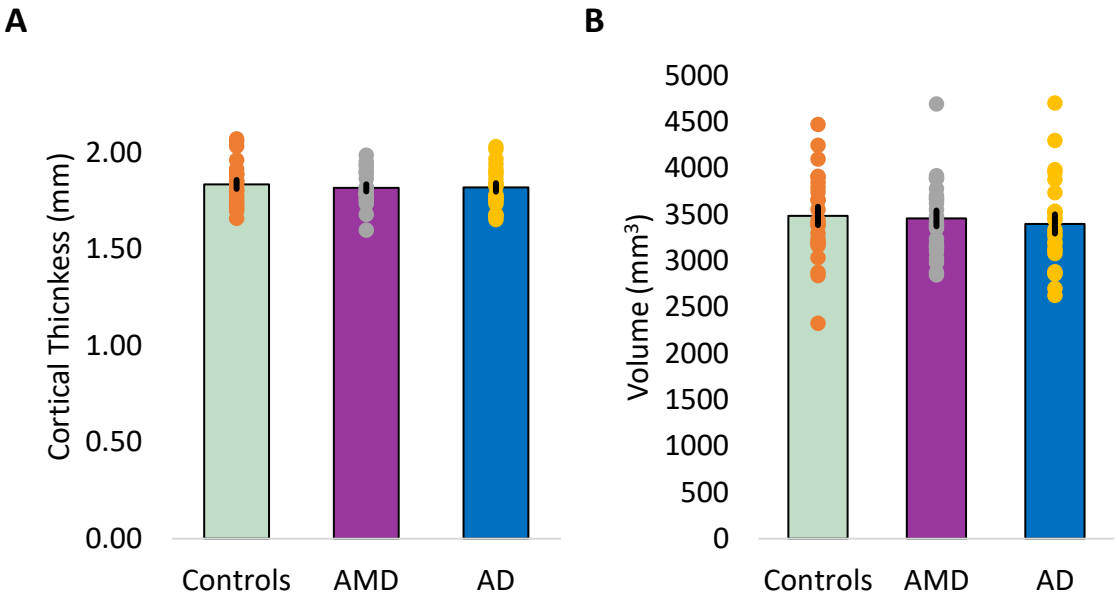


Figure 3-6. Mean occipital pole cross-sectional results for controls, AMD, and AD.
A shows cortical thickness, B shows volume, AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. Dots represent individual participants' cortical measure.

3.4.6 MMSE scores for study 1 and 2 AD participants

The results relating to AD participants show a different pattern to that observed in the first study. In study 1 the AD participant group showed a significant thinning of the angular gyrus whereas a near-significantly thinner cortex was found in this study. To ensure this difference reflects AD progression, the MMSE scores from both sets of AD participants were compared (Figure 3-7). An independent t-test was run on the AD participants MMSE score from study 1 (study 1: M=21.25, SD=1.00) with the MMSE scores from the participants used in this study (study 2: M=22.38, SD=1.97). The results showed that there was a significant difference between the AD participants' MMSE scores in this study compared to AD participants from study 1 ($t(35.95)=2.37$, $p=.023$, Cohen's $d = 0.76$). This might explain why the angular gyrus results are different because the AD participants in this study are in an earlier phase of the mild AD disease course. Both AD groups show non-significant angular gyrus results and assumed to be in roughly the same stage of disease.

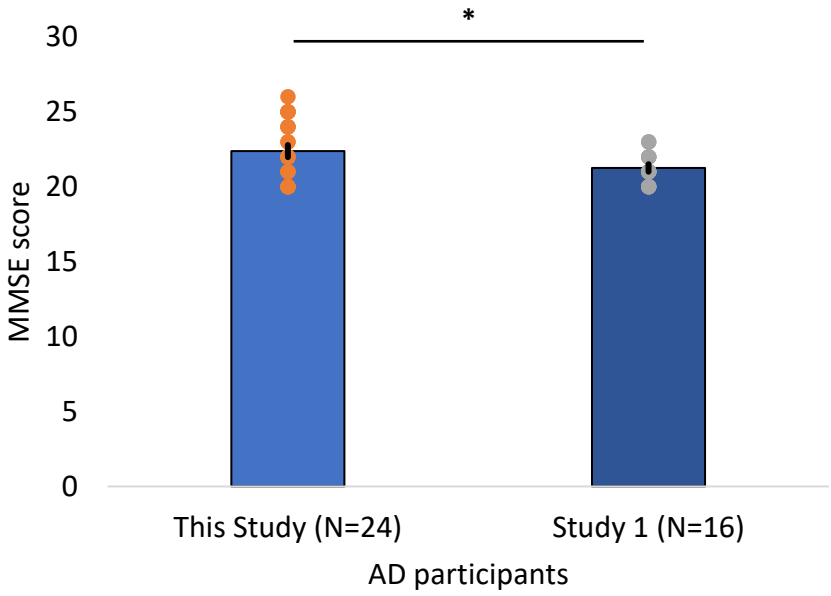


Figure 3-7: Mean MMSE scores for AD participants from study 1 (N=16) and study 2 (N=24).
Error bars show standard error of the mean. Dots represent individual participants' MMSE scores. *p<.05

3.5 Longitudinal Results

3.5.1 Entorhinal Cortex

At baseline, controls had a cortical thickness of 3.50mm (SE=0.12), AMD had a cortical thickness of 3.42mm (SE=0.12) and AD had a thickness of 2.60mm (SE=0.12). The entorhinal cortex thickness results are shown in Figure 3-8. Controls significantly declined at an average of 0.03mm (SE=0.01) per year (t(198)=3.49, p=.001), AMD significantly declined at an average of 0.05mm (SE=0.09) per year (t(198)=4.75, p<.001) and AD significantly declined at 0.09mm (SE=0.01) per year (t(198)=6.60, p<.001) as shown in Figure 3-8A. Only AD declined at a significantly accelerated rate of change compared to controls (t(198)=-3.26, p=.001, beta= -0.05, SE=0.01) and AMD (t(198)=-2.23, p=.027). AMD did not have a significantly different rate of change from controls (t(198)=-0.02, p=.268, beta = -0.02, SE=0.01).

At baseline, controls had a mean volume of 2163.92mm^3 (SE=157.46), AMD had a mean volume of 1991.54mm^3 (SE=157.56), and AD had a mean volume of 1403.21mm^3 (SE=157.71).

The same pattern of results for cortical thickness was observed in volume (Figure 3-8B) where controls significantly declined at 25.01mm^3 (SE=7.46) per year (t(198)=3.35,p=.001), AMD significantly declined at 24.92mm^3 (SE=8.05) per year (t(198)=3.10, p=.002), and AD significantly declined at 64.11mm^3 (SE=10.16) per year (t(198)=6.31, p<.001). AD had a significantly accelerated rate of change compared to controls (t(198)=-39.11, p=.002, beta= -39.11, SE=12.61) and AMD (t(198)=3.02, p=.003) but AMD did not have a different rate of change from controls (t(198)=0.08, p=.993 beta= 0.08, SE=10.97).

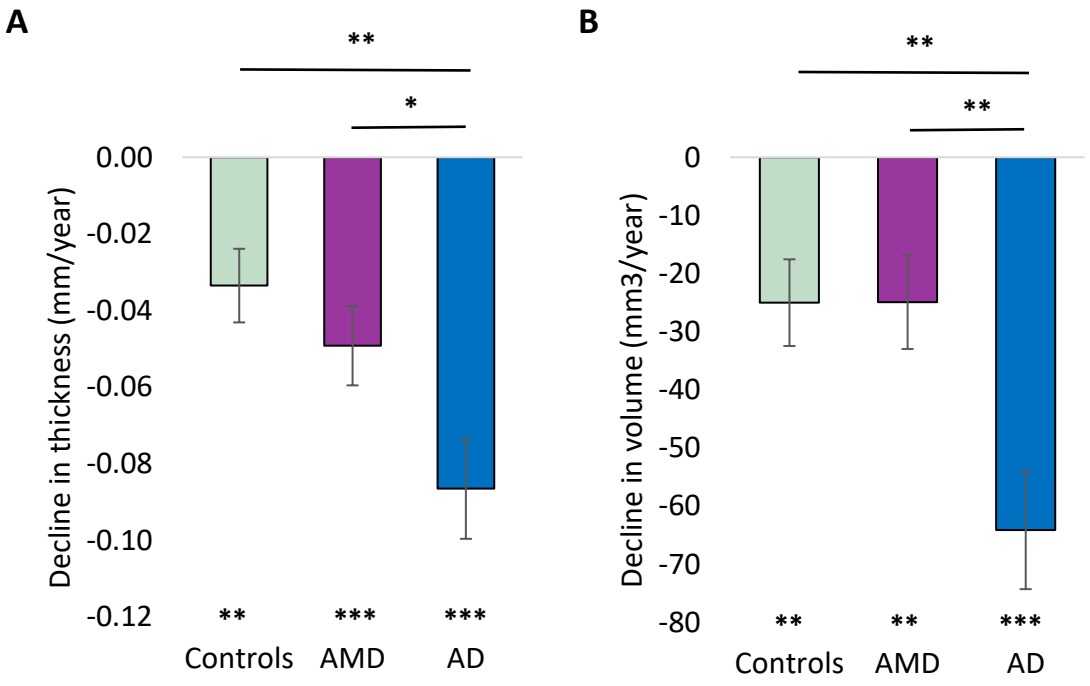


Figure 3-8. Mean entorhinal cortex thickness and volume decline per year for controls, AMD, and AD.
A shows mean cortical thickness and B shows mean volume. AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. *p<.05 **p<.01 ***p<.001

3.5.2 Hippocampus

At baseline, controls had a mean volume of 3633.75mm^3 (SE=197.44) AMD had a mean volume of 3239.28mm^3 (197.51) and AD had a mean volume of 2880.64mm^3 (SE=197.59). All participant groups significantly declined across time (Figure 3-9). Controls declined an average of 49.12mm^3 (SE=9.18) per year (t(198)=5.35, p<.001), AMD declined an average of 54.74mm^3 (SE=9.72) per year (t(198)=5.63, p<.001), and AD declined at an average of 100.57mm^3 (SE=11.14) per year (t(198)=9.03, p<.001). AD showed an accelerated rate of change in hippocampal volume compared to controls (t(198)=-51.45, p<.001, beta=-51.45, SE=14.43) and AMD (t(198)=3.10, p=.002). The rate of change between the controls and AMD were not significantly different (t(198)=-5.63, p=.674, beta=-6.63, SE=13.37).

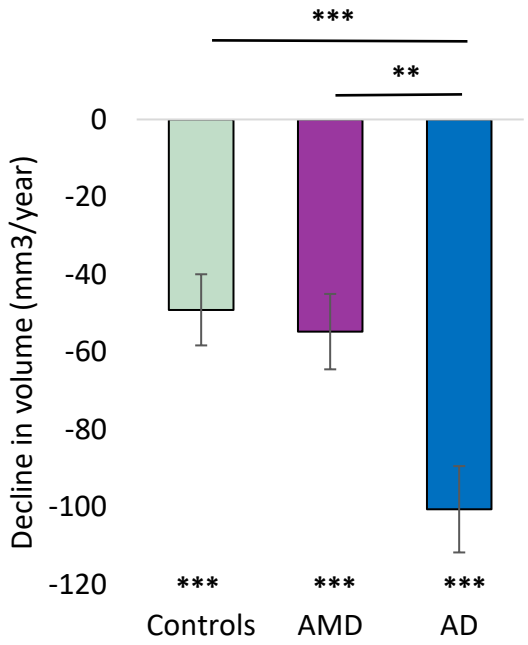


Figure 3-9. Mean hippocampal volume decline per year for controls, AMD, and AD.
AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. **p<.01 ***p<.001

3.5.3 Angular Gyrus

At baseline, controls had a mean cortical thickness of 2.44mm (SE=0.08), AMD had a mean cortical thickness of 2.45mm (SE=0.08) and AD had a mean cortical thickness of 2.24mm (SE=0.08). Angular gyrus results are shown in Figure 3-10. AMD did not significantly decline across time, declining an average of less than 0.01mm (SE=0.01) per year (t(198)=0.57,p=.569), whereas controls significantly declined by an average of 0.022mm (SE=0.01) per year (t(198)=3.57, p<.001), and AD significantly declined by an average of 0.025mm (SE=0.01) per year (t(198)=2.49, p=.014) as shown in Figure 3-10A. Although AD did not have a different rate of change compared to controls (t(198)=-0.25, p=.805, beta=-0.00, SE=0.01) or AMD (t(198)=1.74, p=.084), AMD showed a significantly slower rate of change compared to controls (t(198)=1.97, p=.050, beta=0.02, SE=0.01).

For volume, at baseline controls had a mean volume of 5590.36mm^3 (SE=376.12), AMD had a mean volume of 5216.77mm^3 (SE=376.12) and AD had a mean volume of 4608.40mm^3 (SE=376.97). All participant groups' volumes significantly declined across time (Figure 3-10B). Controls declined an average of 70.74mm^3 (SE=14.49) per year (t(198)=4.88, p<.001), AMD declined an average of 33.11mm^3 (SE=16.02) per year (t(198)=2.07, p=.040), and AD declined an average of 108.62mm^3 (SE=23.61) per year (t(198)=4.60, p<.001). Neither AMD

(t(198)=1.74, p=.083, beta=37.63, SE=21.60) nor AD (t(198)=-1.37, p=.173 beta=-37.87, SE=21.60) had a significantly different rate of change compared to controls, but AMD was significantly slower compared to AD (t(198)=2.65, p=.009).

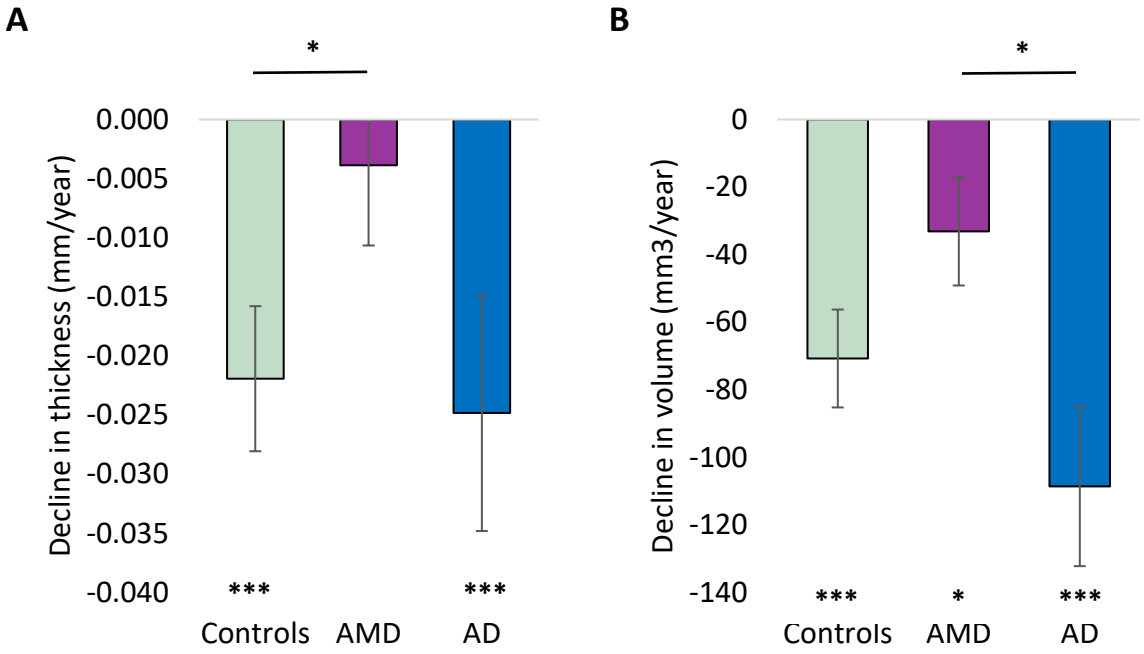


Figure 3-10. Mean angular gyrus volume decline per year for controls, AMD, and AD. A shows mean cortical thickness and B shows mean volume. AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. *p<.05 ***p<.001

3.5.4 Inferior Frontal Gyrus

At baseline, controls had a mean cortical thickness of 2.60mm (SE=0.07), AMD had a mean cortical thickness of 2.56mm (SE=0.07) and AD had a mean cortical thickness of 2.39mm (SE=0.07). The control group's IFG thickness significantly declined by an average of 0.02mm (SE=0.01) per year (t(198)=3.35, p<.001). The AMD group declined by an average of 0.01mm (SE=0.01) per year and AD declined by an average of less than 0.01mm (SE=0.01). Neither AMD (t(198)=0.97, p=.334) nor AD (t(198)=-0.52, p=.601) thickness significantly declined across time. The rate of change for AMD was not significantly different compared to the control group (t(198)=1.54, p=.125, beta=0.01, SE=0.01) but AD was significantly slower compared to controls (t(198)=2.26, p=.025, beta=0.02, SE=0.01). There was no significant difference between AMD and AD rate of change (t(198)=0.99, p=.324; Figure 3-11A).

At baseline controls had a mean volume of 1965.39mm^3 (SE=119.38), AMD had a mean volume of 1927.79mm^3 (SE=119.45) and AD had a mean volume of 1855.35mm^3 (SE=119.58). The results for IFG volume show that both the control and AMD groups showed a significant

decline in volume across time (Figure 3-11B). The control group declined at an average of 27.08mm^3 (SE=4.60) per year (t(198)=5.89, p<.001), and the AMD group declined at an average of 18.22mm^3 (SE=5.04) per year (t(198)=3.62, p<.001). The AD group did not decline significantly across time with an average change of 9.98mm^3 (SE=6.97) per year (t(198)=1.43, p=.153) as shown in Figure 3-16B. The rate of change for the AMD group was not significantly different from controls (t(198)=8.86, p=.195, beta=8.86, SE=6.82) or the AD group (t(198)=0.96, p=.339) but AD was significantly slower compared to controls (t(198)=17.10, p=.042, beta=17.10, SE=8.35).

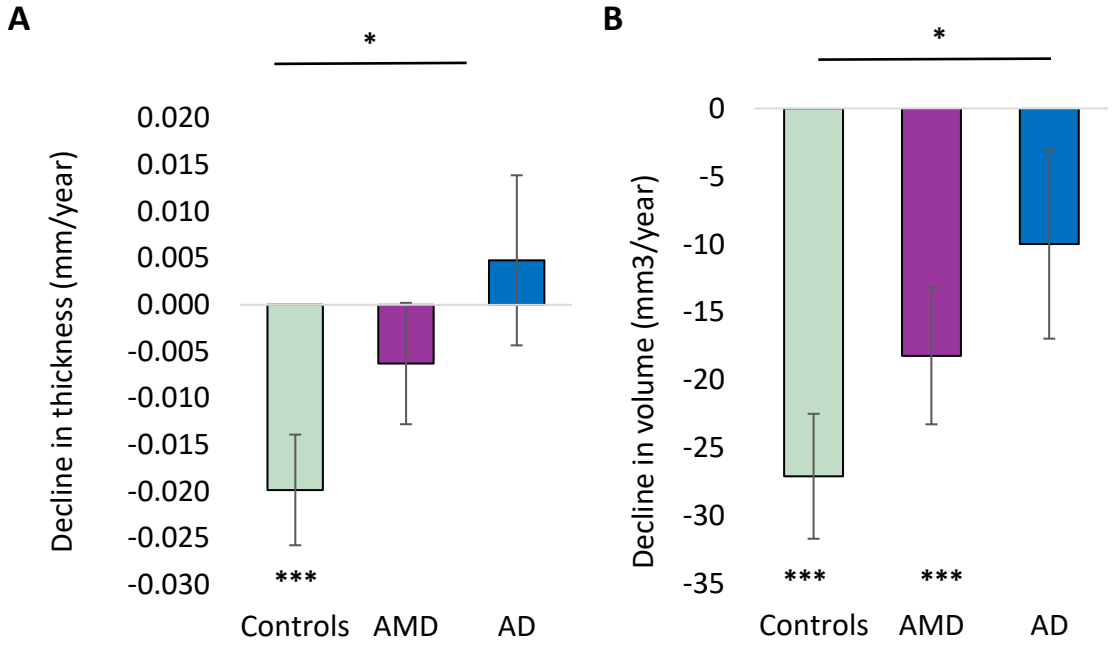


Figure 3-11. Mean inferior frontal gyrus volume decline per year for controls, AMD, and AD. A shows mean cortical thickness and B shows mean volume, AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. *p<.05 ***p<.001

3.5.5 Occipital Pole

At baseline, controls had a mean cortical thickness of 1.86mm (SE=0.05), AMD had a mean cortical thickness of 1.85mm (SE=0.05) and AD had a mean cortical thickness of 1.85mm (SE=0.05). Occipital pole results are shown in Figure 3-12. The control group's occipital pole thickness (Figure 3-17A) significantly declined across time at an average of 0.02mm (SE=0.00) per year (t(198)=3.16, p=.002). AMD did not significantly decline across time, declining an average of 0.01mm (SE=0.01) per year (t(198)=1.05,p=.294), and neither did AD with an average decline of 0.01mm (SE=0.01) per year (t(198)=1.10,p=.273). There was no significant difference in the rate of change for AMD (t(198)=1.34, p=.180, beta=0.01, SE=0.01) or AD

(t(198)=0.77, p=.440, beta=0.01 SE=0.01) from controls, or AMD compared to AD (t(198)=0.09, p=.769).

For occipital pole volume, controls had a mean volume of 3663.81mm^3 (SE=187.15), AMD had a mean volume of 3645.63mm^3 (SE=187.40) and AD had a mean volume of 3533.29mm^3 (SE=187.96). Controls significantly declined at an average rate of 38.37mm^3 (SE=9.88) per year (t(198)=3.88, p<.001), AMD significantly declined an average of 35.80mm^3 (SE=10.92) per year (t(198)=3.28, p=.001) and AD significantly declined by an average of 54.31mm^3 (SE=16.11) per year (t(198)=3.37, p=.001). There was no significant difference in the rate of change from controls compared with AMD (t(198)=0.17, p=.862, beta=2.57, SE=14.72), and AD (t(198)= -0.84, p=.400, beta=-15.94, SE=18.90), and AD was not significantly different from AMD (t(198)=0.95, p=.343; Figure 3-12B).

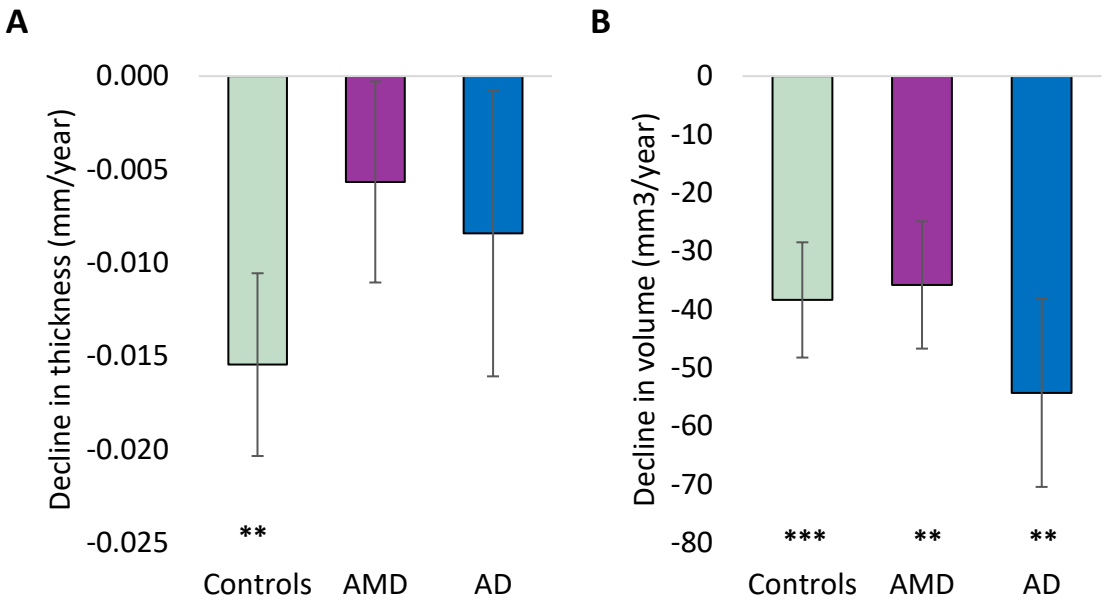


Figure 3-12. Mean occipital pole volume decline per year for controls, AMD, and AD. A shows mean cortical thickness and B shows mean volume, AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. **p<.01 ***p<.001

3.5.6 MMSE scores

Controls had a mean MMSE score of 29.13 (SE=0.63) at baseline and AMD and AD had a mean score of 28.76 (SE=0.64) and 22.94 (SE=0.67) respectively. The MMSE scores are shown in Figure 3-13. Controls and AMD did not show a significant decline in MMSE scores across time, with small reductions in means scores of 0.06 (t(198)=0.44, p=.657) and 0.07 (t(198)=0.48, p=.631) respectively per year. AD did show a significant decrease in mean MMSE score across time (t(198)= 7.72), p<.001) with scores declining an average of 1.64 per year. The rate of

change showed that AMD was no different from controls (t(198) =-0.05, p= .956, beta= -0.01, SE= 0.21) but AD was significantly different (t(198)=-6.21, p<.001, beta = -1.57, SE=0.25).

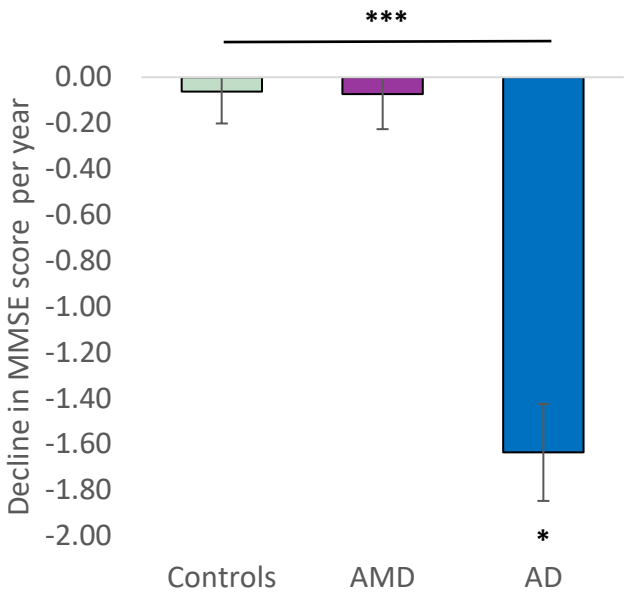


Figure 3-13. Mean MMSE decline per year for controls, AMD, and AD.
MMSE scores shows decline per year. AMD – age-related macular degeneration, AD – Alzheimer's Disease, error bars show standard error of the mean. *p<.05 ***p<.001

3.6 Discussion

The aim of this study was to see whether AD-related atrophy patterns were evident within early AMD cross-sectionally and longitudinally. The cross-sectional results showed that the entorhinal cortex and hippocampus were significantly affected in AD, only hippocampal volume revealed a near-significant finding in AMD compared to controls. Focusing on temporal lobe ROIs (entorhinal thickness and volume, and hippocampal volume), the results showed that despite all regions significantly declining across time in all participant groups, the rate of change was only significantly greater in AD. In the angular gyrus, the control and AD groups significantly declined across time but there was no accelerated rate of change in AD compared to controls. Surprisingly, AMD did not fit this pattern showing both a slower decline across time and slower rate of change compared to controls. This was more evident in cortical thickness where there was no significant thinning across time and the rate of change was significantly decelerated compared to controls. In the IFG, the control group showed a significant decline across time whereas the AD group did not, revealing a significantly slower rate of change in AD. The AMD group showed a different pattern of IFG results based on the cortical measure investigated. Cortical thickness did not significantly decline across time, but

the rate of change was not significantly different from controls. Volume did significantly decline across time with no differences in the rate of change compared to controls. For the occipital pole, all groups' volumes significantly declined with time but only the control group showed significant cortical thinning. The rate of change was not significantly different for AD or AMD compared to controls for either cortical measure.

Cross-sectional analysis was included in this study to confirm the patterns evident in AD and help inform interpretations of results between study 1 and 2. The cross-sectional results showed that the entorhinal cortex and hippocampus were significantly affected in AD. No other regions were significantly different compared to controls. AD findings reflect regions traditionally affected in mild AD. One difference between the AD participants in this study and the previous study is that these participants are earlier in the mild AD stage, evidenced by the lack of difference found in the angular gyrus and supported by the difference in MMSE score (section 3.5.6; Dickerson et al., 2009). As this study wants to compare AMD to very early mild AD the results in this study provide a good baseline from which AMD results can be compared. For AMD, no cortical estimates were significantly different from controls as hypothesised.

Longitudinal findings showed that the control and AD groups' MTL results are consistent with previous literature, where accelerated rates of change were found for AD compared to controls (Davatzikos et al., 2009; Fischl et al., 2002; Fjell et al., 2014; McEvoy et al., 2009; Raji, Lopez, Kuller, Carmichael, & Becker, 2009; Wisse et al., 2018). The results revealed that both the control group and AD group showed significant declines across time in the entorhinal cortex and hippocampus, confirming the involvement of temporal lobes in normal ageing (Driscoll et al., 2009; Fjell, McEvoy, et al., 2013; Fjell, Walhovd, et al., 2009; Pfefferbaum et al., 2013; Raz et al., 2010). The importance of this finding highlights that these MTL regions show a significant decline across time, as a minimum, because of normal ageing and that it is an increase in the rate of change that signifies pathological ageing in these ROIs. This distinction is important in understanding the AMD results.

Although MTL ROIs also significantly declined across time in AMD, statistically the rate of change is not accelerated compared to controls. This pattern is not surprising given the AMD group were screened to ensure cognitively normal function, to prevent confounding results with MCI classified AMD participants. Nevertheless, an acceleration in these regions were found in cognitively normal individuals that converted to MCI in previous literature, regardless of AMD status, compared to those who remained cognitively normal (Jack et al., 2004; Miller et al., 2013; Pacheco et al., 2015). This is the basis from which the hypothesis that an accelerated rate of change would be found in AMD was devised, showing that this result does

not support the hypothesis. However, any patterns of decline could have been further confounded due to ADNI's inclusion and exclusion criteria. Participants were required to have good enough vision to complete cognitive tasks, meaning AMD participants in this study were early in the AMD disease course, where AD is hypothesised to be less likely to develop (section 1.2.1). In a later stage of AMD, an increase in entorhinal cortex rate of change may be revealed to reflect developing prodromal AD, as shown in previous prodromal AD prediction studies (Fjell et al., 2014; Miller et al., 2013; Pacheco et al., 2015). The results show that presumed early AMD participants are no different from normal ageing, and do not show pathological changes associated with AD in these ROIs when considering rate of change only (Davatzikos et al., 2009; Fjell & Walhovd, 2010; Fjell, Walhovd, et al., 2009). The importance of entorhinal cortex and hippocampus in helping to distinguish normal ageing from AD is widely accepted, and thus suggests that the results of the current study do not support the hypothesis that early AMD exhibits AD-related atrophy in the medial temporal lobe.

The next notable region that can help distinguish AD-related brain changes from normal ageing is the IFG. The results showed that the control group had significant thinning and decreasing volumes across time compared to the mild AD group. These results support previous findings showing frontal regions are susceptible to normal ageing and alternatively preserved in mild AD (Head et al., 2005; Singh et al., 2006; Yang et al., 2016). The results further support a frontotemporal pattern of change in normal ageing (Chow et al., 2008) and more widely shows a double dissociation between normal ageing and AD when taking the MTL findings into consideration (Head et al., 2005). The IFG preservation found in mild AD was further highlighted by the significantly slower rate of change for AD compared to controls. This finding supports the hypothesis that a slower rate of change would be found in mild AD. Here the pathological changes in the brain can be identified with change across time and by the rate of change compared to controls, unlike MTL where all groups significantly decline across time. This is important when interpreting the AMD results.

The rate of change is not significantly different from controls for AMD, but while volume is significantly declining across time, aligning with normal ageing, this is not found in cortical thickness. The IFG in AMD does not significantly thin across time, contrary to controls, suggesting a pathological atrophy pattern. The results show a slowing of cortical thinning in IFG consistent with preservation found in AD (Singh et al., 2006; Yang et al., 2016). As critiqued in other studies, if more AMD participants develop MCI or AD than the controls this may account for this slowing. However, conversion rates to MCI and AD are similar between the

AMD and control group, showing that explanation is unlikely to account for this deceleration and that this is a true effect emerging in this AMD group.

Although IFG volume results for AMD showed a similar pattern to controls, the AMD results show a small trend towards a deceleration across time compared to controls (9mm^3 slower per year) and accelerated change (8mm^3 faster per year) across time compared to AD. These results show that despite non-significant rates of change to normal ageing, there may still be pathological patterns of neurodegeneration emerging in AMD. Whilst previous studies have found atrophy in the absence of cognitive decline, the lack of a significant difference given AMD participant's cognitive status is unsurprising. Ultimately, trends in the data may reveal more about potential patterns of atrophy than looking specifically for significant differences in the rate of change, especially as greater rates of change are detectable closer to AD onset (Pettigrew et al., 2017).

Referring to the double dissociation between normal ageing and AD, focusing on frontal and temporal regions, it is relevant to see if other AD-related patterns in AMD data were emerging in the MTL regions, considering IFG cortical thickness results indicate there could be AD atrophy patterns emerging. Consistent with deceleration found in the IFG for AMD participants, a pattern indicative of AD (Head et al., 2005; Singh et al., 2006), there was a non-significant increased rate of atrophy in entorhinal cortex thickness compared to controls, placing AMD atrophy across time between controls and mild AD. This same pattern was not found for MTL volume results. The non-significant increase in entorhinal cortex thinning across time is a noteworthy finding, considering MMSE scores do not show a similarly increased decline across time. This finding supports earlier conclusions that MTL atrophy is a more sensitive marker of disease than cognitive tasks (Jack et al., 2004). The results together show a double dissociation pattern for cortical thickness suggesting these AMD participants sit between mild AD and controls, akin to prodromal AD, and supports a cross-over of neurodegeneration features for AD and AMD.

Mild AD can be detected via the temporoparietal pattern found in AD (Fjell & Walhovd, 2010; Johnson et al., 2012), where damage moves from the MTL to inferior parietal lobe. The angular gyrus results in this study show that AD did not have a significantly increased rate of change compared to controls, and that both participant groups showed similar significant atrophy across time. These results suggest no pathological changes have reached the angular gyrus because AD participants are too early in the mild AD stage, a conclusion supported by previous literature (Dickerson, Bakkour, et al., 2009) and cross-sectional MMSE results (section 3.5.6). The lack of significance here does not deny the presence of AD as AD atrophy moves

throughout the brain in stages (Braak & Braak, 1996), and greater rates of atrophy are evident nearer the onset of each relevant AD stage (Pettigrew et al., 2017). This illustrates how non-significant results cross-sectionally or by rate of change do not always prove the absence of disease when AD patterns are emerging in the data elsewhere; especially as this has been demonstrated here in participants with early mild AD. This argument gives credence to the above conclusion that significant thinning across time reflects a slow neurodegenerative process, despite earlier literature stating that significant differences in rates of change are required to confirm pathological atrophy (Davatzikos et al., 2009; Johnson et al., 2012). Considering normal ageing evolves into pathological atrophy in AD, the nonsignificant increase in atrophy across time in angular gyrus results could represent early signs of a slow pathological neurodegeneration process.

An unexpected finding was that AMD participants did not show the same pattern of change compared to both controls and AD in the angular gyrus, where a significantly slower rate of change and no decline across time was found in cortical thickness. As this is the first longitudinal study to explore AMD grey matter beyond the occipital cortex, this result cannot be compared with previous findings. Further research could establish if this is a consistent finding in other AMD participant groups when compared to controls recruited for that purpose. Preservation in the inferior parietal lobes has not been noted in AD, potentially showing a separate pathological pattern to AD.

The occipital pole revealed largely consistent results between the participant groups. No significant difference in cortical thickness or volume rate of change was found, and volume significantly declined across time in all groups. This result was not unexpected as AMD does not show occipital lobe changes until later in the disease course (Boucard et al., 2009; Hanson et al., 2019; Hernowo et al., 2014; Prins, Plank, et al., 2016) and this group of AMD participants were presumed to exhibit early AMD. The average duration from diagnosis to first scan for the AMD participants in the current study was 3.67 years (SD=2.74), but critically, there was no evidence of visual loss; participants vision was good enough to complete the cognitive tasks as per ADNI's inclusion criterion. One inconsistent result between the groups was found in cortical thickness where controls showed significant thinning across time, but AMD and AD did not. Previous studies have found occipital cortex neurodegeneration in normal ageing and a significant decline in the occipital pole in the control group would fit with these findings (Storsve et al., 2014; Yang et al., 2016). The lack of a significant decline across time in AMD and AD is arguably indicative of further similarities between the two diseases, where preservation

and or no involvement of the occipital cortex, is evident in the early stages of the disease compared to later stages as found in AMD (Hanson et al., 2019) and AD (Karas et al., 2003).

Cross-sectional results mostly aligned with longitudinal results. For entorhinal cortex and hippocampal volume, the cross-sectional results show that AD is significantly affected, corresponding with the accelerated rate of change found in longitudinal results. In AMD, cross-sectional results show a non-significant thinner cortex in entorhinal cortex compared to controls; in the same way that there is a non-significant accelerated rate of change for entorhinal cortex compared to controls longitudinally. This indicates that there could be a slow neurodegeneration process occurring in the entorhinal cortex, where previous atrophy is reflected in the cross-sectional results (nearer the beginning of the disease course) and ongoing atrophy in the longitudinal results (where increased thinning could eventually be found cross-sectionally as the disease progresses (as seen in study 1)). Entorhinal cortex and hippocampal volume do not show this same pattern. Similarly, for longitudinal angular gyrus results the preservation of cortical thickness is shown for AMD in cross-sectional findings, whereas AD indicates involvement of the angular gyrus that is not significant in cross-sectional or longitudinal results. This pattern was also found for the occipital pole where no significant involvement of this region was detected in cross-sectional or longitudinal results in any participant group.

One result showing a differing pattern between cross-sectional and longitudinal results is the IFG. Although there was no significant difference between participant groups in cross-sectional findings, the findings show that AD, and to a lesser degree AMD, are thinner compared to controls whereas the longitudinal results suggest a preservation of this area. The results could be explained by the difference in what cross-sectional and longitudinal studies measure. The results show that there has been a previous degeneration of the IFG in AD that sits within the boundary of normal ageing, but preservation of this region begins when mild AD starts. Controls will show larger thinning in this region compared to mild AD until AD moves into the moderate stage of AD (Busatto et al., 2003; Dickerson et al., 2009; Jack et al., 2010; Singh et al., 2006). This result shows the importance of both cross-sectional and longitudinal studies in understanding changes across time, making the differing methods equally valuable in exploratory research.

One weakness of the study comes with the benefits of using data from a database. Using the ADNI database offers more control and information about participants that would not be collected on a smaller scale research project (such as a PhD project) enabling full exclusion of diseases and conditions that are likely to confound results. This exclusion criteria would be

overly restrictive and a barrier to recruitment in a smaller project, meaning the database offers more flexibility in identifying specific participants. However, AMD participants were screened to be cognitively normal and to remain cognitively normal for the duration of the study. It is likely that strictly ensuring participants were not showing signs of MCI resulted in the participant selection being overly controlled, and not reflective of the patterns of brain changes evident if participants were enrolled in a less rigorous recruitment process (as was the case for study 1). Cognitive information could be collected to assess cognitive status for better exploration of the findings but not to screen participants retrospectively. Although the method used in this study is appropriate for some studies it may not be suitable in this context. During initial recruitment to longitudinal studies, researchers would not be able to predict which participants would begin to experience cognitive impairments during the study, highlighting that the results in this study may not reflect a natural AMD neurodegeneration process, as only cognitively normal AMD participants were used. This reveals a limitation of using the database, where participants would need to self-certify they are cognitively normal on enrolment to a smaller research project. Mostly, cognitive impairment may initially go undetected, but the ADNI database is routinely assessing participants where MCI and AD emergence is likely to be picked up almost immediately.

Future studies would benefit from assessing brain changes across the AMD disease course to establish whether medial temporal lobe regions are involved in the disease whilst tracking cognitive changes. There is some evidence that the frontal lobes are showing early indicators of a differing atrophy pattern to normal ageing, but temporal lobe involvement remains debateable. In study 1, AMD participants showed entorhinal cortex and angular gyrus thinning not found in this AMD group's cross-sectional results. There are two possible reasons for this difference: 1) the first study may have been influenced by younger control group and only revealed age-effects (the current study from ADNI has tightly controlled for age), or 2) because they indicate changes in later-stage AMD that are not evident in early AMD (the current study participants have an early AMD diagnosis). Neither of these possibilities can be excluded from this study's results. Tracking the pattern of atrophy across the AMD disease course will help establish whether a cross-over between AMD and AD atrophy is present in later stage AMD as hypothesised in section 1.2.1.

In conclusion, the results show a pattern of neurodegeneration that suggests AMD sits between normal ageing and AD. Compared to controls, IFG thickness shows a shift towards preservation and entorhinal cortex thickness reveals an increased atrophy that remains within the boundary of normal ageing, indicating AD-related neurodegenerative patterns across time.

These results reflect a slow neurodegeneration process compared to an accelerated neurodegeneration that would be revealed via significantly different rates of change. Age-related macular degeneration participants were in the early stages of AMD and were also cognitively normal throughout the study. These patterns of changes emerged in a highly controlled sample of AMD participants suggesting a true finding in this group of participants. Further research could assess the brain changes across the disease course for a complete insight into whether AMD brain changes naturally follow brain changes seen in prodromal to mild AD.

Chapter 4: Study 3;

Is there evidence of AMD-specific atrophy and does the pattern of atrophy change at different stages of disease?

4.1 Introduction

Main findings from studies 1 and 2 suggest atrophy patterns may change at different stages of the AMD disease course. Particularly in the angular gyrus and entorhinal cortex (studies 1 & 2); regions affected in mild AD (Dickerson et al., 2009; Du et al., 2007; Karas et al., 2004). However, it is still not known whether there are AMD-specific brain changes despite AMD stage or visual status; or how atrophy during different AMD stages change across time. Based on previous findings in studies 1 and 2, it is important to see whether declines across time follow an atrophy pattern suggestive of very mild AD, to further understand potential relationships between AMD and AD.

This study has two aims: first to see if there is any AMD-specific atrophy in the selected brain regions regardless of visual status; and second to see which areas of the brain are affected across time at different stages of AMD. To explore the first aim, all AMD participants from study 1 and 2 were compared with their controls to see if AMD-specific regions were revealed (and to assess database effect on the ROIs). As this participant group consists of an array of participants with mixed visual status and time since diagnosis, it is predicted that any AMD specific changes will be detected in this group of participants. Second, longitudinal changes in early and late AMD are investigated to see what areas of the brain are affected during these different stages of the AMD disease course. This will reveal the pattern of atrophy that occur in early and late stage AMD in a similar way to Braak staging in AD (Braak et al., 2006; Braak & Braak, 1991, 1995).

Only cortical thickness was examined in this study as cortical thickness is more sensitive to AMD atrophy compared to volume (Apostolova et al., 2007; Aycheh et al., 2018; Chandra et al., 2019; Lerch et al., 2005, 2008; Regeur, 2000; Singh et al., 2006). This is highlighted by the emerging atrophy evident in cortical thickness but not volume (studies 1 & 2). For example, in study 1 entorhinal cortical thickness was significantly thinner in late AMD compared to controls with a medium-to-large effect size, but volume was not significantly different between controls and AMD with only a small-to-medium effect size. The inclusion of volume in

earlier chapters was to measure changes against AD, however, volume in AMD is not affected in the same way as in AD and does not show differences compared to controls. Only hippocampal volume was included in this study as Freesurfer does not provide a cortical thickness estimate for this ROI.

Previous studies showed that the entorhinal cortex was significantly thinner in late AMD and was not significantly different in early AMD when compared to controls (studies 1 & 2). Similarly, occipital pole thinning has been found in relation to long standing visual loss in late AMD (Hanson et al., 2019; Hernowo et al., 2014) but this was not found in study 1. Based on these findings, it is hypothesised that entorhinal cortex thinning but not occipital pole thinning will reveal AMD-specific brain atrophy due to the increased sample size. The other ROIs would also show no significant difference compared to controls.

Longitudinal analysis compares late to early AMD; it is hypothesised that no significant differences will be found for rate of change for any of the ROIs (as this represents accelerated neurodegeneration). However, entorhinal cortex thinning was found in late (study 1) but not early AMD (study 2), and preservation of the angular gyrus was found across time (reflecting slow neurodegeneration) in early AMD (study 2) despite thinning in late AMD cross-sectionally (study 1). Based on these findings, the angular gyrus and entorhinal cortex are hypothesised to show accelerated thinning across time in late AMD. It is also hypothesised that accelerated occipital pole thinning will be found across time in late AMD, where participants experience visual loss (Hanson et al., 2019). No other regions are expected to show differences between early and late AMD based on previous findings in studies 1 and 2.

4.2 Methods

4.2.1 Participants

The same cross-sectional AMD and control participants from study 1 (N=16 in each participant group) and 2 (N=24 in each participant group) were used in this study for cross-sectional analysis. The combined AMD (N=40) participants had a mean age of 79.35years (SD = 5.72) with 21 males. The combined controls (N=40) had a mean age of 75.80years (SD= 7.17) with 23 males.

Comparison of the two AMD groups across time used 22 early AMD participants from ADNI (13 male) with a mean age of 78.27 years (SD=5.93) at baseline and all 16 late AMD participants from YNIC with a mean age of 77.00 years (SD=6.85) at baseline (Table 4-1).

Table 4-1. Cross-sectional and longitudinal demographics for the early (ADNI) and late (YNiC) AMD participants.

	Early AMD			Late AMD		
pp	Sex	Cross age	Long age range	Sex	Cross age	Long age range
1	M	91	90-91	M	82	79-82
2	M	73	71-73	F	74	70-74
3	F	77	74-78	F	73	70-73
4	M	85	84-86	M	75	71-75
5	M	73	72-73	M	86	81-86
6	M	87	85-87	F	79	75-79
7	F	75	71-76	M	73	67-73
8	M	75	76-78	M	88	88-88
9	F	77	75-78	F	81	81-81
10	M	77	74-78	F	77	76-77
11	F	72	70-72	F	86	86-86
12	F	78	78-80	M	80	79-80
13	M	85	85-89	M	87	87-87
14	M	75	75-77	F	78	78-78
15	M	80	80-82	M	65	65-65
16	M	85	86-87	F	77	76-78
17	F	86	86-88			
18	F	79	78-82			
19	F	80	78-79			
20	M	80	71-73			
21	F	85	80-83			
22	M	87	83-87			
23	F	78				
24	F	72				

pp = participant in study. Cross age = Age at which scan was used in cross-sectional analysis, Long age range = age at first scan to age at last scan

4.2.2 AMD classification

The clinical features of the two AMD groups differ, with the AMD group from YNiC (Study 1) having verified central vision loss, whereas the AMD group from ADNI (Study 2) had to be able to complete visual aspects of the cognitive tasks unaided, as specified in ADNIs inclusion criteria. Average time from diagnosis to first ADNI MRI scan was 3.67 years (SD=2.74) for the ADNI AMD group, consistent with early AMD. It should be noted that not every participant had a recorded date. Based on these clinical features the AMD groups were split into presumed early-stage AMD – AMD participants from ADNI - and late-stage AMD – AMD participants from YNiC.

4.2.3 Acquisition and Pre-processing

Acquisition of data is explained in studies 1 and 2. Data from York's Neuroimaging Centre was acquired on the GE Excite 3T MRI scanner. ADNI used different MRI scanners (GE Healthcare, Philips Medical Systems, and Siemens Medical Solutions).

Pre-processing followed the same stages outlined in study 1 section 2.2.3 for Freesurfer's cross-sectional analysis (version 6; statistics run in IBM SPSS statistics 25) and study 2 for longitudinal analysis (statistics ran in MATLAB R2018b).

Only cortical thickness is investigated as it is a more sensitive measure of atrophy (Apostolova et al., 2007; Aycheh et al., 2018; Chandra et al., 2019; Lerch et al., 2005, 2008; Regeur, 2000; Singh et al., 2006), except for hippocampal volume because Freesurfer does not provide thickness estimates.

4.2.4 Linear mixed effects model validation

The model was designed pre-data collection based on the research aims. The model in this study consisted of only early AMD participants in one group and late AMD participants in the other, to see if there were differing features across the different stages of the disease course. Decline across time and rate of change were measured (see 3.3.4 for more details on linear mixed effects models). The model was (MATLAB syntax):

ROI ~ 1 + Late + Time + LateAMD*Time + (1+Time|ParticipantID).

Early AMD was used as the reference group in this analysis. Time and participant were added as random effects. Age was assessed and no significant difference was found between early AMD and late AMD groups' baseline ages ($t(36)=0.61$, $p=.544$) so age was not added into the model. Fixed-effects and random-effects were examined in SPSS version 25 and all assumptions were met. Linear mixed-effects models were run in MATLAB R2018b.

4.2.5 Timepoint data

This chapter used the same early AMD participants from study 2. Late AMD participants' longitudinal data has not been used previously. A table of their timepoint data is included in Table 4-2.

Table 4-2. Timepoint information for the early and late AMD participants.

	Time from baseline		Number of MRI images	
	Mean	SD	Mean	SD
Early AMD	2.43	0.98	3.08	0.72
Late AMD	2.21	2.07	3.56	1.21

4.3 Cross-sectional Results

4.3.1 Entorhinal Cortex

A two-way factorial ANOVA assessing the effect of database (ADNI vs YNiC) and participant group (early vs late AMD) on cortical thickness showed no significant interaction between database and participant group ($F(1,76)=0.66, p=.421$, partial eta = 0.01; Figure 4-1A).

For cortical thickness, there was a main effect of participant group ($F(1,76)=7.54$, $p=.008$, partial eta =.09) with AMD having thinner entorhinal cortex (M=2.39mm, SD=0.17) than controls (M=2.44mm, SD=0.17; Figure 4-1B). Effect sizes showed that late AMD (Controls: M=2.55mm, SD=0.12; late AMD: M=2.46mm, SD=0.17) had a larger effect (Cohen's d=0.74) than early AMD (Controls: M=2.37mm, SD=0.16; early AMD: M=2.35mm, SD=0.15; Cohen's d=0.49). There was no main effect of database ($F(1,76)=1.19, p=.278$, partial eta = 0.02).

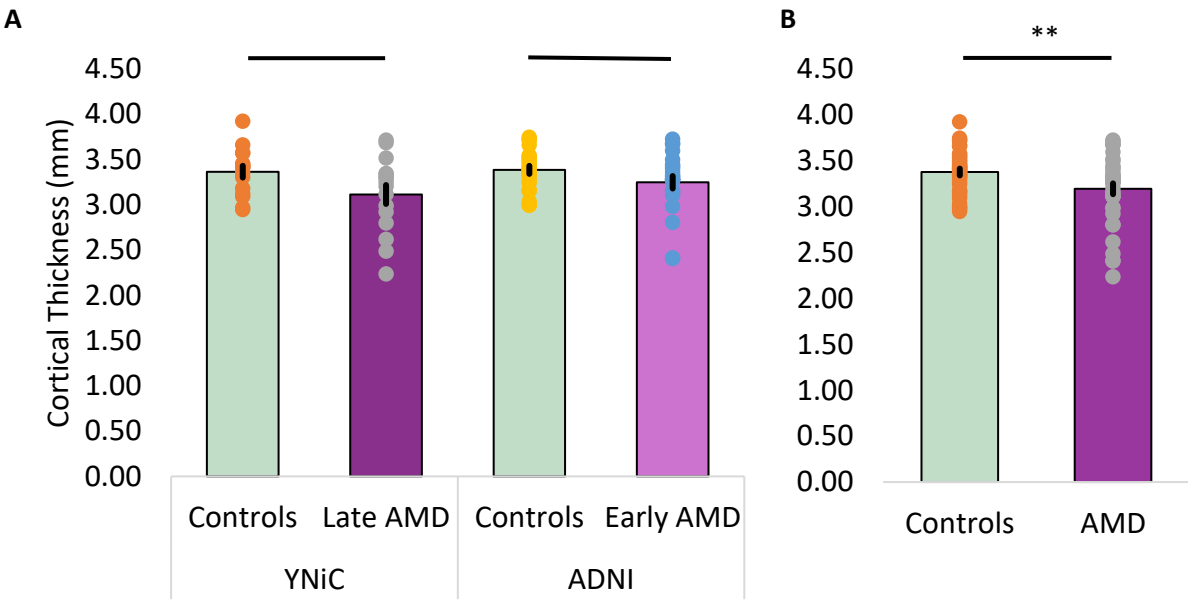


Figure 4-1. Entorhinal cortex results showing group means for AMD compared to controls and via database.
A shows AMD and conrols split by early (ADNI) and late (YNiC) AMD, B shows combined controls compared to AMD. ADNI – Alzheimer's Disease Neuroimaging Centre, YNiC – York Neuroimging Centre, AMD – age-related macular degeeration. Error bars show standard error of the mean. Dots represent individual participant's cortical measure. **p<.01

4.3.2 Hippocampus

A two-way factorial ANOVA showed no significant interaction between database (ADNI vs YNiC) and participant group (early vs late AMD) for hippocampal volume ($F(1,76)=0.93, p=.338$, partial eta = 0.1; Figure 4-2A). There was no main effect of participant group ($F(1,76)=2.02$,

p=.159, partial eta = .03) but AMD did have smaller hippocampal volume (M=3577.76mm^3, SD=609.20) compared with controls (M=3754.38mm^3, SD=528.16; Figure4-2B). Late AMD had a smaller effect (Controls: M=4070.52mm^3, SD=537.91, late AMD: M=4020.37mm^3, SD=527.09; Cohen's d=0.09) than early AMD (Controls: M=3543.61mm^3, SD=410.39, early AMD: M=3282.69mm^3, SD=470.07; Cohen's d=0.59). There was a main effect of database (F(1,76)=33.41,p<.001, partial eta = .31) where hippocampal volume was smaller in ADNI compared to YNiC. Given the aims of the study, this difference in database is not of interest.

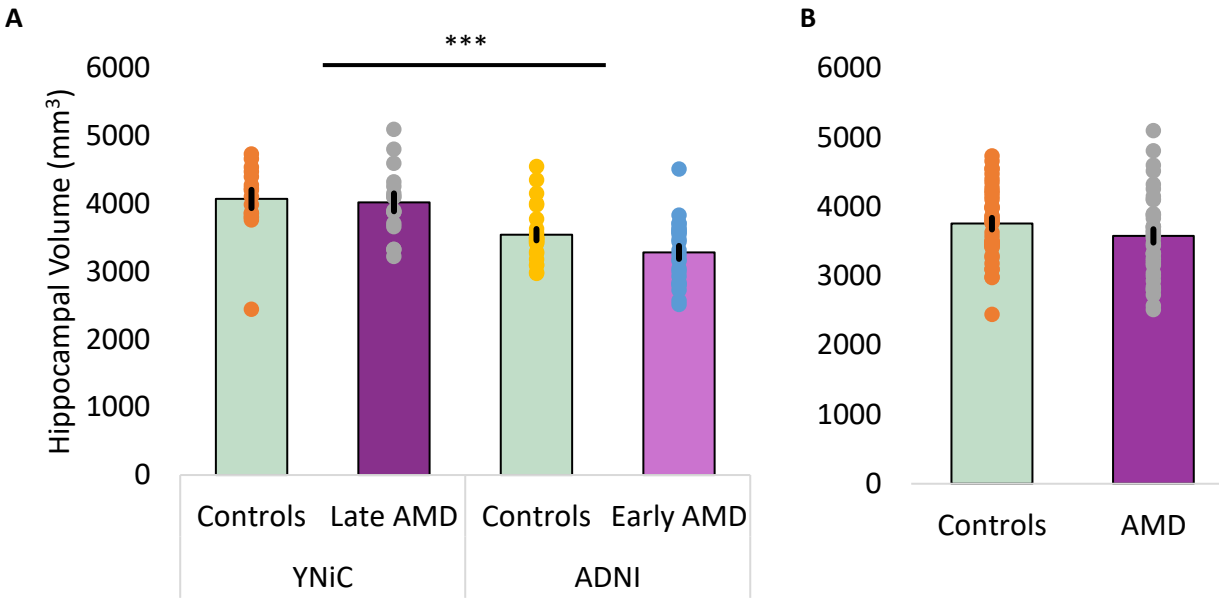


Figure 4-2. Hippocampal volume results showing group means for AMD compared to controls and via database.
A shows AMD and conrols split by early (ADNI) and late (YNiC) AMD, B shows combined controls compared to AMD. ADNI – Alzheimer's Disease Neuroimaging Centre, YNiC – York Neuroimging Centre, AMD – age-related macular degeeration. Error bars show standard error of the mean. Dots represent individual participant's cortical measure. ***p<.001

4.3.3 Angular Gyrus

The two-way factorial ANOVA for angular gyrus cortical thickness showed that there was no interaction between database (ADNI vs YNiC) and participant group (early vs late AMD) (F(1,76)=1.17,p=.283, partial eta =.02; Figure 4-3A). The results revealed no main effect of participant group for angular gyrus thickness (F(1,76)=2.73, p=.103, partial eta =.04), however AMD had thinner angular gyrus (M=2.39mm, SD=0.16) compared to controls (M=2.44mm, SD=0.17; Figure 4-3B). There was a main effect for database where YNiC had thicker cortex compared to ADNI (F(1,76)=17.97, p<.001, partial eta = .19), again this difference in database is not of interest to the main aims of the study.

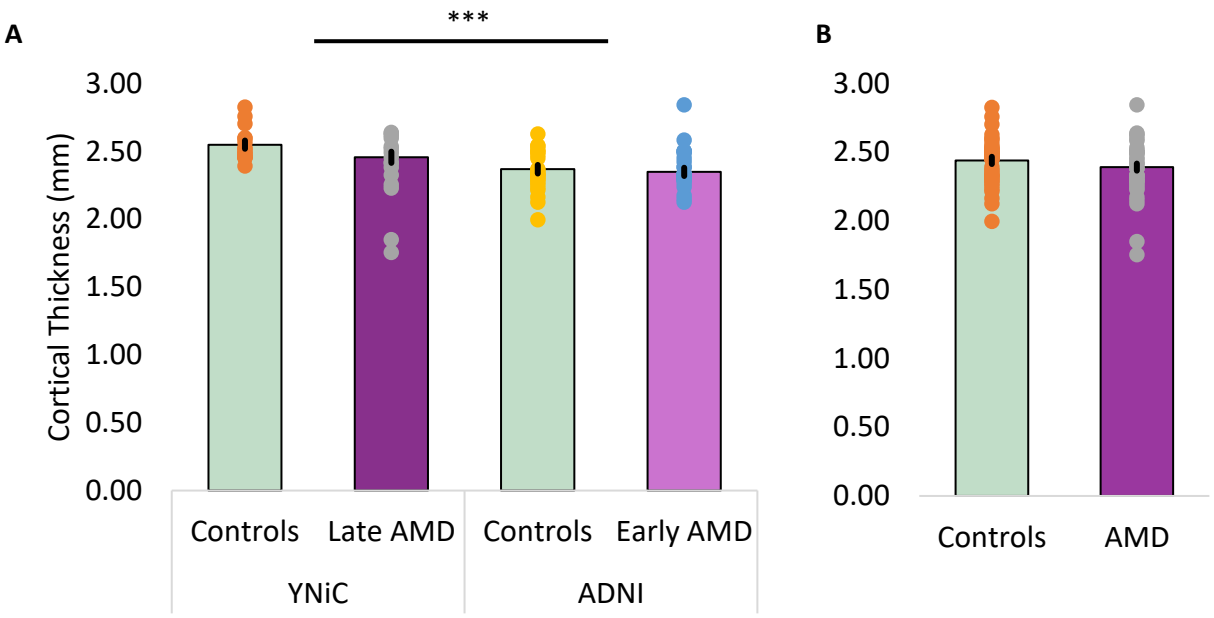


Figure 4-3. Angular gyrus results showing group means for AMD compared to controls and via database.
A shows AMD and conrols split by early (ADNI) and late (YNiC) AMD, B shows combined controls compared to AMD. ADNI – Alzheimer's Disease Neuroimaging Centre, YNiC – York Neuroimging Centre, AMD – age-related macular degeeration. Error bars show standard error of the mean. Dots represent individual participant's cortical measure. ***p<.001

4.3.4 Inferior Frontal Gyrus

A two-way factorial ANOVA assessing the effect of database (ADNI vs YNiC) and participant group (early vs late AMD) on IFG cortical thickness ($F(1,76)=1.75$, $p=.190$, partial eta $=.02$) revealed no significant interaction (Figure 4-4A). The homogeneity of variance assumption was violated however transforming the data did not correct the violation, and the original data was used (Levene's statistic $(3,76) = 5.95$, $p=.001$). The results showed that AMD participants had thinner IFG cortex ($M=2.49$mm, $SD=0.20$) compared to controls ($M=2.55$mm, $SD=0.16$) but there was no main effect for participant group ($F(1,76)=3.00$, $p=.087$, partial eta$=.04$; Figure 4-4B), although it was nearing significance. Late AMD had a larger effect size (Controls: $M=2.61$mm, $SD=0.13$, late AMD$=2.49$mm, $SD=0.28$; Cohen's $d=0.61$) than early AMD (Controls: $M=2.50$mm, $SD=0.16$, early AMD: $M=2.49$mm, $SD=0.13$; Cohen's $d=0.11$). There was no main effect of database ($F(1,76)=1.64$, $p=.204$).

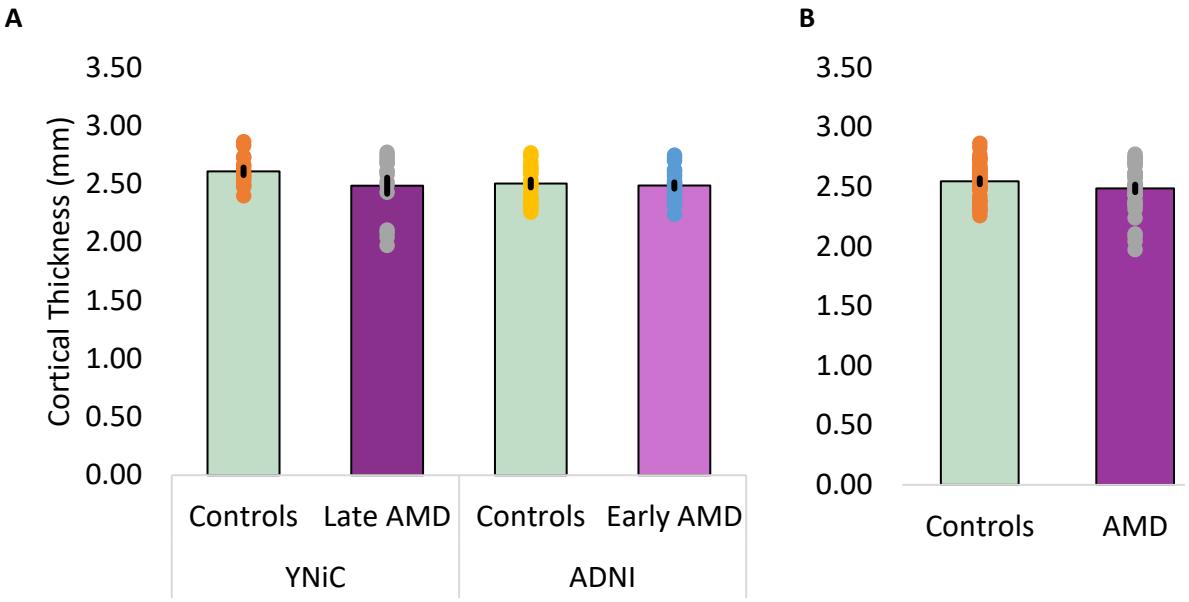


Figure 4-4. IFG results showing group means for AMD compared to controls and via database. A shows AMD and conrols split by early (ADNI) and late (YNiC) AMD, B shows combined controls compared to AMD. ADNI – Alzheimer's Disease Neuroimaging Centre, YNiC – York Neuroimging Centre, AMD – age-related macular degeeration. Error bars show standard error of the mean. Dots represent individual participant's cortical measure.

4.3.5 Occipital Pole

A two-way factorial ANOVA was conducted to assess the effect of database (ADNI vs YNiC) and participant group (early vs late AMD) on the occipital pole's cortical thickness. The results showed that there was no interaction between participant groups and database ($F(1,76)=0.42, p=.518$, partial eta=.01; Figure 4-5A). There was no main effect of participant group ($F(1,76)=1.73$, $p=.192$, partial eta=.02),. Controls mean cortical thickness (M=1.92mm, SD=0.16) was thicker cortex compared to AMD (M=1.88mm, SD=0.14; Figure 4-5B). Effect sizes for early AMD (Controls: M=1.84mm, SD=0.11; AMD: M=1.82mm, SD=0.09; Cohen's d=0.18) is smaller than the effect size for late AMD (Controls: M=2.04mm, SD=0.13; AMD: M=1.99mm, SD=0.14; Cohen's d=0.38) for cortical thickness. There was a main effect of database where YNIC participants had thinner cortex compared to ADNI participants ($F(1,76)=47.39, p<.001$, partial eta=.38). Given the aims of the study this difference in database is not of interest.

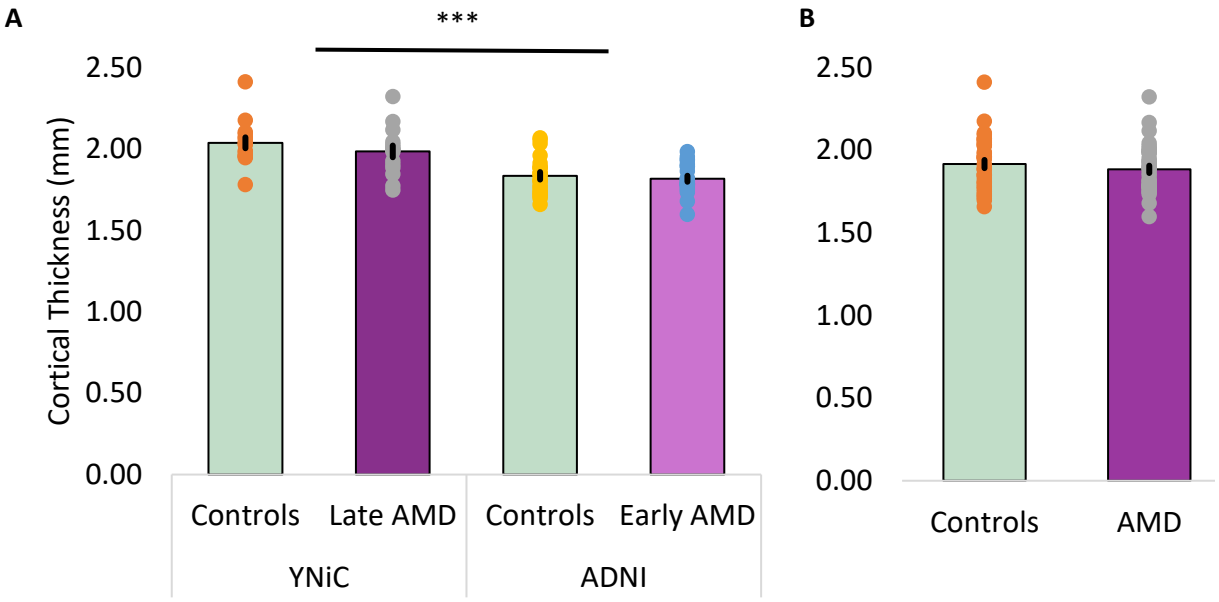


Figure 4-5. Occipital Pole results showing group means for AMD compared to controls and via database.
A shows AMD and conrols split by early (ADNI) and late (YNiC) AMD, B shows combined controls compared to AMD. ADNI – Alzheimer's Disease Neuroimaging Centre, YNiC – York Neuroimging Centre, AMD – age-related macular degeeration. Error bars show standard error of the mean. Dots represent individual participant's cortical measure. ***p<.001

4.4 Longitudinal results

A linear mixed-effects model was used to investigate decline across time in the different AMD participant groups and differences in rate of change for each ROI. The mixed-effects model consisted of only early and late longitudinal AMD data.

4.4.1 Entorhinal Cortex

At baseline, early AMD had a mean entorhinal cortex thickness of 3.42mm (SE=0.13mm) and late AMD had a mean entorhinal cortex thickness of 3.29mm (SE=0.15mm). Entorhinal cortex thickness results are displayed in Figure 4-6. Early AMD significantly declined across time declining an average of 0.05mm (SE=0.01) per year (t(120)=4.17, p<.001), but late AMD narrowly missed significance declining at 0.03mm (SE=0.01) per year (t(120)=1.94, p=.054). Despite the differences in decline across time, there was no significant difference in the rate of change between the two groups (t(120)=1.07, p=.287, beta=0.02, SE=0.02).

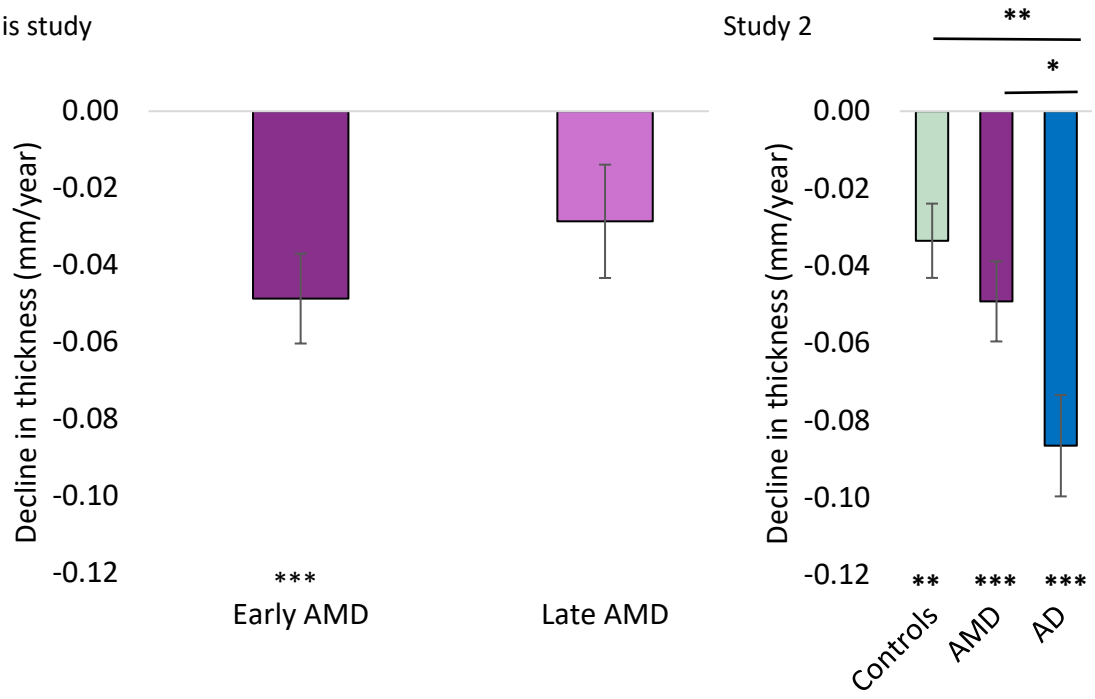


Figure 4-6. Entorhinal Cortex results for this study compared to study 2.
Graph for this study shown on left with the graph showing early AMD from study 2 on the right. Early AMD in this study (left - dark purple) is the same data as AMD from study 2 (right). AMD – age-related macular degeneration. Error bars show standard error of the mean. *p<.05 **p<.01 ***p<.001

4.4.2 Hippocampus

At baseline, early AMD had a hippocampal volume of 3240.07mm^3 (SE=211.62mm^3) and late AMD had a volume of 4093.16mm^3 (SE=247.50mm^3), however there was a significant difference between database meaning these values are not comparable. Hippocampal volume results are displayed in Figure 4-7. Both groups hippocampal volumes significantly declined across time. Early AMD declined an average of 56.01mm^3 (SE=11.26) per year (t(120)=4.97, p<.001) and late AMD declined an average of 50.79mm^3 (SE=14.40) per year (t(120)=3.53, p=.001) where no significant difference was found for the rate of change between groups (t(120)=0.29, p=.776, beta=5.22, SE=18.28).

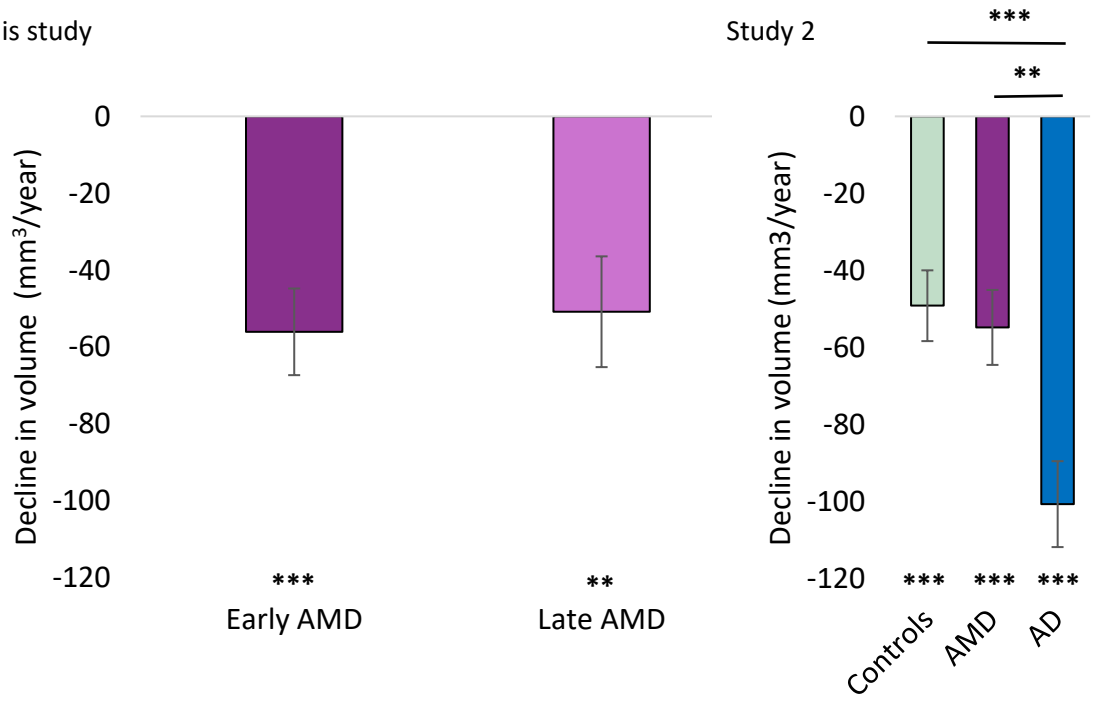


Figure 4-7. Hippocampal volume results for this study compared to study 2.
Graph for this study shown on left with the graph showing early AMD from study 2 on the right. Early AMD in this study (left – dark purple) is the same data as AMD from study 2 (right). AMD – age-related macular degeneration. Error bars show standard error of the mean. **p<.01 ***p<.001

4.4.3 Angular Gyrus

At baseline, early AMD had a thickness of 2.45mm (SE=0.09) and late AMD had a thickness of 2.51mm (SE=0.10), however there was a significant difference between database meaning these values are not comparable. Angular gyrus thickness results are displayed in Figure 4-8. Early AMD had a minimal average decline of 0.004mm (SE=0.01) per year (t(120)=0.55, p=.581), a pattern also observed in late AMD, with a minimal average decline of 0.003mm (SE=0.01) per year (t(120)=0.49,p=.627). There was no significant difference in the rate of change between both groups (t(120)=0.08, p=.940, beta=0.00, SE=0.01).

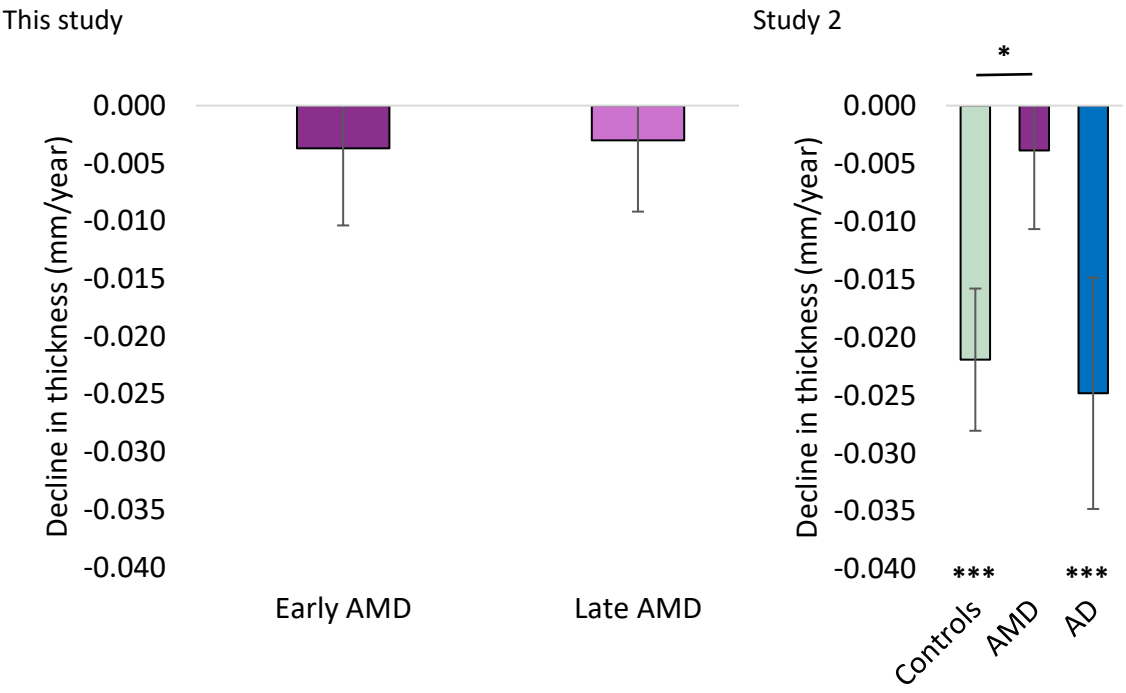


Figure 4-8. Angular gyrus results for this study compared to study 2.
Graph for this study shown on left with the graph showing early AMD from study 2 on the right. Early AMD in this study (left - dark purple) is the same data as AMD from study 2 (right). AMD – age-related macular degeneration. Error bars show standard error of the mean. *p<.05 ***p<.001

4.4.4 Inferior Frontal Gyrus

At baseline, early AMD had a thickness of 2.56mm (SE=0.7) and late AMD had a thickness of 2.58mm (SE=0.08). IFG thickness results are displayed in Figure 4-9. Neither early (t(120)=0.95, p=.346) or late AMD groups (t(120)=1.00, p=.321) significantly declined across time and no significant difference was found in the rate of change (t(120)=0.03, p=.979, beta=0.00, SE=0.01) as both groups declined by an average of <0.01mm (SE=0.01) per year.

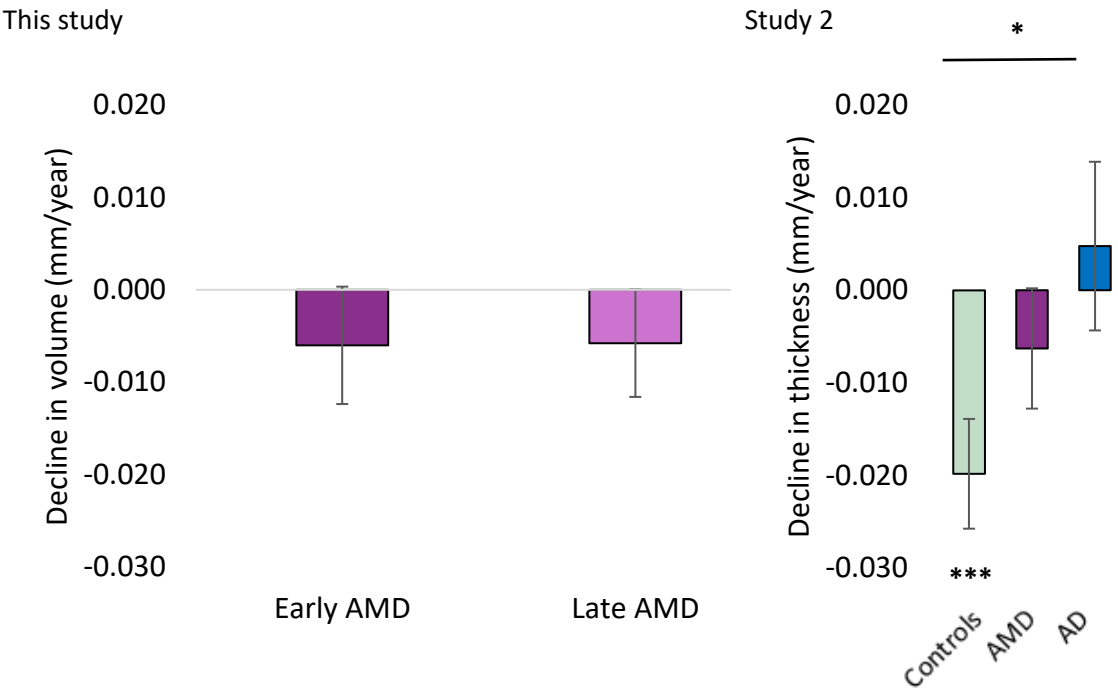


Figure 4-9. Inferior frontal gyrus results for this study compared to study 2.
Graph for this study shown on left with the graph showing early AMD from study 2 on the right. Early AMD in this study (left - dark purple) is the same data as AMD from study 2 (right). AMD – age-related macular degeneration. Error bars show standard error of the mean. *p<.05 ***p<.001

4.4.5 Occipital Pole

At baseline, early AMD had a thickness of 1.85mm (SE=0.00) and late AMD had a thickness of 2.08mm (SE=0.00), however there was a significant difference between database meaning these values are not comparable. Occipital pole thickness results are displayed in Figure 4-10. Early AMD did not significantly decline across time with an average decline of less than 0.01mm (SE=0.01) per year (t(120)=1.03, p=.306), whereas late AMD did significantly decline with an average decline of 0.01mm (SE=0.01) per year (t(120)=2.12, p=.036). However, there was no significant difference in the rate of change between late and early AMD (t(120)=-1.00, p=.330, beta= -0.01, SE= 0.01).

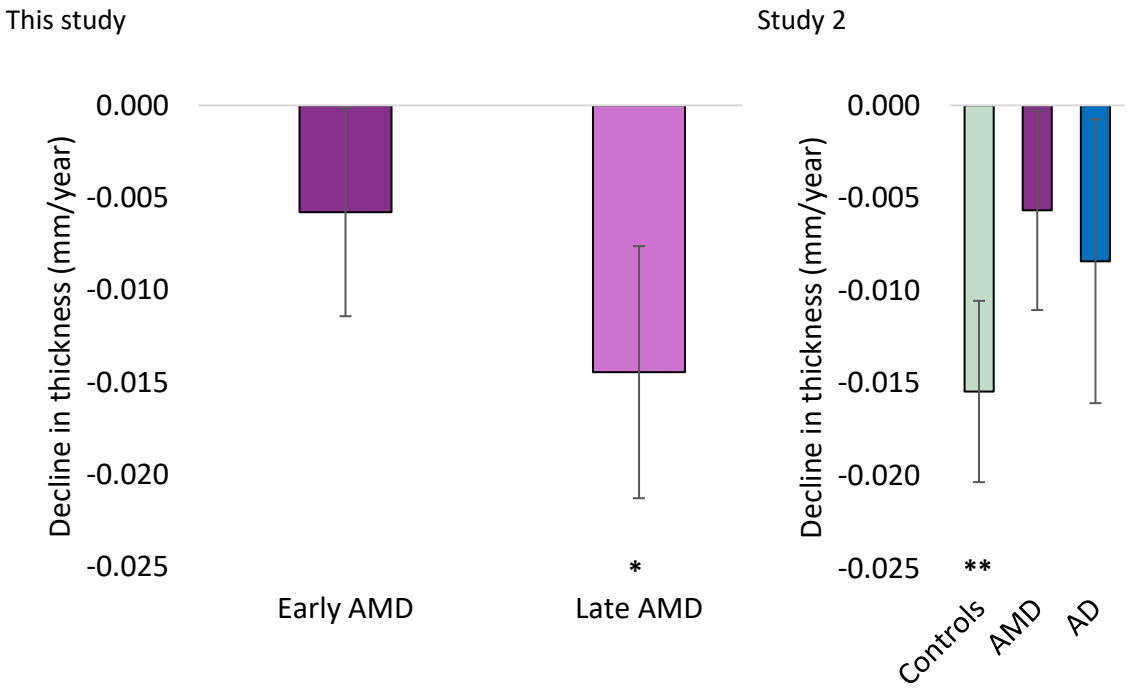


Figure 4-10. Occipital Pole results for this study compared to study 2.
Graph for this study shown on left with the graph showing early AMD from study 2 on the right. Early AMD in this study (left - dark purple) is the same data as AMD from study 2 (right). AMD – age-related macular degeneration. Error bars show standard error of the mean. *p<.05 **p<.01

4.5 Discussion

The aim of this study was to see whether there were any AMD-specific brain changes and to investigate atrophy patterns across time during different stages of AMD. Cross-sectional results indicated that entorhinal cortex thickness is significantly affected in AMD despite stage of disease, supporting the hypothesis. No other ROIs were significantly affected. However, IFG was nearing significance and all regions revealed thinner cortex compared to controls. The longitudinal results revealed no significant difference in the rate of change (accelerated neurodegeneration) for all ROIs, however, for a couple of ROIs differences were found in declines across time (slow neurodegeneration). The IFG and angular gyrus do not significantly decline across time for either early or late AMD, and hippocampal volume significantly declined across time for both participant groups, revealing no difference between early and late AMD for these regions. However early AMD showed a significant decline across time for entorhinal cortex but not occipital pole, whereas late AMD showed a significant decline for occipital pole but not for entorhinal cortex.

Cross-sectional analysis showed that the entorhinal cortex is significantly thinner in AMD indicating AMD-specific atrophy. This is because there is sufficient power after combining all AMD participants (regardless of clinical features) to show the underlying cortical thinning evident for AMD in study 1 and 2 – small-to-medium effect size for early AMD and medium-to-large for late AMD. This finding is particularly important as the 24 early AMD participants (out of 40) in the AMD experimental group are cognitively healthy at the time their brains were scanned; and these participants did not express MCI or AD above conversion rates found in the control group a mean of 6.53 years after baseline (section 3.2.3). It was found that despite evidence of cortical thinning, the chances of converting to MCI or AD are reduced after seven years (Pettigrew et al., 2017). However, there were 8 participants that had passed the seven-year point in the study, leaving 16 participants with the potential to convert to MCI or AD at a later date. As AD-related atrophy is often found closest to AD onset (Pettigrew et al., 2017), any potential future converts will not confound the results at this stage, where AD-related brain changes are less likely to be detected. The results, therefore, suggest entorhinal cortex thinning is a consequence of AMD itself and not due to longstanding visual loss; potential MCI features; or, importantly, age-effects as speculated as a reason for the significant difference found in study 1. The results here show that, not only is entorhinal cortex specifically related to AMD, but this region of the brain is significantly affected before the occipital pole; a finding that aligns with the results in study 1.

AMD atrophy arguably starts in the entorhinal cortex (in these selected regions) because these neurones are vulnerable to AMD as well as AD (Johnson et al., 2012; Przedborski et al., 2003). The clinical significance of AMD specific entorhinal thinning is highlighted, as thinner entorhinal cortex is related to lower cognitive scores in cognitively normal individuals (Olsen et al., 2016; Zdanovskis et al., 2020). This entorhinal thinning may account for the shared cognitive impairment profile between AMD and AD (section 1.1.5.2) where memory impairments present first before executive function impairments in both diseases (Jahn, 2013; Rozzini et al., 2014). When memory is affected, rather than other cognitive domains, the chance of developing AD is more likely compared to other dementias (Li et al., 2012), again indicating a potential relationship between AMD and AD. Confirmation of entorhinal cortex atrophy appearing first in AMD (this study; study 1) and AD (Doherty et al., 2015; Smith, 2002) shows that there are similar brain changes between the two diseases.

Overall, longitudinal results showed no significant differences in rate of change but did find significant differences in decline across time in a couple of regions. Whereas a significant difference in the rate of change represents accelerated neurodegeneration, a difference between participant groups' decline across time represents a slow neurodegenerative pattern. Using decline across time, no significant difference was found between early and late AMD for IFG or hippocampus. This supports the hypothesis that there would be no difference between AMD groups for these regions. However, there is no difference in IFG rate of change per year between early and late AMD (<0.01mm) revealing a preservation of this region (when compared to controls and AMD findings in study 2) that potentially represents very early AD brain patterns (Busatto et al., 2003; Jack et al., 2010; Yang et al., 2016). Alternatively, it can also be argued that preservation in the IFG is a defining feature of AMD, revealing another brain region affected in AD as well as AMD. No involvement of the hippocampus was observed, as predicted based on the results from study 1 and 2. It is unclear whether hippocampal volume changes are not detectable because volume is not affected in AMD, and whether another method of measuring the hippocampus would reveal AMD-related atrophy in this region. The hippocampal volume results are consistent with normal ageing (Fjell et al., 2014, 2012; Raz et al., 2005; Scahill et al., 2003) as both early and late AMD significantly decline at similar rates across time (study 2). However, AD cortical atrophy without the involvement of hippocampal atrophy has been found in pre-symptomatic participants (Sabuncu et al., 2011). This further supports the use of cortical thickness over volume in AMD research.

The results showed no involvement of the angular gyrus, where both early and late AMD showed non-significant declines across time. The results do not support the hypothesis that

late AMD would reveal accelerated thinning compared to early AMD. The thinner angular gyrus in late AMD in study 1 may reflect atrophy that had taken place during an earlier phase of the disease, or because of normal ageing as there is no evidence of angular gyrus involvement based on these findings. These results show that both early and late AMD reveal a pattern of slow degeneration (<0.01mm per year) in groups matched for age. This supports the conclusion that angular gyrus involvement in study 1 is due to age-effects (Fjell & Walhovd, 2010; Wisse et al., 2018) rather than a true AMD atrophy pattern. Further investigation of this region is warranted as studies have found cross-sectional and longitudinal studies can elicit different findings (Du et al., 2006; Wisse et al., 2018; Yang et al., 2016). Due to this, these results may not offer a complete picture of the changes occurring in AMD participants' angular gyrus thickness, as accelerated atrophy may occur at an intermediate stage of AMD.

The entorhinal cortex results did not support the hypothesis that accelerated thinning across time would be found in late AMD, where it was otherwise found in early AMD. The significantly thinner entorhinal cortex in late AMD in study 1 likely represents thinning that occurred in an earlier phase of the disease. This conclusion is supported by previous findings where entorhinal cortex thinning in early AMD shows a non-significant accelerated decline across time compared to controls (study 2). It is likely entorhinal thinning occurs in an intermediate stage between the two AMD groups used in this study; especially as previous studies have classified AMD into several other stages (Clemons et al., 2006; Davis et al., 2005) making this separation of participants overly simplistic. However, an unexpected finding is the non-significant decline across time in late AMD, showing a separate pattern to both AD and normal ageing, where entorhinal cortex significantly declines across time in these participant groups (study 2; Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991; Buckner et al., 2005; Fjell et al., 2014; Pfefferbaum et al., 2013). This suggests that entorhinal cortex atrophy is decelerating in late-stage AMD. This characteristic is not unique to AMD as a sigmoidal shape has been suggested to occur in AD, where areas affected first in AD show deceleration after a period of acceleration (Jack et al., 2013, 2010; Sabuncu et al., 2011). A near-significant decline across time is emerging in late AMD, which would align with the pattern of change in normal ageing. Further investigation to confirm this result is required.

In late AMD, the focus of atrophy shifts towards the occipital pole, revealing significant thinning across time. This supports the hypothesis that the occipital pole will show an accelerated decline across time compared to early AMD and aligns with previous findings that have found visual cortex to be affected once AMD is established (Hanson et al., 2019; Hernowo et al., 2014). The similarity in findings to Hanson et al. (2019) is unsurprising as seven out of

the 16 participants longitudinal data in this study are in Hanson et al.'s (2019) publication. No significant thinning was found to occur across time in early AMD, confirming that the occipital pole is not affected early in the disease course (as also shown in study 2). The significant decline across time for the occipital pole in late AMD also helps show that the occipital pole may not have been significantly thinner in study 1 because some AMD participants were nearer the start of occipital pole atrophy than others. These results demonstrate how longitudinal analysis can reveal differing results from cross-sectional findings (Du et al., 2006; Wisse et al., 2018; Yang et al., 2016) and helps reveal areas of accelerating neurodegeneration in the absence of significantly thinner cortex at one given timepoint.

The pattern of brain changes observed across the AMD disease course may contribute to an increased susceptibility to AD. Cross-sectional results show thinning entorhinal cortex specific to AMD, where thinner entorhinal cortex is related to an increased risk of developing AD. This is supported by the findings of Soldan et al. (2015). In cognitively normal participants a thinner entorhinal cortex was associated with a shorter time to AD onset compared to participants that had thicker entorhinal cortex. Thinning in this region was also associated with development of later cognitive impairment (Pacheco et al., 2015), a feature found in AMD participants (section 1.1.5.2). This suggests that AMD participants are likely to experience cognitive impairment, as a minimum, and supports the cognitive impairment profile reviewed in section 1.1.5.2. However, entorhinal cortex thinning decelerates at the later stage of AMD. This decelerating pattern is not consistent with normal ageing or AD, and shows that a continued gradual decline into AD-related atrophy patterns is not suggested in this data. If AMD-related atrophy is not consistent with AD-related atrophy in cognitive related regions, other factors may be involved in the development of cognitive impairment in late AMD. For example, a thinner entorhinal cortex, among other factors such as reduced cognitive reserve (Pettigrew et al., 2017; Soldan et al., 2015), can increase the risk of developing AD, likely contributing to the mixed findings on AD prevalence in AMD patients (Keenan et al., 2014; Tsai et al., 2015).

It is important to highlight that the longitudinal results demonstrate a separate pattern of changes compared to mild AD. Although IFG results indicate that there may be preservation of this region for early and late AMD there is no involvement of the hippocampus or angular gyrus, regions affected in mild AD. It can be argued that this is because atrophy in these areas starts closer to mild AD onset (Pettigrew et al., 2017), and not expected to be seen in these late AMD participants if they are in the prodromal AD stage. The preservation of the IFG is arguably consistent with prodromal AD however, occipital pole thinning found in late AMD

diverges from prodromal AD where occipital pole thinning is not expected, typically occurring in severe AD (Karas et al., 2003). Even if occipital pole atrophy can be explained by the visual impairment experienced in this group of participants, atrophy in the entorhinal cortex should show a pattern of acceleration in late AMD to mirror prodromal AD atrophy pattens. This is not evident in these results.

A limitation of this study is that each stage of AMD has not been assessed, and their associated atrophy patterns measured. There are more stages to AMD than separating participants into early AMD – functional levels of vision – and late AMD – visual impairment (Clemons et al., 2006). It is possible that further changes are occurring in declines across time to reveal the cross-sectional cortical thinning observed in study 1. For example, angular gyrus declines across time are minimal in this study, but late AMD showed a near significantly thinner cortex compared to controls in study 1 after removing outliers. It is possible that further changes are occurring between the participant groups defined as early and late AMD in this study in an intermediate stage. This is supported by the changes found in AD. Changes from prodromal to moderate AD would also reveal an incomplete picture of disease progression, as atrophy follows a sigmoidal shape with an initial period of acceleration followed by later deceleration (Jack et al., 2013, 2010; Sabuncu et al., 2011). The full pattern of changes across the AMD brain could be assessed by following participant's progression once AMD has been detected. Alternatively, patients with an AMD diagnosis could be recruited and classified into the different stages of AMD to measure cortical atrophy between different AMD participant groups.

In conclusion, the entorhinal cortex was found to be affected by AMD itself. Based on previous literature this could potentially have a negative impact on cognitive functioning and implies susceptibility to AD. However, thinning of the entorhinal cortex is accelerated in early AMD compared to late AMD, a pattern inconsistent with mild AD. The deceleration of entorhinal cortex in late AMD is also accompanied by an acceleration of occipital pole thinning not present in early AMD, again inconsistent with mild AD. The results show that AMD has its own neurodegeneration pattern that affects brain regions beyond that associated with visual regions of the brain.

Chapter 5: Study 4;

Do behavioural factors relate to structural brain changes?

5.1 Introduction

Previous research shows that patients' lives are directly impacted in several ways as a result of visual changes from AMD, including their level of physical activity (Lamoureux, Hassell, & Keeffe, 2004). The definition of physical activity has two subcategories: structured exercise activity, and lifestyle physical activity. Whereas structured exercise is a planned, repetitive task done with the aim of maintaining physical fitness, lifestyle physical activity refers to activities conducted during daily life, including occupational and household activities (Centers for Disease Control and Prevention, 2015).

Reduced activity is associated with thinner or smaller brain structures compared to higher levels of activity (Benedict et al., 2013; Brown et al., 2014; Bugg & Head, 2011; Halloway, Arfanakis, Wilbur, Schoeny, & Pressler, 2019; Ho et al., 2011; Kooistra et al., 2014; Rovio et al., 2010; Ruscheweyh et al., 2011; Tamura et al., 2015). This process could be explained, partially, by the 'use-it-or-lose-it' hypothesis introduced in section 1.2.2. The 'use-it-or-lose-it' hypothesis states that because of changes in behaviour, brain regions associated with that behaviour are not used to the same extent they were previously ('use-it') and as a result neurodegeneration occurs ('lose-it'). This process is found in AMD where visual impairment in central vision results in atrophy of the lesion projection zone (Hanson et al., 2019) – represented by the occipital pole in this thesis. As a secondary effect of reduced vision, lower activity levels may then affect wide-spread areas across the brain. The consequence of neurodegeneration is changes in cognition, that is affected in AMD (Al-Salem & Schaal, 2014; Clemons et al., 2006; Harrabi et al., 2015; Rozzini et al., 2014; Zhou et al., 2016), the final stage in the 'use-it-or-lose-it' hypothesis.

The relationship between brain structure and exercise activity levels is found in both healthy and clinical populations (Bherer, Erickson, & Liu-Ambrose, 2013; Makizako et al., 2015; Varma, Chuang, Harris, Tan, & Carlson, 2015; Varma, Tang, & Carlson, 2016). In a healthy elderly

population exercise activity defends against the reduction of hippocampal volume (Killgore, Olson, & Weber, 2013). Moreover, the intensity of exercise was positively correlated with hippocampal volume in a population experiencing poor mental health (Mittal et al., 2013; Pajonk et al., 2010). Using an intervention study with participants aged 55-80, physical activity was found to help increase hippocampal volume across time. The brisk walking group (intervention) showed a 2% increase in the anterior portion of the hippocampus compared to the stretching and muscle strengthening group (control) where the hippocampus decreased by 1.5% due to the normal ageing process (Erickson et al., 2011). This finding is consistent with an earlier cross-sectional study that showed cardiovascular exercise was related to hippocampal volume (Erickson et al., 2009).

The association of entorhinal cortex with exercise is less researched (Lotaibi, Nauer, Dunne, & Schon, 2019; Whiteman, Young, Budson, Stern, & Schon, 2016). A positive relationship was found between cardio-respiratory fitness and entorhinal cortex volume using voxel-based morphometry (VBM), and revealed that the entorhinal cortex was affected by exercise to the same extent as the hippocampus (Whiteman et al., 2016). However, cardio-respiratory fitness and entorhinal cortex were not found to be associated in another study that examined an elderly population (Lotaibi et al., 2019), suggesting the relationship is unclear in this age group.

Exercise activity also positively correlates with the structure of the frontal and prefrontal cortex (Colcombe et al., 2003). In one study, increased cortical thickness was found in the prefrontal cortex when participants engaged in high levels of physical activity (Walhovd, Storsve, Westlye, Drevon, & Fjell, 2014) where larger frontal volume was found as a result of intense exercise in other studies (Erickson, Leckie, & Weinstein, 2014; Scheewe et al., 2013). Long durations of exercise have also been found to slow age-related cortical thinning in the prefrontal cortex (Lee et al., 2016), again demonstrating a 'use-it-or-lose-it' relationship between brain regions and external behaviour.

Overall, meta-analysis studies show that the impact of exercise is widespread across the brain (Colcombe et al., 2006; Colcombe & Kramer, 2016; Erickson et al., 2010; Erickson et al., 2011; Gow et al., 2012; Rovio et al., 2010; Ruscheweyh et al., 2011; Smith et al., 2010), and not a consequence of age. Using VBM to assess the relationship between cardiorespiratory fitness and brain volume in older adults aged 55-79, participants with higher levels of fitness had larger prefrontal, temporal, and parietal cortex, compared to individuals who had lower fitness levels (Colcombe et al., 2003). This finding was replicated in later studies that found an association between cardiorespiratory fitness and brain volume after controlling for age in their analysis (Erickson et al., 2007; Gordon et al., 2008; Weinstein et al., 2012). Erickson et al.

(2007) and Gordon et al. (2008) found larger volumes for the frontal and temporal lobe, whereas Weinstein et al. (2012) found larger volume in the parietal lobe in addition to these regions after controlling for confounds such as age. These studies show that, even though these studies were conducted in older adults, the effect of age does not contribute to the positive correlations found.

A large body of physical activity research focuses on the association between exercise and brain structure with less research focused on lifestyle activities. However, some studies have explored the association between lifestyle - including occupational, leisure, and social activities – and brain structure with mixed findings.

In a study on London taxi drivers, an occupational activity, the volume of the hippocampus was found to correlate with duration of time driving. The continued use of navigation and memory regions of the hippocampus revealed that repeated and sustained use of these areas through the participant's occupation resulted in larger posterior hippocampal volume (Maguire et al., 2000). The protective effect of occupation was found in participants in older age. The lifetime experience questionnaire (LEQ) measures aspects of education, occupation, reading and writing, socialising, and day-to-day habits in each stage of life. In a study that found a higher LEQ score was related to a larger MTL, in particular hippocampal volume, the contributing factor to this association was whether the participant had supervisory or managerial experience during their midlife. Similarly, it was found that those who had managerial experience had a slower hippocampal atrophy compared to participants who did not (Suo et al., 2012). Furthermore, using an overall LEQ score, Valenzuela, Sachdev, Wen, Chen, & Brodaty (2008) found that a higher score was correlated with a reduced rate of hippocampal atrophy in participants aged at least 60 years old, consistent with Suo et al.'s (2012) findings.

This association between lifestyle activity scores and brain structure has been found in other studies (Kinney et al., 2021; Seider et al., 2016; Raffin 2021). Another study that measured physical, social, and cognitive activities using the Community Health Activities Model program for Seniors found that cognitive activities were associated with greater volume in older adults. This included activities such as using a computer, doing arts and crafts, reading, attending events, and playing a musical instrument (Seider et al., 2016), that are difficult to do if someone is visually impaired. This finding is similar to the one that found increased hippocampal volume in older participants after learning how to juggle (Boyke, Driemeyer, Gaser, Büchel, & May, 2008). Most studies measured volume with lifestyle activities, however cortical thickness was measured more recently. Using a questionnaire that incorporated frequency and duration of leisure and household activities, participants that had higher levels

of activity had thicker cortex in temporal regions compared to inactive participants (Raffin et al., 2021). Kinney et al. (2021) concluded that social and leisure activities may contribute to resilience against pathological effects of disease, because social and leisure activity scores were found to be positively associated with cortical thickness in their study (Kinney et al., 2021).

The relationship between cognition and brain structure was reviewed in section 1.2.5, outlining evidence of a positive association between them. The effect of activity levels on cognition is also evident in previous research, indicating that cognitive dysfunction is the outcome of neurodegeneration following the 'use-it-or-lose-it' hypothesis. For example, increased cardiorespiratory fitness in older adults aged 59-80 was positively associated with hippocampal volume. Participants with larger hippocampal volumes (and therefore higher activity levels) achieved better scores on a spatial memory task than participants with smaller hippocampal volumes. This remained the case after controlling for age and educational attainment (Erickson et al., 2009). Another study also found that exercise was related to entorhinal cortex volume which in turn was positively associated with memory scores (Whiteman et al., 2016).

The current study investigates the relationship between exercise and lifestyle activity levels and cognition and their relationship to brain structure. Based on the relationships found between physical activity and brain structure in the frontal, parietal, and temporal lobes, it is hypothesised that cortical measures in each of the selected regions will be significantly positively associated to activity levels. Following the limited research reflecting the same findings as found with exercise activity, it is hypothesised that lifestyle activity will positively correlate with cortical measures except for the occipital pole. This same pattern is hypothesised to occur with cognitive scores, following the 'use-it-or-lose-it' hypothesis except for the occipital pole where no association is expected to occur.

5.2 Methods

5.2.1 Participants

Six AMD (4 male, M=80.33 years, SD=2.22) and 19 control (12 male, M=69.63 years, SD=1.40) participants were recruited to this study. Some of the controls in this study were recruited with the help of MSc students (Adrian Etale, Anna Hall, Julietta Mikolajczyk, Douglas Scarth, Sharon Thind) using YNI'C's participant pool. The inclusion criteria required AMD participants

to have a confirmed diagnosis of AMD with no perceived indications of memory problems and not seeking medical attention for memory difficulties. The inclusion criteria for controls required them to self-certify they were healthy with no perceived memory difficulties, and they were not seeking medical attention for memory problems, and they had normal or corrected-to-normal vision. Details of participants AMD status can be found in Table 5-1.

Table 5-1. Details of participant's AMD status.

AMD Participant	Details of AMD	Participation	Ability to carry out visual tasks
1	Bilateral dry AMD and receiving no treatment	Behavioural only	Good
2	Dry AMD in one eye and wet AMD in the other for which they were receiving injections	Behavioural only	Good
3	Unilateral wet AMD and receiving anti-VEGF injections	Behavioural and MRI	Good
4	Bilateral dry AMD and receiving no treatment	Behavioural and MRI	Good
5	Bilateral wet AMD and receiving anti-VEGF injections	Behavioural and MRI	Struggled
6	Bilateral dry AMD and receiving no treatment	Behavioural and MRI	Struggled

One participant from each participant group was ineligible for MRI scanning. In addition, MRI data from one control participant was not saved due to technical reasons, and one of the AMD participant's data was not released for research following YNiC's health and safety protocol regarding potential anomalies. Their data was only used in behavioural analysis. However, this reduced participant numbers for MRI data from six to four for AMD (3 male, M=80.17 years, SD=2.21), and 19 to 17 for controls (12 male, M=69.33 years, SD=1.59).

Six more AMD participants were eligible for the study, but their data were not collected before the UK's lockdown in response to COVID-19 and were not collected afterwards due to the impact lockdown may have had on cognition and activity levels (shown in Table 5-2).

5.2.2 Materials

The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was used to assess global cognitive ability. The MoCA was administered following the training and guidelines provided with the task and was standardised with a script (Appendix A)**.** To ensure AMD participants could see the visual part of the tasks they were enlarged. For the MoCA the pictures of the animals were enlarged so that each animal covered one half of an A4 page. This was the same for the cube drawing and clock face tasks that covered half a page of A4 each. The dot-joining task took two thirds of a page of A4 to ensure the letters and numbers were visible at a font size of approximately 36 (Appendix B). The MoCA is scored out of 30, with 30 being an attainable top score.

The augmented Victoria Longitudinal Study (VLS) activity questionnaire explores different aspects of daily activities such as reading, theatre trips, gardening, and DIY (Jopp & Hertzog, 2010). This is a freely available questionnaire shown to be a reliable measure of overall activity levels of daily life in older adults. This augmented version of the questionnaire was also found to correlate better with cognition and health status compared to the original VLS questionnaire, making it ideal for AMD participants where differences in cognition and overall health should be reflected in the data with this higher sensitivity. As well as this, this questionnaire was selected because of the flexibility enabling researchers to pick relevant questions from the questionnaire. For this research, the questionnaire was divided into the two domains of physical activity – exercise (planned repetitive task to maintain physical fitness) - and lifestyle activity (conducted as part of daily life). For each question, the participants rated how often they performed each type of activity over the last two years (or since AMD diagnosis if shorter than 2 years). “Daily” was scored as 8 and “never” scored as 0 with varying options in between. Changes to the wording were made for UK participants, such as changing “state” to “county”, indicated in square brackets (Appendix C).

The summed scores for each question were divided by the number of questions in each section of the questionnaire to obtain an average score for exercise (six questions – numbers 11-16) and lifestyle (51 questions) activity (Appendix C). The top mean score of 8 is unrealistic and not attainable as it is unlikely every activity is engaged in daily. The activity questionnaires were printed in font size 16 (recommended by Macular Society) to aid AMD participants in reading the questionnaire for self-completion. Every AMD participant was able to read the questionnaire without assistance from the researcher.

5.2.3 Procedure

5.2.3.1 AMD participant recruitment

Recruitment of AMD participants required various methods different to that used to recruit controls (advertising via the YNiC participant pool). Participants were recruited via support groups including the York Blind and Partially Sighted (YBPS) Society, Wilberforce Trust, and MySight that are found in York, through the Macular Society's research database, word of mouth by advertising in different community settings, and through opticians via posters and leaflets. Table 5-2 shows the success of various methods of recruitment and the outcome of interested persons during the study.

5.2.3.2 Behavioural data

Participants were tested on the MoCA first followed by the self-completed activity questionnaire. The global cognitive tasks were delivered following a script to ensure each participant was assessed under the same circumstances. Participants were asked if they could see and complete the unmodified tasks, to try and use the task as presented where possible. The MoCA was scored using the scoring guide provided with the task and as specified during MoCA training (a requirement before gaining access to the task). There was the option to have the questionnaires read out aloud by the researcher if participants either preferred this or had trouble reading (in the case of bilateral visual impairment). Participants selected one option per question for the activity questionnaire that was scored following the guidance provided.

5.2.3.3 MRI data

MRI data was collected using the 3 Tesla Siemens Magnetom Prisma scanner using a sixty-four-channel head receiver array. Isotropic T1-weighted MPRAGE images were collected using the following parameters: TR = 2400ms, TE = 2.28ms, TI = 1010ms, flip angle = 8 degrees, voxel size = 0.8 x 0.8 x 0.8mm, matrix size = 256 x 256 x 167mm; following the guidelines from the Human Connectome Project (Glasser et al., 2013).

Freesurfer version 6 used in previous chapters to pre-process data and obtain cortical measures was repeated in this study as described in section 2.2.3.

5.2.3.4 Data analysis

To assess the association of brain measures with behavioural measures, hierarchical regressions were conducted. For each model, participant group was added into the model first to control for any differences already expected because of clinical features. The addition of either the brain region or the behaviour scores were added into the second model, where the

change in R statistics was investigated to see whether there was a significant relationship between the two measures.

For physical activity levels, the predicted association was that activity levels affect the structure of the brain. This meant participant group (model 1) and activity levels (model 2) were added into the model as predictor variables and brain region measures (volume or cortical thickness) were the outcome variables. For MoCA the predicted association was that brain measures would correlate with participant MoCA scores. Participant group (model 1) and region (model 2) were added as predictor variables and MoCA score was the outcome variable. If there is a significant relationship between behavioural measures and brain regions both the main model and the change statistics would have to be significant. This indicates that there is a significant relationship between the two variables of interest (exercise with cortical estimates, lifestyle activity with cortical measures, and cortical measures and MoCA) after controlling for participant group. If the main model is significant but the change statistics are not, then it shows that the association is driven by the difference in participant groups based on differences in clinical features. For example, previous literature has shown that MoCA scores and entorhinal cortex are affected in AMD compared to controls, showing how these features can help drive the model if exercise and entorhinal cortex are not significantly related.

The aim of the hierarchical regression is to understand the importance of the added predictor variable in model 2, to assess the relationship between the predictor and outcome after participants group was controlled for (by using model 1). As making predictions about the models was not important to the aim of this study, the betas were not reported.

All assumptions were met for the relevant models unless otherwise stated.

Table 5-2. Details of interested AMD participants' outcomes during recruitment.

Number of interested person	Where from	Recruited?	Why not?
1	Word of mouth	No	History of stroke
2	Word of mouth	No	Withdrew interest
3	**MySight**	**Yes**	
4	**MySight**	**Yes**	
5	Word of mouth	No	History of stroke
6	**Macular Society**	**Yes**	
7	**Macular Society**	**Yes**	
8	Macular Society	No	Comorbidities
9	Optician	No	Withdrew interest
10	Macular Society	No	Comorbidities
11	**Macular Society**	**Yes**	
12	Optician	Yes	Data not collected (COVID-19)
13	MySight	Yes	Data not collected (COVID-19)
14	**Macular Society**	**Yes**	
15	Optician	Yes	Data not collected (COVID-19)
16	YBPS Support group	No	Withdrew interest
17	Macular Society	Yes	Data not collected (COVID-19)
18	Macular Society	No	Withdrew interest
19	Macular Society	No	Participant information sent before COVID-19 – not followed up
20	YBPS Support group	No	Participant information sent before COVID-19 – not followed up

Data were collected from participants in bold. YBPS - York Blind and Partially Sighted Society

5.3 Results

5.3.1 Behavioural measures

Both exercise (r(23)=0.45, p=.023) and lifestyle (r(23)=0.49, p=.014) activity levels were positively correlated with MoCA scores.

5.3.1.1 Exercise activity levels

The control group (N = 19; M=4.66, SD=1.71) had higher exercise activity levels compared to AMD (N=6; M=1.28, SD=0.49). A Welch's unequal variances t-test was run due to unequal sample sizes and revealed a significant difference between controls and AMD participants in levels of exercise (Welch's F(1,22.99) = 59.13, p<.001, Cohen's d = 3.07; Figure 5-1).

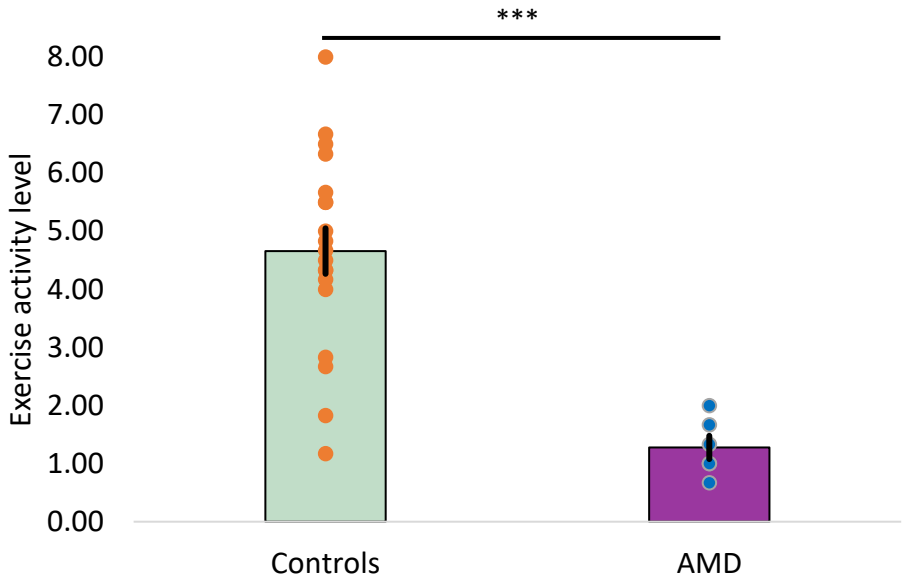


Figure 5-1. Exercise activity level scores for controls and AMD participants.
AMD – age-related macular degeneration, N = 6; control, N = 19. Error bars show standard error of the mean. Dots show individual participant's exercise level. ***p<.001.

5.3.1.2 Lifestyle activity levels

The control group (N = 19; M=3.49, SD=0.62) also had higher lifestyle activity levels compared to AMD (N=6; M=2.23, SD=0.65). A Welch's unequal variances t-test was run due to unequal sample sizes and revealed a significant difference between the groups (Welch's F(1, 8.18) = 17.58, p=.003, Cohen's d =1.98; Figure 5-2).

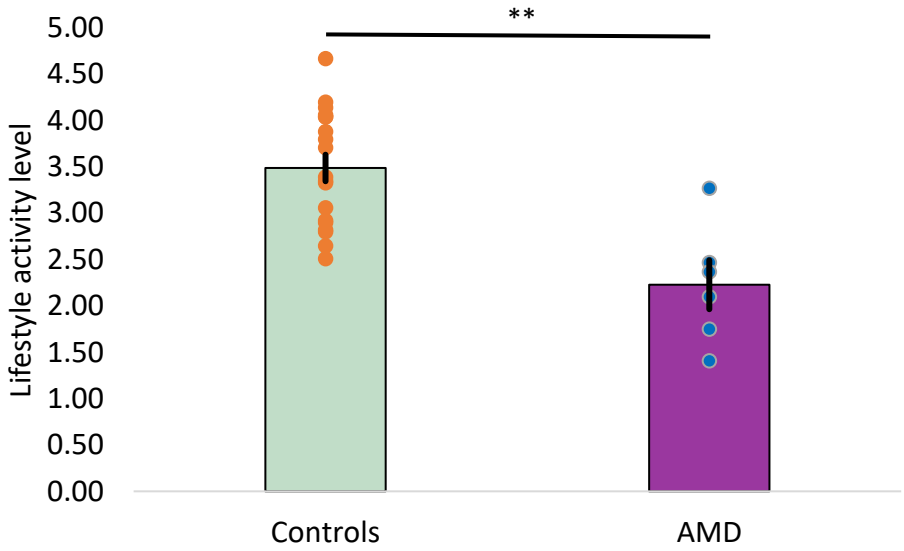


Figure 5-2. Lifestyle activity level scores for controls and AMD participants.
AMD – age-related macular degeneration, N=6; controls, N=19. Error bars show standard error of the mean. Dots show individual participant's exercise level. **p<.01.

5.3.1.3 MoCA scores

The control group (N=19; M=24.21, SD=2.35) had higher MoCA scores compared to AMD (N = 6; M=19.83, SD=2.23). A Welch's unequal variances t-test was run was run on MoCA scores (due to unequal sample sizes) and found a significant difference between the groups (Welch's F(1, 8.82) = 17.14, p=.003, Cohen's d =1.91; Figure 5-3). To exclude the possibility this was due to difference in eyesight, MoCA blind scores were also calculated (controls: M=18.42, SD=1.92; AMD: M=15.33, SD=2.07) and showed a significant difference between groups (Welch's F(1, 7.95) = 10.52, p=.012).

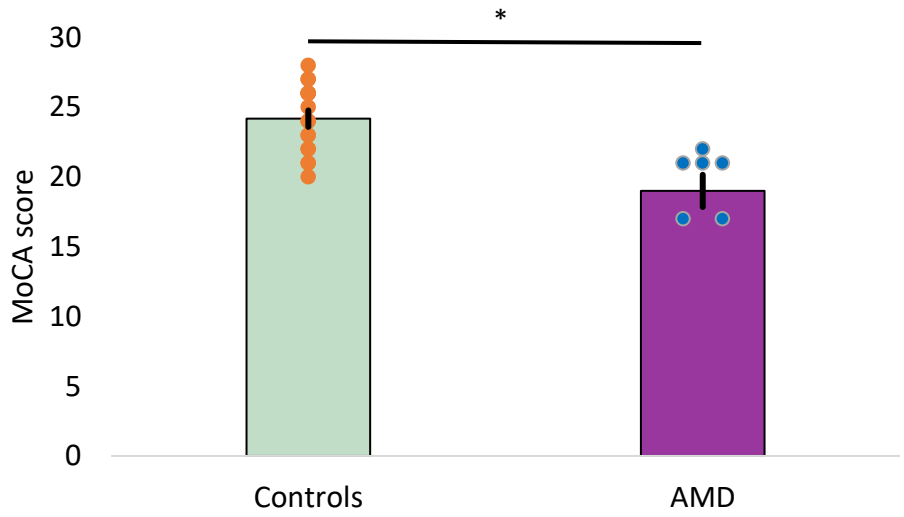


Figure 5-3. MoCA scores for controls and AMD participants.
AMD – age-related macular degeneration. Error bars show standard error of the mean. Dots show individual participant's exercise level. *p<.05.

5.3.2 Cortical measures

The cortical thickness and hippocampal volume estimates for controls and AMD are found in Table 5-3, but this is not a focus in this study. Welch's unequal variances t-test showed there was no significant difference between AMD and controls cortical measures (p>.05; Table 5-3). Entorhinal cortex was closest to significant (p=.169). Mean cortical measures (volume and cortical thickness) in all five brain regions were lower in the AMD group than in the control group.

Table 5-3. Controls and AMD regions' cortical measures.

Regions	Controls		AMD		Cohen's d
	Mean	SD	Mean	SD	
Entorhinal Cortex (mm)	3.73	0.24	3.43	0.33	1.05
Hippocampus (mm^3)	3791.65	222.81	3724.70	489.00	0.19
Angular Gyrus (mm)	2.46	0.25	2.33	0.19	0.59
Inferior Frontal Gyrus (mm)	2.75	0.17	2.66	0.12	0.62
Occipital Pole (mm)	1.87	0.20	1.80	0.17	0.38

AMD - Age-related macular degeneration, N=4; controls, N=17.

5.3.3 Brain-behaviour

5.3.3.1 Exercise and lifestyle activity levels.

Exercise activity levels.

Hierarchical regressions (controls N = 17, AMD N = 4) were conducted to see whether exercise activity levels related to regions' cortical measure estimates after controlling for participant group (Figure 5-4). The results showed that for entorhinal cortex the full model was not significant (R^2=.198, F(2,18)=2.22, p=.138) showing that neither participant group nor exercise activity levels contributed to the entorhinal cortex thickness; although a medium-to-large positive correlation is evident (r effect size = 0.44). The results for hippocampal volume showed that the full model was not significant (R^2=.012, F(2,18)=0.11, p=.896). The results for angular gyrus showed that the full model was nearing significance (R^2=.257, F(2,18)=3.12, p=.069) showing that neither participant group nor exercise activity levels contributed to angular gyrus thickness, with a large negative correlation emerging (r effect size = 0.51). The results for IFG show that the full model was not significant (R^2=.044, F(2,18)=0.42, p=.664). The results for occipital pole showed that the full model was not significant (R^2=.021, F(2,18)=0.19, p=.827).

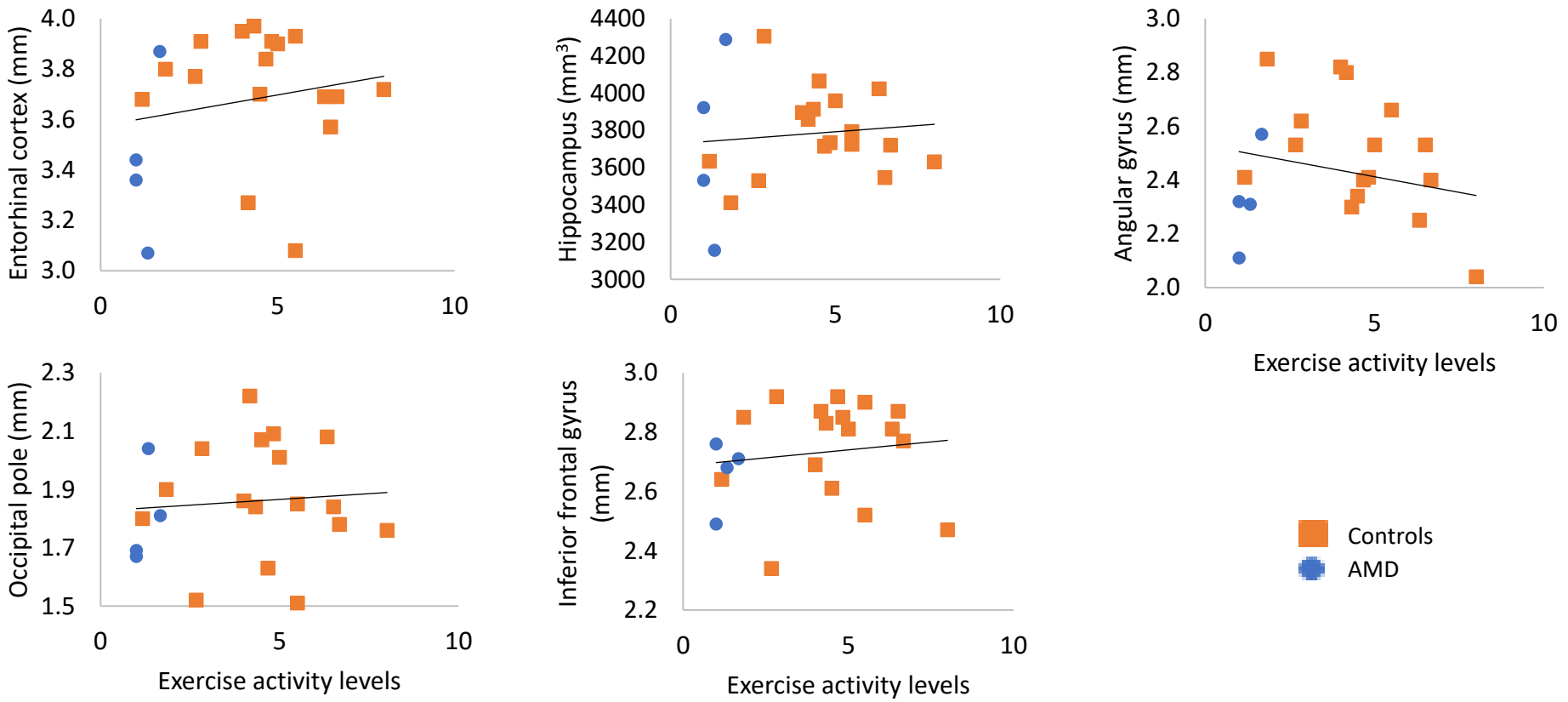


Figure 5-4. Exercise activity level scores shown against the regions of interest cortical measures.
Age-related macular degeneration (AMD) in blue circles, controls in orange squares. Line of best fit is shown for all participant data combined across both groups for each ROI.

Lifestyle activity levels.

Hierarchical regressions (controls N = 17, AMD N = 4) were conducted to see whether activity levels related to regions' cortical measure estimates after controlling for participant group (Figure 5-5).

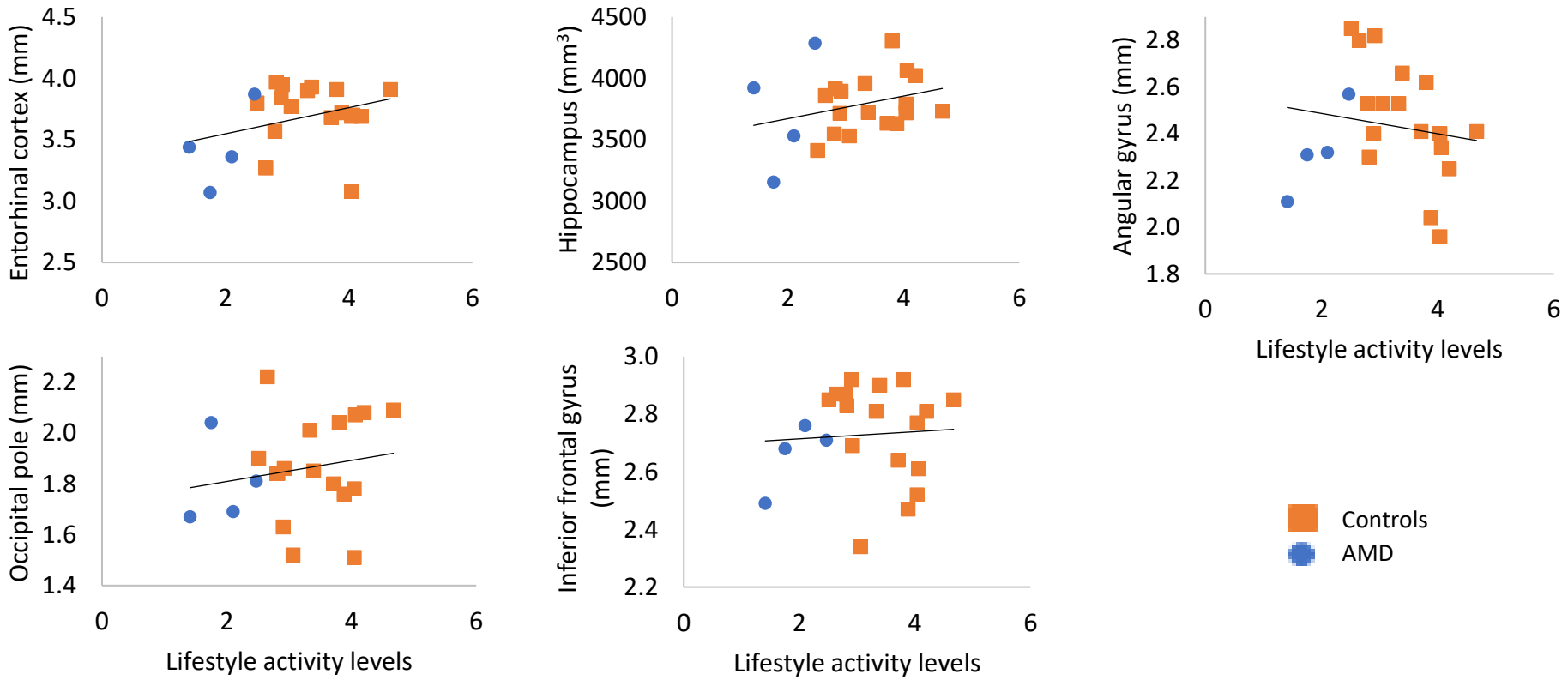


Figure 5-5. Lifestyle activity level scores shown against the regions of interest cortical measures.
Age-related macular degeneration (AMD) in blue circles, controls in orange squares. Line of best fit is shown for all participant data combined across both groups for each ROI.

The results showed that for entorhinal cortex the full model was not significant (R^2 =.186, F(2,18)=2.05, p=.157) showing that neither participant group nor activity levels contributed to entorhinal cortex thickness; although a medium-to-large positive correlation is shown (r effect size =0.43). The results for hippocampal volume showed that the full model was not significant (R^2=.327, F(2,18)=1.08, p=.362) although a medium effect size was found (r effect size =0.33). The results for angular gyrus show that the full model was nearing significance (R^2=.257, F(2,18)=3.11, p=.069) showing that neither participant group nor lifestyle activity levels contributed to angular gyrus thickness, although a large negative correlation is emerging (r=0.51) and the model is nearing significance. The results for IFG show that the full model was not significant (R^2=.057, F(2,18)=0.55, p=.589). The results for occipital pole showed that the full model was not significant (R^2=.035, F(2,18)=0.32, p=.727).

5.3.3.2 MoCA

Hierarchical regressions (controls N = 17, AMD N = 4) were conducted to see whether ROI cortical measures were related to MoCA scores after controlling for participant group (Figure 5-6). The results for entorhinal cortex show that the full model was significant (R^2=.452, F(2,18)=7.43, p=.004). The addition of entorhinal cortex did not significantly contribute to the model (R^2 change = .012, F(1,19)=0.41, p=531). The results for hippocampal volume showed that the full model was significant (r2=.461, F(2,18)=7.69, p=.004) but the addition of hippocampal volume did not significantly contribute to the model (R^2 change = .021, F(1,19)=0.70, p=.416). The results for angular gyrus showed that the full model was significant (R^2=.473, F(2,18)=8.07, p=.003). The addition of angular gyrus did not significantly contribute to the model (R^2 change =.033, F(1,19)=1.13, p=.303). The result for IFG showed that the full model was significant (R^2=.607, F(2,18)=13.90, p<.001). The addition of IFG did significantly contribute to the model (R^2 change =.167, F(1,18)=7.65, p=.013) with a medium-to-large negative correlation (r effect size = 0.41). The results for occipital pole show that the full model is significant (R^2=.471, F(1,18)=8.03, p=.003). The addition of occipital pole did not significantly contribute to the model (R^2 change = .031, F(1,18)=1.07, p=.314). Because the addition of cortical regions did not significantly contribute to the model, this shows that the model was driven by differences in the participant groups.

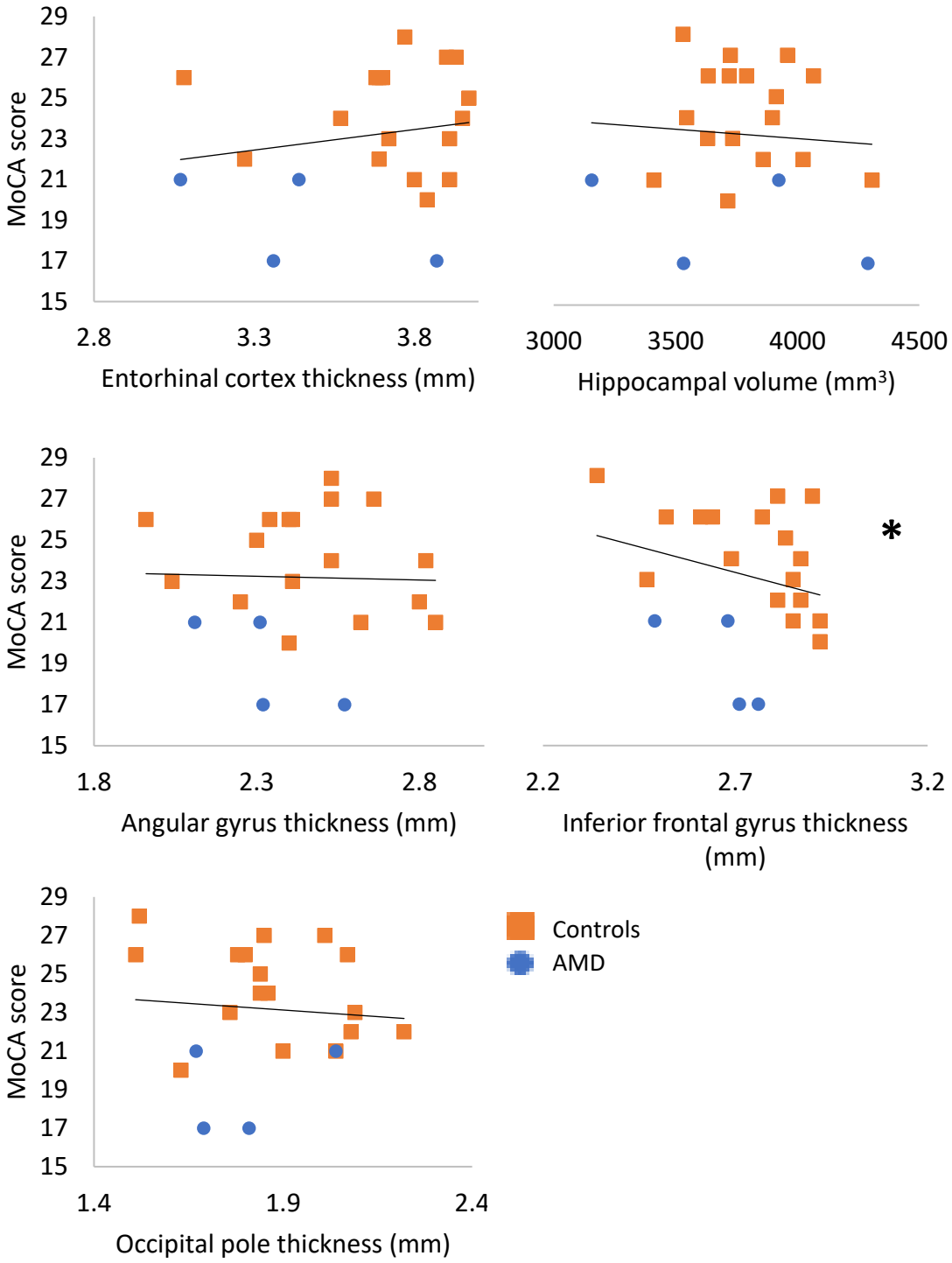


Figure 5-6. MoCA scores shown against the regions of interest cortical measures. Age-related macular degeneration (AMD) in blue circles, controls in orange squares. Line of best fit is shown for all participant's data for each ROI. *p<.05

5.4 Discussion

The aim of this study was to see whether brain structures were related to behavioural factors, although study design and aims were altered due to the impact of COVID-19 on recruitment.

The results show that exercise and lifestyle activity levels, and cognitive scores in AMD are significantly lower when compared to controls. Behavioural measures significantly correlated with each other showing there is an association between them. There was a medium-to-large positive correlation between entorhinal cortex for exercise and lifestyle activity and medium positive correlation between hippocampal volume with lifestyle activity levels but not exercise, although no associations were significant. The angular gyrus showed an unexpected large negative correlation with exercise and lifestyle activity, even though this remained just below the significance threshold for the full model. Only the IFG was significantly related to MoCA scores, where a thinner cortex is associated with a higher score. The main results do not support the hypothesis that brain structure is significantly related to behavioural measures, although hippocampal volume (lifestyle only) and entorhinal cortex show the expected trend with activity levels. Regression analysis is likely underpowered and should be interpreted with caution.

Although cortical measures are not a main focus of this study, thinner entorhinal cortex thickness in AMD paticipants compared to controls is in support of the earlier findings in this thesis (studies 1 & 3). Similar to the age difference in study 1, AMD participants mean age is above the age of 70 and controls is below. Some of the difference between entorhinal cortex thickness means could be due to normal ageing. The significantly reduced MoCA scores for AMD participants was also consistent with previous literature discussed in section 1.1.5.2. Lower activity levels found in AMD participants align with previous findings, where several studies show that reduced vision affects the type of behaviours a person can engage with (Lamoureux et al., 2004), and ultimately reduces their activity levels (Marsiske et al., 1997; Swanson et al., 2012). However, it is important to state that the AMD group only includes data from four or six participants and should be interpreted with caution, even though the findings align with previous research.

A relationship between activity levels and brain measures is known to occur with hippocampal volume, where reduced activity levels are associated with smaller hippocampal volume (Erickson et al., 2009, 2011; Killgore et al., 2013; Makizako et al., 2015; Varma et al., 2015, 2016). The results in this study show a medium positive correlation between hippocampal volume and lifestyle activity levels consistent with previous findings, even though the association was not significant. However, inconsistent with previous literature is the absence of a relationship for hippocampal volume with exercise. Given previous studies focused on a relationship between exercise and hippocampal volume, and not with lifestyle, the opposite finding would be expected - that more subtle changes would be found with lifestyle than found

with exercise. This finding shows that even with slight changes in lifestyle activities, the effects can potentially be detected in relation to brain structure. Lifestyle activity levels are more likely to be impacted in AMD than in non-visually impaired populations (Marsiske et al., 1997; Swanson et al., 2012) highlighting the importance of this finding for AMD. This could have significant implications on clinicians' approach to treating AMD patients where wider advice on maintaining an active lifestyle could be provided.

Anon-significant positive correlation was found for entorhinal cortex thickness with exercise. Although a previous study found a relationship between exercise activity levels and entorhinal cortex in a younger age group (Whiteman et al., 2016), the results in this study align with a previous study that did not find an association between these two measures in the same age group (Lotaibi et al., 2019). Several studies have shown that there can be an age-effect when it comes to the strength of the relationship between activity levels and brain structure. With older adults showing a weaker or different relationship compared to younger adults (Rosario, Kern, Mumtaz, Storer, & Schon, 2021; Williams et al., 2017).Both this current study and Lobaiti et al. (2019) have small sample sizes, and it may be that the slight variation in methods (including the absence of a clinical group in Lotaibi et al. (2019)) has revealed different findings to Whiteman et al. (2016) rather than this being due to age itself. Overall entorhinal cortex thickness may be affected by exercise to some extent.

This current study also shows a positive non-significant correlation between entorhinal cortex thickness and self-reported exercise activity levels, where the effect is stronger than that found for hippocampal volume. This is also contrary to the literature where associations between exercise is stronger and commonly reported with hippocampal volume rather than with entorhinal cortex (Erickson et al., 2009, 2011; Killgore et al., 2013; Lotaibi et al., 2019; Mittal et al., 2013; Pajonk et al., 2010).

The finding of lifestyle activity revealing a non-significant positive correlation with cortical thickness in this study aligns with a previous study that found lifestyle scores on the LEQ was positively associated with cortical thickness in temporal regions (Raffin et al., 2021). This suggests that although there is minimal research in this topic, it is likely a consistent finding. Again, this can have clinical benefits if AMD patients are supported to find alternative ways to keep engaging in lifestyle activities to protect against entorhinal cortex thinning.

A novel finding was the negative correlation between exercise and lifestyle activity levels and angular gyrus thickness, even though this was not significant. Previous studies found positive relationships between the parietal lobe and exercise (Colcombe et al., 2003; Erickson et al.,

2007; Gordon et al., 2008; Weinstein et al., 2012), but the angular gyrus, or inferior parietal lobe, was not specifically stated as the region of interest in these studies. This could account for the difference between previous findings for exercise and lifestyle in this study. This finding does not follow the correlations found in previous literature, but there is no obvious reason why this would have happened in this sample of participants.

No other notable correlations were found between the remaining regions cortical thickness (IFG and occipital pole) and activity levels. The results show that activity is unlikely to impact visual areas potentially because of their role of processing visual information. These findings can also be explained by Heinemann et al.'s (2019) study that showed no effect of reduced visual acuity on activity frequency between controls, early, and late AMD. By extension, thinner or smaller cortex found in late AMD (Burge et al., 2016; Hanson et al., 2019; Hernowo et al., 2014; Prins, Plank, et al., 2016) would not be associated with activity levels as cortical thinning can be found despite stabilised visual acuity (Hanson et al., 2019). The results for the IFG may be because previous studies have focused on larger areas of the frontal or prefrontal lobe, and not specifically the IFG (Colcombe et al., 2003; Colcombe & Kramer, 2016; Gordon et al., 2008; Lee et al., 2016; Smith et al., 2010; Walhovd et al., 2014; Weinstein et al., 2012). This suggests that the IFG is unlikely to be affected by changes in activity levels due to the functional role of this region (related to language ability).

No region showed a positive relationship between the MoCA and cortical measures in this study. This has wider implications for interpretation of the activity results in this study. The strength of the relationship between entorhinal cortex and MoCA is weaker than that found for activity levels. This is despite significant relationships being found between entorhinal cortex and MoCA scores in previous studies (Ogawa et al., 2019; Zdanovskis et al., 2020). In this context it is plausible that the impact of lifestyle and exercise activity levels on entorhinal cortex thinning are more meaningful than indicated in these results. Alternatively, the effect of reduced activity levels on brain structure may not have taken full effect at this stage, showing that cortical thinning is secondary to lower activity levels. This can be explained with the 'use-it-or-lose-it' hypothesis, to some extent, where a change in behaviour is needed before structural brain changes are negatively affected. This is further supported by the effect sizes for activity levels and MoCA with entorhinal cortex. Activity levels, especially exercise, have a larger effect size than MoCA suggesting MoCA scores decline after activity levels decrease.

A negative relationship was found between MoCA scores and IFG thickness. This was not expected when exploring the relationship between cognitively healthy participants MoCA scores and IFG thickness. This is because the frontal lobe is significantly impacted in normal

ageing and not during pathological ageing, for example the preservation found in mild cognitive impairment (Head et al., 2005). The negative relationship between IFG and MoCA can be explained by preservation of this region that is seen in mild AD even when overall MoCA scores are affected at this stage of disease (study 2). Although participants were asked to meet the inclusion criteria before taking part in the study, ten control participants had a score between the range of 20 to 25, that roughly indicates MCI on the MoCA as well as all four AMD participants with scores of 17 or 21. It takes more than one MoCA task to detect MCI and lower scores can be found with lower education levels and depression (Blair et al., 2016; Korsnes, 2020), however this association suggests these participants may have some characteristics of MCI. For AMD participants, preservation of the IFG may be a clinical feature of disease (studies 2 & 3), and this association between IFG and MoCA helps support that conclusion.

A limitation of this study is that the whole participant group was used to assess the relationship between the two measures. The planned analysis was to explore controls and AMD separately, however this was not possible because of the UK's lockdown (March 2020) in response to COVID-19 halting data collection. Had more AMD participants been involved in this study, the brain-behaviour correlations would have better reflected the change of activity levels and associated brain changes from control participants through to the presence of AMD. Similarly, controls with a MoCA score below a certain threshold could have been excluded from the study whilst still maintaining power in the analysis. Although participants confirmed they were cognitively normal, their MoCA scores do not reflect this for every control participant. Future research could also assess the associations between these measures separately for controls and the clinical group, both early and late AMD, to fully understand what impact external factors have on cortical measures and whether trends in the associations are different from controls to AMD. A further weakness is that a measure for activity levels pre-visual impairment and post-visual impairment was not collected, meaning it is not clear whether activities were dropped because of AMD or if AMD participants had lower activity scores in general.

To conclude, although both activity levels are significantly lower in this sample of AMD participants, the results show that changes in behaviour at this stage are not significantly related to cortical measures. However, there were non-significant medium-to-large positive correlation found for exercise and lifestyle activity levels with entorhinal cortex thickness and a medium positive correlation for lifestyle with hippocampal volume. A non-significant negative correlation was found between angular gyrus and activity levels. Despite significantly lower

MoCA scores in AMD participants, no positive association was found for brain structure and MoCA scores except for IFG where the association was negative. The results indicate some support for the 'use-it-or-lose-it' hypothesis in this sample of participants.

Chapter 6: Discussion chapter.

6.1 Thesis aim

The aim of this thesis was to explore whether AMD is related to mild AD using structural MRI, and behavioural data. The basis of this thesis arose from previous research conducted on the link between AMD and AD, where several clinical features identified in one disease were shared with the other.

6.2 Brain structure

6.2.1 Summary of findings

Overall, studies 1, 2 and 3 did not show any significant findings with volume measures. Consequently, only cortical thickness, except for the hippocampus (because cortical thickness is not available in Freesurfer), will be addressed in this summary.

Study 1 confirmed that the pattern of neurodegeneration in AD followed the pathophysiological spread of amyloid beta and phosphorylated tau. The entorhinal cortex, hippocampus, and angular gyrus were significantly affected in mild AD compared to controls. The IFG and occipital pole were not significantly different. In late AMD there was evidence of a similar neurodegenerative pattern. The entorhinal cortex and angular gyrus were significantly thinner in AMD compared to controls, although a near-significant finding was found in angular gyrus once outliers were removed. No significant thinning was found for hippocampus, IFG, or occipital pole in late AMD. Overall, the pattern of neurodegeneration in late AMD indicates some degree of shared atrophy patterns when focusing on cortical thickness findings.

In study 2, cross-sectional and longitudinal analysis was conducted on a sample of (presumed) early AMD participants. The cross-sectional results showed the entorhinal cortex and hippocampus were significantly affected in AD, while a similar pattern was emerging in AMD. When compared to controls, longitudinal results for AD revealed the double dissociation pattern between medial temporal lobe regions and frontal regions. In this pattern, the MTL atrophies at a significantly faster rate in AD compared to normal ageing, while the frontal lobe atrophies at a faster rate in normal ageing compared to AD. The accelerated rate of change was significant for entorhinal cortex and hippocampus for AD participants, and the IFG was

significantly decelerated compared to controls. The results for AMD showed no significant difference in the rate of change compared to controls, but accelerated atrophy was found in entorhinal cortex and decelerated atrophy in the IFG. Although the results for AMD are not significant, the importance of finding similar neurodegenerative patterns to mild AD is that they were found in a sample of participants screened to be cognitively normal. No significant differences in rate of change were found in the occipital pole in either AMD or AD compared to controls, but in AMD the angular gyrus had a significantly slower rate of change than controls, a finding distinct from mild AD.

Study 3 involved cross-sectional analysis comparing all participants from study 1 (late AMD and controls) and 2 (early AMD and controls). Study 3 found significantly thinner entorhinal cortex in the combined AMD participants compared to controls. Although this is partly due to increased statistical power compared to studies 1 and 2, it also revealed an AMD-associated brain change. Other regions did not show any significant atrophy, but all brain regions were smaller or thinner compared to controls. When comparing early to late AMD across time (longitudinal analysis), the results showed that the entorhinal cortex significantly declined in early AMD but not late AMD, and the occipital pole significantly declined in late AMD but not early AMD. The findings showed no difference for hippocampus, IFG, or angular gyrus.

6.2.2 Brain structure discussion

Combining the findings from studies 1, 2, and 3, a hypothesised neurodegenerative pattern for AMD can be established. Cross-sectionally it is evident that entorhinal cortex thinning is a feature of AMD itself. This thinning is more pronounced in late AMD than early AMD cross-sectionally, but overall the entorhinal cortex was found to be significantly thinner after combining participants from study 1 and 2. This is important because this sample includes a mix of participants that have varying experiences of visual impairment (minimal, bilateral and unilateral), clinical features (wet and dry AMD), and a sample that included confirmed cognitively healthy participants (early AMD) showing this feature is shared across different AMD participants.

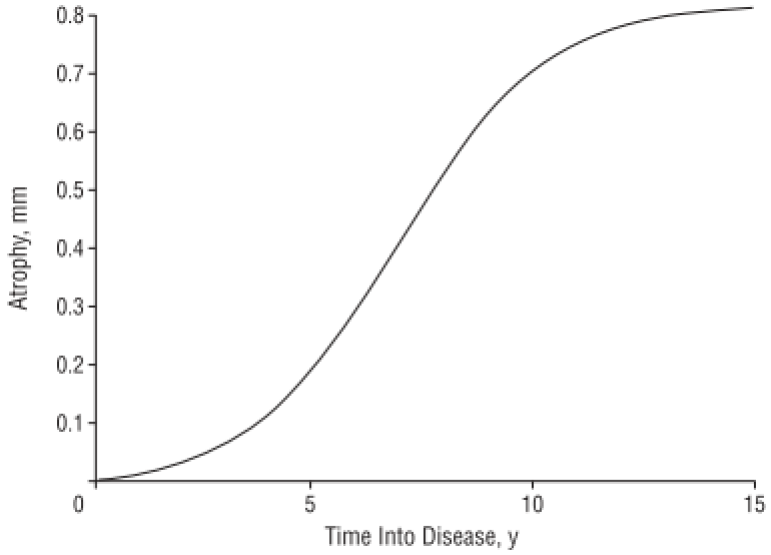
In early AMD, as shown with longitudinal results, the entorhinal cortex follows a non-significantly faster trajectory than that found in normal ageing (study 2). Although the rate of change is not significant, this slow atrophy pattern can have an additive effect over time, whereby this slow decline can then be detected in late AMD cross-sectionally as significantly thinner cortex (study 1). The hippocampus does not seem to be affected in AMD, but it is not clear whether this is because volume is not affected, and another measure would reveal

changes, or whether this region is not affected in AMD in general. The angular gyrus rate of change is significantly slower compared to controls in study 2, and in study 3 there is no difference in atrophy rate in this region between early and late AMD. Together this suggests that this region atrophies slower than seen in normal ageing for both early, as shown in study 2, and in late AMD by association. Whereas cortical thinning findings for entorhinal cortex in cross-sectional and longitudinal analysis align, this is not found with angular gyrus where longitudinal analysis shows this region is preserved in early and late AMD (study 2) and cross-sectional analysis suggests a thinning in late AMD (study 1). Longitudinal results for angular gyrus cast doubt on the near-significantly thinner cortex found cross-sectionally in study 1, where this could be due to an ageing effect rather than clinically related cortical thinning. The IFG shows a non-significantly slower atrophy across time in early AMD compared to controls in study 2, and then no difference between early and late AMD in study 3. Cross-sectional results do not show any difference in thinning across time for AMD in this region compared to controls for early (study 2) or late (study 1) AMD. This shows that the preservation is subtle and not detectable via cross-sectional analysis as found in mild AD.

Collectively, the AMD results above suggest that there is likely to be an intermediate stage of AMD not explored in this thesis. This conclusion can be explained by the sigmoidal shape found with cortical thinning in AD. Areas that show thinning first (such as the entorhinal cortex) decline at rates indistinguishable from those of normal ageing initially (bottom of S shape), they then accelerate to levels beyond that expected with normal ageing (middle part of the S shape), and then slow as the damage moves across the brain (the top part of the S shape) (Sabuncu et al., 2011). As the entorhinal cortex starts to plateau (top of S shape), the frontal lobe in moderate AD would then start to show accelerated atrophy compared to controls before plateauing (top of S shape) in severe AD and so on. This is partly demonstrated in Sabuncu et al. (2011) and Jack et al. (2010, 2013) figures that are shown below (Not for examination: Diagram 3a).

Relating this back to AMD, this idea of a slow atrophy at the start of disease and plateauing nearer the end of disease could further explain the results for both entorhinal cortex and angular gyrus. Cross-sectional entorhinal cortex results for early AMD show no significant thinning compared to controls (study 2) but late AMD does (study 1). However, this change was previously concluded to be due to the slightly accelerated atrophy found in early AMD (study 2), even though this is not significantly accelerated compared to controls. This would then be detected in late AMD cross-sectionally (study 1), where late AMD then shows slowing atrophy (study 3). It is possible that accelerated atrophy (middle part of the S shape) occurs

Not for examination. Diagram 3a.



Hypothetical curve of longitudinal atrophy according to the cumulative diffusion model.

Taken from Sabuncu et al. (2011), page 1041.

Not for examination.

Not for examination. Diagram 3b.

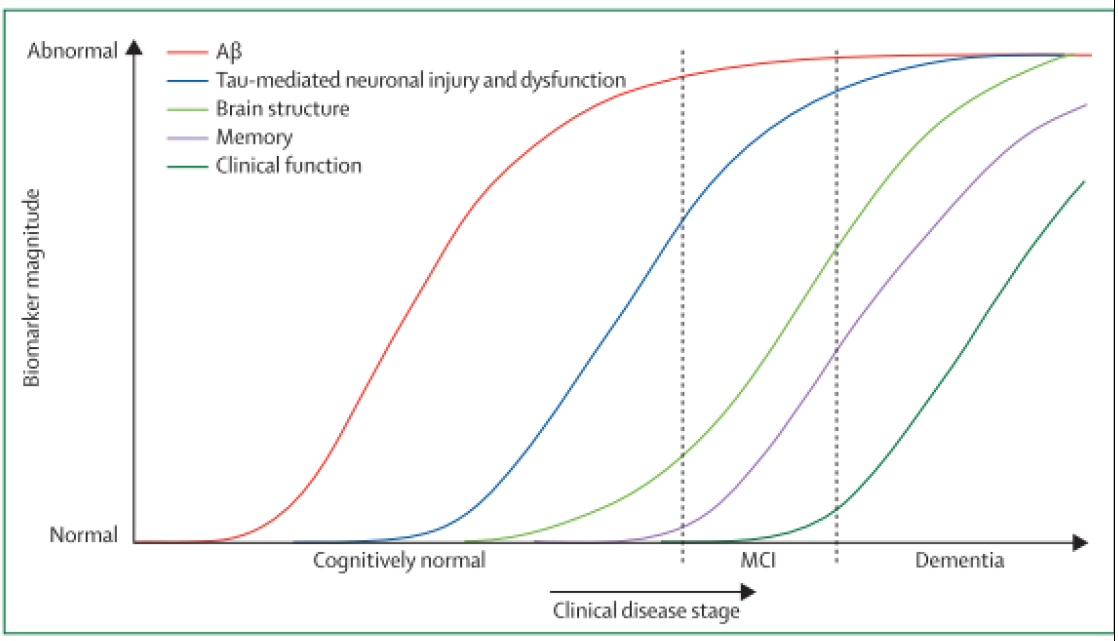


Figure 1: **2010 model of dynamic biomarkers of the Alzheimer's disease pathological cascade**
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose PET. Brain structure is measured by structural MRI. Aβ=amyloid β. MCI=mild cognitive impairment. Reproduced from Jack and colleagues,[18] by permission of Elsevier.

Taken from Jack et al. (2013) page 208, as shown in Jack et al. (2010) page 122.

Not for examination.

between early and late AMD in this study to fully explain the pattern found in this thesis. Applying this to the angular gyrus further shows that an intermediate stage is plausible.

Angular gyrus longitudinal data for early AMD shows a significant deceleration of this region compared to controls where no thinning is found cross-sectionally (study 2). However, late AMD shows near-significantly thinner cortex compared to controls (study 1) but the rates of decline are not different from early AMD (study 3). It could be that the near-significantly thinner cortex in late AMD for angular gyrus is due to an ageing effect; however, these results would also be consistent with accelerated atrophy (middle part of the S shape) in-between early and late AMD explaining the cortical thinning found in late AMD (study 1). This would mean that the decelerated pattern found for early (study 2) and late (study 3) AMD would reflect the bottom of the S shape (early AMD) and top of the S shape (late AMD) respectively.

This plateauing at late AMD, if this is the case, shows that AMD brain changes are not following a pattern to suggest AMD has a direct relationship with AD. Atrophy is starting to decelerate rather than accelerate in the entorhinal cortex and angular gyrus, areas that are known to be affected and have accelerated atrophy from prodromal AD to mild AD. Although cognitive and clinical data is unknown in relation to late AMD participants' cognitive status, it is unlikely they are moving towards moderate AD based on their brain patterns (absence of IFG involvement and brain shrinkage represented by reduced volume) and participants were able to show capacity to take part in an MRI study and lie still in the MRI scanner. It could be argued that, if there is an intermediate stage of AMD following an AD pattern, that the same AD pattern happens to a lesser extent in AMD, where the IFG would be the next affected area with increased duration of patients experiencing late AMD. There is some evidence of this as late AMD shows a medium-to-large effect size for AMD having thinner IFG in study 1 but a small effect for early AMD in study 2.

When comparing this overall pattern with AD, it is evident that AMD does have its own neurodegenerative pattern even if it does share features with AD. Whereas the involvement of occipital pole in late AMD is separate to a pathological neurodegenerative brain change because it is a result of lost visual function, the entorhinal cortex remains a clinically relevant AMD change starting from early AMD. The source of this change, unlike in visually representative areas of the brain, has no known origin other than the presence of AMD itself. A relationship between AMD and AD, based on these findings, would be due to thinner cortices being a risk factor for AD rather than there being a direct relationship.

It can be argued that this research used a stage of AD less likely to be related to the patterns found in AMD and that this research could be repeated in incipient AD as mild AD may be too late in the AD disease course to explore similarities between the two diseases. However, slowing of the entorhinal cortex from early to late AMD is clear evidence that AMD does have a separate pattern to AD, and this is where the similarities between the two groups ends. Furthermore, the angular gyrus is an important region in distinguishing diseases that share neurodegeneration in AD-related regions with AD, from patients that have clinically confirmed AD (Rabinovici et al., 2008; Whitwell et al., 2011). The question of whether there is a direct relationship can be partly answered by this difference as AD is characterised as significant thinning in the entorhinal cortex from incipient AD through to mild AD as shown in study 2 where early mild AD participants are used.

6.3 Brain-behaviour

6.3.1 Summary of findings

Study 4 aimed to see whether activity levels and MoCA scores were associated with cortical measures. AMD had significantly lower scores compared to controls for exercise and lifestyle activity levels, and MoCA scores. The results for activity levels found none of the associations were significant. For exercise, only entorhinal cortex revealed a non-significant positive correlation , while angular gyrus revealed a non-significant negative correlation. Lifestyle activity revealed a non-significant positive correlation with entorhinal cortex and hippocampus, and a non-significant negative correlation with angular gyrus. Only IFG thickness had a significant relationship with MoCA scores, although the association was negative. Participants with thinner IFG cortex scored higher on the MoCA. The results showed some support for the 'use-it-or-lose-it' hypothesis in this sample of participants due to some positive correlations emerging for activity levels and none emerging for cognition.

Structural comparisons of cortical measures between participant groups were not a primary aim of the study and will not be discussed beyond this point, especially as there were only four AMD participants in this analysis.

6.3.2 Brain-behaviour discussion

The findings in study 4 showed that AMD participants had lower levels of exercise and lifestyle activity compared to controls. Reduced activity has been identified as an AD risk factor (Bassuk, Glass, & Berkman, 1999; Kemoun et al., 2010; Kerr et al., 2013; Larson et al., 2006;

Stubbs, Chen, Chang, Sun, & Ku, 2017; Wilson et al., 2002; Zhu et al., 2017). Similarly, higher levels of lifestyle activity is related to preserved cognitive function in older adults with and without dementia (Gronek et al., 2019; Wirth, Haase, Villeneuve, Vogel, & Jagust, 2014). A study that followed participants aged over 65 for 6.2 years found that individuals who exercised three or more times a week had a 32% decreased risk of developing AD compared to those who exercised fewer than three times a week (Larson et al., 2006). Similarly, in a 15-week physical activity program for elderly participants with dementia, increased activity levels slowed cognitive decline (Kemoun et al., 2010). Relating these findings to the exercise activity level results in study 4, it is possible that AMD causes a reduction in activity engaged in, which may contribute to increased AD risk. However, these studies focus on structured exercise or lifestyle-related exercise such as walking, where the effects could differ from cognitive or social aspects of lifestyle activity. Therefore, these previous findings would only apply to exercise activity level findings in study 4. Despite this, studies have found that reading, playing board games, or engaging in musical instruments can help reduce dementia risk (Gronek et al., 2019). This shows that reduced lifestyle activity measured in this study is likely to impact on risk of developing AD to some extent alongside reduced exercise levels.

A correlation was found between exercise and lifestyle activity levels and MoCA scores in study 4 indicating that the 'use-it-or-lose-it' hypothesis is being demonstrated in this study. A previous study on participants with AMD showed that after controlling for other AD risk factors, the number of dropped activities in participants with bilateral AMD was a strong predictor of cognitive decline after three years (Rovner et al., 2009). In participants that dropped three activities they were 3.87 times more likely, and in those who dropped five activities they were 9.54 times more likely, to develop AD compared to participants who didn't drop any activities (Rovner et al., 2009). In Rovner et al.'s (2009) study activity levels did not corelate with cognition at baseline or at the 1-year period in cognitively healthy AMD participants but did later, showing support for the 'use-it-or-lose-it' hypothesis. The main difference between study 4 and Rovner et al. (2009) is that study 4 is devised of controls and AMD participants rather than solely AMD participants. However, this shows that reduced activity levels are a risk factor for developing AD in AMD patients.

6.4 Brain structure and brain-behaviour conclusions

Combining the results across all studies, key findings can be pinpointed and examined to help further understand the relationship between AMD and mild AD. Although brain structure results are limited in how they can be applied to answering this question, the pivotal region is

the entorhinal cortex. This region is proposed to be affected following the sigmoidal shape in AMD prior to visual impairment (studies 1, 2 & 3). The non-significant positive correlation between entorhinal cortex thickness and activity levels shows that decreasing activity levels could have a minimal contributing effect on entorhinal thinning, but not enough to contribute to pathological levels of neurodegeneration.

AMD participants in study 4 were not assessed for stage of disease, rather a confirmed diagnosis was the main requirement for enrolment and their results were combined with controls. It is not clear whether this brain-behaviour relationship for entorhinal cortex and activity would be stronger in a group of participants with only late-stage AMD, or whether activity levels change from diagnosis before vision is affected in early AMD. It could be that activity levels decline from the start of diagnosis and have a minimal long-term negative impact on entorhinal cortex thickness and AD development. Alternatively, it could be argued that because the results show no significant association between cortical thickness and activity levels, the impact of declining activity levels is unlikely to drive the changes found in AMD entorhinal cortex. This could be further supported by hippocampus findings where the association had similar effect size between hippocampal volume and lifestyle activity levels (study 4) but no significant differences were found in hippocampal volume in late AMD (study 1). The data in this thesis is not able to draw strong conclusions on this topic, where further research could provide more convincing evidence for either argument.

Findings that were considered inconsistent across the brain structure and brain-behaviour studies are also important to address. Hippocampus results show a non-significant positive correlation with activity, but no study revealed any involvement of this region in AMD, even in longitudinal analysis (studies 1, 2 & 3). As stated previously, this could be evidence of lower activity levels having minimal impact on volume or could be because volume is not as sensitive as thickness when detecting atrophy. There are unanswered questions as to whether angular gyrus is involved in AMD (studies 1, 2 & 3). If further research showed that this region revealed cortical thinning, either cross-sectionally or longitudinally, then the impact of activity in relation to thickness should be reassessed. The results show that reduced activity levels do not contribute to angular gyrus cortical thinning, showing a non-significant negative correlation between them (study 4). Overall, the results show that the angular gyrus is not affected in AMD and the impact of activity on cortical thinning is not in the expected direction. If reduced activity levels are not associated with thinner cortex, it suggests angular gyrus thinning in AMD is due to another factor and is a possible indicator of prodromal AD. This region was previously identified as a critical region in deciphering AD from other disease (Johnson et al., 2012)

especially as non-AD diseases can have MTL atrophy as part of their neurodegenerative pattern (Barber et al., 2000; Burton et al., 2009; Chan et al., 2001; Fjell & Walhovd, 2010; McKeith et al., 2005).

The IFG and occipital pole are also not related to activity levels. Due to the preservation effect found in the IFG longitudinally, the relationship between possible external drivers and cortical thinning is likely complex. This complexity is demonstrated in IFG thickness as it is unlikely to reveal a difference from normal ageing cross-sectionally, but their external behaviours may be altered (e.g., lower MoCA scores in mild AD). This complex relationship may have resulted in the non-significant findings for IFG. However, this finding does not support the 'use-it-or-lose-it' hypothesis, suggesting this relationship is only found in MTL regions in this participant group. For the occipital pole, the results confirm that any thinning of this region will be because of a loss of visual function rather than related to activity levels. It also shows that occipital pole thickness cannot act as a proxy for measuring disease stage in AMD. A better measure would be contrast sensitivity because it has already been found that visual acuity does not correlate with cognitive score (Clemons et al., 2006; Demırcı et al., 2015) or activity levels (Heinemann et al., 2019).

Overall, the main conclusion is that activity levels were significantly lower but were not significantly associated with cortical measures or determined to be the driver of cortical thinning found in AMD entorhinal cortex. Therefore, these measures are unlikely to contribute to cortical thinning that could increase susceptibility to AD due to thinner cortices (Verfaillie et al., 2016). It is important to remember that reduced activity levels are a known risk factor for AD, and it may be that this effect is stronger in long-term late AMD or would be found in a study that has a larger sample size of purely AMD participants.

6.5 Reviewing the relationship between AMD and mild AD

An increased prevalence of AMD in AD and vice versa was found in the literature previously. In study 2, a binomial test showed there was an increased prevalence of AD in the full (cognitively normal, MRI) ADNI AMD sample than is expected in the general population. This would offer support for there being a direct relationship between AD and AMD. The increased prevalence of AD in AMD, however, could be due to bias related to the data source. Individuals who have a family member affected by AD may be more likely to take part in studies relating to AD, and family history of disease can increase risk of developing AD (Cannon-Albright et al., 2019; Donix et al., 2012).

The contribution of sampling bias was unable to be checked using the cognitively normal controls from ADNI in study 2. Cognitively normal participants were screened to ensure they remained cognitively healthy throughout the cross-sectional and longitudinal study. A different method was used in study 1, where participants scored 30 out of 30 on the MMSE to ensure optimal cognitive ability (because an option to select participant group was not available with that beta search function). This means the two cognitively healthy participant groups from ADNI (studies 1 & 2) would not reflect the wider, randomly selected sample of cognitively healthy participants in ADNI. However, conversion rates to MCI and AD are similar between the AMD and controls in study 2, indicating that sampling bias may be reflected in the binomial test.

Cortical thinning is more sensitive to age-related changes than volume and therefore more likely to detect early pathological changes. The distinct lack of volume involvement in AMD (studies 1 & 2) when entorhinal cortex thickness is showing deceleration of atrophy (studies 1 & 3) is not consistent with AD, where widespread volume decrease is a notable feature of disease. The decision to exclude investigating volume from studies 3 and 4 was based on the findings that AMD showed no difference for volume from controls in studies 1 and 2, and it did not contribute to the overall conclusions earlier in this discussion. In AD, although cortical thinning precedes changes in volume, the results follow the same trend showing a general loss of volume across the disease course. This is evident where volume is smaller in prodromal AD because of the nature of the pathological effects of tau and amyloid in the brain reducing area as well as cortical thickness (Prestia et al., 2013). Although this thesis did not measure amyloid or tau in AMD participants, it is unclear what mechanism is behind cortical thinning observed in AMD and whether this would impact volume. Volume is estimated using area as well as thickness and each is biologically distinct from the other.

To be consistent with AD, late AMD participants would have had to have shown some involvement of entorhinal cortex volume. This was not found in study 1, where participants were in late-stage AMD and a small-to-medium effect size was found for smaller entorhinal cortex volume compared to controls. It is possible that the issues explored in section 1.2.3 about using volume as a measure was not relevant here (that different regions have varying relationships between volume and total intracranial volume, and the relationship between volume and total intracranial volume is reduced in older age, usually factors that confound results). If these potential issues associated with correcting with total intracranial volume do not apply, then under-correcting volume can hide true effects (Im et al., 2008; Schwarz et al., 2016). Differences may have been detected had volume measures been adjusted with total

intracranial volume. However, smaller volume was detected in AD using this same method, suggesting any underestimation of volume atrophy would not be significant and would have been revealed in AMD. This is further supported as there were no significant differences in TIV between participant groups in any of the studies. Based on the findings in this thesis, due to the absence of volume involvement and diverging cortical thickness patterns, brain structure is not considered strong evidence for shared clinical features between AMD and AD.

6.6 Limitations and future research

The primary limitation for forming final conclusions is that study 4 did not fully answer the question of whether lower activity levels contribute to AMD participants brain structure, and subsequently their potential susceptibility to AD. This still needs to be addressed as a central question for the AMD with mild AD relationship debate. Similarly, the contribution of volume should be assessed to see whether using a different method of handling volume estimates produces different findings.

Future research could follow the brain pattern of AMD participants over time whilst assessing their cognitive ability on the MoCA and measuring their physical activity to see if these factors do contribute to AD risk. It has been suggested that some AD neurodegeneration patterns are found in waves as well as with a sigmoid shape. The deceleration of the entorhinal cortex in these late AMD participants could indicate the end of a wave of cortical thinning before another one begins. Further research could better assess the overall pattern of neurodegeneration found in AMD that is beyond the scope of this thesis.

Although expensive to conduct, measuring amyloid beta or tau within the brains of AMD participants would help draw stronger conclusions on whether AMD and AD are related, and help unravel the mechanism behind AMD entorhinal cortex thinning.

6.7 Final conclusions

The combined results from this thesis show that although AMD and AD share many neurodegenerative and cognitive features, they follow slightly different trajectories that may be modified depending on the stage and progression of AMD.

The regions that follow neurodegenerative patterns considered to be shared with AD are the entorhinal cortex and IFG cortical thickness. For the IFG, the non-significantly slower atrophy across time could be the sign of a sigmoidal shape in the time course of changes, where this area will show more thinning, cross-sectionally, nearer to late AMD (some indication of this

can be seen in late AMD in study 1), with slower atrophy in early AMD and plateauing in late AMD (study 3). However, this preservation pattern could be found in AMD regardless of whether there is a relationship with AD as this process is minimal and slow, where no significant findings are found in longitudinal or cross-sectional analysis for IFG. The entorhinal cortex is similar in that it is showing shared patterns with AD, but this is likely to be AMD-specific neurodegeneration, especially as the decelerated thinning in late AMD is not consistent with a relationship between AD and AMD.

The other regions explored in this thesis do not align with an AMD-AD relationship. Limited conclusions can be drawn about the hippocampus because it is measured in volume, a cortical measure not affected in AMD in this thesis. Although cortical thickness is a more sensitive measure to use, the complete absence of reduced volume in studies 1 and 2 show that AMD is unlike AD, where volume is affected in prodromal AD alongside cortical thinning. The angular gyrus is important in identifying AD-related atrophy. For AMD to follow AD patterns, the angular gyrus should follow consistent thinning across the disease course to align with the thinning found in late AMD in study 1. This was not evident from the findings in study 2. The occipital pole is not involved in AD but is involved in AMD as a result of a loss of functional vision. The longitudinal results from early and late AMD participants highlighted that atrophy moves from entorhinal cortex to occipital pole.

Activity levels are significantly reduced in the current AMD sample. Reduced activity levels are a risk factor for AD, and in AMD this risk occurs to the same extent as that found in the general population. This is revealed by the findings in study 4 where similar trajectories are found across the AMD and control group with no significant associations found between activity levels and cortical measures. The significantly reduced MoCA scores show that cognitive impairment is found in AMD possibly due to AMD-specific thinning found in the entorhinal cortex and cortical preservation of the IFG.

Overall, this thesis shows that the similarities between AMD and mild AD do not support a direct link between AMD with mild AD. However, it seems that those who are diagnosed with AMD are more likely to face several risk factors for AD than may be present in the general population. Depending on individual response to AMD (whether someone adapts to new activities or maintains their current activity levels) alongside other risk factors (family history of disease, smoker or non-smoker, amount of cognitive reserve, for example) their individual chance of developing AD will be stronger or weaker than others. This could explain the mixed findings in earlier prevalence studies. The unique finding in this thesis is that AMD appears to

have its own neurodegenerative process in the brain that is associated with cognitive impairment.

Appendices

Appendix A – MoCA script

Visuospatial/Executive (point to the relevant sections)

- Alternating Trail Making:

"Please draw a line going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

- Cube:

“Copy this drawing as accurately as you can.”

- Clock:

Ensure the participant does not look at their watch and that no clocks are in sight.

“Draw a clock. Put in all the numbers and set the time to 10 past 11”

Naming:

“Tell me the name of this animal”

Lion Rhino Camel

Memory:

“This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn’t matter in what order you say them.” Read 1 per second

MEMORY	Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.		FACE	VELVET	CHURCH	DAISY	RED	No points
		1st trial						
		2nd trial						

“I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time”

“I will ask you to recall those words again at the end of the test”

ATTENTION	Read list of digits (1 digit/ sec.).	Subject has to repeat them in the forward order	[ ] 2 1 8 5 4	__/2
		Subject has to repeat them in the backward order	[ ] 7 4 2	

“I am going to say some numbers and when I am through, repeat them to me exactly as I said them”

“Now I am going to say some more numbers, but when I am through you must repeat them to me in the backward order” Record first answer.

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B	__/1

"I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand" Read 1 per second

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65 4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**	__/3

"Now, I will ask you to count by subtracting 7 from 100, and then, keep subtracting 7 from your answer until I tell you to stop."

LANGUAGE	Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]	__/2

"I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: I only know that John is the one to help today."

"Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: The cat always hid under the couch when dogs were in the room."

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)	__/1

"Now, I want you to tell me as many words as you can think of that begin with the letter F. I will tell you to stop after one minute. Are you ready? [Pause. Time for 60 sec.]

Stop."

If the subject names two consecutive words that begin with another letter of the alphabet, the examiner repeats the target letter if the instructions have not yet been repeated.

ORIENTATION	[ ] Date	[ ] Month	[ ] Year	[ ] Day	[ ] Place	[ ] City	__/6

Temporal orientation

"What is todays date?" Year Month Date Season

"Tell me the exact day of the week."

Spatial orientation

"What _____ are we in?"

Country County City

"Are we in a store, University, or home?" Answer:

DELAYED RECALL	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	__/5
Optional	Category cue							
	Multiple choice cue							

1) Free recall

"I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember."

2) Category cue

''I will give you some hints to see if it helps you remember the words, the first word was a body part.''

3) Multiple choice

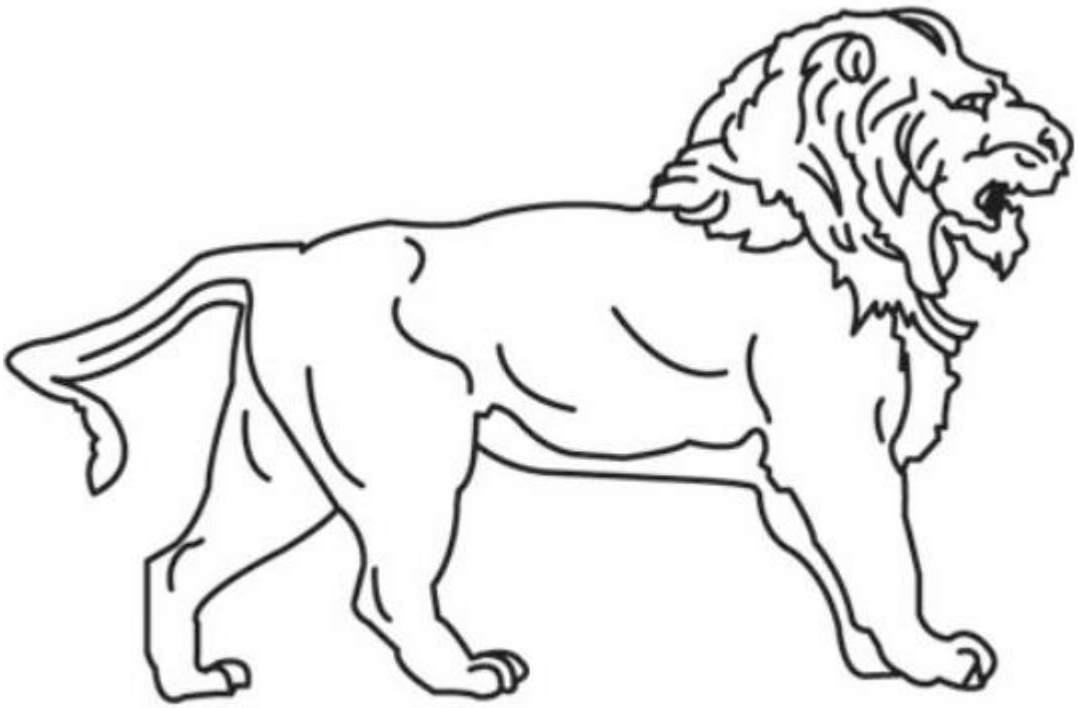
"Which of the following words do you think it was, NOSE, FACE, or HAND?"

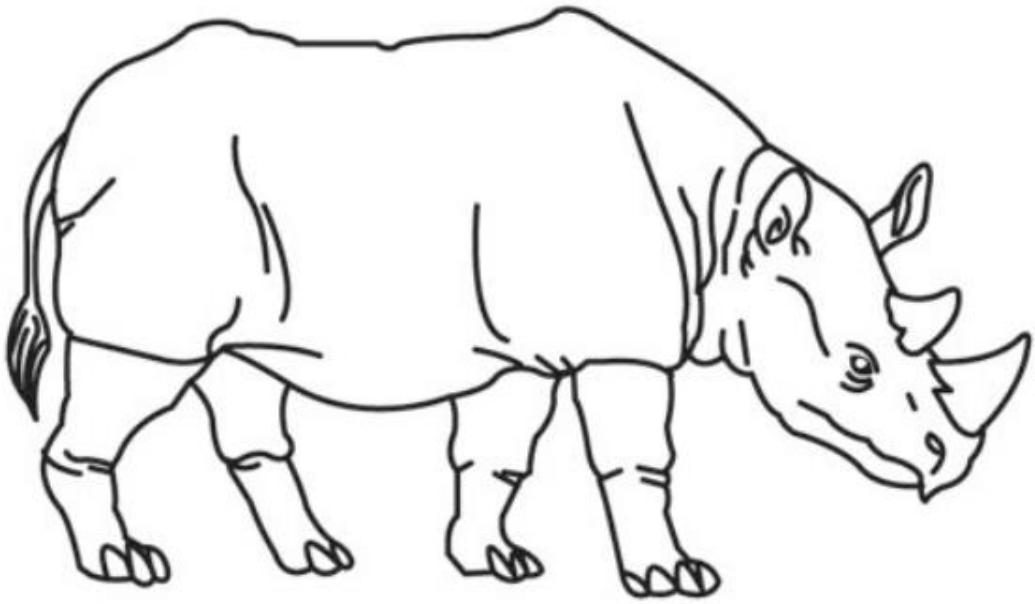
Word	Category cue	Multiple choice
FACE	body part	nose, face, hand (shoulder, leg)
VELVET	type of fabric	denim, velvet, cotton (nylon, silk)
CHURCH	type of building	church, school, hospital (library, store)
DAISY	type of flower	rose, daisy, tulip (lily, daffodil)
RED	colour	red, blue, green (yellow, purple)

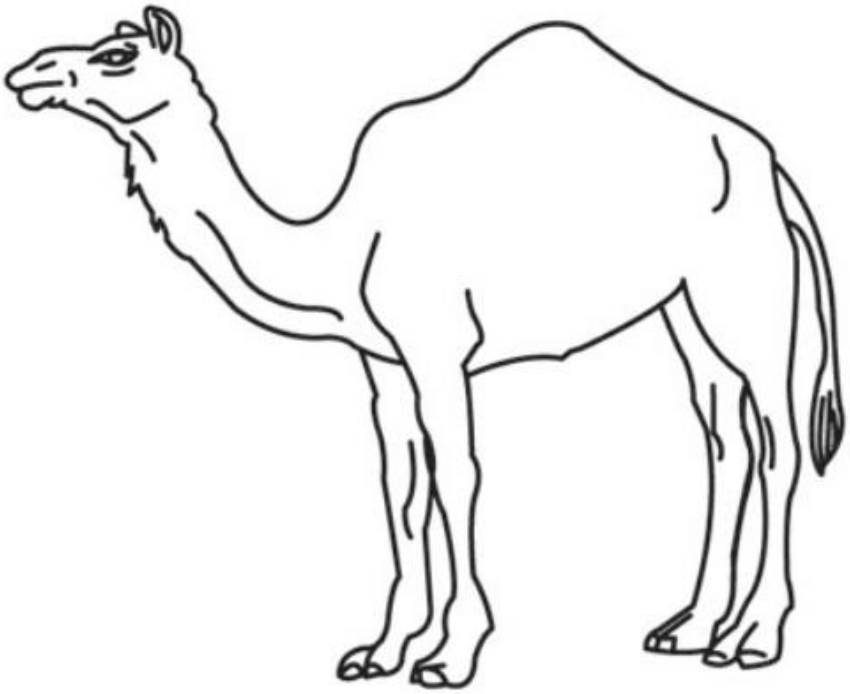
* The words in parentheses are to be used if the subject mentions one or two of the multiple choice responses during the category cuing.

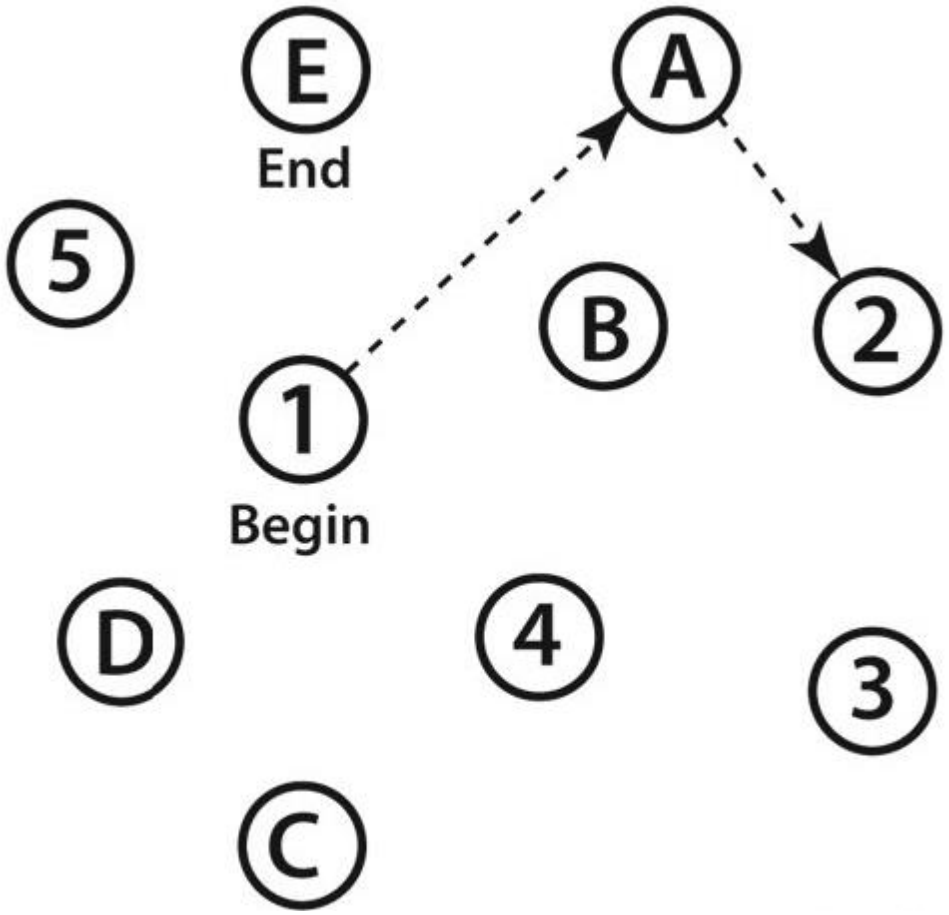
"How many years were you in education?" Answer:

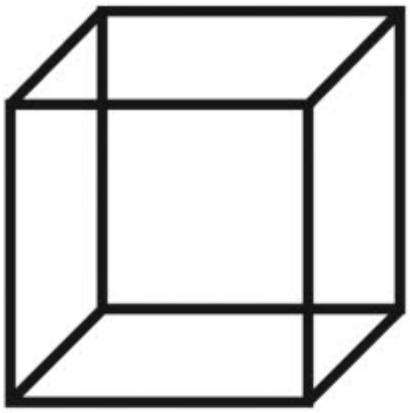
Appendix B – Modified MoCA drawings








E
End
A
5
B
2
1
Begin
D
4
3
C



Copy
cube

Draw CLOCK (Ten past eleven)
(3 points)

Appendix C – Activity questionnaire

ACTIVITIES QUESTIONNAIRE

Our lives are organized to a great extent by the types of activities we participate in. In this questionnaire, you will find a list of activities that different people do in their everyday lives.

You may never have participated in some of these activities. Others you may have participated in several years ago. In this questionnaire, we would like you to tell us how many of these activities you have participated in within the last two years.

You will be asked to indicate how often you engage in each activity. Do not worry if you cannot give an exact figure. Circle the letter that MOST NEARLY describes the frequency with which you have done the activity during the past two years.

Here is an example:

I go shopping at a mall or downtown:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

Let's assume that you go to a mall or downtown once or twice a month most of the time. There may have been a month when you did not go at all, or there may have been a month when you went more often. But once or twice a month most nearly describes what you usually have done over the last two years. Thus alternative f is circled.

For each of the activities listed on the following pages, please circle the letter that most nearly describes the frequency with which you have participated in them during the last two years.

1. I do household repairs (for example, painting, leaky faucets):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

2. I repair a mechanical device (for example, a car or lawn mower):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

3. I purchase a new item requiring some set-up or assembly:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

4. I do woodworking, carpentry, or furniture refinishing:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

5. I play a musical instrument:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

6. I engage in creative writing, writing poems, writing:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

7. I engage in photography:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

8. I collect stamps, coins, dolls, or other memorabilia (also: films, clips, music, stones)

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

9. I engage in sewing, knitting, or needlework:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

10. I garden indoors or outdoors:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

11. I engage in exercise activities (for example, jogging, swimming, bicycling, or walking):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

12. I engage in outdoor activities (for example, sailing, fishing, or backpacking):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

13. I engage in recreational sports (for example, tennis, bowling, or golf):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

14. I do aerobics (for example, cardiovascular, fitness training, workout):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

15. I do flexibility training (for example, stretching, yoga, tai chi):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

16. I do weight lifting, strength training, or calisthenics:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

17. I work crossword puzzles, acrostics, or anagrams:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

18. I play card games (for example, Pinochle or Bridge):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

19. I do jigsaw puzzles:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

20. I play board games (for example, chess or checkers):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

21. I play knowledge games (for example, Trivial Pursuit):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

22. I play word games (for example, Scrabble):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

23. I read newspapers:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

24. I read books or magazines for leisure:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

25. I read books or magazines as part of my job, career, or formal education:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

26. I go to the library:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

27. I watch news programs on television:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

28. I watch documentary or educational programs on television:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

29. I watch game shows on television (for example, Wheel of Fortune or Jeopardy):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

30. I watch comedy, or adventure programs on television:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

31. I write a letter (for example, to a friend, relative, business, etc.; also includes electronic mail such as email, but must be longer and substantial):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

32. I use pre-programmed software on a personal computer (for example, MS Word, Word

Perfect, Eudora, or Netscape):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

33. I use an electronic calculator:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

34. I prepare my own income taxes:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

35. I do arithmetic or mathematical calculations:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

36. I attend films (for example, travel films, commercial movies, etc.):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

37. I attend a public lecture or talk:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

38. I eat out at a restaurant:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

39. I talk on the phone to friends, or relatives:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

40. I visit relatives, friends, or neighbours:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

41. I go out with friends:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

42. I attend parties (e.g., birthday party):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

43. I give a dinner or a party for friends:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

44. I attend church services or synagogue:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

45. I engage in prayer, meditation, or philosophical contemplation:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

46. I attend meetings of clubs (for example, hobby club, book club, discussion club):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

47. I attend organized social events (e.g., activities at the senior centre, fraternity events, church social groups):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

48. I engage in political activities (e.g., neighbourhood organization, environmental club):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

49. I give a public talk or lecture (for example, to a club, service organization, etc.):

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

50. I do volunteer work for an organization (for example, a hospital, church, school, or political party:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

51. I engage in business activities such as investments or real estate transactions not related to my job or career:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

52. I engage in an on-the-job training program:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

53. I enrol in a course at a college or university:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

54. I study or practice a language other than my native tongue:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

55. I travel away from my home to other places in the [UK]

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

56. I travel outside my town to other places in my [county]:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

57. I travel in a foreign country:

a. Never
b. Less than once a year
c. About once a year
d. 2 or 3 times a year
e. About once a month
f. 2 or 3 times a month
g. About once a week
h. 2 or 3 times a week
i. Daily

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Abbreviations

ADNI	Alzheimer's Disease Neuroimaging Initiative
YNiC	York Neuroimaging Centre (University of York)
AD	Alzheimer's Disease
AMD	Age-related macular degeneration
MCI	Mild cognitive impairment
DXSUM_PDXCONV_ADNIALL.csv	Participants' demographic and cognitive details
DXCURRENT	In the DXSUM_PDXCONV_ADNIALL.csv document, indicating the current cognitive state of participants. 1 = cognitively healthy; 2 = Mild cognitive impairment; and 3 = AD.
DXAD	In the DXSUM_PDXCONV_ADNIALL.csv document, indicating the diagnosis of AD given. 1 = probable; 2 = possible
RECMHIST.csv	Recent medical history
MEDHIST.csv	Medical history
MoCA	Montreal Cognitive Assessment
MMSE	Mini-Mental State Examination
IFG	Inferior frontal gyrus
MTL	Medial temporal lobe
TIV	Total intracranial volume
RPE	Retinal pigment epithelium
ANOVA	Analysis of variance

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