Investigating how *APOE* differentially affects memory and perception of ambiguous scenes in young- and middle-aged adults

A thesis submitted for the degree of Doctor of Philosophy

by

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September 2018

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ACKNOWLEDGMENTS

Completing my PhD would not have been possible without the kind support of my colleagues, friends, and family. I will be forever grateful to my supervisor Kim Graham for your support and guidance throughout my PhD. I am especially thankful for the time you have put in over the last few months to help me achieve this thesis, despite your commitments to your family and new job.

The research I have carried out over the last four years has very much been part of a team effort and I will forever enjoy the memories of working alongside such an amazing group of people. Thank you to Andrew Lawrence for always having insightful advice when it was needed most. Thanks also to Carl, Katja, and Mark for always being there when I hit a brick wall. To Rebecca, Beth, Hannah, Martina, Alison, Steph, and Erika, I thoroughly enjoyed sharing an office with you all for the first few years and will miss the office antics, random debates, and much needed pick-me-ups that helped on those long days of data collection. I would also like to thank the many friends I have made in CUBRIC over the years who have made the last four years go by with so much laughter. I will miss working with you all and hope you will all keep in touch.

I would also like to thank Jenny Rusted and her lab at the University of Sussex for kindly hosting me in Brighton during our collaboration. You made me feel incredibly welcome and I had a fantastic time working (and socialising) with you all. I also offer a particularly big thank you to all of the participants, in both Cardiff and Brighton, who so kindly volunteered their time to take part in my research. Without you generously giving up your time and effort this thesis would not have been possible.

Thanks as well to the many friends I have made in Cardiff over the years. I particularly couldn't have done this without the love and support of Laura, Dan, Andrea, Sam, Kelly, Lowri, Ben, Alex, Nia, Jon and Becky. I couldn't have wished for a more amazing group of friends to take my mind off the PhD stresses. Dan, thanks for putting up with me as a housemate for as long as you did and for all of your support, particularly in those final months. Laura, we started at the same time and finished at the same time and have had so many amazing times along the way; thanks for always being there when a bottle of wine seemed like the only fix!

Finally, I will always be grateful to my family whose encouragement and belief carried me along this journey. A huge thank you goes to my amazing mum who has always been there on the end of the phone when I needed her the most, bailed me out when the student stipend was running low, and whose grit and determination in life has taught me that anything is possible if you work hard enough for it.

THESIS SUMMARY

My thesis investigated whether performance on complex scene and object perceptual and memory tasks would be influenced by possession of different variants of the *APOE* gene. A particular focus was on the effect of the *APOE*-ε4 allele on scene processing. *APOE*-ε4 is known to increase risk for Alzheimer's disease (AD) in later life and is associated with structural and functional changes in the medial temporal lobe (MTL) and posteromedial cortex, regions known to be affected early in AD. Previous studies have shown sensitivity to spatial processing in AD, including difficulties in differentiating scene, but not object, stimuli (Lee et al., 2006), impairments remembering scenes over a delay (Bird et al., 2010), and deficits in navigation around spatial environments (Pengas et al., 2010). These findings suggest that difficulties with complex spatial processing may be a hallmark of AD, and that investigation of scene processing in individuals at greater risk of developing AD later in life may be of interest in understanding the genesis of these later life cognitive impairments.

In Chapter 1, I provide an overview of relevant literature on the *APOE* gene and its relationship to AD, and discuss experiments which have demonstrated brain and behaviour differences between *APOE*-ε4 carriers and non-carriers. I interpret these findings in the context of recent models of memory which focus on representational networks, and where distinctions between scene and object processing are a key feature (Bussey & Saksida, 2007; Graham, Barense, & Lee, 2010; Murray, Wise, & Graham, 2017). The subsequent chapters describe experiments which aimed to extend the research described in Chapter 1 by investigating scene perception and memory in carriers of different *APOE* alleles in early- and mid-adulthood. In Chapter 2, I describe findings from applying a novel conjunctive learning task, in which participants were required to discriminate between objects and scenes. In Chapter 3, I report results from applying a new visual paired-comparison task in the same group of participants. Chapter 4 extends the approach outlined in Chapter 3, using the visual paired-comparison task in middle-aged participants, again focusing on the comparison of performance in groups with different *APOE* genotypes. Finally, in Chapter 5, I assess how performance in the tasks used in Chapters 2-4 are related to the volumes of brain regions (in the MTL and extrastriate cortex). As these have been strongly linked to object and scene perception and memory, I was interested in whether volume would be associated with performance on my new tasks. The final chapter summarises the experimental findings from Chapters 2-5 and explains how these build upon our current body of knowledge about how the *APOE* gene affects cognition in both early- and mid-adulthood.

CONTENTS

CHAPTER 1 – GENERAL INTRODUCTION

1.1 Alzheimer's disease and the amyloid-cascade hypothesis

Alzheimer's disease (AD) is a chronic neurodegenerative disease, and is the most common cause of dementia (defined as the progressive loss of cognitive ability) world-wide (Alzheimer's Disease International, 2015). The most recognisable symptom is usually the gradual onset of memory impairment, including forgetting recent events or conversations, misplacing items, and having trouble remembering names of people and places (NHS England, 2018). There are, however, multiple variants that can begin with other symptoms, such as visuospatial disruption (posterior cortical atrophy), attention and executive function impairment (familial AD), or language impairment (logopenic AD), depending on the extent of damage in different brain regions and networks (Lehmann et al., 2013). As AD progresses, patients show greater disruption in cognition, including disorientation, disordered speech and language impairments, personality changes, and mood swings (NHS England, 2018). There are an estimated 50 million people world-wide affected by AD and other dementias, and that number is expected to triple by 2050 (Alzheimer's Disease International, 2015). Concerns about the social and economic impact of the disease have brought AD to the forefront of health research policy, with recent efforts to prevent and/or cure the disease becoming globalised (e.g. World Dementia Council, 2017).

AD is characterised by the presence of two main pathological markers in the brain (Selkoe, 1991): 'plaques' (a large sticky build-up of the amyloid-beta (Aβ) protein) and 'tangles' (excessive levels of tau protein resulting in the formation of neurofibrillary tangles). Extensive plaque deposition leads to vascular damage and neuronal cell loss (Hardy & Higgins, 1992). In turn, this results in the specific cognitive impairments noted above, with the striking impairment in memory seen in many individuals with the disease, making it distinguishable from other types of dementia (Karantzoulis & Galvin, 2011). Alois Alzheimer, the Bavarian psychiatrist who first defined the syndrome,

reported the symptoms of his patient, referred to as August D, as being "progressive memory impairment; disordered cognitive function; altered behaviour including paranoia, delusions, and loss of social appropriateness; and a progressive decline in language function" (Selkoe, 2001). Although Alzheimer originally coined AD to refer to 'pre-senile' dementia—as August D was much younger than would be expected for senile dementia—we now know that he was observing familial (or early-onset) AD (Müller, Winter, & Graeber, 2013), which is very similar to sporadic (or late-onset) AD but occurs in individuals under the age of 65.

In the UK, when individuals initially start becoming worried about potential cognitive change, but where this is not yet sufficient for a clinical diagnosis of a major cognitive disorder, such as AD, patients are often diagnosed with mild cognitive disorder. This is also known as mild neurocognitive disorder (American Psychiatric Association, 2013) or, more commonly, as mild cognitive impairment (MCI). Patients with MCI are characterized by "[an] impairment of memory, learning difficulties, and reduced ability to concentrate on a task for more than brief periods" (World Health Organization, 2016). In cases where an MCI patient has a cognitive deficit where the dominant problem is memory (amnesic-MCI, or aMCI), it is often considered to be the prodrome to AD (Petersen & Morris, 2005; Sachs-Ericsson & Blazer, 2015). Research over the last two decades or so has focused on this early prodromal state, in particular identification of those individuals at greatest risk of converting (declining cognitively) to more obviously fit the pattern typically associated with AD. Conversion rates from MCI to dementia (broadly defined, including AD) greatly vary from around 20% to over 60% depending on the sample investigated and the length of time following diagnosis (Ganguli, Dodge, Shen, & DeKosky, 2004; Morris et al., 2001; Wolf et al., 1998; Sun, van de Giessen, Lelieveldt, & Staring, 2017). Greater conversion is seen in samples where individuals sought treatment compared to those sampling from the general population (Crocco & Loewenstein, 2005; Sachs-Ericsson & Blazer, 2015). A 2008 meta-analysis of fifteen studies estimated that the conversion rate specifically from MCI to AD was 31.4% (Mitchell & Shiri-Feshki, 2008).

Arguably the most dominant model of AD pathogenesis has been the amyloid cascade hypothesis (Hardy & Higgins, 1992; Selkoe, 1991; Selkoe & Hardy, 2016). The theory posits that AD pathology begins with inadequate processing of the Aß42 protein, which eventually results in cognitive decline and dementia. More specifically, it is argued that increased brain activity in specific brain regions triggers amyloid precursor protein (APP) to cleave into Aß peptides, which then oligomerize to form soluble Aß, thought to be the most toxic Aß species (McLean et al., 1999). These soluble Aß oligomers form fibrils, which are the main component of the Aß plaques. Cellular responses to this then accelerate the formation of neurofibrillary tangles and subsequent tau accumulation, which disrupts neuronal functioning and eventually leads to cell death (see Figure 1.1). Selkoe and Hardy (2016) argue that this neurodegeneration may begin between 20-30 years prior to clinical diagnosis. Others posit that the accumulation of Aß42 is a life-long process in some cases, such as in individuals with a genetic predisposition to AD (Jagust & Mormino, 2011). These individuals may have genes that either increase the relative production of Aß42 (e.g. presenilin-1 (*PSEN1)* or 2 (*PSEN2*) genes), or genes that are inefficient at clearing Aß (such as *APOE*-ε4), resulting in the gradual relative rising of Aß42.

Support for the amyloid cascade hypothesis has increased with the accrual of many clinical and preclinical studies, as well as large-scale genome-wide association studies (GWAS) studies (for review, see Selkoe & Hardy, 2016). A more extensive summary of work on the relationship between genes and AD is covered later (in section 1.3), but the identification of a number of risk genes for AD that are implicated in the accumulation or clearance of Aß (see Figure 1.1), suggests a dominant role of Aß accumulation in the pathogenesis of AD. This is further supported by the prevalence of mutations in genes that encode proteins directly involved in the production and cleavage of APP into Aß peptides, such as *APP* or *PSEN1*/2, in individuals with autosomal dominant AD (Ricciarelli & Fedele, 2017). The argument is also augmented by the increased proportion of individuals with Down syndrome—which is attributed

to the triplication and overexpression of the *APP* gene (Glenner & Wong, 1984; D. Hartley et al., 2015)—developing AD in early life (Ricciarelli & Fedele, 2017).

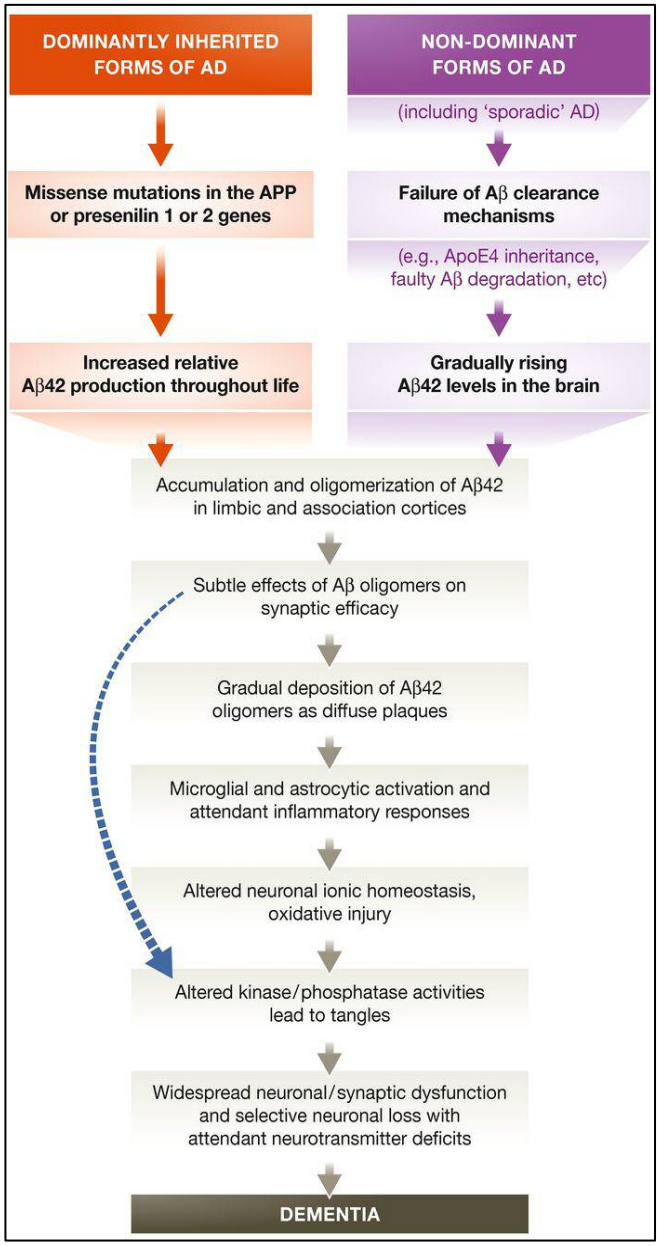

Figure 1.1 – The sequence of major pathogenic events leading to AD proposed by the amyloid cascade hypothesis (Selkoe & Hardy, 2016).

This model is not without contention, however, with some arguing that its hierarchical structure is often not supported by the data (e.g. Herrup, 2015). A number of studies fail to find any association between AD-related cognitive impairment and A*ß* accumulation (Aizenstein et al., 2008; Delaère et al., 1990; Dickson et al., 1992; Fagan et

al., 2009; Katzman et al., 1988; Klunk et al., 2009; Villemagne et al., 2011). For example, Aizenstein et al. (2008) used positive emission tomography (PET) imaging to measure the extent of A*ß* deposition in elderly healthy individuals and separated them into dichotomous groups (amyloid-positive vs amyloid-negative). They found no significant decreases in cognitive performance in the amyloid-positive (compared to the amyloid-negative) group, and even found increased performance on a delayed recall test in the amyloid-positive group. Villemagne et al. (2011) also used positive emission tomography (PET) imaging to measure A*ß* deposition in 239 individuals and compared this with performance on a battery of cognitive tests. They found only a weak relationship between A*ß* burden and cognitive decline, however they did find the A*ß* was predictive of future cognitive decline, suggesting that the downstream effects of A*ß* accumulation may have a more direct effect on AD-related impairment.

There is also criticism regarding the over reliance on transgenic mouse models in support of A*ß*-centric pathological hypotheses (Ricciarelli & Fedele, 2017). Even though sporadic AD makes up over 95% of AD cases, transgenic mouse models often use mutations found in familial AD, which may have distinctive disease progression and cognitive symptoms (Farrer et al., 1990). Mice also appear to respond differently to gene-expression, for example, *APP* and *APP*/*PEN1* mice both overexpress APP (compared to humans), fail to present the tangles and neuronal death that occurs in AD patients, and exhibit reversible cognitive damage, none of which translate across to AD patients (Ricciarelli & Fedele, 2017).

Another focus of contention is the lack of efficacy in anti-A*ß* vaccines, with trials of both active (Farlow et al., 2015; Holmes et al., 2008; Pasquier et al., 2016) and passive (Salloway et al., 2014; Schwarz et al., 2017) immunisations to date reporting no reliable differences in cognitive evaluations. An example of this can be seen in the EXPEDITION3 study (Honig et al., 2016; Schwarz et al., 2017), which used an antibody directed against A*ß* peptides. Despite some improvements to cognition and a reduction in atrophy in the right hippocampus (HC), phase III trials revealed only small differences

in cognition between treatment and placebo groups, using the ADAS-Cog, and so the trial was deemed to be unsuccessful. Although this is seen as evidence against the amyloid cascade hypothesis, it is possible that the lack of effects in anti-A*ß* vaccine trials is due to the overreliance on a single, and relatively outdated, cognitive measure. A later study (Wessels, Matthews, Dowsett, Andersen, & Siemers, 2017) reassessed the data using a combined score from both ADAS-Cog and the Alzheimer's Disease Cooperative Study - instrumental Activities of Daily Living (ADCS-iADL) (Galasko et al., 1997), and found a greater effect of the treatment, increasing over time. This demonstrates that even a small adjustment to the validating measure can have a profound effect on the interpretation of the result. Further, if the impact of A*ß* starts much earlier than we previously thought, decades in advance of the onset of overt cognitive decline, it is possible that anti-A*ß* vaccinations may be being given too late in the disease to result in major positive cognitive changes.

Overcoming the limitations of clinical cognitive tests (such as the ADAS-Cog) becomes increasingly important as the target shifts further away from clinical diagnosis and into much earlier stages of disease pathology. Early and accurate identification of those with a high likelihood of developing AD could provide a number of benefits: Firstly, it would allow the individual to plan ahead and receive practical advice and information while they still have the capacity to make decisions. Secondly, determining and implementing treatments earlier in the lifespan is likely to have more beneficial effects in terms of delaying or preventing neurodegeneration. Thirdly, it enables researchers to progress understanding of how the disease develops. Finding reliable methods of predicting AD earlier on in the lifespan prior to the onset of any cognitive decline (e.g. pre the prodromal phase of AD) could have considerable benefits for patients and society (Alzheimer's Disease International, 2018; Heerema, 2018).

1.2 Impairment of spatial memory in Alzheimer's disease

Arguably one of the biggest problems with clinical tests for AD is an overreliance on the assumption that the primary failure in AD is related to memory failure. Although AD is typically associated with impairments in declarative memory (NHS England, 2018), there are a number of studies that report deficits in AD patients that are specific to spatial memory and learning (Bird et al., 2010; Cherrier, Mendez, & Perryman, 2001; deIpolyi, Rankin, Mucke, Miller, & Gorno-Tempini, 2007; Kalová, Vlcek, Jarolímová, & Bures, 2005; Moodley et al., 2015; Morganti, Stefanini, & Riva, 2013; Pengas et al., 2010). Perhaps one of the most popular tests of spatial memory is the Morris water-maze (Morris, 1984). This task typically requires rodents to navigate around a pool of murky water to find a non-visible platform. Sensory cues are usually placed around the pool, providing allocentric reference points with which the rodent can calculate its position relative to the target. Studies in rats have found this task to be preferentially demanding on the HC (for review, see D'Hooge & De Deyn, 2001), which is a brain region that is recruited during tasks involving spatial perception and memory (Bussey & Saksida, 2007; Graham et al., 2010; Murray et al., 2017) and is thought to be affected early in AD (Dubois et al., 2016; Visser, Verhey, Hofman, Scheltens, & Jolles, 2002).

Virtual reality equivalents of the Morris water-maze have been used in human studies, and have also shown preferential recruitment of the HC (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Cornwell, Johnson, Holroyd, Carver, & Grillon, 2008; Goodrich-Hunsaker, Livingstone, Skelton, & Hopkins, 2010). Laczó et al. (2010) developed a real-world equivalent of the Morris water-maze using a 'Blue Velvet Arena'—a circular tent equipped with cameras, an LED-projected target, and navigational markers on the edges that can be turned on/off when needed. They used this in patients with AD, amnesic-MCI (aMCI), non-amnesic MCI (naMCI), individuals with subjective memory complaints, and healthy controls. They also manipulated which strategies the participant could use to locate the target, by offering either egocentric cues, by indicating either the start-position (from which the target had been previously

learned), or allocentric cues, by showing the navigational markers on the edges. They found that AD patients were significantly impaired on both conditions, compared to all other groups, and aMCI patients were impaired compared to all but the AD patients. These results suggest that AD patients may be particularly impaired at spatial navigation.

Bird et al. (2010) investigated the extent to which spatial/topographical memory was impaired in AD and aMCI patients, compared to fronto-temporal lobe dementia (FTLD) patients and healthy controls, using a four-mountains task. In this task, participants were presented with a target mountainous scene and four options to choose from, one of which was the same scene but from a different viewpoint. In the non-spatial condition, the scenes could be discriminated by looking at a single feature, such as the sky colour or the type of fauna, whereas the topographical condition required participants to mentally rotate the image or consider the spatial boundaries between the different parts of the image. As expected, both AD and aMCI patients were impaired on both conditions, compared to FTLD and controls. In addition, AD patients were disproportionately worse on the spatial condition, suggesting that AD is particularly damaging to spatial compared to non-spatial memory.

There have been a number of other tasks that also demonstrate that AD might be more specifically associated with spatial dysfunction, as well as spatial memory, particularly in comparison to other forms of dementia, such as semantic dementia. Pengas et al. (2010) used a series of tests, including the four-mountains task, a virtual route-learning task, a head-orientation test, and a series of non-spatial standard memory tests, with the aim of identifying which tasks might be most beneficial in accurately identifying AD from both healthy controls and from other dementia types. Of the tasks they used, they found the most clinically-relevant task was the virtual route-learning task, in which participants had to navigate around a virtual town along a specific pre-learnt route. The authors found that AD patients were sufficiently poorer than both

controls and semantic dementia patients, such that the test provided the most ecologically valid method of assessment.

1.3 Genetic risk of Alzheimer's disease

Observing and exploring factors that are causally involved in the genesis of AD, and precede cognitive decline and subsequent clinical diagnosis of AD, is challenging, as we have few reliable methods for identifying individuals that are likely to develop AD. As a result, researchers are increasingly looking at genetic variants implicated in the disease, using these as a proxy for increased risk of poorer later life cognitive health, including AD. One method that has been applied is the study of individuals with a history of familial AD, where we can be very confident that a large number of individuals in a family will go on to develop early-onset AD. In such families, rare mutations in dominant genes such as *PSEN1*, *PSEN2* and *APP* (Bettens, Sleegers, & Van Broeckhoven, 2010; Scheuner et al., 1996) appear to increase the concentration of aβ42(43), a longer variant of extracellular aβ, which forms insoluble aggregates much faster and which are more toxic than the more common aβ40 (Bu, 2009; Scheuner et al., 1996). Individuals carrying one of these genes are almost certain to develop early-onset AD if they live into mid-adulthood, making them an important group of people for researchers interested in the trajectory of cognitive decline to work with. There are, however, only around 500 families worldwide that are known to carry one of these genes, which limits large-scale study (Miller, 2012). As noted above, however, familial AD may have different biological causes to those seen in sporadic AD, which impacts on generalisation of findings to the general population.

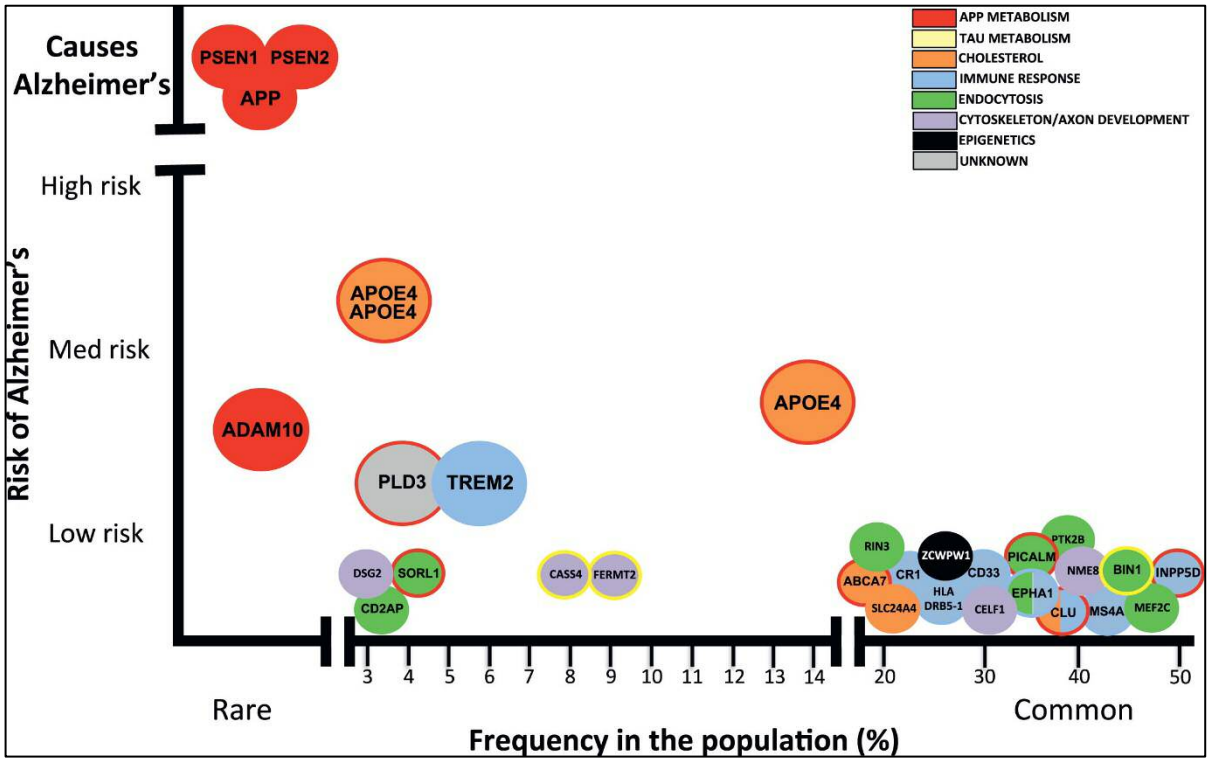

Figure 1.1 – Graphical display of the risk genes associated with AD (as of 2015). The y-axis is ordered by the level of risk for development of AD, with the highest risk genes having certainty of disease progression within an average lifespan. The x-axis is ordered by the frequency of which the gene is found in the general population. The genes associated with a high risk of AD tend to be rare. APOE-ε4 stands out as being relatively common and also having a medium level of AD, which is unusual in genetics. Homozygous carriers of the APOE-ε4 allele has a significantly greater risk than heterozygous carriers. Figure is from Karch and Goate (2015).

The development of revolutionizing technologies, such as genome-wide association studies (GWAS) that allow researchers to evaluate millions of single-nucleotide polymorphisms (SNPs) in thousands of individuals, have enabled the identification of over 20 genes (see Figure 1.2) that appear to increase risk for AD to varying degrees (Escott-Price et al., 2014; Hollingworth et al., 2011; Lambert et al., 2013; for reviews see Giri, Zhang, & Lü, 2016; Karch & Goate, 2015). As already discussed, the majority of genes that have been linked to AD affect Aß production and clearance, either directly (e.g. *PSEN1/2* or *APP*) or indirectly through processes that facilitate production and clearance, such as endocytosis (e.g. *BIN1* or *PICALM*) or cholesterol metabolism (e.g. *APOE* or *CLU*) (Karch & Goate, 2015).

In sporadic AD, the gene which has the strongest influence on later life cognitive health is *APOE*, which codes for a lipoprotein responsible for metabolising lipids (Bu, 2009). The *APOE* gene is located on chromosome 19 and has three main polymorphic

alleles—ε2, ε3 and ε4—which code respectively the isoforms *APOE*-ε2, *APOE*-ε3 and *APOE*-ε4 (Schächter et al., 1994), each being structurally unique. In 1993, Strittmatter and colleagues (1993) found that the *APOE*-ε4 allele greatly increased the likelihood of sporadic AD. An *APOE*-ε4 allele is present in around 25% of the general population, whereas it is found in approximately 40% of patients with AD (Bu, 2009). The most common allele is *APOE*-ε3 (77%) and the least common is *APOE*-ε2 (8%), with the latter believed to offer protective properties against AD (Suri, Heise, Trachtenberg, & Mackay, 2013; Talbot et al., 1994). *APOE*-ε4 heterozygotes carry a lifetime risk of 23% and 30% for men and women, respectively, and this increases to 50% and 60% in ε4 homozygotes (Genin et al., 2011). This intermediate risk of heterozygous ε4 carriers compared to homozygous ε4 carriers suggests that *APOE* is a moderately penetrant gene with semi-dominant inheritance (Genin et al., 2011).

APOE regulates lipid homeostasis in the body by transporting and clearing lipoproteins, fat-soluble vitamins, and cholesterol to the vascular system (Mahley & Rall Jr, 2000). This includes delivering cholesterols that are essential for brain health and repair, such as neuronal growth and synaptic plasticity (Liu, Kanekiyo, Xu, & Bu, 2013; O'Donoghue, Murphy, Zamboni, Nobre, & Mackay, 2018). It is suggested that the *APOE*-ε3 allele is the most efficient at this process (Liu et al., 2013), as, although the *APOE*-ε2 allele appears to offer some protection from AD, it seems this is not associated with Aß deposition, with both the *APOE*-ε2 and *APOE*-ε4 alleles being associated with increased Aß in old age (Berlau, Corrada, Head, & Kawas, 2009; although see Nagy et al., 1995). *APOE*-ε2 also increases the risk of Type III hyperlipoproteinemia—a genetic disorder that can lead to premature atherosclerosis (Mahley, Huang, & Rall, 1999)—which may explain why, from an evolutionary perspective, the allele is still relatively rare.

It is believed that *APOE*-ε4 is associated with deficiencies in Aß clearance, not production (Liu et al., 2013). This is in part due to studies using transgenic mice, which have found that whilst different *APOE* isoforms synthesise (produce) similar levels of

Aß, they vary in the levels of soluble Aß they have (*APOE*-ε4 > *APOE*-ε3 > *APOE*-ε2) prior to the onset of Aß deposition (Castellano et al., 2011). This suggests there is an inefficiency of *APOE*-ε4 to clear away cholesterols and explains why it is also associated with increased risk for other cholesterol-related conditions, such as coronary heart disease (Stengård et al., 1995).

1.3.1 Impact of APOE-ε4 on brain volume, functional networks, and cognition

Magnetic resonance imaging (MRI) studies using *APOE*-ε4 carriers often report inconsistent results. They typically focus on regions within the medial temporal lobe (MTL), such as the hippocampus (HC), entorhinal cortex and parahippocampal cortex (PHC); these are all known to be important for episodic memory, and may underlie the altered cognitive performance seen in early AD. Many structural MRI studies report that *APOE*-ε4 carriers have a reduction in MTL volume (Biffi et al., 2010; Burggren et al., 2008; Hua et al., 2008; Knickmeyer et al., 2014; Lemaître et al., 2005; Plassman et al., 1997; Shaw et al., 2007). For example, Biffi et al (2010) found significant reductions in grey-matter volume in MTL regions, including the HC, entorhinal cortex, and PHC, in elderly *APOE*-ε4 carriers compared to non-carriers, regardless of whether the *APOE*-ε4 carriers had an AD or MCI diagnosis. Given the association between *APOE* and AD pathology, this may seem unsurprising, but this link between *APOE*-ε4 and reduced MTL volume appears to extend much earlier in the lifespan than the pattern reported in elderly individuals. Reduced volume linked to the presence of an *APOE*-ε4 allele has also been reported in healthy adults (Burggren et al., 2008), adolescents (Shaw et al., 2007), and children (Shaw et al., 2007). Further, Knickmeyer et al. (2014) genotyped and scanned the brains of 272 new-born babies, and found significant reductions in grey-matter volume in MTL regions, including the HC and parahippocampal cortex (PHC), in *APOE*-ε4 carriers compared to non-carriers. In addition to these reported grey-matter reductions, age-related reductions in white-matter integrity have also been reported in *APOE*-ε4 carriers,

compared to non-carriers, on structures including the cingulum, corona radiata, corpus callosum, external capsule, internal capsule, and superior longitudinal fasciculus (Heise, Filippini, Ebmeier, & Mackay, 2011). Together, these studies seem to provide strong evidence for an effect of *APOE*-ε4 on grey- and white-matter structure throughout the lifespan.

These findings are not unanimous, however, and a number of experiments have failed to find any structural differences linked to *APOE*-ε4 carriers in both young and elderly adults (e.g. Filippini et al., 2011; Hostage, Choudhury, Doraiswamy, Petrella, & Initiative for the Alzheimer's Disease Neuroimaging, 2013; Westlye, Lundervold, Rootwelt, Lundervold, & Westlye, 2011). For example, Hostage et al. (2013) studied a large cohort of 662 elderly individuals, including AD and MCI patient groups and healthy controls, to look at the relationship between disease, *APOE*-type, and HC volume. Although they found a significant reduction in HC volume associated with the presence of an *APOE*-ε4 allele in MCI and AD groups, there was no significant difference in volume as a result of possessing an *APOE*-ε4 allele in healthy individuals. It is possible, however, that the lack of an effect in the healthy controls reflects other protective factors that might mitigate the effect of *APOE*, such as healthy diet and exercise.

Moreover, some studies have even found increased grey-matter in cognitively healthy elderly *APOE*-ε4 carriers compared to non-carriers (Honea, Vidoni, Harsha, & Burns, 2009; Striepens et al., 2011). In-line with the findings of Hostage et al. (2013), Striepens et al. (2011) found that *APOE*-ε4 carriers with a subjective memory impairment (not sufficient for clinical diagnosis of MCI/AD) had a significantly smaller left HC compared to non-carriers, whereas *APOE*-ε4 carriers without a subjective memory impairment had a significantly larger right HC compared to non-carriers. This also suggests that the relationship between *APOE*-ε4 and volume might be one that is confounded by other genetic and lifestyle factors.

Longitudinal studies looking at the effect of *APOE*-ε4 over time offer greater control over the separate effects of other genetic and lifestyle factors, as these remain relatively consistent over time within an individual. Lu et al. (2011), for example, found that young elderly *APOE*-ε4 heterozygotes (aged 55-75 years) showed a greater reduction in HC volume over approximately five years, compared to a matched control group of *APOE*-ε2 heterozygotes. Other similar longitudinal studies in elderly cohorts have found the same results when comparing between *APOE*-ε4 and *APOE*-ε3 (Cohen, Small, Lalonde, Friz, & Sunderland, 2001) and also looking at other brain structural measures, such as ventricular expansion between *APOE*-ε4 carriers and non-carriers (Roussotte et al., 2014).

There have also been reported differences in white-matter structural integrity that seems to be related to *APOE*. Heise et al. (2011) used diffusion tensor imaging (DTI) in a sample of cognitively healthy individuals (25-78 years). Irrespective of age, *APOE*-ε4 carriers had significantly reduced white-matter integrity (as measured by reduced fractional anisotropy (FA) and increased mean diffusivity (MD)) across the brain, compared to non-carriers. A later study by Hodgetts et al. (2018) looked more specifically at the posterior default mode network—in particular, the parahippocampal cingulum bundle which has high levels of connectivity with the HC and PHC (Heilbronner & Haber, 2014)—and found that young adult *APOE*-ε4 carriers (mean age of 20 years) had increased white-matter integrity selectively in this region, compared to non-carriers. As neuronal activity is known to increase vulnerability to A*ß* deposition, Hodgetts et al. argue that their findings might be indicative of an increased dependence for *APOE*-ε4 carriers on this tract over the lifespan, which eventually leads to an increase in A*ß* accumulation and subsequent atrophy and cognitive decline. This is also supported by evidence that functional connectivity and white-matter integrity in this tract decreases with age in *APOE*-ε4 carriers (Heise et al., 2014), as well as a significant

reduction in the white-matter integrity of this tract in patients with MCI, compared to healthy controls (Metzler-Baddeley et al., 2012).

In further support of this hypothesis, the posterior default mode network has also been associated with increased functional activity in *APOE*-ε4 carriers, even in young adulthood. Shine et al. (2015), used an odd-one-out task involving objects and scenes with young adult *APOE*-ε4 carriers and non-carriers (mean age = 20yrs) whilst looking at brain activity using a functional-MRI (fMRI) task involving perceptual discrimination. In their task, three pictures were presented on screen, either three scenes, three faces, or three objects. In each trial two viewpoints of the same exemplar were shown alongside a third item which was a different scene, object or face. The participant was required to identify which exemplar was the different object, face, or scene. A similar task has previously found that AD patients were impaired on perceptual discrimination for scene, but not face, stimuli (Lee et al., 2006). Shine et al. wished to test whether the same task and conditions would elicit altered brain activity—increased levels of blood-oxygen-level dependent (BOLD)—in *APOE*-ε4 carriers. Whilst Shine et al. found no difference in performance on the task between *APOE*-ε4 carriers and non-carriers, they found that carriers failed to deactivate the posterior cingulate cortex (PCC) (compared to non-carriers) in the scene but not object or face conditions, leading to increased activation in this network over time (see Figure 1.3). This increased activation in the PCC has also been reported in other studies involving young adults (e.g. Dennis et al., 2010; Filippini et al., 2011, 2009; Mondadori, de Quervain, et al., 2007), further suggesting that *APOE*-ε4 carriers have altered patterns of activity in this region, especially related to scene processing and episodic memory.

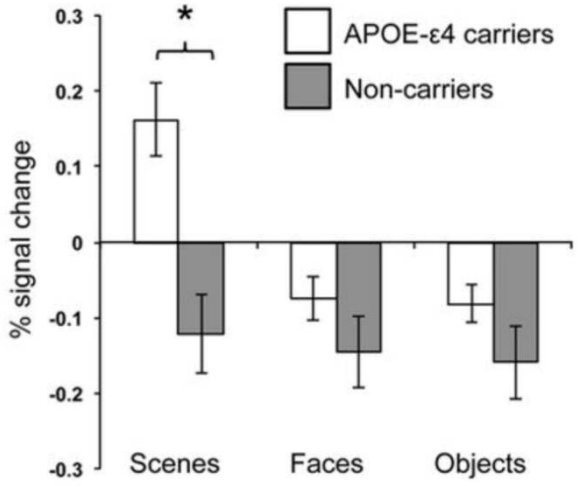

Figure 1.3 – This figure is adapted from Shine et al (2015). It shows the percentage signal change in the posteromedial cortex during an odd-one-out task involving scenes, faces and objects. The graph shows how APOE-ε4 carriers fail to deactivate this region during scene-specific stimuli, leading to higher levels of activity in this network over time.

The argument that increased activity potentiates the secretion of A*ß* and increases the amount of amyloid plaques is underpinned by animal research (e.g. Bero et al., 2011; Nitsch, Farber, Growdon, & Wurtman, 1993; Ovsepian & O'Leary, 2016; Yamamoto et al., 2015). For example, Bero et al. (2011) stimulated the neurons of mice whilst monitoring A*ß* deposition. They found that increasing neuronal activation also increased the secretion of A*ß* in that region, as well as the formation of the plaques that are one of the hallmarks of AD. It is difficult to extend the findings of such studies directly to humans, however, it is worth noting that there is a strong association between 'hubs' that are highly connected to multiple brain regions, such as the PCC, and where there may be high levels of activity, and associations with the level of A*ß* secretion in and around these regions (Buckner et al., 2009; Haan, Mott, Straaten, Scheltens, & Stam, 2012; Jagust & Mormino, 2011). This suggests that the findings in animal work may translate to humans.

It is less clear how these alterations in the brain, linked to the presence of different *APOE* alleles, may affect cognition over the lifetime. A 2018 critical review of literature by O'Donoghue et al. (2018), covering the last 20 years of studies into *APOE* genotypes

and cognition in healthy individuals, noted the lack of a consistent pattern of effects across studies. Unsurprisingly, given the strength of the relationship between *APOE* and AD, the strongest trends appeared in studies looking at elderly *APOE*-ε4 carriers compared to non-carriers (Bondi et al., 1995; Caselli et al., 2009; Rawle et al., 2018; Staehelin, Perrig-Chiello, Mitrache, Miserez, & Perrig, 1999; Wetter et al., 2005; Wisdom, Callahan, & Hawkins, 2011), and particularly when episodic memory tests were applied (Caselli et al., 2009; Rawle et al., 2018). For example, Rawle et al. (2018) conducted a longitudinal study of 815 cognitively healthy individuals aged between 21 and 97 years, measuring their memory using an auditory-verbal learning test every two years. They found that *APOE*-ε4 affected age-related memory, with carriers showing an accelerated decline, compared to non-carriers, from the age of 50 and increasing over subsequent years. The authors do highlight that the majority of their sample was over 50 years, and that it is possible that this effect might extend to younger adults. Indeed, Nao et al. (2017) did find that young adult *APOE*-ε4 carriers (mean age of 28 years) are impaired compared to non-carriers on the same auditory-verbal learning test, suggesting that the effects of *APOE*-ε4 on cognition might exist long before the occurrence of AD.

There are, however, a number of studies that fail to find any *APOE*-related differences in cognition (e.g. Bunce, Anstey, Burns, Christensen, & Easteal, 2011; Caselli et al., 2009; Jorm et al., 2007; Luciano et al., 2009; Richter-Schmidinger et al., 2011; Zhang et al., 2015). O'Donoghue et al. (2018) argue that making cross-study comparisons in this area is challenging, as results are likely to be heavily dependent on methodological factors—such as sample age, sample size, and the cognitive tests that are used—which vary greatly between studies. For example, Bunce et al. (2011) conducted a high powered study including over 6500 individuals, looking for differences between *APOE*-ε4 carriers and non-carriers, from ages 20 to 64 years, on a number of different cognitive measures. Unlike Rawle et al. (2018) and other similarly large sample studies (e.g. Jorm et al., 2007; Luciano et al., 2009), Bunce et al. found no difference in any of their cognitive measures in either young, middle, or older adult age groups. O'Donoghue et al. (2018) argue that

this is potentially due to a lack of sensitivity to *APOE*-related brain changes in the cognitive tasks used, particularly in the younger age-groups. They also argue that it is currently difficult to disentangle whether any observed differences in cognition result from an indirect association with *APOE*, via the increased presence of AD-related pathology in *APOE*-ε4 carriers, or a direct effect of *APOE* on cognition that is independent of future AD diagnosis.

Some studies have taken a more focussed approach in measuring the relationship between *APOE* and cognition, particularly in younger individuals. Acevedo et al. (2010) studied children (aged 7-10 years) who were *APOE*-ε4 carriers and non-carriers on a virtual reality spatial memory task, a human equivalent of the Morris water-maze task used in rodents (Morris, 1984). The task requires participants to navigate around a virtual environment to locate a hidden target, the location of which had previously been learnt. Performance on this task has previously shown to be effected by hippocampal damage in humans (Astur et al., 2002). Acevedo et al. found that *APOE*-ε4 non-carriers spent more time in the quadrant of the environment containing the hidden target compared to the other quadrants, whereas *APOE*-ε4 carriers spent a similar amount of time in each quadrant. This suggests that young *APOE*-ε4 carriers are impaired during spatial learning compared to same age non-carriers.

Zhang et al. (2015) looked at the effect of *APOE*-ε4 on the inhibition of cognitive interference using a Stroop colour-reading task in young adults (16-39 years). This task involves showing participants colours written out as words, but in different coloured ink (e.g. the word BLUE written in red ink). Participants are asked to read aloud the colour of the ink, not the colour spelt out by the word. The authors found that *APOE*-ε4 carriers were slower at reading out the colours compared to non-carriers. This task has been shown to recruit the fronto-parietal attentional network, which includes the anterior cingulate cortex, dorsolateral prefrontal cortex, inferior frontal gyrus, inferior and superior parietal cortex, and insula (Grandjean et al., 2012). Interestingly, this

network also projects to the PCC (Leech & Sharp, 2014), which, as discussed earlier, has been shown to have altered function in *APOE*-ε4 carriers (Dennis et al., 2010; Filippini et al., 2011, 2009; Mondadori, de Quervain, et al., 2007; Shine et al., 2015; Trachtenberg, Filippini, Cheeseman, et al., 2012). Leech and Sharp (2014) argue that the PCC plays a key role in the breadth and focal-direction of attention, between either an external source (such as when viewing a stimulus) or an internal representation (such as an autobiographical memory).

This finding may explain why some researchers have found *APOE*-related differences in performance on tasks involving attention. For example, Rusted et al. (2013) tested young adult *APOE*-ε4 carriers (mean age of 20 years) on two attention tasks: a rapid visual information processing (RVIP) task, which required participants to identify when three consecutive odd or even digits appeared during a rapid presentation of numbers; and a covert attention task, where participants were presented with a left or right cue, followed by the presentation of a stimulus on either the left or right of the screen, as indicated by the cue in 70% of trials. They found that *APOE*-ε4 carriers detected more correct targets in the RVIP task and had greater detection of incongruent trials on the covert attention task, suggesting that there may be an early-life advantage in attentional tasks involving inhibition of incongruent information. This is inconsistent with the findings of Zhang et al. (2015), who found that *APOE*-ε4 carriers (aged between 16 and 39 years) were disadvantaged in the inhibition of cognitive interference, which suggests that differences between *APOE*-ε4 carriers and non-carriers might be sensitive to small changes in tasks that seemly recruit the same cognitive domains.

1.3.2 APOE-ε2: The protective gene?

The majority of studies looking at the effects of *APOE* on cognition have focused on the *APOE*-ε4 allele (O'Donoghue et al., 2018). This is likely due to the increased prevalence of the allele compared to *APOE*-ε2. Of the studies that have looked at *APOE*-

ε2, however, many suggest that there are neuroprotective effects of the allele (for review, see Suri et al., 2013). That said, *ex vivo* neuropathological examination studies report inconsistent findings. For example, Berlau et al. (2009) found that, following an *ex vivo* neuropathological examination, very elderly (90+ years) *APOE*-ε2 carriers were more likely to meet the pathological criteria of AD (the presence of both excessive A*ß* plaques and neurofibrillary tangles) than *APOE*-ε3 carriers, despite having less risk of diagnosis of dementia during their life. This suggests that some other mechanism may be contributing to their maintenance of cognition. Morris et al. (1995), however, found that elderly *APOE*-ε2 carriers (age range from 53-93 years with a mean age of 79 years) had fewer neurofibrillary tangles than non-carriers, but no significant difference in A*ß* plaques. A further study (Nagy et al., 1995), looking at a mostly elderly population (mean age of 79 years), reported a reduction in both A*ß* plaques and neurofibrillary tangles in *APOE*-ε2 carriers. These discrepancies could be, in part, due to differences in the ages of the cohort, which might suggest that *APOE*-ε2 carriers are protected from both A*ß* plaques and neurofibrillary tangles unless they are very old (90+ years), at which point there may be rapid decline associated with pathological hallmarks of AD.

Similar to studies looking at *APOE*-ε4, exactly what effect *APOE*-ε2 has on cognition earlier in life is unclear. Complementing the findings of Zhang et al. (2015), where *APOE*-ε4 carriers were impaired compared to non-carriers a Stroop task, Trachtenberg et al. (2012a) found that middle-age *APOE*-ε2 and *APOE*-ε4 carriers showed similar levels of BOLD during a Stroop task, including increased activation of MTL regions (e.g. the HC, amygdala, and PHC) in both groups (compared to *APOE*-ε3 carriers). In a different study, Trachtenberg et al. (2012b) looked at brain activation at rest and also found increases in BOLD response in middle-aged *APOE*-ε2 and *APOE*-ε4 carriers compared to *APOE*-ε3 carriers. This begs the question of how and why there are such similar effects of *APOE*-ε2 and *APOE*-ε4 alleles on brain activation, in the context

of different patterns of risk of poorer later life cognitive health. This question is, as yet, unanswered.

Not all fMRI studies, however, have found similar patterns of cognitive performance or levels of brain activity between *APOE*-ε2 and *APOE*-ε4 individuals. Mondadori et al. (2007) found that young adult *APOE*-ε4 carriers remembered more items than *APOE*-ε2 and *APOE*-ε3 carriers during a delayed word recall task. They also reported that *APOE*-ε4 carriers had smaller learning- and retrieval-related brain activity increases than *APOE*-ε3 carriers in a number of MTL and frontal regions, including the HC, during a face encoding task (where participants had to remember the association between a face and an occupation). Conversely, *APOE*-ε2 carriers increased their learning-related activity in these regions. The authors argue that the *APOE*-ε4 allele is associated with more economic use of learning-related neural resources, and that the opposite effect is present in carriers of the *APOE*-ε2 allele.

One possible explanation for some of the inconsistencies in reported *APOE*-ε2 research is that carriers of *APOE*-ε2, -ε3, and -ε4 alleles all utilise different strategies to some tasks. Konishi et al. (2016) provided some evidence for this when testing young adults on a virtual reality spatial navigation task. Participants had to find items using pathways that were surrounded by distinct landmarks, and then remember the route they took. There were two possible methods of identifying the items and recalling the previous paths: a spatial strategy that involved using information about the locations relative the distinct landmarks, or a response strategy that involved using a pattern or numbering system (such as "going clockwise, take the first left after leaving the start position, then skip one pathway and take the next two pathways"). Based on a verbal report of how they completed the task, experimenters categorised the participants into either spatial or response learners and tested this against a subsequent probe trial in which the landmarks were removed (which would impair the spatial- but not the response-driven learners). The authors found that *APOE*-ε2 carriers were more likely to

use a spatial than a response strategy, whereas *APOE*-ε3 and -ε4 carriers were more likely to use a response strategy (see Figure 1.4). They also found that the *APOE*-ε2 carriers also had significantly greater HC volume compared to *APOE*-ε3 and -ε4 carriers, suggesting that this group may be more likely to use hippocampus-dependent spatial strategies during a navigation/search task.

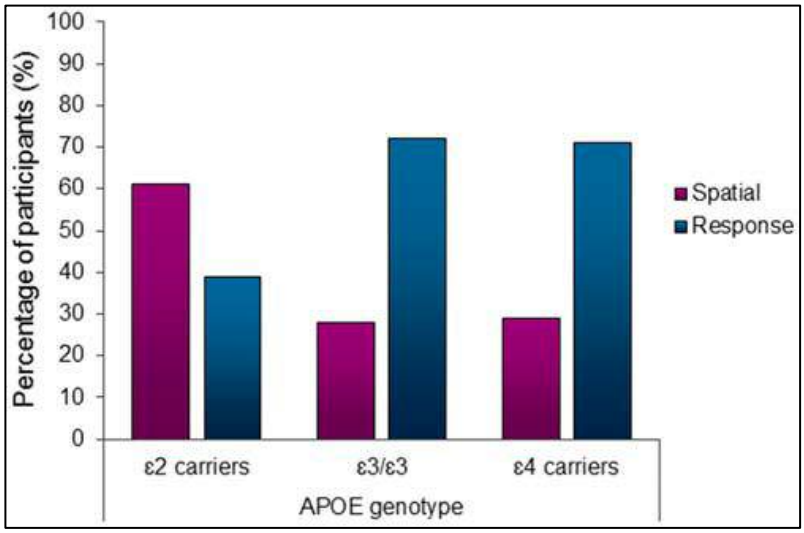

Figure 1.4 – Figure adapted from Konishi et al. (2016), who investigated strategies used during a virtual maze task. Participants who used a spatial strategy utilised landmarks to calculate their position relative to the target. Participants using a response strategy used a pattern system (such as "going clockwise, take the first left after leaving the start position, then skip one pathway and take the next two pathways") to complete the task. They found a significant difference in strategies used in the APOE-ε2 group compared with APOE-ε3 and -ε4.

Very few DTI studies have examined the relationship between *APOE*-ε2 and brain white-matter integrity. Westlye et al. (2012) studied the microstructural properties of white-matter in the brains of 203 individuals ranging from 21 to 70 years (mean = 48 years), and found that *APOE*-ε2 carriers had decreased FA, increased MD and increased radial diffusivity (RD), similar to that of *APOE*-ε4 carriers (and different to *APOE*-ε3 carriers). This finding suggests that both *APOE*-ε2 and *APOE*-ε4 alleles are associated with poorer myelin integrity in the brain, and builds upon the findings of Trachtenberg et al. (2012a; 2012b) that there are comparative functional patterns between *APOE*-ε2 and *APOE*-ε4 groups. Conversely, Chiang et al. (2012) found increased integrity (greater FA)

in the PCC of middle- and old-aged (49-90 years) *APOE*-ε2 carriers, compared to non-carriers. This suggests that the protective effect of *APOE*-ε2 may be specific to certain regions or white-matter tracts, and also that it becomes more pronounced later in life. It also builds on the work discussed in the previous section (e.g. Hodgetts et al., 2018; Shine et al., 2015; Zhang et al., 2015) that suggests that the PCC and associated regions may be critically affected in individuals with both low- and high- risk *APOE* alleles.

In summary, the reported findings from *APOE*-ε2 studies are both limited and inconsistent. This may be largely due to the low prevalence of the allele, leading to sample sizes which are too small to detect subtle differences. Those studies that have found similarities between *APOE*-ε2 and *APOE*-ε4 though are surprising, given that these alleles are thought to have protective and detrimental effects on AD prognosis, respectively. In a comprehensive review of the impact of *APOE*-ε2, Suri et al. (2013) highlight *APOE*-ε2's underrepresentation in the literature, as well as the need for a greater understanding of the mechanisms via which both *APOE*-ε2 and *APOE*-ε4 influence AD pathology and cognition, and how these are affected by age.

1.4 The role of the medial temporal lobe in the perception of objects and scenes

Understanding the role of the MTL in cognition is integral to understanding the relationship between AD-related pathology in these areas and subsequent cognitive decline; specifically because, as noted above, the MTL, and its connections with PCC, are some of the first regions thought to be affected by AD. For many decades, the function of MTL structures (such as the HC, perirhinal cortex (PRC), entorthinal cortex and related subregions) were considered to be specific to episodic memory (e.g. Squire, 1992; Squire, Stark, & Clark, 2004), as evidenced by the striking loss of event memory seen after damage to these structures. A series of experiments—in rodents, non-human primates and humans—have challenged this account, and it is becoming increasingly accepted that the MTL forms part of a visual perception network that supports memory

for different forms of information, rather than being a set of structures specifically dedicated to memory (for reviews, see Graham et al., 2010; Lee, Yeung, & Barense, 2012; Murray, Wise, & Graham, 2016; Saksida & Bussey, 2010).

Bussey and Saksida (2007) presented their views on this by proposing a representational-hierarchical model, arguing that the MTL forms part of a "perceptual representational system" within a wider visual ventral stream. They argue that as information is received in the visual cortex, retinotopic detail is bound into simple features (such as edges, orientations, and colours), which are then further bound together to form increasingly higher-order gestalt representations of objects (see Figure 1.5). As the world around us is made up of multiple objects, the spatial properties of the object-representations can then be bound to form high-order scene-representations. The authors argue that this system seeks to resolve feature ambiguity between objects and environments in order to allow us to rapidly recognise unique items and layouts in the world and distinguish similar ones from each other. They propose that simple representations can be formed in more caudal regions of the visual ventral stream (such as parts of the extrastriate cortex, including lateral occipital complex (Grill-Spector, Kourtzi, & Kanwisher, 2001) or the fusiform face area (Gauthier et al., 2000), for objects and faces, respectively). MTL regions, however, are involved in discrimination of highly complex overlapping representations, with the PRC essential for forming more complex conjunctive representations of objects, for example. Although Bussey and Saksida (2007) do not extensively postulate on the role of the hippocampus, they do suggest it might sit at the top of this hierarchy, with the ability to form representations at a higher level by binding together spatial information to form complex "scene" representations. The work described earlier—which focused on AD, but in particular the possibility that scene processing might be vulnerable in this disorder—is consistent with this hypothesis. There is clear evidence that the HC may be particularly important for scene processing, potentially explained by its early role in generation of a cognitive map in our early animal ancestors (Murray et al., 2017).

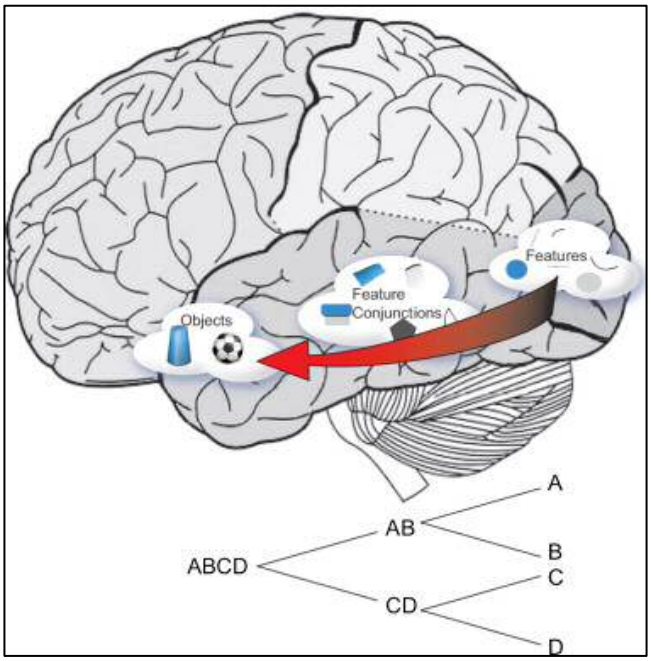

Figure 1.5 – A simplified visualisation of the visual ventral stream according to the representational-hierarchical model. Simple features are processed in the caudal regions of the stream. The more rostral regions are capable of reducing ambiguity by forming more complex gestalt feature conjunctions. (Kent, Hvoslef-Eide, Saksida, & Bussey, 2016)

Bussey and Saksida's representational-hierarchical model is based on extensive research conducted in both animals (Bartko, Cowell, Winters, Bussey, & Saksida, 2010; Buckley & Gaffan, 1997) and humans (Barense et al., 2005; Barense, Gaffan, & Graham, 2007; Barense et al., 2012; Barense, Henson, Lee, & Graham, 2010; Brunec et al., 2017; Erez, Cusack, Kendall, & Barense, 2016; Graham et al., 2006; Lee, Buckley, et al., 2005; Lee, Bussey, et al., 2005; Lee & Rudebeck, 2010; Martin, Douglas, Newsome, Man, & Barense, 2018), as well as computer-simulated models (Cowell, Bussey, & Saksida, 2006). For example, Bartko et al. (2010) tested rats with PRC legions on a series of recognition memory tasks where the rat was rewarded for approaching a specific object whilst in the presence of either a similar or dissimilar distractor, based on the number of features that they shared (out of a total of four features). They found that the rats with PRC legions were impaired when the task required them to distinguish between two similar objects, but not when there were dissimilar objects, compared to control rats without a PRC lesion. The findings suggest PRC is essential for distinguishing multiple objects when the number of overlapping features is high, but not low.

Saksida et al. (2007) also tested rhesus monkeys with HC and PRC legions on an object recognition task. In this study, the monkeys were presented with a pair of images, one correct and one incorrect, and were rewarded when they touched the correct object. In a *concurrent discrimination* condition, the correct object in the pair remained consistent throughout, meaning the monkey only had to remember which object was correct. In a separate *transverse patterning* condition, each image was only correct when it was paired with another specific image (for example, when A and B are presented, A is correct; when B and C are presented, B is correct; and when A and C are presented, C is correct). This latter condition required the monkey to learn the conjunction of stimuli, which the authors argued would be PRC dependent. Indeed, they found that PRC-lesioned animals were impaired, compared to control animals without a lesion, on the transverse patterning condition, but not the concurrent discrimination condition, suggesting that the PRC is essential for discriminating between conjunctions of multiple objects, but not single-object recognition. Interestingly, the authors found that animals with HC lesions were facilitated on the transverse patterning condition (compared to controls), which the authors argue might be due to HC intact animals seeking a spatial solution to the task that is unavailable to subjects with HC lesions.

These findings in animal-lesion studies also translate across to research looking humans with damage to the MTL. Barense et al. (2007) studied human patients with selective damage to the HC, as well as patients with broader MTL damage including the PRC, using an odd-one-out task with various object stimuli with differing levels of feature overlap (minimum, intermediate, and maximum). Participants had to select the object, from an array of seven, which did not have an identical pair. In the minimum overlap condition, none of the distractor pairs had any features that were the same as another pair or the target. In the intermediate and maximum conditions, the pairs/target all had two or four features that overlapped, respectively. The authors found that participants with broader MTL lesions, involving the HC and PRC, were significantly impaired at detecting the target on the intermediate and maximum conditions, compared to patients with HC lesions only and matched healthy control participants.

All groups performed well on the minimum overlap condition. In line with the representational-hierarchical model, this finding suggests that individuals with damage to the MTL are impaired at distinguishing objects that have ambiguous features, but not those where the featural ambiguity is low. Further, performance on this type of object discrimination task is not related to HC damage.

There is an increasing collection of evidence to suggest that the HC is a critical region in forming more complex spatial representations, such as scenes (e.g. Aly, Ranganath, & Yonelinas, 2013; Barense, Henson, et al., 2010; Douglas et al., 2017; Kolarik et al., 2016; Lee, Buckley, et al., 2005; Lee, Scahill, & Graham, 2008). Early work with rodents led to the discovery of place-cells—specific neurons that trigger when the individual is in a particular place in their environment (Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1979)—suggesting a role for the HC in representing space. Hampton et al. (2004) reported findings from rhesus monkeys with HC lesions which are consistent with this hypothesis. Within sight of the monkeys, they hid food under a plant-pot in a room with multiple distractor plant-pots and observed their success at finding the food over different time periods and from different locations. They found that monkeys with HC lesions were successful at finding the food from the location in which they saw the food being placed, but only for a short period of time, after which they were unsuccessful (compared to controls). They also found that the HC lesion monkeys were impaired at finding the food when they were immediately moved to a new location relative to where they had seen the food being hidden. This suggests that the HC is important for forming allocentric (or viewpoint invariant) spatial maps, but also that other brain regions are capable of resolving simple immediate egocentric spatial navigation.

Later studies in humans with HC damage also found evidence of impaired spatial navigation and scene perception (for reviews, see Graham et al., 2010; Murray et al., 2017). Astur et al. (2002) observed performance on a Morris water-maze in patients with HC lesions following epilepsy treatment. Participants had to escape a pool within

a virtual environment by finding a hidden platform. Individuals with HC lesions were impaired at finding the platform, spending a similar amount of time in each quadrant of the pool, compared to controls who were able to rapidly learn the location of the platform relative to the environmental features. Interestingly, these findings are similar to the previously discussed study by Acevedo et al. (2010), who found that young adult *APOE*-ε4 carriers did not spend as much time in the quadrant with the hidden platform (as *APOE*-ε4 non-carriers) on a similar task.

Maguire, Nannery and Spiers (2006) also found that HC legions impair navigation around real-world environments, using a virtual taxi-driver task around the city of London. They argued that the HC is essential for forming new spatial representations as well as for navigating environments based on fine-grain spatial detail, whereas it is not required for navigating around well-known and regularly used simple spatial representations. A number of further studies by this group of researchers working with London taxi drivers has shown the HC to be both essential for complex spatial navigation and also adaptive to increased demand on spatial representations of real-world environments (e.g. Hartley, Maguire, Spiers, & Burgess, 2003; Maguire et al., 2000, 2003).

Lee et al. (2006) investigated the role of the hippocampus in scene perception. They used an odd-one-out task in patients with AD and semantic dementia (SD), including both faces and virtual scenes. SD is a form of dementia in which patients show a progressive decline in their knowledge of the world, in the context of (initially) quite good memory for previous events (Hodges, Patterson, Oxbury, & Funnell, 1992). It is often used as a contrast to AD, where we see early loss of episodic memory in the context of better semantic memory. In Lee et al.'s task, patients were presented with 3 identical faces/scenes, from either the same or different viewpoints, and a different 'target' face/scene, and they were asked to select the target. They found that SD patients were impaired on the face (different viewpoint) condition, but not the scene condition or face (same viewpoint) condition, compared to AD patients and the control groups.

Conversely, the AD patients were impaired on the both of the scene conditions, but neither of the face conditions, compared to SD patients and controls. Critically, MRI scans showed that the AD patients had no evident damage to the PRC but extensive damage to the HC, whereas the SD patients had extensive PRC atrophy but only limited damage to the anterior HC. This double dissociation in cognitive performance suggests that the HC and PRC might play critical roles in disambiguating between scenes and faces, respectively, with PRC being particularly important when discrimination between object viewpoints is required.

HC lesions have also been shown to selectively impair memory for scenes but not faces. Bird et al. (2008) studied patient 'Jon' who suffered from apnoeic attacks as a baby, resulting in a 50% reduction bilaterally in the HC, but not extrahippocampal regions. Using a recognition memory task, whereby 'Jon' and matched controls viewed either novel or familiar images of scenes and faces and rated how on a confidence scale how likely it was that the item was familiar or novel, the authors found that 'Jon' performed comparatively for the face condition, but significantly worse on the scene condition. They proposed that the HC cannot be involved in declarative memory per-se given these findings, but preferentially recruited when processing topographical features, such as complex scenes and spatial layouts, rather than faces.

The work from animal and patient studies also converges with research using fMRI. For example, Barense et al. (2010) tested healthy young adult participants on an odd-one-out task whilst measuring BOLD activity. In this task, participants had to select the unique face, scene, object, or shape from a three-choice selection. In some conditions the same viewpoint of an object, face or scene was presented alongside a foil (a completely different face, object or scene), while in others a different viewpoint of an object, face or scene was presented (again alongside a completely different face, object or scene). When different viewpoint conditions were contrasted with same viewpoint conditions, the authors found a significant increase in BOLD activity in PRC during the object and face conditions, but not scene condition. By contrast, a significant increase in

HC activity for different view scenes compared to same view scenes was evident (with no effect in the face and object conditions). The authors argue that this task does not place any significant demand on memory due to the use of trial unique stimuli and a focus on perceptual discrimination where all items are present on the screen during the decision. The finding suggests that, in line with previous results, the PRC and HC are important for distinguishing between object/face and scene specific stimuli, respectively, regardless of memory demand. More specifically, Barense et al.'s findings suggest that these higher-order regions are critical in forming viewpoint-invariant representations, as opposed to representations from a single viewpoint.

More recently, there have been studies to identify how scene activations associated with the HC may differ from those in scene-sensitive regions within the wider visual ventral stream. Hodgetts et al. (2016) used a one-back task—whereby participants are presented with a series of images and instructed to identify when two identical images are repeated in succession—to identify regions that were activated for scene stimuli, but not object stimuli. They identified that the HC is part of a core scene processing network, which also includes the posterior PHC, retrosplenial cortex, and the transverse occipital sulcus. Similar to Bussey and Saksida's (2007) representational-hierarchical model, they argue that each region supports different aspects of scene processing with activation modulated by changes in low-level spatial features, viewpoint changes, and spatial layout. Similarly, Mundy et al (2012) hypothesised that the visual ventral stream includes a wider scene- and object-processing network, in which specific extrastriate regions are capable of resolving low level ambiguity while MTL regions are critical for higher levels of visual featural ambiguity. They also used a one-back task with scenes, objects and faces, and found that there are distinct extrastriate and MTL regions that are preferentially activated for each type of stimuli. In particular, object processing triggered activity in the lateral occipital cortex (LOC) and the PRC; face processing triggered activity in the fusiform face area (FFA) and the PRC; and scenes triggered activation in the PHC and HC. When testing the impact of manipulating the level of ambiguity between the stimuli, Mundy et al. found that LOC, FFA, and PHC

were preferentially activated when the level of feature overlap was low for their respective stimulus categories, whereas PRC and HC had preferential activation for the high feature overlap conditions, again aligned to their seeming preference for object and scene stimuli, respectively (see Figure 1.6). These findings suggest that caudal regions of the visual ventral stream are capable of low-level disambiguation of similar stimuli, whereas disambiguating stimuli with increased similarity and visual complexity recruits the more rostral brain regions in the MTL.

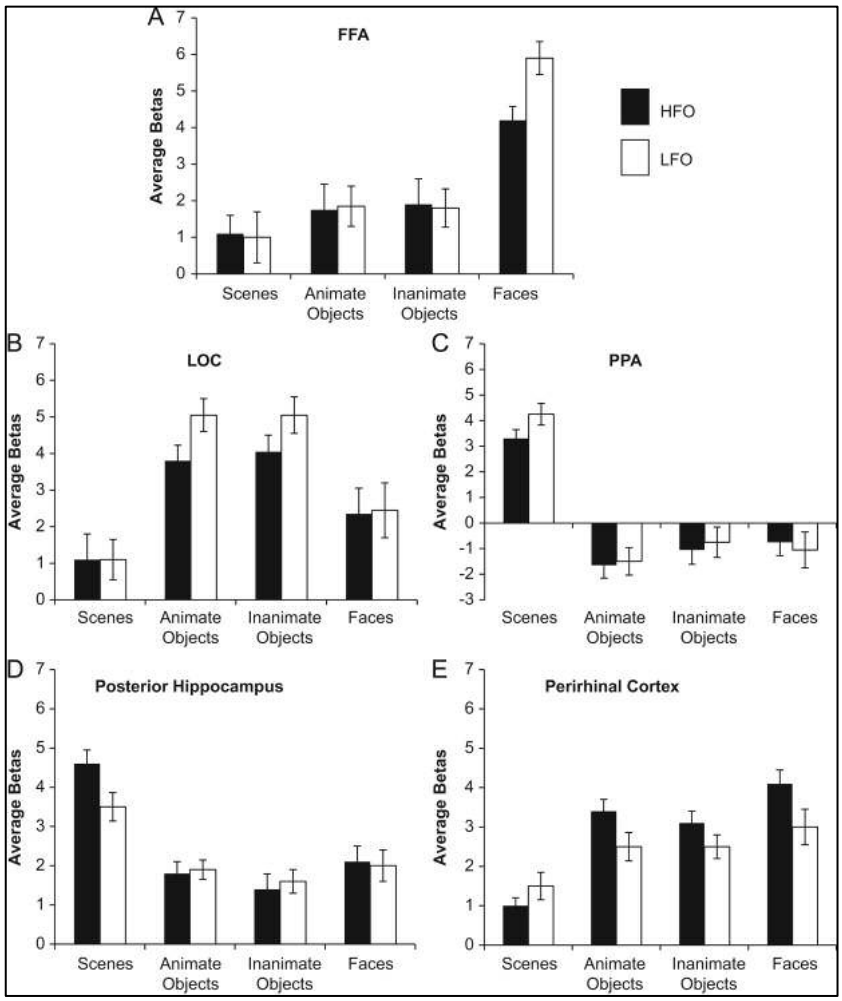

Figure 1.6 – Figure from Mundy et al., (2012). Using a one-back task involving scenes, animate objects, inanimate objects, and faces, the authors plot BOLD activity in (A) the fusiform face area, (B) the lateral occipital complex, (C) the parahippocampal place area, (D) the posterior hippocampus, and (E) the perirhinal cortex.

As discussed earlier in this chapter, the HC and core regions connected to it (e.g., posteromedial cortex) demonstrate structural and functional changes associated with clinical diagnosis of AD (or suspected AD), as well as in those individuals with an

increased genetic risk for AD (Biffi et al., 2010; Burggren et al., 2008; Dennis et al., 2010; Filippini et al., 2011; Heise et al., 2011, 2014; Hua et al., 2008; Knickmeyer et al., 2014; Lemaître et al., 2005; Mondadori, Quervain, et al., 2007; Plassman et al., 1997; Shaw et al., 2007; Shine et al., 2015). This had led to significant efforts to investigate how risk genes for AD, such as *APOE*-ε4, might impact on the functioning of MTL regions, and whether cognitive functioning is particularly vulnerable when tasks involve discrimination of, and memory for, scenes and spatial layouts. Shine et al.'s (2015) study (discussed earlier in this Chapter), found *APOE*-ε4 related functional differences in the PCC specific to scene stimuli, but not to objects or faces. Specifically, this task required participants to discriminate between stimuli from multiple viewpoints, which, as discussed, has been demonstrated—via a series of lesion and neuroimaging studies in rodents, non-human primates and humans—to most likely depend upon high-order, viewpoint invariant scene representations stored within the HC.

1.5 Thesis aims

As highlighted in this chapter, there is extensive evidence to suggest that AD pathology begins many years earlier than overt clinical diagnosis, with some researchers even arguing that the process involves changes across the lifespan, particularly in those with a genetic predisposition for the disease, and other factors which might interact with that risk, such as lifestyle and health (Selkoe & Hardy, 2016). Unfortunately, research into the trajectory of brain and cognitive change across the lifespan has been somewhat hampered by the time and costs involved in identifying individuals at risk. Many of the tests that are used in both clinical diagnosis and research (such as the ADAS-Cog) are arguably outdated, as they assume that function of the regions primarily affected by AD (such as the HC) can best be recruited using memory demanding tasks. The research outlined in the previous section suggests that this may not be the case. For example, Cano et al. (2010) found a substantial ceiling effect in the ADAS-Cog in patients with mild-to-moderate AD, suggesting that the tasks have limited diagnosis effectiveness

even in a patient population. This provides an obvious barrier to improving our understanding of the disease and identifying future risk in younger individuals at risk. Based on recent work looking at the role of spatial and featural disambiguation in selective MTL regions, as discussed in the latter parts of this Chapter, it seems sensible to review the way in which we seek to measure AD-related cognitive impairment, including assessment of that in healthy individuals at genetic risk. In doing so, it might be possible to shift forward diagnosis much earlier in the pathogenesis of AD, and in turn move towards preventative interventions prior to significant cognitive decline.

In this chapter, I discussed how different *APOE* alleles are associated with differential profiles of risk of developing AD later in life. Further there is evidence that this distinct *APOE* alleles may differentially alter brain structure and function, in core networks linked to the onset of AD pathology, potentially decades prior to AD clinical diagnosis. The study of cognition in healthy young individuals with different *APOE* alleles, and distinct risk profiles for AD, provides, therefore, an opportunity to enhance understanding of the *APOE*-related cognitive impacts, and the development of new paradigms which might address the issue of the insensitivity of current tasks used in clinical trials.

The aim of this thesis, therefore, was to investigate whether different alleles of the *APOE* gene selectively impact on perception and memory for scenes (with objects as a control condition). New experimental tasks were developed and applied in young healthy adults to ask whether: (a) there would be a *APOE* dose-linked pattern of performance on tasks in which scenes with a high degree of featural overlap needed to be discriminated (e.g., *APOE*-ε2 < -ε3 < ε4); (b) how any *APOE*-related changes in scene and object perception and memory might differ between young and middle-aged participants; and (c) whether individual performance on new tasks developed in this thesis would be associated with inter-individual variation in the volume of extrastriate and MTL brain regions known to be involved in scene and object processing.

In Chapter 2, I will report work from a conjunctive learning task using both scenes and objects in a population of young adults. This task was designed to require participants to learn which stimulus is rewarded by identifying it based on, for objects, conjunctions of appendages of novel fribbles, or, for scenes, conjunctions of spatial properties of virtual reality rooms. It was predicted that individuals at increased risk of developing AD later in life, via the presence of an *APOE*-ε4 allele, would show poorer performance on the scene, but not object, condition of this task (as measured by both the number of trials to criterion and response times). Individuals with an *APOE*-ε2 allele were expected to show the best performance, in comparison to *APOE*-ε3 and *APOE*-ε4 groups.

In Chapter 3, I developed a visual paired-comparison (VPC) task using eye-tracking to measure free-viewing of two side-by-side stimuli, one familiar and one novel, with both scene and object conditions. It has been previously shown that individuals will preferentially view the novel object in a way which is correlated with their recognition memory for the familiar stimulus. In other words, the more they remember the familiar stimuli, the longer they will spend viewing the novel stimulus. In this study, I manipulated visual similarity, and predicted that individuals at high risk of developing AD, via the presence of an *APOE*-ε4 allele, would show a lower novelty preference for scenes, compared to objects, particularly when the familiar and novel scene pair were visually similar (compared to dissimilar). Individuals at a lower level of risk for AD, such as those with an *APOE*-ε2 allele, would show the highest performance on the scene task, as measured by a longer novelty preference. I predicted no influence of *APOE* genotype on novelty preferences elicited in the object condition, but did hypothesise that similarity would result in smaller novelty preferences due to reduced memory for the previously presented item.

In Chapter 4, I report findings from application of the same VPC task as used in Chapter 3, but in a cohort of middle-aged adults where genotyping information was available to look at *APOE* risk. Similar to the previous chapter, I predicted that higher

risk of AD, as indicated by the presence of an *APOE*-ε4 allele, would be associated with lower novelty preference for similar scenes (compared to dissimilar), but with no evidence of an influence of *APOE* in the object condition.

In Chapter 5, I used MRI scans available from some of the participants reported in Chapters 2, 3 and 4 to ask whether individual differences in performance on the conjunction learning and visual paired-comparison task would be associated with inter-individual variation in the volume of extrastriate and MTL regions. Specifically, with regard to extrastriate cortex, I looked at lateral occipital cortex (LOC), which is known to be preferentially responsive to objects, and parahippocampal cortex (PHC), which is known to be responsive to scenes. For the MTL, I studied perirhinal cortex (PRC) and the hippocampus (HC), which are thought to be differentially involved in object and scene perception/memory, respectively. In the conjunction learning task, I predicted that response times for objects would be related to the volume of object-sensitive regions (e.g., LOC and PRC), but not scene-sensitive regions (e.g., PHC and HC). With regard to response times for scenes, I predicted that this would relate to the volume of scene-sensitive (PHC and HC), but not object-sensitive (LOC and PRC) regions. Similarly, for the VPC task, in both young and middle-aged cohorts, it is expected that individual differences in novelty preference for dissimilar and similar scenes would be positively related to variation in volume of PHC and HC, respectively. For dissimilar and similar objects, I hypothesised variation in novelty preference would correlate with increased volume in the LOC and PRC, respectively.

CHAPTER 2:
THE INFLUENCE OF DIFFERENT *APOE* GENOTYPES ON PERCEPTUAL DISCRIMINATION OF COMPLEX SCENES AND OBJECTS

2.1 Introduction

In Chapter One, I outlined increasing consensus among many neuroscientists (e.g. Bussey & Saksida, 2002, 2007; Bussey, Saksida, & Murray, 2002; Connor & Knierim, 2017; Cowell, Bussey, & Saksida, 2010; Graham et al., 2010; Murray et al., 2017) that the MTL is the apex of a wider visual ventral processing stream that hierarchically organises simple retinotopic visual detail into more complex representations of the objects and their relationship with the environment around us. It has been proposed that these representations are formed by binding together simple features into complex conjunctions (see Figure 2.1), which in turn can be bound to form whole representations of real-world objects and spatial layouts. The most complex representations include conjunctions of the spatial and/or temporal properties of multiple item representations, which allows us to understand and navigate the world around us (Connor & Knierim, 2017; Hsieh, Gruber, Jenkins, & Ranganath, 2014; Murray et al., 2017; Staresina, Duncan, & Davachi, 2011). Proponents of this model argue that this stream starts posteriorly in the visual cortex and extends anteriorly into the PRC and HC as the complexity of the featural and spatial conjunctions increase.

As these representations become more complex, it is argued that they serve to resolve ambiguity between representations (Blumenthal, Stojanoski, Martin, Cusack, & Kohler, 2018; Bussey & Saksida, 2007; Lee, Bussey, et al., 2005). Animal studies, using tasks that require discriminating between stimuli with varying levels of feature ambiguity, found that animals with lesions to the PRC, were unable to correctly distinguish between different objects when the level of feature ambiguity was high, but not when feature ambiguity was low (Buckley & Gaffan, 1997; Bussey et al., 2002; Norman & Eacott, 2004). Saksida et al. (2007) also found that non-human primates with

legions to the PRC were impaired compared to controls at discriminating pairs of images in which all features overlapped, but only the configuration of the images changed. Surprisingly, in this study, animals with HC lesions showed improved performance compared to controls, not evidencing any difficulties with this complex perceptual discrimination task. This finding suggests not only that the HC is not required to make configural discriminations of features, but also that it may actually impair facilitation of this process.

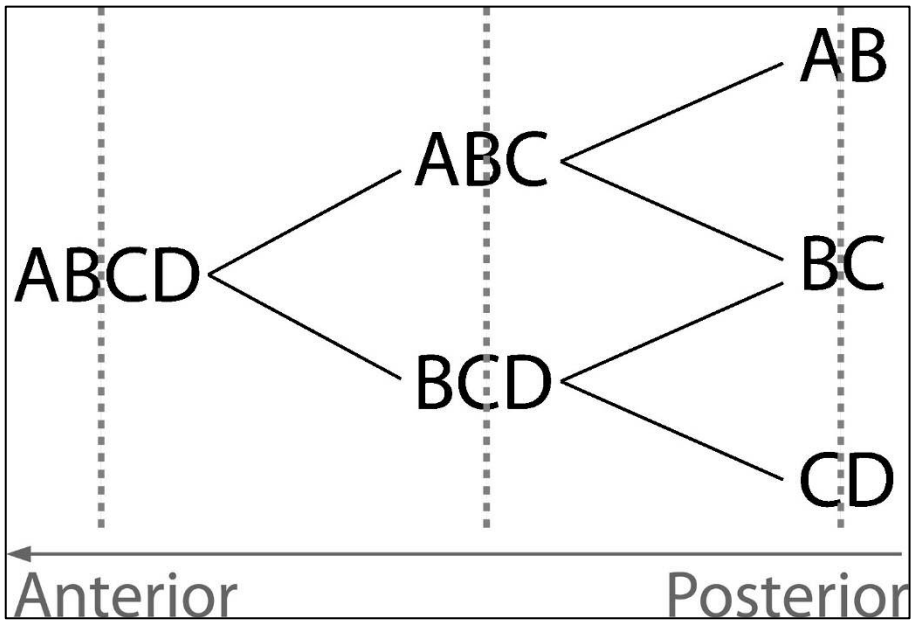

Figure 2.1 – Proposed hierarchical organisation of the visual ventral stream (Cowell et al., 2010). In the anterior regions, such as the PRC, complex object representations are formed from a number of different features that have been combined conjunctively. Figure taken from Cowell et al. (2010).

These results also translate across to human studies. For example, Barense et al. (2005) found that amnesic patients with MTL damage that included injury to the PRC were impaired at discriminating objects when the level of feature ambiguity between exemplars was increased, whereas patients with damage limited to the HC (and not obviously affecting the PRC) performed as well as healthy controls (see Figure 2.2). In this task, selecting the rewarded image was possible by identifying a single feature in the minimum and intermediate ambiguity conditions, but in the maximum condition the participant had to rely on knowing the unique conjunction of two features present in the object. These distinct patterns of impairment after different forms of lesion to the

MTL suggest that distinguishing between object-level representations is dependent on the PRC, particularly when there is a high level of feature ambiguity.

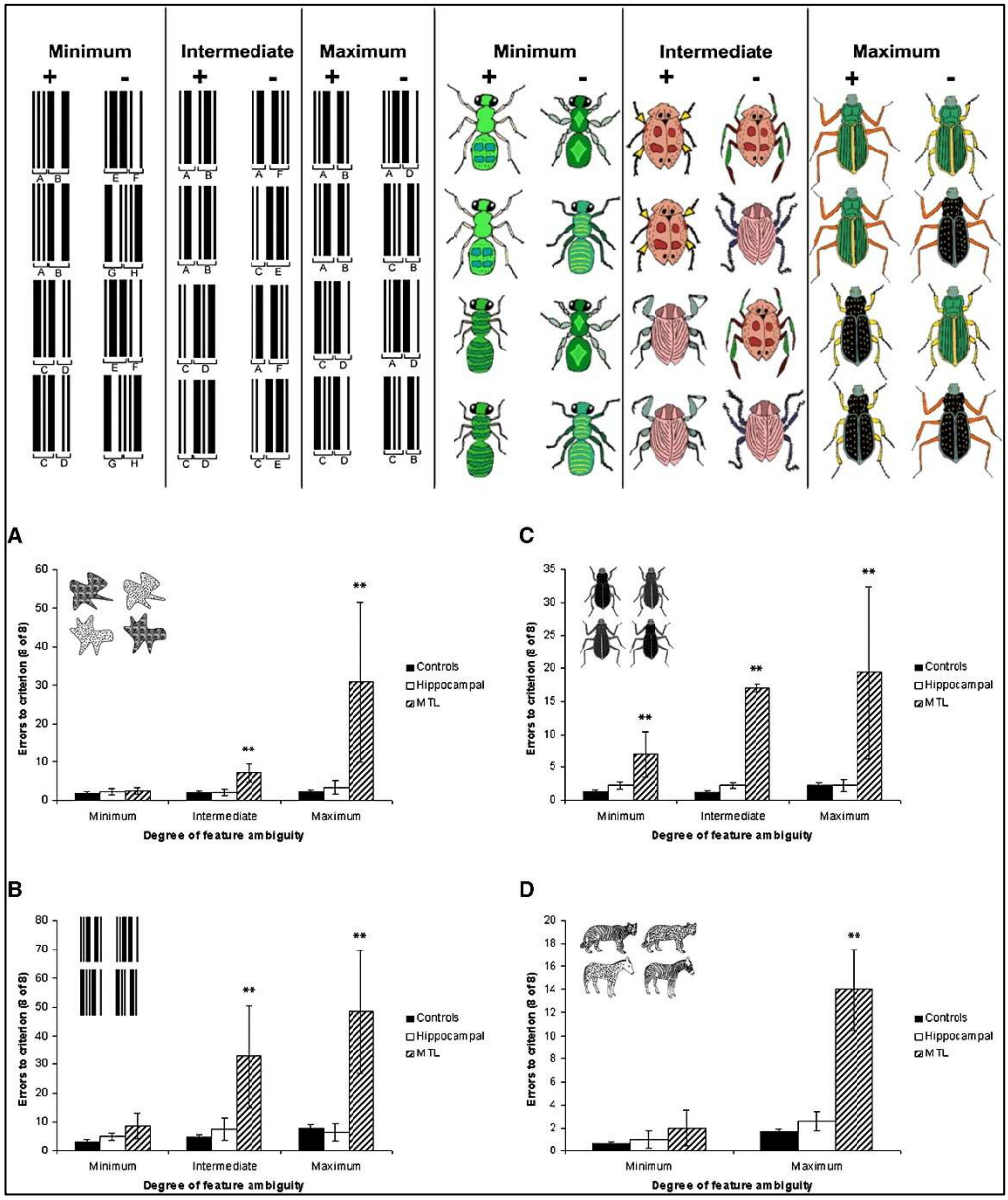

Figure 2.2- Barense et al.'s (2005) study altered feature-ambiguity on a discrimination learning task. Performance of amnesic humans with either restricted hippocampal damage or larger MTL lesions including perirhinal cortex is shown in comparison with age-matched, neurologically intact control participants. Humans with hippocampal lesions learn all the discrimination problems normally, regardless of level of feature ambiguity, but humans with MTL lesions are impaired when there is intermediate or high feature ambiguity. Error bars indicate ± SE. Figure taken from Baxter (2009) based on Figures 2 and 3 of Barense et al. (2005).

Complementary to this, Aly et al. (2013), found that patients with bilateral hippocampal damage were impaired in a task whereby the participants had to decide whether two consecutively presented scenes were the same or different. These scenes

retained the same features and size across two 'different' scenes, but the spatial boundaries between features was altered by pinching or spherizing the images. When reviewing these results alongside those discussed earlier, it appears as though the HC is critical in differentiating between different configurations of spatial properties (particularly when these are ambiguous), but not non-spatial configurations of featural properties.

Although there is much evidence suggesting a key role of the HC in tasks that involve distinguishing between ambiguous spatial stimuli, such as scenes (e.g. Bonnici et al., 2012; Lee, Buckley, et al., 2005; Postans et al., 2014), there are few studies that have looked directly at the role of the hippocampus in processing conjunctions of spatial features within scenes. Buckley, Charles, Browning, & Gaffan (2004) used a conjunctive learning task in non-human primates, where correct responses could only be achieved by learning a combination of spatial features, rather than any single feature of the item (a simple tadpole with a head and tail, which could point in different orientations). They found that learning these configurations of spatial features was impaired after transection of the fornix, the main input-output pathway to the hippocampus, suggesting that this white-matter tract is critical for processing conjunctions of spatial features within an object.

To date, no study has used a similar type of task to that of Buckley and colleagues—focusing on discrimination between highly spatially similar scenes—in humans. Based on the theories discussed in Chapter One and briefly touched upon further in this chapter, hippocampal damage should influence performance in learning to discriminate between such stimuli (an extension to work showing that hippocampal lesions affects odd-one-out performance for scenes (Lee, Buckley, et al., 2005) and categorisation of scenes (Graham et al., 2006)). Such a task should also be sensitive to *APOE*-ε4 if, as noted in Chapter 1.3.1, this semi-dominant allele influences the functioning of the posteromedial/hippocampal brain network involved in spatial processing, and in turn episodic memory. For example, as discussed in Chapter One,

Shine et al. (2015) found an altered pattern of BOLD activity in the PCC—a region affected in the early stages of AD (Zhou et al., 2008)—in *APOE*-ε4 carriers (compared to non-carriers) on a scene condition in an odd-one-out task. One explanation for this pattern was that it reflects altered or compensatory strategies employed by *APOE*-ε4 carriers due to inefficient hippocampal function. If this is the case, it is likely that these inefficiencies may be elicited by difficult behavioural tasks when participants have to distinguish between scene-type stimuli with high levels of feature ambiguity. Note, in Shine et al. (2015), there was no evidence of behavioural differences across *APOE*-ε4 carriers and non-carriers, although behavioural differences between young *APOE*-ε4 carriers and non-carriers have been noted in other studies, typically those involving attention (e.g. Rusted et al., 2013).

Mason et al. (2017) also used an odd-one-out task involving real-world objects, faces, scenes and greebles (novel computer-generated objects). The authors found that healthy middle-aged *APOE*-ε4 carriers were significantly impaired for the greeble condition only, which the authors proposed could be due to a greater level of feature ambiguity in the greeble condition compared to the other conditions, although feature ambiguity was not controlled for systematically in this study, so this hypothesis could not be directly tested. These findings are different to the results that might be predicted based on the literature highlighted in this chapter, where it might be expected that *APOE*-ε4 carriers would show impairments on the scene condition only. One potential explanation, however, is that the greeble stimuli were the only stimulus-type that required processing of specific conjunction of features. If the other stimuli-types could be discriminated using a single-feature comparison, this might engage more caudal regions of the ventral stream located in the extrastriate visual area, such as the LOC (Malach et al., 1995), FFA (Kanwisher, McDermott, & Chun, 1997) and PHC (Epstein & Kanwisher, 1998), that are capable of discriminating between lower-level representations, rather than the hippocampus (Mundy et al., 2012).

Despite the numerous structural and functional changes that have been in reported to occur in the hippocampus of young *APOE*-ε4 carriers (as discussed in Chapter One) (e.g. Alexopoulos et al., 2011; Dennis et al., 2010; Dowell et al., 2013; Filippini et al., 2009; Heise et al., 2011; O'Dwyer, Lamberton, Matura, Tanner, et al., 2012), to date, behavioural impairments have rarely been reported (although see Nao et al., 2017; for review see O'Donoghue et al., 2018). Here, in this Chapter, I was interested in whether different *APOE* genotypes would influence behavioural performance in healthy young participants, tested by using a novel conjunction learning task, similar to that reported by Barense et al. (2005), but where highly ambiguous scene-type stimuli were presented (as well as objects as a control condition).

Based on the literature discussed in Chapter One and earlier in this chapter, it was expected that the new task would preferentially recruit regions involved in forming and reconstructing high-level object and scene representations, namely the PRC and HC, respectively. As discussed in Chapter One, the different *APOE* alleles have a linear effect on risk for AD in later life, with *APOE*-ε2 being considered relatively protective, *APOE*-ε3 having a normal level of risk, and the *APOE*-ε4 allele increasing risk beyond the normal risk of *APOE*-ε3 (Meyer et al., 1998). Therefore, in this study, it was predicted that individuals at a greater *APOE*-related risk of developing AD later on in life would perform worse on the scene, but not object, conjunction learning task, as measured by the number of trials taken to achieve criterion and the average response time (increasing errors and RTs from low-risk < normal-risk < high-risk). Similarly, in a matched sample of *APOE*-ε4 carriers and non-carriers, it is expected that *APOE*-ε4 carriers would perform worse than *APOE*-ε4 non-carriers in the scene condition, but not the object condition.

2.2 Methods

2.2.1 Participants

A total of 138 female participants were recruited from a larger cohort of individuals, in whom *APOE* genotype information was available, via Cardiff University's experiment-management website. Participants took part in the current study in exchange for course credits or cash payment. The cohort was restricted to female participants based on studies that have shown increased effects of the *APOE*-ε4 allele in females, compared to males, in terms of their future risk of developing AD (for review see Ungar, Altmann, & Greicius, 2014). All participants had no self-reported history of depression or psychiatric illness, were not taking any psychoactive medication, were right-handed, had normal or corrected-to-normal vision, and were in their first or second year of their course (to allow for longevity of the cohort for experimental studies).

2.2.1.1 DNA extraction and genotyping of the cohort

The original cohort which had been genotyped for *APOE*-ε4 comprised 229 female Psychology undergraduate students from Cardiff University, ranging in age from 18 to 28 years (mean age (SD) = 20.0 (2.6) years). All participants attended an initial session where they were measured for height, weight, and blood pressure. They also filled out MRI screening forms and provided information about health via a medical history questionnaire. Saliva was provided using the Oragene self-collection methodology (DNA Genotek, Inc., Ontario, Canada); this involves the participant spitting into a tube.

DNA extraction and *APOE*-genotyping were performed in the MRC Centre for Neuropsychiatric Genetics and Genomics at Cardiff University. *APOE* isoforms differ due to a single nucleotide polymorphism (SNP) at two sites in the gene, therefore a single SNP genotyping assay was performed at each site in order to determine *APOE* genotype.

APOE genotypes were determined by KASP genotyping of SNP rs429358 and TaqMan genotyping of SNP rs7412. These were detected on Tecan infinite F200 pro and StepOnePlusTM Real-Time PCR System platforms, respectively. Haplotypes corresponding to *APOE*-ε2, -ε3 and -ε4 were then deduced.

Genotyping was successful in 224 of 229 of the original participants. The distribution of genotypes in those successfully genotyped was ε2/ε2 (0/224, 0%), ε2/ε3 (38/224, 17%), ε2/ε4 (7/224, 3%), ε3/ε3 (125/224, 56%), ε3/ε4 (52/224, 23%), and ε4/ε4 (2/224, 1%). Recruitment for the current study was undertaken from this original sample via highlighting the study on the experimental management system and restricting participants to those who had been previously genotyped. This approach successfully recruited 138 participants.

2.2.1.2 Sub-samples and APOE genotypes

2.2.1.2.1 Comparison by APOE risk

The 138 participants recruited for the study reported in this Chapter had an *APOE* genotype breakdown of: ε2/ε3 = 21, ε2/ε4 = 5, ε3/ε3 = 76, ε3/ε4 = 35, ε4/ε4 = 1. Participants were grouped based on their level of *APOE*-related risk as followed: the low-risk group included individuals with the ε2/ε3 combination (n = 21, mean age (SD) = 19.9 (0.9) years), the normal-risk group included individuals carrying the ε3/ε3 combination (n = 76, mean age (SD) = 19.8 (1.5) years), and the high-risk group included individuals with either the ε2/ε4, ε3/ε4, or ε4/ε4 combinations (n = 41, mean age (SD) = 19.6 (1.37) years). As discussed in Chapter One, individuals with an ε2/ε4 combination are at greater risk of developing AD (Farrer et al., 1997) than those with ε3/ε3, therefore individuals with this combination were included in the high-risk group despite their ε2 allele.

2.2.1.2.2 Matched comparison of APOE-ε4 carriers vs non-carriers

To look more directly at the extent to which the *APOE*-ε4 gene affects performance on the conjunction learning task, a subset of *APOE*-ε4 carriers (ε3/ε4 heterozygotes) (n = 27, mean age (SD) = 20.6 (0.6) years) and *APOE*-ε4 non-carriers (ε3/ε3 homozygotes) (n = 25, mean age (SD) = 20.3 (0.8) years) were selected. These were matched based on age, education, and family history of dementia and provided a more stringent comparison group.

2.2.2 Design and materials

The conjunction learning task included two different conditions: a scene condition using four computer-generated rooms, and a 'fribble' version using four computer-generated animal-like objects comprising of a main body and four appendages (see Barry, Griffith, De Rossi, & Hermans, 2014 for a detailed description). These stimuli had the benefit of being similar to real-world stimuli, but novel to the participants, and enabling controlled manipulations of features within the images to manipulate feature ambiguity.

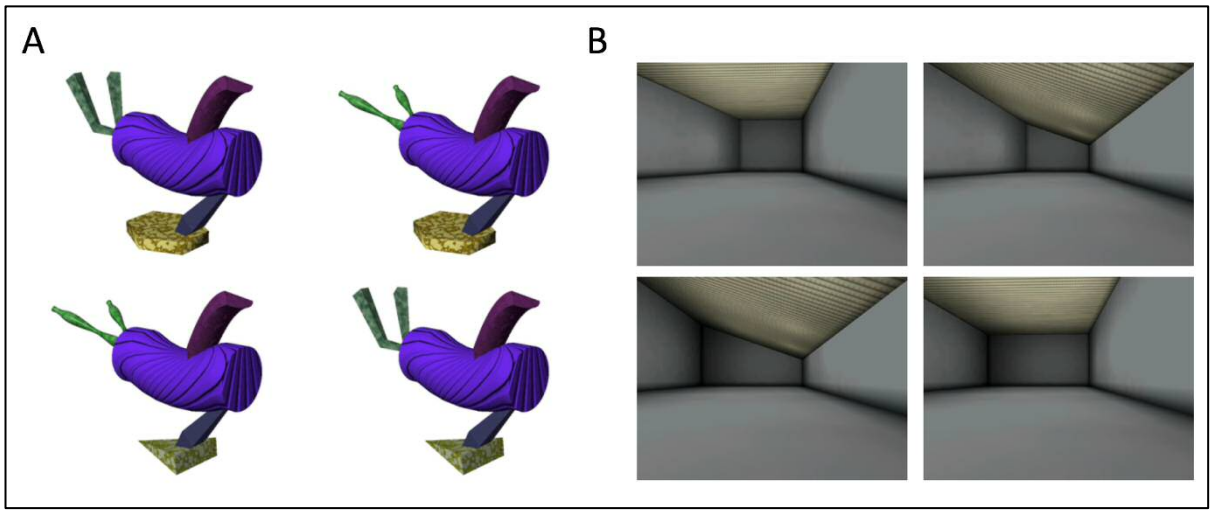

Figure 2.3 – Stimuli used for the Conjunction Learning Task. Set A is the fribble condition and set B is the scene condition.

The four rooms were identical except for manipulations to the width of the room (wide vs narrow) and roof-type (sloped vs flat). The four fribbles were identical except for modifications to the 'base' (hexagonal vs triangular) and 'tail' (squared vs curved) appendages (see Figure 2.3). As there were only two features that could change between stimuli, there was a high-level of feature overlap between the different stimuli.

For each participant, a particular combination of two features of the virtual reality room were allocated as 'correct' (e.g. correct rooms were the one that was narrow with a sloped roof, and the one that was wide with a flat roof). The other two combinations of features (e.g., the room that was narrow with a flat roof, and wide with a sloped roof) were incorrect responses. Likewise, for the fribble stimuli, a set of combinations were also allocated as the 'correct' response (e.g. a fribble with a hexagonal base and curved tail, and one with the triangle base and squared tail). Fribbles with a hexagonal base and squared tail, and triangle base and curved tail were incorrect. The participant was required to learn which images were correct by trial and error. This meant that the only way a participant could accurately identify the 'correct' images was to observe and learn the right combination of feature-conjunctions. Simply learning a single feature of a correct image (e.g. a sloped roof) would not allow a correct response when both images contained that feature.

The entire study was set-up in E-Prime 2.0 software (Psychology Software Tools, Inc, 2016) and presented to participant's view a touch-screen monitor located in a small experimental laboratory.

The study adhered to the British Psychological Society's Code of Ethics and Conduct (The British Psychological Society, 2018) and was approved by Cardiff University School of Psychology's ethics committee.

2.2.3 Procedure

At the start of the study, participants were provided with the following verbal instructions:

"During the study, pairs of images will appear on the screen, one of which is always 'correct' and one is always 'incorrect'. Your task is to tap (using the touch screen) the 'correct' image. If you click on a 'correct' image, you will hear a chime sound and a green box will appear around your choice. If you click on an 'incorrect' image, you will hear a dong sound and a grey box will appear around your choice. You will only learn the 'correct and 'incorrect' images by trial and error. Once you get enough correct in a row the task will end."

During the task, a 'correct' and an 'incorrect' image appeared side-by-side and the participant was required to touch the image they believed was correct, which was immediately followed by audible and visual feedback. As the task progressed, they had to learn which two images were the correct ones and, once the participant correctly identified eight successive trials without an error, the task was completed and the total number of trials to criterion was recorded. For each trial, the response time was also recorded. In the event that the participant failed to meet the criterion of eight successive trials, the task would terminate after a total of 160 trials.

Each participant started with a practice task using the letters 'A' and 'B', sloping either left or right. If the A sloped left then it was 'correct' and if the B sloped right then it was 'correct'. Each participant then completed the two experimental tasks with the room and fribble stimulus sets. The order of the two conditions was counterbalanced across participants and the location of the 'correct' stimulus was also counterbalanced across trials in each task, to avoid using the information about where the item was presented as a clue to the correct decision.

There are two main outputs on the conjunction learning task, the number of trials until the participant met the criterion (of eight successive correct responses) and the average response time across all trials.

2.3 Results

2.3.1 Comparison by APOE risk

2.3.1.1 Number of trials to criterion

To meet the criterion, participants were required to make eight successive correct responses and the total number of trials presented until this criterion was reached was recorded for each participant, for both conditions (see Table 2.1). Three participants (two from the high-risk group and one from the normal-risk group) were removed from the analyses, as they failed to meet the criterion within the 160-trial limit in the fribble condition. None of the participants failed to meet the criterion on the scene condition.

Shapiro-Wilk tests confirmed that the data was not normally distributed for all groups and conditions. As the size of the *APOE*-risk groups were also unbalanced, outliers were present, and the data lacked homoscedasticity, a standard repeated-measures ANOVA model was not appropriate. Instead, a linear mixed-effects (LME) model comparison was constructed, using the lme4 package (Bates, Mächler, Bolker, & Walker, 2015) in R (R Core Team, 2015). This involved building an 'interaction model' which included an interaction of condition (scene vs fribble) and group (low-risk vs normal-risk vs high risk), and a 'null model' which did not include this interaction (see Box 2.1).

TOTAL TRIALS TO CRITERION - *APOE* RISK GROUPS					
		Mean	**Standard Deviation**	**Median**	**Inter-Quartile Range**
LOW RISK	**Scene**	19.76	9.74	16.00	15.00
	Fribble	26.95	31.40	15.00	13.00
NORMAL RISK	**Scene**	18.45	13.13	15.00	8.00
	Fribble	20.49	18.07	14.00	10.00
HIGH RISK	**Scene**	22.21	21.78	13.00	12.00
	Fribble	17.46	8.84	15.00	9.00

Table 2.1 – Summary of results for each group and condition, for the total number of trials to criterion

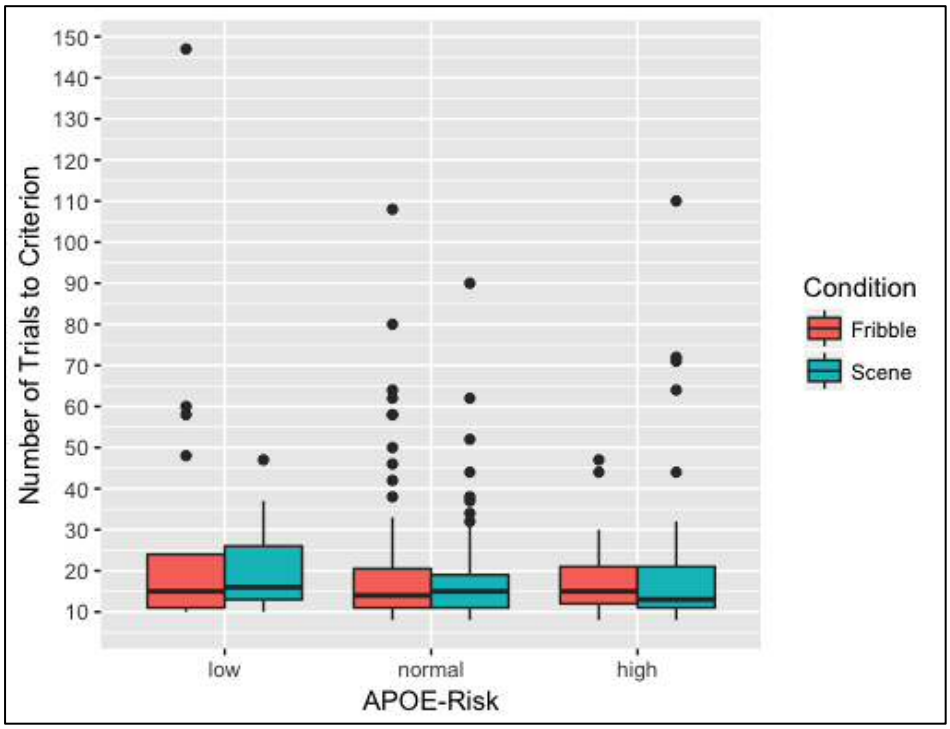

Figure 2.4 – Boxplots showing the number of trials to criterion for each condition across all APOE-risk groups.

The interaction model was then compared to the null model using a likelihood ratio test. This found that the interaction model did not account for any more variance in performance (as measured by the number of trials to criterion) than the null model ($\chi^2(2) = 3.81$, $p = .148$).

2.3.1.2 *Mean response rate*

The mean response time to trials was calculated by taking the mean of the time taken in milliseconds (ms) to make a response across all trials in each task (see Table 2.2). Shapiro-Wilk tests confirmed that the data was not normally distributed in all conditions and groups except for the response times for the fribble condition in the low-risk group.

Interaction model

This model included fixed effects of *APOE*-type and condition as an interaction, and subject as a random effect.

*MEASURED OUTPUT ~ CONDITION * APOEGROUP + (1|SUBJECT)*

Null model

This model included fixed effects of *APOE*-type and condition as separate fixed effects, along with subject as a random effect.

MEASURED OUTPUT ~ CONDITION + APOEGROUP + (1|SUBJECT)

Box 2.1 – Structure of models used in the linear mixed-effects model comparison for the different APOE risk groups (low, normal and high).

Similar to the previous analysis, the size of the *APOE*-risk groups was unbalanced, outliers were present, and the data lacked homoscedasticity. Therefore, a standard repeated-measures ANOVA model was not appropriate. Instead, an LME model comparison was constructed, using an 'interaction model' which included an interaction of condition (scene vs fribble) and group (low-risk vs normal-risk vs high risk), and a 'null model' which did not include this interaction (see Box 2.1).

The interaction model was compared to the null model using a likelihood ratio test; this analysis found that the interaction model did not account for any more variance in performance (as measured by response time) than the null model ($\chi^2(2) = 1.72$, $p = .423$).

MEAN RESPONSE TIMES (MS) – *APOE* RISK GROUPS					
		Mean	**Standard Deviation**	**Median**	**Inter-Quartile Range**
LOW RISK	**Scene**	2130.81	1025.77	2010.55	773.70
	Fribble	2351.79	730.23	2325.64	987.91
NORMAL RISK	**Scene**	2046.13	706.71	1857.69	592.64
	Fribble	2481.06	616.18	2347.93	810.15
HIGH RISK	**Scene**	2006.59	561.10	2035.38	634.87
	Fribble	2420.25	597.76	2346.11	571.62

Table 2.2 – Summary of results for each group and condition, for the mean response times.

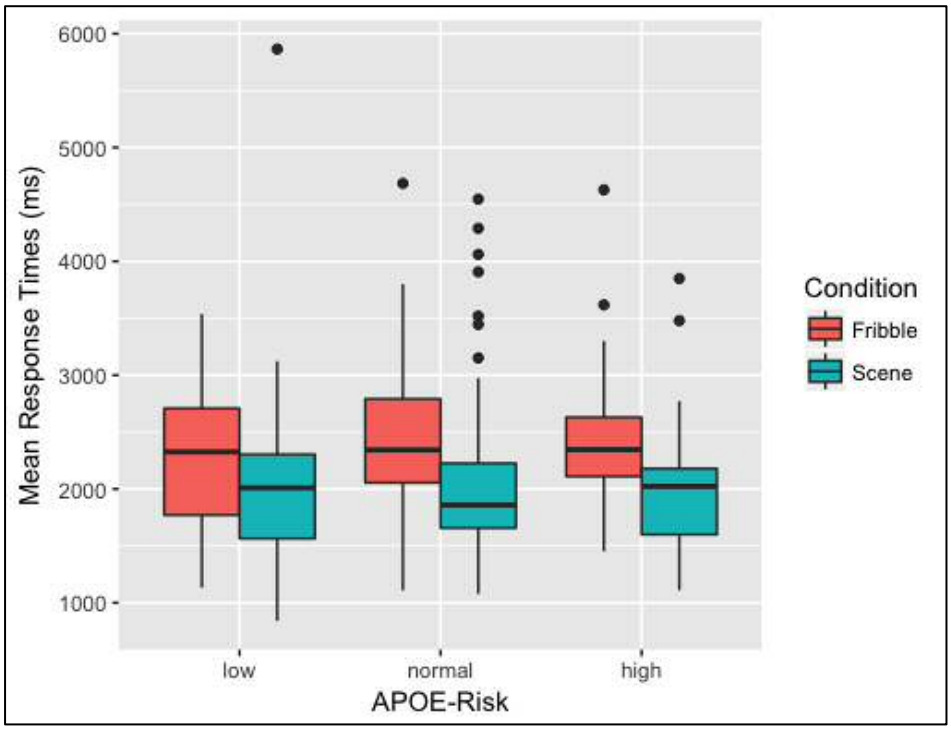

Figure 2.5 – Boxplots showing the mean response times (ms) for each condition across all APOE-risk groups.

2.3.2 *Comparison of APOE-ε4 carriers vs non-carriers*

2.3.2.1 Number of trials to criterion

The total number of trials presented until criterion (eight successive correct responses) was recorded for each participant, for both conditions (see Table 2.3). One participant (*APOE*-ε4 carrier) was removed from the analyses, as they failed to meet the criterion within the 160-trial limit in the fribble condition. None of the participants failed to meet the criterion on the scene condition. Similar to the earlier analyses, Shapiro-Wilk tests confirmed that the data was not normally distributed in all conditions and groups.

TOTAL TRIALS TO CRITERION - CARRIER VS NON-CARRIER					
		Mean	**Standard Deviation**	**Median**	**Inter-Quartile Range**
CARRIER	**Scene**	23.81	24.08	12.50	15.00
	Fribble	17.00	9.56	14.00	9.00
NON-CARRIER	**Scene**	21.32	17.40	16.00	13.00
	Fribble	18.96	21.04	14.00	9.00

Table 2.3 – Summary of results for carriers and non-carriers in both scene and fribble conditions, for the total number of trials to criterion.

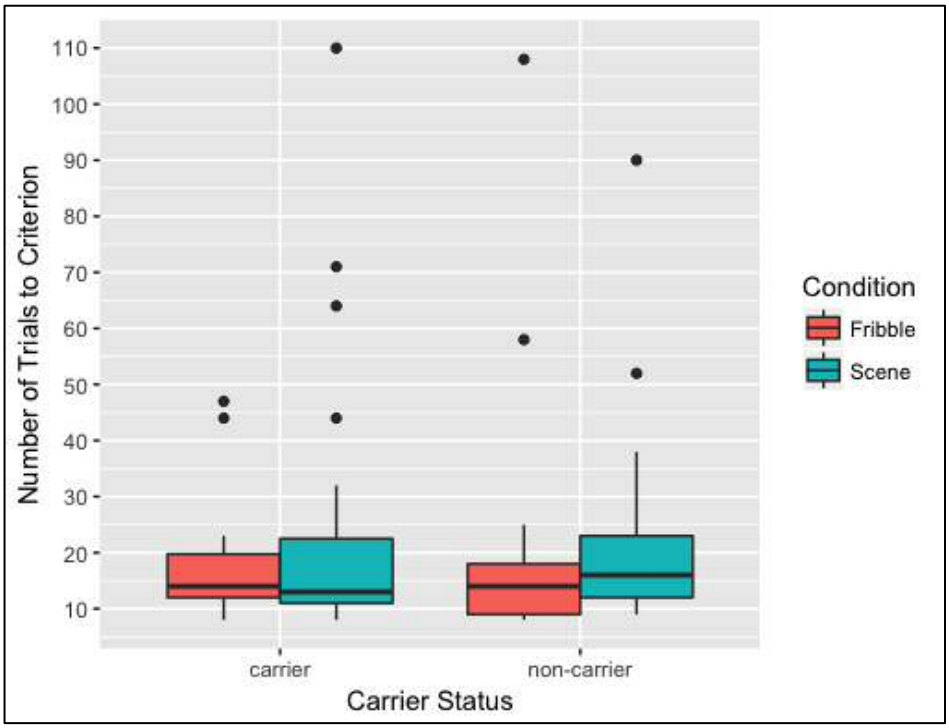

Figure 2.6 – Boxplots showing the number of trials to criterion for each condition between APOE-ε4 carriers and non-carriers.

The LME models were constructed in the same way as they were constructed for the *APOE* risk group analysis. An interaction model consisted of an interaction of the fixed effects of carrier-status and condition, with subject as a random effect. The null model included carrier-status and condition as separate fixed effects with no interaction, as well as subject as a random effect (see Box 2.2). These models were compared using a likelihood ratio test, which found no significant difference between the two models ($\chi^2(1) = 0.02$, $p = .902$).

Interaction model

This model included fixed effects of carrier status and condition as an interaction, and subject as a random effect.

*MEASURED OUTPUT ~ CONDITION * CARRIER-STATUS + (1|SUBJECT)*

Null model

This model included fixed effects of carrier status and condition as separate fixed effects, along with subject as a random effect.

MEASURED OUTPUT ~ CONDITION + CARRIER-STATUS + (1|SUBJECT)

Box 2.2 – Structure of models used in the linear mixed-effects model comparison for carrier vs non-carriers.

2.3.2.2 *Mean response rate*

The final analysis looked at the mean response rate (ms) to all trials, for carriers and non-carriers (see Table 2.4). Data were not normally distributed in all conditions and groups, except for the fribble condition in non-carriers, following Shapiro-Wilks tests of normality.

LME models were constructed as it was in earlier analyses, to measure the amount of variability in response times that can be explained by an interaction model against a null model (see Box 3.2). A likelihood ratio test found that these models were not significantly different ($\chi^2(1) = 0.85$, $p = .356$).

MEAN RESPONSE TIMES (MS) - CARRIER VS NON-CARRIER

		Mean	Standard Deviation	Median	Inter-Quartile Range
CARRIER	**Scene**	2017.05	638.44	1932.40	667.00
	Fribble	2476.96	649.30	2333.22	566.00
NON-CARRIER	**Scene**	1960.50	587.15	1860.19	438.00
	Fribble	2308.20	511.44	2230.20	520.00

Table 2.4 – Summary of results for carriers and non-carriers in both scene and fribble conditions, for the mean response times (ms).

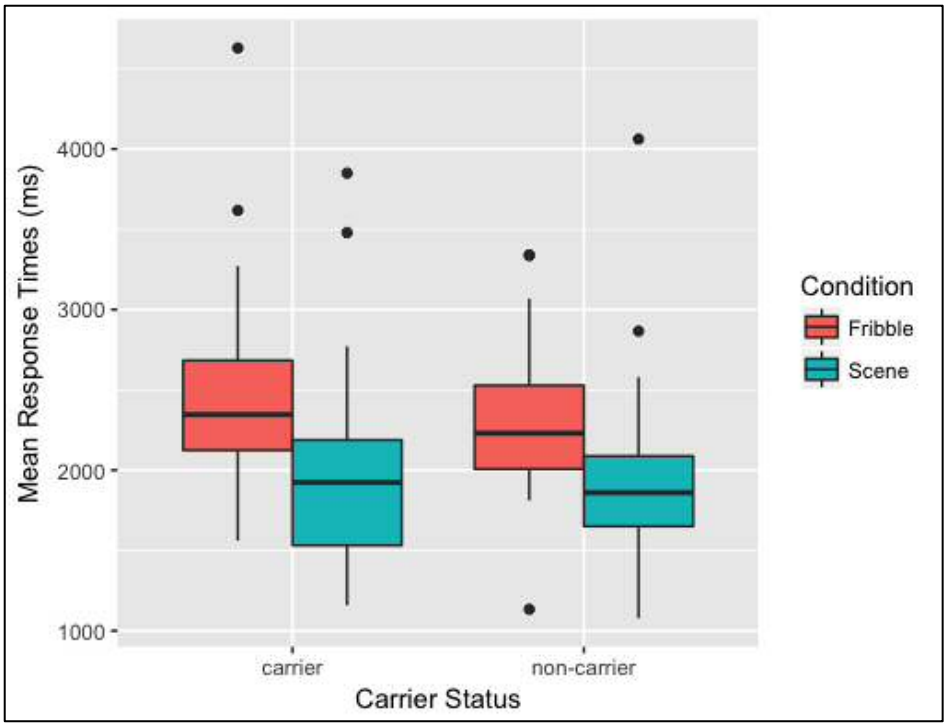

Figure 2.7 – Boxplots showing the mean response times (ms) for each condition between APOE-ε4 carriers and non-carriers.

2.4 Discussion

The aim of this chapter was to investigate whether the presence of different *APOE* genotypes, linked to differing risk profiles for AD in later life, would influence the ability of young adult participants to learn to differentiate between feature-ambiguous scenes and objects based on their unique conjunction of multiple features. To do this, two separate groups were studied. In the first analysis, a large sample of participants were split into low-, normal- and high-risk groups, depending upon their *APOE* genotype. The second analysis focused on a smaller, but matched, subset of *APOE*-ε4 carriers and non-carriers, allowing me to look more specifically at the effect of the *APOE*-ε4 allele on conjunction learning performance.

Carriers of the *APOE*-ε4 gene (the strongest semi-dominant risk gene related to late-onset AD) have been shown to have altered brain activity, compared to *APOE*-ε4 non-carriers, during tasks involving the discrimination of multiple scene but not object stimuli (Shine et al., 2015). Young *APOE*-ε4 carriers have also been shown to have

reduced hippocampal volume compared to *APOE*-ε4 non-carriers (Alexopoulos et al., 2011; O'Dwyer, Lamberton, Matura, Tanner, et al., 2012), a region that has been shown to be required when tasks require processing of high-level spatial conjunctions (Buckley et al., 2004; Lee et al., 2008). As the scene condition used in the conjunction learning task requires processing of spatial (rather than featural) conjunctions, it was predicted that individuals with a high *APOE*-related risk level would perform worse than low and normal risk groups (as measured by both the number of trials to criterion and the average response times) on the scene condition, compared to the object (fribble) condition. Similarly, it was predicted that *APOE*-ε4 carriers would perform worse than their matched *APOE*-ε4 non-carriers in their performance in the scene, but not the fribble, condition, again both in terms of the number of trials taken to meet criterion and the average time to make a response. In the current study, however, *APOE*-ε4 carriers and non-carriers were found to perform at a similar level, with no significant difference in number of trials to criterion and RT. Similarly, *APOE*-risk level—low, normal and high—did not differentially influence performance on the tasks, in terms of learning to identify the correct item over trials as well as the time taken to make those decisions.

Prior to running this study, I predicted that those participants at increased risk of developing AD in later life, as measured by the presence of an *APOE*-ε4 allele (compared to those individuals with low, *APOE*-ε2, or normal level, *APOE*-ε3 risk) would show slower learning of complex scenes (but not objects). This hypothesis was not proven. This is similar to the results from Mason et al. (2017), who found no difference in the ability of *APOE*-ε4 carriers (compared to non-carriers) to discriminate between scenes and objects, even at mid-age. They proposed that this might be due to the stimuli being familiar to the participant, as they did find a difference in *APOE*-ε4 carriers' ability (compared to non-carriers) to discriminate greebles (novel objects). In my study, all the stimuli were novel, and yet performance was similar across all *APOE*

genotypes. This suggests that simply using novel stimuli does not invoke differences across at-risk *APOE* groups, at least in young adults.

One possible explanation for this finding is that the conjunction learning task was not sufficiently demanding enough to stress the conjunctive scene processing dependent upon the hippocampus. In terms of performance, as measured by the number of trials to criteria, scores were mostly clustered around a high-performance level (e.g., most participants completed the task in fewer than 20 trials), suggesting that participants may indeed have found the task too easy. The difficulty of the task could be increased in a future study by using a probabilistic learning paradigm (e.g. Schutte, Slagter, Collins, Frank, & Kenemans, 2017). This method makes the task more difficult by altering the accuracy of the feedback on correct decisions, meaning the participant has to work harder and for longer in order to learn which image is correct.

It is also possible that participants were able to identify the correct scene stimuli by just looking at the shape of the back wall, which is unique depending on the configuration of the roof and room width properties (see Figure 2.3). In other words, it is possible that individuals completed the scene task without processing the conjunctions of spatial properties, as was the focal aim of the task design. Future studies should correct for this possible confound by using stimuli whereby altering the spatial properties of the image does not lead to a unique single feature, such as the back wall.

As touched upon in Chapter One, another possible explanation for the similar levels of performance in this task across different participants, with different *APOE* alleles, is that vulnerability in the networks projecting to and from the HC, might be mitigated by 'brain reserve capacity'—the ability of a brain region to continue to function despite a certain amount of impairment (Stern, 2003)—or 'cognitive reserve'—the more efficient utilization of brain networks or enhanced ability to recruit alternate brain networks in situations where the usual region or network is impaired (Stern, 2002; Vemuri et al., 2011). Studies that have seen altered patterns of activity in networks and regions connected to the HC in young *APOE*-ε4 carriers, compared to non-carriers,

without any changes in cognitive function or performance (e.g. Filippini et al., 2009; Shine et al., 2015), support this theory. For example, Shine et al (2015), found that *APOE*-ε4 carriers had increased activity in the PCC, compared to non-carriers, during a scene-specific oddity detection task. One explanation for this is that *APOE*-ε4 carriers are relying more heavily on attentional networks, which are argued to be regulated by the PCC (Leech & Sharp, 2014), as a result of *APOE*-related inefficiencies in the networks projecting to and from the hippocampus.

If *APOE*-ε4 carriers are recruiting other networks, such as attentional networks, in order to perform comparatively to non-carriers on the conjunction learning task, it stands to reason that *APOE*-ε4 carriers may show better attentional performance. Rusted et al (2013) found that young *APOE*-ε4 carriers do appear to be advantaged during tests of sustained and covert visual attention, compared to *APOE*-ε4 non-carriers (as discussed in Chapter 1.3.1). It is feasible that such an attentional advantage might mitigate any inefficiencies in the ability to form, store, and recall conjunctions of spatial features during the conjunction learning task reported in this chapter.

If *APOE*-ε4 is leading to altered brain function in young adults, as evidenced by some neuroimaging studies (Filippini et al., 2009; Shine et al., 2015), it is likely that, at most, this is having a minimal impact on cognitive performance as measured by standard responses such as accuracy or response time. Although the current task focussed on manipulating spatial feature conjunctions in order to increase demand on the hippocampal complex, it is possible that this alone is not enough to elicit measurable differences in performance in this young and well-educated cohort. There is evidence that factors associated with increased cognitive reserve—such as education, diet, and physical exercise—are also factors that delay the onset of the cognitive symptoms of Alzheimer's disease (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014; Querbes et al., 2009; Scarmeas & Stern, 2003). This suggests that cognitive or brain reserve may offer some cognitive protection against neurodegeneration in regions associated with

Alzheimer's pathology. In this respect, my sample may suffer from a selection-bias, as all participants were engaged in university-level education at a competitive Russell Group university, which is known for its high criteria for acceptance. My participants are therefore all likely to be well educated and may have higher levels of cognitive reserve than the general population.

The aim of this chapter was to identify differences in performance across different alleles of the *APOE* gene when learning conjunctions of spatial properties across ambiguous stimuli. The lack of any difference suggests that the task is not sensitive enough to identify any altered cognitive performance that may exist in young adults with a high risk of developing AD in later life. O'Donoghue et al. (2018) argue that any differences in cognitive performance due to *APOE* is likely to be minimal and difficult to measure using typical measures such as response times or task performance, largely due to any small effect being masked by the many extraneous factors (such as lifestyle differences) that have a much larger effect on cognition.

In the following chapter I will use a different approach to measuring differences in distinguishing between ambiguous scenes and objects. Using a visual paired-comparison (VPC) task, I will use eye-tracking to measure visual recognition memory. Individuals usually show a strong preference to view novel stimuli (Pascalis & de Haan, 2014), and therefore it is possible to measure a person's recognition memory for a familiar stimulus by measuring their novelty preference for an alternative stimulus. Using a modified VPC task, I will measure novelty preference across ambiguous and non-ambiguous scenes and objects in the same groups used in this chapter. As the task measures object/scene recognition implicitly, via a novelty preference, individuals should be less likely to recruit alternative strategies, as the task aim is unknown to them, and therefore it is predicted that this task will be more sensitive to alterations in spatial cognition related to the presence of an *APOE*-ε4 allele.

CHAPTER 3:
PERFORMANCE ON A VISUAL PAIRED-COMPARISON TASK IN YOUNG ADULTS WITH DIFFERENT *APOE* GENOTYPES

3.1 Introduction

Chapter 2 investigated whether young adults at increased genetic risk of late-onset Alzheimer's disease (AD) (via the presence of an *APOE*-ε4 allele) would show a different profile of performance to individuals with a lower genetic risk (such as via the presence of an *APOE*-ε2 allele) in a conjunction-learning task. Specifically, the experiment tested the hypothesis that individuals with greater genetic risk would show altered learning of scenes, but not objects, that overlapped in their visual features. This prediction was not confirmed, with no evidence of a statistical difference in performance between the two groups in either of the conjunction learning conditions. One possible explanation for this finding was that the conjunction learning task was not sufficiently sensitive or demanding to elicit *APOE*-ε4 drive behavioural differences, which are likely to be subtle given the age of the participants. In this chapter, therefore, I outline work carried out using another paradigm, the visual paired-comparison task (VPC).

Typically, in a VPC task, participants view an image (or occasionally multiple images) in an initial familiarisation phase. Following a period of time, the participants are then presented with the original image/s alongside a novel image. A key finding from the task is that cognitively healthy individuals tend to disproportionately focus more on the image, or areas of the image, that are most novel, as opposed to those which they saw in the familiarisation stage. This so-called novelty preference can be calculated by comparing time spent viewing the familiar versus novel stimulus/stimuli (as measured using eye-tracking). The paradigm is commonly used as a measure of recognition memory (Manns, Stark, & Squire, 2000), and has been shown to be sensitive to damage of the hippocampus in rats (Clark, Zola, & Squire, 2000), monkeys (Nemanic,

Alvarado, & Bachevalier, 2004; Zeamer, Meunier, & Bachevalier, 2011; Zola et al., 2000), and humans (Pascalis, Hunkin, Bachevalier, & Mayes, 2009; Pascalis, Hunkin, Holdstock, Isaac, & Mayes, 2004).

For example, Pascalis et al. (2004) used a VPC task, along with a delayed matching to sample (DMS) paradigm, on a patient (YR) with hippocampal damage following a possible ischaemic infarct. The damage was thought to be specific to the hippocampus and there was no damage to the parahippocampal gyrus (including other medial temporal regions such as the perirhinal, entorhinal and parahippocampal cortices). The VPC format involved an object or face stimulus appearing on screen for five seconds, and after a short interval (0s, 5s, or 10s) the same stimulus appeared again alongside a novel object/face. The proportion of time spent looking at the novel stimulus, compared to the familiar one, was recorded. Similarly, the DMS task involved a face or object being shown, but this time YR was asked to indicate which was the previously seen stimulus when presented alongside a novel distractor. YR performed similarly to matched controls on the DMS task and on the 0 second interval of the VPC but, unlike the controls, showed no novelty preference on the 5 and 10 intervals on the VPC. Critically, the major difference between the two tasks was that, during the DMS task, YR was aware that she was being tested on memory, whereas the VPC task measures recognition memory incidentally. These results are similar to findings in studies combining VPC and DMS tasks in non-human primates (Nemanic et al., 2004). Pascalis et al. (2004) argue that the difference in performance between tasks involving implicit and explicit goals might indicate that, when individuals are aware that they are being tested on memory, they might be capable of compensating for their hippocampal damage using alternative strategies for remembering the items. If this is the case, it could make the VPC a more sensitive measure of hippocampal damage, as it is less likely to trigger task-related compensatory strategies.

These findings provide a potential explanation for why the VPC task has been shown to be a sensitive marker of cognition decline in individuals in the early stages of

dementia. For example, Crutcher and colleagues (2009) administered the VPC task to patients diagnosed with MCI and Parkinson's disease—a neurodegenerative disease that is characterised by progressive motor abnormalities (American Psychiatric Association, 2013)—as well as healthy controls. The study aimed to determine whether the VPC task provided a sensitive approach to differentiating between these two different types of neurodegenerative disorders. During a familiarisation phase, two identical images of clip-art objects were displayed side-by-side for 5 seconds followed by a break of two minutes. During the test phase, the original image and a dissimilar novel clip-art object appeared side-by-side for 5 seconds. By measuring eye-movements to the different stimuli during the test phase, the authors found that both healthy controls and patients with Parkinson's disease spent longer looking at the novel images (73% and 71% of total time, respectively) compared to the MCI group (53%).

In another study, Zola and colleagues (2013) recruited MCI patients and elderly controls and used the same VPC procedure as Crutcher and colleagues (2009) to test if the task could be predictive of future cognitive decline (see Figure 3.1). At the point of running the VPC task, 32 participants were diagnosed with amnesic MCI and there were 60 healthy controls. Over the following 3 years, the diagnosis of 13 MCI patients had progressed to AD, and 4 controls originally considered healthy now had a diagnosis of MCI. These 17 participants were categorised as *converted* and the remaining participants categorised as *non-converted*. They found that all but one of the participants with a novelty preference less than 50% were categorised as *converted*. In those with a novelty preference greater than 50% but less than 67% there was less risk of 'conversion'. Importantly, all individuals with a score above 67% were categorised as *non-converted*. These results (see Figure 3.1) suggest that the VPC task may be predictive of future cognitive decline (as measured over the following three years from when the task was originally given to participants), albeit not differentially predictive across diagnostic groups (e.g. healthy vs MCI vs AD).

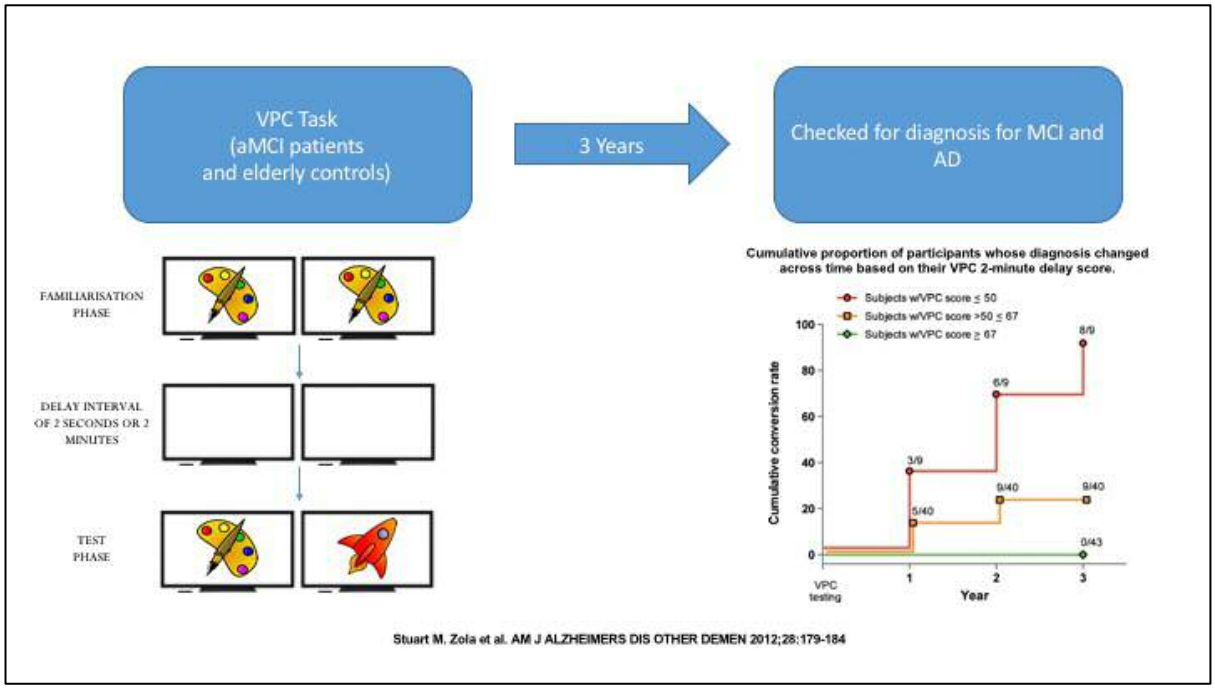

Figure 3.1– Zola et al. (2013) found that the VPC task was predictive of cognitive decline three years after running the VPC task. All but one of the participants scoring at or below chance level (50%) went on to have a change in clinical diagnosis (moving to either MCI or AD) in the subsequent three years. In contrast, no participants with a high novelty preference (>67%) had a diagnosis change in the same period.

What is not clear from this study is the extent to which the VPC task is relying upon hippocampal function—particularly within the context of the hierarchical-representation model discussed in Chapter 1—and how far in advance of a clinical diagnosis for AD this task could be predictive of risk of developing dementia later in life. In a VPC task using simple object stimuli, there is evidence to suggest that dependency on the hippocampus increases with age, with non-human primates with neonatal hippocampal lesions performing normally aged 1.5 months and 6 months, but then subsequently showing delay-dependant impairment at 18 months (Zeamer, Heuer, & Bachevalier, 2010). This intriguing finding suggests that brain structures other than the hippocampus may be capable of supporting incidental recognition memory in early life (as measured by the VPC task), but less so as young non-human primates get older. Interestingly, Pascalis et al. (2004) (discussed earlier in this chapter) report that patient YR showed decreasing ability on the DMS task (in which she previously performed similarly to controls) over time, which, together with the findings from Zeamer et al.

(2010), suggests that cognitive impairment immediately following hippocampal damage could initially be limited, but then increase over time.

Zeamer and colleagues (2013; 2011) found that performance on a VPC task in non-human primates with hippocampal lesions was comparable to that of healthy control animals when the familiar and novel stimuli were dissimilar, but that the lesioned animals showed an impairment when the stimuli were similar both semantically and visually (e.g. two chairs or two aeroplanes). This was further supported in a later study, in which non-human primates encoding for dissimilar object stimuli preferentially relied on recruitment of the perirhinal cortex during a VPC task (Zeamer, Richardson, Weiss, & Bachevalier, 2015), suggesting that, for object-type stimuli that is dissimilar, non-hippocampal structures may be capable of supporting incidental item recognition. Weiss et al. (2017) also found that non-human primates with perirhinal cortex lesions performed worse than controls during a VPC task involving object-type stimuli, but did not find a significant relationship between the extent of the lesions and novelty preference. It seems likely, however, that this was due to a small sample size and a lack of within-group variability rather than the lack of a true effect. In summary, these non-human primate studies support previous evidence (as discussed in Chapter 1.4) suggesting that medial-temporal cortical areas other than the hippocampus, such as the perirhinal and parahippocampal cortices, are capable of incidentally recognising familiar object-type stimuli, particularly when the target and distractor are visually and semantically dissimilar.

Although the VPC task appears, at least to some extent, to recruit the hippocampus (Nemanic et al., 2004; Zeamer et al., 2010), the use of dissimilar object pairings used in the Zola et al. (2013) study may actually be targeting dysfunction in the perirhinal cortex, rather than the hippocampus, as the authors suggest. Considering the models introduced in Chapter 1, it is possible that some of this discrepancy in the literature may arise from use of different forms of stimuli with differential demand on distinct components of the medial temporal lobe. By modifying the design of the VPC

task to incorporate stimuli that have been shown to be preferentially more demanding on the hippocampus, it might be possible to increase the sensitivity of the VPC task to detect differences in recognition memory (as measured by novelty preference) in younger individuals at increased risk of dementia, via the presence of risk genes linked to AD. Use of similar (more ambiguous) stimulus pairs, along with scene-type stimuli (to be compared with the more commonly used object items), could increase dependency on the hippocampus during a VPC task.

In the current Chapter, I develop and test a new version of a VPC task incorporating both scene and object stimuli, as well as a novel manipulation of stimulus similarity (visually similar and dissimilar). Consistent with the approach taken in Chapter 2, I describe the outcomes from testing in two cohorts. First, a large young adult cohort where it was possible to compare individuals with different forms of *APOE* alleles (ε2, ε3 and ε4), and second a subset of that group where it was possible to undertake direct matching across participants to create a group of *APOE*-ε4 carriers versus a group of *APOE*-ε4 non-carriers. In the first analysis, I predict that the *APOE* gene will impact linearly on recognition memory (as measured by decreasing novelty preference for scenes, but not objects) according to the genetic risk-level for AD associated with these alleles (e.g., low-risk > normal-risk > high-risk). In the second analysis, I predict that *APOE*-ε4 carriers will show a smaller novelty preference for scenes (but not objects) than the matched group of *APOE*-ε4 non-carriers. Specifically, *APOE*-ε4 carriers will need to look at the familiar stimuli for longer than *APOE*-ε4 non-carriers, thereby reducing the strength of the novelty preference. Furthermore, I predict that this effect, of a reduced novelty preference for high-risk vs low-risk individuals, will be greater for similar scenes, compared to dissimilar.

3.2 Method

3.2.1 Participants

3.2.1.1 Initial recruitment, DNA extraction and genotyping

The participants for this study were recruited from the same large cohort of females described in Chapter 2. See Chapter 2.2.1.1 for a detailed explanation of DNA extraction, genotyping and the characteristics of the cohort.

Double-blind procedures were followed in that both the experimenter and participants remained blind to genotype.

3.2.1.2 Sub-samples and APOE genotypes

3.2.1.2.1 Comparison by APOE risk

To investigate predicted differences between different alleles of the *APOE* gene (which have different levels of risk associated with onset of AD in later life), I recruited across all participants in whom I had collected saliva samples in exchange for either course credits or a cash payment. A total of 148 participants agreed to take part with an *APOE* genotype breakdown of: ε2/ε3 = 23, ε2/ε4 = 5, ε3/ε3 = 81, ε3/ε4 = 36, ε4/ε4 = 1, failed genotyping = 2. Participants with failed genotyping were removed, leaving a total of 146 participants for analysis. Participants were then grouped based on their level of *APOE*-related risk. The low-risk group included individuals with the ε2/ε3 combination (n=23, mean age (SD) = 21.3 (0.8) years), the normal-risk group included individuals carrying the ε3/ε3 combination (n=81, mean age (SD) = 21.3 (1.3) years), and the high-risk group included individuals with either the ε2/ε4, ε3/ε4, or ε4/ε4 combinations (n=42, mean age (SD) = 20.8 (0.8) years). Compensation for time given to undertake the VPC task was given in the form of either course credits or a cash payment.

3.2.1.2.2 Matched comparison of APOE-ε4 carriers vs non-carriers

To look more directly at the extent to which the *APOE*-ε4 gene affects performance on the VPC task, a subset of 27 ε3/ε4 heterozygotes (carriers - mean age (SD) = 20.6 (0.6) years) and 27 ε3/ε3 homozygotes (non-carriers - mean age (SD) = 20.6 (0.6) years) were matched based on age, education, and family history of dementia.

3.2.2 Design and stimuli

Two main variables were manipulated in this newly designed VPC task: *Stimulus-Type* (Scenes vs Objects) and *Stimulus Similarity* (Similar vs Dissimilar). For the scene stimuli, 36 pairs of natural scenes were used (acquired from Google Images, derived using category terms (e.g. meadow) and the image similarity function), including 18 pairs of similar scenes (e.g. two different snowy mountains) and 18 pairs of dissimilar scenes (e.g. a beach and a rainforest). Similarly, the object stimuli consisted of 36 pairs of real-life objects (acquired from Hemera object database, Vol. 1–3), including 18 pairs of similar objects (e.g. two different kettles) and 18 pairs of dissimilar objects (e.g. a kettle and a laptop computer) (for examples of stimuli pairs, see Figure 3.2).

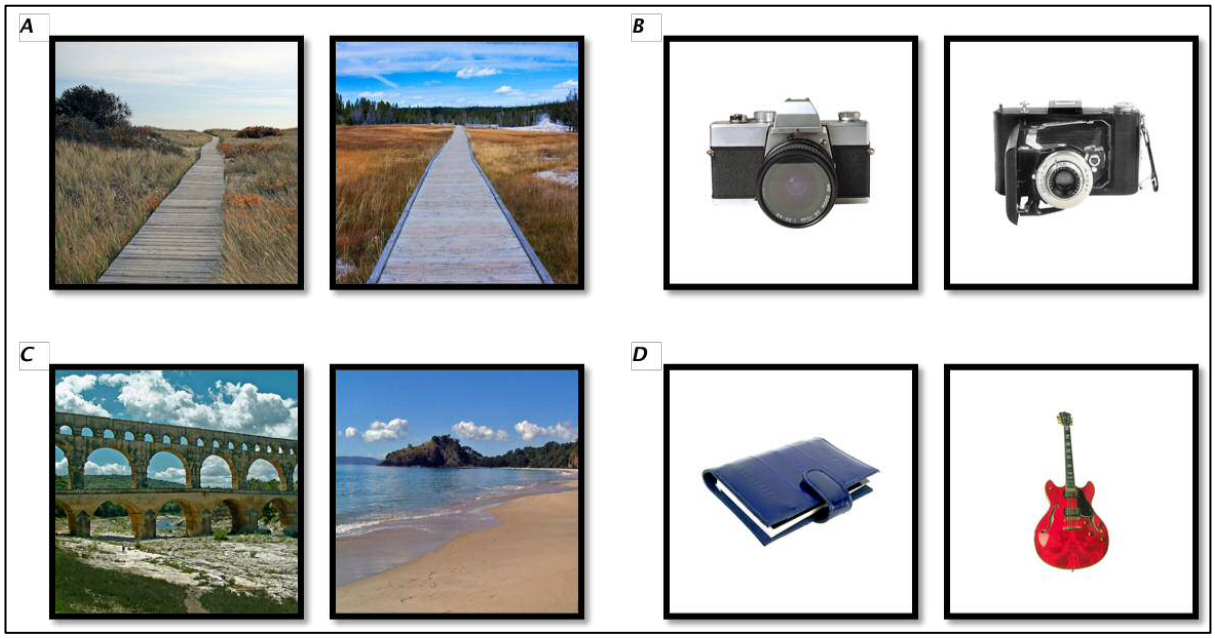

Figure 3.2 – Example of stimulus-pairs used in the current task. This includes Similar Scenes (A), Similar Objects (B), Dissimilar Scenes (C), and Dissimilar Objects (D).

Each stimulus-pair was randomly allocated to one of three blocks. Each block comprised two main phases: The *familiarisation phase,* whereby a series of 24 pairs of identical stimuli were presented on-screen for five seconds per pair. Following this was a break of two minutes (similar to Crutcher et al., 2009; Zola et al., 2013), although the actual break between familiarisation and test of a particular stimulus-pair was ~252 seconds after factoring in the time spent presenting other stimuli (24 x 5s trials + 24 x 0.5s inter-stimulus interval + 120s break). This break length is short enough to exhibit a strong novelty preference (Richmond, Sowerby, Colombo, & Hayne, 2004), but also long enough to observe an effect of cognitive impairment (Crutcher et al., 2009). Following the break, the *test phase* involved 24 pairs of stimuli. One stimulus from the presentation phase (*familiar*) was paired with one *novel* stimulus and appeared on screen for five seconds per trial (see Figure 3.3). The Stimulus-Type, Similarity, and left-right positioning was pseudo-randomised across each block of 24 trials. This process was

repeated a further two times, with a total number of 72 trial-unique trials presented across all three blocks. The entire VPC task lasted around 25 minutes per participant.

The study adhered to the British Psychological Society's Code of Ethics and Conduct (The British Psychological Society, 2018) and was approved by Cardiff University School of Psychology's ethics committee.

3.2.3 Apparatus

The task was developed using Matlab, PsychToolbox-3 and the Tobii SDK 3.0. Eye-movements were recorded using a 300hz static Tobii Pro TX300 eye-tracker attached to a 23" monitor, based in a light and temperature-controlled room. Five-point calibration was carried out prior to each phase. Recorded eye-movements were binocular, and the participant could move their head freely without a chin-rest.

3.2.4 Procedure

On arrival for the study, participants were provided with an information sheet and consent form, in line with the agreed ethics. They were seated at a desk next to the experimenter, but with a divider to prevent any distraction. At the start of each block, participants completed the calibration-process and were then verbally and visually instructed to "relax and just look at the screen as though watching television" during both stages. They were also instructed to stay as still as possible during the process to ensure maximum accuracy from the eye-tracker. When they were ready, they began the familiarisation phase, followed by the two-minute break, followed by the test phase. During the entirety of each block, all eye-movements were recorded. Following each block, participants could take a short break and/or change position before recalibrating the eye-tracker and starting the second and third blocks. At the end of the task, participants were debriefed on the task.

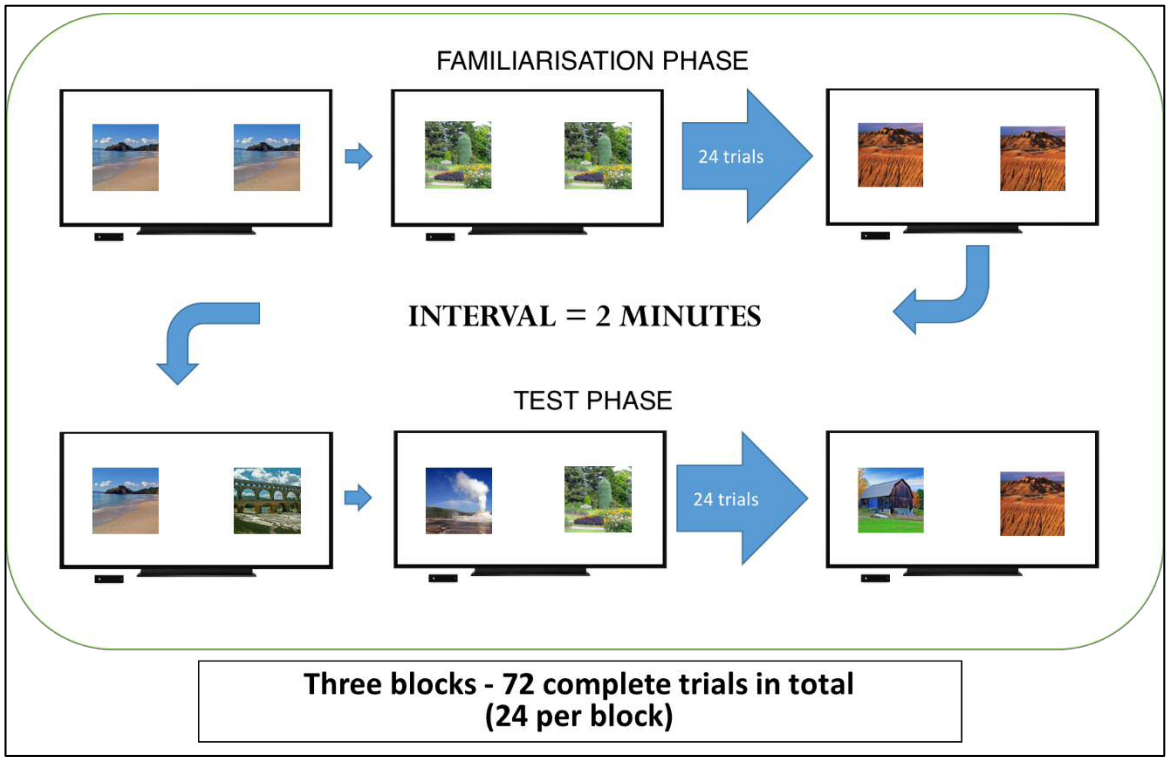

Figure 3.3 – Visualisation of each block structure in the current VPC task.

3.2.5 *Fixation analysis and eye-tracking measures*

The Tobii Pro TX300 eye-tracker outputs a row of gaze-data 300 times per second, each of which include two-dimensional coordinates for where the individual was looking at that time-point. Each data-point was first allocated to a trial based on its timestamp and the data was then separated into individual trials. A velocity-threshold fixation identification method was then used to separate data into saccades and fixations. This method calculated the point-to-point velocity for each data-point in the output. Data-points with a velocity above a threshold of 20 degrees/second were classified as saccades and the data-points in-between saccades were classified as fixations. Consecutive fixation points were then collapsed into fixation groups and the centroid of the group's coordinates were used as the location of the fixation. Any fixations less than 100ms were removed (see Salvucci & Goldberg, 2000 for detailed review of fixation detection methods).

For each trial in the test phase, fixations were allocated to either the novel or the familiar image, depending on the coordinates of the fixation. The time spent fixated on the novel stimulus was divided by the total time spent fixating on both stimuli, resulting in the proportion of time spent fixating on the novel stimulus for each trial. All fixation and data analyses were completed using MATLAB and R.

3.3 Results

3.3.1 Comparison by APOE risk

One-sample *t*-tests confirmed that all groups (low-, normal-, and high-risk), in all conditions (stimulus-type: scenes and objects; similarity: similar and dissimilar), showed a viewing preference to the novel stimulus compared to a chance value of 0.5 (all p's < .001 – see Table 3.1 for descriptive statistics). Shapiro-Wilk tests indicated that, in the ε2/ε3 group, the data was not normally distributed in the Dissimilar Scenes (W = .881, p = .011), Dissimilar Objects (W = .903, p = .029), and Similar Objects (W = .878, p = .009) conditions.

MEAN NOVELTY PREFERENCE (SD)				
	Dissimilar Scenes	**Dissimilar Objects**	**Similar Scenes**	**Similar Objects**
LOW-RISK	.616 (.104)	.634 (.129)	.598 (.107)	.627 (.092)
NORMAL-RISK	.614 (.074)	.601 (.104)	.586 (.070)	.595 (.078)
HIGH RISK	.604 (.066)	.599 (.071)	.582 (.059)	.602 (.062)

Table 3.1 – Mean proportion of time (per trial) spent looking at the novel image (calculated as 'time viewing novel image' / 'total viewing time'), separated for each APOE-type and for each condition.

As the size of the *APOE*-risk groups were unbalanced, outliers were present, and the data lacked homoscedasticity, a standard repeated-measures ANOVA model was not appropriate (see Figure 3.4). Instead, a linear mixed-effects model comparison was

constructed, using the lme4 package (Bates et al., 2015) in R (R Core Team, 2015). This process involved building four models: a 'full model', including an interaction of *APOE*-group, stimulus-type and similarity; a 'stimulus-type model', including an interaction between stimulus-type and *APOE*-group; a 'similarity model', including an interaction between similarity and *APOE*-group; and a 'null model', with no interaction terms included (see Box 3.1). As well as allowing for unbalanced groups, this approach greatly increases the degrees of freedom by including data for every trial, rather than averaging across conditions. Each model therefore factored in subject and stimulus-pairs as random-effects.

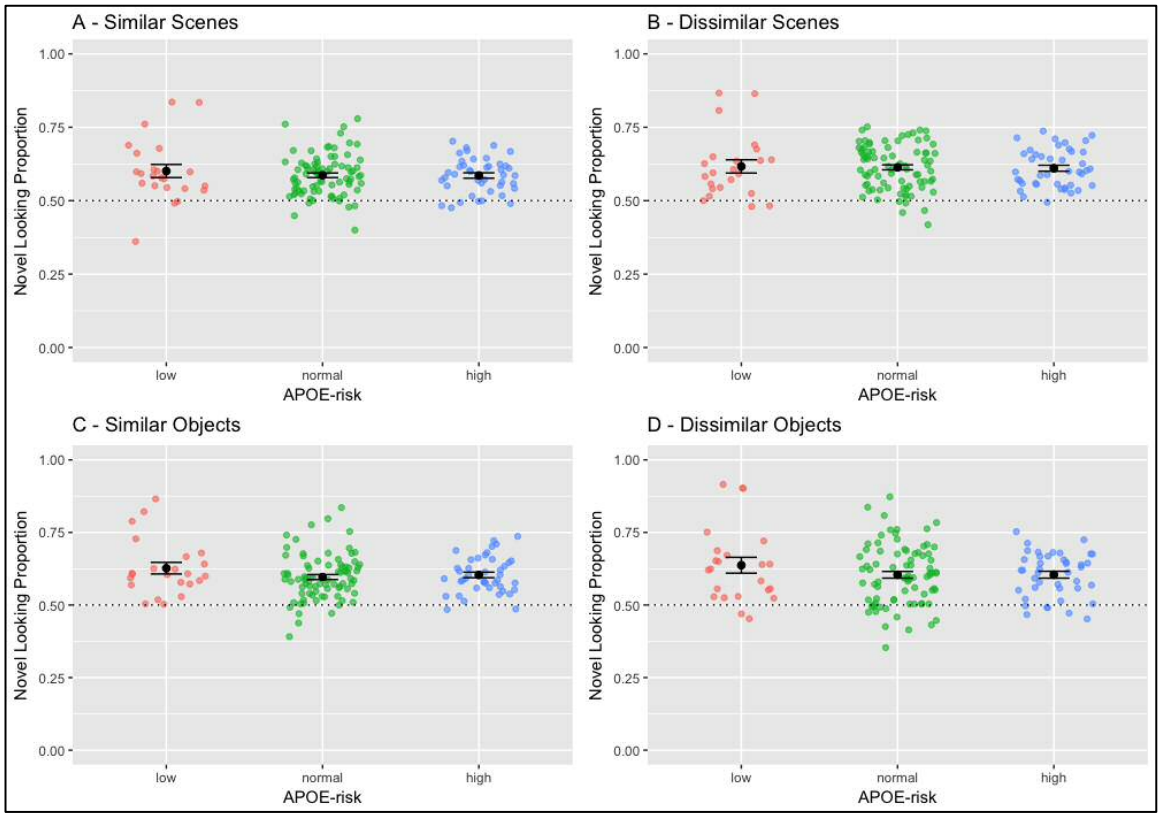

Figure 3.4 – Distribution of data for each group. Each coloured dot represents the mean novelty preference for a single subject. The black dots represent the mean for that group/condition with the bars representing one standard error.

The three interaction models were then compared to the null model using a likelihood ratio test. This found that the full model accounted for the largest amount of variance in novelty preference when compared to the null model ($\chi^2(5) = 15.66$, $p = .008$). The stimulus-type model predicted marginally more variance than the null model ($\chi^2(2)$

= 5.53, $p = .063$), whereas there was no difference between the similarity ($\chi^2(0) = 0.00$, $p > .999$) and null models.

Full model

This model included fixed effects of *APOE*-type, stimulus-type, and similarity as an interaction, and subject and stimulus-family as random effects.

*viewingToNovel ~ stimulusType * similarity * apoeGroup + (1|subject) + (1|familyNo)*

Stimulus-type model

This model included an interaction of *APOE*-type and stimulus-type, had similarity as a separate fixed effect, and subject and stimulus-family as random effects.

*viewingToNovel ~ stimulusType * apoeGroup + similarity + (1|subject) + (1|familyNo)*

Similarity model

This model included an interaction of *APOE*-type and similarity, had stimulus-type as a separate fixed effect, and subject and stimulus-family as random effects.

*viewingToNovel ~ similarity * apoeGroup + stimulusType + (1|subject) + (1|familyNo)*

Null model

APOE-Type, stimulus-type, and similarity as separate fixed effects, along with subject and stimulus-family as random effects.

viewingToNovel ~ stimulusType + similarity + apoeGroup + (1|subject) + (1|familyNo)

Box 3.1 – Structure of models used in the linear mixed-effects model comparison.

Post-hoc analyses of the full model were conducted using the *emmeans* package (Lenth, 2018) in R. This uses estimated marginal means with a Kenward-Roger degrees of freedom method along with a Tukey method of comparison. The analysis indicated that the normal- ($t(1280.30) = 4.10$, $P_{tukey} < .001$) and high- ($t(2922.98) = 3.04$, $P_{tukey} = .029$) risk groups had a significantly lower novelty preference for similar scenes compared to dissimilar scenes, with novelty preference decreasing by an estimated 3.3% (± 0.73 SE) and 2.8% (± 0.94 SE) of total viewing time for normal- and high-risk groups, respectively (see Figure 3.5). The low-risk group, however, showed no significant difference in performance on the similar and dissimilar scenes ($t(5956.61) = 1.47$, $P_{tukey} = .685$).

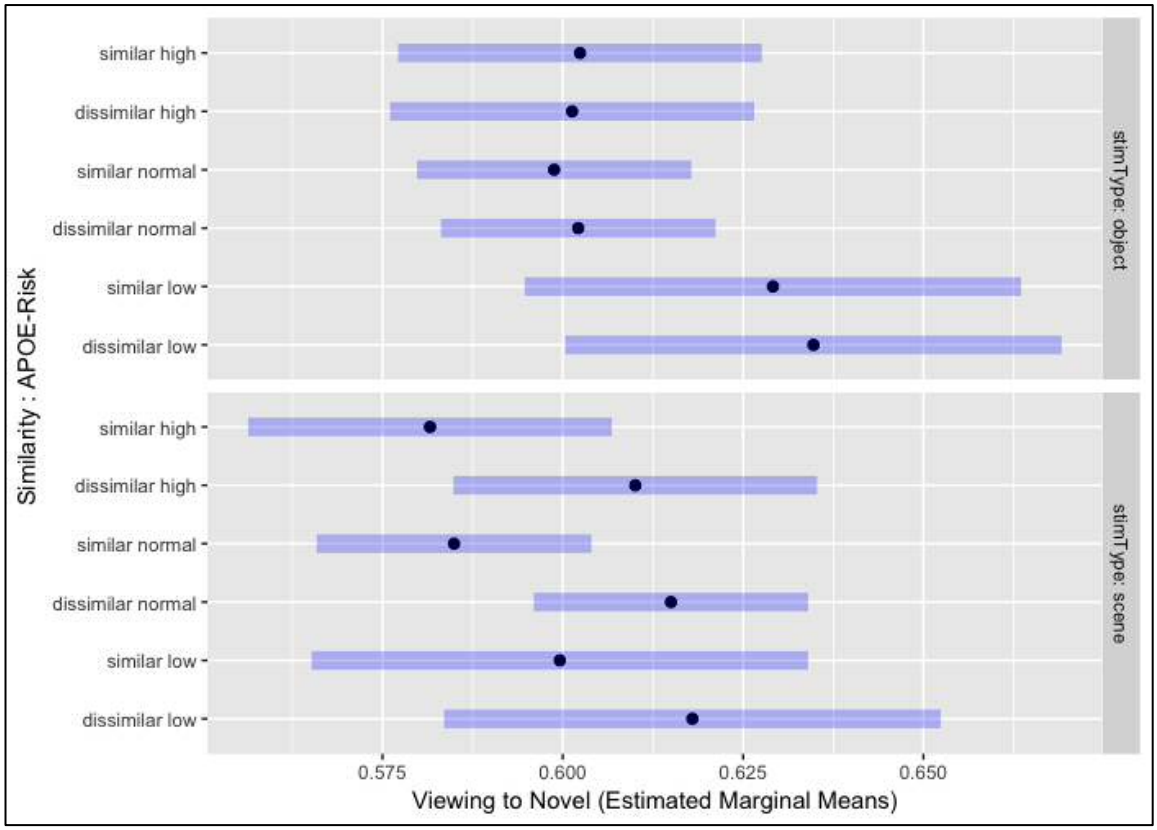

Figure 3.5- This output from the emmeans package shows the estimated marginal means (of viewing proportion to the novel stimulus) for each APOE-risk group (low, normal, high) and level of similarity (similar, dissimilar), separated by stimulus-type (object, scene)

Post-hoc analyses of the stimulus-type model were also conducted using the *emmeans* package (Lenth, 2018) in R, using estimated marginal means with a Kenward-Roger degrees of freedom method along with a Tukey method of comparison. The analysis indicated a marginal difference in novelty preference between scene and object stimuli ($t(10402.45) = 2.75$, $P_{tukey} = .071$) for the low-risk group, with novelty preference decreasing by an estimated 2.3% (± 0.85 SE) of total viewing time for the scene (compared to object) stimuli (see Figure 3.6).

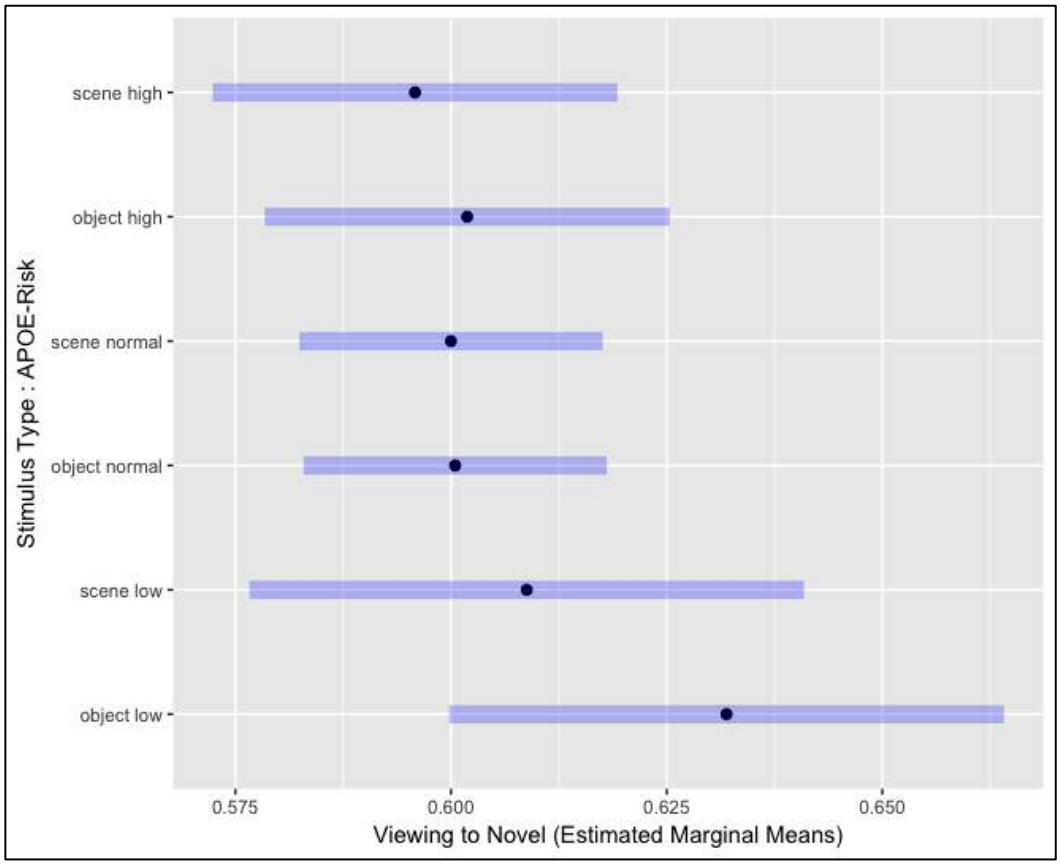

Figure 3.6 – This output from the emmeans package shows the estimated marginal means (of viewing proportion to the novel stimulus) for each APOE-risk group (low, normal, high) and stimulus-type (object, scene). The black dots represent the estimated marginal mean and blue bars represent the 95% confidence intervals.

3.3.2 *Comparison of APOE-ε4 carriers vs non-carriers*

One-sample *t*-tests confirmed that both groups (carriers and non-carriers), in all conditions (stimulus-type: scenes and objects; similarity: similar and dissimilar), showed a viewing preference to the novel stimulus (all p's < .001 – see Table 3.2 for descriptive statistics). Shapiro-Wilk tests indicated that both groups and conditions were normally distributed (all p's > .05).

MEAN NOVELTY PREFERENCE (SD)				
	Dissimilar Scenes	**Dissimilar Objects**	**Similar Scenes**	**Similar Objects**
CARRIERS	.606 (.067)	.600 (.077)	.591 (.063)	.610 (.062)
NON-CARRIERS	.615 (.075)	.611 (.095)	.580 (.064)	.596 (.062)

Table 3.2 – Mean proportion of time (per trial) spent looking at the novel image (calculated as 'time viewing novel image' / 'total viewing time'), separated by carriers and non-carriers for each condition.

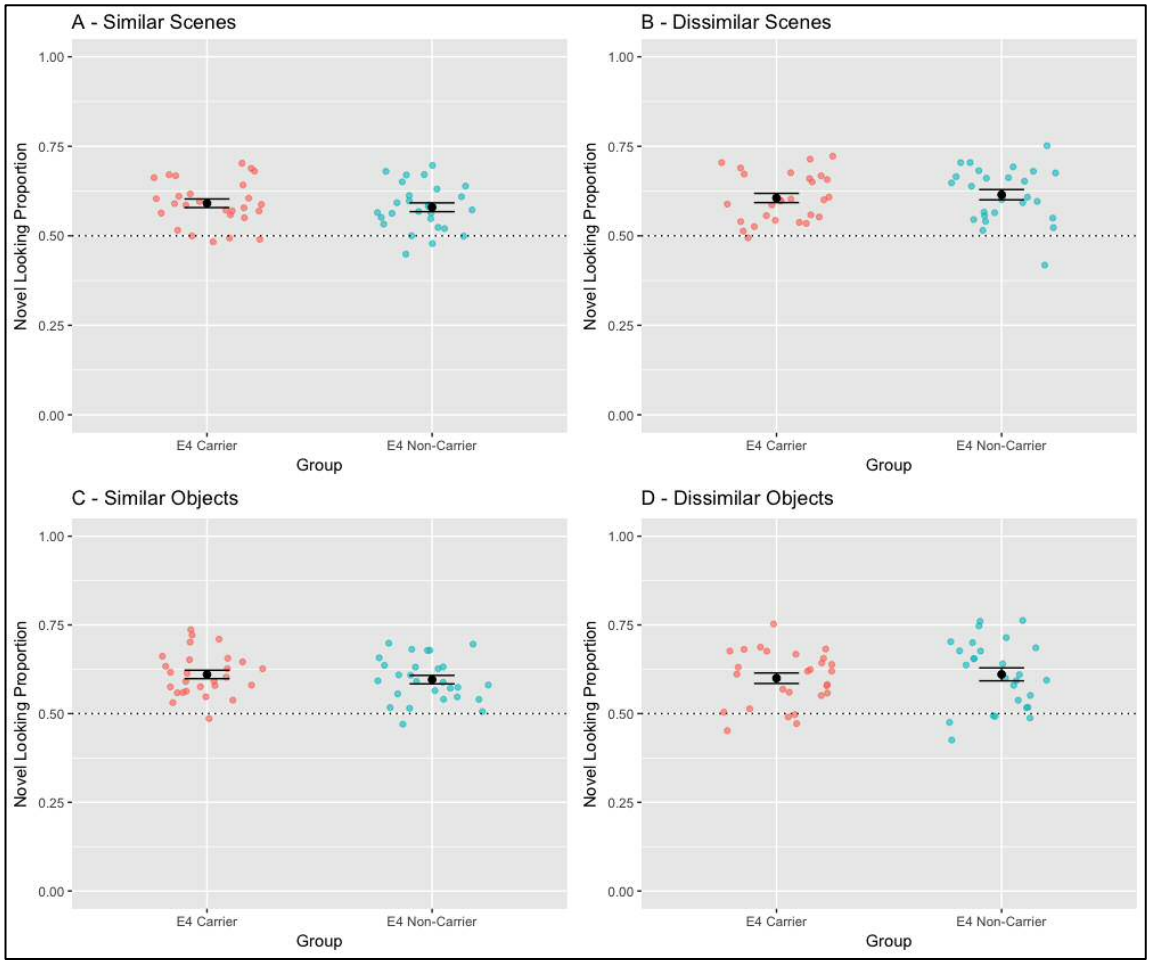

Figure 3.7 – Distribution of data for each group. Each coloured dot represents the mean novelty preference for a single subject. The black dots represent the mean for that group/condition with the bars representing one standard error.

Similar to the previous analysis, an LME model was used to increase the degrees of freedom by factoring in within-subject and stimulus-pair error variance. The same model structure used earlier were constructed but using carrier status as the *APOE*-group instead (see Box 3.1). This resulted in four models: a 'full model', including an interaction of group, stimulus-type and similarity; a 'stimulus-type model', including an interaction between stimulus-type and group; a 'similarity model', including an interaction between similarity and group; and a 'null model', with no interaction terms included. Each model factored in subject and stimulus-pairs as random-effects.

P-values were then obtained using likelihood ratio tests of all three models against the null model. This approach found that the similarity model explained

significantly more of the variance in novelty preference then the null model ($\chi^2(0) = 3.65$, $p < .001$). The full ($\chi^2(3) = 4.71$, $p = .195$) and stimulus-type ($\chi^2(1) = <.001$, $p = .946$) models were not significantly different from the null model.

Post-hoc analyses on the similarity model were conducted using a Kenward-Roger degrees of freedom method along with a Tukey method of comparison on the estimated marginal means from the similarity model (see Figure 3.8). The analysis indicated that the interaction effect was driven by a significant difference between similar and dissimilar stimuli in the *APOE*-ε4 non-carriers ($t(845.22) = 2.90$, $P_{tukey} = .020$), with novelty preference increasing for dissimilar stimuli by an estimated 2.59% (± 0.90 SE) of total viewing time, compared to similar stimuli.

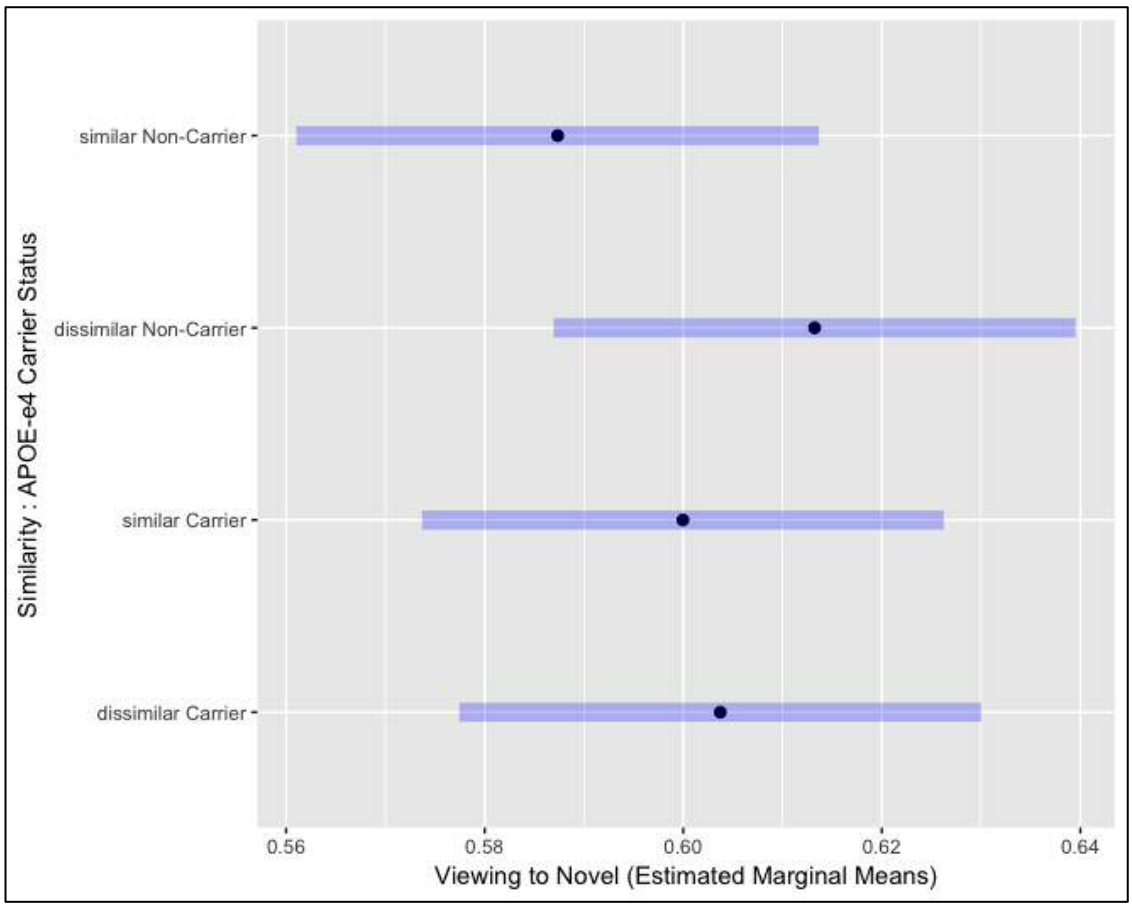

Figure 3.8 – This output from the emmeans package shows the estimated marginal means (of viewing proportion to the novel stimulus) for each group (carriers and non-carriers) and level of similarity (similar, dissimilar), collapsed across stimulus-type. The black dots represent the estimated marginal mean and blue bars represent the 95% confidence intervals.

The difference between the mean similar and dissimilar novelty preference was then calculated for each participant. An independent-samples *t*-test found that the increase in novelty preference for dissimilar compared to similar stimuli was significantly greater for *APOE*-ε4 non-carriers (M = .023, SD = .051) compared to *APOE*-ε4 carriers (M = .002, SD = .040), $t(52) = 1.80$, $p = .039$.

3.4 Discussion

The aim of this chapter was to investigate whether performance on a VPC task using ambiguous scenes and objects would be affected by *APOE* gene status, in a profile aligned to the documented influence of *APOE* alleles on later life risk of developing AD. First, it was predicted that there would be a linear relationship between *APOE*-risk (low-risk > normal-risk > high-risk) and performance for scene-type, but not object-type, stimuli and that this would be particularly evidence for similar (ambiguous) compared to dissimilar, stimulus-pairs. Second, it was predicted that carriers of the *APOE*-ε4 gene would perform worse (less evidence of a novelty preference) than *APOE*-ε4 non-carriers for scene-type stimuli, but not object-type stimuli, and that this difference would increase when the stimulus-pairs were similar compared to dissimilar.

In the analysis by risk-type (low, normal, high), the full model including an interaction of *APOE*, stimulus-type and similarity was found to be significantly more predictive of the variance in novelty preference than a null model without that interaction. Post-hoc tests using estimated marginal means based on the full model did not find support for the hypothesis that there would be a linear relationship between *APOE*-risk groups and novelty preference for similar or dissimilar scenes or objects, although there was a non-significant trend in this direction for the scenes. Instead, the interaction was driven by a significant reduction in novelty preference for similar scenes, compared to dissimilar scenes, in the normal- and high-risk groups, but not the low-risk group. This provides some evidence that young adults with a normal- or high-risk of

developing AD in later life show a lower level of novelty preference for scene stimuli, when the familiar and novel scenes are visually similar. The lack of a significant difference in the low-risk group does not, however, indicate that they are not affected by similarity. Although the estimated marginal means in this group for similar and dissimilar scenes were much closer, the confidence intervals were also larger, which is likely due to the lower size and increased variability in novelty preference in this group.

In addition to the full model, the stimulus-type model also showed a trend for the analysis by risk-type. The post-hoc analyses on this model found this to be driven by a marginal increase in novelty preference for objects, compared to scenes, for the low-risk group. This provides tentative evidence that young adult individuals at a low risk of developing AD in later life, based on the presence of *APOE*-ε2/ε3 alleles demonstrate a stronger novelty preference (linked to better recognition memory) for objects compared to scenes.

These findings provide some evidence, albeit limited, towards a potential cognitive resilience or benefit in *APOE*-ε2/ε3 carriers in the recognition of similar scene-type stimuli compared to dissimilar, and also for objects more generally compared to scenes. Unfortunately, the statistical comparisons between unbalanced groups severely reduces the degrees of freedom, making them underpowered in this sample. This could be improved by sampling matched groups and a-priori analyses in a future study. Looking at broader genetic risk for AD using a polygenic risk score could also increase power, which would allow for more powerful predictive models to include a scaled measure of risk, but also perhaps provide greater specificity for overall genetic risk.

The second analysis carried out in this chapter looked specifically at the high-risk *APOE*-ε4 allele, by comparing a group of *APOE*-ε4 carriers with a specifically matched group of *APOE*-ε4 non-carriers. The results hinted at a potential interactive relationship between *APOE*-ε4 and similarity. As predicted, *APOE*-ε4 non-carriers showed a reduction in novelty preference when the stimulus pairs were similar,

compared to when they were dissimilar. Unexpectedly, however, the *APOE*-ε4 carriers performed comparatively for both similar and dissimilar stimuli, the opposite to the hypothesised results. Although the current study provides no evidence for the mechanisms underpinning these differences, theoretically speaking it is possible that inefficiencies in the hippocampus, or projections to/from the hippocampus, may result in a compensatory overdependence on other MTL regions that are more feature-focussed and less sensitive to gestalt ambiguity between two stimuli.

The lack of power for group-wise comparisons is frustrating as it is difficult to make any confident assumptions about the effects of *APOE* using the current findings. The trends in the data, however, suggest that the current version of the VPC task may be sensitive to very early changes in the brain linked to the *APOE* gene, and this may be useful in improving assessment and diagnostic tools that use a VPC to identify potential future risk of AD (e.g. Neurotrack Technologies, Inc., 2017; Whitehead et al., 2018). It is likely that any cortical changes due to *APOE* will have a minimal effect on cognition in a young adult population, and these changes will be further minimised in individuals scoring both high on intelligence and with a high level of education, which is associated with increased cognitive function (Lee, 2003). There is a large gap between the current cohort and the normal age of clinical diagnosis for late-onset AD, so the current task may be more sensitive *APOE*-related vulnerabilities in a slightly older population in whom there may be a greater impact from *APOE*-related pathology. In Chapter 4, I investigate this using a cohort of mid-age adults using the same VPC task as reported in the current chapter.

It may be possible to increase power in a similar sample to the current study by changing the stimuli that were used here. This could involve developing 'virtual' stimuli-sets that are systematically designed to emphasise novelty and/or ambiguity based on spatial components of a scene. Unfortunately, the extensive piloting I carried out for the current task using varying stimulus-sets revealed low levels of interest from participants in virtual stimuli, which resulted in a low level of overall novelty preference

in the task. An alternative would be to linearize the level of similarity in the current stimuli, which would reduce and control the within-category, between-trial, noise. This could be done using either subjective measures of similarity (e.g. "How similar are the following two images?"), or more complex but objective measures, such as image analysis tools (e.g. the Structural Similarity Index (SSIM) toolbox in MATLAB).

Another way to increase power in young adults would be to use a much larger cohort. With only 14% of the population carrying an *APOE*-ε4 allele (Corbo & Scacchi, 1999), and even fewer (9%) carrying an *APOE*-ε2 allele, the practicalities and cost of genotyping large enough samples to have enough power to detect such small differences is prohibitive. As already mentioned, a better solution (than looking solely at *APOE* alleles) would be to apply polygenic risk approaches, which would factor in other genes that are known to increase risk of developing AD in later life and allow use of the whole cohort in correlational analyses rather than separating participants into different risk groups. Alternatively generating larger sample sizes without the large costs could be done by using existing cohorts in which genetic data is available; however, collecting new data in these cohorts may both expensive and time-consuming, and this is particularly the case with a VPC task that that requires both an expensive eye-tracker and one-on-one interaction with the experimenter.

This approach, however, may change in the future. Eye-tracking technology is rapidly reducing in cost, with basic eye-trackers now available for under £100. Furthermore, application and web developers are now improving the accuracy of tracking eye-movements using a standard webcam (Bott et al., 2017). Others are developing innovative ways of running a VPC task without tracking eye-movements, using a mouse or touch-screen to 'reveal' small parts of the screen and then monitoring how much time individuals spend on the novel-revealed stimuli, rather than the familiar (U.S. Patent No. 9,629,543 B2, 2017).

It is also now possible to investigate some of the mechanisms underpinning potential differences in neuro-cognition during the VPC task using a combination of eye-

tracking and fMRI. Shine et al. (2015) found that young *APOE*-ε4 carriers have differing patterns of activity in the posteromedial cortex during a scene-perception task. This region is functionally connected to networks involving visuo-spatial movement, attentional control, eye-movements and higher-order visuo-spatial perception (Cauda et al., 2010). Perhaps using the current VPC task in fMRI might uncover differences in functional connectivity, and/or the patterns of activation in relevant networks, in individuals possessing different alleles of the *APOE* gene.

If we can further develop our understanding of how the VPC task demands different brain regions and networks related to both scene and object processing, its wider use as a diagnostic tool has some clear benefits. The task requires no motor skills, demands no language comprehension, and has little or no instruction to participants; meaning it is good for assessing populations across the world where there would normally be a language barrier, or where there are varying educational and intellectual abilities. It can also be run with minimal equipment, and when it becomes possible to run the task using just a standard webcam and/or mouse it might be developed—after suitable experimental studies following-on from the intriguing results reported here—into a potential diagnostic tool for use at home, in remote regions, or in countries where expensive equipment is not readily available.

CHAPTER 4:
APOE-RELATED DIFFERENCES IN PERFORMANCE ON A VISUAL PAIRED-COMPARISON TASK IN MIDDLE-AGE ADULTS

4.1 Introduction

In Chapter 3, I used a modified VPC task to investigate recognition memory for similar (vs dissimilar) scenes and objects in young adults with different *APOE* genotypes. I found that individuals with an AD risk that is higher than the population (as evidenced by the presence of an *APOE*-ε4 allele), and in those in whom there is a normal-level degree of risk (as measured by the presence of an *APOE*-ε3 allele), had a lower level of recognition memory (as measured by a novelty preference score) for similar scenes compared to dissimilar scenes. By contrast, individuals in a low-risk AD group (who have an *APOE*-ε2 allele) showed no difference in their novelty preference for similar and dissimilar scenes. Furthermore, there was a trend suggesting that individuals with an *APOE*-ε2 allele have better recognition memory (a greater novelty preference) for objects (whether similar or dissimilar), compared to participants with an *APOE*-ε3 and an *APOE*-ε4 allele. In addition to this, a separate matched *APOE*-ε4 carrier vs non-carrier analysis found that increasing the similarity between stimuli, whether scenes or objects, resulted in a significant reduction in novelty preference in non-carriers, but not carriers. These results suggest that the VPC task may be sensitive to cognitive differences between *APOE*-ε4 carriers and non-carriers, and especially when the target and distractor are visually ambiguous.

The VPC task was chosen as it has previously been shown to be sensitive to early cognitive changes related to AD (Zola et al., 2013). The version of the task used in Chapter 3 involved manipulation of the similarity in objects and scenes, with the aim of increasing the need to resolve featural and spatial ambiguity, which previous lesion studies have shown to be dependent upon MTL structures, such as the PRC and HC (Aly

et al., 2013; Lee et al., 2006; Lee, Buckley, et al., 2005). The level of *APOE*-related risk for sporadic AD increases with age (Jarvik et al., 1995). In this chapter, therefore, I used the same VPC task in middle-age adults (aged 45 to 57 years old) in order to determine whether the effects seen in Chapter 3, in younger individuals, might be more prominent in middle-aged adults. I predicted that individuals carrying *APOE* alleles associated with a greater risk for sporadic AD (e.g. *APOE*-ε4) will have a greater reduction in novelty preference on a VPC task involving similar scenes, compared to dissimilar, than carriers of low-risk alleles (e.g. *APOE*-ε2). I also predict that there will be no difference between different *APOE* groups in the object condition.

As background, as individuals get older, it is thought those with an increased *APOE*-related risk of AD (via the presence of an *APOE*-ε4 allele) will have greater deposits of Aβ, resulting in an increased burden on the function of susceptible regions, such as the HC (Castellano et al., 2011). A number of studies have found that cerebral Aβ deposition and tau levels increase with age in individuals with high-risk *APOE* genotypes, but that this pattern is not in low-risk genotypes (e.g. Kester et al., 2009; J. C. Morris et al., 2010; Small et al., 2009). These *APOE*-age-related biological changes appear to result in a reduction in cognitive function (Yu et al., 2013). For example, Dubé et al. (2013) found that older *APOE*-ε4 carriers are much more likely than non-carriers to have what they describes as "subtle deficiencies in memory or executive functioning that do not fit the definition of dementia but are also abnormal". Remarkably, Deary et al. (2002) conducted a study spanning differences over seven decades. They tested 500 individuals at age 80 using the Mini-Mental State Examination (MMSE) scores and compared results against MMSE scores collected in 1932 at age 11. They found that *APOE*-ε4 had a significant effect at age 80, compared with no effect at age 11, albeit using an unsophisticated measure of cognition.

Lim et al. (2012) also found that the *APOE*-ε4 allele is more specifically associated with a rapid decline in visuospatial learning in older adults. They used a paired associate-learning (PAL) task, which requires participants to learn increasing sets of

pattern-location associations, with each level of difficulty placing greater load on visuospatial memory. They found that individuals with a high level of cerebral Aβ performed significantly worse (than individuals with low levels of cerebral Aβ) on the task. The PAL task has been repeatedly shown to preferentially recruit brain regions associated with complex spatial perception, such as the hippocampal formation (for review see Barnett, Blackwell, Sahakian, & Robbins, 2015), which suggests that Lim and colleagues' findings might be indicative of an increased AD-related pathology on or around HC-connected networks in older healthy *APOE*-ε4 carriers.

It is not just elderly adult *APOE*-ε4 carriers that show impaired cognitive function. In one longitudinal study, Blair et al. (2005) found that middle-age *APOE*-ε4 carriers were also impaired, compared to non-carriers, on tasks involving verbal learning and memory, attention, and psychomotor skills. Although this appears to partly contrast with Lim and colleagues' (2012) suggestion that *APOE*-related impairment might be particularly focussed on visual spatial learning, Blair et al. used a longitudinal design which may be more sensitive than a group-wise comparison. That said, they also did not directly test spatial perception/memory which limits direct comparison with Lim et al. (2012). Blair et al. also note that the changes over time were noteworthy but small. Other studies have also noticed *APOE*-related impairments in visuospatial attention (e.g. Greenwood, Lambert, Sunderland, & Parasuraman, 2005; Greenwood, Sunderland, Putnam, Levy, & Parasuraman, 2005), which might suggest that *APOE*-ε4-related pathology at middle-age impairs the visual attention networks that were previously facilitated, compared to non-carriers, in younger adulthood (Rusted et al., 2013).

These alterations in cognition reflect reported *APOE*-related cortical and functional differences in mid-life. Middle-aged *APOE*-ε4 carriers have been shown to have a reduction in HC volume (Cohen et al., 2001), which may relate to reported impairment in spatial working memory (Greenwood, Lambert, et al., 2005). Trachtenberg et al. (2012) also found increased activation in *APOE*-ε4 carriers of MTL

and frontal lobe regions during memory encoding of scenes. These include increased activation in the PCC, a region found to already to have increased activation for scene-specific discrimination in young adult *APOE*-ε4 carriers (Shine et al., 2015). This suggests that the earlier life functional differences seen in young *APOE*-ε4 carriers extends into mid-life in tasks involving perception and memory for spatially complex stimuli (such as scenes), although it should be noted that increased activation has also been found in *APOE*-ε4 carriers during a recognition memory task for faces (Xu et al., 2009), which may be indicative of *APOE*-related pathology becoming more widespread in middle-age.

Overall these reported changes in structure, function, and cognition in middle-age cohorts seem consistent with both the subtler cognitive alterations seen in earlier life and the likely expected risk for onset of dementia according to the presence or absence of particular *APOE* alleles. A recent meta-analysis, however, sheds some doubt on the potential consistency of the impact of *APOE* on cognition at this age. Lancaster et al. (2017) combined data from 23 studies conducted since 1993 and found no overall effect of *APOE* on any of the measured cognitive domains in middle-age. They do note, however, that many of the studies that have been completed to date use neurocognitive tests that are designed to detect clinically relevant cognitive differences, rather than more subtle and specific changes that might be expected in healthy middle-age *APOE*-ε4 carriers. As discussed in Chapter 1, one way of increasing sensitivity to such small changes could involve taking a more refined approach to understanding how memory might break down in dementia aligned to different systems supporting different forms of memory (e.g. Bussey & Saksida, 2007; Graham et al., 2010; Murray et al., 2017).

As has been discussed in previous chapters, one explanation for the inconsistency between results across studies, particularly when considering functional differences in brain networks between *APOE*-ε4 carriers and non-carriers, could be variation in healthy individuals cognitive reserve or ability to bring to bear compensatory mechanisms to support successful completion of tasks. One advantage of the VPC task is that it measures implicit recognition memory (via a novelty preference

measure), and individuals are not purposefully focussed on remembering the stimuli. It could be argued that this might reduce the likelihood of participants recruiting compensatory strategies, as they might do in a more explicit goal-orientated task, making it more sensitive to any subtle differences there may be in spatial memory.

Using the same VPC paradigm as outlined in Chapter 3, the current chapter focuses whether it is possible to demonstrate behavioural differences in novelty preference for scenes between *APOE*-ε4 carriers and non-carriers, enhancing the reports of scene differences related to *APOE*-ε4 reported in previous studies (e.g. Shine et al., 2015). In this study, as with Chapter 3, I manipulated visual similarity, and predicted that individuals at high risk of developing AD, via the presence of an *APOE*-ε4 allele, would show a lower novelty preference for scenes, compared to objects, particularly when the familiar and novel scene pair were visually similar (compared to dissimilar). Individuals at a lower level of risk for AD, such as those with an *APOE*-ε2 allele, would show the highest performance on the scene task, as measured by a longer novelty preference. I predicted no influence of *APOE* genotype on novelty preferences elicited in the object condition, but did hypothesise that similarity would result in smaller novelty preferences due to reduced memory for the previously presented item.

4.2 Method

4.2.1 Participant recruitment, DNA extraction and genotyping

Forty-seven adults aged between 45 and 57 (mean age = 52.5) were recruited from a cohort of approximately 165 healthy volunteers at the University of Sussex in Brighton, in which genotype data was available. All volunteers in the cohort were non-smoking and spoke English as their daily language. Individuals with a history of vascular health problems, untreated high blood pressure, psychoactive medication use, neurological trauma, or any psychiatric condition within the previous five years were excluded from the cohort. Double-blind procedures were followed during recruitment

so that the experimenter and participants remained blind to genotype; the downside of this for the experiment was that the distribution of individuals across genotypes could not be controlled and would not been known until the data analysis. Participants were given £10 Amazon vouchers for taking part in the experiment.

DNA extraction and genotyping had previously been conducted by researchers at the School of Psychology and Life Sciences at the University of Sussex, in line with Human Tissue Authority and the school Research Ethics Committee's guidelines and approval. DNA was collected by buccal swab, using an Isohelix SK1 kit. Samples were analysed by LGC Genomics (Hertfordshire, www.lgcgroup.com/genomics) to determine the presence of 3 major *APOE* alleles (ε2, ε3 and ε4) on 2 *APOE* SNPs (rs429358, rd7412) using a fluorescent-based competitive allele-specific polymerase chain reaction.

Although 47 participants were recruited for this study, in 6 of these participants there was a system error on the eye-tracker occurring part-way through the task. These individuals were therefore excluded from the final analysis. The *APOE* genotype of the remaining 41 participants consisted of: 1 x ε2/ε2, 4 x ε2/ε3, 28 x ε3/ε3, 7 x ε3/ε4, and 1 ε4/ε4. As outlined in previous chapters, individuals with an ε2/ε2 or ε2/ε3 combination were classified as low-risk (n = 5, mean age = 53.8 years, females = 5), those with ε3/ε3 were classified as normal-risk (n = 28, mean age = 52.3 years, females = 18), and those with ε3/ε4 or ε4/ε4 were classified as high-risk (n = 8, mean age = 52.6 years, females = 7).

The study adhered to the British Psychological Society's Code of Ethics and Conduct (The British Psychological Society, 2018) and was approved by the University of Brighton's School of Psychology and Life Sciences ethics committee.

4.2.2 Design and stimuli

The design of, and stimuli used in, the task was identical to that described in Chapter 3 (see Chapter 3.2.2 for further details).

4.2.3 Apparatus

As reported in Chapter 3, the task was developed and run in MATLAB using the PsychToolbox-3 package and Tobii SDK 3.0. For this study, however, I used a 60hz portable Tobii Pro X2-60 eye-tracker attached to a laptop that was connected to a 23" monitor. The study was conducted in a light and temperature-controlled room. Five-point calibration was carried out prior to each data collection phase. Eye-movement recordings were binocular, and the participants could move their head freely without a chin-rest (although they were asked to minimise any head/body movement to maximise the sensitivity of the measures obtained).

4.2.4 Procedure

On arrival, participants were seated beside the experimenter and provided with an information sheet and consent form, in line with the agreed ethics. At the start of each block, participants completed the calibration-process and were then instructed to "relax and just look at the screen as though watching television" during both familiarisation (the initial presentation of the images) and test (the presentation of the previous images alongside a novel image) phases. They were also instructed to stay as still as possible during the process to ensure maximum accuracy from the eye-tracker. When they were ready, they began the familiarisation phase, followed by the two-minute break, followed by the test phase (see Figure 3.3). During the entirety of each block, all eye-movements were recorded. Following each block, participants could take a short break and/or

change position before recalibrating the eye-tracker and starting the second and third blocks. At the end of the task, participants were debriefed on the task.

4.2.5 Fixation analysis and eye-tracking measures

The Tobii X2-60 eye-tracker outputs a row of gaze-data 60 times per second, each of which include two-dimensional coordinates for where the individual was looking at that time-point. As in Chapter 3, each data-point was allocated to a trial based on its timestamp and the data was then separated into individual trials. A velocity-threshold fixation identification method was then used to separate data into saccades and fixations, with any fixations less than 100ms were removed (for more detail see Chapter 3.2.5).

For each trial in the test phase, fixations were allocated to either the novel or the familiar image, depending on the coordinates of the fixation. The time spent fixated on the novel stimulus was divided by the total time spent fixating on both stimuli, resulting in the proportion of time spent fixating on the novel stimulus for each trial (a novelty preference score). All fixation and data analyses were completed using MATLAB and R.

4.3 Results

One sample *t*-tests confirmed that in all four conditions (scenes, similar and dissimilar, and objects, similar and dissimilar) for each group (low, normal and high risk) there was a significant novelty preference (all p's $< .05$) compared to a baseline of 0.5 (equal viewing of both stimuli). The only exception to this was in the low-risk group, where there was no significant novelty difference on the similar scenes condition ($t(4) = 1.95$, $p = .062$) (see Table 4.1 for descriptive statistics).

MEAN NOVELTY PREFERENCE (SD)				
	Dissimilar Scenes	**Dissimilar Objects**	**Similar Scenes**	**Similar Objects**
LOW-RISK	.658 (.096)	.649 (.151)	.621 (.139)	.659 (.107)
NORMAL-RISK	.606 (.081)	.604 (.111)	.566 (.077)	.586 (.089)
HIGH RISK	.584 (.093)	.614 (.056)	.574 (.077)	.570 (.057)

Table 4.1 – Mean proportion of time (per trial) spent looking at the novel image (calculated as 'time viewing novel image' / 'total viewing time'), separated for each APOE-type and for each condition.

As in Chapter 3, a linear mixed-effects model comparison from the lme4 package (Bates et al., 2015) in R (R Core Team, 2015) was used. Four regression models were considered: a 'full model', including an interaction of *APOE*-group, stimulus-type and similarity; a 'stimulus-type model', including an interaction between stimulus-type and *APOE*-group; a 'similarity model', including an interaction between similarity and *APOE*-group; and a 'null model', with no interaction terms included (see Box 3.1).

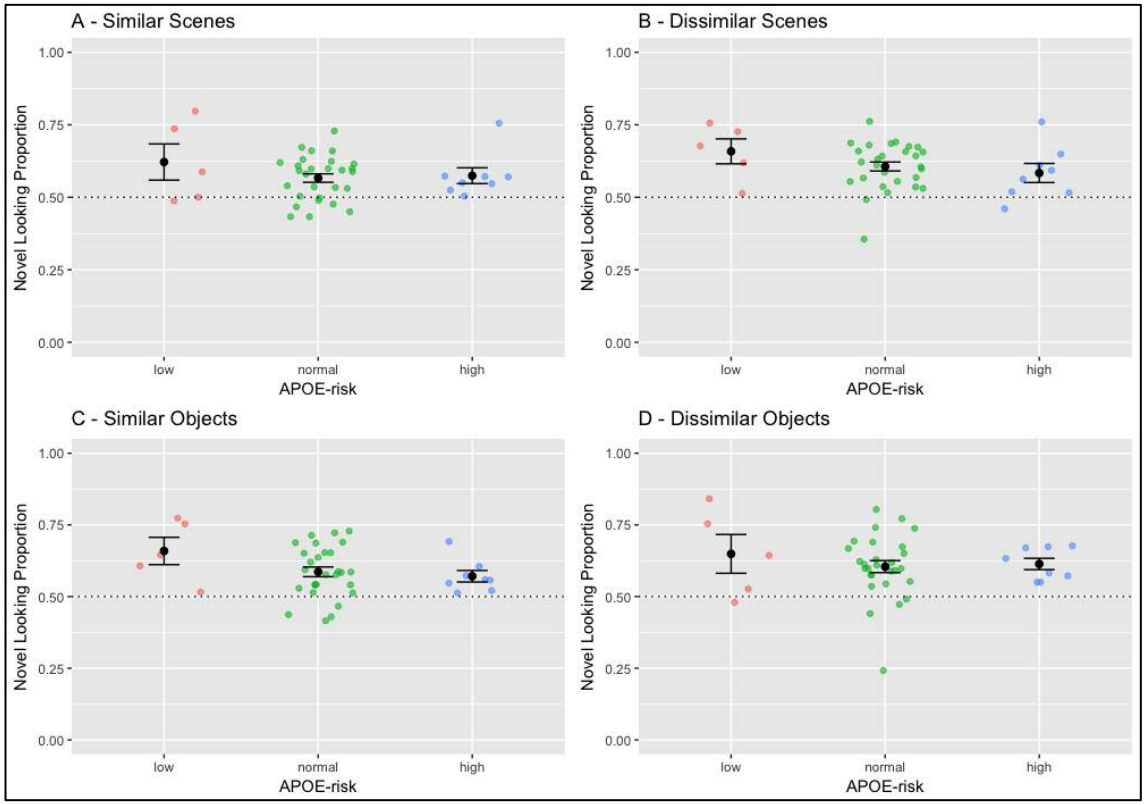

Figure 4.1 – Distribution of data for each group. Each coloured dot represents the mean novelty preference for a single subject. The black dots represent the mean for that group/condition with the bars representing one standard error.

The three interaction models were compared to the null model using a likelihood ratio test, which found that the similarity model predicted significantly more variance in novelty preference than the null model ($\chi^2(0) = 0.54$, $p < .001$). Post-hoc analyses of the similarity model were conducted using the *emmeans* package (Lenth, 2018) in R, using estimated marginal means with a Kenward-Roger degrees of freedom method along with a Tukey method of comparison. This found that the interaction is driven by a difference between the similar and dissimilar stimuli in the normal-risk group ($t(365.86) = 3.59$, $P_{tukey} = .005$), with dissimilar stimuli being viewed for approximately 2.8% (± 0.77 SE) of total viewing time compared to similar stimuli (see Figure 4.2). No other comparison was found to be significant.

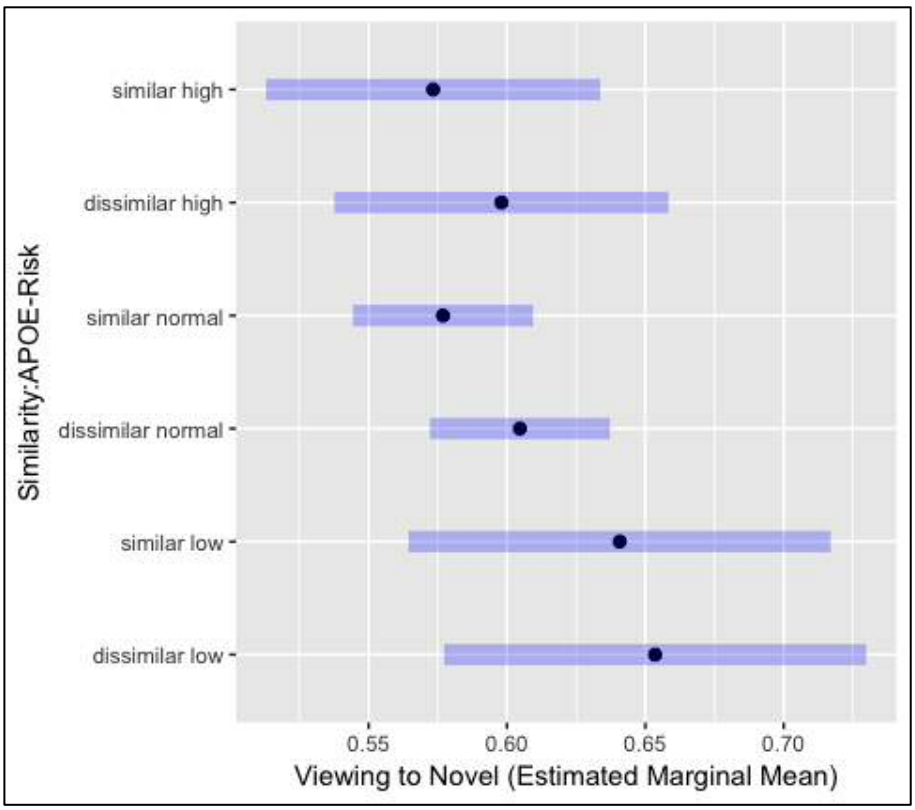

Figure 4.2 – This output from the emmeans package shows the estimated marginal means (of viewing proportion to the novel stimulus) for each APOE-risk group (low, normal, high) for similar and dissimilar stimuli. The black dots represent the estimated marginal mean and blue bars represent the 95% confidence intervals.

4.4 Discussion

The aim of this chapter was to investigate how novelty preference for scenes (as compared to objects), measured using a VPC task, would be influenced by different *APOE* genotypes. It was predicted that there would be a linear relationship between *APOE*-related risk for AD and novelty preference (low-risk > normal-risk > high-risk) for scenes-type (but not object-type) stimuli, and that differences between the groups would be more evident when similar (ambiguous) stimulus-pairs were presented compared to dissimilar stimulus-pairs.

The most predictive model from the LME model-comparison was one that included an interaction of *APOE*-risk and similarity, but not stimulus-type. This result suggests that, in this group of participants, using scene or object stimuli does not preferentially affect recognition memory (novelty preference) in one group of *APOE* genotype participants compared to another. Post-hoc analyses of the interaction between *APOE*-risk and similarity, using estimated marginal means, found that my identified effect was being driven by a difference between similar and dissimilar stimulus-pairs in the normal-risk group. There was no difference between novelty preference for similar and dissimilar stimuli in the low- or high-risk groups, though this finding may be due to very small sample sizes in these groups compared to the group.

The main weakness of this study was poor recruitment. The availability of participants to complete this task was limited, as it was completed over the summer when many individuals were on holiday. Using a double-blind design also meant that I could not check the distribution of *APOE* genotypes until data collection was finished, leading to a skewed group distribution towards the more common *APOE* genotype (*APOE*-ε3/ε3). It is therefore difficult to come to robust conclusions about the effect of *APOE* on the VPC task, as the size of the low- and high-risk groups were likely to be too small to detect differences at an alpha of 0.05. The impact of this problem was partly negated by using estimated marginal means which increases power by comparing all stimulus pairs in the model separately rather than averaging across them. The results of

this show a trend, in which the low-risk group (with an *APOE*-ε2 allele) seem to show a higher novelty preference, and consequently greater recognition memory, compared to the other groups. This finding was not statistically significant, however, and future studies should increase the number of *APOE*-ε2 participants in order to identify whether this is a robust difference in performance in individuals with a different *APOE* genotype.

Many studies conducted to date have focused on comparisons of *APOE*-ε4 carriers and *APOE*-ε4 non-carriers, tending to exclude carriers of an *APOE*-ε2 allele (e.g. Evans et al., 2014) or alternatively including them in the *APOE*-ε4 non-carrier control group (e.g. Chen et al., 2013). Given the numerical difference between *APOE*-ε2 participants seen here, while noting that it was not statistically significant, it seems important moving forward to study *APOE*-ε2 individuals, or at very least to remove them from the control group in order not to inflate any negative impact of *APOE*-ε4. It is worth noting that some studies which have included *APOE*-ε2 in analyses have found a greater beneficial effect of this allele on memory than the corresponding detrimental effect of *APOE*-ε4. For example, Sinclair et al. (2017) found that *APOE*-ε2 carriers showed better performance on verbal learning and episodic memory tasks compared to *APOE*-ε3 and *APOE*-ε4 carriers; with the latter performing similarly. It is impossible to make any assumptions from the current data, but the trend identified in the VPC task would support a suggestion from the literature there that *APOE*-ε2 carriers may show better/enhanced cognitive performance (Suri et al., 2013). Future studies would should focus on a detailed assessment of cognition, including comparison of performance on tasks tapping different representational networks, as well as increasing the size of the cohort to ensure generalisability of finding. It would be very interesting to include a VPC task like that reported here, where it may be possible to study novelty preference to different stimulus-types and levels of ambiguity between stimuli. Such a sample would allow for comparison of difference-scores across groups, which was not possible in this study due to the small group sizes.

Another possible way to investigate potential differences between *APOE* genotypes as individuals' age would be to use a longitudinal design. By repeating the VPC task in the future, it would be possible to look at individual change over time which may be more sensitive to APOE age effects. As discussed earlier in this chapter, Deary et al. (2002) measured change in cognition over a 70 year gap and found significant effects over time that were not present by simply comparing group data at one time-point. Zola et al. (2013) also used a VPC task in a longitudinal design and found that poor task performance was predictive of future cognitive decline, either from healthy cognition to MCI or from MCI to AD.

Collecting data longitudinally has a number of obstacles. It can be difficult to retain the engagement of participants as time passes, leading to a reduction in cohort numbers, which needs to be accounted for in the initial scale of the recruitment. Furthermore, the current task takes around thirty minutes and must be carried out on a one-to-one basis with the participant, making it relatively time-intensive to collect data on a scale needed to have an even distribution of groups large enough to detect differences. For example, to have a low-risk group containing a modest amount of twenty individuals would have required testing approximately 200 people in total (if individuals are not pre-selected by *APOE* genotype for the study, which in itself can have ethical implications). The cost implication is also an issue, as genetic testing is expensive, time consuming, and requires specialist facilities to carry this out. An obvious workaround to these issues is to use an existing cohort of individuals in whom genetic data is already available.

As mentioned at the end of Chapter 3, new technology is making remote eye-tracking on smartphones or via web camera possible (U.S. Patent No. 9,629,543 B2, 2017; Bott et al., 2017). Early research suggests that the VPC task is particularly ideal for remote data collection as there is no need for the type of precision supported by a more expensive eye-tracker, as the only necessary gaze information required is which half of the screen is being viewed (Bott et al., 2017). Neurotrack Technologies (2017) have

developed a version of the VPC based on the work of Zola et al. (2013), that is capable of measuring eye-movements using a laptop and webcam. They claim that the system is capable of detecting early changes and abnormalities in the brain that might lead to impaired memory function. Although the system is new and there are yet to be any peer-reviewed results from such an approach, this tool may provide a suitable platform to test data remotely in a large cohort, depending upon the sensitivity of the task to decline in the neural circuitry thought to be involved in AD.

Aside from the use of different scene and object stimuli, and the manipulation of similarity, the current study also differs from the VPC used by Zola et al. (2013) in that they did not use a block design with multiple stimulus pairs between familiarisation and test phases. The current study used a block design to increase the number of trials and increase cognitive load, whilst also replicating other studies using a similar design (e.g. Manns et al., 2000). It is feasible however, that this change has implications on performance that may partly explain the lack of difference between groups in this study. Zola et al. found that non-converting (to MCI or dementia) participants typically had a novelty preference greater than 67%, which is higher than the mean of any group or condition in my study. This is unsurprising, given the increased number of trials in each block of my study, but it may mean that the task is too challenging to generate sufficient variation to elicit differences between groups. Future studies could test this by varying the number of trials in each block to study the impact this has on performance.

The purpose of modifying the VPC task in my PhD work was to use tasks which had previously been shown to be sensitive to AD, but to additionally include stimuli which other studies have shown to be preferentially dependent upon the MTL regions (e.g. PRC/HC) and their interconnected brain regions (e.g., posteromedial cortex), which we know are some of the earliest regions to be affected by AD pathology (Braak & Braak, 1998; Minoshima et al., 1997; Protas et al., 2013) and where altered function and structure is seen in *APOE*-ε4 carriers (Filippini et al., 2011, 2009; Jack et al., 2008; Shine et al., 2015; van de Pol et al., 2007). Neither the current task, nor the tasks completed in

previous chapters, however, have been shown to be directly dependent upon these brain regions. Chapter 5, therefore, aimed to address this gap by asking whether the LOC and PHC volume in the extrastriate cortex, or PRC and hippocampal sub-field volume in the MTL, would be associated with performance on the tasks I developed and reported in Chapters 2-4. This approach allows me to investigate the neuroanatomical contributions of key brain regions to performance on these cognitive tasks, and whether inter-individual variation in volume would be associated with performance.

CHAPTER 5:
INVESTIGATING THE RELATIONSHIP BETWEEN EXTRASTRIATE AND MEDIAL TEMPORAL LOBE REGION GREY-MATTER VOLUME AND PERFORMANCE ON THE CONJUNCTION LEARNING AND VISUAL PAIRED-COMPARISON TASKS IN YOUNG AND MIDDLE-AGED ADULTS

5.1 Introduction

In the Chapters 2-4, I reported studies applying two distinct and novel cognitive tasks with the aim of testing whether there would be behavioural differences, specifically when scene stimuli were presented, between groups comprising individuals carrying different alleles of the *APOE* gene. As discussed in Chapter 1, healthy *APOE*-ε4 carriers *(APOE*-ε4 is associated with a greater risk of developing AD in later life compared to the normal population risk) have been reported as showing decreased brain volume (Burggren et al., 2008; Chang et al., 2016; Knickmeyer et al., 2014; Shaw et al., 2007) and altered brain function (Dennis et al., 2010; Filippini et al., 2011, 2009; Hodgetts et al., 2018; Mondadori, Quervain, et al., 2007; Shine et al., 2015). This is most often seen in regions and networks (medial temporal lobe and posteromedial cortex) known to be affected early in AD and seems to be evident decades before there is any clinically obvious cognitive change (see Chapter 1.3.1). In the earlier cognitive studies I reported in this thesis, therefore, I predicted that these early alterations in brain network might elicit differences in performance on tasks that have been designed to preferentially engage these regions/networks, specifically between high and low risk groups.

The tasks I developed were influenced by literature showing that the HC is particularly important for aspects of complex scene processing (Graham et al., 2010; Lee et al., 2006; Murray et al., 2017); this region is not only structurally and functionally vulnerable to AD pathology (Fjell, McEvoy, Holland, Dale, & Walhovd, 2014), but it has also been the focal point for previous research that has looked for early behavioural changes that might predict AD (e.g. Crutcher et al., 2009; Zola et al., 2013). One problem

with this approach is that many of the tasks used are based on the theoretical assumption that the HC is solely responsible for declarative memory, which is increasingly being challenged by accounts which focus on representational content as a key influencer of HC involvement in memory (e.g. Graham et al., 2010; Maguire, Intraub, & Mullally, 2016; Murray et al., 2017). As I discussed in Chapter 1, the emerging consensus appears to be that the HC forms part of a visual ventral stream that is responsible for forming increasingly complex representations and, within which, the HC and PRC work to resolve spatial and featural ambiguity, respectively (Bussey & Saksida, 2007; Cowell et al., 2010; Graham et al., 2010; Lee, Buckley, et al., 2005). Given this change in our understanding of the contributions of MTL regions to differentially supporting representational information, a clear next step forward in my research approach was to develop tasks informed by this emerging literature, with the prediction that these might be more sensitive to functional differences in networks aligned to genetic risk of poorer later life cognitive health.

In Chapter 2, I used a conjunction learning task involving scenes and object-like fribbles. The fribble condition in the conjunction learning task was used as a control condition, as this type of object-like stimuli appears to preferentially recruit MTL regions involved in binding conjunctions of distinct features to form complex representations of objects, such as the PRC (Barense et al., 2005). The scene condition, however, was aiming to preferentially recruit the posteromedial/hippocampal brain network, which is thought to be important in distinguishing scenes by forming complex representations based on conjunctions of spatial attributes (Buckley et al., 2004). Both comparisons, including all participants and a matched subset of young adult *APOE*-ε4 carriers and non-carriers, did not show any difference in behaviour between groups. I discussed that this may be due to the possibility that the scene condition could be completed by simply processing the shape of the back wall, which was a unique single feature. In this task, participants may not process the spatial features conjunctively, and the task may,

therefore, be more dependent upon extrastriate brain regions involving in scene processing rather than MTL areas (see Chapter 1.4).

In Chapters 3 and 4, I used natural scenes and objects in a VPC task, varying the level of similarity across the stimulus pairs. The VPC task has previously been shown to be predictive of future cognitive decline (Zola et al., 2013) and atrophy in the HC has been shown to impair performance on the task (Bachevalier, Brickson, & Hagger, 1993; Clark et al., 2000; McKee & Squire, 1993; Nemanic et al., 2004; Zola et al., 2000). It was predicted that modifying the task to use similar and dissimilar scenes, as well as objects, might preferentially increase demand on the HC (for scenes) and PRC (for objects). In the cohorts used in Chapter 3, I found that high- and normal-risk groups had a reduced novelty preference for scenes when the target and distracter were similar, compared to the condition in which the distractor was dissimilar. No such difference between conditions was evident in the low-risk group; specifically they performed as well in both conditions, showing no detrimental influence of closer visual similarity. When looking at a matched comparison between *APOE*-ε4 carriers and non-carriers (taking out any participants with an *APOE*-ε2 allele) there was a significant interaction of group and similarity (collapsed across stimulus-types), with the *APOE*-ε4 non-carrier group showing a significant difference between similar and dissimilar. This was not seen in the *APOE*-ε4 carrier group. A possible explanation for this finding is that the *APOE*-ε4 carrier group are using alternative strategies that are less dependent on hippocampal function and are therefore less influenced by the presence of visual ambiguity across stimuli. Although this theory is speculative, there is some evidence to suggest that young *APOE*-ε4 carriers may benefit from enhanced attentional function (Rusted et al., 2013), which may contribute to this difference between groups.

As discussed in Chapter 1, there is increasing evidence to suggest that HC volume is associated with inter-individual performance on tasks involving scene stimuli. For example, HC grey-matter volume has been found to correlate with degree of HC activity and memory performance for scenes (Walker et al., 2017). Maguire et al. (2000)

also found that London taxi drivers had increased posterior HC grey-matter volume, and decreased anterior hippocampal volume, compared to controls. This relative anterior to posterior redistribution of grey-matter became more pronounced the longer the individual worked as a taxi driver. The authors argued that this pattern was due to localised hippocampal plasticity occurring from the requirement to form complex spatial representations of the spatial (London) environment, which increase in detail and complexity with time and experience. The work also highlights that there may be a distinction between the contributions of anterior and posterior HC regions and their role in spatial perception (Brunec et al., 2018; Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch, 2012; Kim, Jeffery, & Maguire, 2017; Robin & Moscovitch, 2017).

Zeidman et al. (2015) investigated the relationship between activation in different regions of the HC during a scene perception and construction task. In the task, they asked participants to either imagine a scene from a prompt (e.g. an old library) or to hold the presented image of a scene in their *minds eye*, whilst being scanned in an fMRI scanner. The results were compared to a baseline level of activation using objects as a control stimulus. They found that perceiving scenes extensively activated the entire HC bilaterally, whereas constructing a scene involved restricted activation of the anterior HC. The results of this, along with Maguire et al.'s (2000) taxi driver study, suggest that the posterior HC may be preferentially involved in the spatial navigation of our environment, and the anterior HC in scene construction and imagining.

These studies also highlight that the HC is not one unitary structure, but rather a region that contains a number of distinct substructures (Duvernoy, Cattin, & Risold, 2005). Our current understanding of how these subfields map onto how scenes are processed in humans is still limited. The HC can be divided into four subfields: CA1, CA2/3, dentate gyrus (DG), and the subiculum (Hodgetts et al., 2017). Animal research, particularly in rodents, reveal that the CA1 region contains place cells that represent the animals location within its environment (O'Keefe & Dostrovsky, 1971), whereas areas around the subiculum (such as the pre- and parasubiculum) contain grid cells that may

facilitate a framework for spatial representations (Boccara et al., 2010). Boundary vector cells have also been found in the subiculum, presubiculum, and parasubiculum, which represent the positions of the boundaries of a scene (Lever, Burton, Jeewajee, O'Keefe, & Burgess, 2009).

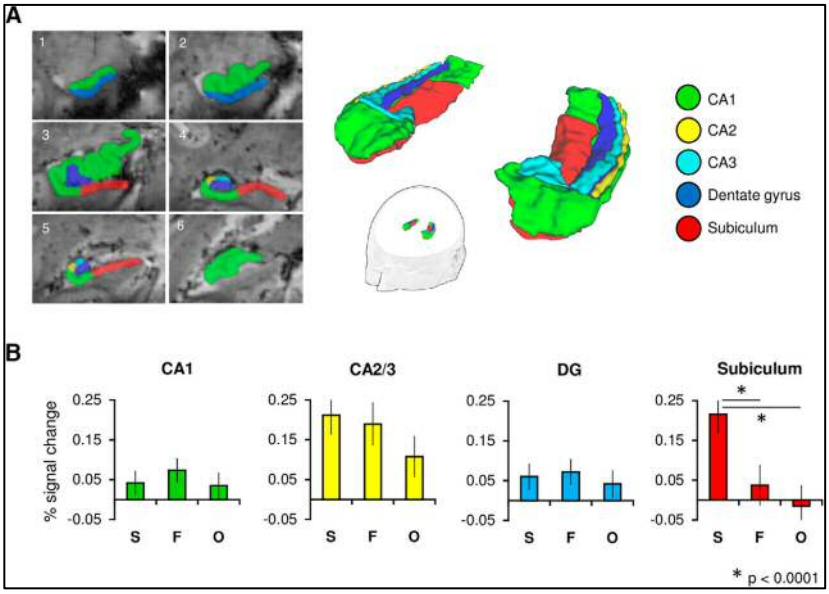

Figure 5.1 – Hodgetts et al. (2017) found preferential activation of the subiculum during the scene condition of an oddity task, but not faces or object conditions. This illustration includes, [A] hippocampal subfield segmentation using ultra-high-resolution MRI, and [B] Mean percentage signal change for the correct scene (S), face (F), and object (O) judgements (relative to size baseline) for each subfield. Error bars represent ± SE. Figure taken from Hodgetts et al. (2017).

Hodgetts et al. (2017) found increased activation in the subiculum during a scene oddity task using ultra-high-field fMRI. Activity elicited while participants performed odd-one-out-judgements for scenes was compared to that evident when performing similar judgements for faces and objects. Subiculum showed increased activity for scenes compared to faces and objects. This was the only hippocampal subfield to show such a distinctive BOLD response to scene stimuli (see Figure 5.1). The authors further segmented the subiculum into anterior-posterior regions; increased activation for scenes was limited to the anterior portion. These findings align with previous suggestions of a preferential role for posterior and anterior hippocampal regions in spatial navigation and constructing scene representations, respectively (Brunec et al., 2018; Zeidman & Maguire, 2016). In the case of the conjunction learning and VPC tasks used in this thesis,

it would seem likely that the scene condition in both tasks would preferentially engage the subiculum and its surrounding regions, as these appear to be areas involved in constructing internal scene representations.

The aim of this final chapter of my thesis was to bridge the gap between the behavioural work outlined in the earlier chapters and brain anatomy, specifically following on from some of the literature outlined above to ask if there would be a relationship between hippocampal subfield volume and performance on the conjunction learning and VPC tasks. Previous work (e.g. Maguire et al., 2000; Walker et al., 2017) suggests that greater HC subfield volume, specifically the subiculum (Hodgetts et al., 2017) would be associated with better performance on the scene conditions in these tasks, assuming they are dependent upon representations stored within the HC. Conversely, the object/fribble conditions would be expected to preferentially engage the PRC which, as discussed in Chapter 1.4 as well as other chapters, is involved in high-order discrimination of objects.

Of note, with regard to my hypotheses, in the conjunction learning task (Chapter 2), there was no relationship between *APOE*-related risk for AD and the speed of learning spatial or featural conjunctions (as measured by both time to criterion and response times). It was proposed that this might be due to the task not being sufficiently difficult, in that—with hindsight—although the stimuli vary only in two features (stressing conjunctive processing) the unique shape of the back wall in the scenes provides another way to solve the task. If this is the case, it is possible that the HC (for scenes) and PRC (for fribbles) will not be preferentially recruited when performing this task. In which case, instead inter-individual variation in response times for the scene condition, but not the objects, might be associated with volume of the PHC (which is involved in low-level perception of scenes). Similarly, for the fribble condition, inter-individual variation in volume of the LOC (which is involved in low-level perception of objects) might predict performance for the object learning condition, but not scenes (as discussed in Chapter 1.4).

In the VPC task (Chapters 3 and 4), I found that young adults with a lower risk of AD (but not normal- or high risk) showed a reduced novelty preference for similar (compared to dissimilar) scenes. When looking more specifically at the relationship between *APOE*-ε4 carriers and non-carriers, there was a difference between similar and dissimilar stimuli (in both stimulus conditions) in the *APOE*-ε4 non-carriers, but not the carriers. Although I had an insufficient sample of individuals with both structural MRI and VPC data to look at the relationship between volume, performance and risk-level, it seemed worthwhile looking at how inter-individual variation in novelty preference was associated with volume of HC sub-regions in the data that was available to me. With regard to this analysis, I predicted that novelty preference for similar scenes would be positively correlated with subiculum volume, but not with other HC subfields. It is further predicted that novelty preference for dissimilar scenes might be more dependent upon the PHC, rather than HC subfields, as those scenes should not require high-order spatial representations. For the object condition, I predicted that inter-individual variation in novelty preference for the similar objects would be related to PRC volume but not the HC. Disambiguating between dissimilar objects, however, might be possible using lower-level object processing, such as those representations stored within the LOC; I hypothesised, therefore, that novelty preference in this condition will be positively related to LOC volume, but potentially not PRC volume. It is expected that these predictions will be true in both the young and middle-age cohorts in which I had available MRI data.

5.2 Method

5.2.1 Analysis 1: Conjunction learning task

5.2.1.1 Participants

As part of a separate study, 51 individuals from the original all-female young adult *APOE* cohort used in Chapters 2 and 3 were invited to attend an imaging session

at Cardiff University Brain Research and Imaging Centre (CUBRIC). This group included 40 of the participants that had also completed the conjunction learning task (mean age = 19.45 years). For the scanning session, participants were recruited via Cardiff University's experiment management system and were offered a cash payment in exchange for their time. Participants were required to pass CUBRIC's MRI screening process, which ensures that individuals with non-removable metal, claustrophobia, or health issues (such as epilepsy) are not included in the scanning. All experimental processes were approved by the Cardiff University School of Psychology's ethics committee and were in accordance with the British Psychological Society's Code of Ethics and Conduct (The British Psychological Society, 2018).

For details of the recruitment process for the conjunction learning task, see Chapter 2.2.1.

5.2.1.2 Conjunction learning task

Details of the conjunction learning task can be found in Chapter 2.2. In summary, the task required participants to learn and identify which one of a pair of images was correct. The same image was always either correct or incorrect, but the images overlapped in all but two visual features with the aim of requiring participants to process conjunctions of features or spatial properties. The task included scene and fribble conditions.

In Chapter 2, it was discussed that the lack of task difficulty resulted in most individuals scoring close to ceiling. This lack of dispersion and inter-individual variation made the measure unsuitable for looking at the relationship with brain volume. Therefore, for this analysis, I used the mean response times to all trials. This measure had greater distribution and would likely reflect the extent to which the participant found the task difficult, with increased difficulty leading to longer time to respond.

5.2.1.3 Image acquisition

Structural imaging was performed at CUBRIC using a Siemens MAGNETOM Prisma 3-tesla MRI scanner (Siemens Healthcare Limited, Camberley, UK). The scanner had a 32-channel head coil and a T1-weighted magnetisation-prepared rapid gradient-echo imaging (MPRAGE) sequence was used (TR = 2500ms, TE = 3.24ms, FA = 9°, FOV = 256mm x 256mm, slices = 176, slice thickness = 1mm).

5.2.2 Analysis 2: Visual paired-comparison (young adults)

5.2.2.1 Participants

Fifty-one participants from the young adult *APOE* cohort were scanned at CUBRIC (see section 5.2.1.1 for details). Forty-one of these individuals had also previously completed the VPC task (mean age = 19.44 years) and were included in this analysis. These were all the same individuals that had completed the conjunction learning task (Analysis 1), but with one additional person. For details of recruitment for the VPC task, see Chapter 3.2.1.

5.2.2.2 VPC Task

Further information about the VPC task protocol used in this analysis can be found in Chapter 3.2. In summary, the task involved participants viewing a series of images, which were then shown again alongside a new image which was either similar or dissimilar to the previously shown image. Stimulus-pairs were either scene or object stimuli. Eye-movements were recorded, and the main measure obtained from the task was the proportion of time spent viewing the novel stimulus, which was assumed to be a measure of implicit recognition memory.

5.2.2.3 Image acquisition

Details of the T1 image acquisition can be found in section 4.2.1.3.

5.2.3 Analysis 3: Visual paired-comparison (mid-age adults)

5.2.3.1 Participants

As detailed in Chapter 4.2.1, the VPC task was also successfully run in 41 middle-aged healthy adults. Within this group, 11 participants (mean age = 51.45 years, females = 9) also had T1 structural MRI data available. Participants were recruited by email from a database of individuals that had previously agreed to be part of a cohort to investigate the effects of *APOE* on cognition at the School of Psychology, University of Sussex and were offered cash payment in exchange for their time. Participants were excluded if they did not meet the Clinical Imaging Sciences Centre's screening criteria (similar to that outlined above for CUBRIC). All scanning was conducted consistent with the protocol that had been approved by the University of Sussex School of Psychology and Life Sciences ethical committee, and was in line with the British Psychological Society's Code of Ethics and Conduct (The British Psychological Society, 2018).

5.2.3.2 VPC task

The VPC task used in this cohort was identical to the one used in Analysis 2 but collected at a different location and using a portable 60hz TOBII eye-tracker (see Chapter 4.2 for further details). The output measure used for the analysis was the mean proportion of time spent viewing the novel stimulus for each of the scene and object conditions.

5.2.3.3 Image acquisition

Structural images were acquired on a Siemens MAGNETOM Avanto 1.5-tesla MRI scanner (Siemens Healthcare Limited, Camberley, UK) using a three-dimensional T1-weighted magnetisation-prepared rapid gradient-echo imaging (MPRAGE) sequence (TR = 1600ms, TE = 4.44ms, FA = 15°, FOV = 230mm x 230mm, slice thickness = 0.9mm).

5.2.4 MRI processing and volume segmentation

Aligned to my hypotheses, I was interested in the relationship between volume of MTL and extrastriate areas known to respond to object and scene stimuli (e.g. Mundy et al., 2012), including the LOC/PRC and PHC/HC, respectively. Volume measures were obtained using Freesurfer 6.0 image analysis suite (which is freely available to download online at http://surfer.nmr.mgh.harvard.edu).

Before undertaking processing with Freesurfer, the T1-weighted MPRAGE files were first converted to the three-dimensional *nifti* format. The Freesurfer software then (a) registers these into Talairach space, (b) normalises for variable intensities caused by inhomogeneities in the radiofrequency field, (c) extracts non-brain volume (such as the skull and extra-meningeal tissues), (d) segregates the hemispheres, (e) removes the brain stem and cerebellum, (f) corrects for topology defects, (g) defines grey-matter, white-matter and cerebrospinal fluid, and (h) parcellates the subcortical region into distinct brain structures (Whelan et al., 2016).

Following reconstruction of the whole HC and surrounding sub-cortical regions, hippocampal subfields were then segmented. In Freesurfer 6.0, the location of each of the subfields is predicted based on a probabilistic atlas built from ultra-high resolution ex-vivo MRI data and manually annotated structures. This newly-revised method has been shown to have a number of advantages over, and be more reliable than, previous automated methods of HC subfield segmentation (Whelan et al., 2016; Yushkevich et al.,

2015), including when used with T1-weighted 3T MR image (Whelan et al., 2016). Freesurfer then outputs the following subfields for each hemisphere: CA1, CA2/3, fimbria, subiculum, presubiculum, parasubiculum, CA4/DG, HC tail, HC fissure, the molecular layer, granule cells in the molecular layer of the DG, and the hippocampal-amygdala transitional area (HATA) (see Figure 5.2).

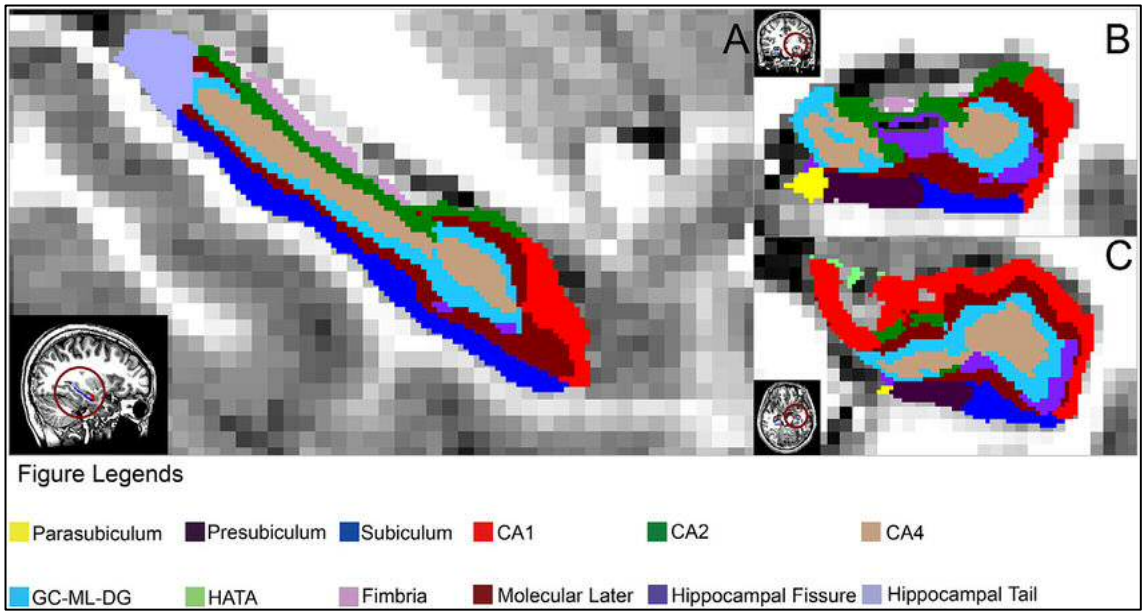

Figure 5.2 – Example of hippocampal subfield segmentation by Freesurfer 6.0. Views include (A) sagittal, (B) coronal, and (C) axial, for a healthy individual. Figure taken from Li et al. (2018).

Using these outputs, I created a subiculum cortex region, comprising of the presubiculum, parasubiculum, and subiculum subfields. I also generated a CA4/DG region, comprising both the CA4/dendrite gyrus and the granule cells in the molecular layer of the dendrite gyrus. These were complemented by CA1, CA2/3, LOC, PRC and PHC, giving seven regions in total. To correct for head-size, all volumes used were divided by the total intercranial volume (ICV) to give a volume ratio of total ICV.

5.3 Results

5.3.1 Analysis 1: Conjunction learning task

Volumes for each of the regions (for both the left and right hemispheres) and for each participant were imported into JASP (JASP Team, 2018), along with the mean

response time in milliseconds for the scene and fribble versions of the conjunction learning task (see Table 5.1 for descriptive statistics). All volumes (LOC, PRC, PHC, CA1, CA2/3, CA4/DG, and subiculum cortex) were entered into a linear regression model using a bidirectional elimination stepwise method with fribble and scene response time as the dependent variables. This method includes or removes one region at each step based on the probability of its F-value, starting with the smallest p-value. Regions were only included if their p-value at that step was lower than .05 and variables included in the model were subsequently removed if their p-value became greater than .1 as a result of the inclusion of another variable. For the fribble condition, the final model indicated that right CA2/3 and right LOC volumes accounted for 23.7% of the variance in response time ($R^2 = .237$, $F(2,37) = 5.74$, $p = .007$), with greater volume in both right CA2/3 ($\beta = -.386$) and right LOC ($\beta = -.372$) being associated with lower response times. For the scene condition, the model included only the right PHC volume, which predicted 16.6% of the variance in response time ($R^2 = .166$, $F(1,38) = 7.56$, $p = .009$). Greater right PHC volume was associated with lower response times ($\beta = -.407$) (see Figure 5.3).

	MEAN	STANDARD DEV
RESPONSE TIMES (MS): SCENES	2125	937.7
RESPONSE TIMES (MS): FRIBBLES	2404	674.0
LOC – RH	.008790	.001178
PHC – RH	.001484	.000183
PRC – RH	.001375	.000201
CA1 – RH	.000447	.000046
CA2/3 – RH	.000139	.000020
CA4/DG – RH	.000371	.000036
SUBICULUM – RH	.000536	.000053
LOC – LH	.008344	.000796
PHC – LH	.001576	.000220
PRC – LH	.001256	.000154
CA1 – LH	.000423	.000041
CA2/3 – LH	.000130	.000017
CA4/DG – LH	.000369	.000033
SUBICULUM – LH	.000552	.000049

Table 5.1 – Table includes the means and standard deviations for response times (in milliseconds) for the scene and fribble conditions of the conjunction learning task, as well as means and standard deviations for all volumes used (as a proportion of total ICV) for the left (LH) and right (RH hemispheres.

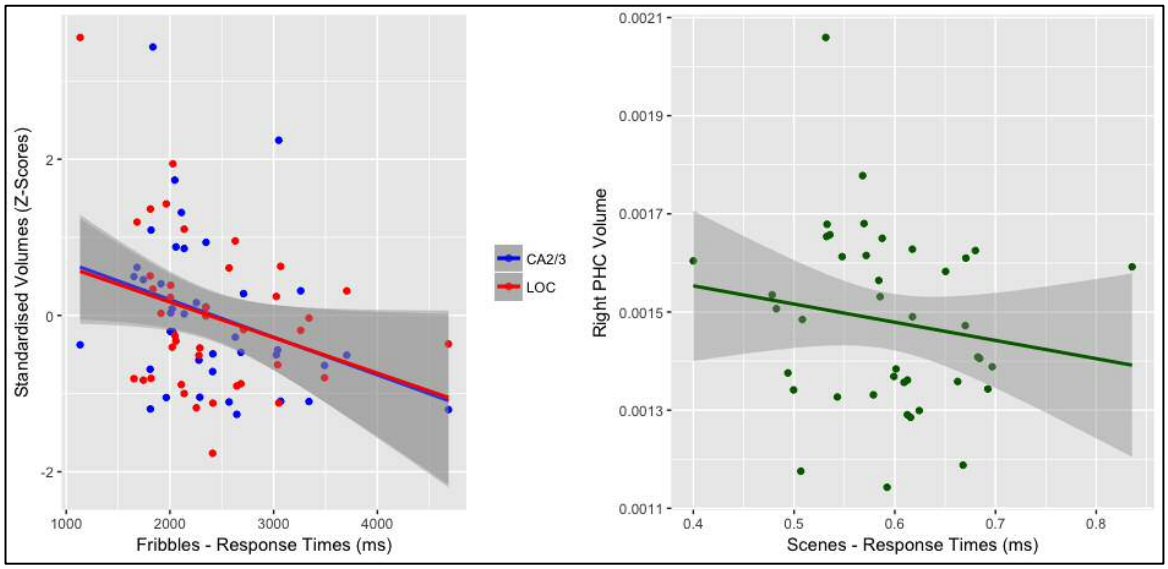

Figure 5.3 – Linear regression slopes for fribbles (left) and scenes (right).

5.3.2 *Analysis 2: Visual paired-comparison (young adults)*

Similar to Analysis 1, volume data for the LOC, PRC, PHC, and HC subfields was imported into JASP along with the corresponding VPC data collected in the young adults (see Table 5.2 for descriptive statistics). A linear regression model was then constructed using a bidirectional elimination stepwise method with all volumes as covariates to predict variance in novelty preference for each of the four VPC conditions: similar scenes, dissimilar scenes, similar objects, and dissimilar objects. Regions were only included if their p-value at that step was lower than .05 and variables included in the model were subsequently removed if their p-value became greater than .1 as a result of the inclusion of another variable. The final regression model included only the right subiculum volume, which accounted for 15.1% of the variance in novelty preference on the similar scene condition ($R^2 = .151$, $F(1,39) = 6.96$, $p = .012$), with greater right subiculum volume being associated with a decrease in novelty preference ($\beta = -.389$). For dissimilar scenes, similar objects, and dissimilar objects, no volume was found to account for variance in novelty preference (see Figure 5.4).

	MEAN	SD
NOVELTY PREF: SIMILAR SCENES	.5935	.0790
NOVELTY PREF: SIMILAR OBJECTS	.5984	.0735
NOVELTY PREF: DISSIMILAR SCENES	.6093	.0783
NOVELTY PREF: DISSIMILAR OBJECTS	.5991	.1064
LOC – RH	.008804	.001166
PHC – RH	.001482	.000182
PRC – RH	.001375	.000199
CA1 – RH	.000446	.000046
CA2/3 – RH	.000139	.000020
CA4/DG – RH	.000370	.000035
SUBICULUM – RH	.000537	.000052
LOC – LH	.008365	.000797
PHC – LH	.001572	.000219
PRC – LH	.001253	.000153
CA1 – LH	.000422	.000041
CA2/3 – LH	.000130	.000017
CA4/DG – LH	.000369	.000033
SUBICULUM – LH	.000553	.000048

Table 5.2 – Data from young adults. Table includes the means and standard deviations (SD) for novelty preference for the similar and dissimilar, scene and object conditions of the VPC task, as well as means and standard deviations for all volumes used (as a proportion of total ICV) for the left (LH) and right (RH hemispheres.

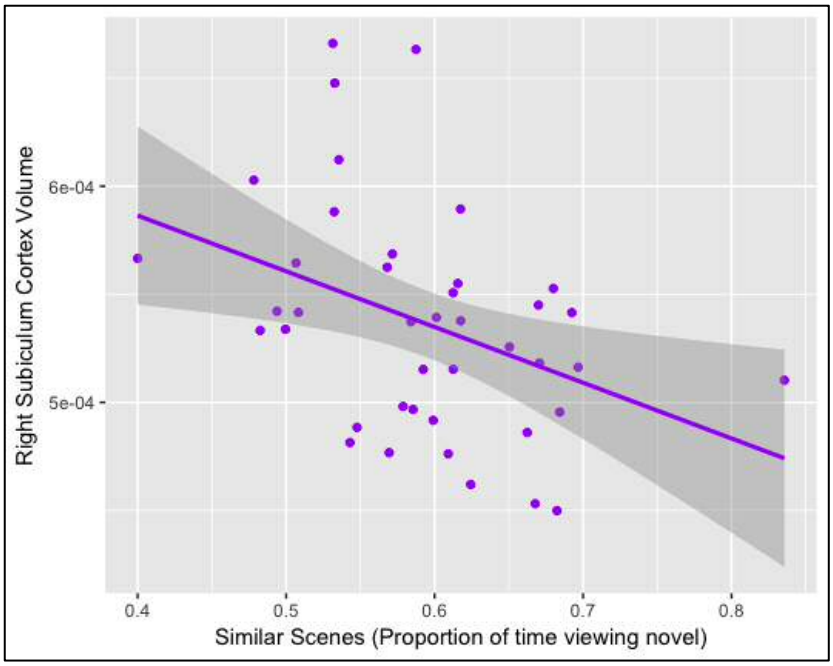

Figure 5.4– Linear regression slope showing how the right subiculum cortex volume negatively relates to novelty preference on the similar scene condition.

5.3.3 *Analysis 3: Visual paired-comparison (mid-age adults)*

In line with the previous analyses, volume data for the LOC, PRC, PHC, and HC subfields, along with the corresponding VPC data collected in the middle-aged adults, was imported into JASP (see Table 5.3). Linear regression models predicting variance in novelty preference for each condition (similar scenes, dissimilar scenes, similar objects, and dissimilar objects) were constructed using a bidirectional elimination stepwise method with all volumes as covariates. Regions were only included if their p-value at that step was lower than .05 and variables included in the model were subsequently removed if their p-value became greater than .1 as a result of the inclusion of another variable. For the both similar scene and similar object conditions, the final model had either not included or removed all regions at each step, leaving no region in the model. The models for the dissimilar scene ($R^2 = .373$, $F(1,9) = 5.34$, $p = .046$) and dissimilar object ($R^2 = .703$, $F(1,9) = 21.26$, $p < .001$) conditions both included only the right subiculum, which accounted for 37.3% and 70.3% of the variance in novelty preference on scenes and objects, respectively. For both dissimilar scenes and objects, greater right subiculum

volume was associated with a larger novelty preference (dissimilar scenes: $\beta = .611$; dissimilar objects: $\beta = .838$) (see Figure 5.5).

	MEAN	SD
NOVELTY PREF: SIMILAR SCENES	.5842	.0533
NOVELTY PREF: SIMILAR OBJECTS	.5973	.0565
NOVELTY PREF: DISSIMILAR SCENES	.6193	.0757
NOVELTY PREF: DISSIMILAR OBJECTS	.6059	.0554
LOC – RH	.007961	.000961
PHC – RH	.001156	.000113
PRC – RH	.001185	.000162
CA1 – RH	.000491	.000033
CA2/3 – RH	.000130	.000013
CA4/DG – RH	.000339	.000023
SUBICULUM – RH	.000520	.000056
LOC – LH	.007390	.000454
PHC – LH	.001314	.000232
PRC – LH	.001129	.000165
CA1 – LH	.000374	.000027
CA2/3 – LH	.000120	.000012
CA4/DG – LH	.000335	.000027
SUBICULUM – LH	.000520	.000046

Table 5.3 – Data from mid-age adults. Table includes the means and standard deviations (SD) for novelty preference for the similar and dissimilar, scene and object conditions of the VPC task, as well as means and standard deviations for all volumes used (as a proportion of total ICV) for the left (LH) and right (RH hemispheres.

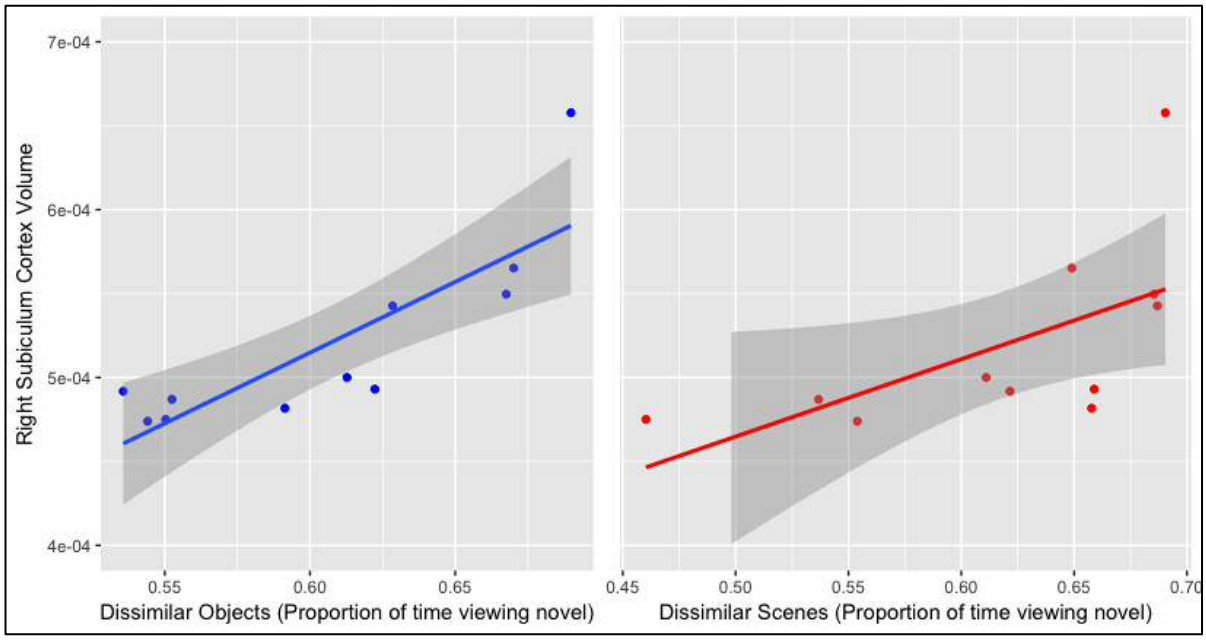

Figure 5.5 – Linear regression slopes for the VPC task in mid-age adults. Graphs show the positive relationship between right subiculum cortex volume and novelty preference on the dissimilar objects (left) and dissimilar scenes (right).

5.4 Discussion

The current chapter aimed to investigate whether there would be an association between the volume of areas within the MTL and extrastriate regions, known to be recruited during object and scene perception (Mundy et al., 2012), and performance on the conjunction learning task (Chapter 2) and VPC task (Chapters 3 and 4). The findings from each of the analyses will be discussed in separate sections prior to a brief summary section.

5.4.1 Analysis 1: Conjunction learning task

In the conjunction learning task, I anticipated that successful performance might be more likely to be driven via low-level representations of scenes and fribbles formed in the extrastriate regions, PHC and LOC, respectively. This reflected the good performance of participants on this task, and the fact that the single shape at the back of the wall could be used to identify the correct stimulus without necessarily processing the more complex featural (conjunctive) overlap across stimuli. I predicted, therefore, that volume of LOC and PHC extrastriate regions would be negatively correlated with

response times on object and scene conjunctive learning conditions, respectively. More specifically, greater volume would be beneficial, resulting in faster decision times. A stepwise regression model inputting the volume for all HC subfields, the PRC, the PHC, and the LOC in each hemisphere found that inter-individual variability in RTs in the fribble condition were, in part, explained by volume of the right LOC, as well as the right CA2/3 subfield. This association was negative, as predicted. The same stepwise regression inputs for scenes revealed a significant contribution from PHC regions to how rapidly individuals undertook a scene discrimination; again, this association was negative in direction.

These findings are mostly in line with my predictions and suggest that the conjunction learning task used in Chapter 2 might not preferentially engage the level of high-order conjunctive processing that would require recruitment of the PRC and HC for fribbles and scenes, respectively. Instead, the findings suggest that extrastriate regions are more predictive of individual variability in performance, at least as measured by response times. This finding is in line with previous research that suggests that disambiguating between simple representations of objects and scenes recruits the LOC and PHC, respectively, located in the extrastriate cortex (Mundy et al., 2012). The conjunction learning task reported in Chapter 2 aimed to elicit behavioural differences in complex conjunctive processing (e.g., complex scene disambiguation), with the expectation that this is dependent upon the HC. The findings here provide some evidence to suggest that this task may not be as strongly HC-dependent as intended, which may explain why there was little evidence of *APOE*-driven modulations of performance (see Chapter 2).

5.4.2 Analysis 2: Visual paired-comparison (young adults)

Analysis 2 undertook a similar analysis to look at the MTL and extrastriate areas contributions to performance on the VPC task reported in Chapter 3 and 4. It was predicted that increased performance (as measured by a greater novelty preference) on

the similar scene and object conditions would be associated with increased volume in the subiculum cortex and the PRC, respectively. Increased novelty preference on the dissimilar scene and object conditions, however, would be related to increased volume in the PHC and LOC, respectively. The results were somewhat surprising, however. In the dissimilar object and scene conditions, and the similar object condition, there was no evidence of an association between any specific brain region and degree of novelty preference. In the similar scene condition there was indeed a significant relationship between the volume of the right subiculum and performance, but in the opposite direction to the predictions, with increased subiculum volume being associated with decreased novelty preference.

One possible explanation for this might be that individuals with a greater novelty preference for these similar scenes have a larger anterior subiculum, aligned with a reduction in volume of the posterior subiculum, or visa-versa (as seen in Maguire et al.'s (2000) study on taxi-drivers). Freesurfer's method of segmenting the subiculum may feasibly include a posterior/anterior bias as the two parts are combined. It is also feasible that combining the pre- and parasubiculum with the subiculum may cause a similar effect. To address this possibility, I looked at the presubiculum, parasubiculum and subiculum separately. Both the presubiculum (R = -.370, p =.017) and subiculum (R = -.424, p =.006) were found to be negatively correlated with novelty preference (large volume associated with a smaller novelty preference). There was no relationship with the parasubiculum (R = .013, p =.936). There was no evidence of distinct patterns of association between volume and novelty preference in subiculum regions. As with the taxi driver study, Hodgetts et al. (2017) also found an anterior/posterior split of the subiculum during an scene oddity task; with anterior subiculum strongly driving the preferential BOLD response to scene stimuli. The lack of either a T2-weighted or ultra-high-resolution image in this dataset limits the possibility of investigating this question further in this study, but would be an interesting future study providing better anatomical resolution around HC subfields.

It is reassuring to note that other studies have found either a negative or a non-linear relationship between cognitive performance and HC subfield volume in cases where the opposite effect might be expected (Foster et al., 1999; Riggins et al., 2018; Schlichting, Guarino, Schapiro, Turk-Browne, & Preston, 2017; Van Petten, 2004). For example, Schlichting et al. (2017) tested children, adolescents, and adults using an associative inference test, whereby participants had to learn multiple pairs of novel objects, after which they were presented with an object and asked to select the object that it was paired with. In some cases, objects were paired twice (e.g. objects A+B and B+C) and the participant would have to remember the indirect connection (e.g. presented with object A and the correct answer is object C). This task therefore required participants to remember not only the item representation, but also the associations of multiple object pairs. They found this task to be sensitive to CA1 HC subfield volume, and interestingly the relationship was negative in children (lower CA1 volume = increased performance) but positive in adults (greater CA1 volume = increased performance).

Van Petten (2004) argues that there are three perspectives to the relationship between HC volume and memory: a *bigger is better* hypothesis, which simply predicts a linear relationship between memory and volume; a *neuropsychological perspective,* that any normal size structure will support normal levels of function, but that loss of tissue (such as AD related atrophy) will result in declined function; and a *developmental perspective,* whereby the fast growth of HC grey-matter (particularly as a proportion of whole brain) during early childhood is reversed during adolescence, during which the brain continues to grow in size, whilst the HC goes through a reduction process called *pruning*. This pruning process is the removal of weak synapses and a decrease in the number of neurons during maturation of the brain (Huttenlocher & Dabholkar, 1997). Considering that this process is removing inefficient synapses and neurons, it could be argued that—in young adults who have gone through adolescence—that smaller grey-matter volume may actually equate to more efficient processing (Kanai & Rees, 2011).

The developmental perspective offers an intuitive explanation for the results found in Analysis 2 where my prediction that inter-individual differences in subiculum volume would be associated with novelty preference was confirmed, albeit that smaller subiculum volume was associated with greater novelty preference. In this task, greater novelty preference is considered better cognitive processing, specifically recognition of the prior presentation of an item. Riggins et al. (2018) investigated the size of hippocampal subfields in children from 4 to 9 years and found that the subiculum begins to decrease in volume relative to brain size during this time. This suggests that the subiculum might be a region that is receptive to cortical pruning. Furthermore, Schlichting et al. (2017) found a nonlinear relationship between the head and body of the HC and age, with volume of the HC-head peaking during adolescence before reducing during adulthood, and the HC-body showing a pruning effect (e.g., decreasing in size) during childhood before increasing again in early adulthood (see Figure 5.6).

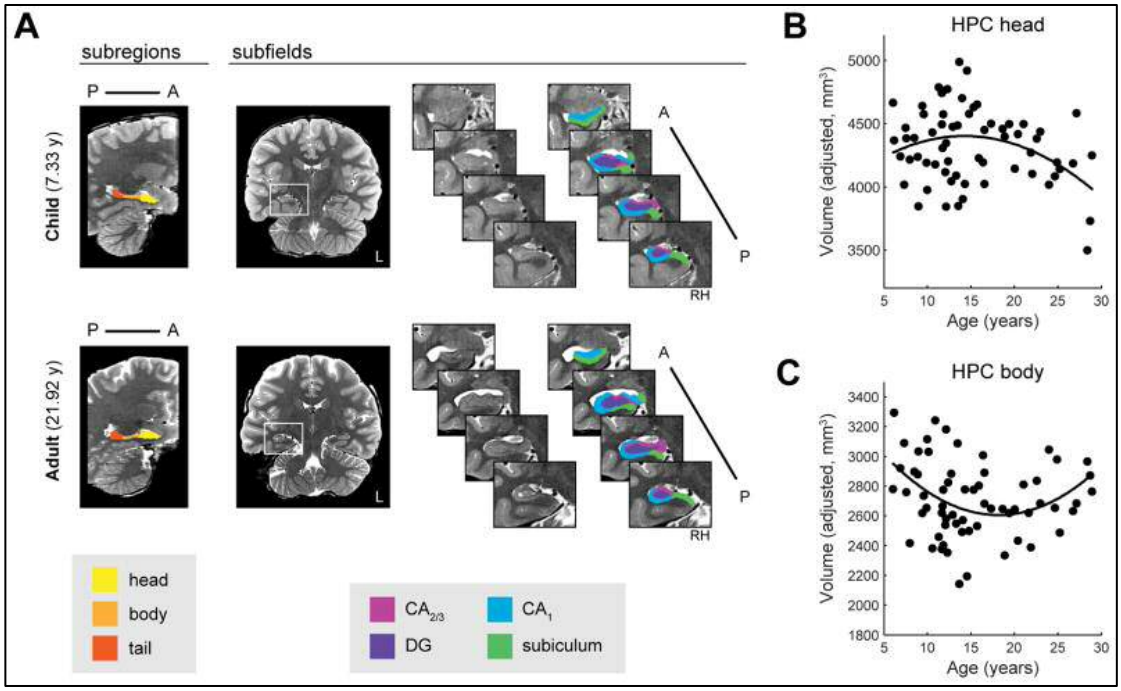

Figure 5.6 – Image of HC volume data taken from Schlichting et al. (2017). (A) Example regions of interest from a representative child (top) and adult (bottom) participant. (B) Relationship between age and volume for the HPC head. (C) Relationship between age and volume for the HPC body.

5.4.3 Analysis 3: Visual paired-comparison (mid-age adults)

In Analysis 3, I looked at the relationship between HC subfields, PRC, LOC and PHC and performance on the VPC task in mid-age adults. As with the analysis with the young adults (Analysis 2), it was predicted that increased volume in the subiculum and the PRC would be associated with better performance (as measured by a greater novelty preference) on the similar scene and object conditions, respectively. By contrast, increased volume in the PHC and LOC would be associated with greater novelty preference on the dissimilar scene and object conditions, respectively. In this analysis I found no significant relationship between volume (of any region included in the analysis) and stimulus-type (for the similar conditions). There was, however, a relationship between novelty preference for dissimilar scenes and objects with right subiculum; unlike in the young adult analysis (Analysis 2) this was in a positive (and predicted) direction.

Firstly, it should be acknowledged that the sample size for this analysis was very small and therefore the results need to be considered cautiously and would need to be replicated to be sure they were robust. That said, both the significant relationships identified in the analysis were very strong, with beta values between right subiculum volume and scenes/objects being .611/.838, respectively. In the dissimilar object condition, right subiculum volume accounted for over 70% of the variance in novelty preference. One potential risk with such a small sample is that outliers inflate the effect. To check for this, I also ran non-parametric Spearman correlations (which are not sensitive to outliers) to see if this reduced the significance of the association; this analysis only increased the strength of the association in both instances, suggesting that outliers are not driving the effect. Furthermore, the findings (at least in terms of the brain region implicated in novelty preference) replicate those reported in young adults (Analysis 2), where there was also a relationship between novelty preference and right subiculum in a separate, larger cohort, albeit that this effect was only evident in the similar scene condition. The lack of effect in the similar conditions in the older group is somewhat

confusing, but may be more easily explained by the small sample size, as low degrees of freedom mean only the very strongest of effects would be significant.

Interestingly, the positive relationship between novelty preference and subiculum volume in older adults fits with the previously made suggestion that cortical pruning is responsible for the inverse relationship found in the young adults. Indeed, it would be a feasible prediction that the effects of synaptic pruning, which peak during late adolescence, would reduce with age. Specifically, a negative association between HC volume and performance (whether novelty preference, discrimination learning or other tasks dependent upon the HC) would be seen in young individuals, while as we age and experience progressive loss of functional flexibility and neurons within the HC this may move towards a positive relationship between volume and performance (novelty preference) as measured in this study.

In summary, this Chapter investigated the relationships between grey-matter volume in extrastriate and MTL regions that are associated with object and scene memory and perception. The findings suggest that the conjunction learning task (Chapter 2) was not sufficiently demanding on MTL lobe regions, and may be more reliant on the simple representations formed in the extrastriate cortex, which may explain why there was no relationship found between task performance and *APOE*-risk. I also found that the relationship between novelty preference on the VPC is sensitive to volume of the subiculum subfield of the HC, but with a negative relationship in young adults and a positive one in older adults, which could be explained by theoretical models of cortical pruning (Van Petten, 2004). In the final chapter, I summarise the findings from the experiments included in my thesis and relate them back to the wider body of literature. I also discuss the how future research could address some of the questions that have been raised following my research.

CHAPTER 6:
GENERAL DISCUSSION

6.1 Thesis summary

One of the strongest genetic risk factors for sporadic AD is the presence of an epsilon-4 allele on the *APOE* gene (Bertram & Tanzi, 2008). The gene codes for a protein that binds to cholesterols and other lipids, and transports them around the body (Bu, 2009). In all animals except humans, there is only one isoform of *APOE* (Bu, 2009). In humans, however, there are three major isoforms—*APOE*-ε2, *APOE*-ε3, and *APOE*-ε4—with *APOE*-ε3 being structurally similar to the *APOE* protein found in other species. Each isoform codes for an *APOE* protein that are both structurally (with *APOE*-ε2 being the most stable and *APOE*-ε4 being the least stable), and functionally unique in their binding preferences (Hatters, Peters-Libeu, & Weisgraber, 2006). It is these differences that are thought to influence variations in the extent to which A*ß* is cleared in the brain, with extensive deposits leading to the formation of the plaques that are a hallmark feature of AD (Selkoe, 1991). Although the exact mechanisms of how different *APOE* isoforms affect AD pathogenesis are still undetermined, the different variants have a linear association with AD risk, with *APOE*-ε4 being associated with an increased likelihood of developing sporadic AD and *APOE*-ε2 reducing this risk (Corder et al., 1993), compared to *APOE*-ε3. The increase or reduction in risk dramatically increases in *APOE*-ε4 and *APOE*-ε2 homozygotes, respectively (Corder et al., 1993).

It has been proposed that the biological impact of *APOE*, and subsequent A*ß* deposition associated with those biological changes, occurs gradually over the lifetime (Selkoe & Hardy, 2016). There have been reports of differences in brain structure between carriers of different *APOE* alleles at different points in the lifespan, with a particular impact on the HC and key regions/networks that project to/from it. This

includes evidence from neonates and children (Knickmeyer et al., 2014; Shaw et al., 2007), young- and middle-age adults (Burggren et al., 2008; Heise et al., 2014; Nao et al., 2017; O'Dwyer, Lamberton, Matura, Scheibe, et al., 2012; O'Dwyer, Lamberton, Matura, Tanner, et al., 2012), and the healthy elderly (Hostage et al., 2013; Hua et al., 2008; Lu et al., 2011). *APOE*-ε4 also impacts on brain function in regions connected to the HC, such as the PCC, in young healthy adults (Dennis et al., 2010; Filippini et al., 2011, 2009; Shine et al., 2015). These findings suggest that each *APOE* allele impacts brain structure and function differently over the lifespan, with a particular focus on the hippocampal networks.

The general aim of this thesis was to investigate whether, and to what extent, the three main *APOE* alleles differentially affect scene perception and memory in young and middle-aged healthy adults. This question was addressed by creating novel tasks comprising of stimuli, such as scenes, that has been previously shown to preferentially recruit the HC (Aly et al., 2013; Barense, Henson, et al., 2010; Douglas et al., 2017; Kolarik et al., 2016; Lee, Buckley, et al., 2005; Lee et al., 2008), and therefore might be sensitive to potential early cognitive changes related to the biological impact of distinct *APOE* alleles on the brain. In particular, recent theoretical models have argued against a unitary role of the HC in memory, in favour of it being part of a wider hierarchical visual ventral stream (Bussey & Saksida, 2007; Graham et al., 2010; Murray et al., 2017). The HC is a key part of this network, as well as the PRC, potentially involved in disambiguating complex spatial and object representations, respectively (Bussey & Saksida, 2007; Graham et al., 2010). Research carried out over the last two decades have identified a dependency on the posteromedial/hippocampal brain network during tasks involving the perception and memory of scenes (e.g. Buckley et al., 2004). Specifically, it appears that the HC is recruited when a problem requires distinguishing between topological environments, such as two similar scenes (Bonnici et al., 2012).

My thesis attempted to address three questions: (a) whether there would be a *APOE* dose-linked pattern of performance on tasks in which scenes with a high degree

of featural overlap needed to be discriminated (e.g., *APOE*-ε2 < -ε3 < ε4); (b) how any *APOE*-related changes in scene and object perception and memory might differ between young and middle-aged participants; and (c) whether individual performance on new tasks, developed in this thesis, would be associated with inter-individual variation in the volume of extrastriate and MTL brain regions known to be involved in scene and object processing.

6.2 Main findings

In Chapter 2, I used a conjunction learning task that required participants to learn which scenes (or objects as a control) were consistently being rewarded. The stimuli combinations had been designed such that the participant should only be able to distinguish the correct scene based on the specific configuration of two spatial properties, the length of the room and the gradient of the ceiling. Once the participant had worked out the conjunction of spatial features, it was assumed that they would then only select the correct images, and, after eight successful correct responses, criterion was achieved. In a control condition, participants saw object-like fribbles in a task with the same design, only this time the conjunctions that the participant had to learn were of a combination of two different appendages, the type of 'tail' and type of 'base'. Based on the previous literature (e.g. Barense et al., 2007; Barense, Rogers, Bussey, Saksida, & Graham, 2010; Lee et al., 2006) I hypothesised that the scene and fribble conditions would preferentially recruit the HC and PRC, respectively. It was therefore predicted that the scene, but not fribble, condition would be sensitive to the early structural and functional changes reported in the posteromedial/hippocampal brain network of *APOE*-ε4 carriers (Filippini et al., 2009; Hodgetts et al., 2018; Shine et al., 2015), resulting in the slower identification (as measured by trials to criterion and mean response times) of spatial conjunctions in the scenes in *APOE*-ε4 carriers compared to *APOE*-ε3 and *APOE*-ε2 carriers.

These predictions, however, did not materialise, and there were no significant differences evident across groups possessing distinct forms of *APOE* allele. There were a number of potential reasons for this that were outlined in the chapter discussion, but the most likely explanation is that the task was simply not demanding enough to elicit any noticeable differences. This is evidenced by the high success rates seen in all groups, leading to a lack of variability in the trials to criterion measure. Upon closer scrutiny, it became evident that the scene stimuli could, in fact, be discriminated by a single stimulus feature - the back wall. As the two spatial changes involved the three-dimensional length of the room and the gradient of the roof, this unexpectedly created a unique feature, in the shape of the back wall, that may have simplified this task. Mundy et al. (2012) reported that simple scene and object discriminations could be resolved in the PHC and LOC, respectively, so it would seem likely that using a single feature (such the shape of the back wall) may not stress the neural network thought to be particularly vulnerable in *APOE*-ε4 carriers.

This hypothesis was partially tested in Chapter 5, when I looked at the relationship between response times on the conjunction learning task and grey-matter volume in the LOC, PHC, PRC, and HC subfields. In both the scene and object condition, there was a strong association between inter-individual variation in response times and grey-matter volume in the PHC and LOC, respectively. Specifically, those individuals with faster responses times showed greater grey-matter volume. This finding implies that discrimination of both scenes and objects in the conjunction learning task may be more dependent upon posterior ventral stream regions, which other studies have shown to be involved in resolving simple, non-conjunctive, representations. The finding from Chapter 5 supports the explanation for the lack of differences between groups in Chapter 2, suggesting that the task was not sufficiently sensitive to changes in the HC, and by proxy, any functional differences in the HC and its related network due to *APOE*-ε4.

In Chapter 3, I modified a VPC task using real-life similar and dissimilar pairs of scenes and objects. Young adult participants were familiarised with a series of images,

following which they were shown the same images alongside either a similar or dissimilar novel image. As healthy individuals normally preferentially attend novel stimuli (Manns et al., 2000), the extent to which they remembered the familiar stimulus can be determined by the extent to which they view the novel stimulus. Distinguishing between similar scenes has been shown to recruit the HC (Bonnici et al., 2012), which is capable of resolving a high level of ambiguity.

Similar to Chapter 2, in this study I predicted that an increased risk for poor later life cognitive health (associated with the presence of different forms of *APOE* allele) would reduce novelty preferences for scenes, but not objects, with the similar scene condition being most likely to elicit a greater reduction in novelty preference than dissimilar scenes. The results suggested that the task may sensitive to *APOE*-related changes, albeit with some reservations. Both normal- (*APOE*-ε3) and high-risk (*APOE*-ε4) groups showed a significant reduction in novelty preference for similar, compared to dissimilar, scenes. The low-risk (*APOE*-ε2) group, however, did not show any significant difference between similar and dissimilar scenes. This may be indicative of a facilitation of *APOE*-ε2 in distinguishing between similar scenes, due to improved HC functioning. It is, however, difficult to make any strong conclusions based on the lack of a significant difference, as it may be, in part, be due to the smaller low-risk group size.

The second analysis looking at matched *APOE*-ε4 carriers vs *APOE*-ε4 non-carrier found that the *APOE*-ε4 non-carriers were significantly affected by similarity (collapsed across stimulus-type), whereas the *APOE*-ε4 carriers were not. The data suggested that the *APOE*-ε4 carriers showed a similar level of performance for both similar and dissimilar stimuli, but that *APOE*-ε4 non-carriers were better for dissimilar stimuli, showing a decrement in performance for similar stimuli. In the chapter discussion, it was proposed that this may be due to the *APOE*-ε4 carriers using an alternative non-hippocampal dependent strategy in order to resolve the featural ambiguity between stimuli. There is some evidence that different alleles of *APOE* vary

dependence on spatial strategies, with *APOE*-ε2 carriers being more likely to use spatial strategies during a navigation task, compared to *APOE*-ε3 and -ε4 (Konishi et al., 2016). There is also evidence that *APOE*-ε4 facilitates attention, with *APOE*-ε4 carriers performing better on tests of sustained and covert attention (Rusted et al., 2013). These factors could impact on the susceptibility to ambiguity in the *APOE*-ε4 carriers, as carriers may utilise non-spatial strategies (that are less sensitive to HC function and structure) or be facilitated by improved attention during the familiarisation phase.

In Chapter 5, I looked at the relationship between the volume of the PHC, LOC, PRC, and HC subfields and inter-individual variation in novelty preference for these young adults in the VPC. This produced some interesting results, with a significant association between increased volume of the right subiculum and decreased novelty preference for similar scenes. This was in the opposite direction to my predictions, as it would be expected that the similar scene condition might be particularly dependent upon the subiculum (Hodgetts et al., 2017), and therefore that greater volume of this subfield would be associated with increased novelty preference. It was discussed in Chapter 5 that this unexpected directionality in the finding may be due to neuronal pruning—where inefficient brain cells are removed and replaced with fewer, more efficient, neurons (Huttenlocher & Dabholkar, 1997). This is thought to occur mostly during adolescence and may result in a negative relationship between volume and cognitive function in some brain regions, including the HC (Kanai & Rees, 2011). As the participants being tested in this study were a group of young adults, this seems a plausible explanation for the findings from the analyses of this cohort in Chapter 5, although it should be noted that this is a speculative explanation.

Chapter 4 reported data from the same VPC task that was used in the young adults, but this time in a cohort of middle-aged adults. There was no evidence of any significant relationship between *APOE* genotype and novelty preference in any condition. There was a trend indicating that the *APOE*-ε2 carriers had better performance compared to the other groups across all conditions, but the very low

numbers of *APOE*-ε2 carriers make this conclusion extremely tentative, requiring further follow-up to be reassured that it is a robust finding.

The results of the comparison between brain volume in the LOC, PHC, PRC and HC subfields in the middle-aged participants (outlined in Chapter 5) were interesting. They suggested a very strong positive association between the right subiculum and novelty preference for dissimilar scenes and objects. The subiculum has previously been shown to be active during scene discrimination (Hodgetts et al., 2017), so it is not a surprise to unveil an association with the scenes and novelty preference from the VPC tasks. It was surprising, however, that there was also a strong association with dissimilar objects, which would be expected to be more closely related to PRC volume (Mundy et al., 2012), and also that there was no significant relationship with similar scenes. Of course, the sample size for these analyses are low, making any interpretation difficult; nevertheless, the strength of the relationships (particularly on the a-priori assumed scene-subiculum association) and the high significance factor make these results tough to ignore. The fact that the relationship in these middle-aged adults is in the direction I expected, suggests that any negative relationship that results from adolescent neuronal pruning may be limited to young-adults.

Unfortunately, it is difficult to make any cross-cohort analysis between the young and middle-aged adults recruited for the VPC task. As I collected the data from the middle-aged participants at the University of Sussex, I used a slightly different setup, with a lower resolution portable eye-tracker and monitor. Although this is unlikely to affect performance on the task, the data obtained from the two cohorts are, consequently, not comparable. There were also a number of other factors that changed between groups that could have affected performance. One obvious difference was in recruitment; the Sussex cohort was comprised mostly of staff from the University of Sussex, which could result in an over-representation of highly educated individuals who may also be more invested in the study as they were less likely to be doing it for explicitly motivated reasons (such as course credits). This may partly explain why the older group had a

slightly higher performance had (a larger overall novelty preference signifying increased implicit recognition memory) than the younger group from Chapter 3.

In summary, these findings suggest that the VPC task may be sensitive to early changes in the brain that result from different risk alleles of the *APOE* gene. Zola et al. (2013) used a simpler version of the VPC in elderly individuals, and found that it was predictive of further cognitive decline over the following three years. My findings suggest that the task sensitivity can be increased by using stimuli in which complex spatial discriminations are required, such as similar scenes. Furthermore, my analyses of brain volume suggest that the subiculum subfield of the HC may be involved in supporting those discriminations, noting that it is this same subfield that has been reported to be the earliest anatomical marker of AD in the HC (Carlesimo et al., 2015).

6.3 Addressing the key questions

With regards to the key questions I posed at the start of this thesis, firstly I asked whether there would be an *APOE* dose-linked pattern of performance on tasks in which scenes with a high degree of featural overlap needed to be discriminated (e.g., *APOE*-ε2 < -ε3 < ε4). The results from my studies to not lead to a conclusive answer. The findings of Chapter 3 provide some evidence that different *APOE* alleles may differentially impact on the ability of participants to resolve feature ambiguity. For example, the low/normal/high risk analysis hinted at the possibility that *APOE*-ε2 carriers may be better able to disambiguate similar scenes. The *APOE*-ε4 carrier/non-carrier analysis also suggested that carriers perform comparatively for both similar and dissimilar, whereas there was a significant difference in non-carriers due to similarity. The results only show within-group differences though, not between-groups, which may be due to the increased power in the within-group linear mixed-effects model comparisons. With no significant evidence of *APOE* related performance differences in either the conjunction learning task (Chapter 2) or the VPC task in mid-age adults (Chapter 4),

there is insufficient evidence in this thesis to be confident of any dose-dependent pattern of performance for scene, or object stimuli.

The second question identified at the start of the thesis was whether any *APOE*-related changes in scene and object perception and memory might differ between young and middle-aged participants? I tried to address this question by studying two different cohorts on the same task, my VPC paradigm, which I ran in young adults (Chapter 3) and middle-age adults (Chapter 4). The hope was that I would see more pronounced differences between *APOE* groups as they became older. Unfortunately, as I was blinded to the genotype status during recruitment (a requirement for ethics and ensuring due diligence in data collection), I was unable to assess how many of each group I was recruiting while collecting data. Additionally, *APOE*-ε2 is a rare allele in the normal, and many individuals need to be recruited in order to ensure a suitably sized sample of this group. In my final studies, the sample-size of both *APOE*-ε2 and *APOE*-ε4 carriers were on the low side, making group comparisons less robust than I would have liked. There were some visible trends suggestion of better cognitive performance for *APOE*-ε2 participants compared to both *APOE*-ε3 and *APOE*-ε4 participants, but these cannot be considered robust due to these sample size issues.

The final question I wanted to address in my research was whether individual performance on new tasks, developed in this thesis, would be associated with inter-individual variation in the volume of extrastriate and MTL brain regions, which are known to be involved in scene and object processing. By obtaining grey-matter volume data from the structural MRI images available in some of my participants, and asking how inter-individual variation in volume was associated with behavioural performance on both the conjunction learning and VPC tasks, I was able to partly answer this question. Evidence of a significant association between volume in the LOC and PHC and response times for objects and scenes, respectively, is in line with previous research suggesting that these regions are involved in low-level object and scene disambiguation (Mundy et al., 2012). The lack of a relationship with the MTL regions suggests that the

task was not as demanding on high-level conjunctive processing as was hoped, although it is also possible that this null relationship is due to a more sensitive relationship between MTL regions and performance than potentially evident for extrastriate regions. Specifically, a null result does not necessarily mean that these regions are not involved in this task. It is worth noting, however, that these results are consistent with the negative association between grey-matter and VPC in young adults reported in Chapter 5.

The identification of this negative relationship between the right subiculum and novelty preference is particularly interesting. Firstly, it augments previous literature suggesting that this subfield is preferentially engaged by scenes (Dalton & Maguire, 2017; Hodgetts et al., 2017). It also aligns with work in rodents and non-human primates that have found an abundance of grid, border, and head direction cells, which are all likely to be critical in disambiguating very similar spatial environments, within the region including the pre/parasubiculum and the subiculum ((Boccara et al., 2010; Lever et al., 2009; Robertson, Rolls, Georges-François, & Panzeri, 1999; Stewart, Jeewajee, Wills, Burgess, & Lever, 2014). The findings in this thesis build upon these findings to suggest that, (a) the subiculum is a key region of interest in recognition memory for similar, but not dissimilar, scenes; and (b) that increased subiculum volume may be associated with reduced memory performance for similar scenes in young adults.

These findings highlight that the relationship between volume and cognition may not be straightforward and may differ at various stages over the lifespan. In particular, reassessing our approach to what we consider to be 'healthier' in terms of brain structure may further our knowledge of how different *APOE* genotypes also affect the brain, particularly in young adults. There is increasing evidence to suggest that different alleles of *APOE* may modulate synaptic pruning (Lane-Donovan & Herz, 2017). This was evidenced by Chung et al. (2016), who used *APOE* knock-out mice to study how different *APOE* genotypes modulate the rate of astrocyte-mediated phagocytosis—a process by which cell debris is removed. They found that *APOE*-ε2 increases and

APOE-ε4 decreases the phagocytic rate, resulting in potentiated and reduced, respectively, efficiency of synaptic elimination. In other words, *APOE*-ε2 appears to increase the efficiency of synaptic pruning in rodents. If this translates into humans, it could have profound effects on how we interpret both grey- and white-matter structural differences in young adults and children with different *APOE* alleles, as well as how these relate to cognition.

6.4 Addressing the limitations with future research

The findings from Chapter 2 suggest that it is likely that the current version of the conjunction learning task does not sufficiently engage conjunctive processing to elicit dose-dependent differences of *APOE*. That does not, however, mean that the task does not have potential. It appears clear that, at least in the scene condition, the task can be completed by observing a single feature; any further versions of that task should ensure that manipulation of the spatial features does not result in a single feature which discriminates the stimuli. It would also be possible to make the task more demanding by introducing a probabilistic learning element (e.g. Schutte et al., 2017), whereby the accuracy of the feedback is systematically reduced to make the learning process more demanding.

The VPC task does appear to be sensitive to *APOE*-related differences in disambiguating similar scenes, potentially even in young adults. Although the results of Chapter 3 did not uncover between-group statistical differences, there were observable differences that were specific to particular alleles. It is likely that a much larger scale study would be required in order to see differences between different *APOE* groups in young adults. Any measurable behavioural differences due to *APOE* at this stage in life are likely to be small, and more closely related to altered functioning in scene networks (e.g. Shine et al., 2015) rather than any obvious cognitive impairment. New technology developments that are making eye-tracking increasingly accessible, such as techniques to use standard web-cams for tracking VPC eye-movements (Bott et al., 2017), may

enable the use of this task in large-scale cohort studies. This could provide the kind of sample sizes that might be needed to detect differences between different *APOE* alleles. The availability of entire genome data may also allow for comparisons by polygenic risk, which take into account other genetic risk variants, which may be a more robust measure of future risk for AD (Escott-Price, Shoai, Pither, Williams, & Hardy, 2017; Escott-Price et al., 2015).

Another limitation of the VPC design used in this thesis is the dichotomic split of similarity. It may be possible to manipulate the stimuli pairs in such a way that similarity is measured in a linear fashion. One way of doing this would be to collect subjective measures of how similar each pair of images are. Another way could use a more objective measure, such as image analysis software that is capable of detecting similarity using a number of low- and high-order parameters (e.g. Kornel, 2018).

In terms of furthering the interesting MRI findings from Chapter 5, future research into whether the findings in rodents, that different alleles of *APOE* modulate synaptic pruning (e.g. Chung et al., 2016), translate into humans is needed. New methods of MRI imaging, such as the new Connectom scanner (Siemens Healthcare Limited, Camberley, UK) that has vastly increased gradient strength, allow for white-matter microstructure to be measured in much finer resolution that we have seen previously. Furthermore, ultra-high resolution 7-tesla MRI allows us to now measure grey-matter in smaller structures, such as hippocampal subfields, with much more validity. It may be possible to combine such methods in a longitudinal study to measure how both grey- and white-matter integrity and volume differentially alters during adolescence between different *APOE* genotypes. Such a study could provide critical information about how *APOE* impacts upon the brain during this important window of time.

6.5 General conclusion

This thesis provides some evidence that the VPC task may be sensitive to future risk of AD, as measured by the presence of low- (*APOE*-ε2) or high-risk (*APOE*-ε4) alleles of the *APOE* gene, in young and middle-aged adults. The detrimental impact of increasing similarity during implicit discriminations of stimulus-pairs appears to be reduced in young *APOE*-ε4 carriers, compared to non-carriers, which may be indicative of them using cognitive strategies that are less sensitive to ambiguity. Furthermore, in middle-aged adults, there was a trend for increased implicit recognition memory (as measured by novelty preference) on the VPC task for *APOE*-ε2 carriers, though the limited sample size made statistical inferences impossible. Data from structural MRI found supporting evidence for a role of the LOC and PHC in distinguishing object and scene representations, respectively, in line with similar previous findings (e.g. Mundy et al., 2012). Furthermore, I found that implicit recognition memory for similar scenes may be selectively dependent upon the size of the subiculum subfield of the HC, with lower volume increasing novelty preference (a measure of recognition memory) in young adults. This furthers our understanding of how synaptic pruning may potentially create a negative relationship between this hippocampal subfield and cognitive performance during this post-adolescent phase of adulthood.

REFERENCES

Acevedo, S. F., Piper, B. J., Craytor, M. J., Benice, T. S., & Raber, J. (2010). Apolipoprotein E4 and sex affect neurobehavioral performance in primary school children. *Pediatric Research*, *67*(3), 293–299. https://doi.org/10.1203/PDR.0b013e3181cb8e68

Agichtein, Y., Buffalo, E., Lagun, D., Manzanares, C., & Zola, S. (2017). *U.S. Patent No. 9,629,543 B2*. Retrieved from https://patentimages.storage.googleapis.com/31/46/af/eb5db6ab34ab7d/US9629543.pdf

Aizenstein, H. J., Nebes, R. D., Saxton, J. A., Price, J. C., Mathis, C. A., Tsopelas, N. D., … Klunk, W. E. (2008). Frequent amyloid deposition without significant cognitive impairment among the elderly. *Archives of Neurology*, *65*(11), 1509–1517. https://doi.org/10.1001/archneur.65.11.1509

Alexopoulos, P., Richter-Schmidinger, T., Horn, M., Maus, S., Reichel, M., Sidiropoulos, C., … Kornhuber, J. (2011). Hippocampal volume differences between healthy young apolipoprotein E ε2 and ε4 carriers. *Journal of Alzheimer's Disease*, *26*(2), 207–210.

Aly, M., Ranganath, C., & Yonelinas, A. P. (2013). Detecting changes in scenes: the hippocampus is critical for strength-based perception. *Neuron*, *78*(6), 1127–1137. https://doi.org/10.1016/j.neuron.2013.04.018

Alzheimer's Disease International. (2015). *World Alzheimer Report 2015: The Global Impact of Dementia*. London. Retrieved from http://www.alz.co.uk/research/world-report-2015

Alzheimer's Disease International. (2018, September 4). Importance of early diagnosis. Retrieved 4 September 2018, from https://www.alz.co.uk/info/importance-of-early-diagnosis

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. Arlington, VA: American Psychiatric Publishing.

Astur, R. S., Taylor, L. B., Mamelak, A. N., Philpott, L., & Sutherland, R. J. (2002). Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. *Behavioural Brain Research*, *132*(1), 77–84.

Bachevalier, J., Brickson, M., & Hagger, C. (1993). Limbic-dependent recognition memory in monkeys develops early in infancy. *Neuroreport*, *4*(1), 77–80.

Barense, M. D., Bussey, T. J., Lee, A. C. H., Rogers, T. T., Davies, R. R., Saksida, L. M., … Graham, K. S. (2005). Functional specialization in the human medial temporal lobe. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *25*(44), 10239–10246. https://doi.org/10.1523/JNEUROSCI.2704-05.2005

Barense, M. D., Gaffan, D., & Graham, K. S. (2007). The human medial temporal lobe processes online representations of complex objects. *Neuropsychologia*, *45*(13), 2963–2974. https://doi.org/10.1016/j.neuropsychologia.2007.05.023

Barense, M. D., Groen, I. I. A., Lee, A. C. H., Yeung, L.-K., Brady, S. M., Gregori, M., … Henson, R. N. A. (2012). Intact memory for irrelevant information impairs perception in amnesia. *Neuron*, *75*(1), 157–167. https://doi.org/10.1016/j.neuron.2012.05.014

Barense, M. D., Henson, R. N. A., Lee, A. C. H., & Graham, K. S. (2010). Medial temporal lobe activity during complex discrimination of faces, objects, and scenes: Effects of viewpoint. *Hippocampus*, *20*(3), 389–401. https://doi.org/10.1002/hipo.20641

Barense, M. D., Rogers, T. T., Bussey, T. J., Saksida, L. M., & Graham, K. S. (2010). Influence of Conceptual Knowledge on Visual Object Discrimination: Insights from Semantic Dementia and MTL Amnesia. *Cerebral Cortex*, *20*(11), 2568–2582. https://doi.org/10.1093/cercor/bhq004

Barnett, J. H., Blackwell, A. D., Sahakian, B. J., & Robbins, T. W. (2015). The Paired Associates Learning (PAL) Test: 30 Years of CANTAB Translational Neuroscience from Laboratory to Bedside in Dementia Research. In *Translational Neuropsychopharmacology* (pp. 449–474). Springer, Cham. https://doi.org/10.1007/7854_2015_5001

Barry, T. J., Griffith, J. W., De Rossi, S., & Hermans, D. (2014). Meet the Fribbles: novel stimuli for use within behavioural research. *Frontiers in Psychology*, *5*. https://doi.org/10.3389/fpsyg.2014.00103

Bartko, S. J., Cowell, R. A., Winters, B. D., Bussey, T. J., & Saksida, L. M. (2010). Heightened susceptibility to interference in an animal model of amnesia: impairment in encoding, storage, retrieval--or all three? *Neuropsychologia*, *48*(10), 2987–2997. https://doi.org/10.1016/j.neuropsychologia.2010.06.007

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, *67*(1), 1–48. https://doi.org/10.18637/jss.v067.i01

Berlau, D. J., Corrada, M. M., Head, E., & Kawas, C. H. (2009). APOE ε2 is associated with intact cognition but increased Alzheimer pathology in the oldest old. *Neurology*, *72*(9), 829–834. https://doi.org/10.1212/01.wnl.0000343853.00346.a4

Bero, A. W., Yan, P., Roh, J. H., Cirrito, J. R., Stewart, F. R., Raichle, M. E., … Holtzman, D. M. (2011). Neuronal activity regulates the regional vulnerability to amyloid-β deposition. *Nature Neuroscience*, *14*(6), 750–756. https://doi.org/10.1038/nn.2801

Bertram, L., & Tanzi, R. E. (2008). Thirty years of Alzheimer's disease genetics: the implications of systematic meta-analyses. *Nature Reviews Neuroscience*, *9*(10), 768–778. https://doi.org/10.1038/nrn2494

Bettens, K., Sleegers, K., & Van Broeckhoven, C. (2010). Current status on Alzheimer disease molecular genetics: from past, to present, to future. *Human Molecular Genetics*, *19*(R1), R4–R11. https://doi.org/10.1093/hmg/ddq142

Biffi, A., Anderson, C. D., Desikan, R. S., Sabuncu, M., Cortellini, L., Schmansky, N., … Alzheimer's Disease Neuroimaging Initiative (ADNI). (2010). Genetic variation and neuroimaging measures in Alzheimer disease. *Archives of Neurology*, *67*(6), 677–685. https://doi.org/10.1001/archneurol.2010.108

Bird, C. M., Chan, D., Hartley, T., Pijnenburg, Y. A., Rossor, M. N., & Burgess, N. (2010). Topographical short-term memory differentiates Alzheimer's disease from frontotemporal lobar degeneration. *Hippocampus*, *20*(10), 1154–1169. https://doi.org/10.1002/hipo.20715

Bird, C. M., Vargha-Khadem, F., & Burgess, N. (2008). Impaired memory for scenes but not faces in developmental hippocampal amnesia: a case study. *Neuropsychologia*, *46*(4), 1050–1059. https://doi.org/10.1016/j.neuropsychologia.2007.11.007

Blair, C. K., Folsom, A. R., Knopman, D. S., Bray, M. S., Mosley, T. H., Boerwinkle, E., & for the Atherosclerosis Risk in Communities Study Investigators. (2005). APOE genotype and cognitive decline in a middle-aged cohort. *Neurology*, *64*(2), 268–276. https://doi.org/10.1212/01.WNL.0000149643.91367.8A

Blumenthal, A., Stojanoski, B., Martin, C., Cusack, R., & Kohler, S. (2018). Animacy and real world size shape object representations in the human medial temporal lobes. *BioRxiv*, 304824. https://doi.org/10.1101/304824

Boccara, C. N., Sargolini, F., Thoresen, V. H., Solstad, T., Witter, M. P., Moser, E. I., & Moser, M.-B. (2010). Grid cells in pre- and parasubiculum. *Nature Neuroscience*, *13*(8), 987–994. https://doi.org/10.1038/nn.2602

Bondi, M. W., Salmon, D. P., Monsch, A. U., Galasko, D., Butters, N., Klauber, M. R., … Saitoh, T. (1995). Episodic memory changes are associated with the APOE-epsilon 4 allele in nondemented older adults. *Neurology*, *45*(12), 2203. https://doi.org/10.1212/WNL.45.12.2203

Bonnici, H. M., Kumaran, D., Chadwick, M. J., Weiskopf, N., Hassabis, D., & Maguire, E. A. (2012). Decoding representations of scenes in the medial temporal lobes. *Hippocampus*, *22*(5), 1143–1153. https://doi.org/10.1002/hipo.20960

Bott, N. T., Lange, A., Rentz, D., Buffalo, E., Clopton, P., & Zola, S. (2017). Web Camera Based Eye Tracking to Assess Visual Memory on a Visual Paired Comparison Task. *Frontiers in Neuroscience*, *11*. https://doi.org/10.3389/fnins.2017.00370

Braak, H., & Braak, E. (1998). Evolution of neuronal changes in the course of Alzheimer's disease. *Journal of Neural Transmission. Supplementum*, *53*, 127–140.

Brunec, I. K., Bellana, B., Ozubko, J. D., Man, V., Robin, J., Liu, Z.-X., … Moscovitch, M. (2017). Differential spatiotemporal representations along the hippocampal long axis in humans. *BioRxiv*, 179655. https://doi.org/10.1101/179655

Brunec, I. K., Bellana, B., Ozubko, J. D., Man, V., Robin, J., Liu, Z.-X., … Moscovitch, M. (2018). Multiple Scales of Representation along the Hippocampal Anteroposterior Axis in Humans. *Current Biology*, *28*(13), 2129-2135.e6. https://doi.org/10.1016/j.cub.2018.05.016

Bu, G. (2009). Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nature Reviews Neuroscience*, *10*(5), 333–344. https://doi.org/10.1038/nrn2620

Buckley, M., Charles, D., Browning, P., & Gaffan, D. (2004). Learning and Retrieval of Concurrently Presented Spatial Discrimination Tasks: Role of the Fornix. *Behavioral Neuroscience*, *118*(1), 138–149. https://doi.org/10.1037/0735-7044.118.1.138

Buckley, M., & Gaffan, D. (1997). Impairment of visual object-discrimination learning after perirhinal cortex ablation. *Behavioral Neuroscience*, *111*(3), 467–475.

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., … Johnson, K. A. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *29*(6), 1860–1873. https://doi.org/10.1523/JNEUROSCI.5062-08.2009

Bunce, D., Anstey, K. J., Burns, R., Christensen, H., & Easteal, S. (2011). Does possession of apolipoprotein E ε4 benefit cognitive function in healthy young adults? *Neuropsychologia*, *49*(7), 1693–1697. https://doi.org/10.1016/j.neuropsychologia.2011.02.042

Burggren, A. C., Zeineh, M. M., Ekstrom, A. D., Braskie, M. N., Thompson, P. M., Small, G. W., & Bookheimer, S. Y. (2008). Reduced cortical thickness in hippocampal subregions among cognitively normal apolipoprotein E e4 carriers. *NeuroImage*, *41*(4), 1177–1183. https://doi.org/10.1016/j.neuroimage.2008.03.039

Bussey, T. J., & Saksida, L. M. (2002). The organization of visual object representations: a connectionist model of effects of lesions in perirhinal cortex. *The European Journal of Neuroscience*, *15*(2), 355–364.

Bussey, T. J., & Saksida, L. M. (2007). Memory, perception, and the ventral visual-perirhinal-hippocampal stream: Thinking outside of the boxes. *Hippocampus*, *17*(9), 898–908. https://doi.org/10.1002/hipo.20320

Bussey, T. J., Saksida, L. M., & Murray, E. A. (2002). Perirhinal cortex resolves feature ambiguity in complex visual discriminations. *European Journal of Neuroscience*, *15*(2), 365–374. https://doi.org/10.1046/j.0953-816x.2001.01851.x

Cano, S. J., Posner, H. B., Moline, M. L., Hurt, S. W., Swartz, J., Hsu, T., & Hobart, J. C. (2010). The ADAS-cog in Alzheimer's disease clinical trials: psychometric evaluation of the sum and its parts. *Journal of Neurology, Neurosurgery & Psychiatry*, *81*(12), 1363–1368. https://doi.org/10.1136/jnnp.2009.204008

Carlesimo, G. A., Piras, F., Orfei, M. D., Iorio, M., Caltagirone, C., & Spalletta, G. (2015). Atrophy of presubiculum and subiculum is the earliest hippocampal anatomical marker of Alzheimer's disease. *Alzheimer's & Dementia : Diagnosis, Assessment & Disease Monitoring*, *1*(1), 24–32. https://doi.org/10.1016/j.dadm.2014.12.001

Caselli, R. J., Dueck, A. C., Osborne, D., Sabbagh, M. N., Connor, D. J., Ahern, G. L., … Reiman, E. M. (2009). Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. *The New England Journal of Medicine*, *361*(3), 255–263. https://doi.org/10.1056/NEJMoa0809437

Castellano, J. M., Kim, J., Stewart, F. R., Jiang, H., DeMattos, R. B., Patterson, B. W., … Holtzman, D. M. (2011). Human apoE Isoforms Differentially Regulate Brain Amyloid-β Peptide Clearance. *Science Translational Medicine*, *3*(89). https://doi.org/10.1126/scitranslmed.3002156

Cauda, F., Geminiani, G., D'Agata, F., Sacco, K., Duca, S., Bagshaw, A. P., & Cavanna, A. E. (2010). Functional Connectivity of the Posteromedial Cortex. *PLoS ONE*, *5*(9), e13107. https://doi.org/10.1371/journal.pone.0013107

Chang, L., Douet, V., Bloss, C., Lee, K., Pritchett, A., Jernigan, T. L., … Pediatric Imaging, Neurocognition, and Genetics (PING) Study Consortium. (2016). Gray matter maturation and cognition in children with different APOE ε genotypes. *Neurology*, *87*(6), 585–594. https://doi.org/10.1212/WNL.0000000000002939

Chen, C.-J., Chen, C.-C., Wu, D., Chi, N.-F., Chen, P.-C., Liao, Y.-P., … Hu, C.-J. (2013). Effects of the Apolipoprotein E ε4 Allele on Functional MRI during n-Back Working Memory Tasks in Healthy Middle-Aged Adults. *American Journal of Neuroradiology*, *34*(6), 1197–1202. https://doi.org/10.3174/ajnr.A3369

Cherrier, M. M., Mendez, M., & Perryman, K. (2001). Route learning performance in Alzheimer disease patients. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, *14*(3), 159–168.

Chiang, G. C., Zhan, W., Schuff, N., & Weiner, M. W. (2012). White Matter Alterations in Cognitively Normal apoE ε2 Carriers: Insight into Alzheimer Resistance? *AJNR. American Journal of Neuroradiology*, *33*(7), 1392–1397. https://doi.org/10.3174/ajnr.A2984

Chung, W.-S., Verghese, P. B., Chakraborty, C., Joung, J., Hyman, B. T., Ulrich, J. D., … Barres, B. A. (2016). Novel allele-dependent role for APOE in controlling the rate of synapse pruning by astrocytes. *Proceedings of the National Academy of Sciences*, *113*(36), 10186–10191. https://doi.org/10.1073/pnas.1609896113

Clark, R. E., Zola, S. M., & Squire, L. R. (2000). Impaired Recognition Memory in Rats after Damage to the Hippocampus. *The Journal of Neuroscience*, *20*(23), 8853–8860.

Cohen, R. M., Small, C., Lalonde, F., Friz, J., & Sunderland, T. (2001). Effect of apolipoprotein E genotype on hippocampal volume loss in aging healthy women. *Neurology*, *57*(12), 2223–2228.

Connor, C. E., & Knierim, J. J. (2017). Integration of objects and space in perception and memory. *Nature Neuroscience*, *20*(11), 1493–1503. https://doi.org/10.1038/nn.4657

Corbo, R. M., & Scacchi, R. (1999). Apolipoprotein E (APOE) allele distribution in the world. Is *APOE * 4* a 'thrifty' allele? *Annals of Human Genetics*, *63*(4), 301–310. https://doi.org/10.1046/j.1469-1809.1999.6340301.x

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., … Pericak-Vance, M. A. (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, *261*(5123), 921–923. https://doi.org/10.1126/science.8346443

Cornwell, B. R., Johnson, L. L., Holroyd, T., Carver, F. W., & Grillon, C. (2008). Human Hippocampal and Parahippocampal Theta during Goal-Directed Spatial Navigation Predicts Performance on a Virtual Morris Water Maze. *Journal of Neuroscience*, *28*(23), 5983–5990. https://doi.org/10.1523/JNEUROSCI.5001-07.2008

Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2006). Why Does Brain Damage Impair Memory? A Connectionist Model of Object Recognition Memory in Perirhinal Cortex. *Journal of Neuroscience*, *26*(47), 12186–12197. https://doi.org/10.1523/JNEUROSCI.2818-06.2006

Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2010). Functional dissociations within the ventral object processing pathway: cognitive modules or a hierarchical continuum? *Journal of Cognitive Neuroscience*, *22*(11), 2460–2479. https://doi.org/10.1162/jocn.2009.21373

Crocco, E. A., & Loewenstein, D. A. (2005). Psychiatric aspects of mild cognitive impairment. *Current Psychiatry Reports*, *7*(1), 32–36. https://doi.org/10.1007/s11920-005-0021-8

Crutcher, M. D., Calhoun-Haney, R., Manzanares, C. M., Lah, J. J., Levey, A. I., & Zola, S. M. (2009). Eye tracking during a visual paired comparison task as a predictor of early dementia. *American Journal of Alzheimer's Disease and Other Dementias*, *24*(3), 258–266. https://doi.org/10.1177/1533317509332093

Dalton, M. A., & Maguire, E. A. (2017). The pre/parasubiculum: a hippocampal hub for scene-based cognition? *Current Opinion in Behavioral Sciences*, *17*, 34–40. https://doi.org/10.1016/j.cobeha.2017.06.001

Deary, I. J., Whiteman, M. C., Pattie, A., Starr, J. M., Hayward, C., Wright, A. F., … Whalley, L. J. (2002). Ageing: Cognitive change and the *APOE* ε4 allele. *Nature*, *418*(6901), 932. https://doi.org/10.1038/418932a

deIpolyi, A. R., Rankin, K. P., Mucke, L., Miller, B. L., & Gorno-Tempini, M. L. (2007). Spatial cognition and the human navigation network in AD and MCI. *Neurology*, *69*(10), 986–997. https://doi.org/10.1212/01.wnl.0000271376.19515.c6

Delaère, P., Duyckaerts, C., Masters, C., Beyreuther, K., Piette, F., & Hauw, J. J. (1990). Large amounts of neocortical beta A4 deposits without neuritic plaques nor tangles in a psychometrically assessed, non-demented person. *Neuroscience Letters*, *116*(1–2), 87–93.

Dennis, N. A., Browndyke, J. N., Stokes, J., Need, A., Burke, J. R., Welsh-Bohmer, K. A., & Cabeza, R. (2010). Temporal lobe functional activity and connectivity in young adult APOE ε4 carriers. *Alzheimer's & Dementia*, *6*(4), 303–311. https://doi.org/10.1016/j.jalz.2009.07.003

D'Hooge, R., & De Deyn, P. P. (2001). Applications of the Morris water maze in the study of learning and memory. *Brain Research Reviews*, *36*(1), 60–90. https://doi.org/10.1016/S0165-0173(01)00067-4

Dickson, D. W., Crystal, H. A., Mattiace, L. A., Masur, D. M., Blau, A. D., Davies, P., … Aronson, M. K. (1992). Identification of normal and pathological aging in prospectively studied nondemented elderly humans. *Neurobiology of Aging*, *13*(1), 179–189.

Douglas, D., Thavabalasingam, S., Chorghay, Z., O'Neil, E. B., Barense, M. D., & Lee, A. C. H. (2017). Perception of Impossible Scenes Reveals Differential Hippocampal and Parahippocampal Place Area Contributions to Spatial Coherency. *Hippocampus*, *27*(1), 61–76. https://doi.org/10.1002/hipo.22673

Dowell, N. G., Ruest, T., Evans, S. L., King, S. L., Tabet, N., Tofts, P. S., & Rusted, J. M. (2013). MRI of carriers of the apolipoprotein E e4 allele-evidence for structural differences in normal-appearing brain tissue in e4+ relative to e4- young adults: MRI OF CARRIERS OF THE APOLIPOPROTEIN E E4 ALLELE. *NMR in Biomedicine*, n/a-n/a. https://doi.org/10.1002/nbm.2912

Dubé, J. B., Johansen, C. T., Robinson, J. F., Lindsay, J., Hachinski, V., & Hegele, R. A. (2013). Genetic Determinants of "Cognitive Impairment, No Dementia". *Journal of Alzheimer's Disease*, *33*(3), 831–840. https://doi.org/10.3233/JAD-2012-121477

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., … Jack, C. R. (2016). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's & Dementia*, *12*(3), 292–323. https://doi.org/10.1016/j.jalz.2016.02.002

Duvernoy, H. M., Cattin, F., & Risold, P.-Y. (2005). *The Human Hippocampus: Functional Anatomy, Vascularization and Serial Sections with MRI, 3rd edition* (3rd edition). Berlin, Germany: Springer.

Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature*, *392*(6676), 598. https://doi.org/10.1038/33402

Erez, J., Cusack, R., Kendall, W., & Barense, M. D. (2016). Conjunctive Coding of Complex Object Features. *Cerebral Cortex (New York, N.Y.: 1991)*, *26*(5), 2271–2282. https://doi.org/10.1093/cercor/bhv081

Escott-Price, V., Bellenguez, C., Wang, L.-S., Choi, S.-H., Harold, D., Jones, L., … Williams, J. (2014). Gene-Wide Analysis Detects Two New Susceptibility Genes for Alzheimer's Disease. *PLoS ONE*, *9*(6), e94661. https://doi.org/10.1371/journal.pone.0094661

Escott-Price, V., Shoai, M., Pither, R., Williams, J., & Hardy, J. (2017). Polygenic score prediction captures nearly all common genetic risk for Alzheimer's disease. *Neurobiology of Aging*, *49*, 214.e7-214.e11. https://doi.org/10.1016/j.neurobiolaging.2016.07.018

Escott-Price, V., Sims, R., Bannister, C., Harold, D., Vronskaya, M., Majounie, E., … Williams, J. (2015). Common polygenic variation enhances risk prediction for Alzheimer's disease. *Brain*, *138*(12), 3673–3684. https://doi.org/10.1093/brain/awv268

Evans, S., Dowell, N. G., Tabet, N., Tofts, P. S., King, S. L., & Rusted, J. M. (2014). Cognitive and neural signatures of the APOE E4 allele in mid-aged adults. *Neurobiology of Aging*, *35*(7), 1615–1623. https://doi.org/10.1016/j.neurobiolaging.2014.01.145

Fagan, A. M., Mintun, M. A., Shah, A. R., Aldea, P., Roe, C. M., Mach, R. H., … Holtzman, D. M. (2009). Cerebrospinal fluid tau and ptau(181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer's disease. *EMBO Molecular Medicine*, *1*(8–9), 371–380. https://doi.org/10.1002/emmm.200900048

Farlow, M. R., Andreasen, N., Riviere, M.-E., Vostiar, I., Vitaliti, A., Sovago, J., … Graf, A. (2015). Long-term treatment with active Aβ immunotherapy with CAD106 in mild Alzheimer's disease. *Alzheimer's Research & Therapy*, *7*(1), 23. https://doi.org/10.1186/s13195-015-0108-3

Farrer, L. A., Myers, R. H., Cupples, L. A., St. George-Hyslop, P. H., Bird, T. D., Rossor, M. N., … Growdon, J. H. (1990). Transmission and age-at-onset patterns in familial Alzheimer's disease. *Neurology*, *40*(3 Part 1), 395. https://doi.org/10.1212/WNL.40.3_Part_1.395

Farrer, Lindsay A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., … Duijn, C. M. van. (1997). Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease: A Meta-analysis. *JAMA*, *278*(16), 1349–1356. https://doi.org/10.1001/jama.1997.03550160069041

Filippini, N., Ebmeier, K. P., MacIntosh, B. J., Trachtenberg, A., Frisoni, G. B., Wilcock, G. K., … Mackay, C. E. (2011). Differential effects of the APOE genotype on brain function across the lifespan. *NeuroImage*, *54*(1), 602–610. https://doi.org/10.1016/j.neuroimage.2010.08.009

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., … Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE-ε4 allele. *Proceedings of the National Academy of Sciences*, *106*(17), 7209–7214.

Fjell, A. M., McEvoy, L., Holland, D., Dale, A. M., & Walhovd, K. B. (2014). What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. *Progress in Neurobiology*, *117*, 20–40. https://doi.org/10.1016/j.pneurobio.2014.02.004

Foster, J. K., Meikle, A., Goodson, G., Mayes, A. R., Howard, M., Sunram, S. I., … Roberts, N. (1999). The Hippocampus and Delayed Recall: Bigger is not Necessarily Better? *Memory*, *7*(5–6), 715–733. https://doi.org/10.1080/096582199387823

Galasko, D., Bennett, D., Sano, M., Ernesto, C., Thomas, R., Grundman, M., & Ferris, S. (1997). An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease. *Alzheimer Disease & Associated Disorders*, *11*, 33.

Ganguli, M., Dodge, H. H., Shen, C., & DeKosky, S. T. (2004). Mild cognitive impairment, amnestic type: an epidemiologic study. *Neurology*, *63*(1), 115–121.

Gauthier, I., Tarr, M. J., Moylan, J., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). The Fusiform "Face Area" is Part of a Network that Processes Faces at the Individual Level. *Journal of Cognitive Neuroscience*, *12*(3), 495–504. https://doi.org/10.1162/089892900562165

Genin, E., Hannequin, D., Wallon, D., Sleegers, K., Hiltunen, M., Combarros, O., … Campion, D. (2011). APOE AND ALZHEIMER DISEASE: A MAJOR GENE WITH SEMI-DOMINANT INHERITANCE. *Molecular Psychiatry*, *16*(9), 903–907. https://doi.org/10.1038/mp.2011.52

Giri, M., Zhang, M., & Lü, Y. (2016). Genes associated with Alzheimer's disease: an overview and current status. *Clinical Interventions in Aging*, *11*, 665–681. https://doi.org/10.2147/CIA.S105769

Glenner, G. G., & Wong, C. W. (1984). Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. *Biochemical and Biophysical Research Communications*, *122*(3), 1131–1135.

Goodrich-Hunsaker, N. J., Livingstone, S. A., Skelton, R. W., & Hopkins, R. O. (2010). Spatial deficits in a virtual water maze in amnesic participants with hippocampal damage. *Hippocampus*, *20*(4), 481–491. https://doi.org/10.1002/hipo.20651

Graham, K. S., Barense, M. D., & Lee, A. C. H. (2010). Going beyond LTM in the MTL: A synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia*, *48*(4), 831–853. https://doi.org/10.1016/j.neuropsychologia.2010.01.001

Graham, K. S., Scahill, V. L., Hornberger, M., Barense, M. D., Lee, A. C. H., Bussey, T. J., & Saksida, L. M. (2006). Abnormal categorization and perceptual learning in patients with hippocampal damage. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *26*(29), 7547–7554. https://doi.org/10.1523/JNEUROSCI.1535-06.2006

Grandjean, J., D'Ostilio, K., Phillips, C., Balteau, E., Degueldre, C., Luxen, A., … Collette, F. (2012). Modulation of Brain Activity during a Stroop Inhibitory Task by the Kind of Cognitive Control Required. *PLoS ONE*, *7*(7). https://doi.org/10.1371/journal.pone.0041513

Greenwood, P. M., Lambert, C., Sunderland, T., & Parasuraman, R. (2005). Effects of Apolipoprotein E Genotype on Spatial Attention, Working Memory, and Their Interaction in Healthy, Middle-Aged Adults: Results From the National Institute of Mental Health's BIOCARD Study. *Neuropsychology*, *19*(2), 199–211. https://doi.org/10.1037/0894-4105.19.2.199

Greenwood, P. M., Sunderland, T., Putnam, K., Levy, J., & Parasuraman, R. (2005). Scaling of visuospatial attention undergoes differential longitudinal change as a function of APOE genotype prior to old age: Results from the NIMH BIOCARD Study. *Neuropsychology*, *19*(6), 830–840. https://doi.org/10.1037/0894-4105.19.6.830

Grill-Spector, K., Kourtzi, Z., & Kanwisher, N. (2001). The lateral occipital complex and its role in object recognition. *Vision Research*, *41*(10–11), 1409–1422. https://doi.org/10.1016/S0042-6989(01)00073-6

Haan, W. de, Mott, K., Straaten, E. C. W. van, Scheltens, P., & Stam, C. J. (2012). Activity Dependent Degeneration Explains Hub Vulnerability in Alzheimer's Disease. *PLOS Computational Biology*, *8*(8), e1002582. https://doi.org/10.1371/journal.pcbi.1002582

Hampton, R. R., Hampstead, B. M., & Murray, E. A. (2004). Selective hippocampal damage in rhesus monkeys impairs spatial memory in an open-field test. *Hippocampus*, *14*(7), 808–818. https://doi.org/10.1002/hipo.10217

Hardy, J., & Higgins, G. (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science*, *256*(5054), 184–185. https://doi.org/10.1126/science.1566067

Hartley, D., Blumenthal, T., Carrillo, M., DiPaolo, G., Esralew, L., Gardiner, K., … Wisniewski, T. (2015). Down syndrome and Alzheimer's disease: Common pathways, common goals. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *11*(6), 700–709. https://doi.org/10.1016/j.jalz.2014.10.007

Hartley, T., Maguire, E. A., Spiers, H. J., & Burgess, N. (2003). The Well-Worn Route and the Path Less Traveled: Distinct Neural Bases of Route Following and Wayfinding in Humans. *Neuron*, *37*(5), 877–888. https://doi.org/10.1016/S0896-6273(03)00095-3

Hatters, D. M., Peters-Libeu, C. A., & Weisgraber, K. H. (2006). Apolipoprotein E structure: insights into function. *Trends in Biochemical Sciences*, *31*(8), 445–454. https://doi.org/10.1016/j.tibs.2006.06.008

Heerema, E. (2018, September 4). Benefits of Early Detection in Alzheimer's Disease. Retrieved 4 September 2018, from https://www.verywellhealth.com/12-benefits-of-early-detection-in-alzheimers-disease-98046

Heilbronner, S. R., & Haber, S. N. (2014). Frontal cortical and subcortical projections provide a basis for segmenting the cingulum bundle: implications for neuroimaging and psychiatric disorders. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *34*(30), 10041–10054. https://doi.org/10.1523/JNEUROSCI.5459-13.2014

Heise, V., Filippini, N., Ebmeier, K. P., & Mackay, C. E. (2011). The APOE ε4 allele modulates brain white matter integrity in healthy adults. *Molecular Psychiatry*, *16*(9), 908–916. https://doi.org/10.1038/mp.2010.90

Heise, V., Filippini, N., Trachtenberg, A. ., Suri, S., Ebmeier, K. ., & Mackay, C. . (2014). Apolipoprotein E genotype, gender and age modulate connectivity of the hippocampus in healthy adults. *NeuroImage*, *98*, 23–30. https://doi.org/10.1016/j.neuroimage.2014.04.081

Herrup, K. (2015). The case for rejecting the amyloid cascade hypothesis. *Nature Neuroscience*, *18*(6), 794–799. https://doi.org/10.1038/nn.4017

Hirshhorn, M., Grady, C., Rosenbaum, R. S., Winocur, G., & Moscovitch, M. (2012). Brain regions involved in the retrieval of spatial and episodic details associated with a familiar environment: An fMRI study. *Neuropsychologia*, *50*(13), 3094–3106. https://doi.org/10.1016/j.neuropsychologia.2012.08.008

Hodges, J. R., Patterson, K., Oxbury, S., & Funnell, E. (1992). Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain : A Journal of Neurology*, *115 (Pt 6)*, 1783–1806. https://doi.org/10.1093/brain/115.6.1783

Hodgetts, C. J., Shine, J. P., Lawrence, A. D., Downing, P. E., & Graham, K. S. (2016). Evidencing a place for the hippocampus within the core scene processing network. *Human Brain Mapping*, *37*(11), 3779–3794. https://doi.org/10.1002/hbm.23275

Hodgetts, C. J., Shine, J. P., Williams, H., Postans, M., Sims, R., Williams, J., … Graham, K. S. (2018). Increased posterior default mode network activity and structural connectivity in young adult APOE-ε4 carriers: a multi-modal imaging investigation. *BioRxiv*. https://doi.org/10.1101/285536

Hodgetts, C. J., Voets, N. L., Thomas, A. G., Clare, S., Lawrence, A. D., & Graham, K. S. (2017). Ultra-High-Field fMRI Reveals a Role for the Subiculum in Scene Perceptual Discrimination. *Journal of Neuroscience*, *37*(12), 3150–3159. https://doi.org/10.1523/JNEUROSCI.3225-16.2017

Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J.-C., Carrasquillo, M. M., … Williams, J. (2011). Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nature Genetics*, *43*, 429–435.

Holmes, C., Boche, D., Wilkinson, D., Yadegarfar, G., Hopkins, V., Bayer, A., … Nicoll, J. A. R. (2008). Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. *Lancet (London, England)*, *372*(9634), 216–223. https://doi.org/10.1016/S0140-6736(08)61075-2

Honea, R. A., Vidoni, E., Harsha, A., & Burns, J. M. (2009). Impact of APOE on the healthy aging brain: a voxel-based MRI and DTI study. *Journal of Alzheimer's Disease: JAD*, *18*(3), 553–564. https://doi.org/10.3233/JAD-2009-1163

Honig, L. S., Hake, A., Sundell, K., Carlson, C., Hoffmann, V. P., Case, M., … Siemers, E. (2016). EXPEDITION3: A Phase 3 Trial of Solanezumab in Mild Dementia

due to Alzheimer's disease. *The Journal of Prevention of Alzheimer's Disease, CTAD 2016 (Clinical Trials on Alzheimer's Disease), San Diego, USA: Addendum*, 1.

Hostage, C. A., Choudhury, K. R., Doraiswamy, P. M., Petrella, J. R., & Initiative for the Alzheimer's Disease Neuroimaging. (2013). Dissecting the Gene Dose-Effects of the APOE ε4 and ε2 Alleles on Hippocampal Volumes in Aging and Alzheimer's Disease. *PLOS ONE*, *8*(2), e54483. https://doi.org/10.1371/journal.pone.0054483

Hsieh, L.-T., Gruber, M. J., Jenkins, L. J., & Ranganath, C. (2014). Hippocampal Activity Patterns Carry Information about Objects in Temporal Context. *Neuron*, *81*(5), 1165–1178. https://doi.org/10.1016/j.neuron.2014.01.015

Hua, X., Leow, A. D., Parikshak, N., Lee, S., Chiang, M.-C., Toga, A. W., … Alzheimer's Disease Neuroimaging Initiative. (2008). Tensor-based morphometry as a neuroimaging biomarker for Alzheimer's disease: an MRI study of 676 AD, MCI, and normal subjects. *NeuroImage*, *43*(3), 458–469. https://doi.org/10.1016/j.neuroimage.2008.07.013

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *The Journal of Comparative Neurology*, *387*(2), 167–178.

Jack, C. R., Petersen, R. C., Grundman, M., Jin, S., Gamst, A., Ward, C. P., … Thal, L. J. (2008). Longitudinal MRI findings from the vitamin E and donepezil treatment study for MCI. *Neurobiology of Aging*, *29*(9), 1285–1295. https://doi.org/10.1016/j.neurobiolaging.2007.03.004

Jagust, W. J., & Mormino, E. C. (2011). Lifespan brain activity, β-amyloid, and Alzheimer's disease. *Trends in Cognitive Sciences*, *15*(11), 520–526. https://doi.org/10.1016/j.tics.2011.09.004

Jarvik, G. P., Wijsman, E. M., Kukull, W. A., Schellenberg, G. D., Yu, C., & Larson, E. B. (1995). Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease: a case-control study. *Neurology*, *45*(6), 1092–1096.

JASP Team. (2018). *JASP (Version 0.8.6)[Computer software]*. Retrieved from https://jasp-stats.org/

Jorm, A. F., Mather, K. A., Butterworth, P., Anstey, K. J., Christensen, H., & Easteal, S. (2007). APOE genotype and cognitive functioning in a large age-stratified population sample. *Neuropsychology*, *21*(1), 1–8. https://doi.org/10.1037/0894-4105.21.1.1

Kalová, E., Vlcek, K., Jarolímová, E., & Bures, J. (2005). Allothetic orientation and sequential ordering of places is impaired in early stages of Alzheimer's disease: corresponding results in real space tests and computer tests. *Behavioural Brain Research*, *159*(2), 175–186. https://doi.org/10.1016/j.bbr.2004.10.016

Kanai, R., & Rees, G. (2011). The structural basis of inter-individual differences in human behaviour and cognition. *Nature Reviews. Neuroscience*, *12*(4), 231–242. https://doi.org/10.1038/nrn3000

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The Fusiform Face Area: A Module in Human Extrastriate Cortex Specialized for Face Perception. *Journal of Neuroscience*, *17*(11), 4302–4311.

Karantzoulis, S., & Galvin, J. E. (2011). Distinguishing Alzheimer's disease from other major forms of dementia. *Expert Review of Neurotherapeutics*, *11*(11), 1579–1591. https://doi.org/10.1586/ern.11.155

Karch, C. M., & Goate, A. M. (2015). Alzheimer's Disease Risk Genes and Mechanisms of Disease Pathogenesis. *Biological Psychiatry*, *77*(1), 43–51. https://doi.org/10.1016/j.biopsych.2014.05.006

Katzman, R., Terry, R., DeTeresa, R., Brown, T., Davies, P., Fuld, P., … Peck, A. (1988). Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. *Annals of Neurology*, *23*(2), 138–144. https://doi.org/10.1002/ana.410230206

Kester, M. I., Blankenstein, M. A., Bouwman, F. H., Elk, V., J, E., Scheltens, P., … M, W. (2009). CSF Biomarkers in Alzheimer's Disease and Controls: Associations with APOE Genotype are Modified by Age. *Journal of Alzheimer's Disease*, *16*(3), 601–607. https://doi.org/10.3233/JAD-2009-0999

Kim, M., Jeffery, K. J., & Maguire, E. A. (2017). Multivoxel pattern analysis reveals 3D place information in the human hippocampus. *Journal of Neuroscience*, 2703–2716. https://doi.org/10.1523/JNEUROSCI.2703-16.2017

Klunk, W. E., Mathis, C. A., Price, J. C., DeKosky, S. T., Lopresti, B. J., Tsopelas, N. D., … Nebes, R. D. (2009). Amyloid Imaging with PET in Alzheimer's Disease, Mild Cognitive Impairment, and Clinically Unimpaired Subjects. In *PET in the Evaluation of Alzheimer's Disease and Related Disorders* (pp. 119–147). Springer, New York, NY. https://doi.org/10.1007/978-0-387-76420-7_6

Knickmeyer, R. C., Wang, J., Zhu, H., Geng, X., Woolson, S., Hamer, R. M., … Gilmore, J. H. (2014). Common Variants in Psychiatric Risk Genes Predict Brain Structure

at Birth. *Cerebral Cortex*, *24*(5), 1230–1246. https://doi.org/10.1093/cercor/bhs401

Kolarik, B. S., Shahlaie, K., Hassan, A., Borders, A. A., Kaufman, K. C., Gurkoff, G., … Ekstrom, A. D. (2016). Impairments in precision, rather than spatial strategy, characterize performance on the virtual Morris Water Maze: A case study. *Neuropsychologia*, *80*, 90–101. https://doi.org/10.1016/j.neuropsychologia.2015.11.013

Konishi, K., Bhat, V., Banner, H., Poirier, J., Joober, R., & Bohbot, V. D. (2016). APOE2 Is Associated with Spatial Navigational Strategies and Increased Gray Matter in the Hippocampus. *Frontiers in Human Neuroscience*, *10*. https://doi.org/10.3389/fnhum.2016.00349

Kornel. (2018). *Image similarity comparison simulating human perception (multiscale SSIM in Rust): kornelski/dssim*. Rust. Retrieved from https://github.com/kornelski/dssim

Laczó, J., Andel, R., Vyhnalek, M., Vlcek, K., Magerova, H., Varjassyova, A., … Hort, J. (2010). Human Analogue of the Morris Water Maze for Testing Subjects at Risk of Alzheimer's Disease. *Neurodegenerative Diseases*, *7*(1–3), 148–152. https://doi.org/10.1159/000289226

Lambert, J.-C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., … Amouyel, P. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease [Letter]. *Nature Genetics*, *45*, 1452–1458.

Lancaster, C., Tabet, N., & Rusted, J. (2017). The Elusive Nature of APOE ε4 in Mid-adulthood: Understanding the Cognitive Profile. *Journal of the International Neuropsychological Society*, *23*(3), 239–253. https://doi.org/10.1017/S1355617716000990

Lane-Donovan, C., & Herz, J. (2017). ApoE, ApoE Receptors, and the Synapse in Alzheimer's Disease. *Trends in Endocrinology & Metabolism*, *28*(4), 273–284. https://doi.org/10.1016/j.tem.2016.12.001

Lee, A. C. H., Buckley, M. J., Gaffan, D., Emery, T., Hodges, J. R., & Graham, K. S. (2006). Differentiating the roles of the hippocampus and perirhinal cortex in processes beyond long-term declarative memory: a double dissociation in dementia. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *26*(19), 5198–5203. https://doi.org/10.1523/JNEUROSCI.3157-05.2006

Lee, A. C. H., Buckley, M. J., Pegman, S. J., Spiers, H., Scahill, V. L., Gaffan, D., … Graham, K. S. (2005). Specialization in the medial temporal lobe for processing of objects and scenes. *Hippocampus*, *15*(6), 782–797. https://doi.org/10.1002/hipo.20101

Lee, A. C. H., Bussey, T. J., Murray, E. A., Saksida, L. M., Epstein, R. A., Kapur, N., … Graham, K. S. (2005). Perceptual deficits in amnesia: challenging the medial temporal lobe 'mnemonic' view. *Neuropsychologia*, *43*(1), 1–11. https://doi.org/10.1016/j.neuropsychologia.2004.07.017

Lee, A. C. H., & Rudebeck, S. R. (2010). Human medial temporal lobe damage can disrupt the perception of single objects. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(19), 6588–6594. https://doi.org/10.1523/JNEUROSCI.0116-10.2010

Lee, A. C. H., Scahill, V. L., & Graham, K. S. (2008). Activating the medial temporal lobe during oddity judgment for faces and scenes. *Cerebral Cortex (New York, N.Y.: 1991)*, *18*(3), 683–696. https://doi.org/10.1093/cercor/bhm104

Lee, A. C. H., Yeung, L.-K., & Barense, M. D. (2012). The hippocampus and visual perception. *Frontiers in Human Neuroscience*, *6*. https://doi.org/10.3389/fnhum.2012.00091

Lee, S. (2003). Education, Other Socioeconomic Indicators, and Cognitive Function. *American Journal of Epidemiology*, *157*(8), 712–720. https://doi.org/10.1093/aje/kwg042

Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain*, *137*(1), 12–32. https://doi.org/10.1093/brain/awt162

Lehmann, M., Madison, C. M., Ghosh, P. M., Seeley, W. W., Mormino, E., Greicius, M. D., … Rabinovici, G. D. (2013). Intrinsic connectivity networks in healthy subjects explain clinical variability in Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(28), 11606–11611. https://doi.org/10.1073/pnas.1221536110

Lemaître, H., Crivello, F., Dufouil, C., Grassiot, B., Tzourio, C., Alpérovitch, A., & Mazoyer, B. (2005). No epsilon4 gene dose effect on hippocampal atrophy in a large MRI database of healthy elderly subjects. *NeuroImage*, *24*(4), 1205–1213. https://doi.org/10.1016/j.neuroimage.2004.10.016

Lenth, R. (2018). emmeans (Version 1.1.2). Retrieved from https://cran.r-project.org/web/packages/emmeans/index.html

Lever, C., Burton, S., Jeewajee, A., O'Keefe, J., & Burgess, N. (2009). Boundary Vector Cells in the Subiculum of the Hippocampal Formation. *Journal of Neuroscience*, *29*(31), 9771–9777. https://doi.org/10.1523/JNEUROSCI.1319-09.2009

Lim, Y. Y., Ellis, K. A., Pietrzak, R. H., Ames, D., Darby, D., Harrington, K., … AIBL Research Group. (2012). Stronger effect of amyloid load than APOE genotype on cognitive decline in healthy older adults. *Neurology*, *79*(16), 1645–1652. https://doi.org/10.1212/WNL.0b013e31826e9ae6

Liu, C.-C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nature Reviews Neurology*, *9*(2), 106–118. https://doi.org/10.1038/nrneurol.2012.263

Lu, P. H., Thompson, P. M., Leow, A., Lee, G. J., Lee, A., Yanovsky, I., … Bartzokis, G. (2011). Apolipoprotein E genotype is associated with temporal and hippocampal atrophy rates in healthy elderly adults: a tensor-based morphometry study. *Journal of Alzheimer's Disease: JAD*, *23*(3), 433–442. https://doi.org/10.3233/JAD-2010-101398

Luciano, M., Gow, A. J., Harris, S. E., Hayward, C., Allerhand, M., Starr, J. M., … Deary, I. J. (2009). Cognitive ability at age 11 and 70 years, information processing speed, and APOE variation: The Lothian Birth Cohort 1936 study. *Psychology and Aging*, *24*(1), 129–138. https://doi.org/10.1037/a0014780

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S. J., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(8), 4398–4403.

Maguire, E. A., Intraub, H., & Mullally, S. L. (2016). Scenes, Spaces, and Memory Traces: What Does the Hippocampus Do? *The Neuroscientist*, *22*(5), 432–439. https://doi.org/10.1177/1073858415600389

Maguire, E. A., Nannery, R., & Spiers, H. J. (2006). Navigation around London by a taxi driver with bilateral hippocampal lesions. *Brain*, *129*(11), 2894–2907. https://doi.org/10.1093/brain/awl286

Maguire, E. A., Spiers, H. J., Good, C. D., Hartley, T., Frackowiak, R. S. J., & Burgess, N. (2003). Navigation expertise and the human hippocampus: A structural brain imaging analysis. *Hippocampus*, *13*(2), 250–259. https://doi.org/10.1002/hipo.10087

Mahley, R. W., Huang, Y., & Rall, S. C. (1999). Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia): questions, quandaries, and paradoxes. *Journal of Lipid Research*, *40*(11), 1933–1949.

Mahley, R. W., & Rall Jr, S. C. (2000). APOLIPOPROTEIN E: Far More Than a Lipid Transport Protein. *Annual Review of Genomics and Human Genetics*, *1*(1), 507–537. https://doi.org/10.1146/annurev.genom.1.1.507

Malach, R., Reppas, J. B., Benson, R. R., Kwong, K. K., Jiang, H., Kennedy, W. A., … Tootell, R. B. (1995). Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. *Proceedings of the National Academy of Sciences*, *92*(18), 8135–8139.

Manns, J. R., Stark, C. E. L., & Squire, L. R. (2000). The visual paired-comparison task as a measure of declarative memory. *Proceedings of the National Academy of Sciences*, *97*(22), 12375–12379. https://doi.org/10.1073/pnas.220398097

Martin, C. B., Douglas, D., Newsome, R. N., Man, L. L., & Barense, M. D. (2018). Integrative and distinctive coding of visual and conceptual object features in the ventral visual stream. *ELife*, *7*, e31873. https://doi.org/10.7554/eLife.31873

Mason, E. J., Hussey, E. P., Molitor, R. J., Ko, P. C., Donahue, M. J., & Ally, B. A. (2017). Family History of Alzheimer's Disease is Associated with Impaired Perceptual Discrimination of Novel Objects. *Journal of Alzheimer's Disease*, *57*(3), 735–745. https://doi.org/10.3233/JAD-160772

McKee, R. D., & Squire, L. R. (1993). On the development of declarative memory. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *19*(2), 397–404.

McLean, C. A., Cherny, R. A., Fraser, F. W., Fuller, S. J., Smith, M. J., Vbeyreuther, K., … Masters, C. L. (1999). Soluble pool of Aβ amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. *Annals of Neurology*, *46*(6), 860–866. https://doi.org/10.1002/1531-8249(199912)46:6<860::AID-ANA8>3.0.CO;2-M

Metzler-Baddeley, C., Jones, D. K., Steventon, J., Westacott, L., Aggleton, J. P., & O'Sullivan, M. J. (2012). Cingulum Microstructure Predicts Cognitive Control in Older Age and Mild Cognitive Impairment. *Journal of Neuroscience*, *32*(49), 17612–17619. https://doi.org/10.1523/JNEUROSCI.3299-12.2012

Meyer, M. R., Tschanz, J. T., Norton, M. C., Welsh-Bohmer, K. A., Steffens, D. C., Wyse, B. W., & Breitner, J. C. S. (1998). APOE genotype predicts when — not whether

— one is predisposed to develop Alzheimer disease. *Nature Genetics*, *19*(4), 321–322. https://doi.org/10.1038/1206

Miller, G. (2012). Stopping Alzheimer's Before It Starts. *Science*, *337*(6096), 790–792. https://doi.org/10.1126/science.337.6096.790

Minoshima, S., Giordani, B., Berent, S., Frey, K. A., Foster, N. L., & Kuhl, D. E. (1997). Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Annals of Neurology*, *42*(1), 85–94. https://doi.org/10.1002/ana.410420114

Mitchell, A. J., & Shiri-Feshki, M. (2008). Temporal trends in the long term risk of progression of mild cognitive impairment: a pooled analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*(12), 1386–1391. https://doi.org/10.1136/jnnp.2007.142679

Mondadori, C. R. A., de Quervain, D. J.-F., Buchmann, A., Mustovic, H., Wollmer, M. A., Schmidt, C. F., … Henke, K. (2007). Better memory and neural efficiency in young apolipoprotein E epsilon4 carriers. *Cerebral Cortex (New York, N.Y.: 1991)*, *17*(8), 1934–1947. https://doi.org/10.1093/cercor/bhl103

Mondadori, C. R. A., Quervain, D., J. -F, D., Buchmann, A., Mustovic, H., Wollmer, M. A., … Henke, K. (2007). Better Memory and Neural Efficiency in Young Apolipoprotein E ε4 Carriers. *Cerebral Cortex*, *17*(8), 1934–1947. https://doi.org/10.1093/cercor/bhl103

Moodley, K., Minati, L., Contarino, V., Prioni, S., Wood, R., Cooper, R., … Chan, D. (2015). Diagnostic differentiation of mild cognitive impairment due to Alzheimer's disease using a hippocampus-dependent test of spatial memory. *Hippocampus*, *25*(8), 939–951. https://doi.org/10.1002/hipo.22417

Morganti, F., Stefanini, S., & Riva, G. (2013). From allo- to egocentric spatial ability in early Alzheimer's disease: a study with virtual reality spatial tasks. *Cognitive Neuroscience*, *4*(3–4), 171–180. https://doi.org/10.1080/17588928.2013.854762

Morris, C. M., Benjamin, R., Leake, A., McArthur, F. K., Candy, J. M., Ince, P. G., … Edwardson, J. A. (1995). Effect of apolipoprotein E genotype on Alzheimer's disease neuropathology in a cohort of elderly Norwegians. *Neuroscience Letters*, *201*(1), 45–48. https://doi.org/10.1016/0304-3940(94)12126-B

Morris, J. C., Roe, C. M., Xiong, C., Fagan, A. M., Goate, A. M., Holtzman, D. M., & Mintun, M. A. (2010). APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Annals of Neurology*, *67*(1), 122–131. https://doi.org/10.1002/ana.21843

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., & Berg, L. (2001). Mild Cognitive Impairment Represents Early-Stage Alzheimer Disease. *Archives of Neurology*, *58*(3), 397–405. https://doi.org/10.1001/archneur.58.3.397

Morris, R. G. M. (1984). Developments of a water-maze procedure for studying spatial learning in the rat. *Journal of Neuroscience Methods*, *11*(1), 47–60. https://doi.org/10.1016/0165-0270(84)90007-4

Morris, R. G. M., Garrud, P., Rawlins, J. N. P., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, *297*(5868), 681. https://doi.org/10.1038/297681a0

Müller, U., Winter, P., & Graeber, M. B. (2013). A presenilin 1 mutation in the first case of Alzheimer's disease. *The Lancet Neurology*, *12*(2), 129–130. https://doi.org/10.1016/S1474-4422(12)70307-1

Mundy, M. E., Downing, P. E., & Graham, K. S. (2012). Extrastriate cortex and medial temporal lobe regions respond differentially to visual feature overlap within preferred stimulus category. *Neuropsychologia*, *50*(13), 3053–3061. https://doi.org/10.1016/j.neuropsychologia.2012.07.006

Murray, E. A., Wise, S. P., & Graham, K. S. (2016). *The Evolution of Memory Systems: Ancestors, Anatomy, and Adaptations*. Oxford University Press.

Murray, E. A., Wise, S. P., & Graham, K. S. (2017). Representational specializations of the hippocampus in phylogenetic perspective. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2017.04.065

Nagy, Z., Esiri, M. M., Jobst, K. A., Johnston, C., Litchfield, S., Sim, E., & Smith, A. D. (1995). Influence of the apolipoprotein E genotype on amyloid deposition and neurofibrillary tangle formation in Alzheimer's disease. *Neuroscience*, *69*(3), 757–761.

Nao, J., Sun, H., Wang, Q., Ma, S., Zhang, S., Dong, X., … Zheng, D. (2017). Adverse Effects of the Apolipoprotein E ε4 Allele on Episodic Memory, Task Switching and Gray Matter Volume in Healthy Young Adults. *Frontiers in Human Neuroscience*, *11*. https://doi.org/10.3389/fnhum.2017.00346

Nemanic, S., Alvarado, M. C., & Bachevalier, J. (2004). The Hippocampal/Parahippocampal Regions and Recognition Memory: Insights from Visual Paired Comparison versus Object-Delayed Nonmatching in Monkeys. *The Journal of Neuroscience*, *24*(8), 2013–2026. https://doi.org/10.1523/JNEUROSCI.3763-03.2004

Neurotrack Technologies, Inc. (2017). Neurotrack. Retrieved 22 March 2018, from https://neurotrack.com

NHS England. (2018). Alzheimer's disease. Retrieved 13 April 2018, from https://www.nhs.uk/conditions/alzheimers-disease/

Nitsch, R. M., Farber, S. A., Growdon, J. H., & Wurtman, R. J. (1993). Release of amyloid beta-protein precursor derivatives by electrical depolarization of rat hippocampal slices. *Proceedings of the National Academy of Sciences of the United States of America*, *90*(11), 5191–5193.

Norman, G., & Eacott, M. J. (2004). Impaired object recognition with increasing levels of feature ambiguity in rats with perirhinal cortex lesions. *Behavioural Brain Research*, *148*(1), 79–91. https://doi.org/10.1016/S0166-4328(03)00176-1

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *The Lancet Neurology*, *13*(8), 788–794. https://doi.org/10.1016/S1474-4422(14)70136-X

O'Donoghue, M. C., Murphy, S. E., Zamboni, G., Nobre, A. C., & Mackay, C. E. (2018). APOE genotype and cognition in healthy individuals at-risk of Alzheimer's disease: a review. *Cortex*. https://doi.org/10.1016/j.cortex.2018.03.025

O'Dwyer, L., Lamberton, F., Matura, S., Scheibe, M., Miller, J., Rujescu, D., … Hampel, H. (2012). White Matter Differences between Healthy Young ApoE4 Carriers and Non-Carriers Identified with Tractography and Support Vector Machines. *PLoS ONE*, *7*(4), e36024. https://doi.org/10.1371/journal.pone.0036024

O'Dwyer, L., Lamberton, F., Matura, S., Tanner, C., Scheibe, M., Miller, J., … Hampel, H. (2012). Reduced Hippocampal Volume in Healthy Young ApoE4 Carriers: An MRI Study. *PLoS ONE*, *7*(11), e48895. https://doi.org/10.1371/journal.pone.0048895

O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, *34*(1), 171–175. https://doi.org/10.1016/0006-8993(71)90358-1

O'Keefe, J., & Nadel, L. (1979). Précis of O'Keefe & Nadel's The hippocampus as a cognitive map. *Behavioral and Brain Sciences*, *2*(04), 487–494. https://doi.org/10.1017/S0140525X00063949

Ovsepian, S. V., & O'Leary, V. B. (2016). Neuronal Activity and Amyloid Plaque Pathology: An Update. *Journal of Alzheimer's Disease*, *49*(1), 13–19. https://doi.org/10.3233/JAD-150544

Pascalis, O., Hunkin, N. M., Bachevalier, J., & Mayes, A. R. (2009). Change in background context disrupts performance on visual paired comparison following hippocampal damage. *Neuropsychologia*, *47*(10), 2107–2113. https://doi.org/10.1016/j.neuropsychologia.2009.04.001

Pascalis, O, Hunkin, N. M., Holdstock, J. S., Isaac, C. L., & Mayes, A. R. (2004). Visual paired comparison performance is impaired in a patient with selective hippocampal lesions and relatively intact item recognition. *Neuropsychologia*, *42*(10), 1293–1300. https://doi.org/10.1016/j.neuropsychologia.2004.03.005

Pascalis, Olivier, & de Haan, M. (2014). Recognition Memory and Novely Preference: What Model? In *Progress in Infancy Research*. Psychology Press.

Pasquier, F., Sadowsky, C., Holstein, A., Leterme, G. L. P., Peng, Y., Jackson, N., … ACC-001 (QS-21) Study Team. (2016). Two Phase 2 Multiple Ascending-Dose Studies of Vanutide Cridificar (ACC-001) and QS-21 Adjuvant in Mild-to-Moderate Alzheimer's Disease. *Journal of Alzheimer's Disease: JAD*, *51*(4), 1131–1143. https://doi.org/10.3233/JAD-150376

Pengas, G., Patterson, K., Arnold, R. J., Bird, C. M., Burgess, N., & Nestor, P. J. (2010). Lost and found: bespoke memory testing for Alzheimer's disease and semantic dementia. *Journal of Alzheimer's Disease: JAD*, *21*(4), 1347–1365.

Petersen, R. C., & Morris, J. C. (2005). Mild cognitive impairment as a clinical entity and treatment target. *Archives of Neurology*, *62*(7), 1160–1163; discussion 1167. https://doi.org/10.1001/archneur.62.7.1160

Plassman, B. L., Welsh-Bohmer, K. A., Bigler, E. D., Johnson, S. C., Anderson, C. V., Helms, M. J., … Breitner, J. C. (1997). Apolipoprotein E epsilon 4 allele and hippocampal volume in twins with normal cognition. *Neurology*, *48*(4), 985–989.

Postans, M., Hodgetts, C. J., Mundy, M. E., Jones, D. K., Lawrence, A. D., & Graham, K. S. (2014). Interindividual variation in fornix microstructure and macrostructure is related to visual discrimination accuracy for scenes but not faces. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *34*(36), 12121–12126. https://doi.org/10.1523/JNEUROSCI.0026-14.2014

Protas, H. D., Chen, K., Langbaum, J. B. S., Fleisher, A. S., Alexander, G. E., Lee, W., … Reiman, E. M. (2013). Posterior cingulate glucose metabolism, hippocampal glucose metabolism, and hippocampal volume in cognitively normal, late-middle-aged persons at 3 levels of genetic risk for Alzheimer disease. *JAMA Neurology*, *70*(3), 320–325. https://doi.org/10.1001/2013.jamaneurol.286

Psychology Software Tools, Inc. (2016). *E-Prime 2.0*. Pittsburgh, PA. Retrieved from http://www.pstnet.com

Querbes, O., Aubry, F., Pariente, J., Lotterie, J.-A., Démonet, J.-F., Duret, V., … Celsis, P. (2009). Early diagnosis of Alzheimer's disease using cortical thickness: impact of cognitive reserve. *Brain*, *132*(8), 2036–2047. https://doi.org/10.1093/brain/awp105

R Core Team. (2015). *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from http://www.R-project.org/

Rawle, M. J., Davis, D., Bendayan, R., Wong, A., Kuh, D., & Richards, M. (2018). Apolipoprotein-E (Apoe) ε4 and cognitive decline over the adult life course. *Translational Psychiatry*, *8*(1), 18. https://doi.org/10.1038/s41398-017-0064-8

Ricciarelli, R., & Fedele, E. (2017). The Amyloid Cascade Hypothesis in Alzheimer's Disease: It's Time to Change Our Mind. *Current Neuropharmacology*, *15*(6), 926–935. https://doi.org/10.2174/1570159X15666170116143743

Richmond, J., Sowerby, P., Colombo, M., & Hayne, H. (2004). The effect of familiarization time, retention interval, and context change on adults' performance in the visual paired-comparison task. *Developmental Psychobiology*, *44*(2), 146–155. https://doi.org/10.1002/dev.10161

Richter-Schmidinger, T., Alexopoulos, P., Horn, M., Maus, S., Reichel, M., Rhein, C., … Kornhuber, J. (2011). Influence of brain-derived neurotrophic-factor and apolipoprotein E genetic variants on hippocampal volume and memory performance in healthy young adults. *Journal of Neural Transmission (Vienna, Austria: 1996)*, *118*(2), 249–257. https://doi.org/10.1007/s00702-010-0539-8

Riggins, T., Geng, F., Botdorf, M., Canada, K., Cox, L., & Hancock, G. R. (2018). Protracted hippocampal development is associated with age-related improvements in memory during early childhood. *NeuroImage*, *174*, 127–137. https://doi.org/10.1016/j.neuroimage.2018.03.009

Robertson, R. G., Rolls, E. T., Georges-François, P., & Panzeri, S. (1999). Head direction cells in the primate pre-subiculum. *Hippocampus*, *9*(3), 206–219. https://doi.org/10.1002/(SICI)1098-1063(1999)9:3<206::AID-HIPO2>3.0.CO;2-H

Robin, J., & Moscovitch, M. (2017). Details, gist and schema: hippocampal–neocortical interactions underlying recent and remote episodic and spatial memory.

Current Opinion in Behavioral Sciences, *17*, 114–123. https://doi.org/10.1016/j.cobeha.2017.07.016

Roussotte, F. F., Gutman, B. A., Madsen, S. K., Colby, J. B., Narr, K. L., Thompson, P. M., & Alzheimer's Disease Neuroimaging Initiative (ADNI). (2014). Apolipoprotein E epsilon 4 allele is associated with ventricular expansion rate and surface morphology in dementia and normal aging. *Neurobiology of Aging*, *35*(6), 1309–1317. https://doi.org/10.1016/j.neurobiolaging.2013.11.030

Rusted, J. M., Evans, S. L., King, S. L., Dowell, N., Tabet, N., & Tofts, P. S. (2013). APOE e4 polymorphism in young adults is associated with improved attention and indexed by distinct neural signatures. *NeuroImage*, *65*(Supplement C), 364–373. https://doi.org/10.1016/j.neuroimage.2012.10.010

Sachs-Ericsson, N., & Blazer, D. G. (2015). The new DSM-5 diagnosis of mild neurocognitive disorder and its relation to research in mild cognitive impairment. *Aging & Mental Health*, *19*(1), 2–12. https://doi.org/10.1080/13607863.2014.920303

Saksida, L. M., & Bussey, T. J. (2010). The representational–hierarchical view of amnesia: Translation from animal to human. *Neuropsychologia*, *48*(8), 2370–2384. https://doi.org/10.1016/j.neuropsychologia.2010.02.026

Saksida, L. M., Bussey, T. J., Buckmaster, C. A., & Murray, E. A. (2007). Impairment and Facilitation of Transverse Patterning after Lesions of the Perirhinal Cortex and Hippocampus, Respectively. *Cerebral Cortex*, *17*(1), 108–115. https://doi.org/10.1093/cercor/bhj128

Salloway, S., Sperling, R., Fox, N. C., Blennow, K., Klunk, W., Raskind, M., … Brashear, H. R. (2014). Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease. *New England Journal of Medicine*, *370*(4), 322–333. https://doi.org/10.1056/NEJMoa1304839

Salvucci, D. D., & Goldberg, J. H. (2000). Identifying fixations and saccades in eye-tracking protocols (pp. 71–78). ACM Press. https://doi.org/10.1145/355017.355028

Scarmeas, N., & Stern, Y. (2003). Cognitive Reserve and Lifestyle. *Journal of Clinical and Experimental Neuropsychology (Neuropsychology, Development and Cognition: Section A)*, *25*(5), 625–633. https://doi.org/10.1076/jcen.25.5.625.14576

Schächter, F., Faure-Delanef, L., Guénot, F., Rouger, H., Froguel, P., Lesueur-Ginot, L., & Cohen, D. (1994). Genetic associations with human longevity at the APOE and ACE loci. *Nature Genetics*, *6*(1), 29–32. https://doi.org/10.1038/ng0194-29

Scheuner, D., Eckman, C., Jensen, M., Song, X., Citron, M., Suzuki, N., … Younkin, S. (1996). Secreted amyloid β–protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. *Nature Medicine*, *2*(8), 864–870. https://doi.org/10.1038/nm0896-864

Schlichting, M. L., Guarino, K. F., Schapiro, A. C., Turk-Browne, N. B., & Preston, A. R. (2017). Hippocampal Structure Predicts Statistical Learning and Associative Inference Abilities during Development. *Journal of Cognitive Neuroscience*, *29*(1), 37–51. https://doi.org/10.1162/jocn_a_01028

Schutte, I., Slagter, H. A., Collins, A. G. E., Frank, M. J., & Kenemans, J. L. (2017). Stimulus discriminability may bias value-based probabilistic learning. *PLOS ONE*, *12*(5), e0176205. https://doi.org/10.1371/journal.pone.0176205

Schwarz, A. J., Sundell, K. L., Lachno, D. R., Case, M. G., Suhy, J., Pontecorvo, M. J., … Siemers, E. R. (2017). EFFECT OF SOLANEZUMAB ON BIOMARKERS OF NEURODEGENERATION IN THE EXPEDITION3 TRIAL IN MILD ALZHEIMER DISEASE. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *13*(7), P605. https://doi.org/10.1016/j.jalz.2017.06.650

Selkoe, D. J. (1991). The molecular pathology of Alzheimer's disease. *Neuron*, *6*(4), 487–498. https://doi.org/10.1016/0896-6273(91)90052-2

Selkoe, D. J. (2001). Alzheimer's Disease: Genes, Proteins, and Therapy. *Physiological Reviews*, *81*(2), 741–766.

Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*. https://doi.org/10.15252/emmm.201606210

Shaw, P., Lerch, J. P., Pruessner, J. C., Taylor, K. N., Rose, A. B., Greenstein, D., … Giedd, J. N. (2007). Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms: an observational study. *The Lancet Neurology*, *6*(6), 494–500. https://doi.org/10.1016/S1474-4422(07)70106-0

Shine, J. P., Hodgetts, C. J., Postans, M., Lawrence, A. D., & Graham, K. S. (2015). APOE-ε4 selectively modulates posteromedial cortex activity during scene perception and short-term memory in young healthy adults. *Scientific Reports*, *5*(1). https://doi.org/10.1038/srep16322

Sinclair, L. I., Pleydell-Pearce, C. W., & Day, I. N. M. (2017). Possible positive effect of the APOE ε2 allele on cognition in early to mid-adult life. *Neurobiology of Learning and Memory*, *146*, 37–46. https://doi.org/10.1016/j.nlm.2017.10.008

Small, G. W., Siddarth, P., Burggren, A. C., Kepe, V., Ercoli, L. M., Miller, K. J., … Barrio, J. R. (2009). Influence of Cognitive Status, Age, and APOE-4 Genetic Risk on Brain FDDNP Positron-Emission Tomography Imaging in Persons Without Dementia. *Archives of General Psychiatry*, *66*(1), 81–87. https://doi.org/10.1001/archgenpsychiatry.2008.516

Squire, L. R. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review*, *99*(2), 195–231. https://doi.org/10.1037/0033-295X.99.2.195

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The Medial Temporal Lobe. *Annual Review of Neuroscience*, *27*, 279–306. https://doi.org/10.1146/annurev.neuro.27.070203.144130

Staehelin, H. B., Perrig-Chiello, P., Mitrache, C., Miserez, A. R., & Perrig, W. J. (1999). Apolipoprotein E genotypes and cognitive functions in healthy elderly persons. *Acta Neurologica Scandinavica*, *100*(1), 53–60.

Staresina, B. P., Duncan, K. D., & Davachi, L. (2011). Perirhinal and Parahippocampal Cortices Differentially Contribute to Later Recollection of Object- and Scene-Related Event Details. *Journal of Neuroscience*, *31*(24), 8739–8747. https://doi.org/10.1523/JNEUROSCI.4978-10.2011

Stengård, J. H., Zerba, K. E., Pekkanen, J., Ehnholm, C., Nissinen, A., & Sing, C. F. (1995). Apolipoprotein E polymorphism predicts death from coronary heart disease in a longitudinal study of elderly Finnish men. *Circulation*, *91*(2), 265–269.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*(3), 448–460. https://doi.org/10.1017/S1355617702813248

Stern, Y. (2003). The Concept of Cognitive Reserve: A Catalyst for Research. *Journal of Clinical and Experimental Neuropsychology (Neuropsychology, Development and Cognition: Section A)*, *25*(5), 589–593. https://doi.org/10.1076/jcen.25.5.589.14571

Stewart, S., Jeewajee, A., Wills, T. J., Burgess, N., & Lever, C. (2014). Boundary coding in the rat subiculum. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1635), 20120514. https://doi.org/10.1098/rstb.2012.0514

Striepens, N., Scheef, L., Wind, A., Meiberth, D., Popp, J., Spottke, A., … Jessen, F. (2011). Interaction effects of subjective memory impairment and ApoE4

genotype on episodic memory and hippocampal volume. *Psychological Medicine*, *41*(9), 1997–2006. https://doi.org/10.1017/S0033291711000067

Strittmatter, W. J., Weisgraber, K. H., Huang, D. Y., Dong, L.-M., Salvesen, G. S., Pericak-Vance, M., … Roses, A. D. (1993). Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer disease. *Proceedings of the National Academy of Sciences*, *90*(17), 8098–8102.

Sun, Z., van de Giessen, M., Lelieveldt, B. P. F., & Staring, M. (2017). Detection of Conversion from Mild Cognitive Impairment to Alzheimer's Disease Using Longitudinal Brain MRI. *Frontiers in Neuroinformatics*, *11*. https://doi.org/10.3389/fninf.2017.00016

Suri, S., Heise, V., Trachtenberg, A. ., & Mackay, C. . (2013). The forgotten APOE allele: A review of the evidence and suggested mechanisms for the protective effect of APOE ε2. *Neuroscience & Biobehavioral Reviews*, *37*(10, Part 2), 2878–2886. https://doi.org/10.1016/j.neubiorev.2013.10.010

Talbot, C., Lendon, C., Craddock, N., Shears, S., Morris, J. C., & Goate, A. (1994). Protection against Alzheimer's disease with apoE epsilon 2. *Lancet (London, England)*, *343*(8910), 1432–1433.

The British Psychological Society. (2018). Code of Ethics and Conduct. The British Psychological Society. Retrieved from https://www.bps.org.uk/sites/bps.org.uk/files/Policy%20-%20Files/BPS%20Code%20of%20Ethics%20and%20Conduct%20%282018%29.pdf

Trachtenberg, A. J., Filippini, N., Cheeseman, J., Duff, E. P., Neville, M. J., Ebmeier, K. P., … Mackay, C. E. (2012). The effects of APOE on brain activity do not simply reflect the risk of Alzheimer's disease. *Neurobiology of Aging*, *33*(3), 618.e1-618.e13. https://doi.org/10.1016/j.neurobiolaging.2010.11.011

Trachtenberg, A. J., Filippini, N., Ebmeier, K. P., Smith, S. M., Karpe, F., & Mackay, C. E. (2012). The effects of APOE on the functional architecture of the resting brain. *NeuroImage*, *59*(1), 565–572. https://doi.org/10.1016/j.neuroimage.2011.07.059

Ungar, L., Altmann, A., & Greicius, M. D. (2014). Apolipoprotein E, Gender, and Alzheimer's Disease: An Overlooked, but Potent and Promising Interaction. *Brain Imaging and Behavior*, *8*(2), 262–273. https://doi.org/10.1007/s11682-013-9272-x

van de Pol, L. A., van der Flier, W. M., Korf, E. S. C., Fox, N. C., Barkhof, F., & Scheltens, P. (2007). Baseline predictors of rates of hippocampal atrophy in mild cognitive impairment. *Neurology*, *69*(15), 1491–1497. https://doi.org/10.1212/01.wnl.0000277458.26846.96

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia*, *42*(10), 1394–1413. https://doi.org/10.1016/j.neuropsychologia.2004.04.006

Vemuri, P., Weigand, S. D., Przybelski, S. A., Knopman, D. S., Smith, G. E., Trojanowski, J. Q., … Jack, C. R. (2011). Cognitive reserve and Alzheimer's disease biomarkers are independent determinants of cognition. *Brain*, *134*(5), 1479–1492. https://doi.org/10.1093/brain/awr049

Villemagne, V. L., Pike, K. E., Chételat, G., Ellis, K. A., Mulligan, R. S., Bourgeat, P., … Rowe, C. C. (2011). Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease. *Annals of Neurology*, *69*(1), 181–192. https://doi.org/10.1002/ana.22248

Visser, P. J., Verhey, F. R. J., Hofman, P. a. M., Scheltens, P., & Jolles, J. (2002). Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. *Journal of Neurology, Neurosurgery, and Psychiatry*, *72*(4), 491–497.

Walker, J. A., Low, K. A., Fletcher, M. A., Cohen, N. J., Gratton, G., & Fabiani, M. (2017). Hippocampal structure predicts cortical indices of reactivation of related items. *Neuropsychologia*, *95*, 182–192. https://doi.org/10.1016/j.neuropsychologia.2016.12.005

Weiss, A. R., Guo, W., Richardson, R., & Bachevalier, J. (2017). Intact perceptual ability, but impaired familiarity judgment, after neonatal perirhinal lesions in rhesus macaques. *Developmental Cognitive Neuroscience*, *28*, 54–64. https://doi.org/10.1016/j.dcn.2017.10.006

Wessels, A. M., Matthews, B. R., Dowsett, S. A., Andersen, S. W., & Siemers, E. R. (2017). THE INTEGRATED ALZHEIMER'S DISEASE RATING SCALE (IADRS): FINDINGS FROM THE EXPEDITION3 TRIAL. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *13*(7), P1521–P1522. https://doi.org/10.1016/j.jalz.2017.07.649

Westlye, E. T., Lundervold, A., Rootwelt, H., Lundervold, A. J., & Westlye, L. T. (2011). Increased Hippocampal Default Mode Synchronization during Rest in Middle-Aged and Elderly APOE ε4 Carriers: Relationships with Memory Performance.

The Journal of Neuroscience, *31*(21), 7775–7783. https://doi.org/10.1523/JNEUROSCI.1230-11.2011

Westlye, L. T., Reinvang, I., Rootwelt, H., & Espeseth, T. (2012). Effects of APOE on brain white matter microstructure in healthy adults. *Neurology*, *79*(19), 1961–1969.

Wetter, S. R., Delis, D. C., Houston, W. S., Jacobson, M. W., Lansing, A., Cobell, K., … Bondi, M. W. (2005). Deficits in Inhibition and Flexibility are Associated with the APOE-E4 Allele in Nondemented Older Adults. *Journal of Clinical and Experimental Neuropsychology*, *27*(8), 943–952. https://doi.org/10.1080/13803390490919001

Whelan, C. D., Hibar, D. P., van Velzen, L. S., Zannas, A. S., Carrillo-Roa, T., McMahon, K., … Alzheimer's Disease Neuroimaging Initiative. (2016). Heritability and reliability of automatically segmented human hippocampal formation subregions. *NeuroImage*, *128*, 125–137. https://doi.org/10.1016/j.neuroimage.2015.12.039

Whitehead, J. C., Li, L., McQuiggan, D. A., Gambino, S. A., Binns, M. A., & Ryan, J. D. (2018). Portable eyetracking-based assessment of memory decline. *Journal of Clinical and Experimental Neuropsychology*, 1–13. https://doi.org/10.1080/13803395.2018.1444737

Wisdom, N. M., Callahan, J. L., & Hawkins, K. A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiology of Aging*, *32*(1), 63–74. https://doi.org/10.1016/j.neurobiolaging.2009.02.003

Wolf, H., Grunwald, M., Ecke, G. M., Zedlick, D., Bettin, S., Dannenberg, C., … Gertz, H. J. (1998). The prognosis of mild cognitive impairment in the elderly. *Journal of Neural Transmission. Supplementum*, *54*, 31–50.

World Dementia Council. (2017). World Dementia Council. Retrieved 24 May 2018, from https://worlddementiacouncil.org/

World Health Organization. (2016). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines* (Version: 2016). Geneva, Switzerland: World Health Organization. Retrieved from http://apps.who.int/classifications/icd10/browse/2016/en#/F00-F09

Xu, G., Mclaren, D. G., Ries, M. L., Fitzgerald, M. E., Bendlin, B. B., Rowley, H. A., … Johnson, S. C. (2009). The influence of parental history of Alzheimer's disease and apolipoprotein E ε4 on the BOLD signal during recognition memory. *Brain*, *132*(2), 383–391. https://doi.org/10.1093/brain/awn254

Yamamoto, K., Tanei, Z.-I., Hashimoto, T., Wakabayashi, T., Okuno, H., Naka, Y., … Iwatsubo, T. (2015). Chronic optogenetic activation augments aβ pathology in a mouse model of Alzheimer disease. *Cell Reports*, *11*(6), 859–865. https://doi.org/10.1016/j.celrep.2015.04.017

Yu, L., Boyle, P., Schneider, J. A., Segawa, E., Wilson, R. S., Leurgans, S., & Bennett, D. A. (2013). APOE ε4, Alzheimer's disease pathology, cerebrovascular disease, and cognitive change over the years prior to death. *Psychology and Aging*, *28*(4), 1015–1023. https://doi.org/10.1037/a0031642

Yushkevich, P. A., Amaral, R. S. C., Augustinack, J. C., Bender, A. R., Bernstein, J. D., Boccardi, M., … Zeineh, M. M. (2015). Quantitative comparison of 21 protocols for labeling hippocampal subfields and parahippocampal subregions in in vivo MRI: Towards a harmonized segmentation protocol. *NeuroImage*, *111*, 526–541. https://doi.org/10.1016/j.neuroimage.2015.01.004

Zeamer, A., & Bachevalier, J. (2013). Long-term effects of neonatal hippocampal lesions on novelty preference in monkeys: Hippocampus and Recognition Memory Development. *Hippocampus*, *23*(9), 745–750. https://doi.org/10.1002/hipo.22139

Zeamer, A., Heuer, E., & Bachevalier, J. (2010). Developmental Trajectory of Object Recognition Memory in Infant Rhesus Macaques with and without Neonatal Hippocampal Lesions. *Journal of Neuroscience*, *30*(27), 9157–9165. https://doi.org/10.1523/JNEUROSCI.0022-10.2010

Zeamer, A., Meunier, M., & Bachevalier, J. (2011). Stimulus similarity and encoding time influence incidental recognition memory in adult monkeys with selective hippocampal lesionsStimulus similarity and encoding time influence incidental recognition memory in adult monkeys with selective hippocampal lesions. *Learning & Memory*, *18*(3), 170–180. https://doi.org/10.1101/lm.2076811

Zeamer, A., Richardson, R. L., Weiss, A. R., & Bachevalier, J. (2015). The development of object recognition memory in rhesus macaques with neonatal lesions of the perirhinal cortex. *Developmental Cognitive Neuroscience*, *11*, 31–41. https://doi.org/10.1016/j.dcn.2014.07.002

Zeidman, P., & Maguire, E. A. (2016). Anterior hippocampus: the anatomy of perception, imagination and episodic memory. *Nature Reviews Neuroscience*, *17*(3), 173–182. https://doi.org/10.1038/nrn.2015.24

Zeidman, P., Mullally, S. L., & Maguire, E. A. (2015). Constructing, Perceiving, and Maintaining Scenes: Hippocampal Activity and Connectivity. *Cerebral Cortex (New York, NY)*, *25*(10), 3836–3855. https://doi.org/10.1093/cercor/bhu266

Zhang, C.-C., Ren, H.-Y., Li, M.-L., Wang, Q., Deng, W., Guo, W.-J., … Li, T. (2015). Apolipoprotein E gene polymorphisms associated with processing speed and executive functions in healthy Han Chinese. *Neuroscience Bulletin*, *31*(3), 368–370. https://doi.org/10.1007/s12264-014-1515-3

Zhou, Y., Dougherty, J. H., Hubner, K. F., Bai, B., Cannon, R. L., & Hutson, R. K. (2008). Abnormal connectivity in the posterior cingulate and hippocampus in early Alzheimer's disease and mild cognitive impairment. *Alzheimer's & Dementia*, *4*(4), 265–270. https://doi.org/10.1016/j.jalz.2008.04.006

Zola, S. M., Manzanares, C. M., Clopton, P., Lah, J. J., & Levey, A. I. (2013). A Behavioral Task Predicts Conversion to Mild Cognitive Impairment and Alzheimer's Disease. *American Journal of Alzheimer's Disease and Other Dementias*, *28*(2), 179–184. https://doi.org/10.1177/1533317512470484

Zola, S. M., Squire, L. R., Teng, E., Stefanacci, L., Buffalo, E. A., & Clark, R. E. (2000). Impaired recognition memory in monkeys after damage limited to the hippocampal region. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *20*(1), 451–463.