Apolipoprotein e4 Influences on Scene Representation in Young Adults

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Thesis Summary

Episodic memory for past and future events, scene imagination, visual scene perception, and navigation, are all supported by a set of brain regions in the medial temporal lobe (MTL) and posteromedial cortex (PMC). It has been proposed that the construction of scenes, also supported by these brain regions, may provide a scaffold which underpins these many related cognitive processes.

Consistent with pathology in the MTL and PMC, Alzheimer's patients are impaired in many of these cognitive processes, including scene construction. APOE e4 is the strongest known genetic risk factor for the development of late onset Alzheimer's Disease. Alterations in brain activity have been found in young adult APOE e4 carriers during scene perception and episodic memory tasks, with however, cognitive performance matched across groups. This thesis combined behavioural, genetic and imaging approaches in order to answer an overarching question: do young adult (age ~20 years) APOE e4 carriers show early behavioural (Chapters 2 and 3) and brain alterations (Chapter 4), compared to non-carriers, on sensitive cognitive paradigms assessing scene representation ability?

Chapter 2 and 3 of this thesis did not detect a significant difference between APOE e4 carriers and non-carriers in overall scene representations. However, APOE e4 carriers were found to describe fewer sensory details about their imagined scenes, suggesting that subtle differences between groups may exist, but subjective experience may not be a sensitive method to detect these. In a further computerised perceptual illusion task, APOE e4 carriers showed a (non-significant) attenuation of the illusionary effect, reflecting alterations in scene representation required for strength of the illusion. Finally, I used ASL imaging (Chapter 4) to investigate scene-selective alterations in APOE e4 carriers during a visual perception task. This study failed to find a significant scene-selective functional difference between APOE e4 carriers and non-carriers, but confirmed that further work is needed to understand BOLD response alterations in young APOE e4 carriers.

The findings of this thesis pave the way for further investigation to understand functional brain changes in young APOE e4 carriers, which aligned to a specific cognitive hallmark of AD, could provide a marker for increased genetic risk, but further, could help us to better understand the influence of genetic risk on brain health.

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1 CHAPTER 1. General Introduction

1.1 Thesis Overview

This thesis focuses on understanding how increased risk of poorer later life cognitive health impacts on visual scene construction and scene perception. Risk of poorer later life cognitive health will be assessed by the presence or absence of an APOE-e4 allele, one of the strongest semi-dominant genetic risks linked to poorer cognition in aging (Genin et al., 2011). Performance on scene perception will be tested using a range of experimental tasks, including scene construction (Chapter 2), boundary extension (Chapter 3), and odd-one-out (oddity) judgement (Chapter 4). Prior to reporting these experiments, this Introductory Chapter covers literature on aging, with a focus on APOE-e4 and its association with Alzheimer's disease (AD), as well as relevant cognitive neuroscience studies using the tasks to be adopted in this thesis. As each experimental chapter Introduction provides detailed consideration of key papers relevant to the reported study, this Introduction focuses on providing an overarching context to the Thesis, outlining the outstanding scientific questions addressed by my research. I will start by discussing current knowledge about scene perception and memory, in the context of scene construction. Following from this, I move on to discuss our current understanding of genetic risk of poorer later life cognitive health, and studies indicating that scene processing may provide a potential marker of later life risk, as well as transition to, Alzheimer's disease.

1.2 Spatial Cognition and Scenes

1.2.1 Brain Networks for Scene Processing: A Scene Construction 'Core' Network

Recall of past events, imagining fictitious future events, and navigation through space are supported by an overlapping set of brain regions often described as a 'core' scene network (Addis et al., 2007; Hassabis et al., 2007; Spiers et al., 2006; Schacter et al., 2007). This 'scene' network has considerable functional overlap with the so-called default network (DN), (Buckner et al., 2008; Raichle et al., 2001), a set of interconnected brain regions which demonstrate increased activation during rest, but deactivation during task

engagement. This brain network includes the hippocampus (Hassabis et al., 2007; Hodgetts et al., 2016), parahippocampal gyrus (Aguirre et al., 1998; Epstein et al., 1998; Epstein et al., 2003), retrosplenial cortex (RSC; Vann et al., 2009; Epstein et al., 2007), posterior cingulate cortex (PCC; Irish et al., 2015), precuneus, temporo-parietal junction, angular gyrus, lateral temporal cortex, ventrolateral prefrontal cortex, and medial prefrontal cortex (Spreng et al., 2009). There have been several theories put forward regarding the functioning of this 'core' network. Buckner et al. (2007) proposed that remembering the past, imagining the future, understanding the viewpoint of others (so called theory of mind) and spatial navigation rely on a common set of cognitive processes. This view alludes to the idea that episodic memory is inherently reconstructive rather than reproductive by nature, and that these reconstructions are crucial for behavioural flexibility, allowing us to extract and manipulate elements of previous experiences and recombine them to simulate imagined future scenarios (Schacter et al., 2007; Murray et al., 2016). Advancing on this theory, it has also been proposed that this core network is also involved in scene construction; specifically, generation and maintenance of complex and spatially coherent scenes, which in turn generate a spatial framework for past, future and mental navigational events (Hassabis et al., 2007; Summerfield et al., 2010; Murray et al., 2017).

Support for this core scene construction network has been evidenced using lesion (Hassabis et al., 2007; Kwan et al., 2010) and neuroimaging studies (Schacter et al., 2007; Addis et al., 2007), (see Chapter 2 for further discussion). Briefly for now, scene construction involves the integration of single perceptual objects and their spatial relations to create a scene. To study this integrative process, Summerfield et al (2010) designed an imaging study, whereby participants were asked to mentally construct scenes, with the number of elements comprising the scene gradually building up over trials. Participants were instructed to mentally integrate the given elements of the scene together, in a way which was realistic, vivid, and spatially coherent. The elements were grouped to be contextually related to help reinforce realistic and vivid imagining. Several regions, including (but not limited to) the hippocampus, parahippocampal gyrus, and retrosplenial cortex (RSC), were found to be activated when elements were integrated to form a scene with reported 'sceneness'. This study demonstrates the involvement of this core network in scene construction.

Further evidence for a core network for scene construction comes from neuroimaging studies which examine functional activation during episodic memories for past events and future fictitious events (i.e. Addis et al. 2007). As mentioned above, such

studies will be described in further detail in Chapter 2, however, so here, I will describe a convergence of these findings from a meta-analysis study. Benoit et al., (2015) set out to provide a more precise and specific quantification of the brain regions (core network) jointly engaged during both episodic memory and 'episodic simulation'. The authors conducted an activation likelihood estimation (ALE), to examine consistency in brain activation patterns across neuroimaging experiments. Studies included in the meta-analysis provided evidence for commonly recruited brain regions through testing for spatial overlap between episodic memory for autobiographical events and episodic stimulation (i.e. fictitious/ hypothetical future events). Importantly, this meta-analysis examined concordance of brain activation patterns across diverse types of episodic simulation, irrespective of the content of the imagined event, with the inclusion of possible future, fictitious episodes and counterfactual episodes (i.e. imagining alternative versions of real experienced events). Seventeen clusters were identified that were consistently engaged in both episodic memory and episodic simulation (Benoit et al., 2015). These regions included the hippocampus, parahippocampal cortex, the anterior cingulate cortex (ACC), the PCC, RSC, the dorsomedial prefrontal cortex, adjacent rostral and ventral prefrontal cortices, lateral surface parts of the temporal cortex, and clusters in the posterior inferior parietal and superior temporal lobes (shown in Figure 1.1). All clusters were predominantly located within the DN, however, notably the DN is generally considered to be broader than this core network (Benoit et al., 2015). Further, a largely overlapping set of regions has also been associated with spatial navigation (Buckner et al., 2007; Spreng et al., 2008, 2010). Therefore, some of the brain areas identified likely contribute to broader cognitive functions, for example, episodic memory, future thinking, spatial navigation. As previously outlined, these capabilities have in common a requirement to build spatial models of the respective situation, that is, scene construction (Hassabis et al., 2007; Mullally et al., 2014).

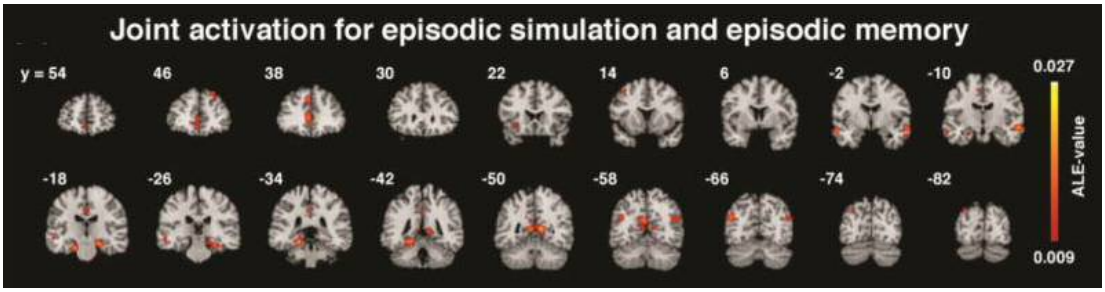

Figure 1.1: From Benoit et al. (2015), Results of an ALE meta-analysis identifying a core network of regions which show consistent engagement during both episodic stimulation (future, fictitious and alternative versions of past events) and episodic memory.

1.2.2 The Hippocampus, Space, Scenes and Episodic Memory

It has long been established that the medial temporal lobe (MTL), particularly the hippocampus, is involved in memory processes (Scoville & Milner, 1957). A traditional view of hippocampal functioning is that it is part, along with other MTL structures (including the PRC, ERC, and parahippocampal cortex), of a unitary memory system (Squire et al., 1991; Squire et al., 2004; Squire et al., 2011). This system exclusively subserves long term declarative memory, that is, conscious memory for events from the past (Cohen and Squire, 1980). This view posits that injury to any structure in this MTL memory system, whether hippocampus, PRC or any other brain region, would impair performance on all tasks tapping declarative memory, and that the degree of this impairment would be proportional to the degree of damage to the MTL structures (Squire et al., 1991; Squire et al., 2004; Squire et al., 2011). Contrary to this unitary view, there are also theories which describe functional segregation within the MTL for memory, with different structures supporting different processes in memory, such as recollection. Here, damage to different MTL structures results in different patterns of memory impairment. According to one theory, the hippocampus mediates recollective memory, where contextual information about the memory is evident, while the PRC is crucial for familiarity based recognition memory (memory that something has been seen before but devoid of the context in which that item has been seen), (Aggleton et al., 1999, Brown et al., 2001; Yonelinas et al., 2010). More controversially, research has also demonstrated that MTL structures may not be solely involved in memory, instead, also contributing to perception and implicit forms of memory (Graham et al., 2010; Buckley et al., 2006; Bussey et al., 2007; Murray et al., 2007). A key aspect of these theories is that the hippocampus is necessary for both complex visual scene processing, as well as episodic memory, which will be discussed later in this chapter.

The discovery of 'place cells' in the hippocampus of rats in the 1970s emphasised a critical role for this structure in aspects of spatial cognition and navigation in an environment (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978). Place cells are cells which selectively fire when an animal is in a specific region within any given environment (see Figure 1.2). This area is referred to as the 'place field'. Jung and colleagues (1994) further investigated the properties of these place fields in rodents, and reported differences in the dorsal and ventral hippocampus (corresponding to posterior and anterior hippocampus in humans, respectively), with changes in the size of the place fields along the longitudinal axis of the hippocampus. Specifically, place cells responded to relatively smaller place fields in the dorsal hippocampus, increasing the size of the place field progressively towards the ventral end of the structure. These findings suggest that the anterior and posterior hippocampus may serve functionally specialised roles in spatial navigation and spatial cognition, depending upon how environmental information about the location of the animal is represented. Place fields in the posterior hippocampus may be involved in representing more detailed spatial representations, conserving the fine details within a smaller spatial reference frame, at the cost of representing the broader environment. Whereas, place fields within the anterior hippocampus may be involved in supporting a re-scaled version of the broader environment, at the expense of preserving high levels of fine-grained spatial detail. This finding fits with neuroimaging evidence in humans. For example, that scene construction compared with perception activates more anterior compared with posterior hippocampal regions (Zeidman., 2015), with a constructive representation of space, being rescaled and therefore subsequently less spatially precise compared with perceiving a scene.

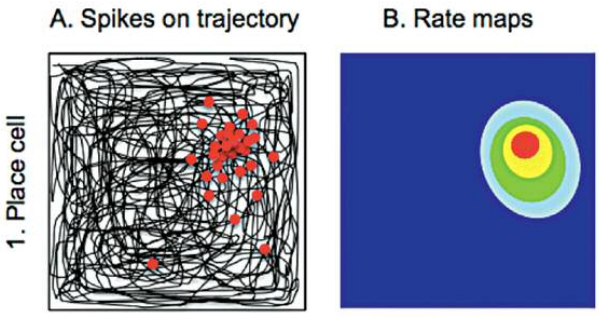

Figure 1.2: From Hafting et al., (2005). An illustrative schematic of a place cell firing from electrodes implanted within the hippocampus of a rat, with each action potential shown by a red dot. Individual place cells fire in one location. Column A shows the path of a rat as it moves within a square arena. Column B shows rate maps for the firing frequency within the environment. Lower wave length colours depict higher rates of firing.

There is evidence of functional specialisation within the hippocampus. This functional specialisation most likely arises due to the differential connectivity of MTL regions with other brain regions (see Figure 1.3). The animal literature on grid cell structure in the entorhinal cortex (ERC) may help to explain this pattern of hippocampus long axis gradient in spatial representations. The ERC feed is the primary cortical input into the hippocampus, and animal studies have replicated the gradient found in place fields along the hippocampus in medial ERC (Moser et al; 2008). Like in the hippocampus, grid cells in different regions of ERC respond to different compressions of the environment. Further, in rodents the portions of the medial ERC where grid cells show this pattern are connected to the ventral hippocampus (corresponding to the anterior hippocampus in humans). The proportional rescaling of the environment supported by these cells may permit an entire spatial environment to be represented; a potential consequence of this rescaling, however, is altered geometry, particularly concerning distances (Stensola et al., 2012). Moreover, some grid cells in parts of the medial ERC do not respond to compressions of the environment in the same way; these medial ERC parts are connected with the dorsal hippocampus in rodents (corresponding to the posterior hippocampus in humans). The minimal rescaling in these grid cells may support representation of highly detailed spatial information through the preservation of geometric information. Therefore, at the network level, due to its internal functional variation along the long axis, and its cortical inputs from wider networks, the anterior hippocampus may be involved in spatial representation which provides a 'sense' of a spatial environment, without accurate geometric information. Whereas the posterior hippocampus is more likely to store representations of specific spatial details within an environment, including precise geometric information. The latter would most likely support discrimination of highly overlapping spatial features. Additionally, this functional specialisation may be important for understanding vulnerability to pathological and non-pathological aging which may differentially effect the anterior and posterior hippocampal regions.

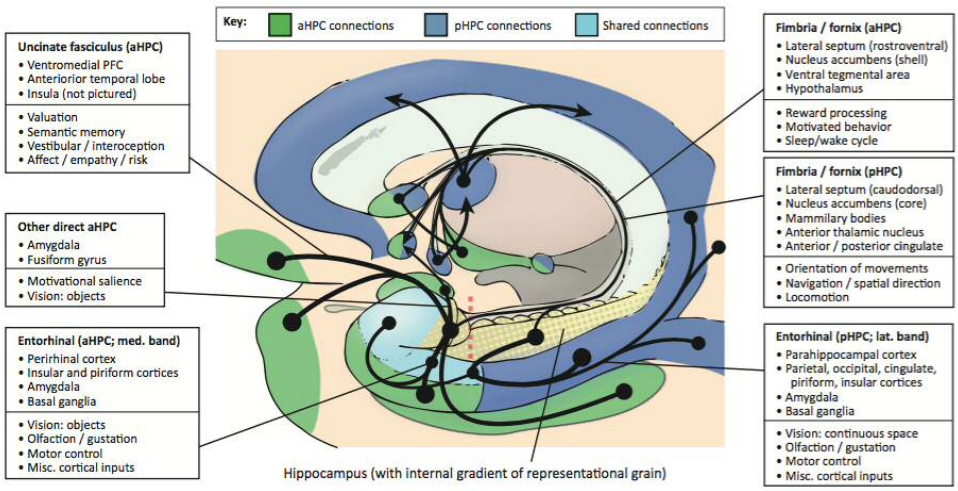

Figure 1.3: From Poppenek et al (2013) Model of long axis specialisation of the hippocampus, showing that specialisation emerges based on two primary mechanisms; 1) the anterior and posterior hippocampus represent information internally at coarse and fine gradients, respectively. Different CA/DG subfield ratios form the basis of this pattern, through their roles in pattern separation and pattern completion. 2) anterior and posterior hippocampus connect to different cortical and subcortical systems, producing an array of different functions that the hippocampus is associated with. In this illustration, hippocampal connections are depicted with thick black lines, with their reciprocal termination points shown in black dots. The information proposed to be associated with each path ways is shown in boxes.

Beyond physiological evidence, further evidence of hippocampal involvement in spatial processing is well known from an influential study by Maguire et al. (2000), where the posterior hippocampus of London taxi drivers, who are required to have a detailed knowledge of complex travel routes within London, was found to be significantly larger compared to bus drivers (who similarly have to drive around the city, but are not required to have the same degree of navigational route knowledge). Moreover, posterior hippocampal volume was found to positively correlate with number of years as a London taxi driver, demonstrating a link between spatial navigation experience and the hippocampus. The highlighted distinction between anterior and posterior functions in spatial navigation seems to extend to aspects of scene construction and perception.

In an fMRI study, Zeidman et al. (2015) sought to investigate the functional overlap and distinction between scene construction and perception, by asking participants to firstly mentally construct and maintain scenes (versus acontextual objects as a control condition), and secondly, view photographs of scenes (and acontextual objects as a control condition)

whilst being scanned. As shown in Figure 1.4 (left), scene perception activated both anterior and posterior regions along the long axis of the hippocampus, whereas scene construction activation was restricted to the anterior hippocampus only. These findings clearly position the hippocampus within the core network for scene construction and perception (going beyond its purported role in episodic memory), but also highlights some potential differences in different parts of the hippocampus, perhaps linked to the many different subfields within this structure. In a recent study using ultra high field fMRI, Hodgetts et al. (2017) found preferential activation of the anteromedial subiculum of the hippocampus, for scene perceptual discriminations, but not for face or object discriminations. The task used was an oddity discrimination task, which as described later in this chapter (and further in Chapter 4), is sensitive to scene perceptual impairments in AD (Lee et al., 2007). The overlap between scene perception and construction in anterior hippocampus suggest that perceiving and discriminating between scenes may also rely on constructive processes. As alluded to earlier in this chapter, provision of visual scene information may be too brief and partial to rely on alone as a mechanism to understand the entirety of a scene, and filling in / construction of components of this may be a critical role of the anterior hippocampus (Intraub et al., 1992).

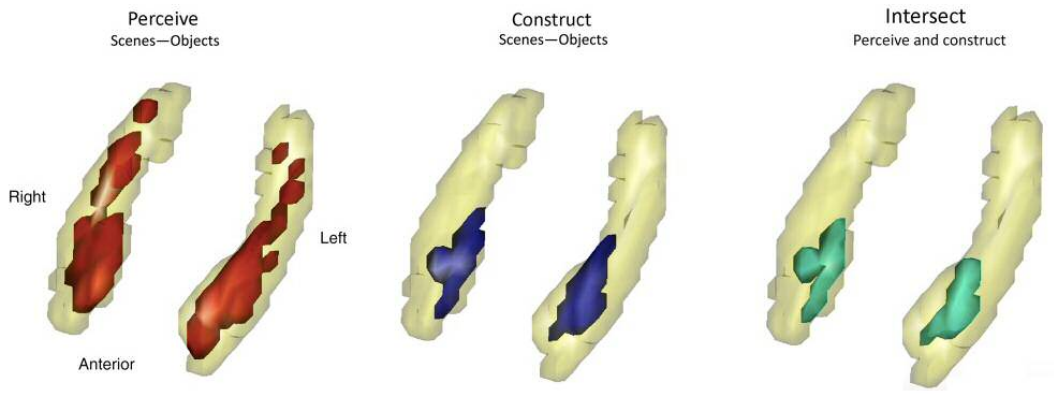

Figure 1.4: From Zeidman et al. (2015) Bilateral hippocampal mask ROI analysis. Shown on a 3D projection of the hippocampus, left: Activation for perceiving scenes, relative to perceiving objects. Middle: Activation for constructing scenes relative to constructing objects. Right: Voxels activated by both scene perception and scene construction.

As alluded to previously in this chapter, the hippocampal contribution to episodic memory may be explained by this brain region's involvement in scene and spatial

processing, with this form of information a critical embedded component of successful event memory retrieval (Murray et al., 2017). Further evidence for the role of the hippocampus in complex scene perception comes from studies in amnesic patients with MTL damage. Lee et al. (2005) tested patients on their ability to make visual discriminations for scenes, and other stimulus categories including faces and objects. In this study, image pairs were presented. The images had been morphed together at varying levels, so that the features they shared ranged between 0-49%. Participants were required to distinguish which of the two stimuli was most similar to a third stimulus, with this third image being one of the stimuli used to create the morphed pairs. Five stimulus categories were tested, including outdoor scenes, faces (famous and non-famous pairs), objects (non-living and animal pairs), abstract art, and colours. Lee et al. (2005) found that amnesic patients who had selective damage of the hippocampus, performed comparably to healthy controls when making discriminations for faces, objects, abstract art and colours. These patients, however, demonstrated a marked impairment for real world scene discriminations, with increasing numbers of errors evident as the percentage of shared features across the pairs of scenes (degree of morphing) increased. Crucially, patients with more widespread MTL damage (including the hippocampus, but also PRC and parts of anterior temporal lobe) also showed discrimination impairments for the scene pairs, but were also impaired on face discrimination compared with controls, alongside a less profound object discrimination deficit. As the stimuli for each trial were all presented simultaneously in an array, this task did not require participants to remember information across multiple trials. Therefore, the findings of this study not only demonstrated the involvement of the MTL in complex visual discrimination, but further, showed that the hippocampus and PRC were differentially involved in scene and object perception, respectively.

In a further perceptual discrimination study, participants were presented with a stimulus array of 4 images in each trial, and their task was to select the 'odd-one-out' from the array (Lee et al., 2005). Again, stimuli were presented simultaneously in the same array, meaning that there was no explicit demand placed on long term memory to perform the task successfully. Stimuli were either virtual reality indoor rooms or unfamiliar faces. For each trial, the stimuli were either presented from the same view point or different viewpoints. The different viewpoint condition was designed to increase the demand placed on processing of multiple spatial relationships between elements within the scene, compared to the same viewpoint condition. Consistent with previous findings, patients with selective hippocampal lesions were found to be severely impaired on the scene discrimination

condition, but only when the scenes were from different (and not same) viewpoints. Performance on the face conditions, both same and different viewpoint, was similar to controls. The patients with more widespread MTL damage (affecting both the hippocampus and PRC) were found to be impaired in both scene and face different viewpoint discrimination. Performance on same viewpoint conditions, for both scenes and faces, was preserved. The findings of this follow-up study further evidenced a critical role for the hippocampus in spatial perception, particularly when processing of complex conjunctions of spatial features within a scene was required (Lee et al., 2005).

A methodological criticism of these studies is that patients may have damage to regions beyond the MTL that are involved in processing scenes (in the case of the hippocampal patients) or also those involved in perception of faces and objects (individuals with additional PRC damage). Functional imaging studies in healthy individuals without MTL damage provide compelling additional support. Applying a similar oddity discrimination task to that used in his patient studies, Lee et al. (2008) found bilateral posterior hippocampus and parahippocampal cortex activations while participants were performing scene oddity judgements (scene oddity minus size oddity). By contrast, performing face oddity judgements activated the left PRC and the anterior hippocampus bilaterally. Further, when the face and scene conditions were contrasted with each other, there was a relative increase for the degree of activation in the associated regions for each condition. This imaging evidence neatly links the functional activation in this region with the impairments presented as a consequence of damage to these structures.

1.2.3 The Posterior Cingulate Cortex and Scene Processing

A further region in the core scene network, which will be a focus throughout this thesis, is the posterior cingulate cortex (PCC). The PCC consists of Brodmann (1909) areas 23 and 31 (see Figure 1.5, A, B), and is located within the posteromedial cortex (PMC), alongside the precuneus, which lies posterior and superior to the PCC. The retrosplenial cortex, also part of PMC, lies adjacent to the PCC. Diffusion tensor imaging (DTI) tractography has shown structural connections from the retrosplenial cortex and ventral PCC to the MTL, alongside dorsal PCC connections to the ventromedial prefrontal cortex via the cingulum bundle (Greicius et al., 2009). Graph theoretical analysis has shown that the PCC is a highly interconnected brain region relative to other brain areas, and given this, it is thought to be a hub region in the brain supporting a range of different cognitive processes (Hagman et al., 2008). Functionally, the PCC shows an extensive and complex

pattern of connectivity (Vincent et al., 2006; Leech et al., 2012), which again supports its role as a key hub, interacting with distinct intrinsic networks throughout the brain (Leech et al., 2012). The PCC has also been found to have a higher rate of metabolism compared with other brain regions (Raichle et al., 2001), and further, PCC metabolism is responsive to cognitive state, in particular how demanding a cognitive task is. In addition, compared to almost all other brain regions, the PCC shows consistently higher levels of cerebral blood flow (CBF) (Pfefferbaum et al., 2011), even when the task results in a relative fall in PCC activity as measured by the BOLD response.

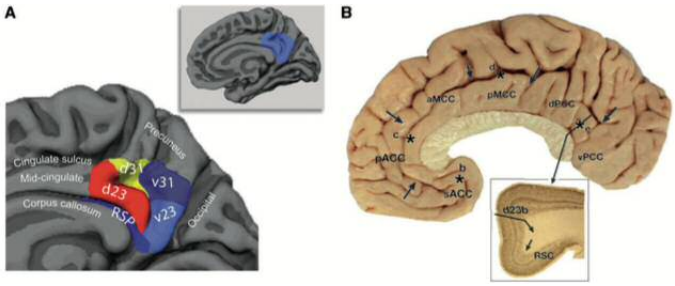

Figure 1.5: From Leech (2014). Anatomy of the PCC. A) An illustration of PCC sub-division locations based on cytoarchitectonics with Brodmann labels overlaid. Areas v23 and the posterior part of area v31 correspond to ventral PCC, and areas d23 and the anterior part of v31 corresponds to dorsal PCC. RSP = retrosplenial cortex. B) Anatomical midline section highlighting different cingulate cortical regions; the PCC, anterior cingulate cortex (ACC), mid-cingulate cortex (MCC), with a sub-section through the dorsal PCC.

Due to its high interconnectivity, it is unsurprising that the functions of the PCC are highly debated, with no clear consensus (Leech et al., 2012). The PCC is implicated as a key region within the default network (DN), which I touched upon at the beginning of this Introduction. As a reminder, this is a network of brain regions that are highly active during task-absent 'rest' and that deactivate when engaged in a task (Gusnard et al., 2001; Raichle et al., 2001). PCC's involvement in the DN led researchers to the view that the PCC deactivates relative to the level of cognitive demand during a task (Mckierman et al., 2003). This view is now considered somewhat outdated, especially given evidence that the PCC also shows increased brain activity during the retrieval of autobiographical memories, future thinking, scene construction, spatial navigation, spatial location imagining of the self, and theory of mind tasks (Addis et al., 2007; Hassabis et al., 2007; Spreng et al., 2008; Guterstam et al., 2015). This finding, considered alongside evidence of increased activity

during rest, has led to the hypothesis that the PCC plays a key role in internally directed cognition (Raichle et al., 2001). With respect to PCC's involvement also in the core network for scene construction (see previous sections), it is worth noting that during task absent 'rest' conditions our mind is likely to be wandering. We may be thinking about recent events, or planning for future events, processes most likely dependent upon scene reconstruction via access to prior experiences, and crucial for the mental imagery we experience during the absence of a specific cognitive task. Therefore, PCC may be involved in internally driven thought through its key role in supporting scene construction. Potential support for this proposal comes from imaging studies which show that the PCC plays an important role in successful episodic memory processing, showing deactivation during memory encoding, with increased activation during retrieval of episodic memories (Daselaar et al., 2009; Huijbers et al., 2012). With episodic memory being reconstructive by nature, this pattern of activation may reflect PCC involvement in scene construction, for which there may be a greater demand during stages of episodic retrieval, as information is drawn via manipulation of internal representations.

Further evidence for the involvement of the PCC in scene construction comes from research in Alzheimer's disease (AD). AD patients demonstrate characteristic impairments in episodic and autobiographical memory retrieval, but also show difficulties with spatial navigation and orientation, associated with neurodegeneration (atrophy) of the PCC (Irish et al., 2012; Irish et al., 2013; Pengas et al., 2012; Tu et al., 2015). Further, in a voxel based morphology (VBM) study with AD patients, Irish et al. (2015) found increased PCC volume to be related to scene construction ability in both patient and control groups, evidencing a role for the PCC in scene construction in healthy individuals as well as through atrophy of this structure. A key part of this thesis focused on this potential vulnerability to scene perception in dementia, not from the perspective of clinical studies but rather whether scene perception is a sensitive cognitive biomarker of AD risk (the latter measured via genetic risk). The next sections focus on describing some background to AD and APOE e4, which is the strongest semi-dominant risk gene for AD.

1.3 AD, APOE e4 and Later-life Cognitive health

1.3.1 Alzheimer's Disease

AD is the most common cause of dementia, accounting for 60-70% of the estimated 47.5 million people living with dementia worldwide (World Health Organisation, 2012). AD is one of the leading causes of death in the US and with an increasing aging population, the number of people diagnosed with AD is projected to substantially increase every year, estimated to be 11 to 16 million in the US alone by 2050 (Alzheimer's Association, 2015). Amnesic AD patients exhibit widespread cerebral cortical atrophy, which is most profound in the medial temporal lobe regions (Braak & Braak., 1991; Braak et al., 2006, see Figure 1.6), but typically spares the primary motor, sensory and visual areas. Alongside atrophy, AD is characterised by the presence of two hallmark pathologies in the brain; extracellular amyloid-beta plaques (Glenner et al., 1984; Masters et al., 1985) and intracellular tangles of hyperphosphorylated tau protein (Braak & Braak, 1998). The plaques consist of a beta amyloid core and 4-kD peptide, surrounded by neurites (projections from the cell body) which are configured abnormally. The temporal and spatial association between these two pathological hallmarks is still not fully understood.

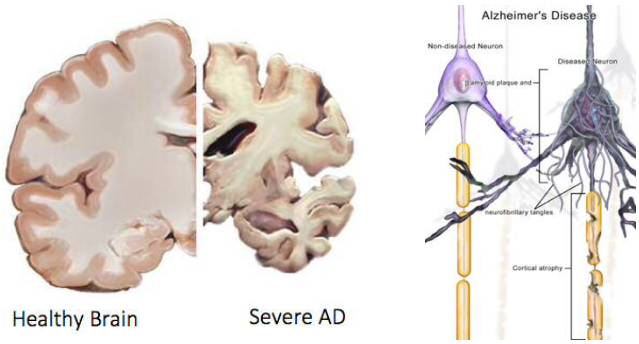

Figure 1.6: Pathology in Alzheimer's Disease. A) Atrophy in the brain in a healthy individual (left) and in advanced AD (right), B) A normal neuron and a diseased neuron showing pathological hallmarks of AD, which include amyloid plaques and neurofibrillary tangles.

Prior to the clinical diagnosis of AD, a prodromal stage of mild cognitive impairment (MCI) is often evident. Criteria for the identification of MCI typically involves a noticeable decline in at least one cognitive domain (Albert et al., 2011; Peterson et al.,

2004, 2001). These cognitive changes can be observed in a variety of cognitive domains, including memory, executive function, language, attention, and visuospatial skills. The most common impairment seen in MCI is in episodic memory, especially in MCI patients who go on to progress to AD. AD is characterised by progressive episodic memory impairment (Salmon et al., 2000) and for many years this was the focus of cognitive studies in the disease. More recently, it has become clear that spatial navigation and scene processing impairments are also a common cognitive symptom of the disease. AD patients have been found to be impaired when remembering previously travelled routes (Delpolyi et al., 2007). They also demonstrate difficulties with spatial navigation around both familiar and unfamiliar environments (Lithfous et al., 2013; Monacelli et al., 2003; Pai et al., 2004). Cushman et al. (2008) showed that AD patients have significant difficulties forming associations between images of scenes and the spatial location of these images. These scene-related cognitive impairments observed in AD will be discussed further in later sections of this chapter.

Despite being regarded as somewhat controversial, the 'amyloid cascade hypothesis' remains one of the best defined conceptual frameworks for the study of AD. This theory proposes that aberrant accumulation of amyloid results in aggregation and formation of the insoluble amyloid beta plaques, which is the initiating event in a pathological process which leads to cognitive decline and dementia (Hardy et al., 2002). A key question, however, that the amyloid hypothesis fails to address is why amyloid deposition occurs in the first place. Evidence has emerged suggesting that neural activity in the brain may regulate the production and secretion of amyloid-beta (Jagust et al., 2011; Nitsch et al., 1993; Kamenetz et al., 2003; Bero et al., 2011; Cirrito et al., 2011). Neural activity, therefore, may be a potential mechanism which mediates the pathogenesis of AD. Studies of transgenic mice provide support for activity dependant amyloid release, but additionally Bero et al. (2011) showed that interstitial amyloid beta fluid levels are associated with regional neuronal activity, and to the later development of amyloid plaques in these regions with high levels of activity.

1.3.2 Genetic Risk of Alzheimer's Disease

The early onset of AD, before the age of 60 (EOAD), is infrequent, and is usually caused by either a mutation of the amyloid precursor protein gene (APP) located on chromosome 21, or more commonly, presenilin 1 and 2 genes (PSEN1/PSEN2) located on

chromosome 14. Individuals who have these disease related mutations are almost certain to develop AD as these genes are fully penetrant. These cases are estimated to account for less than 5% of AD cases (Bertram et al; 2012). Late-onset (sporadic) AD (LOAD), which typically occurs in individuals over the age of 65, is far more common, with no definitive genetic cause. There is accruing evidence of heritability, however, (Gatz et al; 2006) suggesting a genetic component in LOAD risk. This enables studies asking how genetic risk of AD affects brain function and behavioural performance prior to onset of cognitive decline, an approach applied in this thesis.

The strongest identified genetic risk factor for LOAD is the Apolipoprotein e4 allele, located on chromosome 19. APOE e4 is associated with AD risk in a dose dependant manner, with carriers of two copies of the e4 allele being at the highest risk of developing AD, and having an earlier onset than heterozygous carriers (Corder et al., 1993; Locke et al., 1995; Poirier et al., 1993). Genome wide association studies (GWAS) have identified other polymorphisms for AD risk, but these have only marginal risks compared to APOE e4 (Tanzi, 2012). Compared to a 4-fold risk of AD associated with having an APOE e4 allele, typically GWAS studies report a 0.1-0.15-fold risk in other strong risk genes (Bertram et al., 2010). The APOE e4 link to AD has been found to more pronounced in women than men (Payami et al., 1994). A large meta-analysis revealed that women in their sixties with only one copy of the APOE e4 allele have a 4-fold increased risk of LOAD compared with non e4 carriers (Farrer et al., 1997). Whereas risk in heterozygote APOE e4 males does not differ from non e4 carriers until around age 70 years, and still, is significantly reduced compared to risk in female e4 carriers at 70 years (Farrer et al., 1997). Among homozygote APOE e4 carriers, both females and males have a pronounced increased risk compared with APOE e3 homozygotes, however, risk for females is still greater, at around 12-fold compared with non e4 carriers, compared with 10-fold in male e4 homozygotes, compared with non e4 carriers (Farrer et al., 1997).

The Apolipoprotein E (APOE) gene is polymorphic and has three common isoforms; e2, e3 and e4. These alleles differ in their frequencies in the population (e2: 5-10%; e3: 65-70%; e4: 15-20%) giving rise to three homozygous (e4/4, e3/3, e2/2) and three heterozygous (e4/3, e3/2, e4/2) phenotypes (Mahley et al., 2000). These three main isoforms differ from one another by a single amino acid substitution, differences which seem to have an enormous impact on cellular and molecular function. A primary function of APOE is to transport and deliver lipids from one tissue or cell type to another, mediating cellular uptake of lipoproteins through specific cell surface receptors. It is also a major determinant in

cholesterol metabolism and cardiovascular disease (Mahley et al., 2000). APOE e3, the most common of the APOE isoforms, contributes little variation in isoform-specific effects on plasma lipids, and is therefore considered to be 'normal' (or a benchmark) for APOE function. APOE e2 and e4 isoforms, however, are widely described to have a varying, but in some cases quite dramatic, impact on lipid and lipoprotein levels. APOE e4 is associated with increased risk of atherosclerosis (Mahley et al., 1999), heart disease (Schachler et al., 1995), and as previously outlined, AD and vascular dementia (Corder et al., 1993; Liu et al., 2013; Kalaria et al., 1999). Additionally, following acute head trauma, possession of the e4 isoform is associated with a poorer clinical outcome in older adults (Teasise et al., 1997; Crawford., Friedman et al., 1999), regardless of injury severity (Ponsford et al., 2011). Also, a meta-analysis found that APOE e4 is associated with a worse outcome 6-months following the injury (Zhou et al., 2008). These poorer outcomes in e4 carriers might be related to the reduced synapse remodelling and repair ability and protecting against neuronal injury, in comparison with e3 carriers (Bu et al., 2009; Lucido et al., 2015). Further, possession of the e2 allele is described to have a protective effect against AD (Kim et al., 2009; Qiu et al., 2004), and has not been associated with the poor outcomes observed in e4 carriers (Miller et al., 2010).

The way in which APOE modulates neuronal repair, remodelling or protection is key to its role in neurodegenerative diseases (see Kim et al., 2009; Liu et al., 2013). When neuronal damage is caused, neuronal repair of synaptodendritic connections is required. APOE e2 and e3 are suggested to play a particularly effective role in the process of neuronal repair protecting against further damage (Mahley et al., 2000), (as shown in Figure 1.7). Among other neuroprotective effects, e2 and e3 are also associated with inducing neurons to produce long neurites, through lipoprotein transport. Contrastingly, the e4 allele may be comparably ineffective when it comes to neuronal protection and repair but further, this allele is associated with decreased neurite growth and branching (Mahley et al., 2007), a key potential change seen in neurodegenerative diseases.

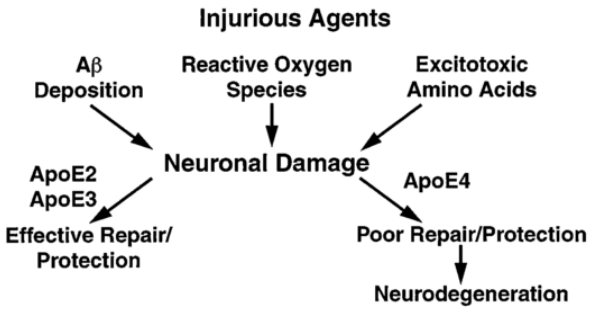

Figure 1.7: From Mahley et al (2000). Isoform specific effects of APOE on neuronal repair, remodelling and protection.

As previously outlined, one of the hallmark pathologies of AD is the presence of vast extracellular amyloid plaque accumulation in the brain. Different APOE isoforms are thought to differentially affect amyloid plaque formation (as shown in Figure 1.8), and/ or beta amyloid peptide metabolism. The lipid-binding region of APOE mediates its interaction with beta amyloid, and whereas lipid free e4 forms a stable-complex with beta amyloid, lipid free e3 does not (Strittmatter et al; 1993). The opposite is found for lapidated (covalently modified with lipid extensions) isoforms, where compared with lipidated e4, lipidated APOE e3 binds to beta amyloid peptide at a 20-fold higher rate, which may increase the clearance of beta amyloid peptide, reducing both the accumulation of beta amyloid and numbers of neurotoxic amyloid species (Kounnas et al., 1995; LaDu et al., 1997).

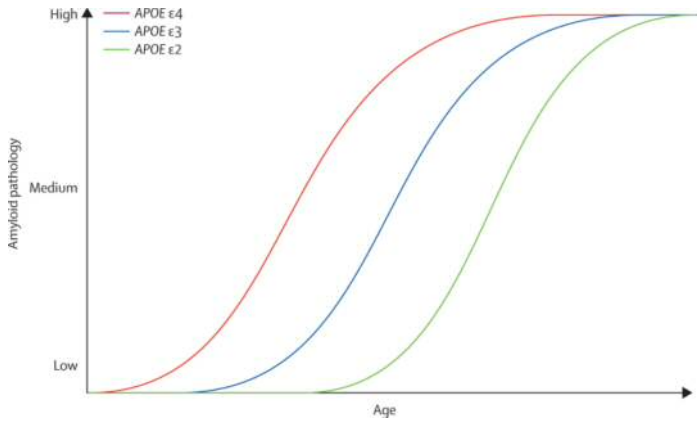

Figure 1.8: From Verghese et al (2011). The effects of Apolipoprotein E on amyloid pathological changes in Alzheimer's Disease. Research suggests that the dominant effect of human APOE isoforms on AD is to shift the onset of disease via changes to the probability of amyloid deposition and the age of onset of pathological changes. APOE e4 is associated with the earliest onset of pathological changes, whereas e2 carriers have a reduced risk of AD, and the disease occurs at a later stage.

1.3.3 APOE e4 and cognition

As noted above, possession of the APOE e4 allele is associated with increased vulnerability to later life poor cognitive health, including dementia (both AD and vascular) (Bookheimer et al., 2009). Cognitive decline can be experienced years before clinical diagnosis of AD (during MCI stage), and there is accruing evidence that subtle structural and functional brain changes – without overt cognitive difficulties – may occur many years in advance of that. These changes are thought to begin earlier in APOE e4 carriers (Bookheimer et al., 2009), as already outlined. As previously discussed, APOE e4 increases AD risk in a dose dependent manner, and this is also consistent with onset of cognitive changes associated with AD. Compared to e4 heterozygotes and non-carriers, homozygote e4 carriers are reported to demonstrate deficits in episodic recall tasks (Nilsson et al., 2006) and higher rates of general cognitive decline over time prior to an official diagnosis of MCI or AD (Caselli et al., 1999; Caselli et al., 2004, 2007). Similar patterns of cognitive vulnerability have also been reported in non-demented heterozygote e4 carriers, with relatively higher rates of gradual memory decline and impairments in abstract reasoning in older adult e4 carriers (Schiepers et al., 2012). In the same study, possession of an APOE e2 allele was not associated with changes in cognitive performance in this cohort. These findings suggest that APOE e4 seems to have non-pathological and pathological effects on

aging (Deary et al., 2002), with that latter being associated with greater amyloid accumulation in older age (Reinvang et al., 2013). This highlights the issue of needing to be able to differentiate between vulnerability to pathological or non-pathological cognitive changes in APOE e4 carriers as early as possible, before these pathological changes begin to occur.

According to the amyloid cascade hypothesis (as previously outlined), beta amyloid deposition is the initiating event in a pathological process potentially leading to AD, which in turn causes alterations in neuronal functioning and poor cognitive health. Neural activity has been found to be associated with the production and secretion of amyloid beta, with greater activity associated with greater amyloid deposition (Jagust et al., 2011). Event-related FMRI studies in middle-aged and older APOE e4 carriers have found increased activation in regions expected to be engaged in a task (i.e. increased hippocampal activation during memory and recall tasks, Bookheimer et al., 2000), compared with non-carriers (Bookheimer et al., 2000; Burggren et al., 2000; Bondi et al., 2005; Wishart et al., 2006; Fleisher et al., 2005). This suggests that these APOE e4 carriers recruit these MTL regions more strongly, which may indicate life span vulnerability to later life poor cognitive health and preclinical changes associated with increased AD risk. Although these functional findings are well established, across these studies there is no clear consensus about the age at which these pre-clinical functional changes begin to manifest.

Studies have reported cognitive changes which suggest a preclinical decrement in middle aged and older APOE e4 carriers for episodic memory (Bondi et al., 1995; Bondi et al., 1999), but also in domains of attention, naming, spatial abilities and executive function (Albert et al., 2001; Bretsky et al., 2003; Greenwood et al., 2005; Twamley et al., 2006; Mickes et al., 2007). In young adult APOE e4 carriers, there is some discrepancy in findings in the literature regarding whether cognitive changes are apparent early in life. Many studies have reported no behavioural differences between young adult e4 carriers (i.e. Filippini et al., 2009; Shine et al., 2015). However, some studies suggest a potential advantage in some cognitive domains in young APOE e4 carriers compared with non-carriers. These have included higher 1Q scores for APOE e4 carriers (Yu et al., 2000), achievement of a higher level of education (Hubacek et al., 2001), and increased 'mental vitality' (i.e., more active, energetic and alert), (Keltikangas-Jarvinen et al., 1993). In a study which examined neuropsychological outcomes following mild to moderate head injury in a military population of young adults, better performance was observed in measures of attention, executive functioning and episodic memory encoding in APOE e4 carriers, relative to non-

carriers (Han et al., 2007). These positive benefits for APOE e4 have been discussed in the context of antagonistic pleiotropy (Rusted et al., 2013; Han et al., 2008), whereby a cognitive advantage in younger adults underlies higher achievements and greater selection benefits, but may increase vulnerability to cognitive decline in older age. There is, however, debate about whether these early cognitive differences exist, and which domains of cognition might be the most important indicators of later life poor cognitive health.

Literature has proposed that the increased functional activity often found in APOE e4 carriers compared with non-carriers, may be associated with a cognitive advantage, particularly in attention (Rusted et al., 2013). However, as will be discussed, APOE related alterations in functional activity are often found in the absence of behavioural alterations (Filippini et al., 2009; Shine et al., 2015). This does not support a relationship between increased activation and a cognitive advantage in APOE e4 carriers. Instead, this suggests that increased activation in specific brain regions is seen in young APOE e4 carriers may reflect compensatory recruitment of regions to facilitate normal cognitive functioning (Han et al., 2008). Over time, it is suggested that this may lead to the pathological alterations, and subsequent cognitive changes observed in older APOE e4 carriers and AD. Therefore, the relationship between activation alterations in APOE and behavioural performance is still in need to be more extensively investigated, to forward our understanding of APOE and AD risk.

Remarkably, task-related functional activation alterations seen in young APOE e4 carriers (Filippini et al., 2009; Shine et al., 2015) are strikingly consistent with the functional deficits we see in older APOE e4 carriers and in patients with AD (Lee et al., 2006). Crucially, these individuals are in their twenties, providing further evidence that possession of APOE e4 may modulate brain function across the life span - not just months or years, but decades before potential onset of the clinical symptoms of AD. In an influential study, Filippini et al. (2009) acquired BOLD fMRI during a resting-state and a 'novel versus familiar' encoding memory paradigm in 18 APOE e4 carriers and 18 non-carriers (Filippini et al., 2009). The encoding task was used because it has been found to robustly activate the hippocampus (Tulving et al., 1994). Given that the earliest pathological changes in AD are in MTL regions, this task was implemented to specifically examine the influence of APOE e4 on hippocampal activation during memory encoding. Greater hippocampal activation (average bilaterally 32% signal increase) was identified in the APOE e4 carriers during the encoding task, without behavioural differences across groups. Notably, no differences in grey matter volume were found in this study, for whole brain or individual structure

measures, including the hippocampus. Filippini's study provides evidence that the APOE e4 genetic variant could contribute towards the manifestation of hippocampal changes through functional brain activity alterations, decades before potential onset of cognitive or pathological symptoms.

Alongside functional alterations in young adult APOE e4 carriers, structural brain changes have also been reported (O'Dwyer et al., 2012; Chang et al., 2016; Shaw et al., 2011). In older individuals with MCI, hippocampal volume reduction is suggested to be a prognostic indicator of subsequent AD (Grundman et al., 2002). As previously outlined, MTL structures including the hippocampus and entorhinal cortex, alongside posteromedial regions including the PCC, are amongst the earliest regions affected by AD pathology (Buckner et al., 2004; Leech et al., 2013; Braak & Braak., 1991, 1997; Pengas et al., 2010), with marked atrophy in these regions being a structural hallmark of the disease (Hyman et al., 1994; Price et al., 1991; Gomez-Isla et al, 1996). Pathological changes in these structures (particularly the hippocampus) are consistent with cognitive changes observed in AD, including impairments in episodic memory, complex scene processing and spatial navigation (Philippi et al., 2015; Lee et al., 2005; lee et al., 2007; Zhou et al., 2012). As described previously in this chapter, possession of the APOE e4 allele is a major genetic risk factor for the development of AD in later life. Alterations in brain structure and function are reported in middle aged and older e4 carriers, relative to non-carriers, in both healthy individuals (Bookheimer et al., 2000; Reiman et al., 2004; Wishart et al., 2006; Bondi et al., 2005), and patients with MCI and AD (Morgen et al., 2013; Filippini et al., 2008; Lehtovirta et al., 1995). Individuals with AD who carry the APOE e4 allele show greatest volume reduction in the hippocampus, compared with non-carriers (Schuff et al., 2009). Further, an APOE e4 dose-dependent effect on MTL atrophy (particularly the hippocampus and ERC) has been reported in AD patients, with greater volume reductions with increasing load of the e4 allele (Frisoni et al., 1999; Du et al., 2006; Filippini et al., 2008; Lehtovirta et al., 1995). Therefore, structural differences in young healthy e4 carriers earlier in life, could be predictive of later life vulnerability to further tissue loss in these regions (such as the hippocampus), but further, could indicate vulnerability to early cognitive alterations associated with this volume reduction in AD.

However, in parallel with structural measures in young adult e4 carriers, O'Dwyer et al. (2012), obtained measures of cognitive performance using standard neuropsychological assessments. These included measures of general intelligence (Mehrfachwahi-Wortschatz test), a verbal intelligence test, a trail making test, Spatial Span

of the Wechsler Memory Scale, Letter Number Sequencing test, the California Verbal Learning Test, and the Brief Visual Memory Test. Despite lower hippocampal volumes in these young adult e4 carriers, no APOE-related differences in cognitive performance were found between groups. Based on the findings of this study, the authors suggest that although there are early hippocampal volume alterations in young e4 carriers, these changes may not be behaviourally-relevant at this young age. However, one of the main arguments of this thesis, is that standard and generalized tests of broad cognitive function, may not be sensitive enough to tap into very early subtle and cognitively specific changes which might be evident in these young adult e4 carriers.

1.4 **Bringing it all together: scenes, AD and APOE e4**

1.4.1 Scene construction in Healthy Aging and Alzheimer's Disease

Healthy aging is associated with structural changes to the brain, including in MTL regions. This brain atrophy is associated with memory decline, alongside impoverished spatial navigation and scene processing abilities. As previously discussed in this chapter, the co-occurrence of episodic memory and scene processing deficits may not be unrelated, with both processes being underpinned by scene representations stored within the hippocampus. Studies have generally shown that increasing age can have a negative impact on spatial imagery (i.e. Craik & Dirkx, 1992). Although earlier research suggested this may occur more broadly (Hertzog et al., 1993), it has since been proposed that the effect of aging on spatial imagery may occur in a non-uniform manner. For example, Dror and Kosslyn (1994) describe age related progressive impairment in image generation and rotation, but not image maintenance or scanning, suggesting that distinct processes underlying spatial imagery are effected by normal (non-pathological) aging, selectively. Maintenance of mental scene imagery (scene construction) involves the flexible manipulation of, and adding and integration of elements into a scene representation, which is described to be a fundamental process for scene construction. Although it should also be noted that scene representations (construction) is argued to underpin multiple cognitive processes including view point manipulation which is involved in mental rotation. It is therefore interesting that this mental imagery maintenance is reportedly comparably spared in non-pathological aging (Dror and Kosslyn, 1994; De Beni et al., 2006), yet as will be discussed, scene construction is impaired in individuals with AD (Irish et al., 2015). This demonstrates that although changes in the MTL may be present in both pathological and non-pathological aging, the

profiles of these changes in spatial cognition differ, and therefore, distinct networks may be more vulnerable to pathological changes associated with AD.

The effects of aging on components of scene construction ability has been investigated in a study comparing healthy younger and older individuals (Rendell et al., 2012). Participants provided verbal descriptions of both atemporal (without time constraints) and future thinking (imposed subjective sense of time) imagined scenarios, alongside self-report ratings of quality (i.e. richness/ vividness) of the imagined events. Compared to younger individuals, older adults showed a reduced capacity for scene constructions across conditions, but were worse for future thinking compared with atemporal scene constructions. These findings suggest a possible age-related decline in scene construction ability, but particularly where a subjective sense of time is involved. In a similar study (also outlined previously in this chapter in relation to regions supporting scene construction), Irish et al. (2015) tested scene construction abilities in AD patients, however, only atemporal constructions and not future thinking scene constructions were assessed. Compared with aged matched controls, AD patients were strikingly impaired across all components of verbal atemporal scene construction, alongside self-report ratings of scene imagination quality, which reflected these marked impairments. For comparability of healthy age related cognitive changes and those associated with AD, it would be useful to have scene constructions for both atemporal and future thinking conditions to investigate how patterns of performance across episodic scene construction categories are related to normal and abnormal cognitive aging.

As described previously in this chapter, studies of patients with MTL and hippocampal damage have directly linked the hippocampus to visual scene perception (Lee et al., 2005). As also previously outlined, the hippocampus and other MTL structures are among the earliest structures affected by AD pathology. In a similar study to the MTL patient study by Lee et al. (2005), patients with AD participated in an oddity discrimination task, with a 4-choice array of scenes and faces (Lee et al., 2006). Their performance was compared to patients with semantic dementia, a different form of dementia which causes a progressive loss of semantic knowledge about the world, in the context of better preserved episodic memory (Kramer et al., 2003). While AD is associated with hippocampal atrophy, SD is associated with PRC atrophy, with less involvement of the hippocampus (Davies et al., 2004). In Lee et al.'s (2006) study, AD patients were found to be impaired for scene discriminations for both same and different viewpoint conditions, compared with controls, however they did not show impairments for face discriminations, regardless of viewpoint.

Conversely, SD patients demonstrated impairments for face discriminations for different viewpoints, compared with controls. They showed no impairment in either of the scene discrimination viewpoint conditions, nor in the same view face discrimination. This double dissociation provides evidence for a selective impairment in scene perception in AD, supported by scene construction impairments in AD (Irish et al., 2015), which suggests that scene processing could be an important cognitive marker for abnormal cognition associated with AD. Further, some of the earliest structural changes in AD have been reported in the CA1 subfield of the hippocampus, with subfields CA2-3 relatively spared (Frisoni et al., 2008). Anatomically, the largest proportion of CA1 is located in the anterior hippocampus, which as I discussed at the beginning of this chapter is associated with scene construction and perception ability (see Zeidman et al., 2015). At which stage changes related to scene processing occur, and how that is linked to genetic risk of AD (e.g., presence or absence of an APOE e4 allele) remains an important question.

In this Chapter, I have proposed that scene construction forms a spatial scaffold underpinning many related cognitive processes, including episodic memory for past and future events, scene imagination, visual scene perception (particularly view point independent discrimination) and spatial navigation. I have discussed studies suggesting that some of these cognitive domains are affected early in AD, and also imaging investigations highlighting effects of the APOE e4 allele on functional activity in the brain, particularly during episodic memory encoding. It is interesting to note that alterations of brain activity have also been seen in young adult APOE e4 carriers during scene perception and working memory tasks (Shine et al., 2015; Filippini et al., 2009). I will briefly overview the Shine et al. (2015) study here, describing it in further detail in Chapter 4 where I extend this work. Shine et al. (2015) used a similar perceptual discrimination (oddity) task to that used by Lee and colleagues to elicit impairments in complex scene, but not face, discriminations in AD patients (Lee et al., 2005, 2006, 2007). Task conditions included odd one out choice arrays of scenes, faces, objects and size. In these young adults, e4 carriers demonstrated a scene selective failure to modulate PCC activity, compared to non-carriers. As previously described, the PCC shows altered functional activity early in MCI (Petrella et al., 2011) and AD (Greicius et al., 2004), but further the PCC is implicated in the core scene network (Irish et al., 2015; Schacter et al., 2007). Therefore, this study suggests that e4 may influence later life vulnerability to poor cognitive health through alterations in the PCC functional activity.

The findings of Shine et al. (2015) highlight a degree of sensitivity in the altered functional response seen in APOE e4 carriers, with differences between APOE e4 carriers

and non-carriers most evident in tasks involving processing of visual scenes. Shine et al. found no behavioural differences across conditions, with APOE e4 carriers performing similarly to non-carriers. The oddity task, however, is a relatively simple discrimination task, and the working memory paradigm also employed in their study only involved a 1 back condition. In this thesis, I expand on the work of Shine et al. in two key ways. First, I will ask whether subtle scene related behavioural differences may be evident between APOE e4 carriers and non-carriers when sensitive behavioural measures (e.g. greater task demand compared with oddity) are applied to examine scene construction (Chapters 2 and 3). Second, I will augment these behavioural studies by running a follow-up study based on Shine et al. (2015) looking at both BOLD, but also a more direct measure of neural activity, cerebral blood flow (Chapter 4). Understanding the neural basis of brain changes in young APOE e4 carriers, aligned to a specific cognitive hallmark of AD, could provide a marker for increased genetic risk, but further, could help us to better understand the influence of genetic risk on brain health. The combined behavioural and imaging approach applied in this thesis allows me to answer an overarching question: do young APOE e4 carriers show behavioural and brain alterations, compared to non-carriers, on sensitive cognitive paradigms assessing scene processing ability?

Lastly in this introduction chapter, I will describe the recruitment and genotyping procedures for a large APOE cohort of participants, which all participants in the experimental chapters of this thesis were recruited from. I will include this information here, to avoid repeating the information throughout chapters. Instead, within individual experimental chapters, the participants from this APOE cohort who took part in the individual study, will be described. Following this participants section here, I will next move on to the first experimental chapter of this thesis, where I will use a verbal scene construction task, to begin to probe subtle scene representation differences which may exist between young adult e4 carriers and non-carriers.

1.5 Participant Cohort for Experimental Chapters in This Thesis

This section details information regarding the participants who will later be described throughout the experimental chapters in this thesis, including how they were recruited for the cohort and information on DNA extraction procedures to determine APOE status. Each experimental chapter will provide additional details of participants included in that particular chapter (e.g. numbers, groups, APOE status information).

1.5.1 Participants and Recruitment

Procedures described in this section, were approved by Cardiff University School of Psychology Ethics committee. Participants gave full written informed consent before taking part in this research. All participants who took part in the studies in this thesis were undergraduate students from the School of Psychology, Cardiff University, Wales. The experimental cohort was formed of 19 participants who were re-recruited from a previous cohort of 30 participants, described by Shine et al (2015). Of the 19 individuals re-recruited, 10 were APOE e4 carriers and 9 non-carriers (APOE e3), with 1 male in each group. These participants were originally recruited from 125 participants who provided a saliva sample for DNA extraction and genotyping for APOE, and signed up to be invited back for future behavioural and imaging studies. To augment this relatively small sample, 229 (female) participants were additionally recruited, providing a saliva sample for DNA extraction and APOE genotyping. Of these 229, a cohort of 84 participants was created, comprised of 42 carriers with one copy of the APOE e4 allele (e3-e4) and 42 non-APOE e4 carriers (e3-e3). These individuals were matched for age, family history of dementia and family history of psychiatric illness, similar to the original sample used in Shine et al. (2015). Participants were not included in this cohort of 84, if they had any self-report history of mental illness or depression. Participants were all right handed and had normal, or corrected to normal vision.

Participants who took part in the imaging study in this thesis (see Chapter 4), included the 19 individuals from the first cohort, and an additional 28 from the second cohort, of which 10 were APOE e4 carriers and 18 were non-carriers, providing an overall total of 20 APOE e4 carriers and 27 non-carriers. The behavioural studies reported in Chapters 3 and 4 include participants re-recruited from the cohort of 84. Further details for each study will be provide in the methods section for each experimental chapter.

During participant recruitment and all testing with this cohort, a double-blind approach was employed, whereby the participants and experimenters who were collecting and analysing the data, were blind to APOE status.

1.5.2 DNA Extraction and Genotyping

The procedure for collecting saliva samples was the same across both cohorts used in this study. Oragene 0G-500 saliva sample kits were used to collect saliva for DNA extraction. The DNA extraction and APOE genotyping was carried out at the MRC Centre for Neuropsychiatric Genetics and Genomics at Cardiff University. To determine APOE genotype, a single SNP genotyping assay was used for the two sites on the APOE gene where the APOE isoforms differ due to a single nucleotide polymorphism. The SNP rs429358 was determined using KASP genotyping and the rs7412 using Taqman genotyping (Butchart et al., 2015; Ide et al., 2016). The Tecan infinite F200 Pro, and StepOnePlus Real-time PCR System platforms were used to detect these. Haplotypes were then deduced for APOE e2, e3 and e4. In the first cohort of 125 participants, 100 saliva samples produced successful genotyping, and 224 out of the 229 in the second cohort. Distribution of genotypes from successful genotyping in the first cohort of 100 was e2-e2 1/100 (1%), e2-e3 10/100, (10%), e2-e4 1/100 (1%), e3-e3 69/100 (69%), e3-e4 19/100 (19%), e4-e4 0/100 (0%). In the second cohort of 224 participants, the genotype distribution was e2-e2 0/100 (0%), e2-e3 38/224 (17%), e2-e4 7/224 (3%), e3-e3 125/224 (56%), e3-e4 52/224 (23%) ande4-e4 2/224 (1%).

2 Chapter 2: Spatially Coherent Scene Imagination in Young Adult APOE e4 Carriers

2.1 Introduction

Episodic memory involves mentally re-living rich, recollective experiences of the everyday personal events which occur throughout our lives. This experience has been likened to mental time travel, given that we are able to re-experience our past in the 'minds-eye' (Tulving, 2002). Episodic memory is widely accepted as a constructive rather than reproductive endeavour (Bartlett, 1932; Schacter et al., 1998), and is underpinned by the mental generation and maintenance of complex and spatially coherent scenes in which past events take place. Importantly, this process of 'scene construction' is not limited to re-experiencing past events; it has also been shown to be recruited during pre-experience of future events, through scene imagination (Schacter et al., 2007; Hassabis et al., 2007; Summerfield et al., 2010).

Consistent with this, functional neuroimaging studies have identified a 'core network' of brain regions involved in recalling past events that are already recruited when imagining fictitious and future events, but when navigating in spatial environments (Buckner et al., 2007). These include medial temporal lobe regions (e.g. the hippocampus and parahippocampal gyrus) but also posteromedial structures such as the retrosplenial cortex, posterior cinglate cortex (PCC) and precuneus (Spreng et al., 2009; Irish et al., 2015). Although many theories have been proposed for the functioning of this core brain network, Hassabis and Maguire et al. (2007, 2009) have suggested that this network is involved in scene construction, consistent with its role in cognitive processes that rely on a spatial-contextual framework.

Considering the hippocampus as an integral structure within the scene construction network, Hassabis et al. (2007) sought to investigate whether patients with acquired hippocampal amnesia (who were impaired in remembering their past experiences) could

imagine new future experiences. Patients and controls participated in a task which involved provision of a verbal cue describing an ordinary, everyday setting or scenario (e.g. 'imagine you are standing on the crowded platform of a train station'). Participants were instructed to imagine and describe their surroundings in the scenario as if they were actually present, effectively in their 'minds-eye'. Participants were told not to construct a scene from a memory, but instead to imagine a scene which is entirely new and a place they had not previously visited. The interviewer was permitted to use limited encouraging-probing questions, for example 'can you see anything else in the scene?'. Following each verbally described scene construction, participants completed self-ratings of the sense of presence and salience (effectively, vividness), alongside completion of a spatial coherence questionnaire. Items in this measure referred to integration or fragmentation of the imagined scene. Hassabis et al. (2007) found that relative to controls, hippocampal amnesic patients who present marked impairments in episodic memory, also present difficulties in scene imagination for fictitious atemporal (free of temporal constraint) and future-thinking scenes. Patients' produced overall fewer details, but further, their constructed scenes lacked spatial coherence and descriptions were fragmented compared with controls. See Table 2.1 for examples of spatially coherent and fragmented statements.

Despite these findings in hippocampal damage patients, the view that episodic past and future events are both supported by the MTL has not remained unchallenged. Squire et al. (2010) found amnesic patients' scene construction performance to be comparable with controls for the imagining of future events. Interpretation of these findings was criticized as neurological damage in the MTL was not quantified, and included extra-MTL regions. Therefore, the question of whether episodic future thinking impairments result from MTL damage, remained outstanding. In an attempt to address this, Race et al. (2011) assessed verbal episodic scene constructions of both past events and imagined future events in patients with MTL/hippocampal damage. Findings were comparable to those presented by Hassabis et al. (2007), with patients producing fewer details in both the episodic past events and future events scenarios, compared with controls (see Figure 2.1). Further, performance in both episodic conditions, were found to be related ($p = < .005$) for both patients and controls.

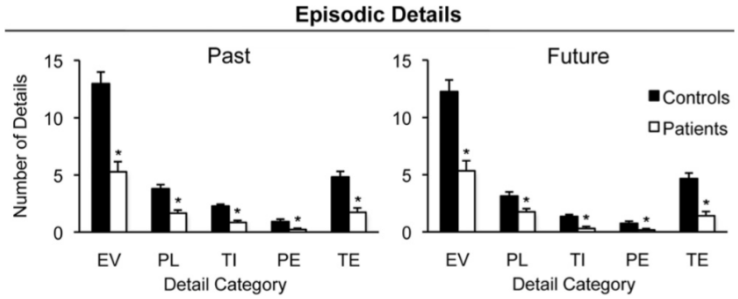

*Figure 2.1: From Race et al. (2011) Mean episodic details produced in the past and future scene imagining conditions for AMTL damage patients and controls. Detail category definitions: EV=event, PL=place, TI=time, PE=perceptual, TE=thought/emotion. Error bars for mean standard error. *p<.05 compared with controls.*

Interestingly, Hassabis et al. (2007) did not find between group differences in self-report ratings of sense of presence and sense of salience. It may be possible that despite scene fragmentation, these comparable self-report ratings reflect an intact simple mental visual imagery (e.g. single objects or faces, or components of a scene) which does not rely on the hippocampus (Kosslyn et al., 2001; Rosenbaum et al., 2004). Importantly, Individuals who have been found to be impaired in both past remembering and future imagining of events have not been found to be impaired in narrative description of pictorial scenes (Race et al., 2011), (see Figure 2.2, A and B). These findings provide evidence that hippocampal integrity is important not just for episodic memory, but instead, for representations of scenes, that form the underpinning spatial framework for multiple, related cognitive processes.

A B

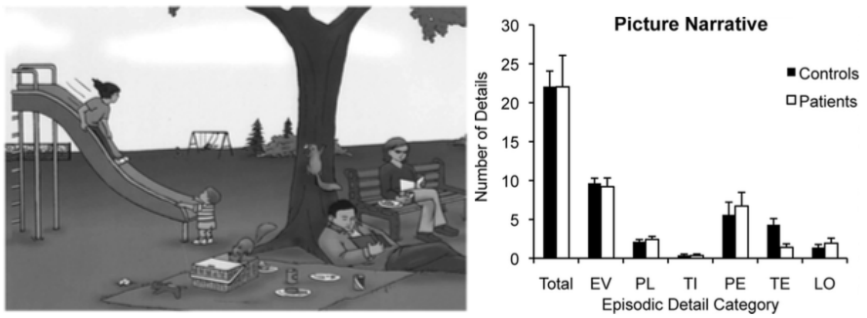

Figure 2.2: Race et al. (2011) A) A representative example of a picture used for the picture narrative task. B) Mean number of details produced in the picture narrative task (EV=event, PL=place, TI=time, PE=perceptual, TE=thought/emotion, LO=object location). Error bars for SEM.

Alzheimer's disease is characterised by degeneration within the core network implicated in scene construction, particularly medial temporal lobe (hippocampus) and posteromedial (posterior cingulate cortex) regions (Braak & Braak, 1991). Consistent with this pattern of atrophy, episodic memory impairment is a prominent clinical characteristic of AD progression. In parallel with these memory impairments, AD patients present difficulties with spatial navigation and scene perception (Lee et al., 2007), which have been attributed to atrophy of the posterior hippocampus and PCC (Pengas et al., 2012; Tu et al., 2015). In a recent study, using a reduced item version of the scene construction task developed by Hassabis et al. (2007), Irish et al. (2015) assessed scene construction for fictitious atemporal scenes in AD patients. Consistent with hippocampal damage patients, scene construction ability was strikingly compromised in the patient group, compared with controls. Patients produced significantly fewer content details in their descriptions, but further, their scores in a spatial coherence measure revealed that patients rated their imagined scenarios as spatially fragmented and more like a collection of images rather than a spatially coherent, integrated scene. Interestingly, AD patients and controls did not differ in their ratings of perceived sense of presence and salience, which is consistent with the findings from Hassabis et el. (2007) in hippocampal damage patients. As there were marked differences between groups across content measures in this task, without differences in reported presence and salience, this could reflect that scene construction differences between these groups are subtle in nature. Further, although one possibility to explain these findings could be that the subjective ratings of presence and salience are systematically

different somehow between groups. For example, because of amnesia, patients may remember their task performance less accurately, or they might not have access to the same rich detail of experiences to imagine.

Previous studies with amnesic patients have attributed scene construction impairments to damage and atrophy in the MTL, particularly the hippocampus (Hassabis et al., 2007; Race et al., 2011). In line with neuroimaging evidence of a core network underpinning scene construction and related processes, Irish et al. (2015) showed that grey matter integrity correlated with a more distributed network (including the hippocampus) in controls, compared to AD patients. In both groups, integrity of the PCC was implicated in scene construction performance in both AD and controls (see Figure 2.3). Therefore, in AD, damage to the PCC is likely to reflect the degeneration of a broader posteromedial network, within which, there is compromised connectivity between the PCC and hippocampus (La Joie et al., 2014).

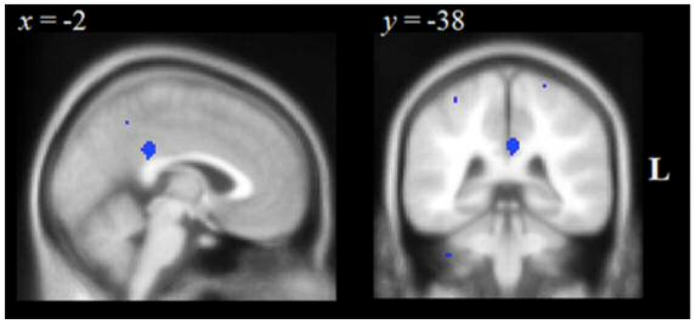

Figure 2.3: From Irish et al; (2015) Inclusive mask results following VBM analysis, showing overlap between AD patients and controls in brain regions associated with scene construction performance. Clusters overlaid on Montreal Neurological institute standard brain.

This convergence of behavioural and imaging evidence suggests atrophy in this core network in AD is not simply limited to detrimental effects on memory in a broad sense, but in fact, may be disrupt representations of space (or scene constructions), the underlying framework for rich episodic memory and future thinking. Functional alterations (failure to deactivate) the PCC of young APOE e4 carriers (who have an increased risk of developing AD later in life) on a scene perception task that is impaired in early AD have also previously been shown (Shine et al., 2015). Furthermore, smaller volume in the hippocampus in young adult APOE e4 carriers relative to non-carriers has previously been reported (O'Dwyer et

al., 2012). As outlined, the hippocampus is a key structure in this core network known to support spatial representations/scene construction (Hassabis et al., 2007). Crucially, these functional and structural alterations in APOE e4 carriers are strikingly consistent with the reported findings in AD and hippocampal amnesia, and beg the question as to whether young APOE e4 carriers might demonstrate analogous aberrant scene construction impairments. Early vulnerability to scene construction alterations could underpin later AD related changes across episodic autobiographical memory and future imagining.

This novel study aimed to investigate whether there were behavioural differences between young adult APOE e4 carriers and non-carriers in verbal scene construction. It was predicted that young adult APOE e4 carriers, compared with non-carriers, would have lower experiential index scores, reflecting richer, more spatially coherent imagined scenes in APOE e4 non-carriers. These predictions were based on the assumption that early functional and structural alterations in the core network underpinning scene construction (including the hippocampus and PCC) will impact the mental generation of rich and spatially coherent, complex imagined scenes.

2.2 Methods

2.2.1 Participants

44 female participants (N = 20 APOE e4 carriers/ N = 24 non-carriers, mean age= 19.8 years, range = 19-22) were recruited from a cohort of 84 undergraduate Psychology students at Cardiff University, for whom we had genetic information regarding APOE status (as described previously in Chapter 1, methods). Participants were awarded study participation credits for their time. As described previously, both the experimenter and participants were blind to APOE status during data collection and analysis.

2.2.2 Task procedure and materials

Participants were interviewed individually, and sat facing the experimenter. Interviews were digitally recorded for later transcription and coding. Task instructions were explained to the participant; that they would be presented with 7 verbal cues to ordinary

every day settings ('atemporal' – without of temporal constraint) and 3 verbal cues which required participants to think about themselves within a scenario in the future. Both conditions required participants to imagine scenes, however only the future thinking condition imposed a subjective sense of time (autonoetic consciousness, Tulving, 1985). For each item participants were instructed that they should take a few moments to imagine the setting, but should not recount an actual memory, instead creating something entirely new and imagining the setting 'in the mind's-eye'. They were required to describe what they could 'see, hear and feel, in as much detail as possible, as if they are actually present'. To ensure there was no bias in scene content, the items covered a variety of scenario settings, covering natural, man-made, busy and empty scenes (atemporal scenes: beach, museum, pub, fishing harbour, forest, street market, train station; future scenarios: next birthday, event this weekend, meeting a friend). Order presentation of items was randomised using an online randomisation calculator (www.randomizer.org).

Following each item, participants were asked to complete a series of self-rating measures, to 'assess quality' of each imagined item. These self-report measures included; 1) perceived difficulty (1-5, very easy - very difficult); 2) how much like a memory the imagined scenario was (1-5, not at all like a memory-exactly like a memory); 3) sense of presence (1-5, 'I did not feel like I was really there at all' - 'felt strongly like I was there'); 4) sense of salience (1-5, I could not really see anything' - 'extremely salient'). In addition, a further measure of spatial coherence of the imagined scenario (SCIQ) was obtained, which required participants to identify which of a set of 12 presented statements they felt described their imagined scenario accurately. Participants were not informed as to the specific purpose of this measure and its items. Of these 12 statements, 8 reflected an 'integrated imagined scene (items 2,3,5,7,8,9,10,12) and 4 reflected a 'fragmented' imagined scene (items 1,4,6,11), see Table 2.1 for items.

Table 2.1: Spatial coherence Index Questionnaire (SCIQ)

1. It was quite fragmented
2. I saw the scene in colour
3. It was similar to looking at a picture or seeing it on TV
4. I could see individual details, but it didn't all fit together as a whole scene
5. I would find it easy to answer questions about the scene
6. It wasn't so much a scene as a collection of images
7. I was able to use some senses other than vision e.g. sound, smell
8. I could see it as one whole scene in my mind's eye
9. I was able to think of details associated with the general theme
10. I would find it easy to give further details of the surroundings in the scene
11. It wasn't a scene you could step into; it wasn't really joined-up
12. I would find it easy to substitute an aspect of the scene for something else

2.2.3 Scoring

The content of each transcribed scene construction was coded for content, according to statements reflecting four categories. These included (1) spatial reference content, (2) describing explicit spatial measurements (e.g., "the room is about 10 metres wide"), (3) directions relative to the participant's vantage point (e.g., "in the corner to my right"), and (4) relative position of entities (e.g., "in front of the window"). Entity content was the described presence of any distinct entities present, such as a person or object within the construction. Sensory description content referred to any statements which described the physical properties of an entity (e.g., 'the floor is wooden', or 'I can feel the warmth from the sun'). Finally, the thought/ emotion/ action content category referred to any statements which described introspective thoughts (e.g., "I have a sense of being alone"), thoughts of others (e.g., "he is wondering why I am here") and intentions or actions of the self or other entities within the scene (e.g., "I am walking towards the bar" or "the man is walking towards the bar"). See Figure 2.4 for an example of scoring of categorization in an example transcribed item. Each production of content/statement for each category was assigned 1 point. Total scores for each category, per scene construction item, were then summed and each category production score capped at a score of 7, in accordance to the methods described by Hassabis et al (2007) whereby a score of 7 reflects sufficient descriptive production per item.

E: 'Imagine you are lying on a sandy beach in a beautiful tropical bay....'

SD SPA SD SD
P: I can feel the sand underneath me, it's warm it's quite quiet there, you can hear like a
SD SD
bird in the background, but, that's kind of it, there's no one else there. And you can sort of
EP SD SD
hear the sea, kind of gently coming in, and the sea is like bright turquoise, and the sand is
SD SD SPA
white and it's not like a big beach, it's a little one, maybe like ten meters across. To get to
TEA EP SD SPA
the beach you have to kind of, climb down this little cliff, it's not a big one, it's like a meter
SD SPA EP
and it's got grass on the top, and up there, there's like a couple of palm trees, and some
EP EP SD
bushes, and some other trees and like, strange fruit on it, that's red. Umm, yeah, the sun's
SD SD SD
out, the sky's really blue and there aren't any clouds.

Figure 2.4: An example of an item description from a participant. Scoring for this item: spatial references (SPA) = 4, entity presence (EP) = 5, sensory description (SD) = (15)7, thought/emotion/action (TEA) = 1. Total content score for this example = 17/28)

As previously outlined, after each construction item, participants provided a self-report quality score for sense of presence, with a rating from 1 - 5 (1, 'I did not feel like I was really there at all' - 5, 'felt strongly like I was there' and a sense of salience rating from 1- 5 (1, 'I could not really see anything' - 5, 'extremely salient'). For analysis, these scores were rescaled from 1 – 5 to 0 – 4. Therefore, each rating contributed a maximum score of 4 in the experimental index. In addition, participants were asked to rate the difficulty of each imagined scenario from 1 – 5 (1, 'very easy'; 5, 'very difficult') and similarity to an actual memory, in part or whole, from 1 – 5 (1, 'nothing like any memories'; -5, 'exactly like a memory'). These scores did not contribute towards the experiential index score, but instead were used to ensure participants were performing the scene construction task as instructed, to 'create something new', rather than recall a memory.

Developed by Hassabis et al. (2007), a spatial coherence index questionnaire (SCIQ) score also contributed to the experiential index, as previously outlined. This score reflects contiguousness and spatial integrity of the constructed scene. Following each scene construction item, participants were presented with 12 statements; 8 of which were qualitative descriptions of an integrated and spatially coherent scene (e.g., 'I could see it as one whole scene in my mind's eye') and the remaining 4 statements describing a fragmented

scene (e.g., ‘’I could see individual details, but it didn’t fit together as a whole scene’). Participants were instructed to simply select only the statements that described their imagined scenario, but they were not informed as to the purpose of the statements (i.e., fragmented versus spatially coherent descriptions). Of the possible 12 items, positive scores were assigned for integrated items and points deducted for negative items. Due to a greater weighting of integrated scores, possible scores were normalised around 0 (- 4 to + 8 = - 6 to + 6). Therefore, a maximum SCIQ score of + 6 contributed to the experiential index.

Each construction was also assigned a subjective quality rating by the experimenter, rated from 0 - 10, reflecting how well the scene construction description evoked a sufficiently detailed picture of the imagined scenario, in their own ‘minds-eye’ (0, no picture – 10, extremely vivid picture). In contribution to the composite score, this quality judgement was a maximum of 18, so the score assigned /10 was multiplied by a factor of 1.8, as 0 - 10 is arguably a simpler and more natural scale for subjective rating.

As described in Hassabis et al. (2007), all of the scoring elements were combined to create a composite score, where:

Composite score (/60) =

content (/28) +

self-report presence & salience (/8) +

SCIQ (/6) +

Quality judgement (/18)

2.3 Results

2.3.1 Experiential Index

Each sub-component of the experiential index was analyzed separately to investigate between group differences in scene constructions. Mean composite scores and mean scores for each sub-component of the experiential index can be found in Table 2.2.

Table 2.2: Means (and standard deviations) for scene construction performance in each episodic imagining condition, for each sub-component of the Experiential Index, according to APOE group.

	Atemporal Scene Constructions (M, SD)		Future Thinking (M, SD)		Total (M, SD)	
	e4 Carriers (N=20)	Non-Carriers (N-24)	e4 Carriers (N=20)	Non-Carriers (N-24)	e4 Carriers (N=20)	Non-Carriers (N-24)
Composite Score Total	33.41 (8.46)	34.66 (7.08)	29.61 (9.29)	30.81 (7.35)	32.36 (8.12)	33.49 (6.34)
Sub-components:						
Content						
Spatial References	2.04 (1.27)	2.26 (1.22)	1.00 (1.17)	.73 (.72)	1.74 (1.13)	1.79 (.97)
Entity Present	4.07 (1.39)	3.79 (.92)	3.75 (1.65)	3.66 (1.12)	3.99 (1.34)	3.73 (.89)
Sensory Descriptions	5.63 (1.09)	6.16 (.85)	3.51 (1.80)	4.50 (1.70)	5.07 (1.13)	5.64 (.93)
Thought/emotion/action	3.40 (2.08)	3.43 (1.83)	4.56 (1.92)	4.95 (1.80)	3.70 (1.99)	3.89 (1.70)
Content Total	15.15 (4.64)	15.66 (3.59)	12.51 (4.35)	13.58 (3.84)	14.40 (4.25)	15.01 (3.27)
Participant Ratings						
Sense of Presence	2.36 (.68)	2.30 (.56)	2.80 (.73)	2.51 (.93)	2.48 (.63)	2.37 (.62)
Sense of Salience	2.44 (.45)	2.48 (.46)	2.71 (.65)	2.72 (.79)	2.51 (.42)	2.55 (.45)
Ratings Total	4.80 (1.05	4.79 (.87)	5.51 (4.64)	5.25 (1.64)	4.99 (1.00)	4.93 (.98)
Spatial coherence Index	2.02 (1.65)	2.11 (1.71)	1.50 (2.41)	1.53 (1.99)	1.91 (1.62)	1.94 (1.52)
Quality Judgement	11.43 (3.29)	12.05 (2.97)	10.08 (4.23)	10.50 (7.35)	11.04 (3.51)	11.58 (2.92)

2.3.2 Composite scores and APOE status

To investigate composite scores and APOE status, a 2x2 repeated measures ANOVA was performed with condition (AT/FT) as a within subject factor, and APOE status (e4 carriers/ non-carriers) as a between subject factor. A significant main effect of condition was identified, $F(1, 42) = 12.67$, $p = .001$, with higher composite scores in the atemporal (AT) condition compared with the future thinking (FT) condition. There was not a significant main effect of APOE group $F(1, 42) = .31$, $p = .57$, and a significant interaction between composite score and APOE group was also not found $F(1, 42) = .00$, $P = .98$. Mean composite scores with condition collapsed, according to group are shown in Figure 2.5.

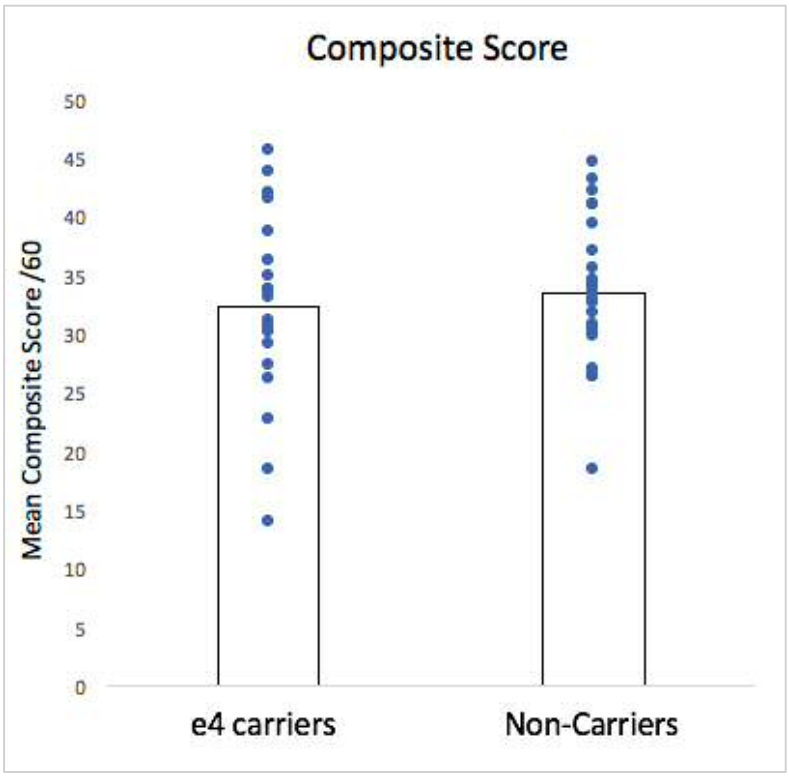

Figure 2.5: Mean composite scores for each participant in the scene construction task, according to APOE status, with AT/FT conditions collapsed.

2.3.3 Content

2.3.3.1 Content score

The 4 content category components of the experiential index were analysed separately, each with a 2X2 ANOVA, with condition (AT/FT) as a within subject factor, and APOE group as a between subject factor. Mean scores for each content category score, according to condition and APOE group, can be found in Table 2.2. Alongside analysis of content scores capped at 7 (as previously described in this chapter, in line with Hassabis et al., (2007)), exploratory analysis of total content produced was also carried out without capping the content scores at 7.

2.3.3.2 Spatial References

With content scores capped at 7 (Hassabis et al., 2007), there was a significant main effect of condition, $F(1, 42) = 61.67$, $p = <.001$, with fewer spatial references made in the future thinking compared to atemporal scene imagining condition. There was no significant main effect of group $F(1, 42) = .004$, $p = .94$. There was no significant interaction between condition and APOE group $F(1, 42) = 2.22$, $p = .14$, with means reflecting (non-significantly) fewer spatial references in the future thinking condition in non-carriers, compared with carriers, as shown in Figure 2.6. Similarly, without capping content scores at 7, there was a main effect of condition $F(1, 42) = 58.58$, $p = <.001$, no significant main effect of group $F(1, 42) = .005$, $p = .94$, and no significant interaction $F(1, 42) = 2.01$, $p = .16$.

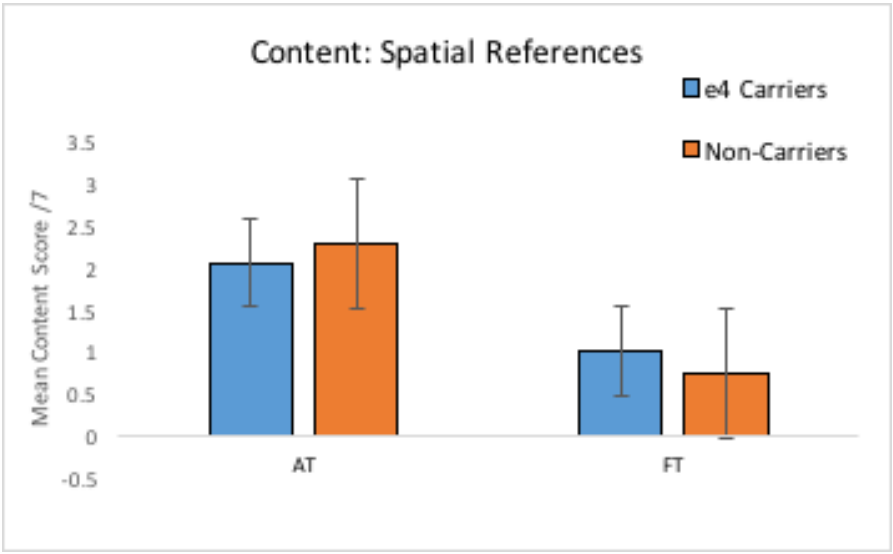

Figure 2.6: Mean scores for production of spatial reference details in scene construction content, for atemporal and future thinking conditions, according to APOE group. Error bars for standard error.

2.3.3.3 Entity Presence

With content scores capped at 7 (Hassabis et al; 2007), there was not a significant main effect of condition $F(1, 42) = 1.85$, $p = .18$. There was also no significant main effect of APOE group $F(1, 42) = .27$, $p = .60$, and no significant condition and APOE group interaction $F(1, 42) = .34$, $p = .56$. Similarly, without content capping at 7, there was no main effect of condition $F(1, 42) = 2.24$, $p=.14$, no main effect of group $F(1, 42) = .61$, $p = .43$, and no significant interaction $F(1, 42) = .22$, $p = .63$. Means are shown in Figure 2.7

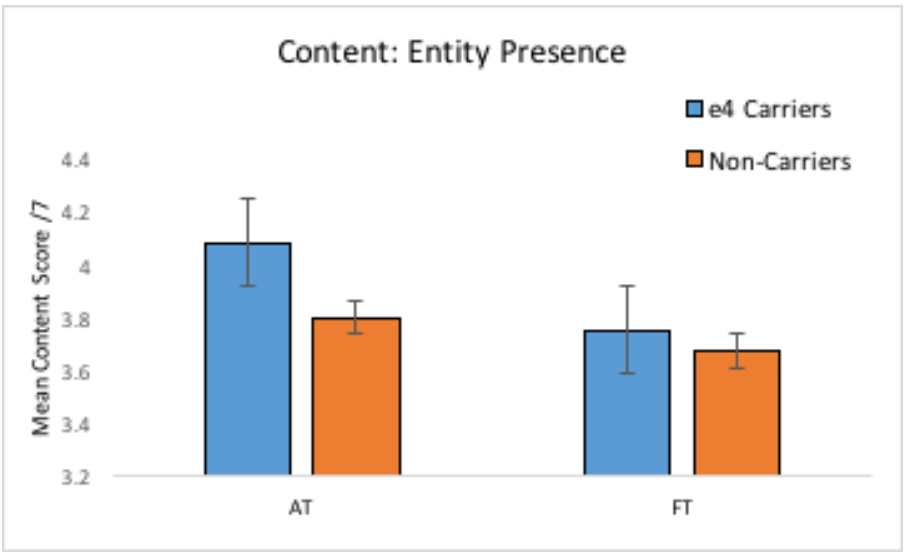

Figure 2.7: Mean scores for production of entity presence details in scene construction content, for atemporal and future thinking conditions, according to APOE group. Error bars for standard error.

2.3.3.4 Sensory Descriptions

With content scores capped at 7 (Hassabis et al; 2007), there was a significant main effect of condition $F(1, 42) = 63.82$, $p = <.001$, again with fewer sensory descriptions in the future thinking compared with atemporal scene imagining condition. There was a significant main effect of group $F(1, 42) = 4.46$, $p = .04$, with fewer sensory descriptions from e4 carriers compared with non-carriers. There was, however, no significant interaction between condition and APOE group $F(1,42) = .93$, $p = .33$. Similarly, without capping content at 7, there was a significant main effect found for condition $F(1,42) = 84.33$, $p = <.001$, a significant main effect of group $F(1,42) = 4.53$, $p = .03$, and no significant interaction between condition and group $F(1, 42) = .30$, $p = .58$. Means shown in Figure 2.8.

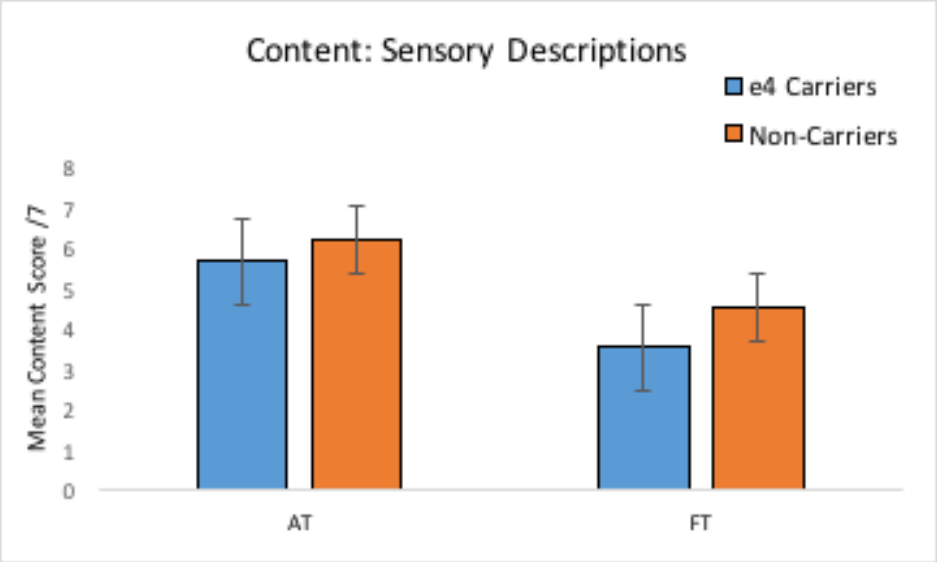

Figure 2.8: Mean scores for production of sensory description details in scene construction content, for atemporal and future thinking conditions, according to APOE group. Error bars for standard error.

2.3.3.5 Thought/Emotion/Action Content

With content scores capped at 7 (Hassabis et al; 2007), there was a significant main effect of condition $F(1, 42) = 49.55$, $p = <.001$. In this category, however, fewer TEA details were produced in the atemporal compared to future thinking condition (rather than the opposite, as for other content categories). There was no significant main effect of APOE group found $F(1, 42) = .15$, $p = .69$, and no significant interaction for condition and APOE group $F(1, 42) = .87$, $p = .35$. Similarly, without capping content scores at 7, a significant effect of condition was found $F(1, 42) = 34.86$, $p = <.001$, no significant main effect of group $F(1, 42) = .009$, $p = .92$, and no significant interaction $F(1, 42) = 1.29$, $p = .26$. Means are shown in Figure 2.9.

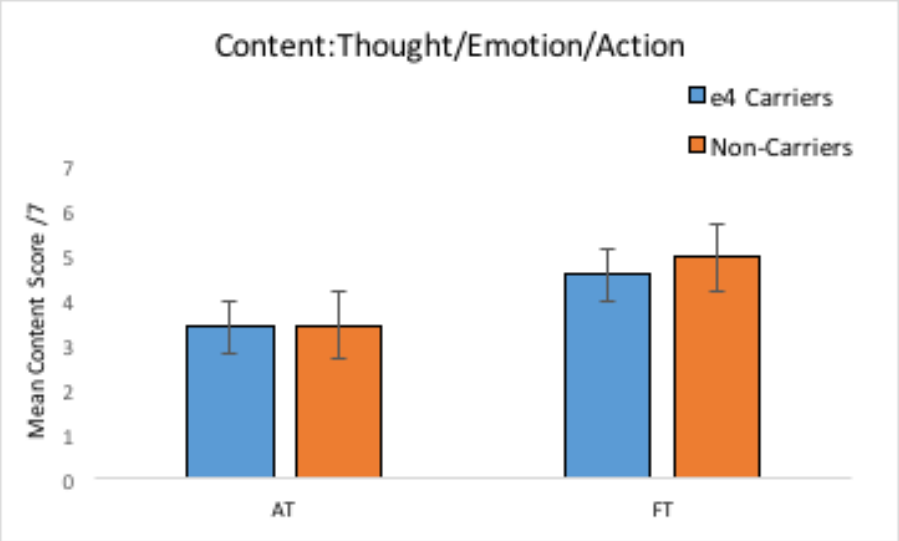

Figure 2.9: Mean scores for production of thought/emotion/action details in scene construction content, for atemporal and future thinking conditions, according to APOE group. Error bars for standard error.

2.3.4 Participant Ratings for Presence and Salience

To investigate APOE status in self-report ratings of sense of presence and sense of salience in scene constructions, A 2x2x2 ANOVA was performed with condition (AT/FT) and ratings of presence and salience as within subject factors, and APOE group (e4 carriers/non-carriers) as a between subject factor. There was no significant main effect of condition $F(1, 42) = 2.14$, $p=.15$. There was also no significant main effect of group identified $F(1, 42) = .19$, $p = .66$. There was a significant main effect of rating measure, $F(1, 42) = 9.27$, $p = .004$, with higher ratings for sense of salience compared with sense of presence. There was no significant interaction between condition and APOE group $F(1, 42) = 2.25$, $p = .14$, self-report measure and APOE group $F(1, 42) = .51$, $p = .47$, or condition and self-report measure $F(1,42) = 1.11$, $p = .29$. Means are shown in Figure 2.10.

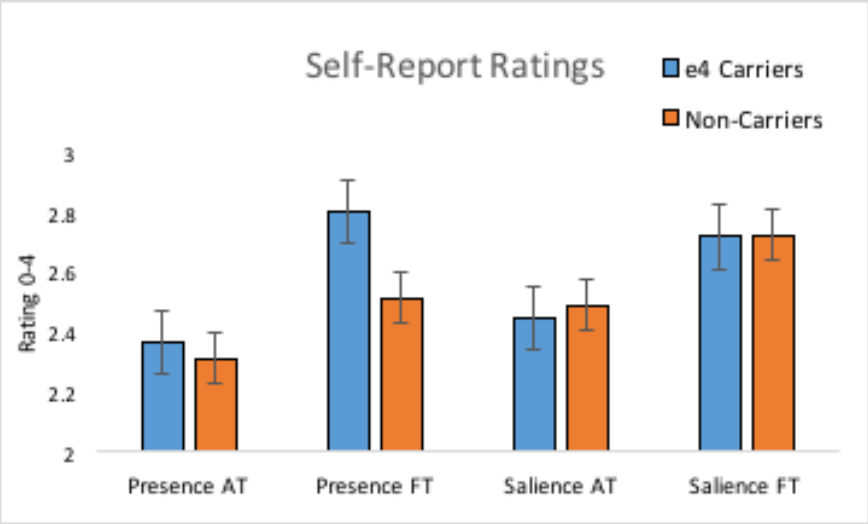

Figure 2.10: Mean self-rating scores for sense of presence and sense of salience for AT and FT conditions, according to APOE status.

2.3.5 Spatial Coherence Index

To investigate spatial coherence index scores and APOE status, a 2x2 repeated measures ANOVA was performed with condition (AT/FT) as a within subject factor, and APOE status (e4 carriers/ non-carriers) as a between subject factor. There was no significant main effect of condition found $F(1, 42) = 2.91$, $p = .09$. Neither was there a significant main effect of group $F(1, 42) = .01$, $p = .90$. No significant interaction between condition and APOE group was evident $F(1, 42) = .008$, $p = .93$. Means for spatial coherence scores with conditions collapsed, according to APOE status, are shown in Figure 2.11.

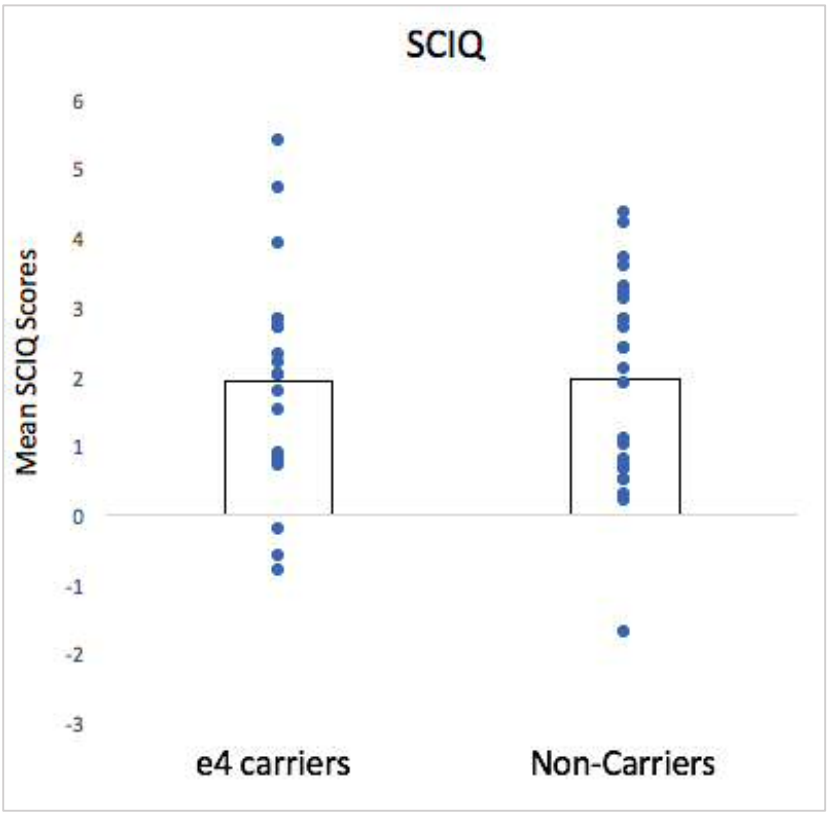

Figure 2.11: Means for spatial coherence index (SCIQ) scores with conditions collapsed, according to APOE status.

2.3.6 Experimenter's Subjective Quality Ratings

First, to investigate the relationship between the subjective quality rated by the experimenter and overall performance in other components of the composite score, quality ratings were correlated with composite scores which excluded quality ratings. A significant positive correlation was found, $r = .75$, $p = <.001$, suggesting that the experimenter's subjective ratings reflected the overall detail and richness of the scene constructions.

Second, to investigate whether there were between group differences in subjective quality ratings of scenario descriptions, a 2x2 ANOVA with condition (AT/FT) as a within subject factor and APOE group (e4 carriers/non-carriers) was performed. There was a significant main effect of condition $F(1, 42) = 30.24$, $p = <.001$, with higher subjective quality ratings for atemporal compared to future thinking scenario descriptions. There was no main effect of group $F(1, 42) = .27$, $p = .60$, and no significant interaction between condition and group $F(1, 42) = 1.15$, $p = .69$.

2.3.7 Self-Report Difficulty and Memory

Additional measures of 'difficulty' of scene imagining and 'likeness to an actual memory' were also obtained, which are not part of the composite score. Participants rated difficulty to imagine the scene and likeness to an actual memory from 1-5 (adjusted to 0-4 for experiential index), with higher scores representing greatest difficulty and greater likeness to a memory. Means can be found in table 2.3. A 2x2x2 repeated measures ANOVA was performed with condition (AT/FT) and rating (difficulty/memory) as within subject factors, and APOE status as a between subject factor (APOE e4 carriers/non-carriers). A significant main effect of condition was found, $F(1, 42) = 3.46$, $p = .001$, with higher ratings in the future thinking compared to the atemporal condition (means are shown in Table 2.3), indicating that participants found the future thinking condition more difficult to imagine and also more like a memory. A significant main effect of rating category (difficulty/memory) was not found $F(1, 42) = 3.90$, $p = .055$, with highest ratings for the memory-likeness ($m = 2.49$, $sd = .49$) compared with difficulty ($m = 2.48$, $sd = .56$). There was no significant main effect of group (APOE e4 carriers/non-carriers), $F(1, 42) = 2.34$, $p = .13$. There was no significant interaction between group and condition $F(1, 42) = 3.46$, $p = .07$, and there was no significant interaction between group and rating $F(1, 42) = .88$, $p =$

.35. A significant interaction was found for condition (AT/FT) and rating (difficulty/memory), $F(1, 42) = 27.86$, $p = <.001$. Inspection of this interaction showed that participants reported comparable difficulty ratings across both scene construction conditions, however for memory ratings, participants reported future thinking constructions as more memory-like compared with atemporal scene constructions.

Table 2.3: Self-report ratings for difficulty (0-4, very easy to very difficult) and likeness to a memory (0-4, nothing like to exactly like), for atemporal and future thinking scenario imagining conditions.

	Atemporal Scene Constructions (M, SD)		Future Thinking (M, SD)		Total (M, SD)	
	e4 Carriers	Non-Carriers	e4 Carriers	Non-Carriers	e4 Carriers	Non-Carriers
Difficulty	2.41 (.66)	2.67 (.53)	2.11 (.69)	2.47 (.91)	2.32 (.59)	2.60 (.51)
Memory	2.35 (.58)	2.17 (.42)	2.90 (.98)	3.22 (.75)	2.48 (.59)	2.49 (.41)

2.4 Discussion

In this chapter, a verbal scene construction task, previously used to demonstrate that AD and hippocampal damage patients have difficulties imagining spatially coherent fictitious scenes, was used to investigate whether there were early behavioural differences in scene imagination in young adult APOE e4 carriers. AD is a degenerative disease which is characterised by marked atrophy of the medial temporal lobe (including hippocampus) and posteromedial cortex (including PCC), brain regions integral for scene construction. The aim of this study was to investigate whether young healthy adults (~20 years old) at increased risk of developing AD later in life (via the presence of APOE e4) would show differences in their scene construction ability compared to non APOE e4 carriers. FMRI has shown altered functional activation (Shine et al., 2015; Filippini et al., 2009) in the hippocampus and PCC in young APOE e4 carriers, and reduced hippocampal volume compared to non-carriers (O'Dwyer et al., 2012). However, whether behavioural abnormalities exist in these young individuals is still inconclusive in APOE literature, but

it was hypothesised in this chapter, that cognitive alterations might potentially may be evident in verbal scene construction.

Composite scores in this study were found to be higher for atemporal scene constructions compared to future thinking scene constructions (shown in Table 2.2). In a previous study, Rendell et al. (2012) compared scene construction performance in older and younger participants, and similarly identified that composite scores were higher for atemporal compared to future thinking scenario imagination. This difference was found to be driven by lower composite scores in older adults in the future thinking condition. In the present study, no group differences were found in composite scores across either condition, or when these were collapsed. APOE e4 carriers and non-carriers performed similarly (as shown in Table 2.2 and Figure 2.5).

Composite scores in this study were comparably lower than control participants in Hassabis et al. (2007), they were effectively similar to that obtained for the amnesic patients. The scores obtained here were relatively similar, however, to the young participants in a further scene construction study by Rendell et al. (2012), where older participants' scores were much lower than those of the HC damaged patients in Hassabis et al. (2007). A comparison of these scores across studies suggests that control participants in Hassabis et al. (2007) were performing exceptionally well compared to all other participant groups across other studies. One explanation for this marked difference might be different tasks demands and context across studies. Perhaps younger, undergraduate students might be more self-conscious when describing what they can 'see' in their imagination, during a laboratory based interview. Although as much was done as possible to encourage participants to feel relaxed, in a non-judgemental environment, the amount of information and detail produced by older control participants in the study by Hassabis et al. (2007) is observably greater compared to the younger participants in the present study.

The difference between scenario imagining conditions in this study (e.g., between AT and FT) was not found to be driven by perceived difficulty, and there was also no difference between performance of the APOE groups for perceived difficulty. Across both conditions, however, difficulty was rated as moderately high, and notably, perceived difficulty was rated greater in this this study, compared to the older controls in Hassabis et al. (2007). A further rating of 'likeness to an actual memory' was obtained to check whether participants were adhering to the task instructions, creating something new, rather than recalling a memory. Scores were moderate, suggesting that participants were doing the task

as instructed. It was found, however, that participants rated imagined scenarios in the future thinking condition to be more like a memory, compared with the atemporal imagined scenes. In line with previous literature, this suggests that the future thinking scene imagining, rather than atemporal, may have relied on past episodic memories for scene constructions. It is argued that compared with atemporal imagining, future imagining is more explicitly relevant to the self, or self-projection (Rendell et al., 2012) and therefore, may be 'more like a memory'.

Participants' rated their sense of presence and sense of salience as comparably high for both atemporal scene construction and future thinking conditions, suggesting that they felt immersed within the scene for the imagined constructions. There were no differences found between e4 carriers and non-carriers for these measures. Notably, Hassabis et al. (2007) reported that these self-report measures were also high in both the hippocampal damage and control groups, with no differences between groups for either of these ratings, despite differences in content and SCIQ scores. The authors postulate that these comparable self-ratings across groups may somehow be systematically different between their groups, for example, that patients do not have the same volume of rich experiences to draw on. It may also be the case that the deficit identified in these patients, of fragmented scene construction, may be too subtle in nature to be reflected by sense of presence and salience, as these measures may not reflect spatial coherence. In the present study, it is not possible to make such inferences, however, lower hippocampal volumes in young adult APOE e4 carriers (O'Dwyer et al., 2012) are likely to be developmental rather than a result of atrophy, and still very little is known about how developmental hippocampal differences may effect cognitive functioning. With regard to sense of presence and salience in one's own imagination, this will be relative to the individual, especially in the case of developmental differences where a cognitive change is not sudden or lost (i.e. in the case of sudden brain injury).

In this study, APOE between group differences were not evident for the Spatial Coherence Index scores (SCIQ). Scores were moderate, and comparable in both atemporal scene constructions and future thinking conditions, indicating that overall, participants were describing their scene constructions to be spatially coherent rather than fragmented. Hassabis et al. (2007) previously found this measure to be particularly sensitive in patients with hippocampal damage (amnesia). These patients reported imagined scenes that were fragmented compared to control participants, with controls reporting scenes as spatially integrated and coherent. Further, Rendell et al. (2012) used the same task to investigate

effects of age in scene construction, and reported significant SCIQ score differences between younger and older participants for both atemporal and future thinking scene constructions. Given that our participants are aged ~20 years and control participants in the Hassabis study were much older than our sample, we might expect that due to normal patterns of age related cognitive decline, our younger sample would show greater scores in this measure than older individuals, perhaps more closely matching scores reported by Rendell et al. (2012) for young participants. In the present study, however, SCIQ scores were much lower than those obtained in the young participants in Rendell et al. (2012), suggesting that imagined scenarios were less spatially coherent across both groups in the present study compared with Rendell et al. (2012).

Teasing apart content scores by content category analysis revealed some interesting differences in content production between the two scene imagining conditions. First, higher content production in atemporal constructions was not uniform across all 4 content categories, which include; 1) spatial reference, 2) entity presence, 3) sensory descriptions and 4) thought/emotion/action. Spatial references and sensory description content was greater in the atemporal constructions, entity presence was matched across conditions, and thought/emotion/action content was greater in the future thinking constructions. Other than content of entities presence in the scenario, this pattern of content is markedly comparable to findings of Rendell et al. (2012) for young individuals. A possible explanation of these patterns could be that in atemporal scene constructions, there is no explicit, imposed subjective sense of time, and therefore participants may be more focused on external properties of the spatial framework, such as spatial relationships between entities, or sensory information about entities present and the imagined environment. The future thinking construction, however, explicitly involves a subjective sense of time and focus on the self, projected in time, within a spatio-temporal framework.

Future thinking has been described to perhaps rely partially on recall of past episodic details, which are then recombined and integrated into a coherent novel event (Addis et al; 2008), termed the constructive-episodic-simulation hypothesis (Schacter & Addis., 2007a; Schacter & Addis., 2007b). This explicit focus on novel episodic events in the future thinking condition, may naturally evoke previous episodic details which may be more initially focused on the self, explaining higher thoughts/ emotions and actions content in future thinking. This notion is further supported by findings in this study of higher self-report of likeness to memory for the future thinking condition compared to the atemporal

scene constructions. These scores, however, were still only moderate, suggesting that participants did not fully rely on memory for future thinking constructions.

Hassabis et al. (2007) found differences between patients and controls for each content category. In the present study, however, this was not the case. The only difference found between APOE e4 carriers and non-carriers was for the production of sensory descriptions, where fewer sensory descriptions were produced by APOE e4 carriers compared with non-carriers. Although this difference was not supported by any group differences self-report ratings of sense of presence or salience, as previously described, this may reflect developmental differences in the richness of imagined sensory experience, which may be relative to the detail individuals have access to. Further, given that damage to the hippocampus has been found to result in fewer sensory descriptions in patients' scene imagination (Hassabis et al., 2007; Maguire et al., 2010), it is possible that reduced access to sensory detail could reflect subtle, early, developmental differences in the richness of imagination in these young adults and could be an indicator of later life poor cognitive health. Further, although not significant, there was an observable trend for fewer content spatial references in APOE e4 carriers for atemporal scene constructions, but the reverse in the future thinking condition, with fewer spatial references for non-carriers compared with e4 carriers. Spatial references were also fewer for future thinking compared to atemporal scene imagining. A speculative interpretation of this trend could be that, given future thinking was found to be experienced as more like a memory than atemporal scenes (in both groups), young adult APOE e4 carriers have reduced access to the mentally generated relative positions of entities, directions or measurements that have not previously been experienced (less like a memory). Specifically, APOE e4 carriers may be more able to draw upon spatial content from previous experiences in order to imagine events within the future which are more like actual memories.

There was no difference between groups for subjective quality of imagined scenarios, rated by the experimenter. Subjective quality rating was identified as a factor which contributed to the difference between the two scene construction conditions, however, with atemporal constructions being rated higher quality than future thinking. These findings are consistent with those reported by Rendell et al. (2012), who suggested that individuals may find scene construction with an imposed sense of time more difficult compared to atemporal construction. In the present study, however, difficultly ratings were comparable across conditions. A possible explanation could be related back to the content category production, whereby it was found that more thought/emotion/action content was

produced in future thinking compared to atemporal, whereas the reverse was found for spatial references. This is perhaps interpreted in subjective quality by the experimenter, with higher quality ratings reflecting less introspective, and more physical descriptions in scene constructions in the atemporal condition.

FMRI studies suggest that in developmental amnesia, there is activation during scene construction in many of the same regions as controls, including the ventromedial prefrontal cortex, PCC and posterior partietal cortices (Mullally et al., 2014). These patients rate their scene constructions as more effortful compared to controls. These findings suggest a non-hippocampal dependent scene construction may be possible in developmental amnesia, which is mediated by semantic strategies which result in a less vivid visualisation of scenes. Importantly, as previously mentioned, acquired hippocampal damage patients may be more acutely aware of an ability that they have lost. This could be an important consideration in young APOE carriers, where smaller hippocampal volumes (as found by O'Dwyer et al., 2012), may be considered developmental. Subsequently, behavioural alterations in young e4 carriers may be incredibly subtle in nature and may reflect a non-hippocampal dependent strategy for scene construction. Future work could use functional imaging to further investigate non-hippocampal strategies in scene construction in these young APOE variant groups.

Previous studies have found functional alterations in the PCC in scene perception (Shine et al., 2015) and in the hippocampus during memory tasks (Filippini et al., 2009) in young adult APOE e4 carriers, with matched behavioural performance. Therefore, an interesting future direction for the scene construction work could be to investigate early functional alterations underlying scene imagination between these groups. The prediction in line with previous findings would be that we would see increased activation in the regions underpinning scene construction in APOE e4 carriers. This prolonged, increased functional activation of these regions, is hypothesized to be related to later life changes in cognitive functions supported by these regions, including the generation of complex, spatially coherent scene constructions, which underpins imagination of past and future events.

In conclusion, there may be subtle scene construction alterations in young e4 carriers compared to non-carriers, whereby less sensory detail is experienced and mnemonic strategies are adopted to imagine scenarios. However, the interview technique employed by this study may have not been sensitive enough to tap into these developmental group differences as subjective experience of scene imagination (e.g., richness/vividness) would

likely be comparable in these young individuals, who have not acquired any damage as a result of sudden injury, to the hippocampus or regions supporting scene construction. In the next study in this thesis, however, I will further probe scene representation ability in young adult e4 carriers compared with non-carriers, using a computerized scene perception task which measures scene representation ability through a perceptual illusion.

3 CHAPTER 3: Boundary Extension in Young Adult APOE e4 Carriers

3.1 Introduction

Our spatially continuous visual world is made up of an infinite set of 'snapshots' of complex, inter-related objects and backgrounds. Whilst our eyes are in motion, vision is suppressed (saccadic suppression (Volkmann et al; 1986)), with each fixation during visual scanning only offering a brief and partial view of a scene - and yet, we do not see the world as a collection of still frames. Precisely how the brain is able to overcome such physical limitations, and create a seamless experience of such a rich, meaningful, spatially coherent and continuous world, has long been a question which has evoked curiosity in perception research. Our visual experience is clearly not limited by these physiological constraints of visual sensory input. Instead, as our eyes move, there is rapid alteration between visual sensory perception, and access to an automatically constructed, internal representation of a scene, which is rapidly updated and maintained (Zeidman et al; 2015). This is a highly adaptive process, allowing us to perceive our world as spatially continuous, despite the fact that our visual sensory input is discontinuous.

In earlier perception and memory research, Hochberg (1978, 1986) described the experience of visual scene perception as much like viewing a moving display through an aperture. Despite not seeing a whole display at one time, viewers make sense of, and perceive the display, as a whole. Hochberg (1978) proposed that this is possible through rapidly integrating partial views with the use of a mental schema, which he described as an 'abstract representation' of spatial layout and major landmarks. This serves as a framework to integrate rapid partial views into a meaningful and understandable whole. Hochberg (1986) also pointed out, that due to the abstract nature of this spatial representation, finer sensory details are less well preserved. Therefore, there is much detail of the world which we do not actually experience. Further evidence to support this comes from research which shows that when objects or properties of a visual scene violate expectation of the content or properties of features within a scene, these can go completely unnoticed (Beiderman et al., 1982). Further, when inconspicuous items placed within a scene are changed for a different

item during a viewpoint shift (change of viewpoint of the receiver), these go unnoticed, even when returning to the original viewpoint with the new item (Simons, 1996).

After viewing a photograph of a scene, we tend to remember a greater expanse of the scene than we actually saw in the photograph. This well-established cognitive phenomenon is known as boundary extension (BE), and is argued to reflect the construction of an internal representation of a scene, which extends beyond the given physical borders (Gottesman et al., 1999; Mullally et al., 2012; Intraub et al., 1989). BE is described as a two-stage process; the first stage being constructive, because despite having visually presented information, we are not limited to this visual sensory input. Instead, we also experience the scene through an automatically constructed and maintained representation of what we have seen. This representation extrapolates well beyond given boundaries, in line with our expectations of a spatially coherent and continuous visual world (Gregory, 1968), forming a spatial framework in which a scene can be embedded. The second phase of BE occurs at retrieval, where BE is revealed behaviourally through what is also described as a subsequent memory error, where we 'misremember' the scene extended beyond the boundary of what we originally saw (Intraub et al., 1992).

For example, when a viewer sees an identical image of a scene for a second time, they tend to see the second viewing as closer up compared with the first. This is due to the restrictive boundaries of the second scene conflicting with their internal representation of the first scene, which has extended beyond the boundaries of the first image. In rapid serial visual presentation (RSVP) tasks, two identical scenes are typically presented sequentially, and participants are asked to indicate whether they think the second image is closer up, the same distance, or farther away than the first. Participants tend to report the second image as closer up compared with farther away, demonstrating BE (Intraub & Richardson., 1989; Intraub et al., 1992; Mullally et al., 2012., Kim et al., 2015; Chadwick et al., 2013). BE also occurs for mismatch views (close to wide angle and wide to close angle views), (Park et al., 2007; Czigler et al., 2013). When a second image is farther away than the first image, participants tend to misremember the image as the same as the first. They do not notice the change of extended visual boundaries for second image. This is because the extended boundaries of the second image, are more fitting with an internal representation which has already extended beyond the boundaries of the first image. When the second image is closer up than the first, the second image appears much closer up, with the closer view change exaggerated as the extrapolated boundaries are physically reduced. Neurophysiological and functional imaging studies support this behavioural asymmetry, with asymmetry in ERP's

mirroring wide to close and close to wide directional error (Czigler et al., 2013) and scene-selective attenuation in the parahippocampal place area and retrospenial cortex evident during the second stage of boundary extension (Park et al., 2007). Crucially, BE occurs only for scenes, and not for objects which are isolated (Intraub, 1998; Intraub & Gottlesman, 2002). Further, BE has been found to occur across all ages tested, from babies (Quinn & Intraub, 2007), to children (Seamon et al., 2002), and adults (Intraub & Richardson, 1989). This emphasizes the adaptive nature of scene perception, allowing us to effortlessly experience a spatially coherent and continuous world, from snapshots of visual information.

BE is a robust effect which is reliably found across many different measures other than RSVP tasks. These include, drawing tasks, where participants are presented with a scene and are then later asked to draw the scene from memory (shown in Figure 3.1, A). Participants tend to draw objects within the scene as smaller, and include more background information than they actually saw (Intraub & Bodamer., 1993; Mullally et al., 2012), (as shown in Figure 3.1, B). BE is also shown in haptic tasks, where blindfolded participants are presented with arrangements of objects into a scene to touch, presented within a fixed wooden border. The borders are then removed and participants asked to put the borders back in their original location using markers. This task has shown that participants have a tendency to put the borders back so that the scene is significantly bigger than the original size (Mullally et al., 2012). A computerized adaptation of this, a border-adjustment task, shows the same BE effect (Intraub, Hoffman et al., 2006). Collectively, findings across these different tasks all demonstrate extrapolation beyond the given boundaries of sensory input, forming a mental representation which is not restricted to presented borders, which becomes apparent as a memory error when we are presented with the image again and it is inconsistent with our internal representation. Moreover, BE is described to occur when the visual stimulus is disrupted for as quickly as $1/20^{th}$ of a second (Dickinson & Intraub., 2008), demonstrating that spatial extrapolation for very briefly seen images, is rapid enough to integrate successive views. The BE effect has also been found when tested ranging from minutes later, up to 48 hours later (Gottesman & Intraub., 2002; Intraub et al., 1992; Intraub et al., 1998., Intraub & Richardson., 1989; Mathews & Mackintosh, 2004).

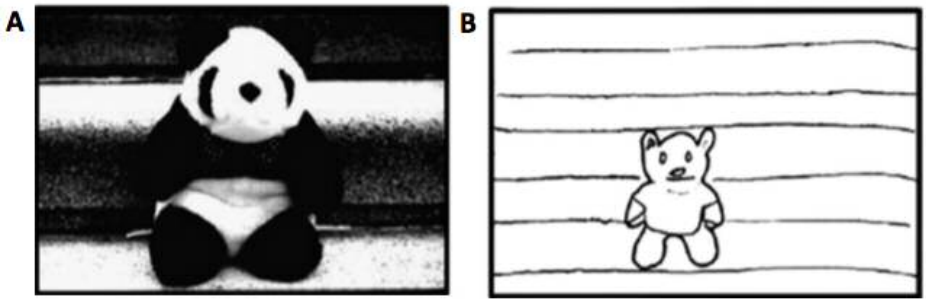

Figure 3.1: From Intraub & Gottesman, (1996). A) Image of an object in a scene; B) Drawing of the same scene from memory, moments after viewing.

As described in previous chapters, the hippocampus, in particular, is considered to play an integral role in constructing internal representations of the environment (Burgess et al., 2002; O'Keefe et al., 1978). Critically, these internal scene representations are not only important for remembering past events, but also vital for the imagination of fictitious and future scenes (Hassabis et al., 2007), and scene perception (Lee et al., 2007). Functional imaging studies have also found that the hippocampus is activated during the 'first stage' (previously described) of BE, demonstrating that this structure supports the extrapolation of scenes beyond visual boundaries (Chadwick et al., 2013; Bird et al., 2010), see Figure 3.2. Patients with hippocampal damage and concomitant amnesia have been found to be unable to imagine spatially coherent scenes (Hassabis et al., 2007). Further, patients with AD (a disease characterised by marked hippocampal atrophy, as well as involvement of other parts of the episodic memory network) demonstrate impairments in scene construction (Irish et al., 2015) and scene perception (Lee et al., 2007). Interestingly, hippocampal damaged patients have also been found to demonstrate attenuated BE effects (Mullally et al., 2012), although this has not yet been tested in AD. Mullally et al. describe their findings as a paradoxical memory advantage in these hippocampal damage patients compared to controls, whereby visually presented scene stimuli are reproduced more accurately to the spatial proportions of the original image viewed (Mullally et al., 2012).

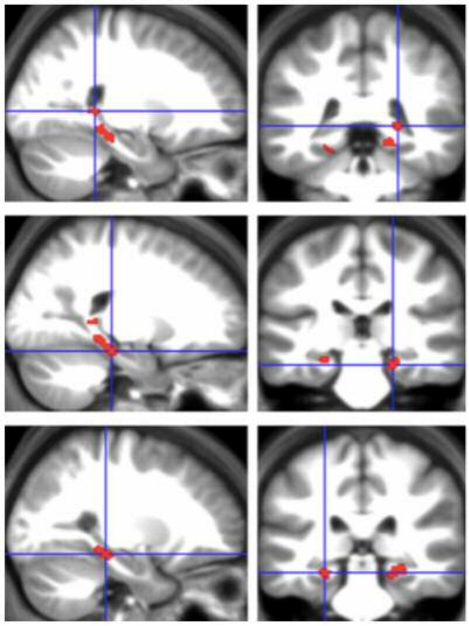

Figure 3.2: From Chadwick et al. (2013). Group average of activation during trials where BE occurred compared to trials where it did not, shown in the sagittal plane, left, and coronal plane, right. Increased engagement was found in the hippocampus during extrapolation of scenes beyond the view. Activity thresholded at p=.005.

This attenuated BE effect in hippocampal damaged patients has been shown across multiple BE tasks. Examples of these include a simple drawing task, whereby participants are briefly presented with an image of an object in a scene and are asked to draw the image from memory (as previously described). Healthy individuals show expected BE effects, whereby they draw the object within the scene much smaller than its presentation in the original image, and included more background information. Hippocampal damaged patients, however, produce a more accurate to-scale drawing, more comparable to the image as it was visually presented (Mullally et al; 2012), as shown in Figure 3.3, A and B. In repeated identical view RSVP tasks, where participants are unaware that every image is always identical ('the same'), healthy individuals rate a high proportion of trials as 'closer up' for the second image, as expected. However, again, hippocampal damage patients show attenuated BE effects in this task, with fewer BE effect 'closer up' responses and more correct 'same' responses, which patients rated confidently (Mullally et al., 2012), as shown in Figure 3.4.

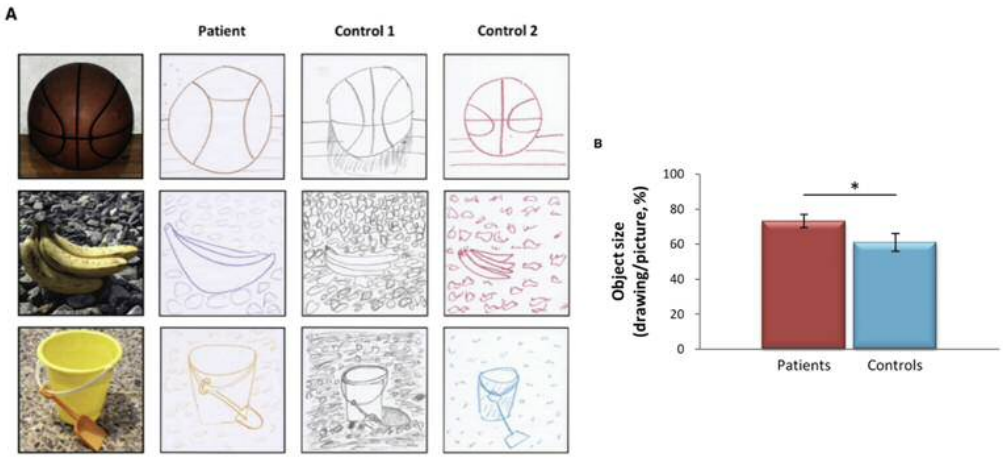

Figure 3.3: From Mullally & Maguire et al. (2012). A) Examples of BE drawing task stimuli from HC damage patients and controls. B) Results for HC damage patients and controls in this task, showing a significant difference between groups for accuracy (% size of object within the scene relative to object size in scene of presented stimuli).

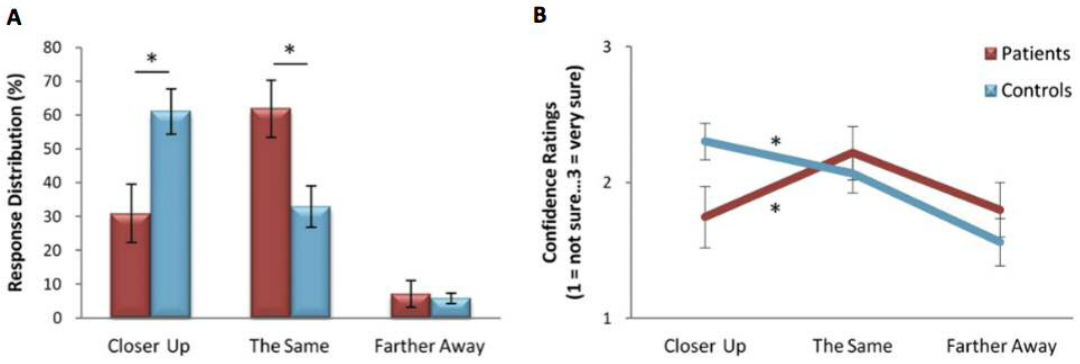

*Figure 3.4: From Mullally & Maguire et al. (2012). A) Proportion of trials classified as 'closer up', 'same' or 'farther away' in a BE RSVP task. B) Confidence ratings for each trial decision in the RSVP task (1= 'not sure', 2= 'fairly sure', 3= 'very sure'). *p = <.05.*

The aim of this chapter is to investigate whether young APOE e4 carriers, who are at increased genetic risk of developing AD later in life, and as reported by O'Dwyer et al. (2012), have reduced hippocampal volume compared to APOE e4 non-carriers, demonstrate BE differences compared to non-carriers. The paradoxical memory advantage as a result of attenuated BE reported in hippocampal damage patients, could be particularly interesting with regard to these young e4 carriers. The antagonistic pleiotropy hypothesis postulates an

evolutionary cognitive advantage of this allele in young individuals. There have been conflicting findings throughout the literature, as to whether this may be the case. Antagonistic pleiotropy does not affect all cognitive domains in the same way, and therefore discrepancies across findings likely reflects variation the of tasks of different cognitive abilities and categories of memory function (Tuminello & Han., 2011). In the case of BE, this task demonstrates how an advantage in one type of memory task, could be related to a restrictive disadvantage in representational ability. For example, Mullally et al. (2012) describe attenuated BE in hippocampal amnesic patients as a paradoxical memory advantage, given that they remember what they actually saw, rather than misremembering, as controls do in the BE illusion. In this study, I will measure BE using a rapid serial visual presentation task (RSVP), similar in method to the task previously used to study BE in hippocampal amnesic patients, described in Mullally et al. (2012). However, advancing upon this task, in line with conditions described by Park et al. (2007), further BE conditions (close to wide and wide to close views) will be included, in attempt to demonstrate behavioural differences between these groups across multiple BE conditions.

It is predicted that young APOE e4 carriers, compared to non-carriers will make more correct 'same' responses when the same stimuli are repeated identical (both for close-close and wide-wide) conditions. So, APOE e4 carriers will show an attenuated BE effect, similarly to previous findings in hippocampal amnesics (Mullally et al., 2012). I also predict that APOE e4 carriers will show relatively less boundary extension in the close-wide condition, reflected by an absence of the typical significant asymmetry which I expected to observe in non-carriers. These predictions are based on assumptions that functional and structural alterations in the network underpinning scene construction (including the hippocampus) in young APOE e4 carriers, will restrict generation of internal representations of scenes beyond the boundaries of the visual presentation, paradoxically improving visual accuracy for scenes.

3.2 Methods

3.2.1 Participants

32 Participants, (N= 14 e4/e3 carriers and N= 18 non-carriers, all e3/e3) were recruited from a cohort of 84 female undergraduate Psychology students at Cardiff University, in whom we had genetic information regarding APOE status, as detailed in Chapter 1 introduction, methods. Participants had normal or corrected to normal vision. As in all studies of this thesis, both the experimenter and participants were blind to APOE status. Participants were awarded Cardiff University Psychology course study participation credits for their time.

3.2.2 Task procedure and materials

3.2.2.1 Rapid Serial Visual Presentation (RSVP) Task

The RSVP task was programmed and presented to participants in Psychopy. Stimuli images included an object within a 'scene', with field-of-view controlled for. The tasks included four intermixed conditions;

1) a 'same' condition where a close-view identical image is both the study and test image;

2) a 'same' condition where a wide-view identical image is both the study and test image;

3) a close-wide, where the test image is a wider view than the study image;

4) a wide-close presentation, where the test image is a closer view than the study image.

Stimuli consisted of 48 'scenes', which formed 96 images; 48 close-view and 48 wide-view versions of the same scenes. Close-view images were created in Photoshop, by cropping the wide-view images by 15% and then resizing them to the same size as the original image (as described by Park et al., 2007; Czigler et al., 2013). The images were then randomly allocated to either a close first (24 scenes) or wide first (24 scenes) condition, and then divided again into the further condition beginning with that view. No two trials

contained the same image stimuli. Therefore, selected close images formed 12 CC and 12 CW trial-unique trials, and wide images formed 12 WW and 12 WC trial-unique trials, similarly to methods described by Park et al. (2007), and Czigler & Intraub. (2013). Objects within the scene for the close view images occupied approximately 45-50% of the scene, which has been described by Maguire and Intraub. (2015) to maximise BE. Each trial presented a 'study' image, for 500ms, followed by a masked interval of 2000ms, then a central fixation for 1000ms, immediately followed by the 'test' image (either: 1) 'identical close' to the study image; 2) 'identical wide' to the study image; 3) a 'closer' view than the study image; 4) 'wider' view than the study image), which required a self-paced response (RT measured). Participants then rated from 5 options, whether the second (test) image was; 'much closer up', 'a little closer up', 'same', 'a little farther away', 'much farther away' than the first (study) image. Next, participants were asked to rate their confidence in this response on a 3-point scale: 1 = 'not sure'; 2 = 'fairly sure'; 3 = 'very sure'; 4 = blank; 5 = 'did not see the image at all'. The 'blank' option was used to create a space between the 3-point confidence ratings and 'not seeing the image at all', to avoid the mistake of participants selecting the highest number as the highest confidence rating. An example trial is shown in Figure 3.5. Trials where participants reported not to see the image were removed from further analysis. Although not always used in BE task analyses, confidence ratings will be important for between-group analyses reported in the present study.

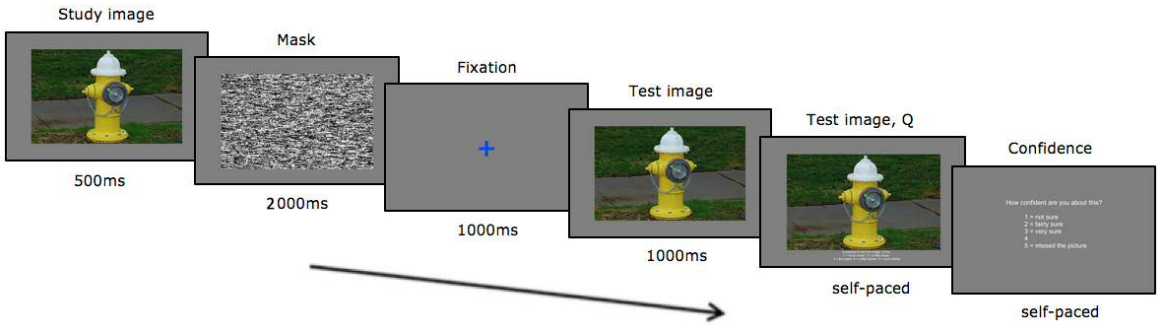

Figure 3.5: A time line of an example trial of the BE study created in this thesis, showing the study image, mask, fixation, test image and response screen presentations.

3.2.3 Memory Task

Participants also completed a memory task, immediately following the BE task. The memory task was presented in Power point and consisted of 48 images, 24 of which were stimuli from the BE task, and the remaining 24 stimuli were comparable images in terms of content and FOV, but were not seen during the BE task, which served as foils. Participants were instructed to work their way through the Power point presentation, scoring a '1' on their answer sheet if the image was 'old' (previously seen) or '2' if the image was 'new' (not previously seen). They also provided confidence ratings on their answer sheet, for each item, scoring '1' = not confident, '2' = fairly confident, '3' = very confident.

3.3 Results

3.3.1 BE mean scores

For each trial, BE scores were determined using the 5-point BE ratings, where 'much closer' was assigned a score of minus 2, 'a little closer' was assigned a score of minus 1, 'same' was a score of 0, 'a little farther' was a score of 1, and 'much farther' was a score of 2. From these scores, mean BE scores were then calculated for each condition. There were no outliers identified in the data (+/- 2.5 sd). No participants reported to have 'missed' the image on any trials, therefore, no trials were excluded from analysis. The expectation with regard to comparison of close-wide (CW) and wide-close (WC) conditions, was that there should be a larger difference from 0 on WC trials compared with CW. To further investigate this observable asymmetry shown in Figure 3. 6, WC scores, (which are all negative) were multiplied by minus 1, to invert them into positive values for comparison with positive scores in CW, using a paired samples t-test. As expected, the magnitude of the CW condition (m = .47, sd = .41) from 0, was significantly smaller than the WC condition (m = 1.46, sd =.27) ratings, $t(31) = -11.84$, $p = <.001$. One sample t-tests showed that both CW and WC scores differed significantly from 0 ($p <.001$), meaning in the CW condition, participants did not judge the test image to be the same as the study image when it was actually further away. The significant asymmetry observed in Figure 6, however, demonstrates a BE effect in this data.

Paired samples t-tests were also carried out for mean BE ratings for close-close (CC) (m = -.58, sd = .27) and wide-wide (WW) (m = -.51, sd = .29) conditions, t(31) = -1.30, p = .20. One sample t-tests identified that mean BE ratings in the CC condition were significantly different from 0, t(31) = -12.22, p = <.001. Mean BE ratings in the WW condition were also significantly different from 0, t(31) = -9.90, p = <.001.

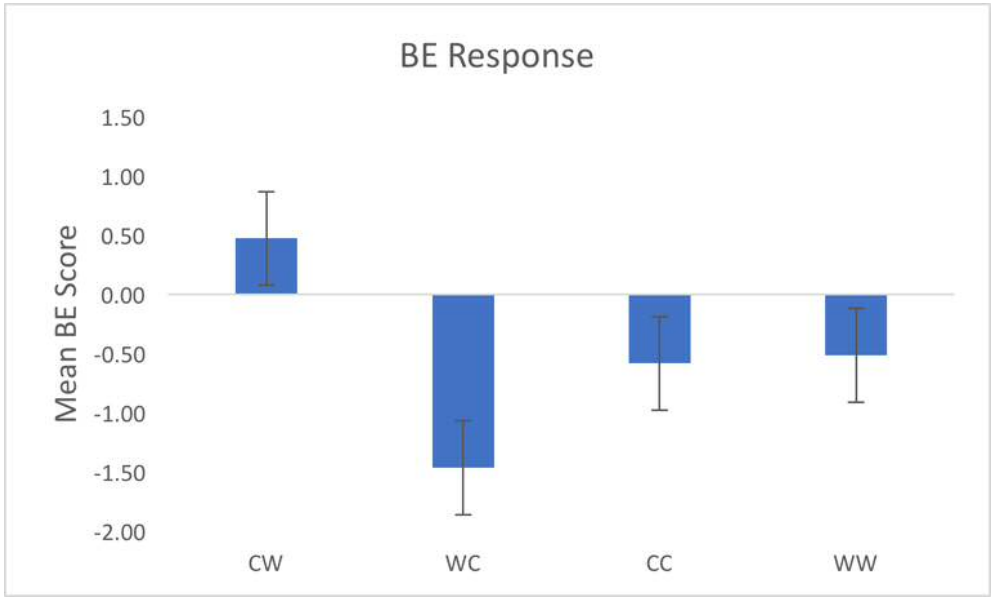

Figure 3.6: Group mean BE responses for each condition, close to wide view (CW), wide to close view (WC), repeated identical close view (CC), repeated identical wide view (WW).

3.3.2 BE mean scores and APOE e4 status

To investigate between group differences in APOE e4 carrier status for BE (e4 carriers N=14, non-Carriers N=18), a 2x4 ANOVA was performed, with group as a between subject factor and condition as a within subject factor. A significant main effect of condition was found (Greenhouse-Geisser corrected), $F(3,75.42) = 363.67$, $p = <.001$. No significant main effect of group was evident, however, $F(1, 30) = .00$, $p = .99$. There was also no significant interaction between condition and group, $F(2.51, 75.42) = 1.60$, $p = .20$. Means are shown in Figure 3.7.

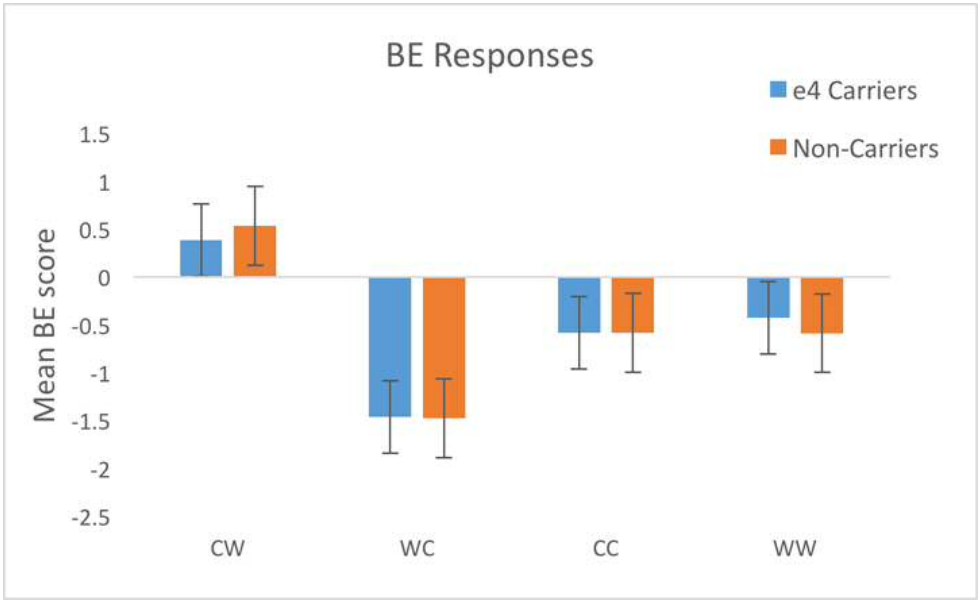

Figure 3.7: Mean BE scores for each condition, according to APOE status.

3.3.3 BE Reaction Times

Mean reaction times (seconds) were examined using a single factor ANOVA. There was no significant main effect of condition $F(2.08, 64.68) = 1.81$, $p = .16$. As shown in Figure 3.8, however, RTs were numerically fastest for the WC conditions, and slowest for CW, which is expected, in line with previous literature.

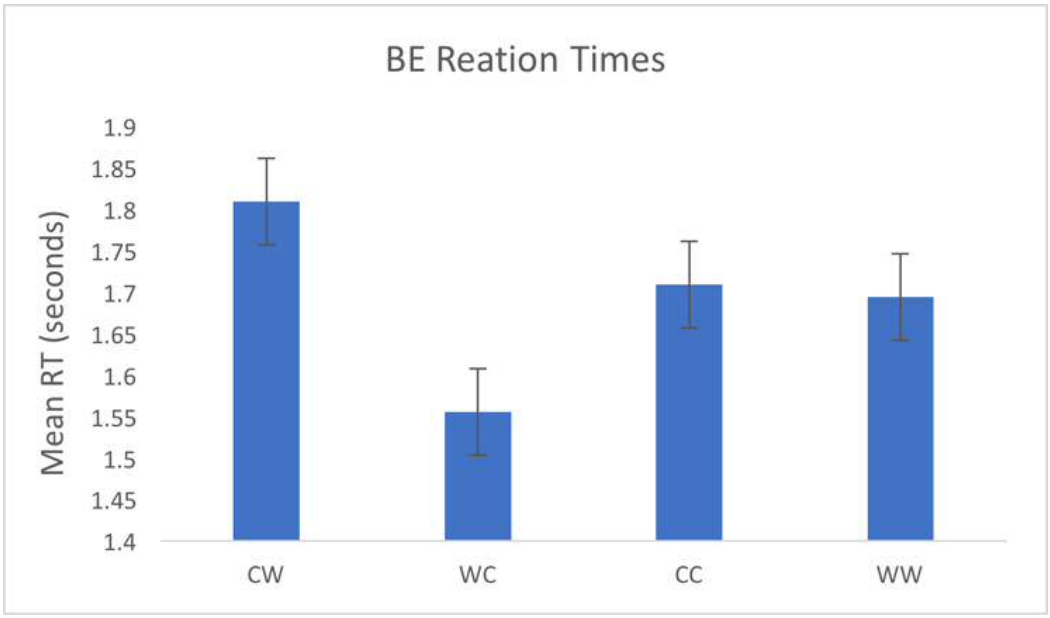

Figure 3.8: Group mean reaction time (seconds) for each condition, close to wide view (CW), wide to close view (WC), repeated identical close view (CC), repeated identical wide view (WW).

3.3.4 BE Reaction times and APOE e4 status

To investigate between group differences in APOE e4 carrier status for reaction times, a 2x4 ANOVA was performed, with group as a between subject's factor and condition as a within subject's factor. There was no main effect of condition ($F(2.12, 63.86) = 1.45$, $p = .24$, Greenhouse-Geisser corrected) nor of group $F(1,30) = .39$, $p = .53$. No significant interaction between group and condition was evident ($F(2.12, 63.86) = .32$, $p = .30$). Mean RTs are shown in Figure 3.9.

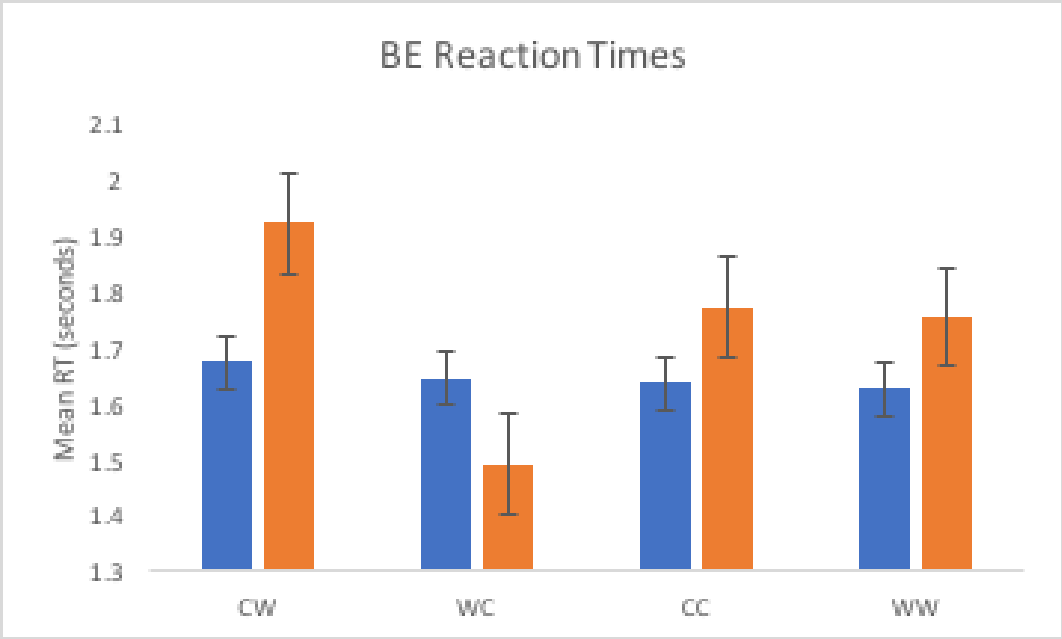

Figure 3.9: Mean reaction times (seconds) for each condition, according to APOE status.

3.3.5 BE Confidence Ratings

Overall, mean confidence ratings across the conditions were high 2.12-2.60/3, as shown in Figure 3.10. In line with previous studies (Czigler & Intraub., 2013), and participant feedback following the task, mean confidence ratings indicate that participants were most confident in their responses for WC, which is consistent with the view that the difference between views is most salient in WC trials. Mean confidence ratings for the 4 conditions (CW, WC, CC, WW) were analysed using a single factor ANOVA. A significant effect of condition was found ($F(3,93) = 38.91$, $p = <.001$), and results of pairwise comparisons (LSD) showed that WC mean confidence ratings were significantly greater than CW ($p = <.001$) and CC ($p = <.001$) conditions, and WW ($p = <.001$). Mean confidence ratings were also significantly higher for CW compared with WW ($p = .01$).

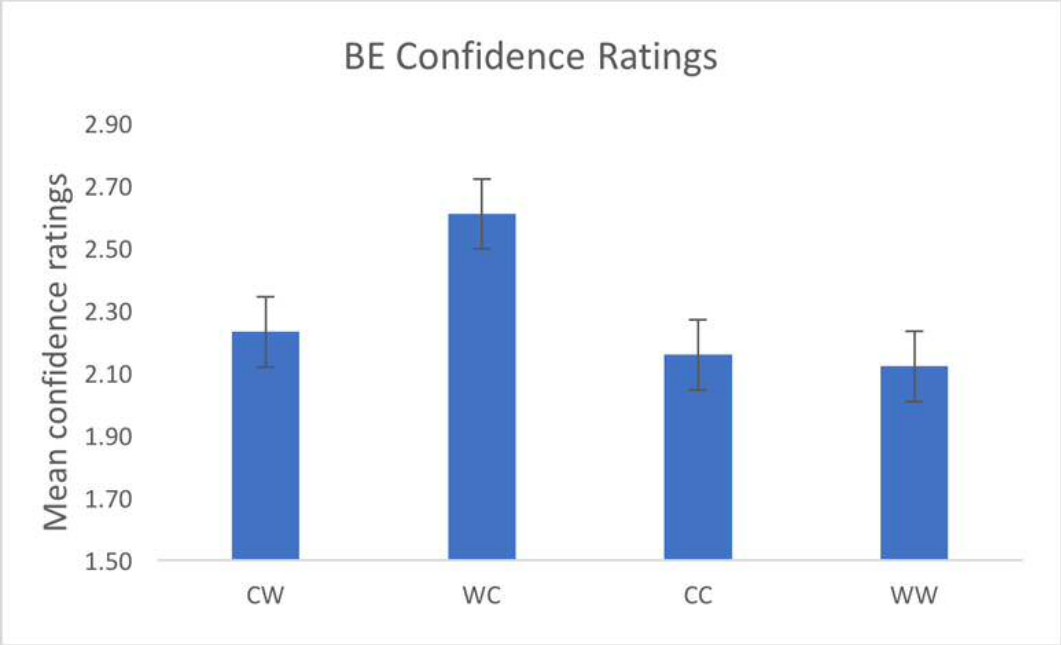

Figure 3.10: Group mean confidence ratings for each condition, close to wide view (CW), wide to close view (WC), repeated identical close view (CC), repeated identical wide view (WW).

3.3.6 BE Confidence Ratings and APOE e4 status

To investigate between group differences in APOE e4 carrier status for confidence ratings, a 2x4 ANOVA was performed, with group as a between subject's factor and condition as a within subject's factor. Again, there was a significant main effect of condition $F(3, 90) = 39.28$, $p = <.001$, in line with findings previously outlined above. There was no significant main effect of group $F(1, 30) = .45$, $p = .50$. There was, however, a significant interaction of condition and group, $F(3,90) = 2.98$, $p = .03$. Follow up investigation of this interaction found that it was driven by differences in the CC condition, where e4 carriers rated their responses more confidently ($m = 2.29$, $sd = .26$) compared with non-carriers ($m = 2.04$, $sd = .39$) $t(30) = 2.04$, $p = .05024$. Means are shown in Figure 3.11.

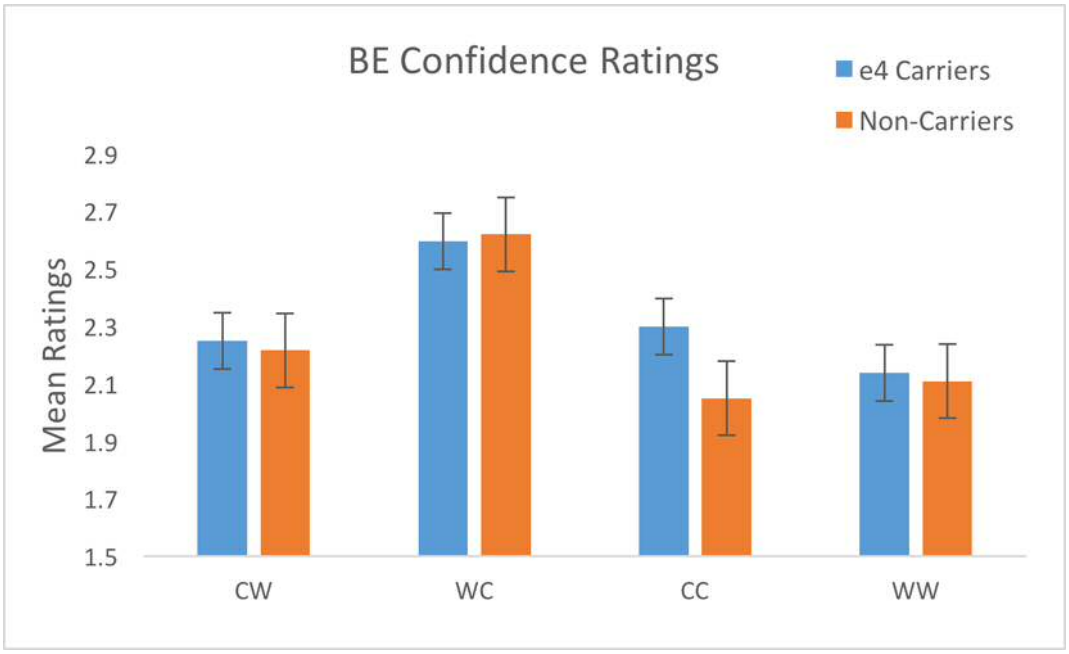

Figure 3.11: Mean confidence ratings /3 (1= not very sure, 2 = fairly sure, 3 = very sure) for each condition, according to APOE status.

3.3.7 BE Proportions

In addition to an asymmetry in BE mean ratings, it was expected that there would be a greater proportion of 'same' ('0') ratings for CW compared to WC. Proportion of BE ratings are shown in Figure 3.14, A & B. A paired samples t-test found that as expected, a significantly greater proportion of 'same' ratings was made for CW (m = .40, sd = 21) compared with WC (m = .05, sd = .10), t(31) = 8.55, p = <.001, demonstrating BE. Further, as reported by Czigler & Intraub (2013), it would be expected that proportions of 'closer' ratings in WC should be significantly greater than proportions of 'farther' ratings in CW. This effect can be observed in Figure 3.12, A & B. A t-test, with close and far conditions collapsed, confirmed that the proportion of ratings of closer for WC (m = .91, sd = .11) were significantly greater than the proportion of far responses in CW (m = .48, sd = .23), t(31) = -9.27, p = <.001.

For the CC and WW conditions (identical images for study and test), BE is demonstrated when participants rate the second scene as closer up than the first scene more often than they rated it as farther away. In Figure 3.14, C and D, it can be observed that the proportion of 'closer' (-2, -1) responses are much greater compared to 'farther' (1, 2) responses, in both CC and WW conditions. To investigate this, values in the closer ratings (-2, -1) were collapsed, and the same was done for farther ratings (1, 2). The CC and WW condition were examined separately. A paired samples t-test showed that in the CC condition, the magnitude of closer ratings (m = .53, SD=.19) was significantly greater than farther ratings (m = .03, sd = .06), t(31) = 13.07, p = <.001, as shown in Figure 3.14, C. This was also the case for the WW condition, with the proportion of closer ratings (m = .46, sd = .19) being significantly greater than farther ratings (m = .04, sd = .05), t(31) = 10.78, p = <.001, Figure 3.14, D. These results demonstrate BE in both of these conditions, with participants rating the second of two identical images as being closer up than the first.

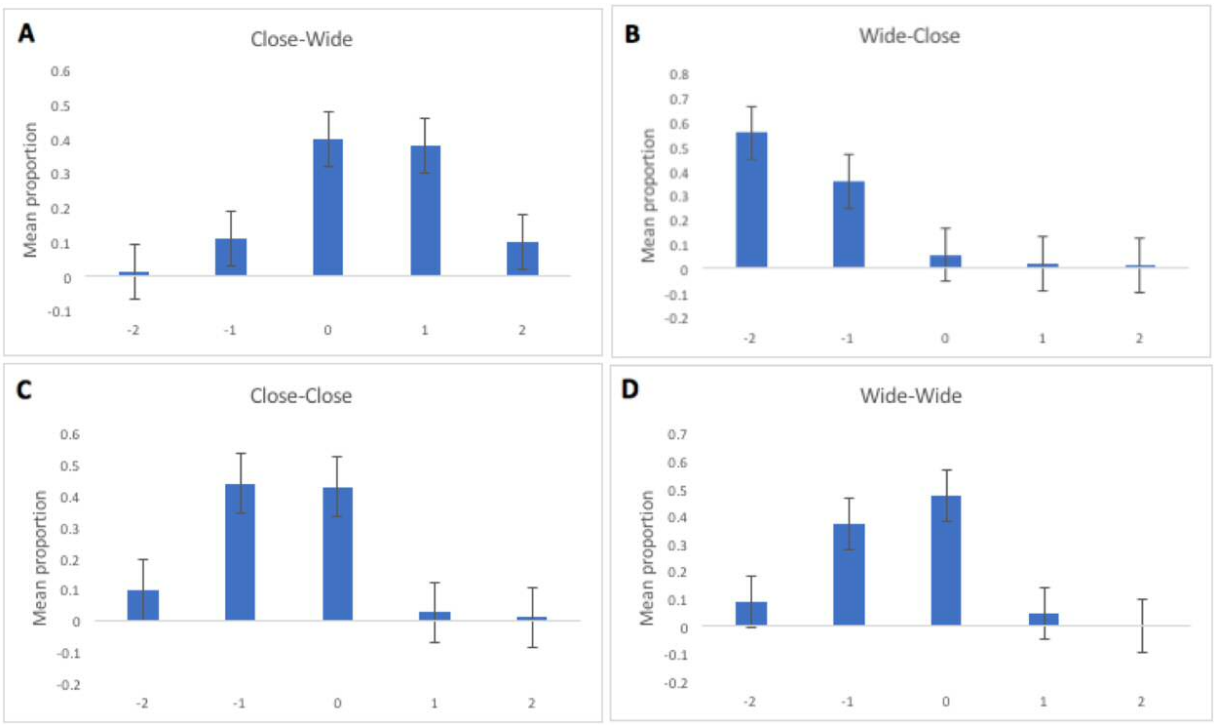

Figure 3.14: Group mean distribution of proportions for each of the conditions. For each condition participants rated the second image to be either '-2 = much closer', '-1 = closer', 0 = the same', '1= farther', '2 = much farther' compared to the first image they saw.

3.3.8 BE proportions and APOE e4 status

Following from the previous analysis, the next step was to investigate these proportion scores according to APOE status. A 2x2 repeated measures ANOVA was performed for 'same' responses in the CW compared with WC condition, with APOE status as a between subject factor. As previously described, there was a significant main effect of condition, as expected, $F(1, 30) = 70.81$, $p = <.001$. There was no significant main effect of group $F(1, 30) = .17$, $p = .67$, nor was there a significant interaction for group and condition, $F(1, 30) = .13$, $p = .71$. A further ANOVA was performed with APOE status as a between subject factor and CW 'farther' and WC 'closer' as within subjects. Again, a significant main effect of condition was found $F(1, 30) = 85.00$, $p = < .001$. No significant main effect of group $F(1, 30) = .005$, $p = .94$ was found, and there was no significant interaction, $F(1, 30) = .52$, $p = .47$. Means are shown in Figure 3.15.

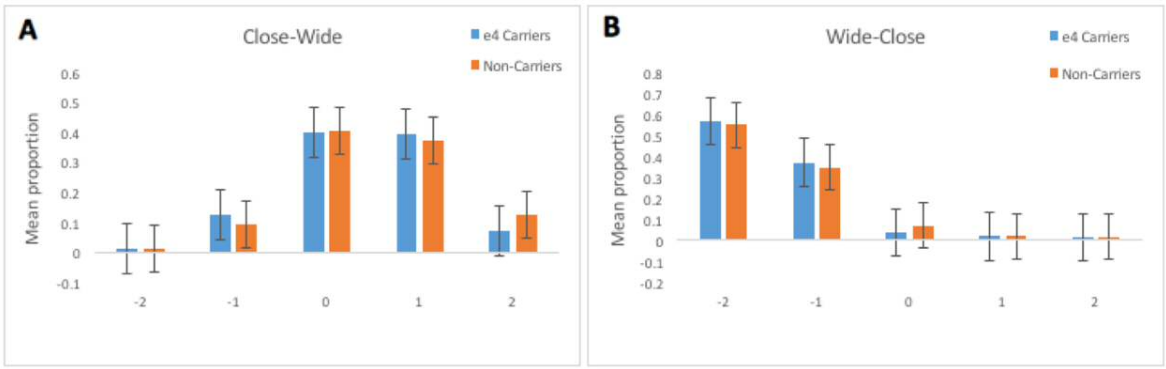

Figure 3.15: Group mean distribution of proportions for CW and WC conditions, according to APOE status. For each condition participants rated the second image to be either '-2 = much closer', '-1 = closer', 0 = the same', '1 = farther', '2 = much farther' compared to the first image they saw.

To investigate APOE status in CC and WW conditions, values in the closer ratings (-2, -1) were collapsed, and the same was done for farther ratings (1, 2). Each condition (CC and WW) was examined separately. Both groups exhibited boundary extension in both conditions, as evidenced by the test image being classified as 'closer up' more often than 'farther away' in CC (e4 carriers 52% vs .03% $p = <.001$, non-carriers 55% vs .04% $p = <.001$), shown in Figure 3.16, A, and WW (e4 carriers 41% vs .05% $p = <.001$, non-carriers 50% vs .05% $p = <.001$), shown in Figure 3.16, B.

In the CC condition, non-carriers correctly classified 41% of trials as the same. APOE e4 carriers correctly classified 45% of trials as the same. A 2x3 repeated measures

ANOVA was performed with APOE status as a between subjects' factor, and distance (closer, same, farther) as within subjects' factors. As previously identified, there was a significant main effect of distance F(1.18, 35.59) = 58.13, p = <.001. As shown in Figure 16, A, these was a numerical trend for e4 carriers to correctly identify the test image as the 'same' as the study image more frequently, compared with non-carriers. This was not statistically significant, however, with no significant main effect of group evident (F(1, 30) = .77, p = .38). No significant interaction of APOE status and distance was found F(1.18, 35.59) = .31, p = .61. In line with Mullally (2012), mean confidence ratings for each of the distance judgements were considered in this analysis. Again, close (-2, -1) and far (1, 2) conditions were collapsed for this analysis.

In the WW condition, non-carriers correctly classified 43% of trials as the same. In comparison, e4 carriers correctly classified 54% of trials as the same. A 2x3 ANOVA was confirmed a significant main effect of distance F(1.16, 34.88) = 52.94, p = <.001, but no significant main effect of group F(1, 30) = 1.44, p = .23. As shown in Figure 16, B, mean proportion scores show a trend in the data which is in line with Mullally (2012), with e4 carriers correctly identifying the test image as the 'same' as the study image more frequently, compared with non-carriers. Also, there was a trend for e4 carriers to judge the distance of the test image as closer than the study image, less frequently compared with non-carriers. There was, however, no significant interaction between APOE status and distance (Greenhouse-Geisser corrected), F(2, 34.88) = 2.23, p = .14.

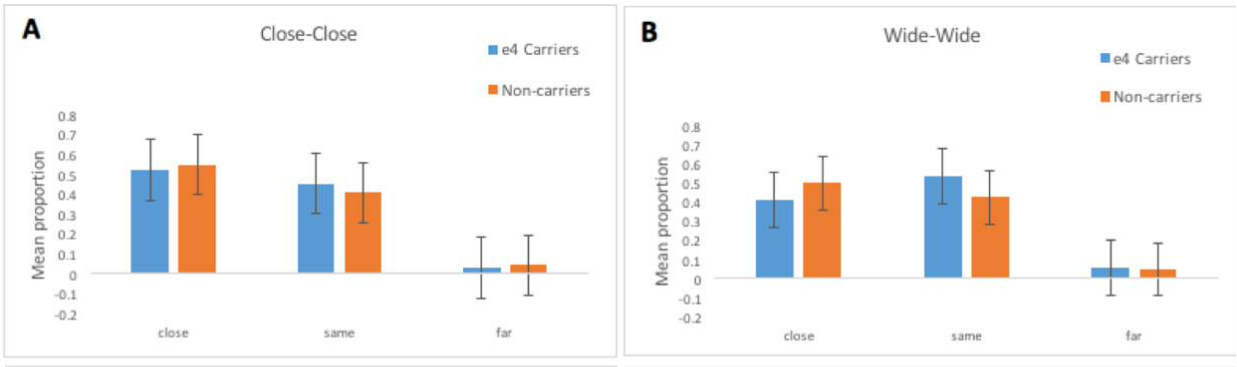

Figure 3.16: A) Group mean distribution of proportions for CC, according to APOE status, B) Group mean distribution of proportions for WW, according to APOE status. Closer ratings -2 & -1 are collapsed and classified as 'close', 0 = 'same' responses, and +1 & +2 are collapsed and classified as 'far' responses.

3.3.9 Memory Task Performance

An independent samples t-test found no significant difference between mean proportion of correct responses in the memory task for e4 carriers (m = .74, sd = .14) and non-carriers (m = .73, sd = .20), t(30) = .24, p = .80. Means are shown in Figure 3.17.

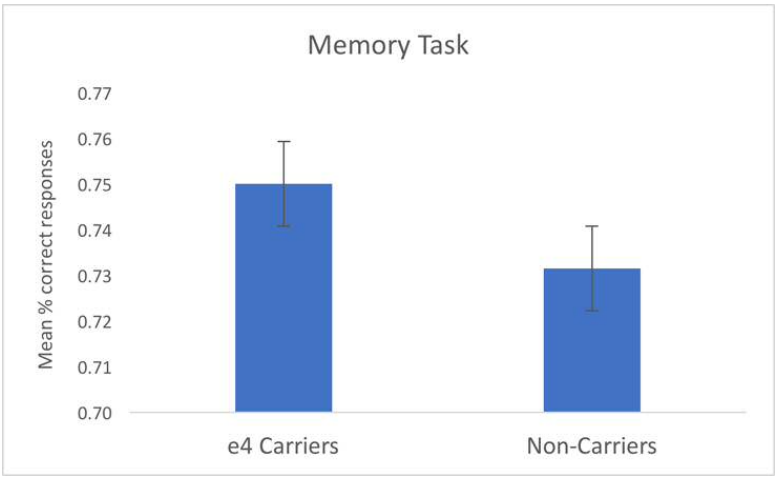

Figure 3.17: Mean % of correct responses in the memory task according to APOE status.

3.4 Discussion

The aim of this chapter was to investigate whether young APOE e4 carriers demonstrate behavioural differences in boundary extension (BE), a cognitive phenomenon, whereby healthy individuals consistently misremember a greater expanse of a scene than they were shown in a given view. Functional imaging studies in healthy individuals have shown that extrapolating beyond a given view during the BE effect recruits the hippocampus (Chadwick et al., 2013). Further, studies of patients with hippocampal damage have been found to exhibit attenuated BE, compared with healthy controls (Mullally et al., 2012). This finding was attributed to these patients having impairments in imagining spatially coherent scenes (Hassabis et al., 2007). Young adult APOE e4 carriers have previously been found to have smaller hippocampal volume compared with non-carriers (O'Dwyer et al., 2012). The question addressed in this chapter was whether healthy, young individuals with an APOE-e4 allele, known to have smaller hippocampal volume, but also, show altered brain activity in the hippocampus and its wide network for episodic memory and for scene

perception, would show subtle differences in the BE effect, potentially indicative of vulnerability in processing of scene representations.

Collapsing across APOE status, I found that the BE effect was observed across all task conditions. This was evident through an asymmetry in mean BE error between mismatch conditions (close to wide (CW) and wide to close (WC) trials), which is typical of BE. In CW views, participants frequently indicated that the view had not changed (in 40% of trials) even though the second image was farther away, and in WC trials, participants frequently reported the view as much closer than the first view they actually saw. BE was also demonstrated in both identical view conditions, close to close view (CC) and wide to wide view (WW), with participants frequently misremembering the second image as closer up than the first view (51% of trials for CC, and 41% of trials for WW). BE in the CC trials was numerically greater (but non-significantly) than WW trials. This is consistent with the existing literature which reports that CC trials, where views are more constrained, yield greater BE, with the effect found to decrease with wider angle views (Intraub & Berkowits., 1996; Park et al., 2007). Across all 4 conditions, the directional error of misremembering is in line with a BE effect whereby individuals extrapolate beyond the given boundaries of the view they are presented with and when presented with a second view, there is a discrepancy between their mental representation of the original view and the second image. Further, the fact that in the WC view condition, there was no boundary restriction, supports the idea that participants did not rely on a prototypic viewing distance of a scene, a finding which is in line with previous research which has also rejected a prototypic view hypothesis (Intraub & Berkowits, 1996). Participants were more confident on WC, compared to identical view (CC and WW) and CW view trials. This is consistent with the idea that the difference between the WC view is more salient than the identical view and the CW view trials. Reaction times are not typically reported in BE literature. They were obtained in the current study as a potentially more sensitive way to investigate between group differences relevant to APOE status. With APOE status collapsed, participants' reaction times to each condition were consistent with confidence ratings, with fastest reaction times in the WC trials, and longest reaction times in the CW trials, indicating that BE occurs more quickly when the view change is more salient.

When considering APOE status, it was found that both APOE e4 carriers and non-carriers exhibited BE, performing comparably across the 4 conditions. In particular, mean BE scores were mostly indistinguishable between groups in the mismatch (CW and WC) conditions, which are conditions that have not previously been considered in hippocampal

damage literature. In the CW condition, e4 carriers misremembered the scenes as no view change (BE effect) in 39% of trials, comparably with non-carriers who misremembered no view change in 40% of trials. Performance in WC trials was equally comparable. For the identical view conditions, although there was not a significant BE difference between groups, a non-significant trend was observed, particularly for the WW condition - which resembles previous findings in hippocampal damage patients, whereby patients show attenuated BE, correctly identifying repeated identical view trials as 'same' more frequently compared with controls (Mullally et al., 2012). In the WW identical view condition of the present study, e4 carriers correctly identified 54% of trials as the same, compared to non-carriers who correctly identified only 43% of trials as the same. Comparably, hippocampal damage patients misremembered only 30% of trials as closer up, in contrast to controls who misremembered 60% of trials as closer up (Mullally et al., 2012). In the current study, e4 carriers showed a similar pattern, misremembering fewer trials as closer up (41%) compared with non-carriers (50%). APOE e4 carriers have previously been reported to have smaller hippocampal volume compared with non-carriers (O'Dwyer et al., 2012). However, this is likely attributed to a developmental mechanism as opposed to acquired damage resulting in reduced volume. Although less available residual tissue during the progression of hippocampal atrophy observed in AD, may be detrimental in later life, the influence of significantly reduced hippocampal volume during development is not yet conclusively understood. Therefore, the same comparable degree of BE attenuation found in patients might not be expected in young, healthy, e4 carriers.

Confidence ratings were comparable between groups for CW, WC and WW conditions. For CC trials, however, e4 carriers rated their responses more confidently, compared to non-carriers, although this was not significant. Mullally et al. (2012) found that patients rated their responses more confidently than controls, and did so when the BE effect was absent (correctly identifying same responses), which they did so more frequently than controls. In the current study, however, e4 carriers (compared with non-carriers) rated their responses more confidently irrespectively of whether they correctly identified or misremembered the viewing distance. Intriguingly, e4 carriers had similar reaction times across all 4 conditions, despite non-carriers' reaction times varying in accordance with varying confidence ratings, which are likely to reflect differences in salience across conditions. This meant that in the 3 conditions considered the least salient, e4 carriers showed a trend towards faster reaction times, whereas in the most salient condition, e4 carriers showed a trend for a slower reaction time compared with non-carriers. This cannot

be explained by differences in BE effect across conditions as these were comparable between groups. Reaction times in this task were not found to be related to either BE scores or confidence ratings for either group. Reaction time is generally considered a more variable measure than accuracy, and here the differences between the groups was not considered to be significant and the sample size was relatively small, these findings do have implications for future investigation of processing speed and efficiency in the young e4 carriers, given that such differences may manifest as a cognitive advantage under some circumstances, but may be inefficient compared to non-carriers, in others.

It is interesting that the (non-significant) pattern in BE proportion scores in the present data, in line with findings of Mullally et al. (2012) was in the wide-angle condition. It is worth considering here, that the CC, rather than WW trials in the present study, are more visually comparable to the identical close-view scenes used in the study with hippocampal patients, with objects within the scene, occupying approximately 50% of the scene composition. Also, although BE was apparent in both CC and WW conditions, there was a greater BE effect in CC trials compared with WW. Wide-view scenes have previously been described to show a decreased BE effect compared to scenes which are closer up, which have a more restrictive view (Intraub & Richardson, 1989; Intraub et al., 1992). It is likely that this is because when you have a centrally located object within a scene in a wide-view image, where the object would be smaller compared with a close view scene, more of the expected information surrounding the object is actually present both in the image and the mental schema. When the object fills the picture (close-view), however, much of the expected surrounding space will not actually be presented in the image, but instead will be contained in perceptual schema which extends beyond the given boundaries. This would result in a greater BE effect for close view compared with wide view angles, as there is more information represented in the mental schema to misremember. So, it is interesting then, that in the present study, although BE was demonstrated in both identical view conditions, the effect was greater for CC compared with WW, and yet, the subtle behavioural trend towards attenuated BE in e4 carriers (which resembled Mullally et al. (2012) findings) was observed in the WW condition. It could be that when the BE effect is less salient, sensitivity to between group differences increases. Mullally et al. (2012) did not use wide-view trials, but it would be interesting to see whether their hippocampal patients would have exhibited further BE attenuation compared to controls.

A further point to consider when comparing the results of the present study with findings from Mullally et al. (2012), is the task design. In the present study, CW, WC and

WW conditions, which haven't previously been used in patient studies, were incorporated to demonstrate between group differences in BE across multiple conditions. It is possible, however, that interleaving these conditions may have led to clues about the directional change in each condition, reducing the BE effect, which may have attenuated between group differences. For comparability, and given that a behavioural pattern was observed in the repeated identical condition in line with Mullally et al. (2012), a future study could more closely replicate the task used in the patient study.

Attenuated BE in hippocampal patients compared to controls has not consistently been found in the literature. A BE study by Kim et al. (2015), also with hippocampal damage patients, failed to replicate the findings described by Mullally et al. (2012) using a repeated identical view RSVP task. The authors report that hippocampal patients and controls performed similarly, with both groups exhibiting BE (defined by more frequent closer up ratings compared to farther away). As evident in the Kim et al. (2015) study, however, was participants in both the patient and control groups correctly identified trials as the 'same' more frequently than they misremembered the trials as closer up, which is inconsistent with Mullally et al. (2012) and in the results presented in this chapter. Kim et al. (2015) did find however, patients to be impaired in a post-BE memory task (no difference was found between groups for memory task performance in the present study). The authors argue that these findings provide evidence that BE does not depend specifically on the hippocampus, and that the sole function of the hippocampus is in memory, rather than spatial cognition, despite compelling evidence from many other research groups that the hippocampus plays a role in scene memory, spatial navigation, scene perception and scene construction (reviewed in Maguire et al., 2013; Graham et al., 2010).

It is most likely that no significant between group differences were found in this chapter, because potentially at this age, it may be too early for behavioural abnormalities in e4 carriers to manifest, or alternatively, task sensitivity may not be sufficient to detect differences. This may be due to the addition of multiple conditions to test BE, but further, the sample size of this study may not have been sufficient to detect subtle between group differences in BE performance. In patient studies which used a similar BE task, hippocampal damage involved profound bilateral damage and therefore differences between patients and controls would be larger than expected in a young healthy genetic risk group. Mullally et al. (2012) used 7 patients with hippocampal damage and 12 controls, compared with the study in this thesis which used 14 e4 carriers and 18 non-carriers. Given

the trend for BE differences in the wide to wide view condition in this chapter, a larger sample size might be more sufficient to detect subtle between group differences.

The RSVP task used by Kim et al. (2015) yielded less BE in both participant groups tested, compared with the study in this chapter, and other tasks in BE literature (Mullally et al., 2012; Chadwick et al., 2013). It is possible that the task stimuli used by Kim et al. (2015) were not sufficient to elicit a strong BE effect. When investigating such between group differences for replication, it might be argued that the stimuli and task used should be as sensitive as the study which the results are being compared with. This would be particularly important in BE, because despite it being a robust effect, there is so much individual variability in BE error. Therefore, in such a small patient group with uncommon selective bilateral hippocampal damage, it would be important that task stimuli yield a large BE effect, comparable to previous patient studies, in order to sensitively investigate between group differences, if they are apparent. In the present study of this chapter, the measure of BE error falls in between that of Mullally et al. (2012) and Kim et al. (2015), so it could be argued that using stimuli which yields an even larger BE effect would be optimal for exploring whether between group differences exist in young e4 carriers and non-carriers. This could perhaps be enhanced by using fewer BE conditions, as previously discussed, given that paradoxically, the BE effect tends to be greater under circumstances typically associated with more accurate memory, such as small trial numbers and distinctive stimuli (Czigler et al., 2013). This point does however highlight a reoccurring criticism of the BE literature: that lack of standardization of methods limits comparability between studies and the subsequent conclusions which can be drawn from them.

In conclusion, young e4 carriers and non-carriers were found to both show comparable BE effects across all BE conditions, however in repeated wide-angle view trials, e4 carriers showed a non-significant trend towards attenuated BE compared with non-carriers, which resembles previous hippocampal patient findings. Because these individuals are young and healthy, behavioural differences in spatial cognition are likely to be subtle, if apparent at all. Therefore, the findings of the present study provide some indications aligned to tasks which might increase sensitivity to BE differences in future studies. These include using a single identical repeated condition, and increasing sample size (number of e4 carriers). Imaging could also be important in a future APOE BE study, providing understanding at a functional level regarding hippocampal contributions to BE effects in young carriers compared to non-carriers. There is evidence from imaging studies to suggest that functional changes may precede behavioural changes early in e4 carriers (Shine et al.,

2015; Filippini et al., 2009). Therefore, we might predict that even in the absence of significant BE attenuation in APOE e4 carriers, we would see increased hippocampal activation in e4 carriers, during the extrapolation of scenes beyond given borders. This may inform us of how possession of the e4 allele influences functional changes which may be indicative of later life poor cognitive health.

This idea leads into the next chapter of this thesis, where I will examine APOE-related scene-selective differences in the BOLD response, during an oddity perceptual discrimination task. This task has been shown to be sensitive to perceptual scene discrimination impairments in AD (Lee et al., 2006, 2007), but also Shine et al. (2015) have previously found a failure to modulate PCC activity in young APOE e4 carrier, compared to non-carriers, specifically for scene perceptual discriminations in this task.

4 CHAPTER 4. Oddity Judgements in Young Adult APOE e4 Carriers

4.1 Introduction

The prior experiments in this thesis (focused on scene construction and boundary extension) did not identify statistically significant evidence of early behavioural changes in young adult APOE e4 carriers. The rationale for these studies was to investigate whether sensitive behavioural paradigms, stressing complex scene processing, could induce subtle behavioural differences in young adult APOE e4 carriers compared to non-carriers. Scene-selective visual discrimination deficits have previously been identified in AD patients (Lee et al., 2006; Lee et al., 2007). For example, Lee et al. (2006) presented computer generated scenes and faces to patients. For each trial, participants were presented with same-category arrays of four images, which included three images of the same scene or face, and a fourth image which was a similar, but different scene or face (see Figure 4.1, 1). One condition presented arrays where images were shown from the same viewpoint; another condition presented items from different viewpoints, and was designed to stress integration of information across the scene. Participants were asked to identify the 'odd one out' in the array of images. Compared with controls, AD patients were impaired specifically in scene discrimination, with their performance in face discrimination matched to that of controls. Further, this impairment was evident regardless of viewpoint (see Figure 4.1, 2). Importantly, in this same study, patients with another form of dementia, semantic dementia (which affects the temporal lobes and leads to a rapid loss of semantic knowledge about the world), demonstrated impairments in face discrimination, but showed normal performance on scene discrimination (as shown in Figure 4.1, 2). Both of these dementias are associated with widespread neurodegeneration (including within the MTL) (Chan et al., 2001; Galton et al., 2001). However, AD is characterized by extensive lesions within the entire hippocampus but less so in the perirhinal cortex, whereas in semantic dementia patients, there is typically greater loss of volume in the perirhinal cortex and less so in the hippocampus (Davies et al., 2004, 2005). Therefore, the findings of this study present a double dissociation where differing profiles of MTL atrophy in these patient groups, impact

different categories of perceptual discrimination, with hippocampal damage resulting in scene impairments, and perirhinal damage, in face impairments.

1. 2.

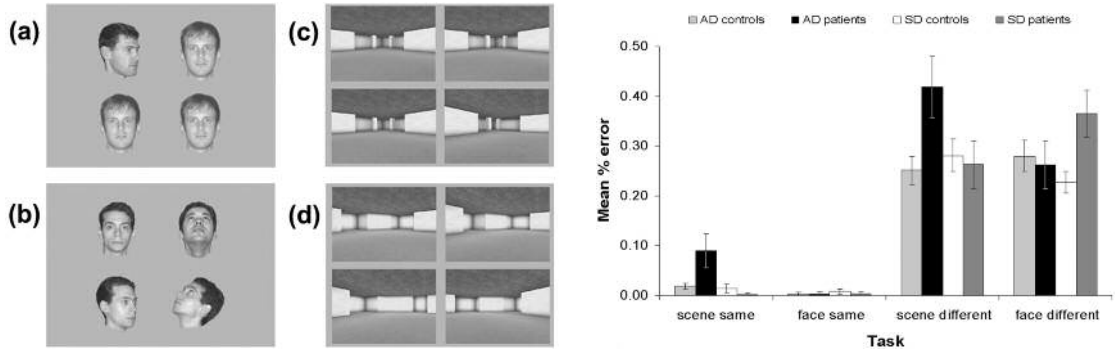

Figure 4.1: From Lee et al. (2006). 1) Example of one trial for a) face same viewpoint, b) face different viewpoint, c) scene same viewpoint and d) scene different viewpoint, in the oddity task (Lee et al., 2006). 2) Means % error and standard error bars for the 4 participant groups for the different oddity conditions.

These findings of a scene-sensitive visual discrimination impairment in AD (Lee et al., 2006) were further replicated using a concurrent discrimination learning paradigm (Lee et al., 2007). The task stimuli in this study included pairs of distinct images of scenes, objects, faces and colour blocks. One item was dedicated the target item while the other was the distractor, see Figure 4.2, 1. for an example trial. Participants were required to discriminate between these pairs of stimuli over successive trials. The stimuli were morphed together providing multiple levels of feature overlap (from low to high), thereby increasing difficulty of the visual discrimination between pairs. Again, relative to controls, AD patients were impaired in discriminating between the scene items (see Figure 4.2, 2), even at the lowest level of morphing where the feature overlap was lowest. Performance for the face, object and colour discrimination items was matched with controls, even at the highest morphing level where feature overlap was greatest. As for the first Lee et al. (2006) study, the performance of AD patients was compared with patients with semantic dementia. They showed a different profile of performance to the AD patients, showing difficulties on face discrimination but not scenes.

1. 2.

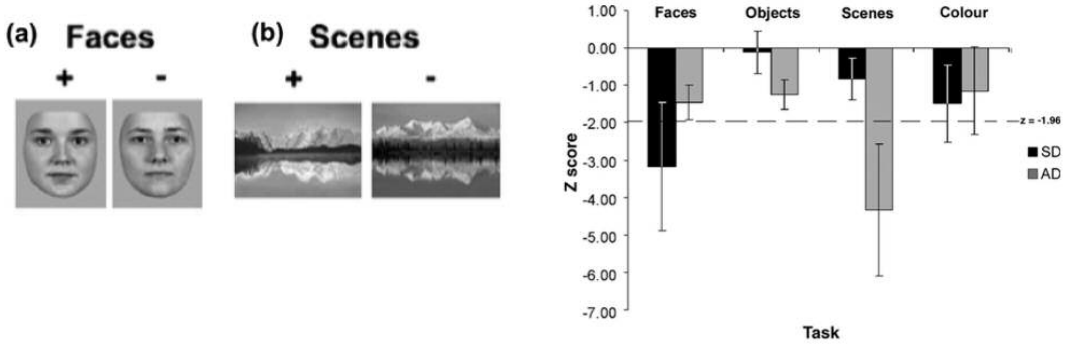

Figure 4.2: From Lee et al. (2007). 1) Example from one trial for a) faces and b) scenes (+ = correct stimulus, - = incorrect stimulus) from the discrimination task. 2) Results showing a z score plot for the two patient groups (AD and SD) compared to the control group for the 4 conditions (scores beyond z=-1.96 indicate significant impairment).

As previously discussed in this thesis, some of the earliest pathological changes in AD occur in the medial temporal lobe, particularly the hippocampus and entorhinal cortex, (Braak & Braak, 1993, 1995). Early changes in AD are also observed, however, in posteromedial regions, including the PCC. For example, abnormally low rates of glucose metabolism have been reported in the PCC of young adult APOE e4 carriers, compared with non-carriers (Reiman et al., 2003). The PCC is a heavily interconnected structure, serving as a key region in the 'default network' (DN), a network which shows greater BOLD activation during 'rest' (e.g., in the absence of a task). The PCC is also implicated in regulating the focus of attention (Gusnard et al., 2001; Hampson et al., 2006), retrieval of autobiographical memories, future planning and scene construction (Addis et al., 2007; Irish et al., 2015). It is also thought to support internally directed cognition (Raichle et al., 2001; Buckner et al., 2008). There is, however, no clear consensus about its function (Leech et al; 2012). Prolonged increased activity in the PCC has been linked to increased amyloid deposition (Jagust et al; 2011), and maybe a potential early cause of the brain atrophy and pathological changes associated with AD. Voxel based morphology (VBM) analysis based on structural MRI, has described the PCC to be associated with performance in scene construction in both AD patients and controls (Irish et al., 2015). This finding highlights the importance of the role of the PCC for scene construction, and suggests the role of PCC

degeneration in AD related impairments. However, early PCC changes in APOE e4 carriers that may be related to later life poor cognitive health, have been less explored.

In a recent fMRI study, Shine et al. (2015) used a similar oddity visual discrimination paradigm as previously used by Lee et al. (2006) in AD. Shine et al. were interested in investigating whether there would be underlying early functional alterations in young adult APOE e4 carriers, specifically related to scene stimuli but not to other complex visual categories (e.g., faces and objects). Stimuli in this study were three-choice arrays of natural outdoor scenes, faces, and objects. Two images in each array were of the same scene, face or object, presented from a different viewpoint, and the third image was similar but of a different scene, face or object. A further condition involved presenting three squares in the array, two of which were identical while the other third square was a different size (size oddity). The participants performed the task in the scanner and were asked to identify the odd one out stimulus in each array. In these young adult e4 carriers, compared with non-carriers, an increased BOLD signal was identified in the PCC during scene oddity judgements, but not while performing face, or object decisions (comparable levels of deactivation were shown for faces and object conditions). Given that the PCC is a central part of the DN (Buckner et al., 2008), the scene-sensitive increased PCC activity found by Shine et al. was interpreted as a failure to effectively modulate (deactivate) PCC activity during scene processing in these young e4 carriers. Moreover, behavioural performance in this task was matched across groups. This study by Shine et al. (2015) is novel, given that previous task related BOLD alterations in young e4 carriers (i.e. Filippini et al., 2009; Suri et al., 2014), have not been interrogated in relation to whether they are cognitively specific to different stimulus categories (scenes, in particular, aligned to the vulnerability of this form of cognition in AD). These findings are consistent with the idea that APOE e4 carriers may have prolonged over-activation in posteromedial cortex regions, such as PCC, from earlier on in life. This may, in turn, be associated with increased amyloid deposition over time, eventually resulting in impairments in cognitive processes supported by this region (e.g., complex scene processing and navigation within environments).

The BOLD signal is described as an indirect measure of underlying neuronal activity, and relies upon many factors including baseline perfusion state, cerebral blood volume, vascular compliance, and coupling relationships between these measures (Buxton et al., 2004; Iadecola et al., 2004; Iannetti & Wise., 2007). Neurovascular coupling relationships are thought to be altered in AD, where increased vascular resistance is observed, alongside differences in coupling of the vascular response with neuronal activity.

During prodromal stages of AD, alterations have been reported in neurovascular measures which subserve neuronal activity, including reduced perfusion (hypoperfusion) (Austin et al., 2011; Liu et al., 2013) and changes in cerebrovascular reactivity (CVR) (Glodzik, 2013). Further, APOE-related perfusion alterations have been reported in healthy middle-aged adults (Fleisher et al., 2008). In Fleisher et al., they found that carriers of at least one copy of the e4 allele had elevated resting perfusion and decreased fractional BOLD and perfusion responses during an encoding task, although differences were not found for absolute blood flow during this task. Therefore, APOE-related differences in the BOLD signal in APOE e4 carriers could potentially be attributed to differences in cerebral perfusion states rather than increased neuronal activity or oxygenation consumption as a result of a task demand.

APOE-related group differences have previously been shown for CVR in young adult APOE e4 carriers, in a study using inhaled carbon dioxide as a vasoactive stimulus (Suri et al., 2014). During an encoding task, the highest BOLD activity in the hippocampus was observed in APOE e4 carriers compared with APOE e2 and e3 non-carriers. The greatest difference, however, in CO2-CVR was between APOE e2 and APOE e4 carriers, with the lowest CO2-CVR values for APOE e4 carriers. The observation of an allele related decrease in CO2-CVR, from e2 to e3 to e4, resembles the likelihood of developing AD later in the lifetime (e.g., where the greatest risk is for APOE e4 carriers, with lowest risk for those with APOE e2). Moreover, when CO2-CVR maps were added as covariates into the BOLD analysis, the number of active voxels in the hippocampus surviving the experimental threshold was hugely reduced. Effectively, APOE-related CO2-CVR differences accounted for ~70% of task-related hippocampal BOLD differences between groups. Blood vessels are known to be sensitive to changes in CO2 levels, initiating a vasodilatory regulatory response when CO2 levels are elevated. This reduction in CO2-CVR in APOE e4 carriers, therefore, may reflect an impaired regulatory response to hypercapnia, with vessels not responding (dilating sufficiently), resulting in a corresponding decrease of oxygen to the tissue. An increased CO2-CVR in APOE e2 carriers could suggest, in contrast, a more efficient regulatory response to hypercapnia. Over the lifetime, this chronic state of mild hypoxia in APOE e4 carriers could contribute to poor cognitive outcomes in older age, whereas efficient regulation in APOE e2 carriers could explain why this allele is associated with 'protection' from AD. Therefore, APOE-related changes to cerebral vasculature may contribute towards the alterations we observe in the BOLD signal. These findings highlight the need to look beyond the BOLD signal to understand changes in the brain in individuals at increased genetic risk of later life poor cognitive health and AD.

This study, therefore, aims to replicate the findings of Shine et al. (2015), in a larger sample size, but critically extending this by also investigating cerebral perfusion in the key posteromedial cortex ROIs of interest (PCC and RSC), which are part of the 'core' scene construction network, described in Chapter 1 (and throughout this thesis). These PMC ROIs were identified as scene sensitive regions in a functional localizer task run in parallel to this study (see methods). An ROI of interest in this study was also the Hippocampus, however, due to a low signal to noise in the MTL, quality of data was poor and therefore analysis of this region was not included in this chapter. I predicted no behavioural differences between young adult e4 carriers and non-carriers on any conditions in the oddity task (consistent with Shine et al., 2015). By contrast, also consistent with Shine et al. (2015), I predicted scene-sensitive differences between APOE e4 carriers compared to non-carriers, specifically a failure to modulate (deactivate) BOLD activity during scene oddity in the PCC and RSC. A comparable pattern was expected for the perfusion (CBF) measures, with scene-sensitive higher CBF in the PCC and RSC ROI for APOE e4 carriers compared with non-carriers.

A further aim of this study was to complement these analyses with CO2-CVR measures to further understand BOLD alterations in young APOE e4 carriers. During the scanning session in this study, measures of end tidal CO2 during a breath holding task were obtained, and CO2-CVR maps were going to be added as a covariate to oddity task BOLD activity. It was predicted that CO2-CVR would be reduced in young APOE e4 carriers, and further, when these measures were added as a covariate to oddity task BOLD activity, CO2-CVR differences would account for predicted APOE-related differences in the BOLD response, but may not account for cognitively specific BOLD alterations as previously found by Shine et al. (2015). Unfortunately, CO2 physiological data quality was found to be too poor in ~70% of participants, due to technical issues with the recording equipment, so this analysis could not be performed. Instead, possible contributions of CVR to task related BOLD and the emerging importance of these measures in APOE studies will be discussed in the final section of this thesis.

4.2 Methods

4.2.1 Participants

Participants in this study were undergraduate students from the Cardiff University Department of Psychology. 19 participants were recruits from a prior cohort of 30 individuals who had previously taken part in the study by Shine et al. (2015). Of these 19 participants, 10 were APOE e4 carriers, and 9 were non-carriers. One individual in each group was male. To augment this sample, a further 27 participants were recruited from a second cohort (2016 APOE cohort) allowing me to increase my sample size to a similar level to that of other published studies (e.g., Filippini et al., 2009 and Suri et al., 2014) had 18 participants in each of the carrier and non-carrier groups). In total, therefore, 46 participants were scanned in this experiment, with a genotype split of n = 21 APOE e4 carriers and n = 25 non-carriers. Five participants were excluded (see Table 4.1 for details of exclusion criteria), resulting in 41 participants (n = 17 APOE e4 carriers/n = 24 non-carriers) in this analysis. All participants had normal or corrected to normal vision.

Table 4.1: Details of participants recruited and included in analysis for APOE groups.

	Total N	Oddity Imaging	Useable CO2 BH data
E4 Carriers	21	17*	6
Non-Carriers	25	24**	8
Total	46	41	14

**= 3 participants were excluded due to excessive movement (exceeding 3mm i.e. 1 voxel) and poor registration (1 male), 1 participant was excluded due to a scanner error, **= 1 participant excluded due to excessive movement and poor registration (exceeding 3mm i.e. 1 voxel).*

4.2.2 Encoding Task as a Functional Localiser

Given that the PMC ROIs used by Shine et al. were derived from a localizer task which was specific to the sample of participants used in that study, in this study, an independent functional localizer was used to define scene sensitive ROIs in the PMC, providing an ROI for the experimental contrast specific to the current participant sample. This localizer imaging study was carried out by another member of the research group, with the same participants who took part in my oddity task. During scanning, participants were presented with eighty 'real world' scenes, and eighty 'real world' faces. Participants were required to make a judgement of 'pleasant' or 'unpleasant' for each of the scenes and faces. Additionally, forty left-facing or right-facing arrows were presented as a control condition. Participants were required to make left or right directional judgements for these. Each stimulus was presented for 4000ms with an average ISI of 1000ms, with two runs of 9 minutes. Responses were made using a finger press button box.

4.2.3 Oddity Task

A series of trial unique stimulus arrays were presented to participants, with their task being to identify the odd one out (see Figure 4.3). Three 'odd-one-out' categories were presented in this version of the oddity task; real world scenes, novel faces, and squares (sizes), as shown in Figure 4.3 A further 'fixation' category was presented, where participants were asked to focus on a fixation cross in the center of the screen. For each trial, 3 (same category) images were presented on the screen at the same time, located to the bottom left and right with the final image presented centrally above those. The scene and face stimuli comprised of two images of the same scene or face, but presented from a different viewpoint, whereas the third image was a different scene or face which was perceptually similar (e.g. the spatial layout and perspective were similar). The squares trials comprised two squares which were of identical size and one square which differed in size by 9-15 pixels. Participants were required to identify which of the scenes, faces or squares was the 'odd one out' in each stimulus presentation.

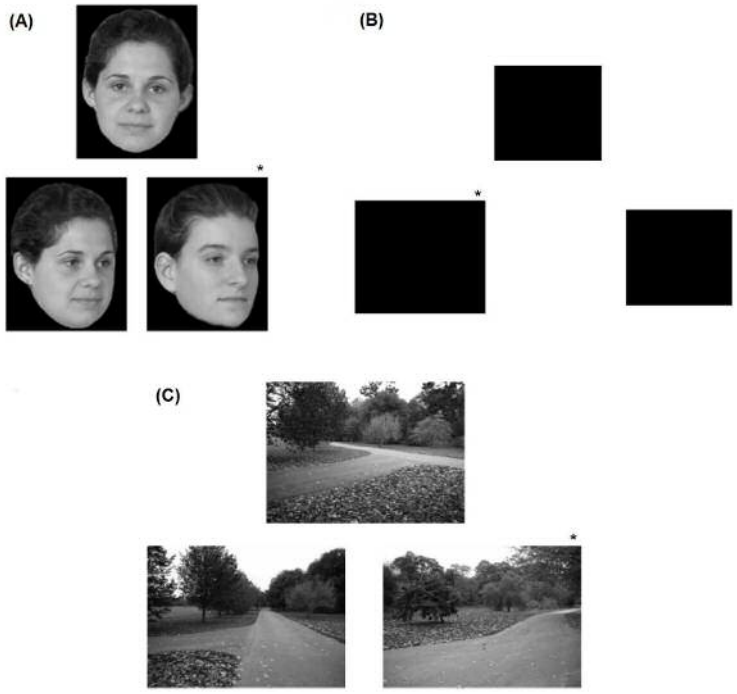

Figure 4.3: Examples of a trial presentation in the oddity task, for each stimulus category a) faces, b) sizes, c) scenes. Correct responses for each category are indicated with a small asterisk.

Fifty-four trial unique arrays were distributed across 3 experimental runs. Each run contained 9 'mini blocks' of trials (3x face, 3x scene, 3x size). Each mini block contained 6 same stimulus category trials and was 33.6 seconds in duration. The fixation trials had a fixation cross maintained on the screen for 33.6s. A Latin square design was used for counterbalancing the 3 runs, where participants were randomly assigned to one of three different sequences of the task runs. The oddity task was programmed and run using E-Prime 2.0 (Psychology software tools). The task was viewed in a mirror mounted on top of the head coil, which allowed participants to view a projector screen located behind the scanner. Task responses in the scanner were made with a key press on a button box.

4.2.4 Memory Task

Post scan, participants completed an oddity memory test, presented in EPrime V 2.0. There were 54 trials in this test. Each trial presented an image of a face or scene in the centre of the screen and the options 'old = 1' and 'new = 2' at the bottom of the screen. Twenty-seven of the trials were the odd-one-out images from the stimulus arrays that were previously seen in the scanner during the oddity task ('old'), and the other 27 were previously unseen images chosen to be perceptually similar (e.g. comparable spatial layout/ perspective) to the targets ('new'). The images in this task were the same for every participant, irrelevant of whether or not they were correctly identified as the odd one out during scanning. The participant was asked to identify whether or not they had seen the presented image during scanning or not. Accuracy and reaction times were recorded, and participants had as long as they wished to take the decision.

4.2.5 Structural Imaging acquisition

Imaging data was acquired on a 3D HD XGE scanner using an 8-channel receiver only head coil. For registration purposes, high resolution 3D anatomical images were acquired for each participant, with a T1-weighted 3D FSPGR sequence comprising of 168 axial slices (TR/TE/TI = 7.8/3.0ms/450ms, flip angle =20°, FOV = 256mm x192mm x176mm, 1mm isotropic resolution), with a 7-minute acquisition time.

4.2.6 Encoding Localiser Task

A gradient-echo EPI sequence was used (TR: 3000 ms, TE: 35 ms, FA: 90°, FOV: 220 mm, interleaved slice acquisition, slice thickness: 2.4 mm, inter-slice gap: 1 mm, in-plane resolution: 3.4 × 3.4 mm). Forty-two whole brain slices were acquired with a 30 degrees axial-to-coronal rotation (posterior down) in order to attenuate signal dropout in the medial temporal lobes (Weiskopf, Hutton, Josephs, & Deichmann, 2006).

4.2.7 Oddity Task

Functional data was acquired using a dual gradient echo, pulsed arterial spin labelling (pASL) sequence. The dual echo provides two images per repetition, TE1 = 'minimum', TE2 = 29.0. The short echo time provides perfusion weighted images, whereas the longer echo time provides BOLD weighted images. A single inversion time (TI) sequence was used for the Oddity task and breath-hold acquisitions, TR=2.2, TE=Min, volumes=184, slices=12, FOV=22, flip angle= 90°, slice thickness=7mm, spacing=1.0. For the resting CBF, a multi inversion time sequence was used (MTI) to allow absolute quantitative measurement of CBF (cerebral blood flow) and AAT (arterial arrival time). 4 post labelling delay times (ms) were used for the short (150,300,450,600) and long (1000,1400,1800,2000) inversion times. Each of the imaging runs began with four dummy volumes, to allow for equilibration of the magnetic field, before onset of the task.

4.2.8 Physiological monitoring

Physiological monitoring was used throughout the entire scanning session. A respiratory belt placed just below the ribs, and finger pulse oximeter recorded respiration and heart rate measurements, and a nasal cannula connected to a sampling line, recorded end tidal O2 and CO2 concentrations. These measures were collected to regress out physiological artefacts which may introduce noise into the ASL data.

4.2.9 Imaging analysis pipeline

4.2.9.1 Encoding Localizer Task

Pre-processing steps included brain extraction (BET; Smith et al., 2002), motion correction using FLIRT (Jenkinson et al., 2002, spatial smoothing (5mm FWHM), intensity normalization, high pass filtering (sigma = 50s), EPI undistortion (field maps), registration to high resolution structural image (MNI template) and modelling of the HRF using double gamma. Five explanatory variables were used including, Scenes hits; Scenes misses; Faces hits; Faces misses, and Arrows. Whole-brain analyses of encoding data was performed, focusing on the following contrasts: activation elicited for Scenes > Faces and Faces >

Scenes. A cluster extent threshold was corrected for $p < .05$. Scene- and face-sensitive activation clusters in the whole brain were then intersected with the Harvard anatomical probabilistic mask of the posteromedial cortex (see Figure 4.4). Two scene sensitive ROIs were identified within the Harvard PMC mask: these included a PCC region (see Figure 4.5, A) and an retrosplenial cortex (RSC) region (see Figure 4.5, B). These two ROIs were used for the main analysis of the Oddity task. The overlap between the PCC ROI identified in this localizer task, compared with the PCC ROI from Shine et al. (2015), is presented visually in Figure 4.6. It should be noted that the PCC ROI in Shine et al. was a unilateral ROI, whereas the PCC ROI in the present study was bilateral.

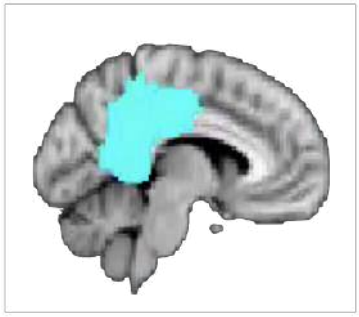

Figure 4.4: Harvard Atlas Tools Posteromedial Cortex anatomical mask, used for intersection of scene and face sensitive ROIs with the Encoding localizer task.

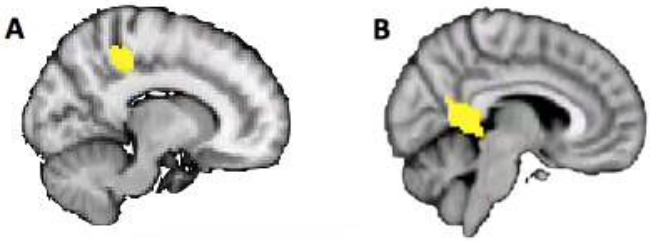

Figure 4.5: Scene sensitive Posteromedial Cortex ROIs (A) PCC and B) RSC derived from the Encoding Task localizer, used in the Oddity task analysis.

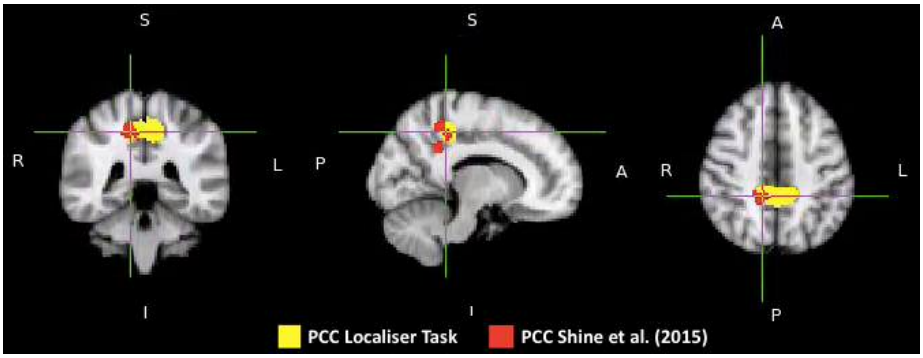

Figure 4.6: Visual comparison of PCC ROI used in Shine et al (2015) (red), with PCC ROI identified in the encoding localiser task (yellow), overlaid in standard MNI space.

4.2.9.2 Oddity Task

The dual echo data was separated into both BOLD and CBF time series. Physiological noise correction was carried out in Matlab, with an image based retrospective correction (RETROICOR), using in house Matlab scripts. Estimates of the contribution of physiological cardiac noise were regressed out of each BOLD and CBF time series before imaging analysis. Analysis was carried out using FSL FEAT (FMRI expert analysis tool, http://www.fmrib.ox.ac.uk/fsl/). Preprocessing consisted of brain extraction (BET; Smith et al., 2002), motion correction using FLIRT (Jenkinson et al., 2002, surround averaging (TE2) and surround subtraction (TE1), spatial smoothing using a Gaussian kernel of 5mm and a high pass filter cut off of 100 seconds. Each run was examined to ensure good quality of data. Data which exceeded movement of 3mm was excluded from analysis (see section 4.2.1 for details of excluded data). For first level analysis, each of the 3 oddity runs was modelled separately. Four explanatory variables (EVs) were defined, three which were the stimuli categories (scenes, faces, sizes) and a fourth EV of incorrect trials. Incorrect trials were defined from the start time of each trial which corresponded with an incorrect response in each participants E-Prime output. Incorrect trials across each run were used as a regressor in the analysis. To use size category as a baseline, two contrasts were defined, 1) scenes minus size and 2) faces minus size. CBF analysis was performed according to the block design of the task, whereby the signal was modelled according to block duration, which included responses to all trials, whether correct or incorrect. BOLD analysis was performed in two separate ways: 1) with a block design consistent with the approach to the CBF; and 2) applying an event related analysis, whereby three EVs included only correct responses

only to scenes, faces and sizes and consistent with the BLOCK analyses, the fourth EV was incorrect responses, again used a regressor. A fixed effects higher level analysis was performed to combine the runs, using the same contrast as previously defined. Finally, percent signal change values were then extracted for each of the contrasts (scenes minus size and faces minus size) for each of the two ROIs derived from the encoding task (PCC and RSC), see Figure 4.5.

4.2.9.3 Resting (multi-inversion time) CBF

The short and long multi-inversion time (MTI) time series were motion corrected (MCFLIRT), and T1 scans were brain extracted, then segmented into grey matter, white matter and CSF using FAST. The CSF image was registered to the perfusion image using FSL FLIRT and a mask of the lateral ventricles was used to calculate M0 CSF. This mask was made by applying a 95% threshold of the maximum intensity signal to the CSF image, and the AFNIs 3dclust was used to find the largest cluster of voxels, covering 5 slices over the ventricles. With CSF as a reference, the equilibrium magnetization for arterial blood (M0 blood) was then calculated (See Wong et al., 1998). CBF maps were scaled with M0 blood to quantify CBF in ml/100g/min. The whole brain grey matter mask was then used to extract values of CBF (ml/100g/min), aCBV (%) and AAT (seconds). Next, the PCC mask was transformed from standard into native space using FSL FLIRT. This mask was then multiplied with the grey matter mask of native space in each individual. This PCC grey matter mask was then multiplied by the perfusion, aCBV and AAT images to extract mean measures of CBF (ml/100g/min), aCBV (%) and AAT (seconds) at the PCC ROI.

4.3 Results

4.3.1 Behaviour

4.3.1.1 Oddity Task

Forty-one (n = 17 APOE e4 carriers, n = 24 non-carriers) participants were included in this analysis for consistency with the imaging analysis. A 2x3 repeated measures ANOVA was carried out for accuracy (% correct), with oddity condition as a within subject factor, and APOE status as a between subject factor. There was a high level of accuracy across all stimulus categories, for both groups, as shown in Figure 4.7, A. No significant

main effect of stimulus category was found F(1.65,64.48) = .38, P = .64 (Greenhouse-Geisser corrected). Nor was there a significant main effect of group, F(1, 39) = 2.04, p = .16, nor was there a significant interaction for stimulus category and group, F(2, 64.48) = 2.86, p = .07, as shown in Figure 4.7, A. A 2x3 ANOVA was also carried out on reaction time (ms). A significant main effect of stimulus condition was found, F(2, 64.43) = 113.84, p = <.001, with comparable reaction times for scenes and faces (p=.22), but faster reaction times for size stimuli compared with scenes and faces (both p = <.001). Reaction times were matched across groups F(1,39) = .14, p = .70, and there was no significant interaction for stimulus category and group F(2, 64.43) = .42, p = .61, as shown in Figure 4.7, B.

A. B.

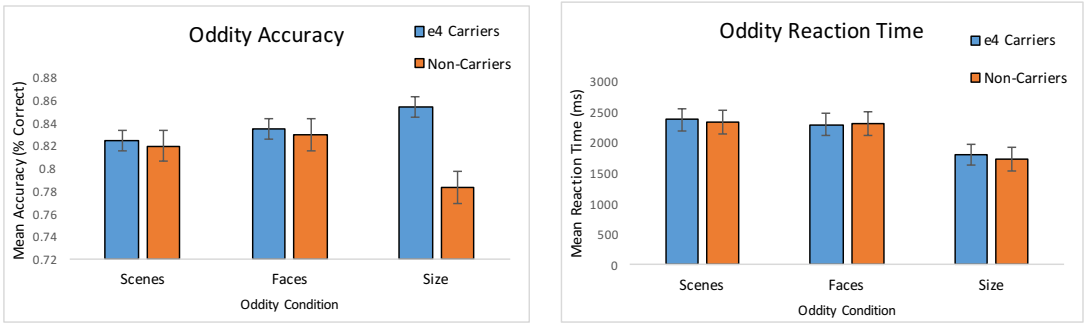

Figure 4.7: A) Mean accuracy scores, shown as % correct for each stimulus condition (scenes, faces, sizes) for the oddity task in the scanner, according to APOE status. B) Mean reaction time (ms) for each stimulus condition (scenes, faces, sizes) for the oddity task in the scanner, according to APOE status

4.3.1.2 Subsequent Memory

Memory scores were poor for both stimuli types as shown in Figure 4.8, where I present percentage of correct responses as hits minus false alarms. Thirty-seven participants were included in this analysis as in 4 participants (n= 1 e4 carrier and 3 non-carriers) data was lost due to technical errors and therefore could not be included. A 2x2 repeated measures ANOVA was performed, with stimulus category (scenes/faces) as a within subjects' factor, and APOE status (APOE e4 carriers/non-carriers) as a between subjects' factor. A significant main effect of condition was found, $F(1,35) = 27.02$, $P = <.001$, with higher memory scores for scenes (mean = .31, SD = .10) compared with faces (mean = .20, SD = .12). There was no significant main effect of group, $F(1, 35) = .1.80$, $p = .18$, but there was a significant interaction for stimulus category and group $F(1,35) = 5.10$, $P = .03$, with e4 carriers having lowest accuracy scores for faces.

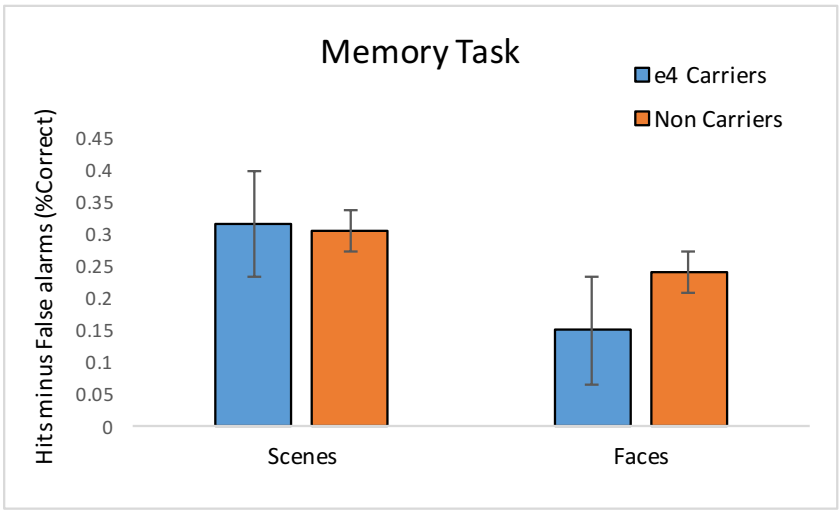

Figure 4.8: Mean scores (hits-false alarms) shown as % correct, for the post scan oddity memory task, for each stimulus category (scenes, faces), according to APOE status.

4.3.2 Imaging

4.3.2.1 Oddity Task Event related BOLD % Signal Change

For both the ROIs identified from the encoding localizer (PCC and RSC), a 2x2 ANOVA was performed, with stimulus category (scenes/faces) as a within subject factor and APOE status (e4 carrier/non-carrier) as a between subject factor.

In the PCC ROI, a significant main effect of stimulus category was identified, $F(1, 39) = 29.37$, $p = <.001$, with greater activity for scenes (mean = -.05, SD = .08) compared with faces (mean = -.12, SD = .08). No significant main effect of group was evident $F(1,39) = 1.65$, $p = .20$, nor was there a significant interaction between stimulus category and group $F(1,39) = .72$, $p = .40$, see Figure 4.9, A.

In the RSC ROI, a significant main effect of stimulus category was found $F(1,39) = 124.13$, $P = <.001$, with greater activity for scenes (mean = .13, SD = .16) compared with faces (mean = -.13, SD = .11). There was no significant main effect of group $F(1,39) = .10$, $p = .75$, and nor was there a significant interaction between stimulus category and group $F(1,39) = 3.09$, $p = .09$. See Figure 9.B for graphical representation of this ROI, see figure 4.9, B.

A. B.

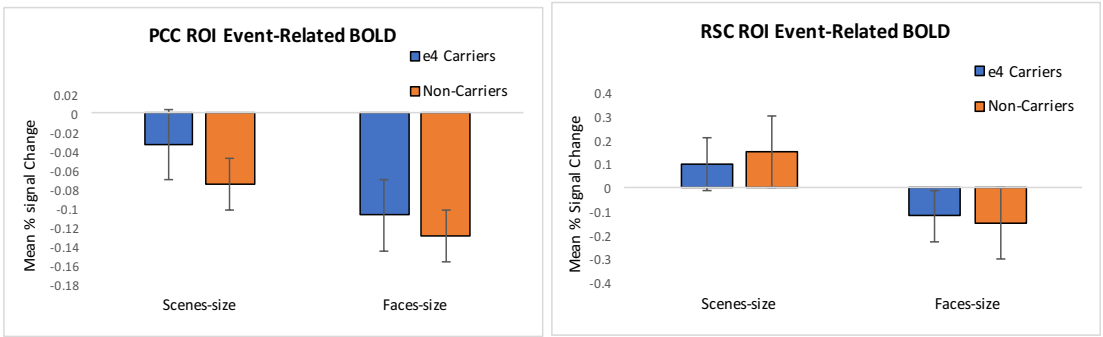

Figure 4.9: Event related analysis BOLD % Signal change extracted from ROIs A) PCC, B) RSC

4.3.2.2 Oddity Task Block design BOLD % Signal Change

For both ROIs, a 2x2 ANOVA was performed, with stimulus category (scenes/faces) as a within subject factor, and APOE status (e4 carrier/non-carrier) as a between subject factor.

In the PCC ROI, a significant main effect of stimulus category was found $F(1, 39) = 22.69$, $p = <.001$, with increased BOLD % signal change for scenes (mean = -.08, SD = .10), compared with faces (mean = -.15, SD = .09). There was a significant main effect of group $F(1,39) = 4.46$, $p = .04$, with greater BOLD % signal change in e4 carriers (mean = -.17, SD = .18) compared with non-carriers (mean = -.28, SD = .15). No significant interaction was found between stimulus category and group $F(1,39) = .86$, $p = .35$, as shown in Figure 4.10, A.

In the RSC ROI, there was a significant main effect stimulus category $F(1, 39) = 156.11$ $P = <.001$, with increased BOLD % signal change for scenes (mean = .17, SD = .18), compared with faces (mean = -.15, SD = .14). No significant main effect group was evident $F(1, 39) = .05$, $p = .83$, and there was no significant interaction between stimulus category and group $F(1, 39) = 3.68$, $p = .06$, as shown in Figure 4.10, B).

A. B.

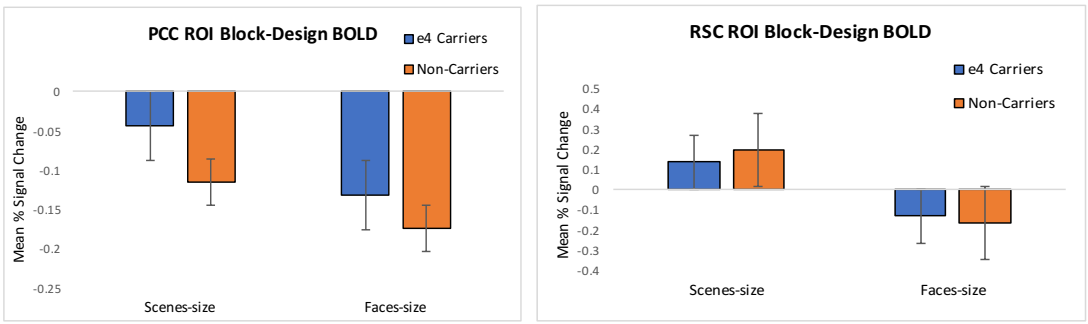

Figure 4.10: Block analysis BOLD % Signal change extracted from ROIs A) PCC, B) RSC

4.3.2.3 CBF (Block design)

For both ROIs, a 2x2 ANOVA was performed, with stimulus category (scenes/faces) as a within subject factor, and APOE status (e4 carrier/non-carrier) as a between subject factor.

In the PCC ROI, a significant main effect of stimulus category was evident $F(1, 39) = 36.49$, $p = <.001$, with greater CBF in the PCC ROI during scenes oddity (mean = .008 sd = .01) compared with faces (mean = -.006, sd = .01). There was no significant main effect of group $F(1,39) = .03$, $p = .84$, and no significant interaction was present between stimulus category and group $F(1,39) = .74$, $p = .39$. This is shown in Figure 4.11, A.

In the RSC ROI, a significant main effect of stimulus category was evident, $F(1,39) = 84.64$, $p = <.001$, with greater CBF for scene oddity (mean = .03, sd = .02), compared with face odd-one-out judgements (mean = .003, sd = .01). No significant main effect of group was found $F(1, 39) = .22$, $p = .63$, and nor was there a significant interaction between stimulus category and group $F(1, 39) = .07$, $p = .78$, see Figure 4.11, B.

A. B.

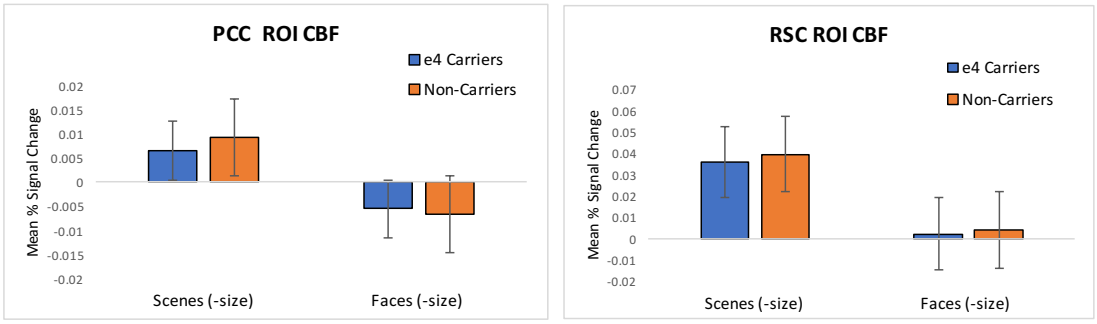

Figure 4.11: CBF % Signal change extracted from ROIs A) PCC, B) RSC

4.3.2.4 Resting CBF

No between group differences were found in whole brain grey matter CBF (ml/100g/min) for e4 carriers (m = 53.46, sd = 9.32) and non-carriers (m = 50.50, sd = 13.87), t(38) = .74, p = .46, aCBV (%) between e4 (m = .22, sd = .06) and non-carriers (m = .20, sd = .06), t(38) = .91, p = .36, or AAT (seconds) e4 carriers (m = .709, sd = .034) and non-carriers (m = .706, sd = .039), t(38)=.20, p = .83.

No between group differences were found in the PCC for CBF (ml/100g/min) in e4 (m = 29.60, sd = 13.60) and non-carriers (m = 30.01, sd = 12.48), t(38) = -.09, p = .92, or aCBV (%) for e4 (m= 11.12, sd = 21.32) and non-carriers (m = 7.75, sd = 9.50), t(38) = .68, p = .49, or AAT (seconds) for e4 carriers (m= .30, sd = .05) and non-carriers (m = .32, sd = .05), t(38) = -1.19, p = .24.

4.4 Discussion

The experiments presented in previous chapters of this thesis investigated potential behavioural markers of altered scene processing in APOE e4 carriers. This is based on evidence that scene construction and discrimination is a sensitive marker of AD, alongside data demonstrating involvement of brain structures linked to scene processing in early AD (in particular the hippocampus and PMC), (Lee et al., 2006; Lee et al., 2007; Irish et al., 2015). No statistically significant behavioural effects were evident in young adult APOE e4 carriers in these studies. The absence of early behavioural changes in young adult e4 carriers is not unusual in the APOE literature, although no studies have undertaken as detailed an investigation of complex scene processing as undertaken in the experiments outlined earlier. The lack of behavioural effect could be due to the insufficient sensitivity of the cognitive tasks I used, or indicate that behavioural changes linked to poorer later life cognitive aging are relatively difficult to detect early in life.

By contrast, there is an increasing body of evidence to suggest that functional changes in brain activity may be apparent in young adult e4 carriers (Fillippini et al., 2009; Shine et al., 2015), decades before the cognitive abnormalities associated with AD are seen. Consistent with this, there is evidence that the BOLD response shows changes over the

lifespan, with younger APOE e4 carriers showing increased activation (compared to non-carriers), which then flips, with older APOE e4 carriers showing decreased activation compared to non-carriers (Filippini et al., 2011). Increased activation early on in the lifespan (e.g., greater than that normally seen in APOE e4 non-carriers), may reflect increased neural effort in regions such as the hippocampus and PCC, to maintain a normal level of cognitive performance. Over time this high level of neuronal activity cannot be maintained and leads to reduced activity, perhaps associated with neuropathological changes in these key brain structures. More specifically, the change from increased to reduced activation (compared to non-carriers) may reflect activity-related neuronal degeneration in posteromedial cortex over the lifespan (Buckner et al., 2009; de Hann et al., 2012). In addition to this, more recently, evidence is emerging to suggest that these alterations in BOLD activation may not reflect increased neuronal activity as such (given that BOLD is an indirect measure of neuronal activity), but may in fact be driven by APOE-related microvascular differences (Mackay et al., 2014). Less efficient cerebrovascular reactivity in young adult APOE e4 carriers may result in reduced oxygen delivery to the tissue of specific regions, which over time may lead to neuropathological changes, and in turn poor cognitive health. The aims of the study in this chapter, therefore, were to replicate previous findings of scene-selective PCC increased activation in APOE e4 carriers compared with non-carriers (Shine et al., 2015), but further, to understand perfusion in the PCC (via consideration of two ROIs, PCC and RSC). However, unfortunately due to the poor quality of CO2 data obtained in this study, it was not possible to investigate the contributions of potential differences in CVR between e4 carriers and non-carriers in this study (as previously described in the introduction section of this chapter).

Consistent with the previous behavioural findings reported by Shine et al. (2015), both APOE e4 carriers and non-carriers performed comparably well in the oddity task. It should be noted, however, that there was a trend towards greater accuracy in APOE e4 carriers compared with non-carriers, driven by differences on the size discrimination condition. This trend was not present in Shine et al. (2015). Reaction times were fastest across both groups for the size condition, compared with the scene and face conditions, which is to be expected, given that the size category requires discrimination of less visually and contextually complex information than in the faces and scenes conditions. Although the trend for improved performance in APOE e4 carriers in this task was not statistically significant, there is a body of literature suggesting that young APOE e4 carriers can show better performance than non-carriers in some cognitive tasks/domains, a pattern not evident

in older APOE e4 carriers (who typically show matched ability or cognitive impairments in these tasks, see Wisdom et al., 2011 for a meta-analysis). Conditions in which APOE e4 carriers have been shown to evidence better performance than non-carriers include executive function (Marchant et al; 2010), verbal fluency (Alexander et al., 2007; Marchant et al., 2010), processing speed (Han et al., 2007; Marchant et al., 2010) and various measures of attention (Marchant et al., 2010; Rusted et al., 2013). These findings have previously been interpreted as evidence in support of antagonistic pleiotropy, whereby the APOE e4 allele confers a specific cognitive advantage early in life. However, in the present study, the trend towards a group difference was driven by poorer performance of the APOE e4 non-carriers on the size discrimination condition, which is arguably is the least demanding of the conditions used in this experiment. In the post-scan oddity memory task, groups were matched on performance for scenes, but APOE e4 carriers performed more poorly than non-carriers in the face condition. Both groups, however, performed well below 50% chance level for accuracy across both scene and face conditions of the post-scan memory task. It was concluded that memory for the stimuli presented in the scanner, was too poor and therefore not meaningful, and this finding will not be further in this thesis.

In the present study, no APOE related differences in the BOLD response were found in the RSC ROI for the block design or event related design analysis. In the PCC ROI, however, there was significantly greater BOLD activation (interpreted as task-related decreased deactivation in this region) in e4 carriers, relative to non-carriers. This was only evident, however, in the block analysis, not in the event related analysis (where there was a trend). This finding of greater BOLD activation in young e4 carriers, relative to non-carriers, is consistent with previous literature reporting these findings in MTL regions (Filippini et al., 2009; Suri et al., 2014) and in the PCC (Shine et al., 2015). This finding in Shine et al. however, was found to be driven by a significant scene-selective decreased deactivation for scenes in APOE e4 carriers, which was not replicated in the present study. Although, it should be noted that there was a trend towards a scene-sensitive decreased deactivation in the PCC for e4 carriers in both the block and event related design analysis in the present study. No APOE-related CBF differences were found in this study in the PCC or RSC, for either the block or event related analysis. Also, no between group differences were found in resting CBF, aCBV or AAT, in either the whole brain or the PCC.

Firstly here, I will address some methodological reasons for why significant APOE-related BOLD differences were identified in the block design analysis, but not the event related analysis. The block design analysis was comparable to the way in which the

CBF analysis was performed, with the BOLD signal modelled to stimulus presentation of each mini block, for each stimulus category. This block analysis included all responses to each trial, whether correct or incorrect (however, incorrect trials were added as a regressor to the analysis). In ASL imaging, the tag (where the blood is magnetically inverted before entry to the brain) and control images (without tagging – blood magnetization is fully relaxed) are acquired in an interleaved fashion, reducing the temporal resolution of the experiment (Liu et al., 2001). By surround subtracting or surround averaging the tag and control images, a CBF or BOLD time series can be formed, respectively, to eliminate contamination of the alternative echo. This method involves calculating the difference between each image and the average of its two nearest neighbours. Therefore, modelling the ASL signal over block durations is a more appropriate method to avoid introducing a greater ratio of temporal noise to signal into the data. Given that performance in the oddity task was generally good across all conditions, and the number of trials that were incorrect was low (scenes 18%, faces 17%, size 19% incorrect trials), the block BOLD signal was therefore modelled to a high-performance level across each block, reflecting high task engagement and ability. The second BOLD analysis I carried out was an event related analysis, comparably to Shine et al. (2015). Incorrect trials were excluded from each block for analysis and the BOLD signal was modelled across correct trials only, within each mini block. Given that ASL imaging, compared with fMRI, is inherently lower in temporal resolution, with a lower signal to noise ratio, removing time points from the modelled signal may have resulted in a reduction of temporal signal to noise, and may explain why a significant APOE-related difference in task-related BOLD response was not found in the event related analysis.

Regarding the interpretation of these results in comparison with Shine et al. (2015), it should first be noted that as described in the methods section of this chapter, the scene sensitive PCC ROI in the present study was defined using a different localiser task from the one used in Shine et al. (2015). Specifically, while Shine et al. used a working memory (n-back task), here I used an encoding task involving scenes and faces. Additionally, the localizer task used by Shine et al. (2015) identified scene selective BOLD APOE group differences in a unilateral scene sensitive PCC ROI (in the right hemisphere), whereas in the present study, this scene sensitive PCC ROI was bilateral (and larger in size). There was, however, a degree of overlap in these masks in the right hemisphere, as presented in the methods section of this chapter (Figure 7). In older adult APOE e4 carriers, compared with non-carriers, greater right hemispheric BOLD activation has previously been found in

multiple regions including the PCC and precuneus, during a verbal paired associate learning task, with matched behavioural performance in the task (Han et al., 2007). The author interpretation of these findings was that right hemisphere brain regions may be involved in compensating for APOE e4 deficiencies associated with verbal episodic memory. Therefore, perhaps further examination of hemispheric differences in these PCC regions might reveal more sensitive cognitively specific between group differences in the study in this chapter. Further, the size of the PCC ROI in this chapter was relatively large in comparison to that used by Shine et al. (2015). Given that the PCC covers a relatively large area of the cortex and is a highly connected region, found to deactivate during many types of cognitively demanding tasks (Leech et al., 2014), the differences in mask size between these studies may account for some of the difference between findings. For example, a larger PCC mask in the present study may have been a less sensitive measure of cognitively specific (scene-selective) deactivation found by Sine et al. (2015).

Despite a non-significant trend for a group and condition interaction in my analysis, a further reason why this study may not have replicated the findings reported in Shine et al. (2015) could be attributed to the inherent differences in the image acquisition sequences used. Firstly, as previously discussed, ASL BOLD has a low signal to noise ratio (SNR), with fewer slices acquired and larger slice thickness, compared with fMRI BOLD. The BOLD signal is tied to the veins and venules (Dunong et al., 2002), and therefore within the larger slice thickness specificity of signal in particular regions can be attenuated. The temporal resolution of ASL BOLD is also poorer than fMRI BOLD, given that a tag and control image pair for ASL is acquired over a longer duration of time to allow the blood delivery to the tissue of interest for tagging. In an ASL sequence, one tag and control image pair is acquired approximately every 4 seconds, whereas in a BOLD fMRI sequence, acquisition time can be as low as 100 milliseconds, but is typically 1-2 seconds (Liu et al., 2007). Therefore, ASL BOLD has a lower signal to noise ratio, and is also less favourable for event related task designs than fMRI BOLD, which may be a more sensitive measure in a behavioural study such as this, where incorrect trials within blocks may introduce unwanted noise.

In addition to these methodological differences, although non-significant, there was a trend in the oddity behavioural data for improved performance in APOE e4 carriers, which was driven by size discrimination performance, not found by Shine et al. (2015). Consistent with Shine et al. (2015), size was used as a baseline condition for the imaging analysis in this study, due to its low-level processing requirement. Given that alterations in the BOLD

signal are associated with both task engagement and performance, it might be hypothesized that in fact, differences in size oddity performance may be reflected by group differences in size oddity BOLD activity. Potential group differences in baseline size BOLD response may result in a distorted representation of scene and face APOE group differences.

There were no significant APOE-related differences between groups for CBF in the PCC or RSC ROIs. This finding is consistent with previous research which has reported no APOE-related differences in CBF in young APOE e4 carriers (Suri et al., 2014), however, Suri et al. (2014) examined MTL regions rather than PMC regions which were explored in this chapter. Despite APOE group differences in the BOLD response (increased in e4 carriers) and CO2-CVR (reduced in e4 carriers), Suri et al. (2014) did not find APOE group differences in task-related CBF, or resting CBF, cerebral blood volume (CBV) or arterial arrival time (AAT). This, alongside the potential decline in metabolic activity as a result of reduced oxygen availability, suggests that APOE e4 carriers have higher venous oxygen saturation compared with non-carriers, which would explain why APOE e4 carriers in their study had the lowest CO2-CVR but highest BOLD activation. Although CVR and the BOLD signal are not evidenced to be directly linked, CO2-CVR is thought to account for individual variability in the BOLD signal in aging (Liu et al., 2013). Therefore, APOE-related changes to cerebral vasculature may contribute towards the alterations we observe in the BOLD signal. Consistent with findings in this chapter, however, Suri et al. (2014) found increased task related BOLD activity in e4 carriers, compared with non-carriers (e3 homozygotes), alongside no group differences in task CBF. Given that I was unable to examine the contribution of CO2-CVR to the APOE-related differences in the BOLD response in this study, it is not possible to conclude here how this may explain my findings. However, interpretation of the possible contribution of CO2-CVR to the BOLD signal is complicated by Shine et al.'s (2015) findings (and the trend found in this chapter), as cognitively specific increased BOLD activation may not be explained by these measures. This highlights the need for further investigation of CVR in young APOE e4 carriers, to understand how vascular differences may influence cognitively specific alterations in brain function which increases vulnerability to a poor cognitive outcome later in life.

In conclusion, attenuation of BOLD deactivation in the PCC of young adult e4 carriers, relative to non-carriers, was found during a perceptual discrimination task in this chapter. The present study, however, failed to replicate significant findings of a scene-sensitive failure to modulate PCC activity in APOE e4 carriers compared with non-carriers (Shine et al., 2015). As outlined in this discussion there are a number of reasons why this

failure to replicate may have occurred, not least that use of a perfusion study – involving different methodological approaches – may have reduced the sensitivity of the study to eliciting this difference. A replication study should typically employ methods that are directly comparable and as sensitive as the measures of the study in question; a next step would be to re-run an identical version of Shine et al.'s (2015) paradigm to more directly determine the robustness of the scene effect identified by these authors. A further advance beyond this study would be to investigate scene selective BOLD activation differences and the contribution of CO2-CVR between APOE e2, APOE e3 and APOE e4 carriers, given that APOE e2 and APOE e4 carriers are reported to show similar levels of increased BOLD activity, reduced CO2-CVR, with APOE e4 carriers at greater risk of later life poor cognitive health.

5 CHAPTER 5: General Discussion

The main aim of thesis was to investigate whether young healthy adults at increased genetic risk of poorer later life cognitive health, via the presence or absence of an APOE-e4 allele, would show brain and behavioural alterations that were topographically and functionally overlapping with those seen in AD. To achieve this goal, scene construction and scene perception abilities were tested in young adult APOE e4 carriers and non-carriers, using verbal scene construction (Chapter 2), boundary extension (Chapter 3), and odd-one-out (oddity) judgement (Chapter 4) paradigms. Investigation of functional alterations related to possession of the APOE e4 allele was investigated using ASL imaging to investigate APOE e4 related group differences in functional BOLD activity and CBF associated with scene perception in the oddity task (Chapter 4). The combined behavioural and imaging approaches applied in this thesis allowed me to address the overarching question: do young APOE e4 carriers show behavioural and brain alterations, compared to non-carriers, on sensitive cognitive paradigms assessing scene processing ability? The answer to this question is important for advancing our knowledge and understanding of the very earliest functional and behavioural changes seen in APOE e4 carriers, and, in turn, investigating how meaningful these may be for understanding later life risk of poorer cognitive outcomes as we age.

In this general discussion, I will summarise and review the main findings of the behavioural and imaging studies in the thesis, outline methodological limitations of the studies and provide ideas for future work which could extend the work in this thesis.

5.1 Summary of findings

5.1.1 Evidence that scene representation in young APOE e4 carriers is comparable to non-carriers

It has been proposed that the mental construction of spatially coherent scenes (scene construction) forms a scaffold which underpins many related cognitive processes including episodic memory for past and future events, scene imagination, visual scene perception

(particularly view point independent discrimination), and spatial navigation (Maguire et al., 2010; Hassabis et al., 2007; Mullally et al., 2012). This has been evidenced through patient studies, whereby damage to regions within a core network (in particular, the hippocampus), results in impairments in scene construction ability, but also poorer episodic memory, episodic future thinking (Hassabis et al., 2007) and scene perception (Mullally et a; 2012). Alongside these hippocampal lesion studies, impairments in scene construction have also been found in AD (Irish et al., 2015). Importantly, although AD is characterised by hippocampal atrophy, scene construction ability in this task was found to be associated with PCC integrity (volume) across both AD patients and controls (Irish et al., 2015).

Previous literature investigating whether cognitive alterations are evident in young APOE e4 carriers compared to non-carriers has typically suggested no major cognitive changes linked to this genetic variant (Filippini et al., 2009). By contrast, some studies have reported cognitive advantages in APOE e4 carriers, for example, higher general IQ scores have been reported (Yu et al., 2000), achievement of a higher level of education (Hubacek et al., 2001) and improved attention (Rusted et al., 2013), compared with non-carriers. However, there is somedebate about whether these early cognitive differences exist, and which domains of cognition might be the most important indicators of later life poor cognitive health. A key argument of this thesis is that these tasks may not be as sensitive in detecting the very earliest changes in these young healthy e4 carriers, at least compared to tasks involving scene processing.

This hypothesis was investigated in Chapters 2-4, where different scene construction and perception tasks where given to young healthy adult APOE e4 carriers. I hypothesized that young e4 carriers would demonstrate early subtle cognitive alterations in scene processing in the sensitive tasks used in Chapters 2 and 3, where I focused on scene construction and boundary extension. The overall finding across the behavioural experiments, however, was that there were no marked differences between APOE e4 carriers and non-carriers. This was true when imagining spatially coherent scenes (Chapter 2) or during scene perception (Chapter 3 and 4). In the verbal scene construction task used in Chapter 2, however, categories of content production were teased apart to examine possible subtle differences between the APOE e4 carrier and non-carrier group in their construction of scenes. It should be noted here, that in hippocampal damage and AD patient studies, fewer details are typically found across all categories compared with healthy controls (Hassabis et al., 2007; Irish et al., 2015). In this thesis, e4 carriers were found to produce significantly fewer sensory details about their constructed scenes compared with

non-carriers. Although it might be expected that fewer sensory details may be associated with a less vivid experience of an imagined scenario, reflected by lower self-report ratings of sense of presence and salience, this was not found to be the case. Therefore, fewer sensory details may instead reflect developmental differences in the richness of imagined sensory experience, which may be relative to the detail individuals have access to. This point relates back to previous findings by O'Dwyer et al. (2012) of lower hippocampal volume in young APOE e4 carriers. Unlike patients who acquire hippocampal damage via injury/ disease, developmental differences in scene imagination may not be reflected in self-report vividness or richness, given that these individuals would not have an alternative mental experience possibly richer/ more vivid), which changed as a result of injury, as a comparison. Therefore, it is possible that reduced access to sensory detail could reflect subtle, early, developmental differences in the richness of imagination in these young adults. However, as highlighted here, this could be difficult to tease out behaviourally, given that the subjective experience of an imagined scene would be relative to a developmental formed ability, rather than a sudden change in quality or experience as a result of injury.

A further finding in this study, although not statistically significant, was fewer content spatial references in APOE e4 carriers for atemporal scene constructions, but with fewer spatial references for non-carriers compared with e4 carriers for future thinking scenarios. Across both groups, spatial references were fewer for future thinking compared to atemporal scene imagining. Given that future thinking was found to be experienced as more like a memory than atemporal scenes (in both groups), this finding could be interpreted as young adult APOE e4 carriers have reduced access to mentally generated relative positions of entities, directions or measurements that have not previously been experienced (less like a memory). Therefore, APOE e4 carriers may be more able to draw upon spatial content from previous experiences to imagine events within the future which are more like actual memories. This might suggest a mnemonic strategy could be adopted by young e4 carriers, which may be cognitively transferable when generating scenes which are more memory-like, but less so when scene construction requires the mental generation of something not previously experienced. Although, it should be noted that spatial references produced by both groups in this study were relatively few compared with spatial references in young healthy individuals in previous studies (i.e. Rendell et al., 2012), which will be further discussed as a limitation of this study, in a later section of this discussion chapter (5.2).

Following on from this verbal scene construction study, I next sought to investigate whether a rapid computerised scene perception task, which placed a demand on scene construction, would provide a sensitive measure of potential behavioural changes linked to scene processing in young adult e4 carriers (Chapter 3). Importantly, Shine et al. (2015) did not identify APOE group differences across scene perceptual discrimination in an oddity task. As mentioned, however, this was a relatively simple discrimination task, yet scene-selective BOLD alterations were identified in APOE e4 carriers in a scene-sensitive PMC region, interpreted by the authors as a failure to modulate brain activity specifically during scene perception. Therefore, my aim was to investigate whether these functional imaging alterations could manifest in behavioural changes in APOE e4 carriers, using a task which places a greater demand on scene construction (i.e. measured by the ability of participants to compare two scenes which are presented one after another (BE) rather than concurrently (oddity).

Expanding on previous BE studies in patients with hippocampal damage (which used close view to close view, identical repeats) this study incorporated multiple BE conditions, including close view to close view and wide view to wide view identical repeats of scenes, as well as wide to close view, and close to wide view scene presentations. Although not significant, in the identical view conditions, showed the most prominent pattern for a BE difference between groups, particularly for the WW condition which resembled previous findings by Mullally et al. (2012) whereby patients with hippocampal damage showed attenuated BE, correctly identifying repeated identical view trials as 'same' more frequently compared with controls. In this thesis, APOE e4 carriers were found to correctly identify 54% of the identical repeat wide view trials as the same, compared to non-carriers who correctly identified only 43% of trials as the same. Comparably, Mullally et al., (2012) reported that patients with hippocampal damage misremembered only 30% of trials as closer up, in contrast to controls who misremembered 60% of trials as closer. A similar pattern was found in my study with APOE e4 carriers misremembering fewer trials as closer up (41%) compared with non-carriers (50%).

Again, APOE e4 carriers have previously been found to have lower hippocampal volume compared with non-carriers, which is likely attributed to be a developmental influence of APOE e4 rather than reduced volume due to brain atrophy. The influence of this smaller measure of hippocampal volume on cognition is not yet conclusively understood. Therefore, the same comparable degree of BE attenuation found in patients might not be expected in young, healthy, APOE e4 carriers. Further, additional BE

conditions were included in this study with the aim of increasing sensitivity to performance differences between APOE e4 carriers and non-carriers. It is possible, however, that the multiple conditions included may in fact have made this task less sensitive to subtle changes in BE between groups. I will discuss this potential methodological concern in a later section of this chapter (5.2).

5.1.2 Evidence of increased BOLD signal in young e4 carriers, which does not reflect scene selective functional alterations

The final experimental chapter in this thesis aimed to replicate a scene-sensitive failure to modulate BOLD activity in the PMC during a perceptual discrimination task, previously reported by Shine et al. (2015). To advance on this previous study, I additionally used ASL imaging to investigate whether APOE dependent alterations in blood flow could further our understanding of these scene-sensitive BOLD alterations. Behavioural performance in this task was matched across APOE e4 carriers and non-carriers in Shine et al.'s (2015) task. The finding of increased BOLD activation in e4 carriers compared with non-carriers, alongside matched behavioural performance, has also been previously reported by Filippini et al. (2009) and Suri et al. (2014). However, these studies looked at MTL regions, in particular, the hippocampus, during encoding tasks. Increased task-related BOLD activation in MTL regions has also been shown in middle aged and older e4 carriers (Bookheimer et al., 2000; Bondi et al., 2005; Fleisher et al., 2009), thus suggesting that APOE e4 influences alterations in functional activity, potentially decades before the onset of cognitive impairments. It has been suggested that these functional alterations may be related to increased amyloid deposition (Fleisher et al., 2009), increasing vulnerability of these individuals to later life cognitive poor cognitive heath and AD. The PCC was of interest in Shine et al. (2015), and carried into the study in this thesis, rather than MTL regions (i.e. the hippocampus), given the early involvement of the PCC in individuals who later develop AD (Chetelat et al., 2006; Hamalainen et al., 2007). Further, the PCC has been shown to be an important region in scene construction (Irish et al., 2015). Prior to Shine et al. (2015), the cognitive specificity of previously reported functional alterations in young e4 carriers were not examined, nor have these differences been examined in the PCC of young e4 carriers.

In line with findings of Shine et al. (2015) performance in the oddity task in this thesis, was matched across APOE e4 carriers and non-carriers. However, this study failed

to replicate the scene-sensitive BOLD alteration evidence in the PMC (specifically PCC ROI), previously found by Shine et al. (2015). In this thesis, significantly greater PCC BOLD activity (interpreted as task-related decreased deactivation in this region) was found in APOE e4 carriers, relative to non-carriers, but, as a combined effect across all conditions. Interestingly, this was only found to be significant in a block design analysis, and was not found in the event related analysis. Task-related increased BOLD activity in young APOE e4 carriers, relative to non-carriers, is consistent with previous literature reporting these findings in MTL regions (Filippini et al., 2009; Suri et al., 2014) and in the PCC (Shine et al., 2015). However, inconsistent with Shine et al., this difference was not found to be cognitively specific to scene oddity. Although importantly, it should be noted that there was a pattern in the data which resembled Shine et al. (2015), towards a scene-sensitive decreased deactivation in the PCC for APOE e4 carriers in both the block and event related design analysis in the present study. Methodological limitations for the lack of replication of the findings of Shine et al. will be further discussed later in section 5.2. Findings of increased BOLD activation in APOE e4 carriers in this study, however, is in line with several other studies that have also reported a similar pattern of activation in these young healthy adults. As will be discussed in section 5.3, however, using tasks which may be more sensitive to subtle early cognitive changes in e4 carriers (possibly BE) could potentially better our understanding of vulnerability to later life poor cognitive health. Further, given that no APOE differences in task or resting CBF were found in the oddity task in this thesis, it could be that BOLD response alterations in young e4 carriers do not reflect an increased blood flow demand for neuronal activity, but instead, this increased BOLD signal may reflect a higher venous oxygen saturation and consequently, lower resting deoxyhemoglobin compared with non-carriers.

5.2 Methodological considerations and Limitations

5.2.1 Sensitivity of behavioural tasks

There are several limitations to the behavioural tasks used in this study. First, compared with Hassabis et al. (2007), the composite scores obtained in my scene construction experiment were comparably lower than those seen in the control participants in the patient study of Hassabis et al. Effectively, the scores across both APOE groups here were more comparable to the scores obtained for the patients with hippocampal damage described in Hassabis et al. In comparison with a further scene construction study by

Rendell et al., (2012), however, who examined behavioural differences in younger and older heathy individuals, young participants scene construction scores in Rendell et al. were similar to those obtained in my experiment. Further, the older participants' scores in Rendell et al., (2012) were comparable to the hippocampal damaged patients in Hassabis et al. (2007). Therefore, it may be possible that particularly good performance in scene construction in Hassabis et al control patients may have magnified between group differences in this particular sample. That said, in a further scene construction task by Irish et al. (2015), these between group differences were still evident between patients and controls, and in fact, scores from both groups were both relatively increased. A large variation between composite scores across studies, could pose as a limitation for the interpretation of findings, particularly given that assumptions are being made about young healthy APOE e4 carriers and prospective cognitively specific decline. This variation across studies could be a consequence of the interview technique of this study. An interview technique was critical for this study, to obtain rich details of imagined scenarios. Although it may be useful to obtain measures of functional activation during this scenario imagining (for example as Nadel et al., 2012 have done previously), an interview technique enabled me to extract finer details about constructed scenes, as they were being constructed. However, younger, undergraduate students might be more self-conscious when describing what they can 'see' in their imagination, during a laboratory based interview, compared to the healthy older control participants in Hassabis et al. (2007). This interview technique was therefore considered a more sensitive measure to investigate subtle changes in these young healthy individuals. Despite efforts to make participants feel relaxed during the interview, this may well be an inherent problem with this technique and may reduce sensitivity to detect subtle between group differences.

Mental construction of scenes relies upon the intricate interplay of many components such as spatial relationships, entities within a scene, sensory characteristics and emotions that may be evoked, which were all measured through verbal content analysis in this task. My assumption was that subtle differences in scene construction would exist between carriers and non-carriers, given that in APOE e4 carriers, structure and function of regions supporting the spatial framework for which imagined scenarios are built upon, is altered. The production of spatial references in this study was particularly low across both groups, compared to other content categories. A similar pattern was observed in patient studies, however, with this pattern particularly evident in patients compared with controls (Hassabis et al., 2007; Irish et al., 2015). An interpretation of this finding therefore, is that

this task may not have been tapping into spatial components of scene construction, which may be where between group differences related to APOE e4 may emerge. Further, Hassabis et al. (2007) found that the SCIQ (also used in this thesis), a measure of scene coherence or fragmentation, was a particularly sensitive measure in patients with hippocampal damage. Patients described their imagined scenes as spatially fragmented, compared with controls, who reported their imagined scenes as spatially coherent, with all of the components of the scene integrated appropriately in mental visualisation. In the present study, however, scores were moderate and matched across groups. Interestingly, compared with Rendell et al. (2012), the SCIQ scores in the present study were lower, suggesting that imagined scenarios were less spatially coherent across both groups. This may however, relate back to the limitations of the interview technique discussed previously, whereby potentially participants in this study were concentrating less on their mental visualisation of scenes and more on the interviewing situation.

Limitations of behavioural sensitivity to between group differences in scene construction also emerged from the findings in the BE task. In the present study, alongside identical view repeat conditions used in previous patient studies (Mullally et al., 2012), close to wide and wide to close view conditions which haven't previously been used in patient studies, were incorporated into the task. These further conditions were included with the aim to probe subtle between group differences in APOE e4 carriers and non-carriers, through testing BE differences under multiple BE conditions. Given that the only (non-significant) between group differences for attenuated BE in e4 carriers, however, was in the identical repeat condition used in patient studies, it is possible, that interleaving these conditions may have led to clues about the directional change in each condition, reducing the BE effect. This should be a consideration for future research, to investigate this effect further. In addition to this, the sample size of the BE study may have been a problem for detection of subtle between group differences. Sample size in the patient study reported by Mullally et al. (2012) was relatively smaller, 7 patients with bilateral hippocampal damage and 12 controls, compared with 14 APOE e4 carrier sand 18 non-carriers in this thesis. However, given that the participants in the patient study had quite pronounced damage to the hippocampus, smaller sample sizes would be sufficient to detect these large effects on BE. Unfortunately, despite recruitment efforts, many of the students recruited for this APOE cohort had vacated Cardiff by the time of this study. Therefore, consideration of extending this sample size would be useful to further investigate a between group BE effect difference which may be suggested by this thesis.

5.3 Outstanding questions and future directions

5.3.1 Investigating the relationship between brain structure and behaviour

A major outstanding question of this thesis is that concerning the relationship between brain structure and performance in behavioural tasks. The hippocampus is an important structure for scene construction (Hassabis et al., 2007; Maguire et al., 2010), with the subiculum preferentially activated for perception of scenes (Hodgetts et al., 2016) and the CA1 subfield important for episodic memory (Fouquet et al., 2012). Critically, there is evidence that these subfields are selectively effected by early AD pathology (Pievani et al., 2011), consistent with impairments shown in AD patients in episodic memory (Backman et al., 2001) and scene perception (Lee et al., 2007). In this thesis, particularly where patterns in line with hypotheses were observed for behavioural differences between APOE e4 carriers and non-carriers, for example in the repeated identical view condition of the BE task, it would be interesting to test whether these measures would be correlated with hippocampal and PCC volume. Volume reduction has been reported in the PCC of cognitively normal older adults who subsequently develop cognitive decline (Haller et al., 2017). Therefore, PCC volume in young adult e4 carriers would be interesting to explore in the context of tasks which might tap into early structural changes in this region. An outstanding question, therefore, is how might the structural alterations in young e4 carriers, particularly in the hippocampus as previously identified by O'Dwyer et al. (2012), map onto cognitive performance on demanding scene processing tasks, such as those used in Chapters 3 and 4 of this thesis. Further, this work could be extended by firstly investigating whether there are selective subfield volume differences between e4 carriers and non-carriers in the subiculum and CA1, which are regions selectively effected earliest in AD pathology (Braak & Braak, 1991; Braak, 1993; Mueller & Weiner, 2009; Mueller et al. 2010), and has not yet been looked at in young adult APOE literature. Secondly, future work should investigate whether measures of hippocampal subfield volume (in particular the subiculum and CA1) in these young APOE e4 carriers, is related to scene construction and scene perception ability.

5.3.2 Cognitively specific functional alterations and APOE

A further outstanding question of this thesis, and APOE literature more broadly, is whether alterations in the BOLD response between APOE e4 carriers and non-carriers (e.g. Filippini et al., 2009), could be made more sensitive via application of more cognitively specific tasks. Typically, in this literature studies have focused on episodic memory (encoding and recall), tasks which have yielded APOE dependent differences in BOLD activity in younger (Filippini et al., 2009) and older (Bookheimer et al., 2000; Bondi et al., 2005; Fleisher et al., 2009) participants. For example, Bondi et al. (2005) identified increased BOLD activation in multiple brain regions (including the right hippocampus and right parahippocampal cortex) in middle aged APOE e4 carriers, during a picture encoding task using indoor and outdoor scenes. The control condition in this study involved pictures of autumn leaves. Although this increased BOLD activity in APOE e4 carriers may reflect functional alterations during perception of scene images, a more robust design for interpretation of such findings, was demonstrated by Shine et al. (2015), where scene-sensitive BOLD alterations were found in young APOE e4 carriers, compared with face, object and size (control) perception. Shine et al. (2015) showed that the BOLD alterations in APOE e4 carriers can be cognitively specific, and map onto the pattern of functional decline evident in AD (Lee et al., 2005). This is a strong methodological approach to demonstrate a potentially valuable association between specific later life cognitive changes and brain activity patterns seen decades prior to older age.

Unfortunately, the oddity replication study in this thesis failed to find strong evidence for the scene-sensitive functional alterations seen by Shine et al. (2015) in their APOE e4 group, which could be, at least in part, due to methodological differences between my study and that of Shine et al. One of the comparable findings across both studies was the absence of behavioural differences between groups. As noted earlier, the oddity task is not a particularly challenging cognitive task, with the aim to ensure that participants are performing at a reasonably good level during scanning. A direction for future research may be to investigate whether more sensitive cognitively specific BOLD alterations exist between young APOE e4 carriers and non-carriers using for example, an adapted BE task using identical view repeats only, which in Chapter 3 were found to elicit the largest between group differences in performance (although non-significantly). A possible task adaptation could include scenes, acontextual objects and face identical view repeats allowing further testing of the stimuli-sensitivity of BOLD changes in PCC (and MTL), while allowing perception to be tested in a non-concurrent way. Further, the MTL was not

explored in this study, due to my focus on replicating Shine et al.'s (2015) findings which were focused on PMC, as previously described. A further concern with the replication in Chapter 4 is that the ASL technique employed resulted in a low signal to noise ratio in the MTL. A future research direction would be to examine MTL regions during oddity, as well as my suggested BE experiment above. Further, given that the subiculum has been found to be preferentially activated in healthy young adults specifically for scene oddity discrimination (Hodgetts et al., 2017), and this is a region which may be structurally compromised early in AD (Mueller & Weiner, 2009; Mueller et al. 2010), it might be valuable to undertake 7T MRI where it would be possible to look at APOE related BOLD activity in the subiculum and other hippocampal subfields (see Hodgetts et al., 2017).

5.3.3 Interpretation of BOLD alterations in young e4 carriers using CO2-CVR

One of the aims of this thesis, which could not be addressed due to poor quality of physiological end tidal CO2 data (~70% of participants), was whether young adult APOE e4 carriers show differences in CO2-CVR compared to non-carriers, and to determine what the contribution of these measures was to any identified BOLD alterations found between APOE e4 carriers and non-carriers in the oddity task. Neurovascular coupling relationships are thought to be altered in AD, where increased vascular resistance is observed, alongside differences in coupling of the vascular response with neuronal activity. These alterations include reduced cerebrovascular reactivity (CVR) (Glodzik; 2013). Further, middle aged APOE e4 carriers have shown elevated resting perfusion and decreased fractional BOLD and perfusion responses during an encoding task, although differences were not found for absolute blood flow during this task (Fleisher et al., 2008). A consideration when interpreting the findings of BOLD alterations in e4 carriers in this thesis (and more generally), is that no task or resting CBF differences were found between APOE groups. Although in this thesis, it was not possible to examine the contribution of CO2-CVR to these APOE BOLD differences, Suri et al. (2014) found that reduced CO2-CVR in young e4 carriers, accounted for ~70% of the difference in BOLD response between e4 carriers and non-carriers. Therefore, elevated BOLD signal in APOE e4 carriers could potentially be attributed to cerebral perfusion states rather than increased neuronal activity or oxygenation consumption.

The reduction in CO2-CVR in APOE e4 carriers found by Suri et al. (2014) has been interpreted as an impaired regulatory response to hypercapnia, with vessels not

responding (not dilating sufficiently), resulting in a corresponding decrease of oxygen to the tissue. This, alongside the potential decline in metabolic activity due to reduced oxygen availability, suggests that APOE e4 carriers have higher venous oxygen saturation compared with non-carriers, which would explain why APOE e4 carriers demonstrate greater BOLD activation compared with non-carriers, without APOE differences in task or resting CBF (Suri et al., 2014). Therefore, APOE-related changes to cerebral vasculature may contribute towards the alterations we observe in the BOLD signal. These findings highlight the need to look beyond the BOLD signal to understand changes in the brain in individuals at increased genetic risk of later life poor cognitive health and AD. Future BOLD imaging studies in APOE should certainly aim to incorporate CO2-CVR, perhaps using a CO2 inhalation challenge, to further examine underlying APOE related differences in the BOLD response.

5.4 Concluding remarks

In this thesis, I set out to investigate whether sensitive behavioural and imaging methods could be applied to detect early subtle differences in scene construction between young APOE e4 carriers and non-carriers. I hypothesised that young APOE e4 carriers, compared with non-carriers, would show functional alterations in brain regions which support scene construction, and this would be reflected by subtle behavioural changes in scene construction ability. This aim was achieved firstly testing scene construction and scene perception across several sensitive behavioural experiments which have previously been found to be sensitive to cognitive impairments in patients with hippocampal damage and AD. Finally, I investigated functional and blood flow activity underlying scene perception in young APOE e4 carriers and non-carriers, with the aim to identify whether scene-selective functional alterations exist in these young carriers, which may indicate vulnerability to later life poor cognitive health. Taken together, the findings across the experiments in this thesis failed to produce strong evidence of behavioural scene construction alterations in young APOE e4 carriers, and functional differences, although evident, did not support my hypothesis of scene-selective functional alterations between these groups. Several interesting patterns in line with existing literature were found across the behavioural and imaging studies, which suggests further work, with a larger sample size, would be valuable in probing these potentially subtle alterations in scene construction and scene perception.

6 References

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