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The Influence of *APOE* ε4 on the Hippocampus and Hippocampus-Dependent Memory

EVA STENING

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Abstract
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APOE ε4 is the major genetic risk factor for Alzheimer's disease, a dementia characterized by memory impairment and hippocampal atrophy. While associated with episodic impairment and reduced hippocampal volume in healthy aging, *APOE* ε4 has been related to increased episodic memory performance in young adults. The effect of *APOE* ε4 on hippocampal volume in young age is uncertain, with studies showing comparable or smaller volumes in ε4 carriers. This thesis aims to further explore the effects of *APOE* ε4 on episodic memory and hippocampal volume in young adults. In addition to episodic memory, spatial memory will also be assessed, as both these memory types are hippocampus-dependent. Furthermore, potential modulating effects of sex are assessed, as sex differences has been found in relation to *APOE*-related pathology, episodic and spatial memory and hippocampal volume. **Study I** examined the effects of *APOE* ε4 on episodic and spatial memory and hippocampal volume in young adults. Hippocampal volume was assessed by manual tracing of the hippocampal head, body and tail. **Study II** considered whole-brain structural covariance patterns of the anterior and posterior hippocampus. Furthermore, the association between these patterns and episodic and spatial memory performance was assessed. **Study III** investigated the effects of *APOE* ε4 on episodic and spatial memory and hippocampal volume in three different age groups. This was done in order to further explore the different effects of *APOE* ε4 on cognition and hippocampal volume seen in young and older age. **In summary**, *APOE* ε4 was positively associated with spatial function and episodic memory in young adults. Although there were no effects of *APOE* ε4 on hippocampal volume, structural covariance patterns of the anterior and posterior hippocampus differed as a function of *APOE* ε4 and sex. Thus, structural covariance may provide an early measure of *APOE* ε4-related effects on brain structure. Moreover, sex was found to modulate the effects of *APOE* ε4 to the disadvantage of women. This was seen in both age-related hippocampal volume effects and in structural covariance patterns in young adults, as well as in spatial memory performance across age groups.

Keywords: APOE ε4, episodic memory, spatial memory, hippocampus

Eva Stening, Department of Psychology, Box 1225, Uppsala University, SE-75142 Uppsala, Sweden.

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

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II Stening, E., Persson, J., Eriksson, E., Wahlund, L-O., Zetterberg, H., & Söderlund, H. Specific patterns of whole-brain structural covariance of the anterior and posterior hippocampus in young *APOE* ε4 carriers. *Manuscript submitted for publication.*

III Stening, E., Nordin, K., Persson, J., Kalpouzos, G., Larsson, E-M., Eriksson, E., Wahlund, L-O., Zetterberg, H., & Söderlund, H. Age effects on hippocampal volume and episodic and spatial memory vary as a function of *APOE* status and sex. *Manuscript.*

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Abbreviations

APOE	Gene coding for apolipoprotein E
DMN	Default Mode Network
fMRI	functional Magnetic Resonance Imaging
ICV	Intracranial Volume
LV	Latent Variable
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
PLS	Partial Least Squares
ROI	Region of Interest
SPM	Statistical Parametric Mapping

Introduction

The genetic influence on the development of an organism has been the focus of a great deal of research in recent years. With the completion of the Human Genome Project (HGP) in 2003, which successfully mapped the genetic makeup of the human being, this area of research is more relevant, and easy accessible, than ever before. Additionally, research not directly affiliated with the HGP has explored the genetic influence on pathology development, with genetic markers for schizophrenia (Ripke et al., 2013), Parkinson's disease (PD; Trinh & Farrer, 2013), depression (Dunn et al., 2015) and Alzheimer's disease (AD; Tanzi, 2012) the most commonly explored. Building on this acquired knowledge, the next step has been to turn attention to the genetic influence on healthy development in hopes of finding early behavioral signs of possible future pathologies. Many pathologies also include behavioral changes and deficits, and therefore many researchers have set out to find correlations between genetics and accompanying symptoms rather than just the physiological symptoms. This, in turn, has generated attempts to pinpoint the genetic influence on psychological domains, such as cognitive functioning.

One of the most studied genes in this regard, and also the focus of this thesis, is the major genetic risk factor for AD; apolipoprotein E, *APOE*. As I will describe further on in this thesis, AD is a neurodegenerative disease with two main physiological and behavioral correlates: brain atrophy and memory impairments. The brain region most vulnerable to AD-related atrophy is the medial temporal lobes (MTL). The hippocampus, as we will see below, is a structure within this region that has been the focus of much research due to its importance for memory functioning. The majority of work on the association between *APOE* and cognition has been focused on healthy aging and thus has examined healthy elderly individuals. In this thesis, I will mainly explore the influence of *APOE* on the hippocampus and two hippocampus-dependent memory types in young adults in an attempt to assess how *APOE* influences healthy cognition earlier in life. However, this will also be assessed in middle-aged and older individuals in the third study of this thesis. But first, we need to start with the hippocampus.

Anatomy of the hippocampus

The hippocampus is an evolutionarily ancient structure located in the MTL, on the floor of the lateral ventricle. It is an elongated bi-hemispheric structure that is common to most mammals. Because of this, and its involvement in behavioral functions (which I will describe later on), it has been extensively studied in animals, mainly rodents but also birds and non-human primates. In humans, it is a well-studied brain structure, mainly because of its involvement in long-term memory. However, animal studies, in addition to post-mortem examinations in humans, have made it possible to study in detail the intricate anatomy of the hippocampus. Below, I will shortly describe the most important aspects of the hippocampal anatomy – its structure and cell properties – as well as heterogeneity along its longitudinal axis.

Anatomically, the hippocampus is a heterogeneous structure and consists of several distinct cytoarchitectonic subfields. It is a bilaminar structure, meaning that it consists of two layers (or laminae) that form two interlocking c-shapes. This is especially evident when studying the hippocampal anatomy in a cross-sectional plane orthogonal from its longitudinal extension. The two c-shaped laminae are the Cornu Ammonis (CA), also known as Ammon's horn) and the dentate gyrus (DG). Together with the subiculum, these laminae make up the definition of hippocampus used in this thesis. The DG, named after its resemblance to teeth, runs through the whole longitudinal length of the hippocampus (Duvernoy, 2005; Kandel, 2013). The CA region is further divided into subfields: CA1 through CA4, which consist mainly of pyramidal cells packed in various densities depending on the subfield. The DG, in turn, is built up of three layers of granule cells. Moreover, the DG is the main site of neurogenesis in the adult human brain (Eriksson et al., 1998).

The hippocampus is thus a complex structure, and differences are also found along its longitudinal extension. Due to the differing morphology, the hippocampus is sometimes divided into three subsegments along its anterior-posterior axis: head, body, and tail (Duvernoy, 2005; Malykhin et al., 2007). However, a simpler division into an anterior and a posterior part is commonly made when assessing the hippocampus' anatomical heterogeneity in relation to function. The anterior hippocampus includes the hippocampal head, while the posterior hippocampus includes both hippocampal body and tail. In

this thesis, both accounts of hippocampal division are used. In Study I the hippocampus is divided into head, body and tail, while in Study II, the anterior-posterior division is used.

Hippocampus-dependent memory

In the following paragraphs, I will describe two memory types that are heavily dependent on the hippocampus: episodic and spatial memory. It can be argued that they are sometimes similar; episodic memory can, for example, contain spatial components and vice versa. However, they are also quite different from each other and as we shall see, they largely depend on different parts of the hippocampus.

Episodic memory

Episodic memory is the memory for personally experienced events that are tied to a specific place in space and in time. This kind of memory depends on conscious recollection and typically evokes a feeling of mental time travel and a subjective awareness of re-experiencing the event. This phenomenon has been dubbed "autonoetic awareness" and is a prerequisite for episodic memory. Another aspect of episodic memory is that it is highly dependent on contextual cues (Tulving, 1983; Tulving, 2002).

Much of our knowledge about hippocampal involvement in episodic memory originates from lesion studies. Perhaps the most famous case study of hippocampal lesions is that of Henry Molaison (H.M.). H.M., who had been suffering from intractable epileptic seizures, had his MTLs surgically resected in an attempt to alleviate symptoms. During the surgery, a large part of his bilateral MTL was removed, including the anterior hippocampus, parahippocampal gyrus and the amygdala. Although the surgery was a success with regard to seizure frequency, it also resulted in both retrograde and anterograde amnesia for personally experienced events. It was only this type of memory that was affected by the medical resection of H.M. His intellectual abilities, perception and reasoning were all intact (Scoville & Milner, 1957). Priming and classical conditioning were not affected by the resection, and neither was working and procedural memory. For example, H.M had no trouble acquiring new skills and showed typical progress in learning and performing new motor tasks, while having no recollection of having performed the task before (Corkin, 1968; Milner, Squire, & Kandel, 1998). There are many more cases where hippocampal damage have led to impaired episodic memory; patients P.B. (Penfield & Milner, 1958), K.C.

(Rosenbaum et al., 2005; Endel Tulving, 2002) and "Jon" (Vargha-Khadem et al., 1997) to name a few. However, a description of the case of H.M. will suffice for this thesis.

The significance of the hippocampus for episodic memory has been further established using functional and structural magnetic resonance imaging (f/MRI), both in amnestic and healthy individuals. In healthy individuals, increased activation of the hippocampus has been seen during the performance of episodic memory tasks (Addis, Wong, & Schacter, 2007; Mayes & Montaldi, 2001; Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Stark & Squire, 2000). With regard to hippocampal volume, episodic memory impairment has been linked to smaller hippocampal volumes in patients suffering from amnesia but without surgically induced MTL damage (Squire, Amaral, & Press, 1990).

Spatial memory

Hippocampal lesions have also been informative in the exploration of spatial memory. H.M. was found to have trouble navigating familiar surroundings (Scoville & Milner, 1957), and patient "Jon" (Vargha-Khadem et al., 1997) showed impaired spatial recognition when the viewpoint at testing was different than during encoding (King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002). In addition, a London taxi driver with hippocampal lesions was able to navigate a virtual London map using main routes only, but when the task required retrieval of detailed spatial representations, performance was impaired (Maguire, Nannery, & Spiers, 2006).

In contrast to episodic memory, which cannot easily be assessed in animal studies, spatial memory is easy to measure in animals. There is a large amount of studies on spatial memory and spatial navigation in rodents, and our initial knowledge of the neural underpinnings of spatial memory comes from this. Seminal work by Tolman showed that trained rats could easily and very quickly adjust their routes toward a food reward when the original route was blocked, suggesting they had access to a cognitive map-like representation of the immediate environment (Tolman, 1948). O'Keefe and Dostrovsky later pinpointed the neural correlates behind this behavior: the hippocampal place cells (O'Keefe & Dostrovsky, 1971). These cells are mainly found in the CA1 region of the hippocampus (O'Keefe, 1976) and fire whenever the rat enters a specific area of its environment, thus creating an internal representation, or map, of said environment. The hippocampus' role in navigation and spatial memory has since been continuously demonstrated. In a widely used task, the Morris Water Maze (Morris, Garrud, Rawlins, & O'Keefe, 1982), a platform is hidden below the surface in a pool of water. When the

location of the platform is held constant, rats learn to swim directly to the platform, even when their own starting point differs between trials. The performance of rats with hippocampal lesions is, however, drastically impaired. The Morris Water Maze has also been adapted for human use by creating computerized versions of the task (Astur, Ortiz, & Sutherland, 1998; Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005; Persson et al., 2014). In general, virtual tasks have spurred on spatial research. Hippocampal involvement in spatial memory can now easily be assessed by having people navigate virtual environments such as buildings or towns, while lying in a scanner during an fMRI session (Hartley, Maguire, Spiers, & Burgess, 2003; Pine et al., 2002). As it happens, the perhaps most famous example of the association between the hippocampus and spatial memory comes not from virtual tasks but from real-life navigation. As it also gives valuable insight into a division of function along the anterior-posterior axis of the hippocampus, I will describe it further below.

Differences along the longitudinal axis related to episodic and spatial memory

By studying London taxi drivers, Maguire et al. (2000) found that they had larger posterior bilateral hippocampi compared to non-taxi drivers, who in turn had larger anterior hippocampi. Furthermore, time on the job was positively correlated to volume of the right posterior hippocampus and negatively correlated with right anterior volume (Maguire et al., 2000). This finding was further verified by Schinazi, Nardi, Newcombe, Shipley and Epstein (2013), who found that right posterior hippocampal volume was positively associated with "offline" cognitive mapping ability. This was measured as the ability to, from a given viewpoint, accurately judge relations between locations in an environment previously traversed. Functionally, the connection between the posterior hippocampus and navigation has also been seen. In virtual navigation tasks, the right posterior hippocampus has been found to be consistently activated throughout navigation (Persson et al., 2013; Xu, Evensmoen, Lehn, Pintzka, & Håberg, 2010). The posterior hippocampus has also shown preferential activation for memory of spatial relations (Hoscheidt, Nadel, Payne, & Ryan, 2010; Nadel, Hoscheidt, & Ryan, 2012; Ryan, Lin, Ketcham, & Nadel, 2010). These findings strongly suggest that the posterior hippocampus is associated with spatial memory. In addition, common to all of these studies except for Hoscheidt et al. (2010) is that they all show that the right posterior hippocampus seems to be especially involved in spatial memory and navigation.

With regard to episodic memory, findings are not as clear as for spatial memory. However, we can recall that H.M.'s surgery removed the anterior

MTL (including the anterior hippocampus) and that he suffered from episodic impairments as a result. In addition, the size of the hippocampal head has been positively associated with verbal episodic memory (Hackert et al., 2002). A recent meta-analysis also supports the notion that the hippocampus is functionally segregated with regard to episodic and spatial memory (Kühn & Gallinat, 2014). This analysis found that while spatial tasks were associated with activation of the posterior hippocampus (and during retrieval, the right posterior hippocampus in particular), episodic memory was associated with more anterior activations. Furthermore, the anterior and posterior parahippocampal cortex also showed activations consistent with this pattern. This latter notion is supported by findings on the functionality of brain structures surrounding the hippocampus. Davachi (2006) concluded that the hippocampus receives information about items and objects from the adjacent perirhinal cortex (located in the anterior parahippocampal gyrus), while contextual information comes in via the parahippocampal cortex (located in the posterior hippocampal gyrus). Stimulus type may also be a factor when assessing the anterior-posterior distribution of function, with verbal and pictorial stimuli engaging the anterior and posterior hippocampus, respectively (Persson & Söderlund, 2015).

Thus, there appears to be a functional division of labor within the hippocampus, with episodic memory processing mainly depending on the anterior hippocampus and spatial memory depending on the posterior hippocampus. I will now move on to describe what we know of *APOE* and how it affects the hippocampus and cognition.

Apolipoprotein E – *APOE*

Apolipoprotein E is a major lipoprotein present in both the peripheral nervous system (PNS) and the central nervous system (CNS) of the human body. Although within the CNS, apolipoprotein E is mainly produced in astrocytes, gene expression of apolipoprotein E can occur in neurons in response to injury (Xu et al., 2006). The main functions of apolipoprotein E include cholesterol transport, anti-inflammatory activities, neuronal repair and dendritic growth (Lahiri, 2004; Mahley, Weisgraber, & Huang, 2006).

APOE is the gene coding for apolipoprotein E, and has its locus on chromosome 19. The *APOE* gene has three possible allelic variations, ε2, ε3 and ε4, depending on the position of cysteine and arginine on positions 112 and 158 of chromosome 19 (Mahley, 1988). *APOE* ε2 has cysteine on both positions, *APOE* ε3 has cysteine on position 112 and arginine on position 158, and *APOE* ε4 has arginine on both positions (Lahiri, 2004). The three alleles differ in population frequency. The ε3 allele is the most common with a frequency of approximately 78%, while the ε2 and ε4 alleles have a population frequency of approximately 6% and 14%, respectively (Eisenberg, Kuzawa, & Hayes, 2010). Humans have two *APOE* alleles, which results in a total of 6 possible genotypes; ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4. *APOE* ε2 has been suggested as a protective factor against the development of AD (Farrer et al., 1997). However, the specific effects of *APOE* ε2 are out of scope for this thesis, which hereafter focuses on the ε4 allele.

APOE ε4 and pathology – Alzheimer's disease

Although the focus of this thesis is not *APOE* in relation to pathology, a little should be said on the topic. One of the main pathologies with which *APOE* is associated is AD. There are two different forms of AD: early onset, which is relatively rare and occurs in individuals under 65 years of age, and late-onset, which occurs after the age of 65 (Rossor, Fox, Mummery, Schott, & Warren, 2010; Sá et al., 2012). For the purposes of this thesis, all references made to AD hereafter will refer to the late-onset variety.

APOE ε4 has commonly been pointed out as a major risk factor for developing AD, being second only to age. In patients suffering from AD, approximately 40% carry the ε4 allele (Bertram & Tanzi, 2008) and individuals that

are heterozygous ε4 carriers (meaning that they carry only one ε4 allele) are three times as likely to develop the disease than those who have none. There appears to be a gene-dose effect of *APOE* ε4, meaning that the presence of two ε4 alleles increases the susceptibility to pathology compared to having just one allele. Indeed, homozygous ε4 carriers are eight times more likely to develop AD than those who have none (Corder et al., 1993). Moreover, *APOE* ε4 is also linked to a decrease in age of disease onset (Blacker et al., 1997; Corder et al., 1993; Filippini, Rao et al., 2009).

APOE ε4 is associated with the two main neurodegenerative mechanisms of AD – formation of amyloid β peptides (also known as "plaques") and neurofibrillary tangles. Of these two, neurofibrillary tangles typically develop within the MTL (Arnold, Hyman, Flory, Damasio, & Hoesen, 1991), mainly in the entorhinal cortex but also in the hippocampus. Neurofibrillary tangles are cytoskeletal abnormalities that originate from hyper-phosphorylation of tau protein in neurons. Tau, when normally regulated by phosphorylation, acts as a stabilizer of microtubules in the cell. When this process is disturbed, the abnormal accumulation of tau causes the protein to disassemble, leading to loss of neuronal function (Kandel, 2013; Lim & Lu, 2005). *APOE* ε4 is associated with hyper-phosphorylation of tau, while *APOE* ε3 is believed to protect against hyper-phosphorylation. *APOE* ε4 also stands out compared to *APOE* ε2 and ε3 with regard to neuronal maintenance. The apolipoproteins coded for by the *APOE* ε2 and ε3 variants are very involved in the repair of neurons, while the apolipoprotein coded by *APOE* ε4 is less so. In addition, *APOE* ε3 is associated with neuronal growth while *APOE* ε4 is not (Holtzman et al., 1995; Li et al., 2009; Mahley et al., 2006). In line with this, hippocampal atrophy is seen early in the development of AD and also in the progression from initial stages to fully developed AD (Henneman et al., 2009; Pol et al., 2006). Furthermore, *APOE* ε4 has been associated with increased hippocampal atrophy in both AD and mild cognitive impairment (MCI), a prodromal stage to AD (Aguilar et al., 2014; Lehtovirta et al., 1995; Manning et al., 2014).

Taken together, *APOE* ε4 is associated with the neurodegenerative processes common to AD. As many of these processes are structurally related to the hippocampus, it is highly relevant to assess how hippocampal volume is related to *APOE* ε4. In the following, I am going to focus on how *APOE* ε4 is related to hippocampal volume in the absence of pathology.

APOE and hippocampal volume

Healthy aging

Given the association between *APOE* ε4 and hippocampal atrophy in AD described above, many have also assessed the structural effects of *APOE* ε4 in healthy aging. The idea is that hippocampal atrophy in healthy *APOE* ε4 carriers may constitute an early sign of future pathology. Indeed, longitudinal studies have found that cognitively intact, healthy elderly *APOE* ε4 carriers show higher degrees of hippocampal atrophy over time than non-carriers (Li et al., 2016; Lu et al., 2011; Moffat, Szekely, Zonderman, Kabani, & Resnick, 2000; Risacher et al., 2010; Shi et al., 2014). Smaller hippocampal volumes in ε4 carriers compared to non-carriers have also been seen in cross-sectional samples (Lind et al., 2006; Tohgi et al., 1997). It should be noted that there are also studies showing no effect of *APOE* ε4 carrier status on hippocampal volume in healthy elderly samples (Bondi, Houston, Eyler, & Brown, 2005; Du et al., 2006).

With regard to differences within the hippocampal structure, some studies show that the differences are most pronounced in the right hippocampus (Lind et al., 2006; Lu et al., 2011; Tohgi et al., 1997), while others have found smaller volumes in the left hippocampus (Shi et al., 2014; Striepens et al., 2011). *APOE* ε4 has previously been associated with reduced volume in CA1 (Kerchner et al., 2014), CA3 and DG (Mueller, Schuff, Raptentsetsang, Elman, & Weiner, 2008). However, to my knowledge, the effects of *APOE* ε4 have not been assessed with regard to either the head-body-tail or the anterior-posterior division.

Young adults

If the effect of *APOE* ε4 on hippocampal volume is a potential early marker of future pathology, then it is of interest to assess how early *APOE* ε4-related volume effects can be detected. Although quite commonly assessed, findings of reduced hippocampal volume in relation to *APOE* ε4 in young adults are sparse. There are some reports of smaller hippocampal volumes in young healthy ε4 carriers (Alexopoulos et al., 2011; O'Dwyer et al., 2012), with the latter study also finding smaller right hippocampal volume in young adults. However, others have found no differences in hippocampal volume

between ε4 carriers and non-carriers (Dennis et al., 2010; Dowell et al., 2013; Filippini et al., 2009; Matura et al., 2014).

Thus, the association between *APOE* ε4 and hippocampal volume in relation to age is inconclusive, with studies finding smaller hippocampal volume in older ε4 carriers, and comparable and smaller hippocampi in young ε4 carriers. It is unclear whether *APOE* ε4 interacts with age in terms of hippocampal volume or if *APOE* ε4 is associated with smaller volume regardless of age. This thesis aims at further exploring the association between *APOE* ε4 and hippocampal volume in mainly young adults but also in middle-aged and older individuals.

Furthermore, given that the hippocampus is a functionally heterogeneous structure, it is possible that assessing differences in hippocampal volume in relation to *APOE* ε4 with this in mind may yield different results. It is therefore highly desirable to consider subsegments of the hippocampus when assessing potential effects of *APOE* ε4.

Gray matter volume patterns related to *APOE* ε4

Given the inconsistency of the relation between *APOE* genotype and hippocampal volume in healthy young individuals, it is possible that the differing cognitive profile of *APOE* ε4 carriers is reflected in more global measurements of brain structure, rather than in specific and isolated regions. Indeed, in the literature assessing hippocampal function, this factor is being taken into account. Assessing how *APOE* ε4 is related to connectivity between different brain regions, findings suggest that changes related to how brain regions function together as networks may be more indicative of detrimental effects of genotype, rather than functional changes of a specific structure (Filippini et al., 2009; Machulda et al., 2011; Petrella, Sheldon, Prince, Calhoun, & Doraiswamy, 2011). Indeed, it may be useful to consider also brain structure in terms of global rather than local patterns, as the brain is a dynamic system, which relies on interactions between both neurons and structures. As the focus of this thesis is on structural and not functional brain measures, I will go on to describe how this way of thinking has been implemented in the structural literature.

Although it is most common to study gray matter differences when assessing structural effects of *APOE* ε4, differences in white matter networks have also been found. *APOE* ε4 has been related to disrupted white matter integrity and increased rates of myelin breakdown in both healthy elderly (Bartzokis et al., 2006; Nierenberg et al., 2005; Persson et al., 2006) and young adults (Heise, Filippini, Ebmeier, & Mackay, 2011, but see Dowell et al., 2013).

With regard to gray matter volume, it may be informative to assess volume of a structure given the volume of other brain regions it may interact with. I will hereafter refer to this as structural covariance. Previous studies have shown associations between functional connectivity in the absence of a task, (so called resting-state functional connectivity) and structural covariance of different brain regions (Alexander-Bloch, Raznahan, Bullmore, & Giedd, 2013; Seeley, Crawford, Zhou, Miller, & Greicius, 2009), thus indicating a functional relevance of structural covariance. Assessing structural covariance in relation to *APOE* ε4, Spreng and Turner (2013) found that in ε4 carriers, increasing age was associated with lower degrees of structural covariance between regions within the most prominent resting network in the brain, the default mode network (DMN).

In this thesis I will further assess structural covariance in relation to *APOE* ε4. In Study II, I will explore whether the anterior and posterior hippocampus differs in their respective structural covariance with the rest of the brain as a function of *APOE* ε4 in young adults.

APOE ε4 and hippocampus-dependent memory

Healthy aging

Cognitive deficits are common in AD. As with hippocampal volume, the strong connection between *APOE* ε4 and the disease has sparked an interest in examining potential associations between *APOE* ε4 and cognition in healthy populations. Studies have shown that in healthy aging, *APOE* ε4 is associated with worse performance in many cognitive domains, including global cognitive ability, executive functioning, perceptual speed and memory (Honea, Vidoni, Harsha, & Burns, 2009; and see meta anlysis by Wisdom, Callahan, & Hawkins, 2011).

Episodic memory

Within the memory domain, episodic memory has been found to be especially vulnerable to both increasing age and *APOE* ε4 (Nilsson, Nyberg, & Bäckman, 2002). A considerable amount of the findings stem from large longitudinal studies that have shown a negative impact of *APOE* ε4 on episodic memory performance in healthy aging (Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012; Nilsson et al., 2006) as well as more rapid decline (Caselli et al., 2009; Wilson et al., 2002). The association between *APOE* ε4 and episodic memory impairment has also been corroborated in cross-sectional studies (Bondi et al., 1995; Helkala et al., 1995) and meta-analyses (Small, Rosnick, Fratiglioni, & Bäckman, 2004; Wisdom et al., 2011).

Spatial memory

The effect of *APOE* ε4 on spatial memory in healthy aging has not been as thoroughly explored as the associations to episodic memory. However, considering *APOE*'s structural effects on the hippocampus, and that the hippocampus is involved in both episodic and spatial memory, it is of great interest to also assess possible associations between *APOE* ε4 and spatial memory. Visuospatial attention and spatial working memory have been assessed, and found to be reduced in *APOE* ε4 carriers (Greenwood, Sunderland, Friz, & Parasuraman, 2000; Greenwood, Lambert, Sunderland,

& Parasuraman, 2005), but findings regarding spatial ability with a navigational component are lacking. As described above, navigation is highly dependent on the hippocampus and it is therefore of importance to specifically assess this spatial memory domain in relation to *APOE* ε4. One study that did assess spatial memory with a navigational task found that ε4 carriers performed significantly worse compared to non-carriers (Berteau-Pavy, Park, & Raber, 2007).

Young adults

Interestingly enough, the association between cognition and *APOE* ε4 in younger populations is quite different than that in healthy aging. Rather than being linked with worse cognitive performance, the presence of the ε4 allele has instead been related to better attention (Rusted et al., 2013), working memory (Mondadori et al., 2007), decision making and prospective memory (Marchant, King, Tabet, & Rusted, 2010), verbal fluency (Alexander et al., 2007), and executive functioning (Han et al., 2007) in young adults. However, there are also studies showing no such beneficial effect of *APOE* ε4 on cognition (Bunce, Anstey, Burns, Christensen, & Easteal, 2011; Ihle, Bunce, & Kliegel, 2012).

Episodic memory

The cognitive advantage of young *APOE* ε4 carriers appears to also include episodic memory. Two studies have shown that in young adults, episodic memory performance benefits from the presence of an ε4 allele (Han et al., 2007; Mondadori et al., 2007). Although the positive effects of *APOE* ε4 on episodic memory early in life need to be further demonstrated, it is especially interesting considering the episodic memory impairments seen in older healthy *APOE* ε4 carriers.

Spatial memory

Visuospatial ability and spatial working memory have been assessed in young adults, but no *APOE* ε4-related difference has been found (Bloss, Delis, Salmon, & Bondi, 2010; Marchant et al., 2010). To the best of my knowledge, only two studies have assessed spatial navigation in relation to *APOE* ε4 in young individuals, one in children aged 7-10 (Acevedo, Piper, Craytor, Benice, & Raber, 2010) and one in young adults aged 18-22 (Yasen, Raber, Miller, & Piper, 2015). Both of these studies used the same virtual navigational test in which the task is to navigate to a hidden target. While there was no effect of *APOE* ε4 in young adults, children *APOE* ε4

carriers showed worse memory retention of the target's location compared to non-carriers.

APOE – a case of antagonistic pleiotropy?

What is evident from the previous chapter is that *APOE* ε4 appears to be differently associated with episodic memory in healthy older individuals than it is in young adults. It has been proposed that *APOE* is a gene showing antagonistic pleiotropy (Alexander et al., 2007; Han & Bondi, 2008; Wright et al., 2003). Antagonistic pleiotropy is a concept that was first introduced by George Williams (Williams, 1957) and may help explain why some genes are still present in the gene pool in spite of the negative effects they may have on organisms. It means that a given genotype gives rise to more than one phenotype of which at least one is negative. As, for example, when *APOE* ε4 has beneficial effects in young age with the cost of decreased cognitive ability and detrimental biological development in older age.

The hypothesis of *APOE* being an example of antagonistic pleiotropy prompts the question of when the negative effects of *APOE* ε4 begin to emerge. When assessing cognition in relation to *APOE* ε4 across different age groups, ε4 carriers showed better performance compared to non-carriers up to the age of 57, while the relationship shifted after that age (Jochemsen, Muller, van der Graaf, & Geerlings, 2012). However, worse performance in *APOE* ε4 carriers compared to non-carriers has also been shown in the fourth decade of life (Flory, Manuck, Ferrell, Ryan, & Muldoon, 2000). Thus, providing *APOE* is a gene showing antagonistic pleiotropic properties, the onset of the shift is not fully known. In Study III, this will be assessed in relation to episodic and spatial memory specifically.

Sex differences in relation to *APOE* ε4

Sex has been shown to be an influential factor in all of the domains described thus far in this thesis. In the cognitive domain, sex differences in episodic and spatial memory are a common finding. These findings are most robust with regard to spatial performance, with men outperforming women on visuospatial tasks such as mental rotation (Burton, Henninger, & Hafetz, 2005; Voyer, Voyer, & Bryden, 1995) and on navigational memory tasks (Astur, Ortiz, & Sutherland, 1998; Lawton & Morrin, 1999; Piper et al., 2011). Women on the other hand, have been found to excel in episodic memory tasks, and especially those of a verbal nature (Herlitz, Nilsson, & Bäckman, 1997; Herlitz & Rehnman, 2008).

There is also a sex difference with regard to susceptibility to *APOE* ε4-related pathology. The association between *APOE* ε4 and the development of AD has been shown to be stronger in women than in men (Bretsky et al., 1999; Corder et al., 2004; Payami et al., 1996). In addition, cognitive decline in healthy elderly ε4 carriers appears to be more pronounced in women than in men, suggesting that sex influences the association between cognition and *APOE* ε4 (Bartrés-Faz et al., 2002; Hyman et al., 1996; Mortensen & Høgh, 2001).

With regard to hippocampal volume, there are studies reporting larger hippocampal volume in women compared to men (Giedd et al., 1996; Perlaki et al., 2014; Persson et al., 2014; Szabó, Lancaster, Xiong, Cook, & Fox, 2003) although others find no differences between sexes (Bueller et al., 2006; Lange, Giedd, Xavier Castellanos, Vaituzis, & Rapoport, 1997; Mu, Xie, Wen, Weng, & Shuyun, 1999). Furthermore, in a study of individuals with MCI, the association between *APOE* ε4 and hippocampal volume reduction was more pronounced in women (Fleisher et al., 2005).

Taken together, the literature on sex difference suggests that it is important to assess how sex might potentially modulate the effects that *APOE* ε4 and age may have on episodic and spatial memory performance and hippocampal volume. Therefore, sex will be included as a factor of interest in this thesis.

Aims

The general aim of this thesis was to move on from the knowledge of the effects of *APOE* ε4 on cognition and hippocampal volume in dementia and healthy aging, and explore the effects it has in healthy young adults. Specifically, episodic and spatial memory are assessed, as these cognitive functions are both dependent on the hippocampus. Furthermore, the hippocampus will not be assessed as a whole, but rather by dividing it into subsegments along its anterior-posterior axis.

More specifically, the aims of this thesis are to explore:

- Whether episodic and spatial memory performance is related to *APOE* ε4 carrier status in healthy young adults (Study I)
- Whether the volume of the hippocampus in terms of the head-body-tail division is associated with *APOE* ε4 carrier status in young adults (Study I)
- Whether *APOE* ε4 affects how anterior and posterior hippocampal volume covary with volume in the rest of the brain (Study II).
- As sex differences are often found in relation to episodic and spatial memory, and effects of *APOE* may be modulated by sex, the effects of sex (and potential interactions with *APOE*) on cognitive performance and hippocampal volume (Studies I and III), and structural covariance of the hippocampus (Study II) are assessed.
- Whether there is evidence for the antagonistic pleiotropy hypothesis, by assessing *APOE* ε4-related effects on episodic and spatial performance as well as hippocampal volume in young, middle-aged and elderly individuals (Study III)

Methods

Magnetic Resonance Imaging (MRI)

MRI is a method used to create high-resolution anatomical images of the brain. It is well suited to assess regional morphology and volumetric assessment of structures, both in medical settings as well as in research. MRI makes use of the fact that hydrogen protons within the brain align themselves along with a strong static magnetic field. During an MRI scanning, a subject is placed within the strong magnetic field yielded by the scanner. A radiofrequency pulse is then emitted and this in turn, excites the protons and makes them break alignment with the magnetic field. When the radiofrequency pulse is switched off, the proton will once again realign with the magnetic field. This process is repeated many times under the scanning sequence. It is the protons movement back to alignment that is measured and used to construct the anatomical image of the brain. Functional images are also possible by using fMRI. In short, this method makes use of the fact that oxygenated and deoxygenated hemoglobin responds differently to the magnetic field. The levels of oxygenation varies depending on the neuronal activity, thus fMRI is used as a measure of brain activity (Huettel, Song, & McCarthy, 2009).

Project overview

Study I, II and III are based on three data collections made at the Department of Psychology, Uppsala University and at the Uppsala University Hospital. During the first data collection, memory tasks were performed during scanning with fMRI, while during the second data collection, tasks were instead performed in the lab at the Department of Psychology while structural MRI was performed at the hospital. In the third data collection, some participants performed the memory tests during fMRI scanning at the hospital while others were tested at the Department of Psychology. Although no fMRI data, only memory scores are included in the present thesis, it is worth noting that parts of the thesis study sample performed the memory tasks under different circumstances from the others. Study I and II includes data from the first and second data collection, whereas Study III includes data from all three data collections.

Participants

Data was collected from a total of 252 participants, of which 245 (124 women, 121 men) were included in the studies included in this thesis. Attrition was due to mainly two factors; some participants were from a pilot study of the cognitive test and therefore did not have MRI data, and some declined to leave saliva for genetic evaluation. For others, *APOE* ε4 carrier status was not possible to establish. For the first and second data collection participants between the ages 18 and 35 were recruited from the Uppsala University campus area. For the third data collection individuals from two age cohorts (40-50 and 60-70 years of age) were recruited from the population registry and by local newspaper advertisements. The final sample consisted of 123 young adults, 59 middle-age and 63 older individuals (see Table 1 for demographical information of the sample). The 97 participants in Study II was a subsample of that from Study I, and were also included in Study III. All participants were right-handed with no contraindications of MRI, had no history of substance abuse, neuropsychological or neurological disease or brain injury. Participants gave informed consent as approved by the regional ethics review board in Uppsala and were reimbursed for their involvement in the studies.

Table 1. *Demographical information of Study I, II and III*

	Study I	**Study II**	**Study III**		
n	123	97	Young = 97 †	Middle-age = 59	Older = 63
Age, yrs. (*M, SD*)	23.8 (3.3)	24.3 (3.4)	24.3 (3.4)	44.6 (3.1)	65.0 (3.0)
Age range	*19-35*	*20-35*	*20-35*	*40-50*	*60-70*
Sex (female/male)	62/61	48/49	48/49	30/29	32/31
Education, yrs. (*M,SD*)*	14.9 (1.7)	15.1 (1.7)	15.1 (1.7)	16.5 (4.0)	16.2 (4.1)
APOE					
ε4 carriers (female/male)	40 (18/22)	29 (11/18)	29 (11/18)	24 (13/11)	17 (8/9)
non-carriers (female/male)	83 (44/39)	68 (37/31)	68 (37/31)	35 (17/18)	46 (24/22)

* Significant difference between age groups at $p < .05$ (young < middle-age = older)

† Note that the young group is the same as in Study II

Procedure

MRI data were collected from all participants at the Uppsala University Hospital. As mentioned above, cognitive testing took place either in the scanner at the hospital or in the lab at the Department of Psychology. For those who were tested at two separate occasions, the scanning and the cognitive testing were scheduled as close in time as possible. In conjunction to testing, all participants included in this thesis gave a saliva sample for genetic assessment. Participants also gave a blood sample for assessment of hormones and other variables, not included in this thesis.

MRI scanning protocol

Scanning was performed on a Philips Achieva clinical whole-body 3 T scanner with an 8-channel head coil (Achieva X-series, Philips Medical Systems, Best, The Netherlands). Structural T1-weighted images were obtained with a 3D magnetization prepared rapid gradient echo sequence (repetition time = 9 ms; echo time = 4 ms; inversion time = 900 ms; shot interval = 3000 ms; flip angle = 9°; field of view = 240 x 240 mm; voxel size = 1 mm^3 isotropic voxels; 170 slices).

Genotyping

Saliva samples were subjected to *APOE* (gene map locus 19q13.2) genotyping using TaqMan Allelic Discrimination technology. Genotypes were obtained for the two SNPs that are used to unambiguously define the ε2, ε3, and ε4 alleles (rs7412 and rs429358). The total thesis sample consisted of 1 ε2/ε2 homozygote (0.5%), 17 ε2/ε3 heterozygotes (7.7%), 131 ε3/ε3 homozygotes (59.8%), 4 ε2/ε4 heterozygotes (1.8%), 60 ε3/ε4 heterozygotes (27.4%) and 6 ε4/ε4 homozygotes (2.7%). Specific allele frequencies for the separate studies are presented below. For all studies, ε2/ε4, ε3/ε4 heterozygotes and ε4/ε4 homozygotes were grouped together as ε4 carriers and the rest were grouped together as non-ε4 carriers. Thus, the question of the possible gene-dose effect of APOE ε4 is not assessed in this thesis due to the too small number of ε4 homozygotes.

Materials

Four tasks assessing episodic and spatial memory were created for this project.

Episodic memory tasks

Word List

In this verbal episodic task, participants viewed 80 nouns presented in white type on black background at the center of a computer screen. Only nouns with a frequency of between 50 and 149 per million were included in the

task. Each noun was presented for 2 s and during this time, participants had to make an abstract/concrete judgment of the word. Recognition memory was tested by having participants make an old/new decision of the 80 target nouns and 80 new nouns serving as distractors. Each noun was again presented for 5 s or until an answer was given by the participant. Adjusted recognition rate was calculated by subtracting the false alarm rate from the hit rate, and was used as the outcome measure in Studies II and III, whereas d-prime (d') was used in Study I.

In the third data collection, a slightly different version of this word list task was used. In this version, 50 nouns were presented during the encoding phase and 25 new nouns served as distractors during recognition. In Study III, word list data from the two different versions of the tasks were used together and this difference were controlled for in all analyses including this measure.

Object Location task

The object location task introduces a spatial component in the episodic memory testing. In this task, 88 drawings of objects (Snodgrass & Vanderwart, 1980) were presented in a 2 x 2 grid on a computer screen. The objects were presented in one of the four quadrants of the screen. Participants were instructed to classify the objects as either man-made or naturally occurring, while memorizing the objects and their locations. In a subsequent recognition test, the targets were presented together with 44 new object drawings serving as distractors. Participants had to make an old/new decision for each object and if they stated that the object was old, they were asked to indicate in which quadrant it had been presented. The item memory outcome measure was d', and the location memory outcome measure was the rate of correctly recalled locations. The object location task was only used in the first and second data collection and is thus not included in Study III. The reason for it being omitted in Study III was the need to shorten the test procedure due to the age of the participants.

Spatial memory tasks

Pointing task

The "Pointing task" is based on a similar task (Lawton & Morrin, 1999), and consists of a virtual maze environment presented on a computer. The mazes included in the task differed in length between trials. There were mazes with 2, 4 or 6 right-angle turns and two layouts of each length including mirrored counterparts, resulting in a total of 12 unique maze layouts. No alternative paths were possible and the distance between each turn was held constant across all mazes. Participants were instructed to make their way through each maze, by means of pressing buttons that allowed forward

movement and left and right turns. While traveling the maze, they were instructed to keep track of the direction to the original starting position. When reaching the end point, their task was to point an arrow towards their starting position. The outcome measure was the amount of errors made in the pointing phase, as measured by the deviation in degrees from the correct pointing angle.

Water Maze task

This task is a virtual version of the Morris Water Maze task which was adapted from the rodent literature on spatial learning (Morris et al., 1982). In a virtual room presented on a computer screen, participants were instructed to swim (by means of buttons that allowed forward movement and left and right turns) in a circular pool of water while searching for a hidden platform within the pool. The room was empty, with the exception of four visual cues that were placed on the four walls of the room: two paintings and two windows. When the platform was found, participants were given a few seconds to rotate left and right in order to memorize their location within the virtual environment. For each new trial, participants were positioned at one of three starting locations in the pool and were again to search for the platform (which was always at the same location throughout the task). The outcome measure was the time (s) and swimming distance (cm) it took to reach the platform.

Neuropsychological measures

Mental Rotation

A redrawn version of the classic Mental Rotations Test (Peters et al., 1995; Vandenberg & Kuse, 1978) was used. In this task, participants had to identify the two (out of four) 3D-rotated geometrical figures that match a target. There were 20 targets in total, and there was a 10-minute time limit to complete as many items as possible. The number of incorrect identifications was subtracted from the number of correct identifications, resulting in "corrected hits" which was used as the outcome measure. Although mental rotation is categorized as a neuropsychological measure here, in Studies I and II it is included as measure of spatial function.

Trail-Making Test (TMT) A and B

The TMT is a connect-the-dots task used to assess visual search, processing speed, flexibility and executive functioning (Reitan, 1958; Tombaugh, 2004). In TMT A, 25 dots with numbers should be connected in increasing order, while in TMT B, it is required to alternate between numbers and letters, also in an increasing order. The task is performed on a time limit.

Verbal Fluency

In this task, participants are asked to orally generate as many words as possible beginning with a given letter during one minute. The letters given are F, A, and S. This task is a measure of cognitive flexibility and speed as well as semantic memory functioning (Lezak, 2004).

Verbal knowledge

To assess general verbal knowledge, a synonyms test was administered, consisting of 30 multiple-choice items with five alternatives each (Dureman, 1960).

Letter Digit Substitution

In this task participants are instructed to substitute digits (1-9) with letters according to a pairing key that they are allowed to practice on for 10 items. After the practice, they have to complete as many consecutive items as possible in one minute. This task measures psychomotor speed, flexibility and sustained attention (Elst, Dekker, Hurks, & Jolles, 2012; Lezak, 2004).

Corsi Block tapping task

In this task, which measures executive functions and visuospatial attention, the participant is to observe and then repeat the order in which an increasing number of blocks are tapped (Corsi, 1972).

Mini Mental State Examination (MMSE)

In the third data collection, MMSE was administered in order to rule out dementia in participants in the older age group.

Segmentation of the hippocampus

As mentioned in the introduction, the studies included in this thesis have implemented two types of hippocampal division along its anterior-posterior axis. This is done to explore the possible effects of *APOE* ε4 on hippocampal volume in light of the proposed heterogeneity of the hippocampus with regard to episodic and spatial function. In Study I the head-body-tail division is used, while the anterior-posterior division is used in Study II. The two different divisions were made using different methodologies, which I will describe below.

Manual tracing

Manual tracing is, albeit time consuming, considered the golden standard of brain segmentation. It allows for exact and detailed delineation of brain

strucutres, and was the method chosen in Study I. Manual tracing on raw structural images was used to divide the hippocampus into head, body and tail. The hippocampus was traced using a mouse-driven cursor using the ITK-SNAP software (Yushkevich et al., 2006) where all planes where visible simultaneously. Tracing of the hippocampal head, body and tail (see Figure 1 A-B), was done according to established protocols (Malykhin et al., 2007; Pruessner et al., 2000) All tracings were done in the coronal plane, starting at the most anterior slice. The tracing protocol is described in Study I, but for the sake of completeness it is also include it here.

Tracing of the hippocampal head

The most anterior slice was the slice where the parahippocampal white matter was visible. The parahippocampal white matter marked the inferior border of the hippocampal head in the coronal plane. The medial border of the hippocampal head was defined by the alveus. The uncinate gyrus was excluded from the hippocampal head in more anterior slices, and included in more posterior slices. The subiculum was included both inferior and medial to the hippocampus. The entorhinal cortex was excluded from tracing. The most posterior slice of the hippocampal head was the most posterior slice where the uncus was clearly visible.

Tracing of the hippocampal body

The fimbria was consistently included in the tracing of the hippocampal body. The parahippocampal gyrus separated the entorhinal cortex from the subiculum, which was included in the tracing. The lateral border of the hippocampal body was marked by the inferior horn of the lateral ventricle.

Tracing of the hippocampal tail

The most anterior slice of the hippocampal tail was the most anterior slice where the crus of fornix was clearly visible. The fornix was consistently excluded from the tracing of the hippocampal tail whereas the fimbria was included.

Anterior-posterior division of the hippocampus

For Study II, an automated segmentation procedure was used. This was done in order to assure comparability with previous work from our lab (Persson et al., 2014). In order to use this automated approach, the structural brain images were first preprocessed using Statistical Parametric Mapping (SPM 8; Wellcome Department of Cognitive Neurology, University College London, www.fil.ion.ucl.ac.uk/spm). In short, the images were segmented into gray matter, white matter and cerebrospinal fluid (CSF) using the New Segment function implemented in SPM (Ashburner & Friston, 2005). All individual gray matter images were warped to the same template, and aligned to the

Montreal Neurological Institute (MNI) space and smoothed using a kernel of 8 mm full width at half maximum (FWHM). This is done so that all brains are placed within the same space and so that potential distortions in the images due to movement and different brain size are reduced to a minimum.

The anterior-posterior division of the hippocampus was made by using an existing hippocampus mask from the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) from the Wake Forest University PickAtlas (WFUPickatlas) toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003). The mask was superimposed on an average image of all individual structural images included in the study. The hippocampus mask was then divided into four seed regions of interest (ROIs); anterior and posterior bilaterally, in concordance with previous studies (Persson et al., 2014; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). The anterior and posterior masks spanned from -2 to -18 and -24 and -42 along the y-axis, respectively (see Figure 1 C).

Controlling for intracranial volume

In order to assess group differences in the volume of specific brain structures, these volumes need to be corrected for brain size. In Study I, intracranial volume (ICV) was obtained by manual tracing following the guidelines from Eritaia et al. (2000) and Malykhin et al. (2007). In short, tracing was done along the dura mater, including gray and white matter as well as CSF. Every 10th slice was manually traced in the sagittal plane. The ICV for each subject was then estimated by multiplying the summed total volume by 10. Where automated volume estimation was used (Studies II and III), ICV was calculated by summing the gray matter, white matter and CSF images. Hippocampal volume estimates for each individual were subsequently corrected by dividing them with the corresponding measure of ICV.

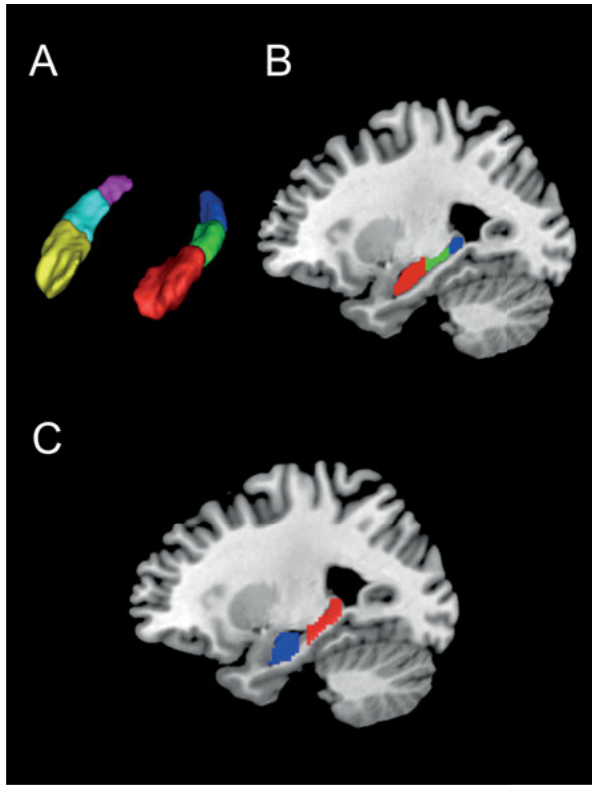

Figure 1. A) Manual segmentation of the hippocampal head, body and tail in 3D space and B) 2D space overlaid on a sagittal slice (B). Left hippocampus: Head = red, Body = green, Tail = blue. Right hippocampus: Head = yellow, Body = cyan, Tail = magenta. C) View of the anterior (red) and posterior (blue) division of the hippocampus

Partial Least Squares

In Study II, structural covariance patterns of the bilateral anterior and posterior hippocampal subsegments are assessed. This is done by partial least squares (PLS; Anthony Randal McIntosh & Lobaugh, 2004; McIntosh, Bookstein, Haxby, & Grady, 1996). PLS is a multivariate analysis approach that in relation to brain measures mainly has been used with fMRI and positron emission tomography (PET) but also for analysis of structural brain images (Spreng & Turner, 2013). Structural PLS assesses the relationship between patterns of gray matter volume in the whole brain to other measures, be it a behavioral variable or, as is the case here, the volume of a seed region. These relationships are expressed as orthogonal latent variables (LVs), similar to factors in common factor analysis. Permutation testing is

used to assess the statistical significance of the LVs, while the reliability of the saliences is estimated using a bootstrapping procedure resulting in a voxel-wise bootstrap ratio (BSR). For Study II, 5000 permutations and 5000 bootstraps were performed. LVs were considered significant at a threshold of $p < .05$, and a voxel BSR of at least 3.3 (corresponding to a p-value of .001) was considered reliable. Owing to the multivariate approach taken, significance testing is made on the entire set of LV's, avoiding the common issue of mass significance.

For each LV, a set of measures are obtained, characterizing that particular LV. Each voxel is ascribed a weight (salience) reflecting its contribution to the pattern described by that LV. These saliences can be either positive or negative. By using these voxel saliences to calculate a weighted sum of all voxel volumes, a brain score is obtained for each individual for a given LV, reflecting how much that individual adheres to the volumetric pattern expressed by the LV. These brain scores, in turn, can be correlated against the volumes of each seed region, as a function of group, to assess how each seed region is related to that LV's pattern, for each group. As such, the structural covariance of an LV is reflected in these brain score - seed volume correlations. Finally, brain scores can be correlated with a behavioral measure, such as cognitive performance. Such a correlation is informative of the functional relevance of that covariance pattern.

Summary of studies

Study I

Background

As *APOE* ε4 is the major genetic risk factor for AD, which is associated with episodic impairment, the association between *APOE* ε4 and episodic memory function has also been assessed in healthy individuals. Findings indicate a negative association between *APOE* ε4 and episodic memory in elderly (Wisdom et al., 2011), and a positive association in young adults (Han et al., 2007; Mondadori et al., 2007). The presence of *APOE* ε4 has also been shown to be negatively associated with gray matter volume of the hippocampus in healthy elderly while the findings are inconclusive in young adults. Given that the hippocampus is a structure important for both episodic and spatial memory, it is of interest to assess the effect of *APOE* ε4 also on spatial memory. By doing so, it is possible to assess if the positive effect of *APOE* ε4 on episodic memory in young adults can be extended to another hippocampus-dependent memory type. Study I aims at exploring the association between *APOE* ε4 and episodic and spatial memory in healthy young adults. In addition, due to the hippocampus being important for both memory types and *APOE* ε4 having negative effects on hippocampal volume in aging, differences in hippocampal volume as a function of *APOE* ε4 carrier status is also assessed.

Methods

A total of 123 adults (62 women/61 men) between 19 and 35 years of age (M=23.8, SD=3.3) with 12 to 20 years of education (M=14.9, SD=1.72) participated in Study I. The *APOE* allele distribution was: 8 ε3/ε2 heterozygotes (6.5%), 75 ε3/ε3 homozygotes (61%), 5 ε4/ε2 heterozygotes (4,1%), 32 ε4/ε3 heterozygotes (26%) and 3 ε4/ε4 homozygotes (2.4%). All individuals carrying one or more ε4 alleles were grouped together as ε4 carriers (n= 40) and the rest were grouped together as non-carriers (n= 83).

In Study I, the word list and object location tasks were used to assess episodic memory, while spatial memory was assessed using the pointing and water maze tasks. Mental rotation was included as a test of spatial function. Rather than using these tasks as single measures, a principal component

analysis (PCA) was performed in order to create composite scores. The Keiser-Meyer-Olkin measure of sampling adequacy was .66, and Bartlett's test of sphericity was significant (χ^2 [21] = 155.73, $p < .001$). Two factors (with eigenvalues > 1) that explained 57 % of the total variance were extracted and subsequently rotated using an oblique rotation (direct oblimin). Object location item and location memory loaded together on one factor, making up a composite variable of Object Location Memory. The word list task did not show high loadings on any of the factors and was used as a single measure. Mental rotation (corrected hits), pointing (error) and water maze (time) loaded together on one factor, making up a composite variable of Spatial Function and Memory. Data for the composite measures were z-transformed and averaged.

To assess potential effects and interactions of *APOE* ε4 and sex on the cognitive composite measures, 2 x 2 ANCOVAs controlling for age and education were conducted.

The manual tracing method described above was used to assess hippocampal volume. The effects and interactions of *APOE* ε4 and sex on volume of the left and right hippocampal head, body and tail were assessed by ANCOVAs also controlling for age and education. All statistical analyses were performed in the SPSS software package.

Results

APOE ε4 carriers outperformed non-carriers in Spatial Function and Memory and Object Location memory, but there was no effect of *APOE* ε4 on Word List performance. Furthermore, *APOE* ε4 carrier status did not have an effect on hippocampal volume. There was a sex difference in Spatial Function and Memory performance, with men outperforming women (see Figure 2). The only effect on hippocampal volume was also related to sex, with women having larger hippocampal body volumes (see Table 2). There were no interactions of *APOE* ε4 and sex on neither the composite measures nor hippocampal volume.

Conclusions

In this study, we extend previous knowledge of better cognitive performance in young ε4 carriers compared to non-carriers and show that also spatial memory performance is positively associated with the presence of *APOE* ε4. *APOE* ε4 carrier status was not related to performance on the episodic Word List task, but there was a positive association between *APOE* ε4 and Object Location memory performance. This may be due to the spatial components of this task. The superior performance of ε4 carriers cannot be explained by differences in volume, since no *APOE*-related differences in volume of the hippocampal head, body or tail volume were

found. This lack of volume effects is in line with previous research (Filippini et al., 2009; Matura et al., 2014).

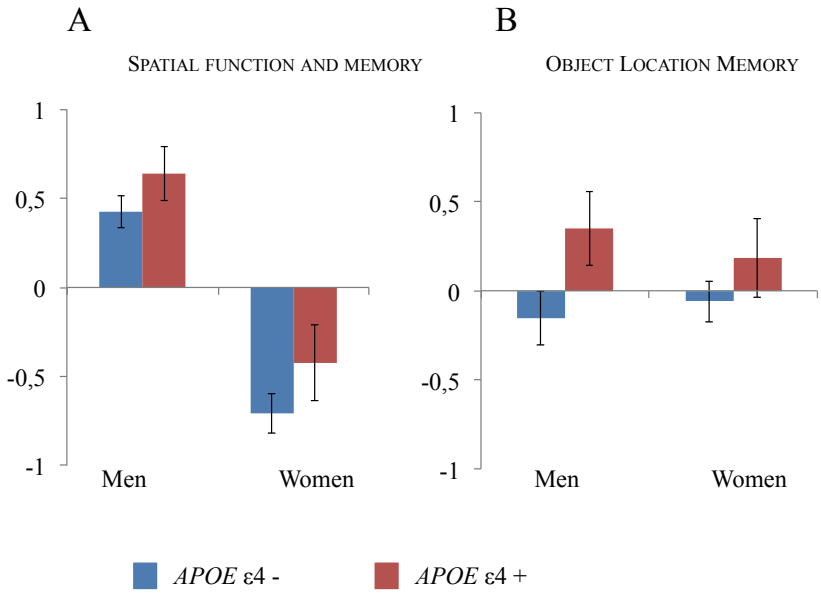

Figure 2. Performance (mean z scores) as a function of *APOE* ε4 status and sex on the Spatial Function and Memory (A) and Object Location Memory (B) composite measures. *APOE* ε4 carriers (red) consistently performed better than non-ε4 carriers (blue) regardless of sex.

Table 2. *ICV and ICV corrected hippocampal volume (mm^3) in men and women as a function of APOE ε4 status (+ or -). Means and standard deviations in parentheses.*

	Men		Women	
	APOE ε4 + (n=18)	*APOE* ε4 - (n=32)	*APOE* ε4 + (n=11)	*APOE* ε4 - (n=37)
Intracranial Volume (ICV)***	1 561,756.7 (113,127.9)	1 563,874.1 (86,414.2)	1 382,380.9 (125,699.2)	1 384,972.4 (93,405.1)
Left hippocampus				
Head	1,146.0 (203.5)	1,128.6 (193.3)	1,074.0 (116.2)	1,107.8 (143.4)
Body***	645.2 (100.6)	625.6 (113.9)	762.8 (90.0)	724.7 (142.9)
Tail	282.6 (47.3)	262.1 (55.8)	287.2 (75.1)	281.7 (56.7)
Total	2,073.9 (201.7)	2,015.8 (221.6)	2,123.9 (140.8)	2,114.1 (206.1)
Right hippocampus				
Head	1,204.5 (155.8)	1,244.1 (178.4)	1,209.3 (251.4)	1,258.7 (183.1)
Body**	651.9 (117.3)	646.2 (121.6)	784.5 (177.9)	714.3 (132.1)
Tail	298.5 (63.9)	293.5 (59.9)	308.3 (92.2)	297.5 (65.0)
Total*	2,154.8 (245.7)	2,183.3 (262.6)	2,302.1 (270.4)	2,270.6 (228.4)

* Men and women differ at $p < .05$

** Men and women differ at $p < .01$

*** Men and women differ at $p < .001$

Study II

Background

While *APOE* ε4 is negatively associated with episodic memory in healthy aging, it has been positively associated with episodic memory performance in young adults. As episodic memory is hippocampus-dependent, the association between *APOE* ε4 and hippocampal volume has been explored in young adults (Dennis et al., 2010; Filippini et al., 2009; Matura et al., 2014; Mondadori et al., 2007). However, findings are inconclusive with most studies reporting no differences. Moreover, when differences in relation to *APOE* ε4 are found in young adults, they tend to point towards smaller volumes

in ε4 carriers (Alexopoulos et al., 2011; O'Dwyer et al., 2012). The inconclusive findings regarding structural differences related to *APOE* ε4 could possibly stem from the fact that most have assessed this using univariate methods. However, the brain is a dynamic system, and cognition is largely shaped by interactions between structures in the form of global brain networks. Hence, Study II uses a multivariate approach to explore how hippocampal volume covaries with gray matter volume in the rest of the brain. The relationship between episodic and spatial performance and structural covariance of the hippocampus is also assessed.

Furthermore, the hippocampus is most often assessed as a whole structure. However, research suggests that it might be useful to study the hippocampus in terms of its anterior and posterior subsegments, especially when assessing memory functions that are most probably differently distributed along the anterior-posterior axis of the hippocampus (Kühn & Gallinat, 2014; Poppenk & Moscovitch, 2011). Thus, in Study II we assessed the hippocampus as four subsegments: left and right, anterior and posterior.

Methods

In this study, 97 participants (48 women/49 men) between 20 and 35 years of age (M=24.3, SD=3.4) with 12 to 20 years of education (M=15.1, SD=1.7) were included. There were 4 ε3/ε2 heterozygotes (4.1%), 64 ε3/ε3 homozygotes (66%), 4 ε4/ε2 heterozygotes (4.1%), 22 ε4/ε3 heterozygotes (22.7%) and 3 ε4/ε4 homozygotes (3.1%). As in Study I, all individuals carrying one or more ε4 alleles were grouped together as ε4 carriers (n= 29) and the rest were grouped together as non-ε4 carriers (n= 68).

Like in Study I, a PCA was used to create composite scores. The Keiser-Meyer-Olkin measure of sampling adequacy was .70, and Bartlett's test of sphericity was significant (χ^2 [21] = 156.16, $p < .001$). Two factors (with eigenvalues > 1) that explained 62 % of the total variance were extracted and rotated using an oblique rotation (direct oblimin). In this study, word list, object location item and location memory all loaded together on one factor, making up a composite variable of Episodic Memory. Mental rotation (corrected hits), pointing (error) and water maze (time) loaded together on one factor, making up a composite variable of Spatial Function and Memory. To calculate the composite measures, the included test values were z-transformed and averaged. All statistical analyses related to cognition were performed in SPSS.

Hippocampal volume was assessed using the anterior-posterior division described above. To assess the covariance patterns of the four hippocampal subsegments, PLS was used (see method section). The covariance patterns emerging from the PLS analysis were subsequently correlated with performance on the episodic and spatial composite measures. This was done separately for men and women, and for *APOE* ε4 carriers and non-carriers in

order to assess the association between structural covariance of the anterior and posterior hippocampus and cognition in relation to *APOE* ε4 status and sex. Due to the large number of tests, false discovery rate (FDR) was computed to correct for multiple comparisons.

Results

From the PLS analysis, two significant LVs emerged. The first LV (named LV2 in accordance with Study II) revealed a three-way segment x sex x genotype interaction, with *APOE* ε4 women showing a different structural covariance pattern of the bilateral anterior hippocampus compared to the other groups (see Figure 3). In female ε4 carriers, anterior hippocampal volumes covaried with volumes of the superior, middle and inferior frontal gyrus, the anterior cingulum and occipital gyri. In all other groups the whole hippocampus (anterior and posterior) showed structural covariance with the precuneus, cerebellum, putamen, the inferior frontal gyrus and middle cingulate cortex.

The second significant LV (named LV4 in accordance with Study II) revealed a segment x genotype interaction, with the patterns of structural covariance of the anterior hippocampus in non-carriers being different from that of the posterior hippocampus in ε4 carriers (see Figure 4). In non-carriers, volume of the bilateral anterior hippocampus covaried with volume in the frontal and postcentral gyrus. In ε4 carriers, the volume of the bilateral posterior hippocampus covaried with volume in the inferior parietal lobule and the orbital, angular and inferior frontal gyri. Worth noting is that in ε4 carriers, this pattern was less reliable in women, albeit significant.

APOE ε4 was positively associated with the Spatial Function and Memory composite, but there was no association between *APOE* ε4 and Episodic Memory. There was also a sex difference in Spatial Function and Memory, with men showing better performance compared to women.

The relationship between the covariance patterns and episodic and spatial performance was assessed, however no correlation was significant after multiple comparison correction.

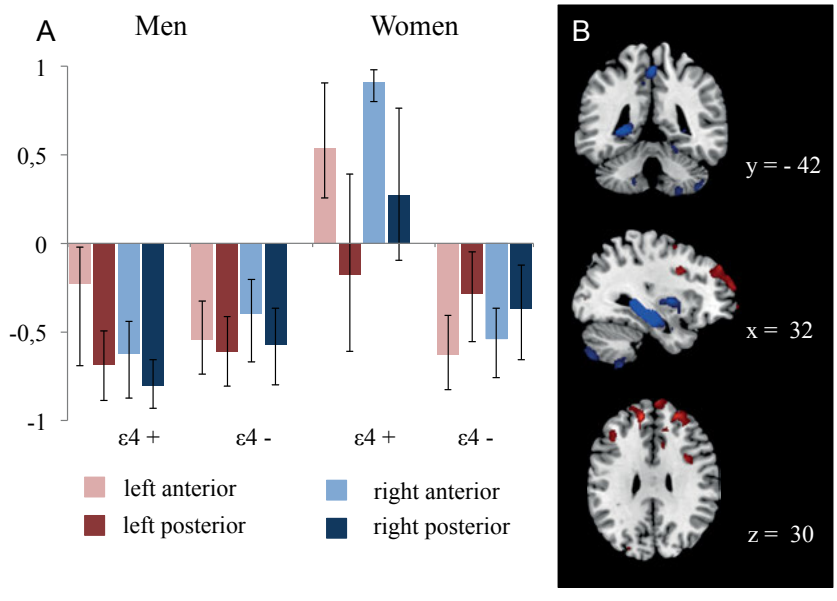

Figure 3 A) Seed-brain score correlations for LV2 as a function of sex, *APOE* ε4 carrier status and hippocampal segment. There was differential connectivity of the bilateral anterior hippocampus in female ε4 carriers compared to that of the anterior and posterior hippocampus in the other groups. B) Structural covariance captured by LV2. The red and blue colors correspond to positive and negative saliences, respectively. Red areas show covariance with the bilateral anterior hippocampus in female ε4 carriers. Blue areas show structural covariance with both anterior and posterior hippocampus in male ε4 carriers and all non-carriers.

Conclusions

Taken together, Study II indicates that young ε4-carriers and non-carriers differ in structural covariance of the hippocampus and that there are differences as a function of sex and subsegment. There was a distinct structural covariance pattern of the anterior hippocampus in female *APOE* ε4 carriers, which was not shared by any other group. This can be interpreted in relation to earlier findings of female ε4 carriers showing differential hippocampus-related resting-state connectivity compared to male ε4 carriers and female non-carriers (Heise et al., 2014).

The structural covariance pattern of the posterior hippocampus in ε4 carriers described by the second significant LV includes regions that are part of the DMN (Greicius, Krasnow, Reiss, & Menon, 2003). The finding of a specific

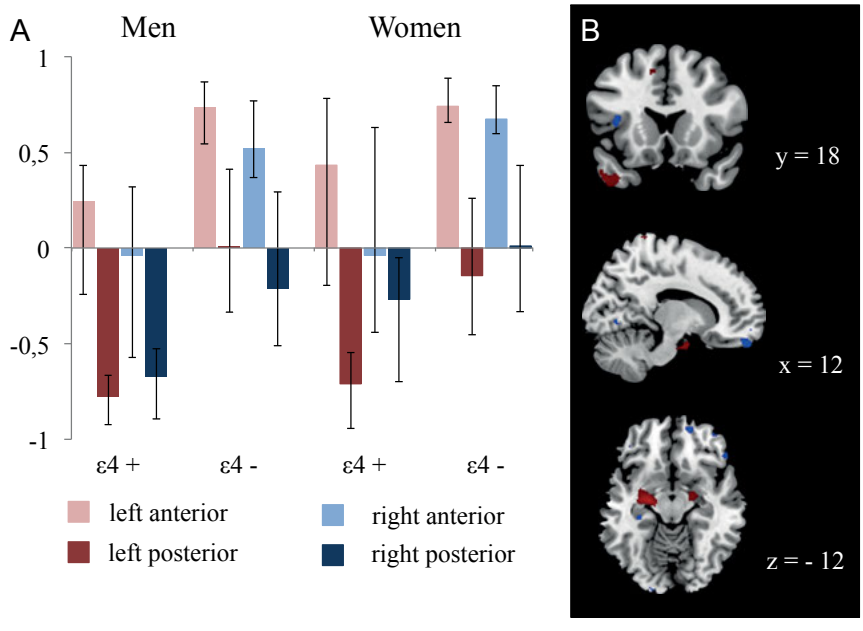

Figure 4 A) Seed-brain score correlations for LV4 as a function of sex, *APOE* ε4 carrier status and hippocampal segment. There were dissociating patterns of structural covariance of the bilateral posterior hippocampus in ε4 carriers and the bilateral anterior hippocampus in non-carriers, regardless of sex. B) Structural covariance captured by LV4. Red areas show covariance with the bilateral anterior hippocampus in all non-carriers. Blue areas show structural covariance with the bilateral posterior hippocampus in all ε4 carriers.

structural covariance pattern of the hippocampus with these regions as a function of *APOE* is in line with reports of increased hippocampal-DMN connectivity in both young ε4 carriers compared to non-carriers (Filippini et al., 2009).

There were no significant associations between structural covariance and episodic and spatial performance after multiple comparisons correction, suggesting that other factors underlie the differences in performance observed between carriers and non-carriers in spatial performance.

Study III

Background

As seen in the literature, *APOE* ε4 has different effects on episodic memory in different age groups. In healthy elderly ε4 carriers, episodic memory is often impaired while *APOE* ε4 has been associated with better episodic performance in young adults. This has lead to the hypothesis that *APOE* may constitute an example of antagonistic pleiotropy (Alexander et al., 2007; Han & Bondi, 2008), meaning that positive effects early in life may counterweigh the damaging effects in older age. Previous research suggests that a shift in cognitive performance in relation to *APOE* ε4 may take place around mid-age (Evans et al., 2014; Jochemsen et al., 2012). Relating to the findings of better spatial function seen in young adults in Studies I and II, the aim of Study III was to assess whether the effect of *APOE* ε4 on episodic and spatial memory differs between young, middle and older age.

Findings of *APOE* ε4-related differences with regard to hippocampal volume in relation to age are inconclusive, with studies on young adults showing both comparable and smaller hippocampal volumes in ε4 carriers (Alexopoulos et al., 2011; Dennis et al., 2010; Filippini et al., 2009; Matura et al., 2014; O'Dwyer et al., 2012). Thus, it is unclear whether *APOE* ε4 interacts with age in terms of hippocampal volume or if *APOE* ε4 is associated with smaller volume regardless of age. Study III aims to further explore how *APOE* ε4 is related to hippocampal volume in healthy young, middle-aged and older individuals.

Methods

A total of 219 participants (110 women; 109 men) were included in Study III. The study sample consisted of three age groups: young (20-35 yrs., n= 97, M=24.3, SD=3.4), middle aged (n= 59, 40-50 yrs., M=44.6, SD=3.1) and older (n= 63, 60-70 yrs., M=65.0, SD=3.0). The *APOE* allele frequency distribution was 1 ε2/ε2 (0.5%), 17 ε3/ε2 (7.8%), 131 ε3/ε3 (59.8%), 60 ε3/ε4 (27.4%), 4 ε4/ε2 (1.8%), and 6 ε4/ε4 (2.7%). ε4/ε2, ε4/ε3 heterozygotes and ε4/ε4 homozygotes were grouped together as ε4 carriers (n=70) and the rest were grouped together as non-ε4 carriers (n=149).

In Study III, episodic memory and spatial memory were measured by the Word List and Pointing tasks. Hippocampal volume was assessed with the SPM 12 software (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK). In SPM 12, an ANCOVA controlling for ICV with age group as a factor was performed to assess the effect of age alone. Modulating effects of *APOE* ε4 and sex were then assessed in hippocampal clusters showing age effects. Age, sex and *APOE* ε4 were included

as factors of interest in ANCOVAs with hippocampal volume as dependent measures, controlling for ICV.

In order to assess the potential association between hippocampal volume and episodic and spatial memory performance, hippocampal volumes were first extracted from normalized and modulated gray matter images using an in-house script. The left and right, anterior and posterior hippocampus was used as ROIs. These were modified from the existing hippocampus mask from the AAL atlas included in the WFUPickatlas toolbox (Maldjian et al., 2003) and chosen due the importance for these hippocampal subsegments in episodic and spatial memory (Kühn & Gallinat, 2014). The anterior and posterior masks spanned from -2 to -18 and -24 and -42 along the y-axis, respectively. After the volumes were corrected for ICV, they were correlated with episodic and spatial memory performance scores separately for each age group. FDR was computed to correct for multiple comparisons.

Results

There were no main effects of *APOE* ε4 on any of the cognitive measures. Age on the other hand, had a negative effect on performance on both spatial and episodic memory. The oldest group showed worse performance compared to the middle-aged and young groups on the spatial task. On the episodic task, the middle-aged group performed significantly better compared to the older group, but there were no differences between the young and middle-age groups or between the young and older groups.

There was a significant effect of sex on spatial memory, with men outperforming women. No effects of sex were found in episodic memory performance. In addition, there was an interaction between *APOE* and sex, with women carrying the ε4 allele showing worse performance compared to all other groups (see Figure 5).

Although there were no effects of *APOE* or sex on hippocampal volume, there was an effect of age in the bilateral hippocampus, with the older group having smaller hippocampal volume compared to the young group in the left and right anterior and left and right posterior hippocampus. These clusters corresponds to the anterior-posterior division of the hippocampus used in Study II, and were subsequently used as ROIs to further assess potentially modulating effects of *APOE* ε4 and sex. Two three-way interactions between age, *APOE* and sex were found in the bilateral posterior hippocampus. In male *APOE* ε4 carriers, volumes were comparable in young and middle-age, while the older group had significantly smaller volume. In women, *APOE* ε4 was significantly associated with age-related volume decline across all age groups.

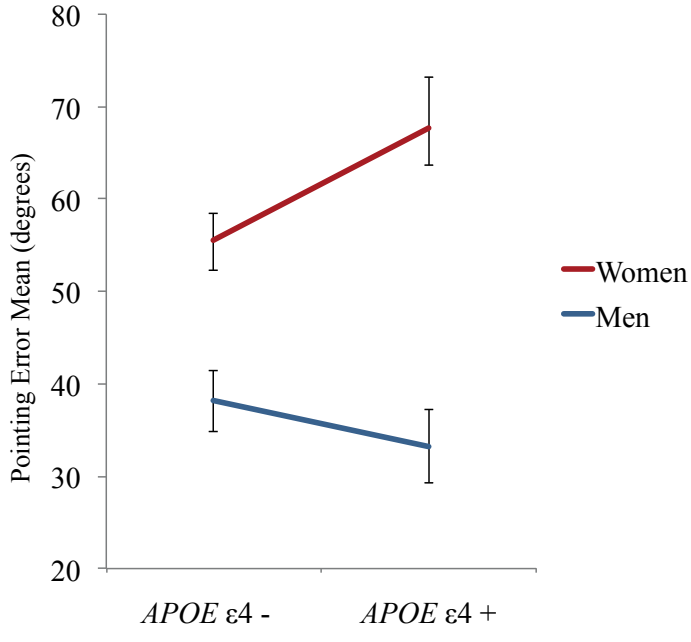

Figure 5. The significant interaction between *APOE* ε4 and sex on pointing performance. High values indicate worse performance.

In male non-carriers, all groups showed significant age-related decline in volume, whereas in women volumes were comparable in young and middle-age, while the older group had significantly smaller volume. These effects were seen in both the left (see Figure 6) and right (see Figure 7) posterior hippocampus.

Furthermore, there were main effects of age and sex in the left anterior hippocampus due to the older group having smaller volumes compared to the middle-aged and young groups, and young and middle-aged men having larger volumes compared to women.

There were no significant correlations between neither episodic nor spatial memory performance and hippocampal volume for any of the three age groups.

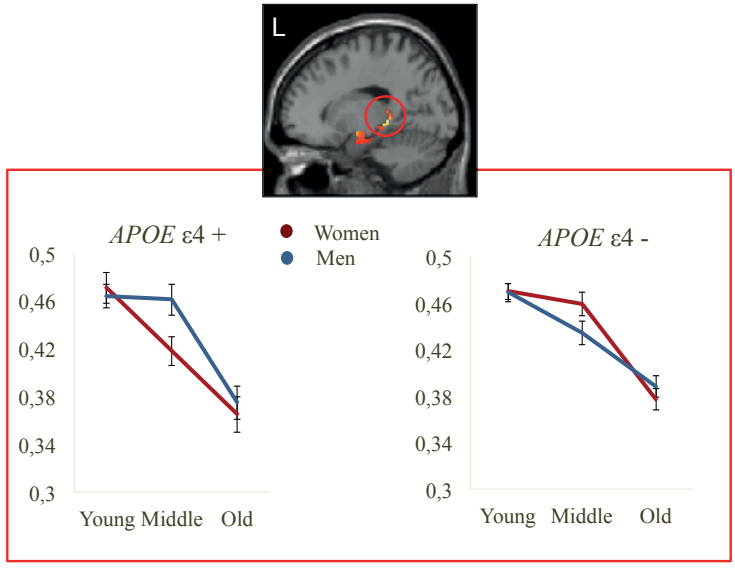

Figure 6. Graph showing the significant three-way interaction of *APOE* ε4, age, and sex on hippocampal volume seen in the left posterior hippocampal cluster showing a main effect of age.

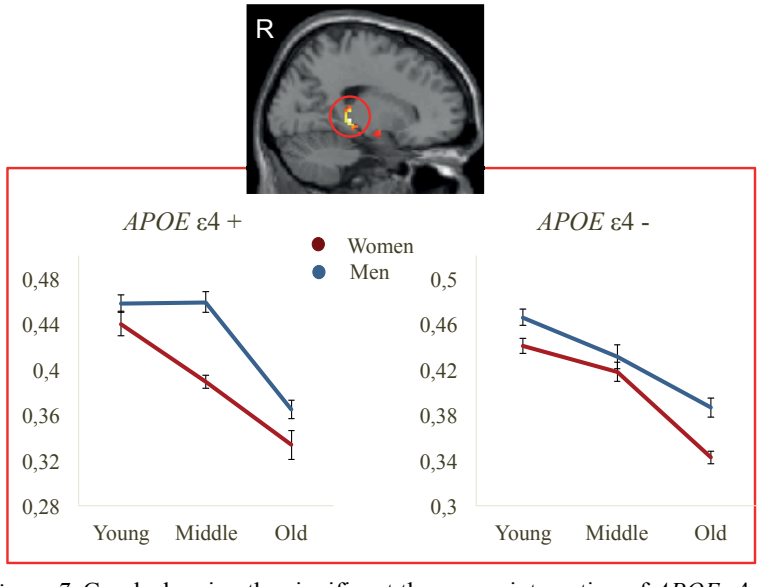

Figure 7. Graph showing the significant three-way interaction of *APOE* ε4, age, and sex on hippocampal volume seen in the right posterior hippocampal cluster showing a main effect of age.

Conclusions

In Study III there were no overall effects of *APOE* ε4, or interactions of age and *APOE* ε4 memory performance. Hence, this study indicates no antagonistic pleiotropy of *APOE* with regard to episodic and spatial memory. However, other interesting interaction effects emerged. First, there was an interaction between *APOE* ε4 and sex on spatial memory performance, with female ε4 carriers showing worse performance compared to both male ε4 carriers and all non-carriers. This supports earlier findings of women being especially susceptible to detrimental effects of *APOE* ε4 (Hyman et al., 1996; Lehmann et al., 2006), and shows that this effect is seen also in spatial memory. Second, there was a three-way interaction between *APOE* ε4, age and sex in the posterior hippocampus, which was due to *APOE* ε4 being differently related to hippocampal volume in middle-aged men and women. In male ε4 carriers, posterior hippocampal volumes were comparable between the young and middle-aged groups, whereas the older group had smaller volume. Meanwhile, in female *APOE* ε4 carriers, there was age-related decline across all age groups. In non-carriers, this pattern was reversed with comparable volumes between young and middle-age being seen in women, while men showed age-related decline in hippocampal volume. These patterns can be interpreted as *APOE* ε4 counteracting the negative effects of age on hippocampal volume seen in men but not women (Pruessner, Collins, Pruessner, & Evans, 2001), and are in line with previous reports of *APOE* ε4 being especially detrimental for women. The findings in Study III indicates that even in the absence of overall effects of *APOE* ε4 on spatial cognition and hippocampal volume, differences related to genotype emerge as function of sex and age.

General discussion

The three studies included in this thesis constitute an approach to further study the effect of *APOE* ε4 in healthy young individuals. *APOE* ε4 was assessed in relation to hippocampal volume and to both episodic and spatial memory, as these memory types are both highly hippocampus-dependent. Although the focus of the thesis has been on assessing the effect of *APOE* ε4 in young adults, middle-aged and older individuals were included in Study III. This was done in order to further explore the proposed antagonistic pleiotropic properties of *APOE* ε4.

The main findings that will be further discussed are presented in the list below:

- *APOE* ε4 was positively associated with spatial cognition (Studies I and II) and episodic memory performance in young adults (Study I)

- There was an overall interaction between *APOE* ε4 and sex, with female ε4 carriers showing the worst spatial memory performance compared to all the other groups (Study III)

- In young adults, structural covariance of the hippocampus differed as a function of *APOE* ε4 status (Study II)

- Young female ε4 carriers showed a unique pattern in how the volume of the anterior hippocampus covaried with volume of the rest of the brain (Study II)

- There was an interaction between *APOE* ε4, age and sex on measures of bilateral posterior hippocampal volume. In men, *APOE* ε4 was associated with comparable volumes in young and middle-age, and smaller volume was seen in the older group. In women, *APOE* ε4 was instead associated with age-related decline in volume across all three age groups. In non-carriers, men showed age-related decline in volume across age groups, while in women, volumes were comparable in young and middle-age whereas the older group had smaller volume (Study III)

Association between *APOE* ε4 and spatial cognition

One of the main findings of this thesis is the positive association between *APOE* ε4 and spatial function and memory in young adults observed in Study I and II. Study I is, to the best of my knowledge, the first to show evidence of such a relationship. It was previously assessed by Yasen et al. (2015) in a sample of comparable age, but while their findings did show sex to have an effect on spatial performance, no effect was found for *APOE* ε4. It should be noted that in Studies I and II, the mental rotation task was included in the spatial composite measures. Two problems may arise from this. First, mental rotation is not a memory task per se, but rather taps into general spatial function related to visuospatial ability and mental imagery processes. Second, mental rotation is not usually considered a hippocampus-dependent task, and is rather functionally associated with the precuneus (Suchan et al., 2002) and the parietal lobules (Jordan, Wüstenberg, Heinze, Peters, & Jäncke, 2002; Weiss et al., 2003). However, one study did indeed find that successfully matching a mentally rotated stimulus to a target involved the bilateral posterior hippocampus (Hannula & Ranganath, 2008). Even so, the findings presented here suggest that in healthy young adults, *APOE* ε4 is positively associated to spatial cognition rather than spatial memory specifically.

Association between *APOE* ε4 and episodic memory

With regard to episodic memory, there was a positive effect of *APOE* ε4 on object location memory in Study I. However, the only episodic memory task used in all three studies included in this thesis, the word list task, did not show any association with *APOE* ε4. Although a positive effect on episodic memory performance in young adults is thus far only supported by two studies (Han et al., 2007; Mondadori et al., 2007), the negative relationship between *APOE* ε4 and episodic memory with increased age is well established (Caselli et al., 2009; Josefsson et al., 2012; Nilsson et al., 2006; Wilson et al., 2002). It is therefore surprising that there was no effect of *APOE* ε4 on word list performance in the elderly group in Study III. Instead, the overall finding of the work presented here is in line with earlier studies reporting no findings of episodic impairment in relation to *APOE* ε4, in either healthy elderly (Luciano et al., 2008) or young adults (Bunce et al., 2011; Ihle et al., 2012).

Two factors may explain the divergent findings of the two episodic tasks used in this thesis. First, the object location task constitutes a measure of

source memory and includes an associative component during both encoding and retrieval. The word list task, in contrast, does not include any of these elements. Second, object location retrieval requires recollection of the stimuli locations, while the retrieval phase of the word list task constitutes a measure of recognition memory rather than recollection. Research has indicated that free recall is sometimes a more robust measure of episodic memory, and especially so when assessing dementia-related cognitive impairment (Bäckman, Jones, Berger, Laukka, & Small, 2005; Howieson et al., 1997; Tulving & Thomson, 1973). Although episodic recognition has, similar to episodic recollection, also been shown to depend on hippocampal functioning, both in lesion studies (Manns, Hopkins, Reed, Kitchener, & Squire, 2003) and in brain imaging of healthy subjects (Merkow, Burke, & Kahana, 2015; Stark & Squire, 2000), it is possible that the lack of effects related to the word list task in this thesis is due to the lack of recollection components in this task.

In Study I, the effect of *APOE* ε4 on object location memory may be explained in light of the effect of *APOE* ε4 seen in spatial function and memory. It can be argued that object location encoding includes certain spatial elements, since the participants are explicitly asked to remember the location of the objects. Indeed, the lack of associations of *APOE* ε4 and word list performance in combination with the effect on spatial performance, makes it plausible to interpret the effect of *APOE* ε4 on object location performance in the light of the task's spatial components.

What role does sex play in *APOE* ε4-related effects on episodic and spatial memory?

The association between *APOE* ε4 and episodic impairment has been found to vary as a function of sex, with women being more susceptible to the detrimental effects of *APOE* ε4 on episodic memory performance (Hyman et al., 1996; Lehmann et al., 2006). It is possible that sex is an important underlying factor that may drive any effects on cognition that *APOE* ε4 may have. Thus, the lack of sex differences in episodic memory in this thesis may provide an explanation for why no effects of *APOE* ε4 on episodic memory performance was observed. This line of reasoning can also be applied to the findings of *APOE* ε4-related effects on spatial memory. In all three studies included in this thesis, we found sex differences in spatial performance. In Study III there was also an interaction between *APOE* ε4 and sex on pointing performance. This suggests that *APOE* ε4 may enhance already existing sex differences. Although *APOE* ε4 alone had no effect on spatial performance in Study III, it is possible that the interaction between sex and *APOE* ε4 may emerge with increasing age. Indeed, the studies reporting sex differences in

relation to the association between *APOE* ε4 and cognitive performance were conducted on elderly populations (Bartrés-Faz et al., 2002; Hyman et al., 1996; Lehmann et al., 2006; Mortensen & Høgh, 2001).

It should be noted that even though all studies included in this thesis showed the expected sex difference favoring men in spatial performance, none of them found a female advantage in episodic memory. Spatial advantage in men is a robust finding, and one explanation is that the spatial advantage is upheld by cultural norms that encourage boys to play in ways that promote development of spatial abilities. With regard to episodic memory performance, it is worth noting that sex differences were also absent in the neuropsychological tests in Studies I and II. The letter digit substitution and verbal fluency tasks are known to elicit superior performance in women (Burton et al., 2005; Elst et al., 2012), which they did not do here. One possible explanation is that the sample in Studies I and II consists of high achieving university students and that differences in verbal ability are therefore not as prominent as they could have been using a more diverse sample. This is in line with previous work from Herlitz and Rehnman (2008), that suggests that while sex differences in episodic memory is a globally common phenomena, the magnitude of the differences is related to education and sociocultural factors. In accordance with this, there was a sex difference in performance in the letter digit substitution task when controlling for education in Study III, and additional analyses showed that the significance of this difference was indeed increased when this covariate was removed.

APOE ε4 and hippocampal structure

Hippocampal volume

There were no effects of *APOE* ε4 on hippocampal volume in young adults in Study I. Thus, we were not able to replicate earlier findings of smaller hippocampal volume in young ε4 carriers (Alexopoulos et al., 2011; O'Dwyer et al., 2012). Instead our findings are in line with the studies showing no volume effects related to *APOE* ε4 in young individuals (Dennis et al., 2010; Dowell et al., 2013; Filippini et al., 2009; Matura et al., 2014). One factor that may explain why Study I failed to find an effect of *APOE* ε4 on hippocampal volume relates to the presence versus absence of ε2 carriers. Alexopoulos et al. (2011) compared ε4/ε3 heterozygotes to ε2/ε3 heterozygotes, and it is possible that the comparison of *APOE* ε4 against *APOE* ε2 is sensitive enough to detect volume differences in young ε4 carriers. Indeed, studies reporting no differences have typically excluded ε2 carriers (Dowell et al., 2013; Filippini et al., 2009; Matura et al., 2014). In Study I, ε2 carriers

are included but also represent a portion of both the ε4 carrier and non-carriers groups.

Previous studies on the effects of *APOE* ε4 on hippocampal volume have either assessed whole-brain volume or treated the hippocampus as a whole structure. The work presented in Studies I and II instead assessed volume of hippocampal subsegments, since the hippocampus is an anatomically complex structure and function has been shown to vary along its longitudinal axis (Kühn & Gallinat, 2014; Poppenk & Moscovitch, 2011). Study I assessed volume of the hippocampal head, body and tail, while Study II used an anterior-posterior division. Of these, only the anterior-posterior division showed an effect of *APOE* ε4, in that the anterior and posterior hippocampus differed in their whole-brain structural covariance. Volume effects related to sex were found with both subsegment divisions. In Study II, sex interacted with *APOE* ε4 and subsegment, which will be further discussed below. In Study I, women were found to have larger bilateral hippocampal body volumes compared to men. In an overlapping sample to that in Study I, Persson et al. (2014) has previously shown that women have larger posterior hippocampi compared to men. Thus, the head-body-tail division enabled us to locate this difference to the hippocampal body.

In Study III, the only effect of *APOE* ε4 on hippocampal volume was seen in an interaction with age and sex. This interaction was seen in the bilateral posterior hippocampus, in clusters showing age-related volume effects. This suggests that *APOE* ε4 and sex may be modulating factors on age effects in the hippocampus. Young and middle-aged male ε4 carriers had comparable posterior volumes, whereas the older group had smaller volume. In female ε4 carriers there was instead an age-related decline in volume across all three age groups. In non-carriers, the patterns were reversed with young and middle-aged women having comparable volumes, while men showed an age-related decline in volume across age groups. Noteworthy is that this pattern emerged in the area of the hippocampus especially important for spatial memory, the posterior hippocampus. In addition it did so in groups showing the expected sex differences in spatial memory. However, as there was no significant association between hippocampal volume and cognitive performance in Study III, this remains purely speculative.

The findings presented in Study III indicates that *APOE* ε4 is specifically linked to sex-related volume differences in middle age in that it is associated with delayed reduction of hippocampal volume in men but not women. Previous research has shown a negative relationship between increasing age and hippocampal volume in men but not in women (Pruessner et al., 2001). It is possible that *APOE* ε4 counteracts the negative effects of aging on hippocampal volume in men, which would explain the interaction seen in Study

III. This interpretation is also in line with previous findings of women being more susceptible to detrimental effects of *APOE* ε4.

Structural covariance patterns of the hippocampus

The association between sex and *APOE* ε4 discussed previously in relation to spatial performance was evident also in the structural covariance patterns of the hippocampus in Study II. In all groups except female ε4 carriers, volume of the whole hippocampus (anterior and posterior) covaried positively with volume of the putamen and precuneus, two regions that are involved in spatial learning, navigational and spatial judgment (Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch, 2012; Ragozzino, Leutgeb, & Mizumori, 2001; Weniger, Ruhleder, Wolf, Lange, & Irle, 2009). This finding suggests that all groups except female ε4 carriers showed structural covariance of the whole hippocampus and regions important for spatial functioning. Due to the way PLS works, volume of the brain regions that covaried positively with the whole hippocampus in all men and female non-carriers (the bars pointing downward in Figure 3A), covaried negatively with the bilateral anterior hippocampus in female ε4 carriers (the bars pointing upward in Figure 3A). Thus, anterior hippocampal volume in female ε4 carriers was negatively correlated with volume of spatially important regions, while their posterior hippocampi showed no significant covariance patterns at all. That female ε4 carriers show a unique structural connectivity pattern is in line with previous studies assessing resting-state connectivity. Reduced connectivity between hippocampus and precuneus in healthy older female ε4 carriers has been reported (Heise et al., 2014), which is in line with volumes of these two regions covarying negatively in female ε4 carriers in Study II.

The lack of covariance pattern of the posterior hippocampus in young female ε4 carriers could be interpreted as an underlying factor to the inferior performance seen in female ε4 carriers in Study III, although the latter is seen across the three different age groups. This interpretation is purely speculative since there were no clear associations between structural covariance patterns and spatial memory in Study II, but should nonetheless be considered for further studies.

The PLS analysis in Study II also revealed different patterns of structural covariance as a function of *APOE* ε4 status. In ε4 carriers, volume of the bilateral posterior hippocampus covaried positively with volume in parietal areas, such as the inferior parietal lobule and angular gyrus, and with multiple frontal regions. The structural covariance of the inferior parietal lobule and the posterior hippocampus is in line with previous findings of resting-state connectivity between the inferior parietal lobule and hippocampus in general (Uddin et al., 2010) and the posterior hippocampus in particular (Poppenk & Moscovitch, 2011). Furthermore, the regions included in the

structural covariance pattern of the posterior hippocampus of the ε4 carriers are common to the DMN (Greicius et al., 2003; Raichle et al., 2001; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009). Previous research has shown that older ε4 carriers have reduced structural covariance of DMN regions compared to non-carriers (Spreng & Turner, 2013), and the findings presented here indicates that the reverse may be true for young ε4 carriers. Our findings are also in line with previous studies showing increased resting-state connectivity between the hippocampus and the DMN in young ε4 carriers (Filippini et al., 2009), further indicating a functional relevance of structural covariance measures.

Taken together, the findings presented here shows that there were no *APOE* ε4-related differences in hippocampal volume in young adults, and only in tandem with age and sex in a larger age span. However, there was an effect of *APOE* ε4 on structural covariance of the hippocampus in young adults. It is possible that *APOE* ε4-related effects on hippocampal volume per se are more commonly seen with increasing age. This would explain why the effects of *APOE* ε4 were only seen in tandem with the age effects in Study III. At the same time, these findings indicate that *APOE* ε4-related differences in structural covariance of the hippocampus may be already detectable in young age. Given the inconclusive findings of volume differences related to *APOE* ε4 in young adults, with most studies reporting no differences, it is possible that structural covariance patterns of the hippocampus in young adults may offer a clue to an early structural architecture of the brain in relation to *APOE* ε4.

The association between cognitive performance and hippocampal volume

It should be noted that no significant associations between memory performance and hippocampal volume and structural covariance were found in the studies included in this thesis. This can be due to multiple factors. First, the sample sizes of the studies included may simply be too small to detect such associations. Second, it is possible that hippocampal volume within the normal range supports cognitive function within the normal range without an obvious linear association, while a more drastic decrease in volume as in the case of pathology, is followed by cognitive impairments (Van Petten, 2004). The participants included in this thesis were all healthy and well functioning, suggesting that even though there were cognitive differences associated with age in Study III, the performance of these age groups were still within the normal range, thus not eliciting any associations with hippocampal volume. Third, the lack of associations between cognitive function and hippocampal

volume may be due to the fact that this thesis is based on the episodic-spatial division of hippocampal function. Although the functional dependence of spatial memory on the posterior hippocampus is a robust finding, there are many views on the functional heterogeneity of the hippocampus with regard to episodic memory. One such view is that the neural basis for episodic encoding and retrieval differs along the longitudinal axis of the hippocampus (Kim, 2015; Lepage, Habib, & Tulving, 1998). Verbal and pictorial stimuli have been shown to differently engage the anterior and posterior hippocampus (Persson & Söderlund, 2015), thus suggesting that stimulus type may be a factor to take into account when assessing functional differences within the hippocampus. Moreover, the anterior hippocampus has been suggested to be especially susceptible to novelty effects, whereas increased familiarity increases posterior activations (Strange, Fletcher, Henson, Friston, & Dolan, 1999). Thus, it is possible that the use of one of these functional divisions may elicit associations between memory and volume of hippocampal subsegments, in addition to possible associations with *APOE* ε4.

APOE ε4, memory and other brain regions

Although the focus of this thesis is on the effects of *APOE* ε4 on hippocampus and episodic and spatial memory, it should be noted that there are other brain regions involved in these memory processes that have shown *APOE* ε4-related effects. In studies of regions adjacent to the hippocampus, *APOE* ε4 has been associated with thinning of the entorhinal cortex in adolescent (Shaw et al., 2007) and middle-aged (Burggren et al., 2008) individuals. The entorhinal cortex contains grid cells important for spatial navigation in both rats (Hafting, Fyhn, Molden, Moser, & Moser, 2005) and humans (Jacobs et al., 2013). Furthermore, thickness of the parahippocampal cortex has been positively associated with episodic memory performance in young ε4 carriers (Dowell et al., 2016). The entorhinal and parahippocampal cortices are both input regions to the hippocampus (Davachi, 2006; Eichenbaum, Yonelinas, & Ranganath, 2007), and it is therefore interesting that associations with *APOE* ε4 has been found in these regions. Furthermore, *APOE* ε4 has been related to reduced cortical thickness and reduced gray matter volume in frontal regions (Fennema-Notestine et al., 2011; Wishart et al., 2006), as well as reduced volume of the caudate (Liu et al., 2010), regions involved in episodic memory and spatial processing, respectively. Thus, it is possible that further studies using a broader assessment of brain volume may yield more comprehensive associations with *APOE* ε4.

Antagonistic pleiotropic properties of *APOE*

With regard to the antagonistic pleiotropic properties of *APOE*, this thesis offers no conclusive evidence in either direction. Although young ε4 carriers showed better episodic memory performance in Study I, and better spatial cognition in Studies I and II, compared to non-carriers, there was no interaction between age and *APOE* ε4 on episodic or spatial memory performance in Study III. Antagonistic pleiotropic properties of *APOE* with regard to hippocampus-dependent memory are therefore not supported in the findings of this thesis. It should however be noted that the interaction between *APOE* ε4 and sex on spatial memory performance was only seen in Study III, and thus in a sample including middle-age and older individuals. Thus, it is possible that *APOE* ε4 does indeed affect spatial memory differently in young and older age, albeit in tandem with sex effects. Also with regard to hippocampal volume in Study III, interactions between *APOE* ε4 and age was seen together with sex effects. Thus, sex appears to be an important factor for age-related effects of *APOE* ε4 on cognition and brain structure. The possible antagonistic pleiotropy of *APOE* needs to be studied further with this in mind.

APOE ε4 and sex

The work presented here adds to the growing body of literature on sex differences in relation to *APOE* ε4. In addition to the negative effects in women already mentioned in connection to AD (Bretsky et al., 1999; Elizabeth H. Corder et al., 2004; Payami et al., 1996), cognitive impairment (Hyman et al., 1996; Lehmann et al., 2006; Mortensen & Høgh, 2001) and hippocampal volume (Fleisher et al., 2005), female ε4 carriers have also been shown to be especially vulnerable to development of vascular dementia (Chen et al., 2016) and depression in AD (Delano-Wood et al., 2008). The reasons as to why women are more susceptible to the detrimental effects of *APOE* ε4 are still under debate, but many studies have found associations between *APOE* ε4 and both female and male sex hormones.

Estrogen has been positively associated with cognitive function and it has been suggested that it may prevent development of AD (Wharton et al., 2009). Estrogen therapy in post-menopausal women has also been shown to modulate *APOE* ε4-related cell aging (Jacobs et al., 2013). Testosterone has been positively associated with cognitive performance in male humans (Moffat et al., 2002) and have been shown to increase spatial learning and memory in association with *APOE* ε4 in mice (Raber, Bongers, LeFevour, Buttini, & Mucke, 2002). Furthermore, lower levels of testosterone in asso-

ciation with *APOE* ε4 has been linked to increased risk of developing AD (Moffat et al., 2004).

Thus, it is possible that levels of estrogen and testosterone are underlying factors of the interactions between *APOE* ε4 and sex seen in spatial memory performance and posterior hippocampal volumes seen in Study III. Decreased estrogen levels may also explain why these interactions emerged only in a sample including middle-aged and older individuals. Estrogen and testosterone level assessment was out of scope for this thesis, but should be nonetheless be considered in future studies.

Other influences on *APOE* ε4-related effects on the hippocampus and memory

There are a multitude of factors that may affect one or many of the questions asked in this thesis. Certain KIBRA (coding for KIdney/BRAin protein) polymorphisms have been linked to both episodic memory performance and hippocampal functioning (Kauppi, Nilsson, Adolfsson, Eriksson, & Nyberg, 2011; Milnik et al., 2012; Papassotiropoulos et al., 2006), and the Met allele of the brain derived neurotrophic factor (BDNF) gene has been associated with reduced hippocampal volume (Bueller et al., 2006; Pezawas et al., 2004). Furthermore, there is always the possibility of gene-gene interactions at play. For example, the CR1 (complement receptor 1) gene has been shown to interact with *APOE* ε4 in episodic decline (Keenan et al., 2012), while the combination of *APOE* ε4 and BDNF Met has been associated with decreased activation of the right hippocampus during episodic encoding (Kauppi, Nilsson, Persson, & Nyberg, 2014). All of these factors provide valuable information about the complex associations between *APOE* ε4, cognition and brain structure and function, and should be further explored in relation to the questions assessed in this thesis.

Limitations and future directions

The studies presented here are not without limitations. One of these concerns the inclusion of carriers of the *APOE* ε2 allele. All three studies in this thesis included ε2 carriers, which may indeed be an issue when interpreting the findings. ε2 carriers are commonly excluded from studies due to the proposed protective properties of this allele (Farrer et al., 1997). In Studies I and III, data were analyzed both with and without ε2 carriers and the resulting findings did not differ, which is why they were kept in the analyses overall. Thus, the inclusion of ε2 carriers does not appear to have biased the results

of this thesis. Furthermore, *APOE* ε4 group sizes in this thesis are rather small, especially when including sex as a factor. To be able to get satisfactory group sizes when assessing both *APOE* ε4 and sex, it would be necessary to screen participants according to *APOE* genotype and then match groups for sex. This approach should indeed be considered for further studies. Another limitation is that some of the tasks used differed between data collections. For example, given the finding of better object location memory in young *APOE* ε4 carriers in Study I, it would have been valuable to assess this also in the middle-aged and older individuals in Study III.

The work presented in this thesis opens up many questions for future research. The association between *APOE* ε4 and structural covariance patterns seen in Study II should be further assessed in older individuals, and preferably in a longitudinal setting. This approach would make it possible to assess whether volume differences related to *APOE* ε4 in older age can be related to the early patterns of structural covariance of the hippocampus. Furthermore, as *APOE* appears to affect susceptibility to pathology, cognition, brain structure and function in a dose-dependent manner (Corder et al., 1993; Greenwood et al., 2005; Liu et al., 2010), future samples should be screened to ensure comparable group sizes and to enable the analysis of ε4 homozygotes.

Conclusions

This thesis aimed at exploring the effect of *APOE* ε4 on hippocampus-dependent memory and hippocampal volume in healthy young adults. However, healthy middle-aged and older individuals were included in Study III to explore possible antagonistic pleiotropic properties of *APOE*. In Study I, there was an effect of *APOE* ε4 in an episodic memory task with spatial components as well as on spatial function, although the latter may not necessarily be hippocampus-dependent. Furthermore, in Study III there was an interaction of *APOE* ε4 and sex on spatial memory performance. Across age groups, women carrying the ε4 allele performed worse compared to female non-carriers and all men. This thesis does not support the hypothesis that *APOE* is an antagonistic pleiotropic gene, as no interactions between *APOE* and age were found for the episodic and spatial tasks. No hippocampal volume differences as a function of *APOE* ε4 were found in young adults in Study I, but Study II showed that structural covariance of the anterior and posterior hippocampus differed as function of *APOE* ε4 and sex. In Study III, there was an interaction between *APOE* ε4, age and sex on bilateral posterior hippocampal volume across young, middle-aged and older individuals. This suggests that *APOE* ε4 and sex acts as modulating factors on age-related differences in hippocampal volume. Although *APOE* ε4-related ef-

fects on hippocampal volume were only seen in relation to age in Study III, structural covariance might provide a tool to detect *APOE* ε4-related effects on brain structure earlier in life. Furthermore, the work presented here strongly indicates that sex is an important factor that may further explain effects of *APOE* ε4 on brain structure and cognition.

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