Specific patterns of whole-brain structural covariance of the anterior and posterior hippocampus in young *APOE* ε4 carriers

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Abstract

Apolipoprotein E (*APOE*) ε4 has been associated with deteriorated episodic memory and spatial function in old age, but also with better performance in young individuals. The hippocampus is important for both episodic memory and spatial function, and it is suggested that these functions depend on the anterior (aHC) and posterior (pHC) hippocampus, respectively. Although an increase in hippocampal volume has been related to cognitive improvement, there are no conclusive findings on the effect of *APOE* on hippocampal volume. Previous studies assessing hippocampal volume in relation to *APOE* has done so using univariate methods and without considering differences along the longitudinal axis of the hippocampus. Here, we used a multivariate method; partial least squares, and assessed the whole-brain structural covariance of the aHC and pHC in young adults (n=97) in relation to *APOE* carrier status and sex. Two significant patterns emerged: 1) structural covariance of the aHC unique to *APOE* ε4 women, and 2) distinct structural covariance of the pHC in ε4 carriers and the aHC in non-carriers. There was an association between adherence to the first pattern of structural covariance and spatial performance in male ε4 carriers, and episodic performance in male non-carriers. For female ε4 carriers and male non-carriers, there was an association between the second pattern of structural covariance and spatial performance, and for episodic performance in female non-carriers. These findings indicate that there is an association between *APOE* and hippocampal volume, and that it differs as a function of sex and hippocampal segment. The present study further supports the need to look at the hippocampus as a heterogeneous structure, and highlights the benefits of multivariate methods in assessing group differences in the brain.

Highlights

- Whole-brain structural covariance of the anterior/posterior hippocampus is assessed
- The covariance patterns found depend on hippocampal segment, *APOE* genotype and sex
- The *APOE* and sex related patterns were associated with cognitive performance

1. Introduction

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The gene coding for apolipoprotein E; *APOE*, has three different alleles, ε2, ε3 and ε4. The ε4 allele, in addition to being a risk factor for the development of Alzheimer's disease (AD; Corder et al., 1993; März et al., 1996), has been linked to declining episodic (Josefsson et al., 2012; Wisdom et al., 2011) and spatial memory function (Berteau-Pavy et al., 2007) in healthy elderly. In young adults, however, *APOE* ε4 has been associated with better episodic memory performance (Han et al., 2007; Mondadori et al., 2007). We have recently complemented the findings of superior episodic memory performance in young *APOE* ε4 carriers, showing also a positive association between *APOE* ε4 and spatial memory and function in young adults (Stening et al., 2016). Given the hippocampus' importance for both episodic and spatial memory (Kühn and Gallinat, 2014), several studies have assessed hippocampal volume and function in *APOE* ε4 carriers compared to non-carriers. Findings are however mixed, and it is unclear what the neural correlates of *APOE* ε4 are that underlie this better memory performance in young age.

Healthy elderly ε4 carriers have been found to have smaller hippocampal volumes, and especially so in the right hippocampus (Lind et al., 2006; Lu et al., 2011; Tohgi et al., 1997). However, there are also studies reporting no volumetric differences associated with *APOE* genotype in the elderly (Bondi et al., 2005; Du et al., 2006). Findings of hippocampal volume differences in young ε4-carriers are uncommon. O'Dwyer et al. (2012) found that young ε4 carriers had smaller right hippocampal volumes compared to non-carriers, in line with some findings in elderly adults, but far more studies find no difference in hippocampal volume related to *APOE* in young adults (Dennis et al., 2010; Filippini et al., 2009; Matura et al., 2014; Stening et al., 2016) or adolescents (Khan et al., 2014).

In terms of hippocampal function, there are observations in healthy elderly ε4 carriers of both increased activation in the right hippocampus (Bondi et al., 2005; Han et al., 2007) and decreased activation in the left hippocampus (Bondi et al., 2005; Filippini et al.,

2011) as compared to non-carriers during episodic memory tasks. In young ε4-carriers, similarly to the elderly, there are observations of both increased (Dennis et al., 2010; Filippini et al., 2009; Matura et al., 2014) as well as decreased bilateral hippocampal activity during episodic memory tasks (Mondadori et al., 2007). Considering hippocampal activity in relation to that of other brain areas, Harris et al., (2015) observed lower connectivity in older *APOE* ε4 carriers compared to non-carriers between the left hippocampus and cortical areas during episodic memory performance. In young *APOE* ε4 carriers, Dennis et al. (2010) observed both increases and reductions in connectivity between the medial temporal lobes and areas involved during successful memory encoding.

Given the mixed findings of the relation between *APOE* genotype and hippocampal volume and function, it is possible that the differing cognitive profile of *APOE* ε4 carriers is reflected in more global brain patterns, as the brain is a dynamic system that is shaped by interactions between structures. As such, it may be more informative to assess brain architecture using a multivariate approach that considers, for example, the volume or activity of a region given the volume or activity of other regions it may interact with. Using such a multivariate approach, we have previously shown that young men and women differ in how their anterior and posterior hippocampal volumes covary with patterns of volume in the rest of the brain (Persson et al., 2014). In terms of *APOE* genotype, Spreng and Turner (2013) found that elderly *APOE* ε4 carriers had a lower degree of structural covariance between regions of the default mode network (DMN) compared to non-carriers. Functionally, there are observations of lower resting state functional connectivity between the bilateral hippocampus and connected structures in older *APOE* ε4 carriers compared to non-carriers (Sheline et al., 2010; Shu et al., 2014). In young ε4 carriers, instead, increased resting state coactivation between the bilateral hippocampus and the DMN has been observed (Filippini et al., 2009).

It hence seems that older *APOE* ε4 carriers differ compared to non-carriers in how their brain is organized, in terms of the DMN and hippocampal resting state connectivity. Similarly, hippocampal resting state connectivity differs between young *APOE* ε4 carriers and non-carriers, but less is known about the structural organization of the brain. Here, we departed from our earlier findings of superior spatial function in young *APOE* ε4 carriers, which was not paralleled by any differences in hippocampal volume (Stening et al., 2016), and assessed patterns of structural covariance of the hippocampus as an alternative explanation of these behavioral differences.

Although it is well known by now that the hippocampus is not a homogeneous structure, most studies assessing *APOE* genotype in relation to hippocampal function and volume, albeit including laterality as a factor, do not consider the longitudinal segments of the hippocampus (but see Harrison et al., 2015). Episodic and spatial memory and function are thought to be related to the anterior (aHC) and posterior (pHC) hippocampus respectively (Kühn and Gallinat, 2014; Persson and Söderlund, 2015). It is therefore highly desirable to consider subregions of the hippocampus when assessing potential variations as a function of *APOE* genotype, as the effects on episodic and spatial memory may differ. Here, we assessed whether gray matter structural covariance of the aHC and pHC with the rest of the brain differs as a function of *APOE* genotype. Because of our finding that the structural covariance patterns of the aHC and pHC differ between men and women (Persson et al., 2014) we included sex as a factor to assess possible interactions between sex and *APOE* genotype. Finally, we examined whether structural covariance patterns are related to episodic and spatial memory.

2. Methods

2.1 Participants

A total of 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=1.8) took part in the study. There were no differences in age or years of education between men and women or *APOE* groups (see Table 1 for demographics). Participants were recruited through advertisements across the Uppsala University campus, and were screened to only include healthy individuals with no history of brain injury or neurological disease, right-handedness and to assure they were able to undergo magnetic resonance imaging (MRI; e.g., having no metal implants or claustrophobia). Participants gave written informed consent approved by the regional ethics board in Uppsala and were given compensation for their participation.

2.2 Procedure

2.2.1 Genotyping

TaqMan Allelic Discrimination technology was used to genotype saliva samples for *APOE* (gene map locus 19q13.2). Genotypes were obtained for the two SNPs that are used to unambiguously define the ε2, ε3, and ε4 alleles (rs7412 and rs429358). In this study, 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%). ε4/ε2, ε4/ε3 heterozygotes and ε4/ε4 homozygotes were grouped together as ε4 carriers (n= 29) and the rest were grouped together as non-ε4 carriers (n= 68). These two groups were then subsequently used for analyses.

ε2 carriers are sometimes removed because of the proposed protective properties of this allele. However, as this is not always the case (Bergfield et al., 2010; Richter-Schmidinger et al., 2010; Tohgi et al., 1997), and because we previously found no difference in hippocampal volume or cognitive performance after removing ε2 carriers (Stening et al., 2016), we included them in the analyses here.

2.2.2 Structural MRI data acquisition

Scanning was performed using 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^2; voxel size = 1 mm^3 isotropic voxels; 170 slices).

2.2.2.1 Preprocessing

Preprocessing of the data was performed using Statistical Parametric Mapping (SPM 8; www.fil.ion.ucl.ac.uk/spm). The T1-weighted images were segmented using the New Segment function implemented in SPM (Ashburner & Friston, 2005). The gray and white matter segmentations were then used to create a template with the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) tools. All individual gray matter images were warped to this template, resliced to 1.5 mm isotropic voxels and aligned with the Montreal Neurological Institute (MNI) space and smoothed using a kernel of 8 mm full width at half maximum (FWHM). Finally, the total intracranial volume (TIV) was calculated for each individual brain, by summing the voxels values of gray and white matter and cerebrospinal fluid segmentations. By scaling the voxel intensities of the normalized images with TIV, the final images represent proportional regional gray matter volume where individual differences in overall brain size have been accounted for.

2.2.2.2. Regions of Interest (ROI)

The aHC and pHC seed regions used in this study were modified from ROIs taken from the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) from the Wake Forest University PickAtlas (WFUPickatlas) toolbox (Maldjian et al., 2003). This was done by superimposing the anatomical labels onto an average of all individual structural images from the present data set. The hippocampus was divided into four seed

regions; left and right aHC and left and right pHC, in concordance with previous studies (Poppenk et al., 2013; Persson et al., 2014). The aHC and pHC masks spanned from -2 to -18 and -23 and -39 along the y-axis, respectively. For each individual preprocessed gray matter image, the voxels that were identified as belonging to each of the four regions were summed and multiplied by the voxel volume to quantify the volume of that region, relative to TIV. This volume extraction was done on unsmoothed images to avoid contamination from adjacent brain regions.

2.2.3. Partial Least Squares (PLS) analysis of structural covariance

The covariance patterns of the volumes of the aHC and pHC were assessed using structural partial least squares (PLS; McIntosh & Lobaugh, 2004; McIntosh et al., 1996; Spreng & Turner, 2013), implemented in MATLAB. PLS is a multivariate analysis approach that, in addition to analysis of other modalities (e.g., fMRI), can be used to assess the relationship between patterns of gray matter volume in the brain to other measures, such as a behavior or the volume of a seed region. These relationships are expressed as orthogonal latent variables (LVs). For each LV, each voxel has a weight (salience) reflecting its relationship to the pattern described by that LV, and can be either positive or negative. Statistical significance of the LVs is assessed using a specific number of permutations, and reliability of the saliences is estimated using a bootstrapping procedure. The latter is expressed as a voxel-wise bootstrap ratio (BSR; the ratio of the salience to the bootstrap error). No correction for multiple comparisons is necessary as PLS considers all voxels simultaneously. A brain score for each participant is obtained for each LV by taking the dot product of the group result image and the individual gray matter image. The brain scores reflect how much of the voxel pattern captured by the LV is expressed in each individual.

Here, structural seed PLS was used to identify patterns of volume in the brain that relate to the gray matter volumes of the left and right aHC and pHC, and how these

patterns potentially differ as a function of APOE ε4 carriers status and sex. The TIV-scaled gray matter images were entered into a PLS analysis together with the left and right aHC and pHC volumes as seeds. Male ε4 carriers, male non-carriers, female ε4 carriers and female non-carriers were entered as different groups, resulting in a total of four groups. The analysis was performed using 5,000 permutations and 5,000 bootstraps. LVs were considered significant at a threshold of $p < .05$, and a voxel BSR of 3.3 or more (corresponding to a p-value of .001) was considered reliable.

2.2.4 Cognitive testing

We have previously reported the cognitive function and episodic and spatial memory of the participants included here (Stening et al., 2016). For sake of completeness, and to relate performance to the structural covariance of the hippocampus, we report them here together with a brief description of the included tests.

To assess the participants' general cognitive abilities and to ensure comparability across them, a battery of neuropsychological tests was administered, including a test of synonyms (SRB; Dureman, 1960), verbal fluency, a letter digit substitution test (LDST; Jolles et al., 1995) and Trail Making Tests A and B (TMT A and B; Reitan, 1958).

2.2.4.1 Spatial and episodic memory tasks

Spatial memory and ability was measured using three different tasks; a virtual version of the Morris Water maze (Morris et al., 1982), a virtual navigation task, and mental rotation. Episodic memory was assessed using an object location task and a word recognition task. The tasks have been described elsewhere (Persson et al., 2014, 2013) but a short summary is presented here.

Water Maze task

In a virtual room presented on a computer screen, participants were instructed to swim (using the computer key pad) in a circular pool of water while searching for a hidden

platform within the pool. 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 latency (s) and swimming distance (cm) it took to reach the platform averaged over all trials.

Pointing task

In this navigational task, participants were instructed to move forward, using the computer key pad, in a virtual maze environment. At the end of each maze, their task was to point an arrow in the direction of their starting position at the beginning of the trial. The outcome measure was deviations in degrees from the correct pointing angle averaged over all trials.

Mental Rotation

Participants performed a mental rotation task in which they had to identify the two out of four 3D-rotated geometrical figures that match a target (Vandenberg and Kuse, 1978). There were 20 targets in total, and participants had a maximum of 10 minutes to complete as many as possible.

Object Location task

In this task, drawings of objects (Snodgrass and Vanderwart, 1980) were presented in a 2 x 2 grid on a computer screen. Participants were instructed to memorize the objects and their locations for subsequent tests while making a man-made/naturally occurring classification of the objects. In the subsequent recognition memory test, the targets were presented together with new 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 previously been presented.

Word List task

In this episodic memory task, participants viewed 80 nouns presented on a computer screen. Subsequent recognition memory was tested by having participants make an old/new decision of the 80 target nouns and 80 new nouns serving as distractors. As an outcome measure of recognition, d-prime was calculated by subtracting the z-transformation of false alarms from the z-transformation of hits.

2.2.5 Assessment of structural covariance-behavior relationship

To explore the relationship between structural covariance patterns and cognitive performance, individual brain scores for each significant LV were correlated with scores of cognitive performance. Correlational analysis was done separately for ε4 carriers and non-carriers, and for men and women. Correlations were considered significant at $p < .05$.

3. Results

3.1 Cognitive performance

APOE ε4 carriers performed better compared to non-carriers on TMT A (t[95]= 2.3, $p < .05$) and B (t[95]= 2.6, $p < .05$), and male *APOE* ε4 carriers were superior to male non-carriers on word fluency (t[35]= -2.2, $p < .05$; see Table 1 for neuropsychological performance as a function of group).

With regards to the episodic and spatial tests, *APOE* ε4 carriers performed better compared to non-carriers on mental rotation (t[72]= -3.1, $p < .01$). ε4 carriers had higher Object Location d' scores compared to non-carriers (t[95]= -1.8, $p = .07$), but this fell just short of significance. There was a sex difference favoring men in mental rotation (t[72]= 6.9, $p < .001$), the Pointing task (t[95]= -7.7, $p < .001$), and latency in the Water Maze task (t[94]= -5.1, $p < .001$). For all episodic and spatial results, see Table 2.

3.2 Structural covariance of the hippocampus

The PLS analysis produced two significant LVs, LV 2 and LV 4 (see Figure 1 for the bootstrapped correlation between seed values and brain scores and Table 3 for a cluster report of reliable voxels).

LV 2 ($p < .001$; accounting for 18% of the cross-correlation variance) revealed a significant three-way axis x sex x genotype interaction, due to *APOE* ε4 + women showing a different covariance pattern of the bilateral aHC with the rest of the brain compared to both *APOE* ε4 + men and *APOE* ε4 – men and women (see Fig. 1). The volume of the aHC of *APOE* ε4 + women covaried positively with volume in the bilateral superior and middle frontal gyri, the right inferior frontal gyrus, the right anterior cingulum, the right inferior temporal gyrus, the right superior occipital gyrus and the bilateral middle occipital gyrus (see Table 3 for all saliences). In *APOE* ε4 + men and *APOE* ε4 - men and women volume in all seeds (left and right aHC and pHC) covaried positively with volume in the hippocampus itself, the precuneus, bilateral cerebellum, left putamen, right inferior frontal gyrus and the left middle cingulate cortex. At the same time, regions covarying positively with the aHC of the *APOE* ε4 + women also covaried negatively with volume in the whole hippocampus in the other groups, whereas the volume in the regions covarying positively with the whole hippocampus in *APOE* ε4 + men and *APOE* ε4 – men and women covaried negatively with the volume of the aHC in *APOE* ε4 + women.

The left anterior hippocampus in *APOE* ε4 + men was close to not being reliably part of the described pattern, and so was the bilateral pHC in *APOE* ε4 – women. In this sense, the patterns were almost opposite in women, who then showed different patterns of covariance of the aHC as a function of *APOE* genotype. Also, *APOE* ε4 + men differed from *APOE* ε4 – men in that their left aHC was close to not sharing the covariance pattern of the rest of the hippocampus.

The second significant LV, LV 4 (p = .035; accounting for 10% of the cross-correlation variance), showed a significant axis x genotype interaction, separating whole brain connectivity of the pHC in *APOE* ε4 carriers from that of the aHC in *APOE* non-carriers. In both male and female ε4 carriers the volume of the bilateral pHC covaried positively with volume in the bilateral superior orbital gyrus, left inferior parietal lobule, bilateral angular gyrus and bilateral inferior frontal gyrus. In ε4 women, this pattern was somewhat less reliable in the right pHC. In parallel, in both male and female non-carriers the volume of the bilateral aHC covaried positively with volume in the right middle frontal gyrus and left postcentral gyrus. Regions covarying positively with the pHC in ε4 carriers covaried negatively with the aHC in in ε4 non-carriers, and regions covarying positively with the aHC in in ε4 non-carriers covaried negatively with the pHC in in ε4 carriers.

Taken together, female *APOE* ε4 carriers showed a distinct structural covariance pattern of the aHC, which was not shared by any other group. In addition, both male and female *APOE* ε4 carriers showed a particular structural covariance pattern of the pHC, which was opposite that of non-carriers' structural covariance pattern of the aHC.

3.3 Associations between structural covariance patterns and cognitive performance

To examine potential associations between covariance patterns and cognitive performance, we assessed the correlations between each individual's brain scores for each of the two LV's and cognitive performance and as a function of group (*APOE* ε4 + men; *APOE* ε4 + women; *APOE* ε4 - men; *APOE* ε4 - women).

For LV 2, male ε4 carriers showed significant correlations between the brain scores and performance in TMT A (r = -.49; p < .05), SRB synonyms (r = .48; p < .05) and Object Location, location (r = .49; p < .05), indicating that male ε4 carriers showing this covariance pattern to a larger extent perform better on these tasks. There were no significant associations between this LV and cognitive performance in female ε4 carriers. In non-carriers,

there were significant associations between the brain scores and performance on the Word List task (r = .57; p = .001) in men and on FAS (r = .46; p = .01) in women, reflecting that non-carriers showing this covariance pattern perform better on these tasks.

For LV 4, male ε4 carriers did not show any significant associations between brain scores and cognitive performance. In female ε4 carriers, there was an association between this LV's brain scores and the amount of time spent searching for the platform in the Water Maze task (r = -.64; p = .05), an association also present in male non-carriers (r = -.37; p < .05). This reflects that higher degree of adherence to this covariance pattern in these groups is related to better performance on this task. For female non-carriers, there was a signification association between the pattern of this LV and Object Location, location performance (r = .34; p < .05).

4. Discussion

Although the *APOE* ε4 allele is associated with impaired episodic memory in the elderly, young ε4 carriers have shown superior episodic memory as well as spatial memory and function. The neural correlates of this cognitive advantage are not fully understood, and in the present study we used a multivariate approach to assess whether young *APOE* ε4 carriers differ from non-carriers in their patterns of whole-brain structural covariance of the aHC and pHC. Two significant patterns emerged, indicating distinctive structural covariance in *APOE* ε4 women compared to everyone else on one hand, and distinguishing *APOE* ε4 carriers from non-carriers on the other. These two patterns correlated with cognitive function, but with different tests in different groups.

The first pattern thus expressed whole-brain structural covariance patterns of the hippocampus that distinguished female *APOE* ε4 carriers from all other groups. In female ε4 carriers, the volume of the aHC covaried with volume in frontal regions, the anterior cingulum, the inferior temporal gyrus and occipital areas, whereas the volume of both the

aHC and pHC in all other groups covaried with volume in the inferior frontal gyrus, putamen, precentral gyrus, precuneus and cerebellum. We have previously shown a sex difference in the structural covariance of the aHC and pHC, where women's aHC in particular covaried with volume in other brain areas. In men, it was the whole hippocampus and the pHC that showed different covariance patterns with the rest of the brain (Persson et al., 2014). The structural covariance pattern presented here partly repeats that previously observed in men, with the whole hippocampus covarying with the thalamus, middle cingulate cortex and cerebellum. There were also additional areas, not covarying with the hippocampus in men in the earlier study, such as the inferior frontal gyrus, putamen and precuneus. This addition may be due to this pattern also being shared by female non-carriers, in whom the pattern was somewhat more reliable in the aHC than the pHC. The pattern observed in female ε4 carriers, on the other hand, showed covariance of the aHC with frontal, temporal, and occipital areas. In women overall we previously observed covariance between aHC and anterior and middle temporal areas (Persson et al., 2014), and although we did observe covariance with the middle as well as the inferior temporal gyrus here, additional areas may be specific to women carrying the ε4 allele.

There are indications that learning may be reflected in increases in gray matter volume (Draganski et al., 2006; Maguire et al., 2000), although greater volume is not always related to greater performance (van Petten, 2014). It is, however, reasonable to hypothesize that regions that function together may also increase in volume together. Several of the regions covarying with the whole hippocampus in men and female non-carriers in the present study are regions important spatial functions. The putamen is one of the main locations of head directions cells (Mizumori et al., 2000), and is believed to be important for spatial learning in rats (Ragozzino et al., 2001). The precuneus is involved in spatial judgment (Hirshhorn et al., 2012) and performance in the Water Maze task (Weniger et al., 2009), and

the cerebellum has recently been proposed to be involved in the creation of hippocampal spatial representation maps (Rochefort et al., 2013). Our findings hence suggest a covariance pattern that may relate to spatial ability in men and female non-carriers. However, this does not parallel our previous behavioral findings of both male and female ε4 carriers being superior in spatial function and memory (Stening et al., 2016), and suggests that this superior performance is due to some other difference in structure and function. The covariance pattern observed in female ε4 carriers may capture an aspect of hippocampal organization that is not directly related to a particular cognitive function.

Our finding of female ε4 carriers showing a unique structural connectivity pattern is in line with functional connectivity findings, suggesting differential resting state connectivity in older healthy female ε4 carriers with reduced hippocampal (Heise et al., 2014) and precuneal (Damoiseaux et al., 2012) connectivity. In addition, the aHC volume of female ε4 carriers covaried negatively with the precuneus, which can be directly related to the reduced resting connectivity between the hippocampus and precuneus observed by Heise et al. (2014). The reason for the present finding of an interaction between sex and *APOE* genotype is unclear, but it has been suggested that estrogen can modulate the effects of the *APOE* ε4 allele (Jacobs et al., 2013) which may contribute to differential effects in men and women.

Female non-carriers followed the same pattern of covariance as all men, regardless of *APOE* carrier status, but they expressed this covariance pattern to a higher degree in the bilateral aHC, while both male groups expressed it to a higher degree in the pHC. The pHC has frequently been shown to be involved in spatial processing, both functionally (Kühn and Gallinat, 2014) and structurally (Maguire et al., 2000). Men usually outperform women in spatial tasks (Astur et al., 1998; Piper et al., 2011), which may be

related to our finding that all men showed more reliable covariance of the pHC compared to the aHC with the brain regions expressed by this LV.

The second significant pattern to emerge from the analysis showed differential structural covariance of the aHC and pHC depending on *APOE* carrier status. In ε4 carriers, volume of the bilateral pHC covaried positively with the volume of parietal areas, such as the inferior parietal lobule and angular gyrus, as well as multiple frontal regions. This is at least partly in line with earlier reports on the connections between the inferior parietal lobule and pHC (Poppenk and Moscovitch, 2011; Uddin et al., 2010), and corresponds well with the pHC structural covariance we have previously observed in men (Persson et al., 2014). In female ε4 carriers, this pattern was less reliable for the right pHC, possibly due to women commonly being more verbal than spatial (Burton et al., 2005; Lewin et al., 2001). This structural covariance pattern of ε4 carriers was comprised the inferior parietal lobule, angular gyrus and orbitofrontal areas, all regions common to the DMN (Greicius et al., 2003). Increased connectivity during rest in ε4 carriers between regions of the DMN and the hippocampus has previously been shown, both in young (Filippini et al., 2009) and middle aged and elderly (Westlye et al., 2011). Furthermore, the pHC has been associated with the DMN in relation to episodic retrieval success (Kim, 2015). This, together with our previous findings of better Object Location memory in ε4 carriers (Stening et al., 2016), can be extended to the present finding of structural covariance between pHC and DMN regions, suggesting this pattern may be associated with performance in ε4 carriers.

In non-carriers, the bilateral aHC showed structural covariance with somatosensory and motor areas, as well as the lingual gyrus, important for visual processing (Bogousslavsky et al., 1987). It also covaried with the middle frontal gyrus, which is in line with Trachtenberg et al. (2012), who found that ε3 carriers showed more distinct functional connectivity in this network comprised of the aHC and middle frontal gyrus, compared to

carriers of the ε2 and ε4 allele. The pattern of structural covariance presented here was common to both men and women and can instead be interpreted as an effect of *APOE* carrier status. We have previously shown a sex difference in the structural covariance of the aHC in that women show structural covariance between the aHC and mainly temporal areas (Persson et al., 2014). It is possible that the divergence here is due to the group adhering to this pattern consists also of men.

The relationship between cognitive performance and the structural covariance of the aHC and pHC was different for the two patterns. For the first pattern, there was a positive association with location memory in Object Location in male ε4 carriers. The Object Location task is an episodic task with spatial components, which may explain its positive associations with the aHC and pHC covariance with spatial areas as mentioned above. There was also a positive association between this pattern and Word List performance. It is notable that the left aHC in male non-carriers more reliably contributed to the first pattern compared to in ε4 carriers, which may explain the strong correlation with Word List performance given this area's involvement in verbal memory (Persson and Söderlund, 2015).

For the second pattern, there were negative associations between time needed in the Water Maze task and structural covariance of the bilateral aHC in male non-carriers, and the bilateral pHC in female ε4 carriers. This indicates that the more these groups adhered to this pattern of structural covariance, the faster they were. In female non-carriers, there was an association between structural covariance of the bilateral aHC and Object Location performance. This is in line with findings of Kim (2015) who reported that the aHC and the middle frontal gyrus show episodic encoding related connectivity. The fact that different groups showed associations between their brain pattern and different cognitive tasks may relate to interindividual variation in what brain areas are involved when a task is carried out.

Previous studies that have found *APOE* related differences in resting state functional connectivity networks, and especially the DMN, also report no gray matter differences between groups (e.g., Filippini et al., 2009; Westlye et al., 2011). This is usually commented on as that variance in DMN connectivity can be found in the absence of volume differences. However, the findings presented here, as well as those in Spreng & Turner (2013), suggest that there are differences in structural covariance that correspond to other APOE related differences, e.g., within the DMN. Here, we have further explored this idea and showed that differences between groups in structural covariance between groups can also be dependent on hippocampal segments. Furthermore, previous claims of no volume differences related to *APOE* carrier status (e.g., Filippini et al., 2009; Stening et al., 2016; Westlye et al., 2011) have all been made using univariate methods. Our findings presented here further emphasize the usefulness of multivariate methods.

One possible limitation of the present study is the relatively low number *APOE* ε4 carriers in the study sample. The reason for this is that there was no screening for *APOE* carrier status before including participants in the study. Nonetheless, the final sample distribution of *APOE* ε4 lies around 30 %, which is above the worldwide frequency distribution of ≈ 14 % of the ε4 allele (Eisenberg et al., 2010; Ordovas et al., 1987).

Taken together, we have shown that the way aHC and pHC volume covaries with volume in the rest of the brain differs as a function of *APOE* genotype in young adults. On one hand, this difference is apparent in women, where *APOE* ε4 carriers and non-carriers show opposing covariance patterns of their aHC, and where non-carriers' pHC shows similar covariance as their aHC. On the other hand, the pHC in male and female *APOE* ε4 carriers covaries with brain regions which are the opposite of those that the aHC in male and female non-carriers covaries with. These differences that suggest differing hippocampus-whole brain interactions may relate to differences in cognitive performance, and future research should

elucidate whether such interactions change over time and underlie the impaired memory function that is commonly associated with the *APOE* ε4 allele in older age.

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