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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 smaller hippocampal volumes in healthy aging, while findings in young adults are inconclusive. Previous studies have mostly used univariate methods, and without considering potential anterior/posterior differences. Here, we used a multivariate method, partial least squares, and assessed whole-brain structural covariance of the anterior (aHC) and posterior (pHC) hippocampus in young adults ($n = 97$) as a function of *APOE* ε4 status and sex. Two significant patterns emerged: (1) specific structural covariance of the aHC with frontal regions, temporal and occipital areas in *APOE* ε4 women, whereas the volume of both the aHC and pHC in all other groups co-varied with frontal, parietal and cerebellar areas; and (2) opposite structural covariance of the pHC in ε4 carriers compared to the aHC in non-carriers, with the pHC of ε4 carriers covarying with parietal and frontal areas, and the aHC of ε4 non-carriers covarying with motor areas and the middle frontal gyrus. *APOE* ε4 has in young adults been associated with better episodic and spatial memory, functions involving the aHC and pHC, respectively. We found no associations between structural covariance and performance, suggesting that other factors underlie the performance differences seen between carriers and non-carriers. Our findings indicate that *APOE* ε4 carriers and non-carriers differ in hippocampal organization and that there are differences as a function of sex and hippocampal segment. They stress the need to consider the hippocampus as a heterogeneous structure, and highlight the benefits of multivariate methods in assessing group differences in the brain.

1. Introduction

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 [1,2], has also been linked to smaller hippocampal volumes in healthy elderly ε4 carriers, and especially so in the right hippocampus [3–5], compared to non-carriers. However, there are also studies reporting no volumetric differences associated with *APOE* genotype in the elderly [6,7]. Findings of hippocampal volume differences in young ε4-carriers are uncommon. OíDwyer et al. [8] 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 [9–12] or adolescents [13].

In terms of hippocampal function, there are observations in healthy elderly ε4 carriers of both increased activation in the right hippocampus [6,14] and decreased activation in the left hippocampus [6,15] as compared to non-carriers during episodic memory tasks. In young ε4-carriers, similarly to the elderly, there are observations of both increased [9–11] as well as decreased bilateral hippocampal activity during episodic memory tasks [16]. Considering hippocampal activity in relation to that of other brain areas, Harrison et al. [17] 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

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APOE ε4 carriers, Dennis et al. [9] 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. There are indications that learning may be reflected in increases in gray matter volume [18,19], although greater volume is not always related to greater performance [20]. It is, however, reasonable to hypothesize that regions that function together may also increase in volume together. Using a multivariate approach, we have previously shown that young men and women differ in how their anterior and posterior hippocampal volumes co-vary with patterns of volume in the rest of the brain [21]. In terms of *APOE* genotype, Spreng and Turner [22] 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 [23]. In young ε4 carriers, instead, increased resting state coactivation between the bilateral hippocampus and the DMN has been observed [10]. 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.

APOE ε4 has been linked to declining episodic [24,25] and spatial memory function [26] in healthy elderly. In young adults, however, *APOE* ε4 has been associated with better episodic memory performance [16,27]. 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 [12]. Here, we depart from our earlier findings of superior spatial function in young *APOE* ε4 carriers, which was not paralleled by any differences in hippocampal volume [12], and instead assess patterns of structural covariance of the hippocampus as an alternative explanation of these behavioral differences.

Episodic and spatial memory and function are thought to be related to especially the anterior (aHC) and posterior (pHC) hippocampus, respectively [28,29]. 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. 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. [17]).

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 [21], we included sex as a factor to assess possible interactions between sex and *APOE* genotype. Furthermore, we examined whether possible differing structural covariance patterns of the aHC and pHC due to *APOE* genotype is associated with memory functions linked to these subregions.

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 12–20 years of education (M = 15.1, SD = 1.7) 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). Seventy-four individuals were also included in our previous study of hippocampal structural covariance [21]. For the sake of comparison, the *APOE* distribution of this subsample is provided in Supplementary Table 1. Participants were recruited through advertisements across the Uppsala University campus, and were screened to only include right-handed healthy individuals with no history of brain injury or neurological disease, 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–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 subsequently used for analyses.

ε2 carriers are sometimes removed because of the proposed protective properties of this allele. However, as this is not always done [5,30,31], and because we previously found no different results in hippocampal volume or cognitive performance after removing ε2 carriers [12], we included them in the analyses.

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 × 240 mm; voxel size = 1 mm^3 isotropic voxels; 170 slices).

2.2.3. 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 [32]. 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 intracranial volume (ICV) 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 ICV, the final images represent proportional regional gray matter volume where individual differences in overall brain size have been accounted for.