



Neuroimaging

Familiarity deficits in cognitively normal aging individuals with *APOE* ϵ 4: A follow-up investigation of medial temporal lobe structural correlates

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Abstract

Introduction: The apolipoprotein E ϵ 4 (*APOE* ϵ 4) allele is a well-documented risk factor for Alzheimer's disease (AD). Accordingly, aging individuals carrying one or more ϵ 4 alleles are at considerably greater risk of developing AD over time. In an effort to characterize early cognitive manifestations of AD, we previously outlined selective deficits in familiarity-based recognition in otherwise asymptomatic carriers of the *APOE* ϵ 4 allele (Schoemaker et al., 2016). In this follow-up report, we aimed to explore the neural correlates of this selective cognitive impairment.

Methods: For this purpose, within the same population and using high-resolution structural neuroimaging, we explored relationships between volumes of the hippocampus, entorhinal, and perirhinal cortices and performance in recollection and familiarity.

Results: Overall, our results revealed significant positive relationships between familiarity performance and volumes of the perirhinal and entorhinal cortices in aging individuals with *APOE* ϵ 4. In *APOE* ϵ 4 carriers, a positive correlation between recollection performance and hippocampal volume was also found. In contrast, no correlation reached statistical significance in the group of noncarriers.

Conclusion: These findings suggest that familiarity performance might be a useful marker of the integrity of the rhinal cortex, especially in populations at risk of AD.

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Keywords:

Apolipoprotein E; Aging; Alzheimer's disease; Cognition; Familiarity; Recollection; Structural neuroimaging; Hippocampus; Entorhinal cortex; Perirhinal cortex

1. Introduction

According to dual-process theories, recollection and familiarity are two distinct processes contributing to recognition performance [1]. Studies investigating the neural correlates of recollection and familiarity have revealed a functional dissociation of these two processes within medial temporal lobe structures. More precisely, as recollection has been linked with hippocampal integrity, evidence suggests

that familiarity is associated with the integrity of the entorhinal cortex and/or perirhinal cortex [2,3]. Interestingly, these areas are the very first to be affected by neurofibrillary tangles in the course of Alzheimer's disease (AD) [4]. Thus, familiarity impairments could represent one of the earliest cognitive manifestations of this disease. In accordance with this hypothesis, we recently outlined a selective impairment in familiarity in cognitively normal aging individuals carrying the apolipoprotein E ϵ 4 allele (*APOE* ϵ 4), a significant risk for the development of AD [5]. In this follow-up investigation, and within the same population, we now aimed to explore the medial temporal lobe structural correlates of this selective impairment.

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2. Methods

A total of 21 *APOE* $\epsilon 4$ carriers and 60 noncarriers aged 55 to 80 years (mean 64.76 years; standard deviation 6.42) participated in this study. Both groups were similar in age, education, and gender representation. Participants underwent a comprehensive cognitive evaluation and completed a computerized task to assess their recollection and familiarity performance. Evaluation procedures as well as demographic and cognitive characteristics of both groups have been previously described in greater detail [5].

For each participant, a T1-weighted magnetic resonance imaging (3D MP-RAGE) scan was acquired on a 3T Siemens Tim Trio scanner (Siemens Healthineers, Erlangen, Germany), with a 32-channel head coil. Before segmentation, neuroanatomical images were denoised [6], corrected for nonuniformity [7], and linearly registered to Montreal Neurological Institute standard space [8]. The volumes of the hippocampal, entorhinal, and perirhinal cortices were then automatically segmented using a previously described technique [9,10] and manually corrected based on published segmentation guidelines [11,12]. Volumes obtained in the standard space were transformed to the native space, using scaling factors derived from the linear registration. Finally, to account for variations in head size, all volumes were normalized for total intracranial volume ([raw volume/total intracranial volume] $\times 10^3$).

Difference in normalized structural volumes between *APOE* $\epsilon 4$ carriers and noncarriers were assessed using a one-way analysis of variance. Pearson correlations were computed between the combined left and right hemispheric normalized volumes of each segmented structure and performance on the recollection/familiarity task. Correlation analyses were carried using the full sample as well as separately for the group *APOE* $\epsilon 4$ carriers and noncarriers. Owing to the small sample size of the $\epsilon 4$ carriers' group and the preliminary nature of research hypotheses, we did not correct for multiple comparisons and reported correlations with a *P* value of $<.05$ as significant.

3. Results

As previously reported, the familiarity rate was significantly reduced in *APOE* $\epsilon 4$ carriers, as compared with noncarriers [$F(1, 79) = 7.80; P = .007$] [5]. When estimates of familiarity were computed to account for the process independence assumption [13], the group difference in familiarity remained significant [$F(1, 79) = 3.99; P < .05$] [14]. There was no significant group difference with regards to the hit rate, the recollection rate or the false alarm rate. Furthermore, no other cognitive measure was significantly reduced in *APOE* $\epsilon 4$ carriers.

There was no significant difference in the total normalized volumes between *APOE* $\epsilon 4$ carriers and noncarriers for the hippocampus [$F(1, 79) = 1.02; P > .05$], the perirhinal cortex [$F(1, 79) = 0.35; P > .05$], and the entorhinal cortex [$F(1, 79) = 0.45; P > .05$].

In the full sample, results revealed a significant positive correlation between the recollection rate and the total normalized hippocampal volume ($r = 0.26; P < .05$). No other correlation reached statistical significance. When considering the two groups separately, no correlations reached statistical significance in the group of *APOE* $\epsilon 4$ noncarriers. In contrast, in *APOE* $\epsilon 4$ carriers, significant positive correlations were found between the total normalized hippocampal volume and the recollection rate ($r = 0.49; P < .05$). Both the familiarity rate ($r = 0.61; P < .01$) and the familiarity estimate ($r = 0.54; P < .05$) derived from Jacoby's formulas (1991) were positively and significantly associated with the total normalized perirhinal cortex volume. A significant correlation was also noted between the familiarity rate and the total normalized entorhinal cortex volume ($r = 0.46; P < .05$); however, the correlation between the total normalized entorhinal cortex volume and the familiarity estimate derived from Jacoby's formulas was only of marginal significance ($r = 0.42; P = .06$). Detailed results of these correlational analyses are presented in Table 1 and illustrated in Fig. 1.

Table 1

Correlations between recollection and familiarity performance and normalized volumes of medial temporal lobe structures

Volumes	Full sample (<i>N</i> = 81)			<i>APOE</i> $\epsilon 4$ noncarriers (<i>N</i> = 60)			<i>APOE</i> $\epsilon 4$ carriers (<i>N</i> = 21)		
	Recollection rate	Familiarity rate	Familiarity estimate	Recollection rate	Familiarity rate	Familiarity estimate	Recollection rate	Familiarity rate	Familiarity estimate
Normalized HP volume	0.26*	-0.01	0.10	0.18	-0.05	0.04	0.49*	-0.05	0.19
Normalized PC volume	0.16	0.02	0.12	0.18	-0.14	-0.03	0.12	0.61 [†]	0.54 [†]
Normalized EC volume	0.15	0.01	0.11	0.19	-0.13	-0.01	0.10	0.46*	0.42 [‡]

Abbreviations: *APOE* $\epsilon 4$, apolipoprotein E $\epsilon 4$; EC, entorhinal cortex; HP, hippocampus; PC, perirhinal cortex.

NOTE. Summary of correlational analyses between performance in recollection and familiarity and normalized volumes of medial temporal lobe regions of interest. Analyses are presented for the full sample, as well as for *APOE* $\epsilon 4$ carriers and noncarriers separately. *N* is the sample size of each group. Recollection rate is the proportion of recognition responses based on recollection. Familiarity rate is the proportion of recognition responses based on familiarity. Familiarity estimate derived from Jacoby's formulas (1991) to account for the process independence assumption. Total normalized volume represents the combined volume of the left and right hemispheres normalized for total intracranial volume.

*Significant correlation as per an $\alpha = 0.05$ threshold.

[†]Significant correlation as per an $\alpha = 0.01$ threshold.

[‡]Correlation of marginal significance as per an $\alpha = 0.10$ threshold.

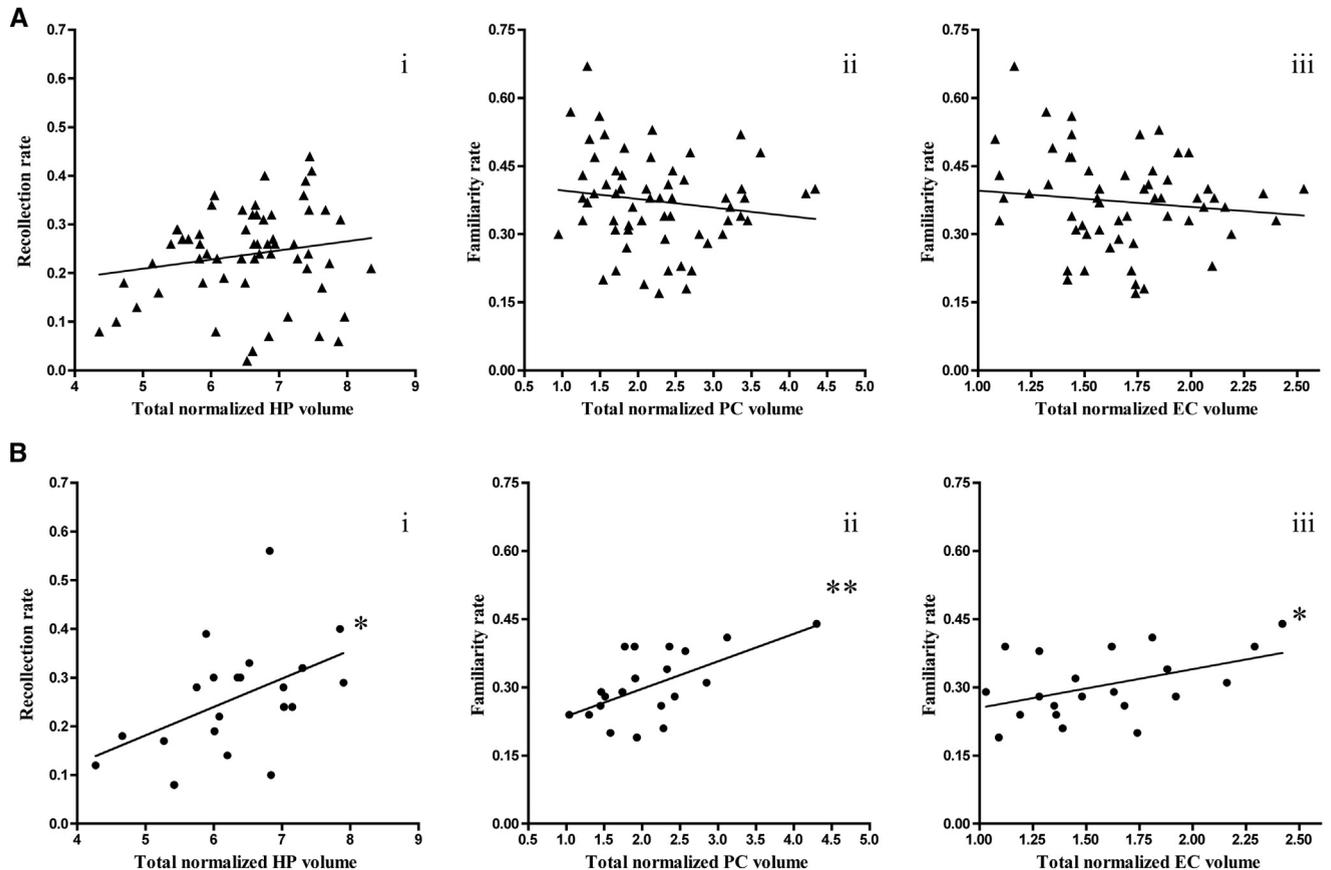


Fig. 1. Correlations between recollection and familiarity performance and normalized volumes of medial temporal lobe structures in *APOE* $\epsilon 4$ carriers and noncarriers. Figure illustrating correlations between recollection and familiarity rates and normalized volumes of medial temporal lobe regions of interest, separately for *APOE* $\epsilon 4$ noncarriers (A) and *APOE* $\epsilon 4$ carriers (B). *APOE* $\epsilon 4$ carriers ($N = 21$) are represented by full-black circles and *APOE* $\epsilon 4$ noncarriers ($N = 60$) are represented by full-black triangles. Specifically, plots show correlations between recollection rate and the total normalized hippocampal (HP) volume (i); familiarity rate and the total normalized entorhinal cortex (EC) volume (ii); and familiarity rate and total normalized perirhinal cortex (PC) volume (iii). Total normalized volume represents the combined volume of the left and right hemispheres normalized for total intracranial volume. * indicates a significant correlation as per an $\alpha = 0.05$ threshold. ** indicates a significant correlation as per an $\alpha = 0.01$ threshold.

4. Conclusion

The *APOE* $\epsilon 4$ allele is an important risk factor for the development of AD [15]. In this study, we investigated relationships between the volumes of the hippocampal, entorhinal, and perirhinal cortices and recollection and familiarity performance in cognitively normal aging individuals with and without the *APOE* $\epsilon 4$ allele.

In a previous article, we highlighted a significant and selective impairment in the familiarity performance of *APOE* $\epsilon 4$ carriers [5]. Here, we provide evidence that the familiarity deficit in *APOE* $\epsilon 4$ carriers is related to the structural integrity of the perirhinal cortex and, although to a lesser extent, the entorhinal cortex. This is convergent with previous human lesion studies and functional magnetic resonance imaging (fMRI) experiments linking familiarity performance to the integrity of the rhinal region [2,3]. Thus, familiarity deficits in *APOE* $\epsilon 4$ individuals might represent early cognitive changes resulting from an increased frequency of

individuals harboring AD pathology affecting the rhinal areas in this population. Familiarity performance might, therefore, be a sensitive cognitive marker of rhinal integrity and of preclinical phases of neurodegeneration, especially in populations at increased risk of AD. However, studies using longitudinal designs and validated AD biomarkers are needed to confirm the utility of familiarity assessment in the detection of preclinical AD.

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RESEARCH IN CONTEXT

1. Systematic review: The relevant literature was reviewed using online databases (PubMed; PsycINFO). Lesion studies have revealed that familiarity performance is dependent on the integrity of rhinal areas. These regions are among the first to be affected by neurofibrillary tangles in Alzheimer's disease (AD). These sources are appropriately cited in the report. In a previous study, we highlighted a selective familiarity deficit in aging individuals with apolipoprotein E $\epsilon 4$ (*APOE* $\epsilon 4$). In this follow-up report, we aimed to characterize the structural correlates of this selective impairment.
2. Interpretation: Our findings suggest that the familiarity deficit outlined in *APOE* $\epsilon 4$ carriers is related to the integrity of the perirhinal cortex and, to a lesser extent, the entorhinal cortex. This suggests that familiarity performance might be a sensitive cognitive marker of rhinal integrity and, thus, might contribute to detection of early cognitive changes associated with AD.
3. Future directions: Using longitudinal designs and validated biomarkers, future studies should aim to characterize associations between familiarity performance and subsequent cognitive decline due to AD.

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