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Selective familiarity deficits in otherwise cognitively intact aging individuals with genetic risk for Alzheimer's disease

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Abstract

Introduction: Familiarity has been associated with integrity of the rhinal cortex. Thus, impairment in familiarity is expected in very early stages of Alzheimer's disease (AD). The apolipoprotein E (*APOE*) ε4 allele is a major risk factor for AD. Here, we investigated the effect of the *APOE* ε4 status on familiarity in cognitively normal aging individuals.

Methods: Eighty-one individuals aged between 55 and 80 years, 21 carriers and 60 noncarriers, were used in these analyses. A cognitive evaluation was performed on all participants to document the absence of objective cognitive deficits. The effect of *APOE* ε4 status on familiarity was tested using independent sample *t* test and an analysis of covariance controlling for age, gender, and education.

Results: The groups did not differ in term of age, education, and male/female ratio. *APOE* ε4 carriers showed a significant reduction in familiarity. No other cognitive deficit was observed in the group of ε4 carriers, relative to noncarriers.

Discussion: *APOE* ε4 is associated with a reduction in familiarity in the absence of other cognitive deficits. These results suggest that performance in familiarity could represent an early cognitive marker for individuals at risk of AD.

Keywords: Aging; Apolipoprotein E; Familiarity; Recollection; Cognitive marker; Alzheimer's disease

1. Introduction

Owing to the aging of the population, a worldwide phenomenon, the burden of Alzheimer's disease (AD) is expected to increase dramatically over the next decades [1]. Because of its insidious progression, AD is often only detected at a relatively advanced stage of neurodegeneration, when clinical manifestations and functional impairments are observable. Detecting AD at an earlier stage could contribute to the development of new interventions (pharmaceutical or not) to slow or halt the progression of the disease. The development of new cognitive tests sensitive to early cognitive changes associated with impending AD could contribute to this objective.

AD is a progressive and neurodegenerative condition that develops over several decades [2]. In the first stages of AD, also known as transentorhinal stages, the entorhinal and perirhinal cortices (EC/PC) are targeted by neurofibrillary tangles [3]. Histopathologic studies have demonstrated important neuronal loss in the EC at the earliest stages of dementia. A study by Gómez-Isla et al. [4] revealed that individuals with a clinical dementia rating scale score of 0.5 presented 32% less neurons in the EC relative to aged-matched controls. Magnetic resonance imaging volumetric studies also reported significant EC volume reduction in individuals with mild AD, with one study revealing a volume loss as high as 40% in this region for patients with AD [5]. The functionality of the EC/PC region is also altered in the course of pathologic aging. A longitudinal positron emission tomography study showed that glucose metabolism in the EC accurately predicted cognitive decline over a period of

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3 years [6]. In comparison with other regions in the temporal and frontal lobes, the EC was found to be to the most accurate predictor of cognitive changes over time. These findings demonstrate that the EC/PC region is very sensitive to early pathologic alterations associated with AD. Thus, detecting an impaired functionality of these regions could allow early and specific identification of subjects with preclinical AD. However, this is hindered by the fact that transentorhinal stages of AD, also referred to as "silent stages," are believed to occur before observable clinical manifestations [3].

The functional role of the EC/PC has been extensively studied over the past decades, but the vast majority of studies investigating its function have been performed in animals. Hence, its role in human cognition continues to be a matter of debate. Recent evidence suggests that the EC/PC is associated with familiarity [7,8]. According to dual-process models, familiarity and recollection are two distinct and independent processes involved in the recognition of previously seen material. Recollection can be defined as a recognition episode accompanied by retrieval of contextual details associated with the encoding sequence. In contrast, familiarity is perceived as a recognition based on a feeling of "knowledge" that a stimulus has previously been encountered, despite a lack of retrieval of contextual details associated with the encoding episode. The existence of two distinct processes involved in recognition has received a substantial amount of empirical support (see Yonelinas 2002 for a review [9]).

Human lesion studies reveal impairment in familiarity following EC/PC lesions [7,10]. In contrast, hippocampal lesions lead to impairment in recollection with preservation of familiarity [7]. These studies highlight a functional double dissociation between the hippocampus and EC/PC region, the latter being associated with familiarity. This was further corroborated by functional magnetic resonance imaging (fMRI) studies showing that activation in the EC/PC was associated with familiarity-based recognition but not with recollection [8,11]. Taken together, these results support the involvement of the EC/PC region in familiarity-based recognition.

Recent articles have reviewed the literature looking at familiarity and recollection in aging individuals with normal cognition, mild cognitive impairment (MCI), and AD [12,13]. Overall, these reviews suggest that, although recollection is impaired in the course of normal aging, familiarity is preserved [12]. The presence of familiarity deficits in MCI and AD patients is not corroborated by all studies. However, the results of these reviews indicate that familiarity deficits tend to be present in MCI individuals at increased risk of AD. Looking at familiarity performance in cognitively normal individuals at increased risk of AD could help defining whether the presence of familiarity deficits represents an early cognitive marker for the development of AD.

The apolipoprotein E (*APOE*) gene is involved in regulating metabolism and the transportation of lipids, such as cholesterol [14]. It is also involved in the growth and repair of neuronal and axonal membranes during development, and following lesions [14]. The *APOE* locus contains two alleles that are polymorphic and exist in three variants: ε2, ε3, and ε4. The ε3 allele is the most common and found in 78% of individuals [15]. The ε4 and ε2 alleles are far less common and are represented in 15% and 7% of individuals, respectively [15]. The ε4 allele of the *APOE* gene, the *APOE* ε4, is a well-documented risk factor for both familial and sporadic AD [16]. The ε4 allele has widely been associated with a higher risk and a younger age of onset of AD [17]. Furthermore, the risk related to the ε4 allele is "dose dependant": individuals with only one ε4 allele show a 2.8–4.4 times increased risk for AD, whereas individuals with two ε4 alleles show a 7.0–19.3 times increased risk [16,18]. Consequently, cognitively intact aging individuals with *APOE* ε4 are more likely to harbor neurofibrillary tangles at the transentorhinal level than noncarriers. Accordingly, a study showed a volume reduction in the medial temporal lobe of nondemented aging individuals, *APOE* ε4 carriers [19].

The objective of this study was to investigate the performance in familiarity of aging individuals carrying an *APOE* ε4 allele and compare it with aging individuals who are noncarriers. Owing to an increased likelihood of harboring AD neuropathology at a subclinical stage, we hypothesized that nondemented individuals with *APOE* ε4 will show decreased performance in familiarity-based recognition.

2. Methods

2.1. Participants

Older Caucasians adults aged between 55 and 80 years were recruited via advertisements in community newspapers. To be eligible for the study, participants had to meet the following criteria: French or English as a first language; absence of current or past neurologic, psychiatric, or severe medical conditions; no current or past history of substance abuse; no current medication known to cross the blood-brain barrier or alter cognitive functioning; >10 years of formal education; and geriatric depression scale [20] and Beck anxiety inventory [21] scores within the normal range. All data were collected as part of a larger fMRI study. The Douglas Mental Health University Institute's research ethics board approved the protocol of the study, and all participants provided informed written consent. Recruited participants underwent a cognitive test battery to allow the exclusion of individuals with suspected cognitive impairment, as defined by a performance of >1.5 standard deviations lower than age-adjusted mean. Participants were also asked to provide a saliva sample to determine their *APOE* genotype. They were informed that results from this genetic test would not be disclosed to them. A total of 88 older individuals completed all testing procedures. Four participants were removed from analyses because of suspected MCI. Three