Neurobiology of Aging 69 (2018) 221–229

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

APOE ε4 status in healthy older African Americans is associated with deficits in pattern separation and hippocampal hyperactivation

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ARTICLE INFO

Article history:
Received 14 March 2018
Received in revised form 16 May 2018
Accepted 18 May 2018
Available online 26 May 2018

Keywords:
APOE
Pattern separation
High-resolution fMRI
Hippocampus
Alzheimer's disease

ABSTRACT

African Americans are 1.4 times more likely than European Americans to carry the apolipoprotein E (APOE) ε4 allele, a risk factor for Alzheimer's disease (AD). However, little is known about the neural correlates of cognitive function in older African Americans and how they relate to genetic risk for AD. In particular, no past study on African Americans has examined the effect of APOE ε4 status on pattern separation—mnemonic discrimination performance and its corresponding neural computations in the hippocampus. Previous work using the mnemonic discrimination paradigm has localized increased activation in the DG/CA3 hippocampal subregions as being correlated with discrimination deficits. In a case-control high-resolution functional magnetic resonance imaging study of 30 healthy African Americans, aged 60 years and older, we observed APOE ε4–related impairments in mnemonic discrimination, coincident with dysfunctional hyperactivation in the DG/CA3, and CA1 regions, despite no evidence of structural differences in the hippocampus between carriers and noncarriers. Our results add to the growing body of evidence that deficits in pattern separation may be an early marker for AD-related neuronal dysfunction.

1. Introduction

We applied task-activated functional magnetic resonance imaging (fMRI) to examine the effects of apolipoprotein E (APOE) ε4 allele on medial temporal lobe (MTL) dysfunction in a population of cognitively healthy African Americans. The APOE ε4 allele is the strongest identified genetic risk factor for Alzheimer's disease (AD) (Potter and Wisniewski, 2012). Its presence has been reported to be associated with heightened episodic memory–related dysfunction in the MTL (Bookheimer et al., 2000; Dennis et al., 2010; Filippini et al., 2009; Michaelson, 2014), which is one of the earliest pathological changes that occur in AD (Gomez-Isla et al., 1996; Price et al., 2001). Despite the fact that African Americans are at elevated risk for AD (Alzheimer's Association, 2018; Tang et al., 2001) and have a higher frequency of the APOE ε4 allele compared with European Americans (Logue et al., 2011), the neural changes that occur in older African Americans and how they relate to genetic risk factors for AD remain unclear. In particular, no previous study on African Americans has examined the effect of APOE ε4 status on the neural computations for "pattern separation," that is, separating similar representations into distinct, nonoverlapping representations while encoding and retrieving episodic memories. This neural computation depends on hippocampal circuitry as demonstrated by a number of empirical reports across species and approaches (Leal and Yassa, 2018).

Our study examined this by comparing a group of healthy African American APOE ε4 carriers (ε4+) to age- and education-matched same-race noncarriers (ε4−) using high-resolution fMRI during a mnemonic discrimination task where participants were asked to distinguish between novel, repeated (old), and similar (lure) information. The neurocomputational mechanism underlying this paradigm is pattern separation, which functions to reduce the mnemonic interference by encoding distinctive representations for similar input patterns (Leal and Yassa, 2018). We therefore tested the hypothesis that APOE ε4 genetic risk is associated with impairments in

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https://doi.org/10.1016/j.neurobiolaging.2018.05.023

pattern separation, that is, behavioral discrimination deficits and the corresponding neural dysfunction in the hippocampus.

1.1. Background

An estimated 5.5 million Americans aged 65 years and older are living with AD as of 2018 (Alzheimer's Association, 2018). In particular, African Americans are at elevated risk for age-related cognitive decline and memory loss, with double the prevalence of AD compared with European Americans (Alzheimer's Association, 2018; Tang et al., 2001). The causes of this health disparity in AD are not sufficiently understood. Furthermore, little is known about the neural correlates of cognitive function in older African Americans and how they relate to genetic risk factors for AD.

The hippocampus is among the earliest loci for pathological changes in AD (Gomez-Isla et al., 1996; Price et al., 2001), with converging evidence suggesting that hippocampal dysfunction may be an early indicator of the neurodegenerative process associated with AD. Several studies have shown that patients with mild cognitive impairment (MCI) exhibit increased activation, or hyperactivation, in the hippocampus during encoding and retrieval of episodic memories (Celone et al., 2006; Dickerson et al., 2004, 2005; Hämäläinen et al., 2007; Kircher et al., 2007; Miller et al., 2008b; Yassa et al., 2010). Similar patterns of hyperactivation have also been observed in individuals at genetic or familial risk for AD (Bassett et al., 2006; Bondi et al., 2005; Bookheimer et al., 2000; Quiroz et al., 2010), healthy older adults who perform poorly on the task (Miller et al., 2008a), and amyloid positive, mildly impaired older adults (Sperling et al., 2009).

An accelerated rate of AD-related pathology in the hippocampus has been associated with the inheritance of the APOE ε4 allele, the strongest identified genetic risk factor for AD (Potter and Wisniewski, 2012). One ε4 allele can increase the risk of AD 2–3 times and 2 ε4 alleles can increase the risk 12 times (Michaelson, 2014). Furthermore, it confers greater AD risk in women compared with men (Altmann et al., 2014). Healthy APOE ε4 carriers show heightened age-related decreases in MTL cortical thickness and hippocampal volume decades before the onset of AD (Michaelson, 2014). Even young APOE ε4 carriers show hyperactivation in the MTL (Dennis et al., 2010), specifically in the hippocampus (Bookheimer et al., 2000; Filippini et al., 2009) during an encoding task, indicating that the APOE-related functional changes in the hippocampus can manifest several decades before cognitive decline.

Growing evidence suggests that the hippocampus possesses a unique circuitry that is computationally capable of resolving mnemonic interference during the encoding and retrieval of episodic memories by using pattern separation, the ability to independently represent and store similar experiences (Leal and Yassa, 2018). Hence, mnemonic discrimination paradigms that are sensitive to the functional changes related to pattern separation can be used to detect alterations in the hippocampus and surrounding medial temporal cortices that may confer vulnerability to AD. Impaired mnemonic discrimination is associated with aberrant hyperactivation in the dentate and CA3 subfields of the hippocampus in nondemented older adults (Dickerson et al., 2005; Reagh et al., 2017; Yassa et al., 2011a,b) as well as in individuals with MCI (Bakker et al., 2012, 2015; Tran et al., 2017; Yassa et al., 2010), the extent of which predicts discrimination deficits.

Past studies examining the relationship between mnemonic discrimination of objects, neural pattern separation, and APOE ε4 status have yielded mixed results. In MCI patients, 1 study reported no differences in hippocampal hyperactivation or mnemonic discrimination between carriers and noncarriers (Tran et al., 2017). Another study reported a link between APOE ε4 homozygotes and performance on a brief mnemonic discrimination task in AD patients (Wesnes et al., 2014). A group of cognitively intact older adult carriers of APOE ε4 was found to perform worse than noncarriers on a spatial mnemonic discrimination task (Sheppard et al., 2016). African Americans are 1.4 times more likely than European Americans to carry the APOE ε4 gene variant (Logue et al., 2011); however, to date, no study has examined whether APOE carrier status in cognitively healthy older African Americans may be associated with impaired pattern separation, involving discrimination deficits, coincident with hippocampal hyperactivation.

1.2. Present study

In the present study, we directly test the hypothesis that the APOE ε4 allele is associated with impaired mnemonic discrimination performance as well as hyperactivation of hippocampal dentate and CA3 subfields in older nondemented African Americans. To ensure that the differences are attributable to APOE genetic risk, and not due to other health and lifestyle factors, subjects also underwent a battery of standardized neuropsychological assessments, physical fitness tests, and reported daily habits.

2. Methods

2.1. Participants

Participants in this study were recruited through the African-American Brain Health Initiative: A University-Community Partnership at Rutgers University-Newark (see www.brainhealth.rutgers.edu). From a larger parent study of 60 individuals, participants in the present study were selected for analysis in a case-control–matched design. Of the parent sample, 15 individuals were homozygous or heterozygous for APOE ε4. We then matched these 15 APOE ε4+ individuals (ε4/ε4: n = 2; ε2/ε4: n = 3; ε3/ε4: n = 10) with 15 individuals who were APOE ε4– (ε2/ε2: n = 2; ε2/ε3: n = 3; ε3/ε3: n = 10) based on age and years of education. Similar to the methodology of Foster et al. (2017), we retained all ε4+ heterozygotes, including ε2/ε4 individuals, as any individual with an ε4 allele is at greater risk of AD than individuals without ε4 alleles (Liu et al., 2013). Therefore, the present study included 30 healthy adults, aged 60-90 years, with an average age of 69 years (Table 1).

Participants exhibiting any signs of dementia as revealed in the standardized neuropsychological assessments (detailed below), and those who took medications that could affect cognition were excluded from the study. Other exclusion criterion included history of excessive alcohol intake and/or drug use, psychiatric disorders (including Bipolar Disorder and Schizophrenia), Epilepsy or related seizure disorders, and significant cardiovascular and cerebrovascular diseases. Participants were also required to be native English speakers. All participants completed written informed consent before participation in the study.

2.2. Physical fitness assessment

In addition to measuring blood pressure, heart rate, and body mass index, a battery of physical assessments was administered to characterize fitness. Aerobic fitness (VO_2 max) was assessed using the Six Minute Walk Test. Participants were instructed to walk a premeasured length on a flat surface for 6 minutes, covering as much ground as possible (McGavin et al., 1978, 1976); total distance was recorded (Noonan and Dean, 2000). Participants' maximal oxygen consumption was approximated using

$$VO_2\ \text{max} = \text{MAX}\,[4.948 + (0.023 \times \text{Distance (in meters)}), (0.03 \times \text{Distance (in meters)}) + 3.98]$$

Table 1
Demographics, neuropsychological tests, fitness, and lifestyle measures

Measure	APOE ε4+	APOE ε4−	Difference (*t*-test)
Sample Size	15	15	
Age	69.5 (6.74)	69.2 (8.0)	
Education (y)	14.7 (1.98)	14.67 (2.38)	
BMI	31.98 (7.38)	30.89 (6.27)	$p = 0.667$
BP—diastole	80.4 (10.99)	83.47 (11.32)	$p = 0.458$
BP—systole	148.53 (29.0)	141.07 (20.9)	$p = 0.426$
Heart rate (bpm)	73.27 (16.09)	68.87 (10.03)	$p = 0.376$
BDI	7.33 (4.64)	8.4 (5.43)	$p = 0.568$
Social support	66.07 (8.98)	68.07 (14.23)	$p = 0.653$
MMSE	27.87 (1.77)	28.20 (1.9)	$p = 0.622$
Digit Span	23.27 (4.03)	23.60 (3.9)	$p = 0.820$
NAART	35.13 (9.94)	36.27 (14.66)	$p = 0.812$
RAVLT—immediate	11.27 (2.02)	12.93 (2.22)	$\mathbf{p = 0.040}$
RAVLT—delayed	9.33 (2.22)	12.73 (2.91)	$\mathbf{p = 0.001}$
Exercise	2.17 (2.04)	1.66 (1.97)	$p = 0.495$
TV (h/d)	4.13 (1.32)	4.97 (1.96)	$p = 0.184$
Sitting (h/d)	4.46 (2.24)	5.30 (2.0)	$p = 0.3$
Sleep quality	3.47 (0.92)	3.07 (1.03)	$p = 0.271$
Gait speed test	4.76 (1.20)	4.86 (1.42)	$p = 0.834$
Repeated chair stand (s)	12.43 (8.83)	17.74 (12.4)	$p = 0.193$
TUG (s)	11.16 (2.10)	10.8 (3.41)	$p = 0.732$
VO_2	12.62 (4.15)	15.26 (3.45)	$p = 0.065$

Data are presented as mean (standard deviation).
Sleep quality: 1 = very poor, 2 = poor, 3 = satisfactory, 4 = good, 5 = excellent.
Group differences were assessed via simple pairwise t-tests.
Any statistically significant differences ($p < 0.05$) are bolded.
Key: APOE, apolipoprotein E; BDI, beck depression inventory; BMI, body mass index; MMSE, mini mental state exam; TUG, timed up and go; RAVLT, rey auditory verbal learning test.

This measure of maximal oxygen consumption (VO_2 max) is widely recognized as both a representation of the functional limitations of the cardiovascular system as well as a measure of aerobic fitness (Taylor et al., 1955).

The Short Physical Performance Battery was used to evaluate static balance when standing, gait speed at a regular pace, and movements consisting of sitting down and standing up. To assess static balance, the participant is asked to maintain up to 3 hierarchical standing postures for up to 10 seconds. First, the participant stands with feet together. If the participant can maintain this posture for 10 seconds, they then perform a semitandem stance position. If semitandem is held for 10 seconds, it is followed by a tandem stance posture. For the gait speed test, the participant is asked to walk at his or her comfortable speed across a 4-m distance. Finally, the participant is asked to stand from a standard chair without upper extremity assistance. If they can stand 1 time, they then are instructed to complete 5 sit-to- stands as quickly as possible without upper extremity assistance. Performance was measured by the time spent during each test. This battery is a reliable measure to assess general physical performance in older adults (aged 60 years and older), and has been found to be predictive of future decline in health status and function (Studenski et al., 2003).

The Timed Up and Go test was used to assess functional mobility and dynamic balance. In this test, participants are seated and then stand and walk 3 m before turning around and walking back to sit. In a 2-year study, Timed Up and Go completion time predicted future disability for basic activities of daily living in older adults free of disability at baseline (Donoghue et al., 2014).

2.3. Standardized neuropsychological assessments and self-reported measures

Before magnetic resonance imaging (MRI) scanning, a neuropsychological battery consisting of the Mini Mental State Exam (broad assay of cognitive impairment), Rey Auditory Verbal Learning Test (RAVLT) Immediate and Delayed Recall (sensitive to verbal memory), North American Adult Reading Test (NAART35) (sensitive to verbal intellectual ability), and Wechsler Adult Intelligence Scale Digit Span (sensitive to working memory) was administered to characterize cognition (Table 1). The Beck Depression Inventory was administered to measure characteristic attitudes and symptoms of depression. Participants also reported health and lifestyle factors such as sleep quality, daily exercise and activity levels, and, answered a social support questionnaire.

2.4. fMRI behavioral paradigm: mnemonic discrimination task

Participants were given a verbal explanation of the task and completed pretraining with mock stimuli outside the scanner. As shown in Fig. 1, the task consisted of an explicit 3-alternative forced choice task (for more details see Kirwan and Stark [Kirwan and Stark, 2007]), in which participants viewed novel (new), repeated (old), and lure (similar) stimuli. Stimuli were colored photographs of common objects. Each participant completed a single run consisting of 96 similar pairs, 96 identical pairs, and 192 unrelated novel items (foils), totaling 576 trials. All trial types were fully randomized throughout the run. Each stimulus was presented for 3 seconds with a 0.5-second interstimulus interval. The number of trials separating similar and identical pairs randomly varied between 10 and 40 trials. Participants were instructed to make a judgment as to whether the object seen was new (i.e., novel items), old (i.e., repeated items) or similar but not identical (i.e., lure items). Of critical interest were the participants' responses on the lure items. A response of "old" to a lure (i.e., similar) item would constitute a failure of discrimination (possibly indicative of reduced capacity for pattern separation), whereas an accurate response of "similar" to a lure would constitute a successful discrimination (Yassa et al., 2010, 2011a). As in prior work, a lure discrimination index (LDI) was calculated as p("Similar"|Lure)−p("Similar"|Foil), which accounts for response bias.

2.5. MRI data acquisition

MRI data were acquired on a 3T Siemens Allegra, using a 32-channel Multiband parallel encoding coil, at the Rutgers University Brain Imaging Center at Rutgers University, Newark. If required, MRI-compatible glasses were used on the day of scanning. A high-resolution 3D magnetization–prepared rapid gradient echo structural scan was acquired in the sagittal plane for each participant: repetition time = 1900 ms, echo time = 2.52 ms, 9° flip angle, 176 slices (no gap), voxel size 1.0 × 1.0 × 1.2 mm, and field of view = 270 × 254 × 212, with a total acquisition time of 9 minutes. High-resolution Multiband echo-planar images were collected using a field of view of 208 × 208 × 125, a repetition time of 664 ms, an echo time of 30 ms, a flip angle of 30°, an isotropic resolution of 1.8 mm with no gap, and a Multiband acceleration factor of 5. Forty-five axial slices were acquired covering the entire brain. Multiband parallel imaging enabled the acquisition of high-resolution functional images, with large sampling rates for full-brain coverage, through the acquisition of multiple slices simultaneously. This resulted in significantly reduced acquisition time, which also limited distortion resulting from magnetic susceptibility. Furthermore, the high temporal efficiency has been shown to provide greater statistical power (Feinberg et al., 2010).

2.6. fMRI data analysis

2.6.1. Preprocessing

Analysis of imaging data was conducted using FSL (FMRIB Software Library; www.fmrib.ox.ac.uk/fsl). Skull stripping was conducted using the FSL brain extraction (Smith, 2002) with the center

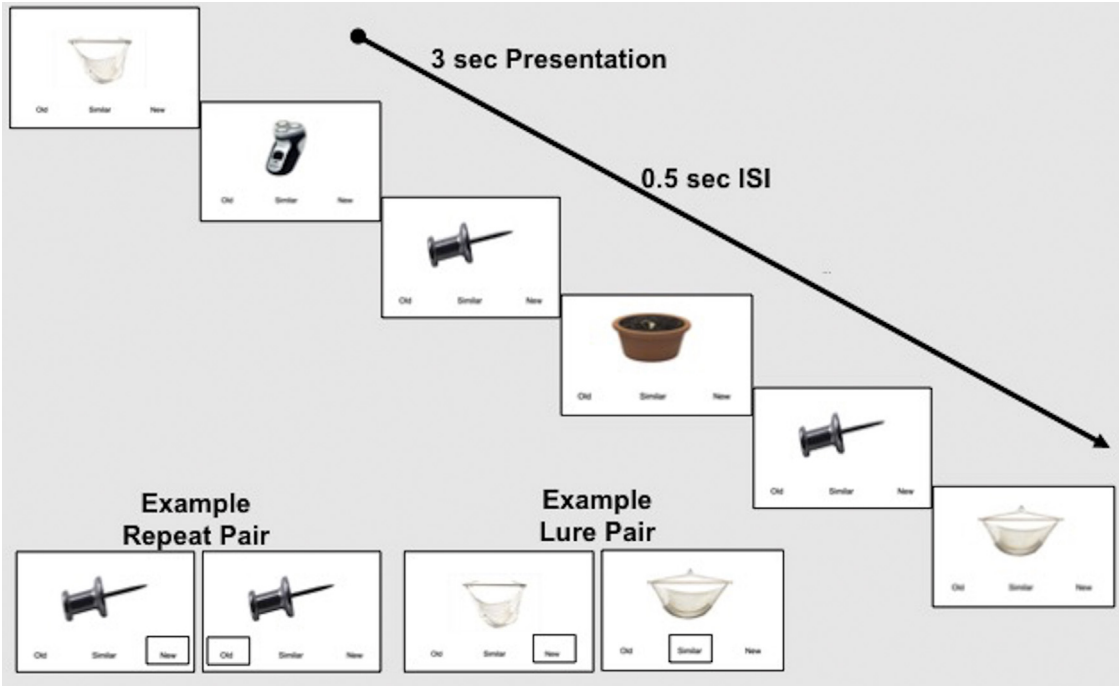

Fig. 1. An example of the mnemonic discrimination behavioral task. Each item was presented for 3 seconds with a 0.5-second interstimulus interval. Novel (new), repeated (old), and lure (similar) items were fully randomized throughout the run. Examples of a repeat pair (left) and a lure pair (right) are shown.

of gravity of each image as a reference point. Functional images were motion corrected using MCFLIRT (FMRIB's motion correction linear image registration tool) (Jenkinson et al., 2002), smoothed using a 5.0-mm Gaussian FWHM kernel, and coregistered to their skull-stripped structural images (degrees of freedom, 9; cost function, normalized mutual information; interpolation, sinc function) using FSL's linear registration tool (Jenkinson and Smith, 2001; Jenkinson et al., 2002). We used Advanced Normalization Tools (Avants et al., 2011) to warp each individual participant's structural scan into an in-house high-resolution 0.65-mm isotropic template using a diffeomorphic nonlinear registration algorithm (Klein et al., 2009). The transformation parameters were then applied to the coplanar functional data to align them to the custom template, for individual and group level general linear model (GLM) analyses.

2.6.2. Analysis

Behavioral vectors based on trial type and behavioral responses were used to model the data in a GLM analysis conducted using the fMRI Expert Analysis Tool utility. A trial averaging window of 3.5 seconds was used beginning from trial onset. The novel foils that were not subsequently tested served as an arbitrary baseline, against which other conditions were compared. The resultant fit coefficients (betas) therefore estimated activity versus baseline (novel foils) for a given trial type. Based on Yassa et al. (2010, 2011a), our critical contrasts of interest were encoding: the first presentation of lures subsequently called "similar" compared with lures subsequently called "old," and retrieval: lures called "similar" compared with lures called "old." For these contrasts, the resultant fit coefficients estimated an increase in the difference between correct rejections and false alarms. At the group level, differences in separation-related activity were examined, by conducting a whole-brain GLM analysis comparing APOE ε4+ risk group versus ε4- group during our critical encoding and retrieval contrasts. The FLAME 1 (FMRIB's Local Analysis of Mixed Effects) mixed-effects model was used and group level Z statistic maps were generated for each contrast with the FSL cluster correction at $Z = 1.65$ and a family-wise error threshold of $p = 0.05$.

2.6.3. Extracting region of interest voxels

Based on our a priori hypothesis, the effects of the contrasts were examined in the MTL cortex and hippocampal subfields. Voxels were selected for subsequent analyses based on combining the voxels that showed group differences during encoding and/or retrieval, with anatomical regions of interest (ROIs) that were based on manual delineations of the subfields and regions of interest on the custom template. ROIs in the MTL were segmented based on published protocols (Reagh et al., 2017). Voxel Z statistics from the resulting hybrid functional/structural ROIs were averaged and all subsequent statistical analyses were conducted on these averages.

2.7. Genetic data collection and processing

Saliva samples were collected using Oragene kits during the neuropsychological testing visit before MRI scanning. DNA extraction and genotyping were conducted at the Rutgers University Human Genetics Institute. APOE SNP genotyping (rs429358 and rs7412) was carried out by real-time polymerase chain reaction on an Eppendorf Mastercycler thermal cycler, using TaqMan SNP Genotyping assays (C_3084793_20 and C_904973_10 for rs429358 and rs7412, respectively).

3. Results

3.1. Behavioral results

All participants underwent an extensive battery of standardized neuropsychological, health, fitness, and lifestyle assessments as well as measures of education and verbal fluency. Participants included in our analyses were within the age- and education-adjusted norms (Table 1). No differences were observed on measures of cognitive intactness (Mini Mental State Exam, Digit Span, NAART), physical health/fitness (body mass index, blood pressure, heart rate, gait speed, repeated chair stand, timed up and go, VO_2 max), depression (Beck Depression Inventory), social support, or self-reported lifestyle measures (exercise, time spent in a sedentary state, and sleep

quality). As seen in Table 1, there was a significant difference in short-term (RAVLT—Immediate, $p = 0.04$) and long-term auditory-verbal memory (RAVLT—Delayed, $p = 0.001$). Participants who were in the APOE ε4-group exhibited stronger immediate (M = 12.93, SD = 2.22) and delayed recall (M = 12.73, SD = 2.91) than those in the APOE ε4+ risk group (M 11.27, SD = 2.02; M = 9.33, SD = 2.22).

The mnemonic discrimination task is depicted in Fig. 1 and described in Methods. Briefly, participants were shown a series of photographs of common objects, which were old targets (previously seen images), similar lures (images that were similar but not identical to ones previously seen), and dissimilar foils (never before seen images). For each image, participants were instructed to indicate if it was new (i.e., novel items), old (i.e., repeated items), or similar but not identical (i.e., lure items). Those in the APOE ε4+ risk group were much more likely to generate "false alarms" to items that were similar (i.e., "lures") than the APOE ε4-group (Fig. 2). The ε4+ risk group successfully labeled 23.4% (SD = 15) of the lure trials as "similar," whereas ε4-group did so on 39.1% (SD = 19.5) of the lure trials; $t(28) = 2.49$, $p = 0.019$. The ε4+ risk group demonstrated a significant impairment on the key LDI measure; $t(28) = 2.53$, $p = 0.018$. Furthermore, there was a significant positive correlation between LDI scores and RAVLT immediate ($r(30) = 0.435$, $p = 0.016$) and delayed ($r(30) = 0.532$, $p = 0.002$) recall.

3.2. Functional neuroimaging results

To examine group differences in separation-related activity, we compared ε4+ risk group versus ε4-group activity during our critical contrast (lures called "similar" minus lures called "old") during both the initial presentation and subsequent presentations. As detailed in the Methods section, the first contrast was based on the first presentation of items that were subsequently tested with a lure, whereas the second contrast was based on the actual lure presentation. Given that our hypotheses were specific to MTL regions, we conducted ROI analyses in MTL cortex and hippocampal subfields. As shown in Fig. 3, during both encoding (initial presentation) and retrieval (subsequent presentations), the APOE ε4+ risk group showed increased activity in the left DG/CA3 hippocampal subfield (encoding: $t(28) = 2.453$, $p = 0.021$; retrieval: $t(28) = 2.236$, $p = 0.033$). Increased activation was also observed bilaterally in the CA1 region of the hippocampus (encoding: $t(28) = 3.122$, $p = 0.004$; retrieval: $t(28) = 3.012$, $p = 0.005$). Similar to the methodology of Yassa et al. (2011a), the contrasts used in the aforementioned analyses are not relative to baseline but rather relative to a zero difference between false alarms and correct rejections. An increase in activation therefore represents an increase in the difference between correct rejections and false alarms.

To investigate the potential link between the behavioral ability to pattern separate and observed hyperactivity in the DG/CA3 and CA1 regions, we performed a correlational analysis between each participant's LDI and activity during the encoding (lures subsequently called "similar" minus lures subsequently called "old") and retrieval (lures called "similar" minus lures called "old") contrasts. Correlations were assessed at the level of ε4+ risk group, ε4-group, and collapsed across the entire sample (Fig. 4). During the retrieval contrast, LDI scores across groups were negatively correlated with activity in left DG/CA3 for the ε4-group ($r = -0.683$, $p = 0.005$) and the entire sample ($r = -0.451$, $p = 0.012$). A similar negative

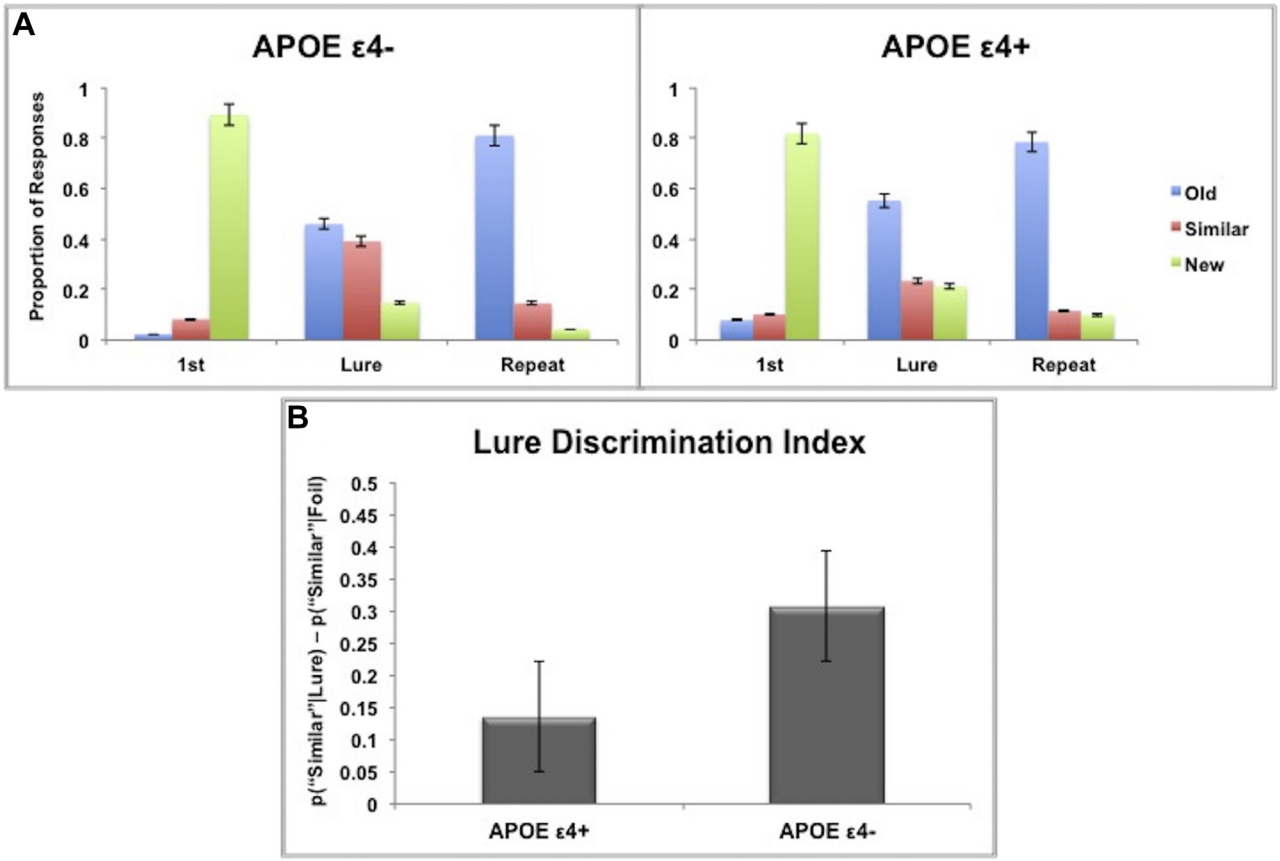

Fig. 2. Performance on the mnemonic discrimination task based on APOE ε4 status. (A) shows response proportions on different trial types in APOE ε4 carriers (ε4+) and non-carriers (ε4−). There was a significant difference between groups on the critical lure items, where APOE ε4+ group were more likely to generate false alarms to the lure items, mischaracterizing them as "old" items instead of "similar". (B) shows the difference between the 2 groups on the Lure Discrimination Index. Those in the APOE ε4+ group had a significantly lower discrimination index score. Abbreviation: APOE, apolipoprotein E.

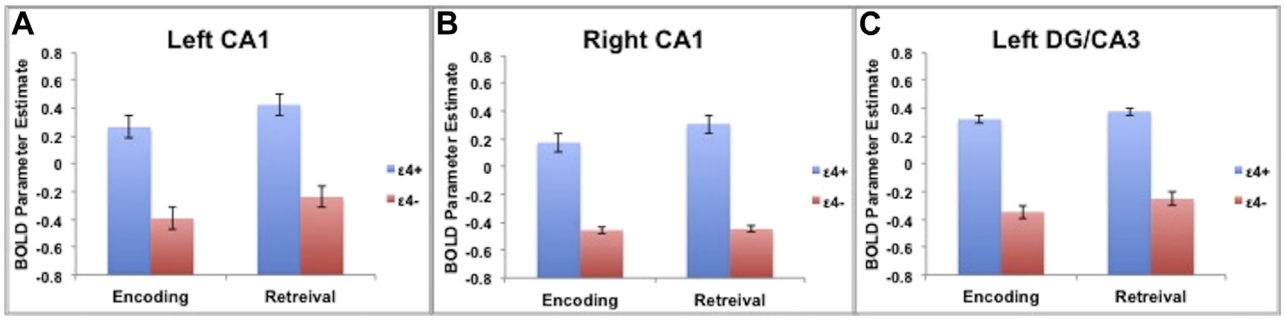

Fig. 3. Activation level during the critical contrast (lures called "similar" minus lures called "old") based on hybrid anatomical/functional ROIs, for both the initial presentation (encoding) and subsequent presentations (retrieval) based on APOE ε4 carrier status. During both encoding and retrieval, the APOE ε4+ risk group showed increased hippocampal activity bilaterally in the CA1 (A, B) and, in the left DG/CA3 (C). Abbreviations: APOE, apolipoprotein E; ROI, region of interest.

correlation was observed in the left CA1 for the ε4-group ($r = -0.545$, $p = 0.036$) and the entire sample ($r = -0.430$, $p = 0.018$). In the right CA1, we found a significant negative correlation between LDI and activation across the entire sample ($r = -0.381$, $p = 0.038$), but neither group featured a significant correlation individually. No significant correlations were found at the individual group level or across the entire sample during encoding.

Furthermore, a hierarchical linear regression revealed that during retrieval, APOE ε4 status significantly modulates the association between LDI and activity in the left DG/CA3 (R^2 change = 0.116, $F(1,26) = 4.74$, $p = 0.038$) and left CA1 (R^2 change = 0.112, $F(1,26) = 4.4$, $p = 0.046$).

3.3. Structural MRI results

Volumetric analyses across MTL regions and hippocampal subfields showed no significant group differences in either volume (Fig. 5A) or surface area (Fig. 5B).

4. Discussion

The present study tested the hypothesis that APOE ε4 genetic risk in nondemented older African Americans is associated with performance on a mnemonic discrimination task and its corresponding neural computations in the MTL. We observed APOE ε4–related impairments in mnemonic discrimination, coincident with specific hyperactivity in the left DG/CA3 and CA1. Moreover, activity in both DG/CA3 and CA1 was negatively correlated with discrimination performance, and this association was moderated by ε4 status. Importantly, there were no structural differences between carriers (ε4+) and noncarriers (ε4−) in volume and surface area of MTL regions and hippocampal subfields. There were also no group differences on standardized neuropsychological tests (with the exception of RAVLT), physical fitness assessments, or health and lifestyle measures.

Lure discrimination was found to be significantly decreased in the APOE ε4+ group compared with the noncarrier group, indicating that there is a behavioral episodic memory deficit associated with APOE ε4 that can be characterized as a shift in bias from pattern separation to pattern completion. Consistent with this, APOE ε4 carriers also showed lower scores on RAVLT immediate and delayed recall, another measure of episodic memory. Discrimination performance on the task was positively correlated with RAVLT scores, further validating pattern separation as a facet of episodic memory. Notably, in our study, no group differences were observed on broad measures of cognitive intactness, suggesting that the presence of an APOE ε4 allele disrupts episodic memory in older adults who are otherwise cognitively healthy. These results add to

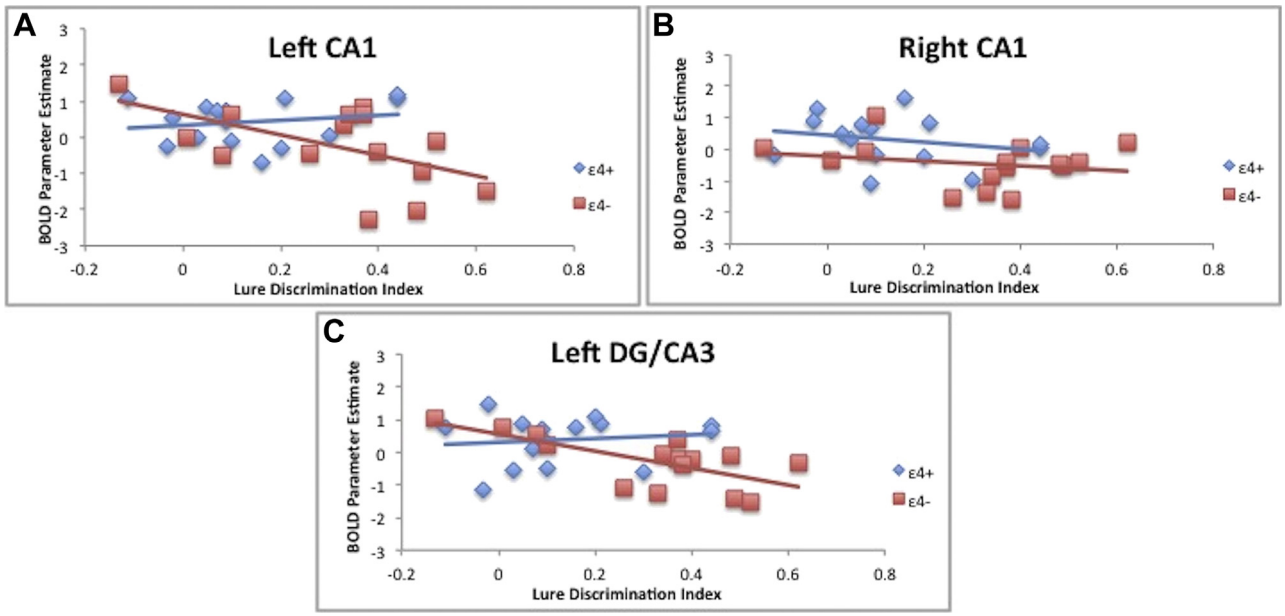

Fig. 4. Correlations between Lure Discrimination Index and activation in the CA1 (A, B) and left CA3/DG during retrieval. Across groups, there was a significant negative correlation between behavioral discrimination and functional activation.

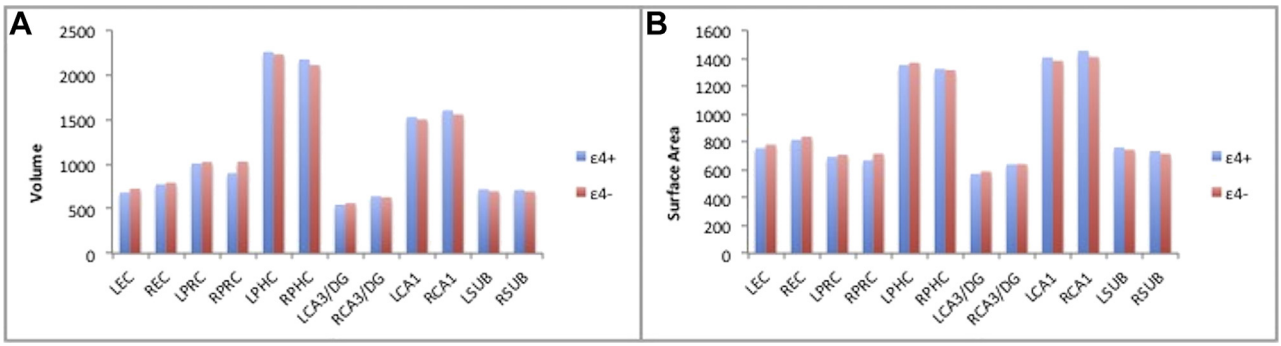

Fig. 5. Volumetric analyses of volume (A) and surface area (B) of MTL regions and hippocampal subfields for the 2 groups, APOE ε4+ versus APOE ε4−. There were no significant group differences in either volume or surface area. Abbreviations: APOE, apolipoprotein E; MTL, medial temporal lobe.

the growing body of evidence on the association between APOE ε4 and episodic memory in the elderly (Caselli et al., 2011; Liang et al., 2017; Mayeux et al., 2001; Nilsson et al., 2006). Moreover, the mnemonic discrimination paradigm is particularly sensitive to the core constructs taxed by MTL pathology, compared with other episodic memory tasks, such as RAVLT, as demonstrated by previous research showing strong correlations between behavioral discrimination with both preclinical hippocampal hyperactivity and perforant path integrity (Yassa et al., 2010, 2011b).

A similar discrimination deficit has been demonstrated in a previous study that examined the effects of APOE ε4 on spatial pattern separation (Sheppard et al., 2016). However, recent studies specifically investigating object pattern separation, as examined in the present study, found no differences based on ε4 status in aMCI patients (Tran et al., 2017), and in AD patients, an impairment in difficult (but not easy) discrimination was found exclusively in ε4 homozygotes (Wesnes et al., 2014). We build significantly on these lines of research by providing evidence of object pattern separation deficits in cognitively healthy ε4 carriers, irrespective of whether they had 1 or 2 copies of the ε4 allele.

Commensurate with behavioral impairments, during task-activated fMRI, APOE ε4 carriers showed significantly increased activation in the hippocampus, localized to the left DG/CA3 and CA1 subregions. This hyperactivity was inversely associated with participants' discrimination performance on the task, suggesting that the increased activation is maladaptive and is a marker for neuronal dysfunction. Pathological hippocampal hyperactivity, specific to the DG/CA3 subfield, is now well established in nondemented older adults (Reagh et al., 2017; Yassa et al., 2011a,b) as well as MCI patients (Bakker et al., 2012, 2015; Tran et al., 2017; Yassa et al., 2010). However, we also found a moderating effect of APOE ε4 status on the negative correlation between performance on the mnemonic discrimination task and activation in the left DG/CA3 and left CA1 subfields, such that this association was significantly stronger in the noncarrier group. Further work is required to understand the significance of this result, but it could potentially indicate that the ε4-related pathology results in abnormal hippocampal recruitment that may not be linked with cognitive effort. As a result, APOE ε4 carriers show dysfunctional hippocampal hyperactivity that is not strongly inversely proportionate to discrimination performance, as observed in noncarriers. This interpretation requires further exploration, focusing particularly on whether the moderation effect may be driven by individuals who are homozygous for the ε4 allele.

Increased hippocampal activation in cognitively normal APOE ε4 carriers has been reported in a number of studies, but the imaging methods used in those previous studies had insufficient resolution to localize that activation to a specific hippocampal subregion (Bookheimer et al., 2000; Burggren et al., 2002). Our results are therefore well in line with these findings, and with high-resolution imaging, extending them to suggest a specific role for the DG/CA3 and CA1 subfields. This is also consistent with animal models of APOE ε4 (Andrews-Zwilling et al., 2010; Palop and Mucke, 2009), predicting that hippocampal hyperactivation, localized particularly to the DG/CA3 region would be observed in ε4 carriers. Furthermore, volume and surface area measures of the MTL regions and hippocampal subfields did not differ between APOE ε4 carrier and noncarrier groups, confirming that the observed functional decline in DG/CA3 and CA1 were not due to measurable structural differences. Hence, our findings provide compelling evidence for an APOE ε4–related deficit in mnemonic discrimination, which likely results from DG/CA3 and CA1 hyperactivation. This suggests that nondemented older persons with a genetic risk for AD have alterations in MTL function without obvious morphologic or behavioral indications of impending disease. Whether these results are specific to African Americans, who are at elevated risk for AD and have a higher frequency of the APOE ε4 allele, remains a significant question.

The present results stand in contrast to those of Tran et al. (Tran et al., 2017), who found that the presence of the APOE ε4 allele did not contribute to increased DG/CA3 activation during pattern separation. The discrepancy between our results and theirs likely arises from differences in the population studied; although our study examines cognitively healthy individuals, Tran et al. (Tran et al., 2017) compared APOE ε4 carriers versus noncarriers in patients with aMCI. As such, this difference has important implications, inviting the hypothesis that the presence of the APOE ε4 allele may initiate an earlier onset of AD or it may be associated with more widespread dysfunction during the preclinical stage of AD, but has little effect on the disease's course once individuals progress to a clinical diagnosis of aMCI or AD. Thus, deficits in pattern separation (impaired mnemonic discrimination coupled with hyperactivation in DG/CA3 and CA1) may be an early marker for AD-related neuronal dysfunction, and in conjunction with genetic risk, may enhance our ability to detect individuals likely to develop AD before actual disease onset.

The results of this study also advance our understanding of racial differences when examining genetic risk factors for cognitive decline to AD. Previous research has found that lower levels of education and socioeconomic status, limited physical activity, and a sedentary lifestyle are more common among African Americans and influence cognitive decline (Yaffe et al., 2013; Alzheimer's Association, 2018). These factors not only place older African Americans at a heightened risk for AD, but could potentially influence the predictive effect of APOE ε4 allele on cognition. The present study used a cross-sectional design that was restricted to African Americans living in and around Newark, New Jersey, thereby decreasing the between-group variability on the various environmental and health variables that may influence racial

differences in the effect of APOE ε4 on cognitive decline. Our participants were demographically matched for age and education levels, and they come from urban areas and community dwellings that are fairly homogeneous for socioeconomic status. Furthermore, we did not find any differences on physical fitness, health, or lifestyle assessments between ε4 carriers and noncarriers, confirming that the observed impairment in pattern separation in older African Americans is not due to any of these factors, but, rather, attributable to genetic variations. We therefore expect these results to apply to other groups, such as Caucasians, but further investigation is required to elucidate the inter-racial generalizability of the relationship between APOE status and pattern separation.

There are several study limitations and specific future directions that should be acknowledged. First, the relatively small samples may not provide enough power to detect subtle effects of APOE genotype, particularly differences between carriers of 1 (heterozygotes) versus 2 (homozygotes) ε4 alleles. In addition, there was a gender imbalance in our study with just 1 male participant. Although the association between AD and the APOE gene has been confirmed worldwide, it appears to differ by ancestral background, such that the overall effect of APOE on AD is lower in African Americans as compared with Caucasians (Tang et al., 2001). In comparison, the ABCA7 genetic variation is the strongest AD genetic risk factor for African Americans (outside of the APOE ε4 allele) with an odds ratio of 1.8 in African Americans (Reitz et al., 2013). Furthermore, APOE ε4 confers greater AD risk in women (Altmann et al., 2014), which may be driving the current results. Hence, future studies with a larger sample size are required to explore interactions between race and gender differences in the effects of APOE ε4 on pattern separation, as well as the effects of ABCA7 variations.

5. Conclusions

The results of the study show that APOE ε4 contributes to maladaptive hyperactivation in DG/CA3 and CA1 hippocampal subregions during pattern separation in cognitively healthy subjects without any structural degradation or behavioral symptoms associated with the clinical diagnosis of aMCI or AD. This work has important implications for future assessments to understand how genetic risk may facilitate early biomarkers in uncovering neuronal dysfunction in the nonsymptomatic, preclinical phase of the disease. Such research is necessary to develop more specific interventions targeting both older, nondemented individuals and younger individuals who are decades from the earliest symptoms of the disease. Further research is also necessary to be sure that findings that link genetics, neuroimaging, and AD risk are studied in different racial groups whose genetic risk factors for AD may differ.

Disclosure statement

The authors confirm that there are no known conflicts of interest associated with the publication of this article.

Acknowledgements

This work was supported by a grant to Mark A. Gluck from the NIH/National Institute on Aging (R56-AG053961) and by support from the Chancellor and Provost's offices at Rutgers University-Newark. Additional support came from grants to Michael A. Yassa from NIH/National Institute on Aging grants P50AG05146, R21AG049220 and R01AG053555. The authors thank Stephen Hanson for his guidance in developing the Multiband fMRI acquisition protocol, and, the staff of the Rutgers University Brain Imaging Center (RUBIC), for their support in the brain imaging data collection.

Our ongoing research studies with older African Americans in the Greater Newark, New Jersey, area would not be possible without the guidance, input, and support of these members of the African American Brain Health Initiative's Community Advisory Board: Tania Cajuste (East Orange Office of Senior Services), Margaret Cammarieri (American Heart Association | American Stroke Association), Honorable Mildred Crump (City of Newark City Council), Mary Dawkins (Hillside Senior Citizen Center), Mildred English (St. James AME Church), Jaklyn De Vore (Essex County Office of Senior Services), Deacon Francis Dixon (The New Hope Baptist Church), Deborah Flamengo (OUCP/AABHI Community Outreach Coordinator), Robin Lateef-Pharms (Bethany Senior Center), Louise Layton (Rutgers Aging Advisory Council), Yolanda Mack (Jehovah-Jireh Praise and Worship Center), Reverend Dr Jacqueline Reeves (St. James AME Church), Joan Reeves (East Orange Office of Senior Services), Donna Sparks (Bethany Baptist Church), Sheltry Ward (New Jersey Black Nurses Association), Pastor Glenn Wilson (Pilgrim Baptist Church), Geri Woods-Coles (Bethany Baptist Church), and Glenda Wright (New Jersey Association of Public and Subsidized Housing).

Data availability: The data used to support these findings are available from the first author on request.

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