

RESEARCH ARTICLE

A profile of brain reserve in adults at genetic risk of Alzheimer's disease

 Gillian Coughlan¹ | Peter Zhukovsky² | Aristotle Voineskos² | Cheryl Grady^{1,3}
¹ Rotman Research Institute, Baycrest, Toronto, Canada

² Kimel Family Translational Imaging Genetics Laboratory, Centre for Addiction and Mental Health, Toronto, Canada

³ Departments of Psychiatry and Psychology, University of Toronto, Toronto, Canada

Correspondence

 Dr Gillian Coughlan, Rotman Research Institute, Baycrest, Toronto, Canada.
 Email: gcoughlan@research.baycrest.org

Gillian Coughlan and Peter Zhukovsky contributed equally to this study.

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Abstract

Introduction: The apolipoprotein E (APOE) $\epsilon 4$ allele is the greatest genetic risk factor for Alzheimer's disease (AD). Our aim was to identify the structural brain measures that mitigate the negative effect of APOE $\epsilon 4$ on cognition, which would have implications for AD diagnosis and treatment trial selection.

Methods: A total of 742 older adults (mean age: 70.1 ± 8.7 years) were stratified by APOE status and classified as cognitively normal (CDR 0) or with very mild dementia (CDR 0.5). Regional brain volume and cognitive performance were measured.

Results: There were significant interactions between APOE and CDR on the left precuneus and on bilateral superior frontal volumes. These regions were preserved in CDR-0 $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ carriers but were reduced in CDR-0.5 $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ carriers, compared to their respective $\epsilon 3/\epsilon 3$ counterparts. Educational attainment predicted greater brain reserve.

Discussion: This pattern of preserved brain structure in cognitively normal $\epsilon 4$ carriers with comprised medial temporal volume is consistent with the theory of brain reserve.

KEYWORDS

Alzheimer's disease, APOE, episodic memory, genetic risk, genotype, neuroimaging genetics

1 | BACKGROUND

The worldwide prevalence of Alzheimer's disease (AD) is increasing as younger age mortality declines.¹ AD neuropathology is characterized by accumulation of amyloid beta ($A\beta$) plaques and intraneuronal tangles of hyperphosphorylated tau. Progressive cognitive impairment and regional gray matter atrophy are triggered by amyloid and tau deposition.²⁻⁴ The apolipoprotein E (APOE) $\epsilon 4$ allele represents the greatest genetic risk factor for AD onset in late life,⁵⁻⁷ significantly accelerates the initial and progressive accumulation of amy-

loid plaques,⁸⁻¹⁰ and is associated with earlier AD symptom onset.¹¹ Depending on $\epsilon 4$ load, a single $\epsilon 4$ allele results in AD onset at 78 years of age and homozygote $\epsilon 4$ carriers typically experience symptom onset at 68 years of age.^{5,11,12} Despite lifelong influences of APOE $\epsilon 4$, not all $\epsilon 4$ carriers develop cognitive decline.¹³⁻¹⁵ This makes cognitively normal older homozygous and heterozygous $\epsilon 4$ carriers a compelling population in which to study neural resources that may mitigate the effects of genetic vulnerability to AD.

In the AD prodrome, referred to as mild cognitive impairment (MCI), APOE $\epsilon 4$ in its homozygote and heterozygote form accelerates cognitive decline,¹⁶⁻¹⁸ as well as cortical and sub-cortical brain atrophy, particularly in the hippocampus, amygdala, precuneus, and entorhinal cortex.^{16,19-26} In cognitively normal individuals, subtle but stable effects of both APOE $\epsilon 4$ variants on accelerated forgetting and memory-guided attention are evident,²⁷⁻³⁰ although evidence for

Abbreviations: AD, Alzheimer's disease; AMG, amygdala; APOE, apolipoprotein E; BNT, Boston Naming Test; CDR, Clinical Dementia Rating; ENT, entorhinal; GLM, general linear models; HPC, hippocampus; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; OASIS, Open Access Series of Imaging Studies; PREC (L), precuneus left; PREC (R), precuneus right; SFL, superior frontal lobe; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS, Wechsler Memory Scale; MTL, medial temporal lobe

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changes in brain structure is mixed. In fact, most studies report no effects of the APOE $\epsilon 4$ allele on gray matter volume in cognitively normal adults.^{19,31–33} Among the few studies that include an independent homozygote $\epsilon 4$ carrier group, however, volumetric reductions in AD vulnerable brain regions are reported, even in the absence of cognitive impairment.^{32,34} Of interest, larger superior frontal gray matter volumes in cognitively normal $\epsilon 4$ carriers with gray matter atrophy have also been reported.^{33,34}

Brain reserve has been defined as a cumulative improvement of neural resources that mitigates the effects of genetic or environmental factors leading to age- or disease-related decline.³⁷ The role of brain reserve in cognitively normal genetically at-risk APOE $\epsilon 4$ older adults has not been widely understood, however.^{37–40} To investigate this, we first undertook a detailed literature review to identify APOE $\epsilon 4$ and AD vulnerable brain regions including the hippocampus, amygdala, precuneus, superior frontal, and entorhinal cortex.^{16,19,43,20–25,41,42} We used the Open Access Series of Imaging Studies (OASIS) sample of APOE genotyped cognitively normal adults and adults with very mild dementia defined by the established Clinical Dementia Rating (CDR) scale (423 $\epsilon 3/\epsilon 3$ carriers, 271 $\epsilon 3/\epsilon 4$ carriers, and 48 APOE $\epsilon 4/\epsilon 4$ carriers). These adults were approaching or at the expected age of AD onset ($\epsilon 3/\epsilon 4$: 76 years; $\epsilon 4/\epsilon 4$: 68 years¹¹). Crucially, we capitalized on a group of cognitively normal (CDR-0) ultra-high-risk $\epsilon 4/\epsilon 4$ individuals at the expected age of disease onset that only one another study has examined in a similar context, given the low population prevalence (2%) of the $\epsilon 4/\epsilon 4$ allele.⁴⁵ Unlike previous studies, we also examined both memory and non-memory performance, including accelerated forgetting after delayed recall of episodic story units, as well as psychomotor fluency and word naming.^{21,23,24,31,32,35}

In order to then investigate brain reserve, we examined interactions between CDR and APOE status to identify regions that are negatively affected by APOE $\epsilon 4$ in those with very mild dementia (CDR-0.5) but were not affected by APOE $\epsilon 4$ in CDR-0 participants. We expected to find increased or preserved brain volumes (indicative of brain reserve) in CDR-0 $\epsilon 4$ carriers on cortical regions outside of the medial temporal lobe (MTL), given that the MTL is particularly vulnerable to the presence of APOE $\epsilon 4$.⁴⁴ Finally, we examined the cognitive profile with well-defined cognitive phenotypes. Similar to the interactive effects of APOE and CDR on brain volumes, we hypothesized that CDR-0 $\epsilon 4$ carriers would show better (or equal) memory performance than their non-risk $\epsilon 3/\epsilon 3$ counterparts. On the other hand, we expected APOE $\epsilon 4$ to negatively impact memory recall in the CDR-0.5 group, given that memory recall is a predictor of cognitive decline due to AD. Because education promotes reserve,^{37,45} we also expected educational attainment to be positively associated with the signatures of reserve identified here.

2 | METHODS

2.1 | Data

Data used in the preparation of this article were obtained from the Open Access Series of Imaging Studies (or OASIS) database

RESEARCH IN CONTEXT

- 1. Systematic review:** We undertook a literature review (PubMed) investigating the genetic risk conferred by apolipoprotein E (APOE) $\epsilon 4$ gene in Alzheimer's disease (AD). APOE $\epsilon 4$ carriers showed an increased risk of cognitive decline and amyloid accumulation, yet many carriers do not develop AD. Although protective lifestyle factors have been identified, the neuroimaging markers of brain reserve to APOE $\epsilon 4$ are yet unclear.
- 2. Interpretation:** In a large cohort of over 700 APOE genotyped older adults, our findings show that select cortical brain volumes may mitigate risk factors associated with the APOE $\epsilon 4$ allele. Specifically, the integrity of the precuneus cortex and superior frontal gyrus appear to form a profile of brain reserve that may explain individual differences in susceptibility to AD pathology.
- 3. Future directions:** Although these findings help the selection of individuals at a higher or indeed lower risk of cognitive decline, future studies are needed to determine whether the pattern of reserve protects against symptom onset in amyloid positive adults with, or without, tau burden.

(<https://www.oasis-brains.org/> accessed: 4 April 2020) collected by the Washington University Knight Alzheimer Disease Research Center over the course of 15 years. OASIS-3 provides volumetric measures from the FreeSurfer pipeline,⁴⁶ APOE status, and neuropsychologic test scores along with clinical dementia ratings. All necessary patient/participant consent was obtained and the appropriate institutional forms have been archived.

2.2 | Participants

We used the cross-sectional OASIS data set consisting of 914 participants over the age of 50 years with brain imaging data. Participants were excluded if they were carrying one or more of the APOE $\epsilon 2$ alleles ($N = 141$), since this group cannot be considered a control group due to interactive effects on neuroprotection.^{47,48} Participants were also excluded if they had an active psychiatric or neurological disorder diagnosis including epilepsy ($N = 1$), alcoholism ($N = 1$), or head trauma ($N = 1$), and/or had a current diagnosis of cardiovascular disease ($N = 2$), Parkinson's disease ($n = 4$), or frontotemporal dementia ($N = 1$) and other active neurological disorders ($n = 21$). History of a single stroke or transient ischemic attack was not an exclusion criterion unless it was related to symptomatic onset of cognitive impairment. Following exclusions, 742 participants were stratified by APOE, resulting in 423 $\epsilon 3/\epsilon 3$ carriers (mean age 70.4, SD 8.7), 271 $\epsilon 3/\epsilon 4$ carriers (mean age 70.8, SD 8.4), and 48 $\epsilon 4/\epsilon 4$ carriers (mean age 67.9, SD 7.9). Of the entire sample, 74% were cognitively normal and 26% showed CDR scores indicative of very mild dementia.⁴⁹ Individuals with a CDR

TABLE 1 Participant demographics, neuropsychology, and neuropsychiatry

	CDR-0			CDR-0.5		
	$\epsilon 3/\epsilon 3$	$\epsilon 3/\epsilon 4$	$\epsilon 4/\epsilon 4$	$\epsilon 3/\epsilon 3$	$\epsilon 3/\epsilon 4$	$\epsilon 4/\epsilon 4$
N	345	178	29	78	93	19
Age	69.1 (8.7)	68.5 (8.2)	67.7 (8.8)	75.9 (6.4)	75.1 (6.8)	68.4 (6.5)
Sex (F)	217	95	19	30	49	12
Race (AA/A/C)	45/1/277	26/1/140	8/0/18	8/0/65	10/0/78	4/0/14
Ethnicity (H/NH)	2/321	1/166	0/26	2/71	0/88	0/18
MMSE	29.1 (1.1)	29.0 (1.4)	28.8 (1.6)	27.3 (2.6)	26.6 (2.7)	26.7 (3.6)
Years of education	16.0 (2.6)	15.9 (2.8)	16.0 (2.6)	15.1 (3.1)	14.5 (3.0)	15.5 (2.7)

Data shown include means and standard deviation in parentheses. Statistical effects of APOE and CDR were assessed using Chi-square tests for categorical variables (sex), and F-tests for continuous variables; * $P < 0.05$ ** $P < 0.01$. CDR, Clinical Dementia Rating; CDR 0, cognitively normal; CDR 0.5, cognitively impaired; MMSE, Mini Mental State Examination; AA, African American; A, Asian; C, Caucasian; H, Hispanic NH, non-Hispanic; 47 people did not have race and ethnicity data recorded.

of 0 were classified as cognitively normal. Individuals with a CDR of 0.5 were clinically classified as having cognitive impairment (or incipient AD). APOE groups were matched as close as possible for age and sex (Table 1), although the $\epsilon 4/\epsilon 4$ carriers were younger than $\epsilon 3/\epsilon 3$ carriers and $\epsilon 3/\epsilon 4$ carriers. For this reason, age was included as covariate in all subsequent analyses.

2.3 | APOE genotyping

Single nucleotide polymorphism (SNP) genotyping data were available for all participants. Genomic DNA was extracted from blood samples using QIAmp DNA blood mini kits from Qiagen Inc. (Valencia, CA). Genomic DNA was refrigerated at 2-4°C and then extracted using a DNA extraction kit (Qiagen, Hildenberg, Germany), following the manufacturer's instructions. APOE genotyping was performed using polymerase chain reaction (PCR) amplification of a 244-bp fragment followed by restriction enzyme HhaI digest.^{46,50}

2.4 | Neuropsychology assessment

Cognitive status and neuropsychological assessment included the following: The Clinical Dementia Rating (or CDR) scale, a Dementia Staging Instrument, was used to characterize cognitively normal (CDR-0) or very mild dementia (CDR-0.5) participants. The Mini Mental State Examination (MMSE)⁵¹ indicated participants' global cognitive function in the domains of memory, orientation, attention, language, and construction.

2.5 | Cognitive testing: Episodic memory, information processing speed, and naming ability

Immediate and delayed episodic memory recall was assessed using Logical Memory II subtest of the Wechsler Memory Scale (WMS; story units recall version).^{52,53} Psychomotor speed was assessed with

the Wechsler Adult Intelligence Scale revised (WAIS-R) digit symbol (digit-symbol pairs completed in 90 seconds)^{52,54} and aphasic word retrieval was measured on the Boston Naming Test (BNT; 30-item version).⁵⁵

2.6 | Identifying the APOE $\epsilon 4$ structural signature of reserve

We undertook a literature review in PubMed, using the search terms (APOE) or (apolipoprotein) or (Alzheimer's disease) and (brain structure) or (cortical volume) to identify the regions previously found to undergo structural atrophy due to APOE $\epsilon 4$ and or AD. In our analysis, we included regions that were most commonly affected by AD and/or APOE $\epsilon 4$ in cognitively normal and cognitively impaired individuals: the hippocampus, amygdala, precuneus, superior frontal, and entorhinal cortex.^{16,19,43,20-25,41,42} Superior frontal gyrus was included given that increases in superior frontal volumes have been reported in cognitively intact $\epsilon 4$ carriers compared to their $\epsilon 3/\epsilon 3$ counterparts.^{35,36} Regional brain volumes were downloaded obtained from structural T1-weighted images by applying cortical surface reconstruction and volumetric segmentation in FreeSurfer version 5.3.0 (<http://freesurfer.net/>). The FreeSurfer automated processing stream includes motion correction, removal of non-brain tissue, automated Talairach transformation, intensity correction, volumetric segmentation, cortical surface reconstruction, and parcellation.^{56,57} We considered right and left brain regions because although brain atrophy tends to be asymmetric in AD patients,⁵⁸ it is not clear if atrophy is asymmetric in the earlier stages of dementia (when CDR scores typically range from 0.5 to 1⁵⁹) or whether APOE $\epsilon 4$ predicts atrophy bilaterally.⁶⁰

2.7 | Statistical analysis

Separate general linear models (GLMs) were used to analyze the effects of APOE and CDR on regional brain volumes, while control-

ling for total intracranial volume, sex, and age. Furthermore, separate GLMs tested the effects of APOE and CDR on WMS Logical Memory (episodic memory recall), WAIS-R digit symbol test psychomotor speed), and the BNT (naming ability), while controlling for age and sex. APOE x CDR interactions were also examined. Within each GLM, multiple comparison correction was performed using Sidak post hoc tests of main effects. Whenever a significant interaction was present in one of the above GLMs, two follow-up linear models were run to assess the effects of APOE genotype on the CDR-0 and CDR-0.5 groups separately. Finally, we used partial correlations between regional volumes with the above cognitive performance outcomes and years of education. Bonferroni corrections were used to correct for multiple comparisons and 95% confidence intervals (CIs) were used to compare Pearson's correlation coefficients. All corrections were adjusted for age, sex, and total intracranial volume.

2.8 | Data availability

Data used in the preparation of this article were obtained from the OASIS-3 database (<https://www.oasis-brains.org/>) and are freely available after registration.

3 | RESULTS

3.1 | Neuropsychological assessment

Participants' demographic and neuropsychological assessment scores are presented in Table 1. APOE genotype groups did not differ by age, sex, race, ethnicity, or years of education. Across the entire sample, a significant effect of APOE on MMSE was found while controlling for CDR, age, and sex ($F(2,725) = 5.4, P = 0.005$; lower scores were seen in $\epsilon 3/\epsilon 4$ vs $\epsilon 3/\epsilon 3, P = 0.015$, and in $\epsilon 4/\epsilon 4$ vs $\epsilon 3/\epsilon 3, P = 0.045$). As expected, neuropsychological scores were affected by CDR after controlling for APOE status, age, and sex, with reduced scores on the MMSE ($F(1,725) = 89.4, P < 0.001$) in cognitively impaired participants (Table 1). The CDR-0 group completed more years of education compared to the CDR-0.5 group ($F = 7.2, P = 0.007$), consistent with previous studies showing that educational attainment enhances cognitive reserve^{61,62} and low attainment predicts cognitive decline.⁶³

3.2 | Effects of APOE genotype and CDR on relative brain volumes

We first examined the hippocampus and the amygdala (Figure 1, Tables S1 and S2), as well as the entorhinal cortex, the precuneus, and the superior frontal gyrus (Figure 2), as a function of APOE genotype and CDR. Significant main effects of APOE and CDR were found with respect to the hippocampus, amygdala, and entorhinal volumes. Post hoc tests (Sidak multiple comparison corrected) revealed lower vol-

umes of the hippocampus, amygdala, entorhinal, and the precuneus in the CDR-0.5 group ($P < 0.001$), compared with the CDR-0 group. In terms of the main effect of APOE, compared to $\epsilon 3/\epsilon 3$ carriers, $\epsilon 4/\epsilon 4$ carriers showed lower volumes of the hippocampus ($P = 0.01$), amygdala ($P = 0.005$), and left entorhinal cortex ($P = 0.024$), across the entire sample. APOE $\epsilon 4/\epsilon 4$ carriers also showed lower amygdala volumes relative to $\epsilon 3/\epsilon 4$ carriers ($P = 0.018$), irrespective of CDR. No significant differences between the $\epsilon 3/\epsilon 4$ and $\epsilon 3/\epsilon 3$ carriers were found ($P > 0.05$) on amygdala volumes. No interactions between APOE and CDR were present for the hippocampus, the amygdala, or the entorhinal cortex.

Crucially, we found an interaction between APOE and CDR interaction on left precuneus volume (Table 2) and bilateral superior frontal cortex volume. In the CDR-0.5 group, precuneus volume was significantly reduced in $\epsilon 4/\epsilon 4$ carriers ($P = 0.046$) and a trend reduction was observed in $\epsilon 3/\epsilon 4$ carriers ($P = 0.06$) compared to the $\epsilon 3/\epsilon 3$ carriers. However, no differences in left precuneus volume were found between $\epsilon 4/\epsilon 4$ or $\epsilon 3/\epsilon 4$ carriers and $\epsilon 3/\epsilon 3$ carriers in CDR-0 individuals ($P > 0.9$). No significant effects on the right precuneus volumes were found (Table 2). Furthermore, there was a significant APOE x CDR interaction on superior frontal volumes. The superior frontal cortex was larger in CDR-0 $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ carriers, compared to their $\epsilon 3/\epsilon 3$ counterparts, whereas smaller volumes were observed in CDR-0.5 $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ carriers, compared to their $\epsilon 3/\epsilon 3$ counterparts. The effect on the superior frontal cortex must be interpreted with some caution, as post hoc tests with Sidak correction did not reach statistical significance ($P > 0.05$). (Effect sizes for all main effects can be found in Table S1; mean values for brain volume are presented in Table S2.)

3.3 | Effects of APOE genotype and CDR on cognition

We then examined APOE x CDR interactions on cognition commonly impaired in early AD, namely episodic memory, psychomotor speed, and naming performance. There was an APOE x CDR interaction on delayed episodic memory recall and a trend toward significance on immediate episodic memory recall. Specifically, delayed recall of logical story units in the WMS-R was worse in CDR-0.5 $\epsilon 4/\epsilon 4$ carriers ($P = 0.011$) and $\epsilon 3/\epsilon 4$ carriers ($P = 0.006$), compared to $\epsilon 3/\epsilon 3$ carriers. By contrast, CDR-0 $\epsilon 4/\epsilon 4$ carriers did not differ significantly from their healthy $\epsilon 3/\epsilon 3$ counterparts ($P = 0.994$), and $\epsilon 3/\epsilon 4$ carriers showed only small decrements in delayed memory ($P = 0.026$), relative to their healthy $\epsilon 3/\epsilon 3$ counterparts (Figure 3A). This pattern largely mirrors the interactive effects of APOE and CDR on precuneus volumes, which were found to be greatly reduced in $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ carriers in the CDR-0.5 group but were preserved in the CDR-0 participants with the same genetic risk. We also found an effect of CDR and APOE on immediate episodic memory recall across the entire sample, with significantly worse performance in CDR-0.5 group compared to the CDR-0 group, as well as in $\epsilon 3/\epsilon 4$ carriers ($P = 0.001$), and a trend for worse performance in $\epsilon 4/\epsilon 4$ carriers ($P = 0.094$) compared to $\epsilon 3/\epsilon 3$ carriers. There were large effects of CDR, but not APOE, on all other cognitive tasks (Table 2).

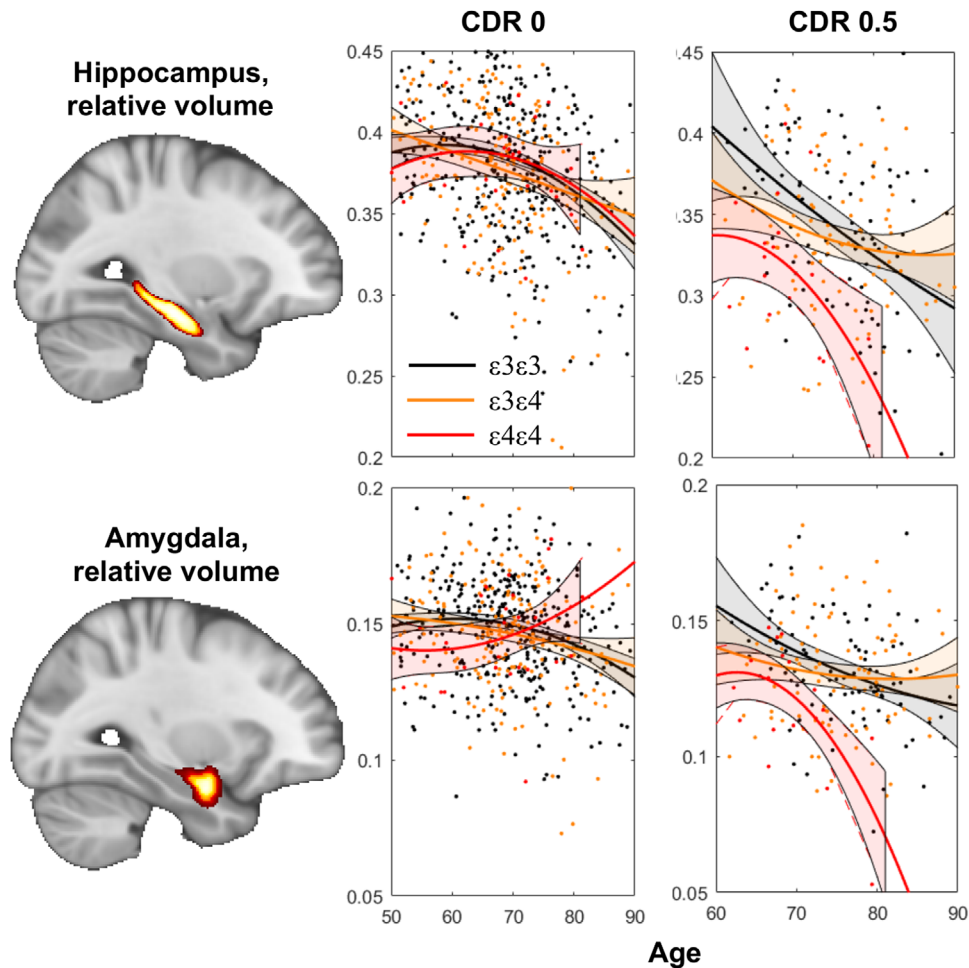


FIGURE 1 Cross-sectional trajectories of relative volumes of the hippocampus and amygdala in cognitively normal (CDR-0) and cognitively impaired (CDR-0.5) participants with the three most common apolipoprotein E gene (*APOE*) variants. Regions of interest were taken from the Harvard-Oxford Atlas and are shown at Montreal Neurological Institute (MNI) X = -29. Non-linear (quadratic) trajectories with 90% confidence intervals are shown for greater precision in visualization. Statistical analyses involved general linear models testing for the effects of *APOE* status, Clinical Dementia Rating (CDR) scale, age, sex, and total intracranial volume. Relative volumes were calculated by dividing regional volumes by total intracranial volume

In terms of brain-behavioral relationships, based on non-overlap of 95% CIs, all cognitive measures were associated with hippocampal volume more strongly than any other region and survived multiple comparison correction, with the exception of naming performance, which was equally strongly associated with hippocampal and entorhinal cortex volume (Figure 3B-C). The left precuneus cortex was positively correlated with delayed recall of logical story units and psychomotor speed, but did not survive multiple comparison correction (see Table S3 for Pearson correlation values).

3.4 | Educational attainment and reserve

Finally, we examined the predictive role of education on reserve (see Figure S1). Higher education was associated with increased left precuneus volumes in $\epsilon 4/\epsilon 4$ carriers but not in $\epsilon 3/\epsilon 4$ or $\epsilon 3/\epsilon 3$ carriers. Higher education was associated with lower superior frontal volumes

in $\epsilon 3/\epsilon 3$ carriers only and with higher delayed recall scores in all *APOE* groups. These results suggest that more years of education has a protective effect on memory performance and on precuneus volumes, especially in the $\epsilon 4/\epsilon 4$ carriers. Further details on the role of education, as well as associations between years to expected age of onset of AD and brain volumes, can be found in the Supplementary materials.

4 | DISCUSSION

We aimed to characterize brain reserve in cognitively healthy older adults who carry at least one copy of the *APOE* $\epsilon 4$ allele. We capitalised on a large cohort of 742 cognitively normal (CDR-0) and adults with very mild dementia (CDR-0.5), including 48 homozygote *APOE* $\epsilon 4/\epsilon 4$ genotype carriers, who are approaching or passed the expected age of AD onset. We found i) preserved or greater cortical volumes in cogni-

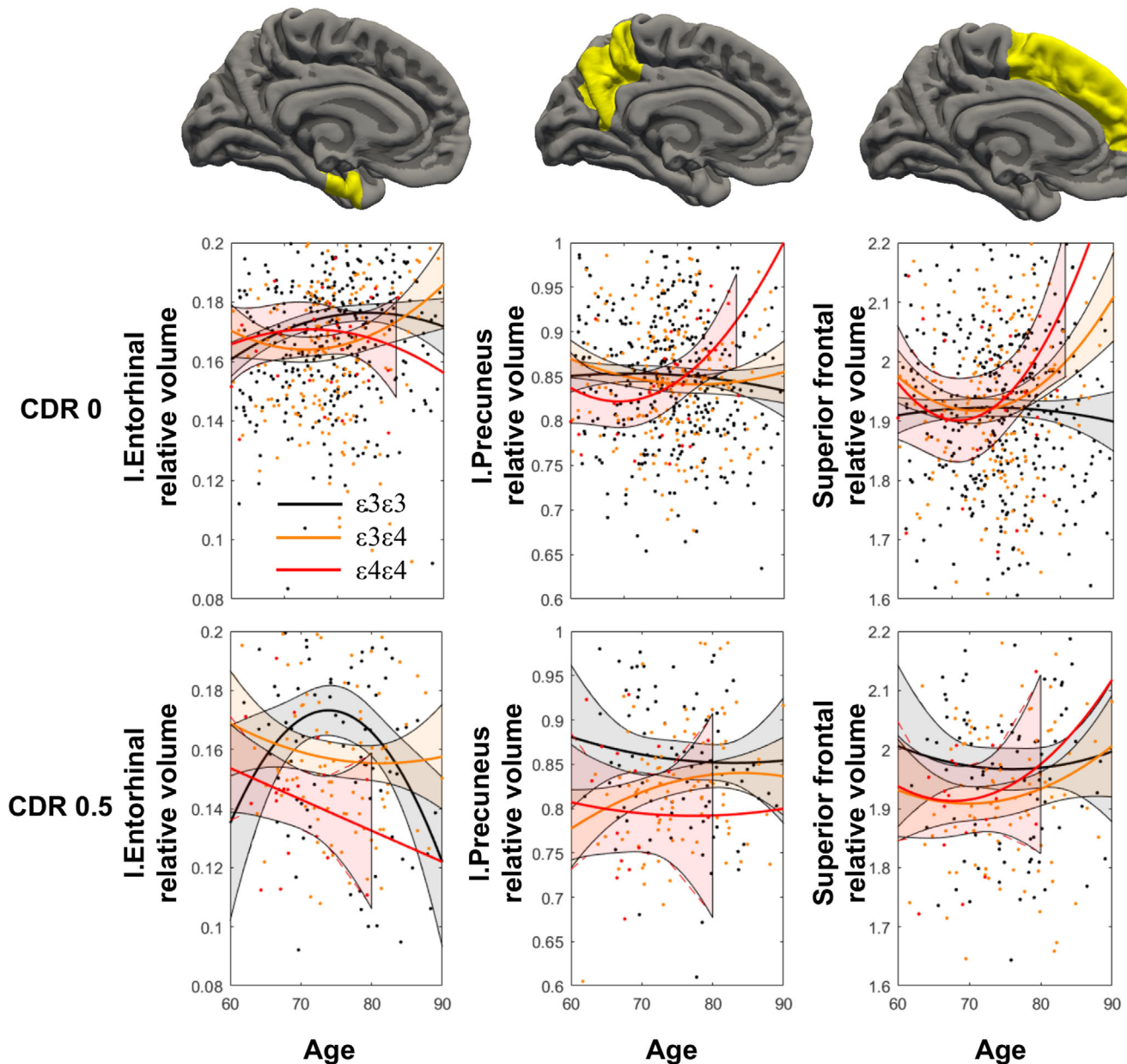


FIGURE 2 Cross-sectional trajectories of relative volumes of the left entorhinal (I.Entorhinal) and left precuneus (I.Precuneus) and bilateral superior frontal gyrus in cognitively normal (CDR-0) and cognitively impaired (CDR-0.5) participants with the three most common apolipoprotein E (APOE) variants. Regions of interest were taken from the Desikan-Killiany Atlas⁵⁶ and are overlaid on the pial surface of the *fsaverage* brain. Non-linear (quadratic) trajectories with 90% confidence intervals are shown for greater precision in visualization. Statistical analyses involved general linear models testing for the effects of APOE, CDR, age, sex, and total intracranial volume. Relative volumes were calculated by dividing regional volumes by total intracranial volume. Vertical red and orange lines represent the expected mean age at AD onset for $\epsilon 4/\epsilon 4$ and $\epsilon 3/\epsilon 4$ carriers, respectively. CDR, Clinical Dementia Rating scale

tive normal APOE $\epsilon 4$ carriers ii) cortical effects persisted in the context of similar levels of atrophy in MTL regions across cognitive normal and impaired $\epsilon 4$ adults iii) cortical volume weakly correlated with better delayed memory retrieval and psychomotor speed across the whole group and iv) greater educational attainment correlated with cortical volumes in APOE $\epsilon 4$ carriers and episodic memory across the whole group.

Two cortical regions emerged as important for brain reserve: the superior frontal cortex and the precuneus cortex. Genetic group com-

parisons in the CDR-0 group suggested that reserve could be profiled by increased superior frontal volume in healthy (CDR-0) APOE $\epsilon 4$ carriers who also showed superior episodic memory ability. Of interest, APOE $\epsilon 4$ carriers with very mild dementia showed significant volumetric reductions in the precuneus cortex, as well as episodic memory deficits, compared to their cognitively impaired $\epsilon 3/\epsilon 3$ counterparts, suggesting the preservation of precuneus volume may play a role in the profile of brain reserve in cognitively healthy APOE $\epsilon 4$ carriers. Also notable, there were no interactions between APOE genotype and CDR

TABLE 2 Summary of statistical effects of APOE and CDR on cortical and subcortical volumes

	APOE			CDR			APOE x CDR		
	F(2,733)	P	ηp^2	F(1,733)	P	ηp^2	F(1,733)	P	ηp^2
Relative brain volumes									
Hippocampus	4.42	0.012	0.012	885.2	<0.001	0.547	2.03	0.132	0.006
Amygdala	5.05	0.007	0.014	67.2	<0.001	0.084	2.72	0.067	0.007
Entorhinal (L)	4.68	0.010	0.013	16.2	<0.001	0.022	1.22	0.294	0.003
Entorhinal (R)	2.94	0.053	0.008	15.3	<0.001	0.020	0.64	0.530	0.002
Precuneus (L)	5.17	0.006	0.014	4.21	0.041	0.006	3.40	0.034	0.009
Precuneus (R)	1.36	0.258	0.004	1.01	0.315	0.001	1.01	0.365	0.003
Superior Frontal	0.40	0.673	0.001	0.18	0.671	0.000	4.52	0.011	0.012
Cognitive outcomes									
WMS-R Immediate Recall (df _{Error} = 541)	7.86	<0.001	0.028	66.1	<0.001	0.109	2.88	0.057	0.011
WMS-R Delayed Recall (df _{Error} = 541)	12.1	<0.001	0.042	102.1	<0.001	0.159	5.64	0.004	0.020
WAIS-R Digit Symbol (df _{Error} = 535)	2.37	0.095	0.009	38.0	<0.001	0.062	0.54	0.583	0.002
Boston Naming Test (df _{Error} = 539)	2.98	0.052	0.011	35.1	<0.001	0.061	1.99	0.138	0.007

APOE, apolipoprotein E gene; x, interaction; WMS-R, Weschler Memory Scale-Revised; WAIS, Weschler Adult Intelligence Scale-Revised; df, degrees of freedom; P: P-value; ηp^2 , partial eta-squared, effect size.

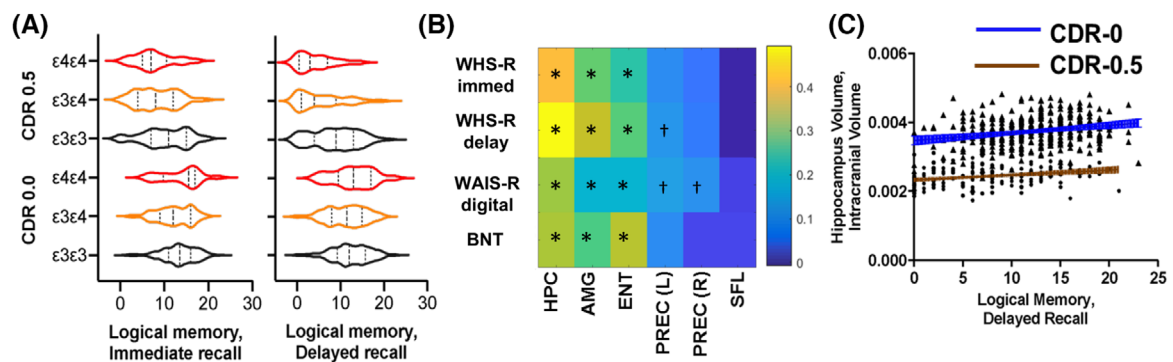


FIGURE 3 Differential effects of apolipoprotein E (APOE) in cognitively normal (Clinical Dementia Rating scale, CDR-0) and cognitively impaired (CDR-0.5) participants (A). Although cognitively normal participants with the high-risk $\epsilon 4/\epsilon 4$ allele showed better memory performance than the non-risk $\epsilon 3/\epsilon 3$ carriers, the opposite pattern was seen in the cognitively impaired participants. Brain-behavior correlations between the neuropsychological tests and regional brain volumes are shown in (B). Correlations were tested for significance using Bonferroni corrected p -values shown as “*,” $P < 0.0025$ (0.05 divided by 25 correlations), with correlations that did not survive multiple correction “†.” An example correlation between relative hippocampal volume and delayed recall is shown in (C). CDR, Clinical Dementia Rating scale; HPC, hippocampus; AMG, amygdala; ENT, entorhinal; PREC (L), precuneus left; PREC (R), precuneus right; SFL, superior frontal lobe; WHS-R immed, immediate episodic recall on the Wechsler Memory Scale-Revised; WHS-R delay, delayed episodic recall on the Wechsler Memory Scale-Revised; WAIS-R Digital, Digital span on the Wechsler Adult Intelligence Scale-Revised; BNT, Boston Naming Test

on the entorhinal cortex, hippocampus, and amygdala volume, but the APOE $\epsilon 4$ -related volume reduction of the hippocampus and amygdala was up to 10 times stronger in adults with very mild dementia.

The precuneus cortex and the superior frontal cortex have been shown to play significant role in episodic memory retrieval^{64,65} despite only a weak correlation with precuneus volume found here. The precuneus plays a significant role in the etiology of AD,^{36,66,67} is the first regions to undergo cognitive thinning up to 8 years before AD onset in familial mutation carriers,⁴¹ and was significantly lower in homozy-

gote APOE $\epsilon 4$ carriers compared to non-APOE $\epsilon 4$ carriers with very mild dementia in the present study. Educational attainment was associated with higher volumes of the precuneus in normal APOE $\epsilon 4$ carriers in this study, potentially explaining why some of the participants at high genetic risk for AD ($\epsilon 4/\epsilon 4$) show higher precuneus volumes alongside better episodic memory, whereas other $\epsilon 4/\epsilon 4$ carriers show cognitive impairment and low precuneus volumes. High levels of amyloid and tau are also associated with cortical thinning (primarily in the precuneus and superior parietal regions) and with subsequent cognitive deterior-

ration in non-demented participants.⁶⁸ This adds weight to our theory that maintained precuneus volumes in APOE $\epsilon 4$ carriers contribute to brain reserve that may mitigate the negative neural effects caused by APOE $\epsilon 4$ and potentially distinguish between APOE $\epsilon 4$ carriers who are more/less likely to convert to AD. Of interest, the precuneus cortex is recruited by cognitive normal APOE $\epsilon 4$ carriers to maintain successful navigation, highlighting the compensatory role of this region in maintaining cognition in the face of enriched genetic risk for AD.⁶⁹

As expected, superior frontal volume contributed to the brain reserve in cognitively normal APOE $\epsilon 4$ carriers. This is consistent with previous studies that show increased superior frontal volumes in cognitively normal $\epsilon 4$ carriers^{35,36}. Prefrontal brain volume is also associated with resistance to higher global amyloid load patients with mild cognitive impairment, again supporting its role in brain reserve.⁷⁰ Moreover, in the context of brain network function, convergent evidence for a compensatory role of the prefrontal cortex comes from task-based functional magnetic resonance imaging (fMRI),⁷¹ showing that even patients with AD can recruit prefrontal cortical resources to compensate for loss of MTL function linked to neurodegeneration. Moreover, prodromal AD patients with intact frontal lobe connectivity maintain episodic memory relatively well, further supporting a role of the prefrontal cortex in brain reserve.⁷²

Replicating and extending previous evidence,^{23,24,34,73,74} we show that the APOE $\epsilon 4$ genotype has detrimental effects on MTL regions, particularly if very mild dementia is already present, which is signified by a CDR score of 0.5 in our study. Although hippocampal volumes were lower in APOE $\epsilon 4$ carriers with very mild dementia compared to cognitively normal APOE $\epsilon 4$ carriers,^{43,75} it was previously unclear when along the dementia continuum (asymptomatic vs symptomatic) the $\epsilon 4$ effect is evident (eg, in CDR-0, CDR-0.5, CDR-1, or CRD-2 individuals). In our sample (CDR-0.5), APOE $\epsilon 4$ carriers show progressed hippocampal atrophy at an early symptomatic stage. Similarly, Zhang et al (2020) also reported that prodromal APOE $\epsilon 4$ carriers show volumetric reductions in the left amygdala and bilateral hippocampus, as well reduced entorhinal thickness,²² linked to elevated amyloid beta and tau pathology. Of interest, APOE $\epsilon 4$ carriers with very mild dementia showed significantly more precuneus atrophy compared to non-APOE $\epsilon 4$ carriers in our sample. These convergent findings suggest that the neural signature of genetically enriched early AD is characterized by advanced structural atrophy, not only in the hippocampus and amygdala, but also in the cortex. Potential mechanisms underlying this volumetric reduction in $\epsilon 4$ carriers include impaired maintenance of cell membranes and synapses, as well as a dysfunctional blood-brain barrier, leading to greater amyloid deposition and reduced amyloid plaque clearance, compared to the $\epsilon 3$ carriers.^{8,33,76-79}

The theory that reserve partially compensates for the effect of amyloid load on cognitive decline,³⁹ combined with our finding that APOE $\epsilon 4$ lowers MTL volume irrespective of CDR group, suggests that amyloid burden in our cognitively normal APOE $\epsilon 4$ carriers may be similar to APOE $\epsilon 4$ carriers with very mild dementia. Moreover, education was higher in cognitively normal participants compared to those with very mild dementia and predicted greater brain reserve in the $\epsilon 4/\epsilon 4$ carriers. These findings should be followed up with studies including tau

and amyloid biomarkers of AD to determine whether precuneus and superior frontal cortex integrity is also part of a brain reserve in the presence of AD pathology in addition to enriched genetic risk from the APOE.

The assessment of neuroimaging markers of brain reserve may improve AD clinical trial selection and design, which requires knowledge about individuals susceptibility to pathology and future cognitive decline.⁴⁰ Pre-screening with a short anatomical imaging sequence may enhance participant selection and/or help determine how aggressive treatment intervention should be. However, limitations in our study need to be considered in interpreting our results and designing future neuroimaging marker studies. First, although we identified precuneus and the superior frontal gyrus regions as key brain reserve regions protecting against genetic risk for AD, the correlations between these regions and memory performance across participants did not survive multiple comparison correction, so the protection on an individual level may not be strongly expressed. More sensitive behavioral measures, such as spatial navigation assessments, may offer greater individual cognitive validation of reserve.^{80,81} Furthermore, there may be other regions beyond the superior frontal gyrus and the precuneus whose structural integrity contributes to brain reserve, but which we did not examine here. In addition, environmental factors, occupational attainment and stimulating environments have also been linked previously to cognitive reserve, as they can delay the onset of AD symptoms.^{39,82}

In conclusion, left precuneus and bilateral superior frontal volumes emerged as markers of brain reserve in the presence of the APOE $\epsilon 4$ allele. Future studies should clarify the association between protective lifestyle factors beyond education (such as aerobic exercise, cardiovascular health, and leisure activities in later life) and the reserve phenotype presented here. Such investigations may uncover the mechanisms underlying preserved brain structure and enhanced memory in older adults protected from the genetic risk for AD.

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CONFLICTS OF INTERESTS

None to declare.

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