APOE4 Status is Related to Differences in Memory-Related Brain Function in Asymptomatic Older Adults with Family History of Alzheimer's Disease: Baseline Analysis of the PREVENT-AD Task Functional MRI Dataset

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Abstract.
Background: Episodic memory decline is one of the earliest symptoms of late-onset Alzheimer's disease (AD). Older adults with the apolipoprotein E ε4 (+*APOE4*) genetic risk factor for AD may exhibit altered patterns of memory-related brain activity years prior to initial symptom onset.
Objective: Here we report the baseline episodic memory task functional MRI results from the PRe-symptomatic EValuation of Experimental or Novel Treatments for Alzheimer's Disease cohort in Montreal, Canada, in which 327 healthy older adults were scanned within 15 years of their parent's conversion to AD.

Methods: Volunteers were scanned as they encoded *and* retrieved object-location spatial source associations. The task was designed to discriminate between brain activity related to spatial source recollection and object-only (recognition) memory. We used multivariate partial least squares (PLS) to test the hypothesis that +*APOE4* adults with family history of AD would exhibit altered patterns of brain activity in the recollection-related memory network, comprised of medial frontal, parietal, and medial temporal cortices, compared to *APOE4* non-carriers (–*APOE4*). We also examined group differences in the correlation between event-related brain activity and memory performance.
Results: We found group similarities in memory performance and in task-related brain activity in the recollection network, but differences in brain activity-behavior correlations in ventral occipito-temporal, medial temporal, and medial prefrontal cortices during episodic encoding.
Conclusion: These findings are consistent with previous literature on the influence of *APOE4* on brain activity and provide new perspective on potential gene-based differences in brain-behavior relationships in people with first-degree family history of AD.

INTRODUCTION

Late-onset sporadic Alzheimer's disease (AD) accounts for an estimated 70% of dementia cases worldwide [1, 2]. Typically appearing after 65 years of age, this form of AD greatly increases in incidence beyond 85 years of age and has grown in prevalence with increasing life expectancy [3]. Despite the rising prevalence and burden of AD, there are currently no widely effective treatments to prevent or delay symptom progression [2]. Moreover, new AD drug trials fail at a rate of over 100 : 1 [4].

Given the current challenges of developing effective treatments for AD, increasing focus surrounds early identification, intervention, and prevention of AD in asymptomatic adults at higher risk of developing the disease [5]. Such risk factors include having an apolipoprotein E ε4 (*APOE4*) allele as well as first-degree family history (i.e., parent or sibling) of the disease [6]. The combination of these factors appears to have an additive effect on AD risk and may influence the age of symptom onset beyond the effects of *APOE* genotype alone [7]. Evidence further indicates that subtle neurological changes may precede symptom onset by as many as 20 years, during a period known as the 'silent' preclinical stage of AD [8, 9]. Therefore, studies have increasingly focused on searching for early neural biomarkers or cognitive indices that could help predict AD development—particularly in individuals at higher risk of AD—at a period in which neurocognitive systems remain relatively intact [10–12]. Such early risk identification would permit access to interventions aimed at preventing or delaying AD onset (e.g., physical and cognitive exercise, control of blood pressure and cardiovascular conditions, improved diet,

etc.) before the disease has progressed, and may help decrease the social and economic burdens associated with AD [13–15].

Declines in memory of past personal events (i.e., episodic memory) represent one of the earliest symptoms of AD [16] and associate with preclinical or pre-symptomatic AD-related neuropathology [17]. Thus, the neural systems supporting episodic memory may be key candidate sites in which the first signs of AD-related neuropathology arise during the 'silent' phase of the disease [18, 19]. Consistent with this theory, differences in task-related brain activity in people with mild cognitive impairment and AD, compared to healthy older adults, appear to reflect declines in memory and attention processing [20, 21], and may index changes related to AD progression [22, 23]. Moreover, brain activity related to memory encoding in regions that subserve episodic memory, including hippocampal, parahippocampal, posterior parietal, and lateral prefrontal cortex, appears different in healthy aging, mild cognitive impairment, and AD [24]. Notably, although recollection of rich contextual details related to a past event tends to decline even in healthy aging [25, 26], recognition of previously encountered objects or events appears more severely impacted in pathological aging [27]. Episodic memory tasks that can differentiate the neural systems associated with familiarity, compared to recollection, may therefore be particularly helpful in identifying early signs of AD related neuropathology in healthy, at-risk adults.

Our past work demonstrated an association between episodic memory performance and changes in task-related functional magnetic resonance imaging (fMRI) detectable as early as middle age [28] and more pronounced in *APOE4* carriers or those with

family history of AD [29]. These distinct associations appear in the absence of measurable behavioral differences and may be greater for the encoding and retrieval of contextual details associated with a past event, compared to general sense of familiarity [28]. Examining brain-behavior relationships during episodic memory task performance may therefore provide new insights for identifying early AD markers. In particular, exploring differences in episodic memory-related brain function in older adults with and without risk factors such as an *APOE4* allele and family history of AD may help better understand the impact of AD on memory systems [30–33].

The present study

Here we primarily aimed to report data from the functional neuroimaging task used in the PREVENT-AD program (https://douglas.research. mcgill.ca/stop-ad-centre), in a sample of older adults at higher risk of AD due to a parental or multiple-sibling family history. Previous studies on AD risk, particularly those investigating the contribution of genetic profile on cognitive symptoms, have not always considered family history despite evidence for its impact on AD development beyond genetic composure [7]. Failure to account for such combined gene-environment contributors may lead to an inaccurate estimate of *APOE4* influence on AD and individual risk profiles [34]. Because our sample uniformly contained older adults with first-degree family history of AD, we aimed to examine the potential influence of *APOE4* on episodic memory performance and related brain activity over and above the influence of family history.

Moreover, whereas previous studies have largely drawn on univariate analytical tools, comparatively few have examined the relationship between *APOE4* and whole-brain functional changes. Thus, we further sought to examine the potential influence of carrying an *APOE4* allele (i.e., +*APOE4*) on whole-brain activity during encoding and retrieval of objects (i.e., recognition) and their location (i.e., source recall), in cognitively healthy older adults with parental history of AD.

To achieve this, we performed partial least squares (PLS) analyses, a data-driven method to objectively assess patterns of whole-brain activity in *APOE4* carriers versus non-carriers. Although traditional methods such as univariate contrast-based, voxel-wise approaches can also evaluate task-related differences in brain activity, PLS has several advan-

tages. First, PLS-based approaches do not rely on pre-defined contrasts, revealing the most stable and robust effects using permutation testing and bootstrapping. In addition, PLS does not rely on the assumptions associated with linear modeling (e.g., normality of sample distribution, equal sample sizes). Finally, PLS offers a sensitive, data-driven multivariate approach that captures the complex relationships between whole-brain patterns of brain activity and exogenous factors (e.g., episodic memory performance) in a single mathematical step [35, 36]. Thus, PLS is the ideal method to examine memory-related patterns of brain activity and the relationship of such activity with performance in our sample of *APOE4* carriers versus non-carriers.

We hypothesized that, relative to –*APOE4*, +*APOE4* would display different patterns of brain activity unrestricted to the hippocampus or medial temporal lobe during episodic encoding and retrieval. We further anticipated that the difference in task-related brain responses between *APOE4* carriers versus non-carriers would interact with object recognition and recall of spatial context. Specifically, given that source recollection performance and associated brain activity may change even in healthy aging [25, 26], we anticipated that differences in brain-behavior relationships would primarily reflect a deficit in object recognition in +*APOE4* compared to –*APOE4* individuals.

METHODS

Participants: PREVENT-AD Cohort

Participants were recruited for the longitudinal PRe-symptomatic EValuation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD) program, an observational cohort study of asymptomatic older adults with a parental or multiple-sibling family history of AD in Montreal, Canada [37]. We evaluated baseline data from 327 older adults ($M_{age} = 63.40 \pm 5.24$ years, 234 women) who were enrolled up to August 31, 2017 (i.e., data release 5.0) and participated in the task fMRI portion of the study (see below).

We excluded participants on the basis of confounding genetic factors (i.e., *APOE2* carriers, $n = 34$; *APOE44*, $n = 7$; unavailable genotype, $n = 3$); having below-chance performance or fewer than eight trials per response type in the task fMRI protocol ($n = 95$); and poor fMRI image resolution ($n = 32$). Our final sample comprised 172 older adults

($M_{age} = 63.42 \pm 5.12$ years; 128 women), including 103 *APOE33* (i.e., –*APOE4*; 76/103 = 74% women) and 69 *APOE34* heterozygotes (i.e., +*APOE4*; 52/69 = 75% women).

Protocol

Enrolment criteria for the PREVENT-AD trial are described elsewhere [37]. Briefly, all participants had at least one parent or multiple siblings diagnosed with sporadic AD or a condition suggesting AD-like dementia within 15 years [38]. At baseline and during each subsequent follow-up assessment, participants performed neuropsychological tests as well as an object-location memory task in the scanner, described below. Here we focus on baseline analyses of the task-related fMRI based on *APOE4* genotype. We describe longitudinal analyses of this task fMRI protocol in a forthcoming report. For more information on PREVENT-AD, see: douglas.qc.ca/page/prevent-alzheimer-the-centre.

Determination of family history of AD

If a documented expert medical history was not available, a brief questionnaire from the Cache County Study on Memory Health and Aging (Utah, USA) determined that a parent or multiple siblings: 1) had trouble with memory or concentration that was sufficiently severe to cause disability or loss of function; 2) had insidious onset or gradual progression of the condition that was not an obvious consequence of a stroke or other sudden insult.

APOE genotyping

Genetic characterization was completed via blood draw, as previously described [39]. DNA was isolated from 200 μl of the blood sample using QIASymphony and the DNA Blood Mini QIA kit (Qiagen, Valencia, CA, USA). *APOE* gene variant was determined using pyrosequencing with PyroMark Q96 (Qiagen, Toronto, ON, Canada). For further detail on the methods used in the PREVENT-AD cohort, see Tremblay-Mercier et al. [40].

Neuropsychological testing

Neuropsychological assessments took approximately 40 minutes to administer and were completed prior to every testing session. The test battery included:

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a battery of neuropsychological assessments aiming to identify abnormal cognitive decline in older adults [41]. The RBANS provides scaled scores for five cognitive indices: immediate memory, visuospatial construct, language, attention, and delayed memory. We included these scaled scores, as well as the total score, in our analyses. Different versions of the RBANS were used in follow-up sessions to prevent practice effects.

The Alzheimer-Dementia Eight Scale (AD8), an eight-item screening tool. The AD8 items index memory, orientation, judgment, and function. A score of two or above suggests impaired cognitive function [42].

The Clinical Dementia Rating (CDR), a five-point scale used to characterize memory, orientation, judgment & problem solving, community affairs, home & hobbies, and personal care [43]. The information for each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g., family member).

The Montreal Cognitive Assessment (MoCA), a brief cognitive screening tool sensitive to mild declines in cognitive function [44].

Task fMRI: Behavioral protocol

Participants were instructed to lie supine in a 3T Siemens Trio scanner (see below), while performing a source memory task programmed in E-Prime version 1.0 (Psychology Software Tools, Inc). During an initial encoding phase, participants were cued (10 s) to memorize a series of 48 colored line drawings of common objects from the BOSS database [45] in their spatial location (i.e., to the left or right of a central fixation cross). Each object was presented for 2000 ms followed by a variable inter-trial interval (ITI; durations of 2200, 4400, or 8800 ms; mean ITI = 5.13 s) to add jitter to the fMRI data collection [46]. Following the encoding phase, there was a 20 min delay during which participants received structural MRI scans.

Following the 20 min delay, a cue (10 s) alerted participants to the beginning of the retrieval phase. During retrieval, participants were presented with 96 colored drawings of common objects: 48 'old' (i.e., previously encoded) stimuli and 48 novel objects, in randomized order. Each object was presented in the center of the screen for 3000 ms, with variable ITI (2200, 4400, or 8800 ms). All participants used a fiber-optic 4-button response box to make

task-related responses, and had an opportunity to familiarize themselves with the response choices during a practice session prior to testing. For each retrieval object, participants made a forced-choice between four alternative answers: i) "*The object is FAMILIAR but you don't remember the location*"; ii) "*You remember the object and it was previously on the LEFT*"; iii) "*You remember the object and it was previously on the RIGHT*"; and iv) "*The object is NEW*". Thus (i) responses reflected object recognition, which may associate more closely with familiarity versus recollection-based retrieval processes, whereas (ii) and (iii) responses reflect associative recollection of object-location associations, and (iv) responses reflected either correct rejections of novel objects or failed retrieval ("misses"). Responding (i)–(iii) to new objects reflected false alarms.

fMRI data acquisition

Functional magnetic resonance images were acquired with a 3T Siemens Trio scanner using the standard 12-channel head coil, located at the Douglas Institute Brain Imaging Centre in Montreal, Canada. T1-weighted anatomical images were acquired after the encoding phase of the fMRI task using a 3D gradient echo MPRAGE sequence (TR = 2300 ms, TE = 2.98 ms, flip angle = 9°, 176 1 mm sagittal slices, $1 \times 1 \times 1$ mm voxels, FOV = 256 mm). Blood oxygenated level dependent (BOLD) images were acquired using a single-shot T2*-weighted gradient echo-planar imaging (EPI) pulse sequence with TR = 2000 ms, TE = 30 ms, FOV = 256 mm. Brain volumes with 32 oblique slices of 4 mm thickness (with no slice gap) were acquired along the anterior-posterior commissural plane with in-plane resolution of 4×4 mm.

A mixed rapid event-related design was employed to collect task-related BOLD activation during performance of the memory task (see above). Visual task stimuli were generated on a computer and back-projected onto a screen in the scanner bore. The screen was visible to participants lying in the scanner via a mirror mounted within the standard head coil. Participants requiring correction for visual acuity wore plastic corrective glasses.

Data analysis

Preprocessing of fMRI data

We converted reconstructed images to NIfTI format and preprocessed them using in Statistical Parametric Mapping software version 12 (SPM12). Images from the first 10 s of scanning were discarded to allow equilibration of the magnetic field. All functional images were realigned to the first image and corrected for movement artifacts using a 6-parameter rigid body spatial transform and a PLS approach. Functional images were then spatially normalized to the MNI EPI-template using the "Old Normalize" method in SPM12 at $4 \times 4 \times 4$ mm voxel resolution, and smoothed using an 8 mm full-width half-maximum (FWHM) isotropic Gaussian kernel. Participants with head motion exceeding 4 mm in the x, y, or z axis during encoding and retrieval were excluded from further analyses. Participants with movements that could not be sufficiently repaired, resulting in distorted brain images as judged by an examiner, were excluded from further analysis. To be included in further analyses, all participants were required to have a minimum of eight observations per event type (i.e., object recognition and source recollection).

Behavioral analyses

We performed behavioral data analyses on neuropsychological tests and episodic memory task performance using SPSS version 24 with a significance threshold of $p = 0.05$, Greenhouse-Geisser corrections for sphericity, and Bonferroni corrections for multiple comparisons, where applicable. Because evidence suggests meaningful sex/gender differences in the neural and behavioral correlates of episodic memory and cognition in aging [47–49], we also investigated self-reported sex as a factor in our analyses.

Neuropsychological tests

We tested for group differences in AD8, MoCA, CDR, and RBANS scores using multivariate analysis of variance (MANOVA), with genotype (*APOE34*, *APOE33*) and self-reported sex (male, female) as independent factors, and test scores as dependent variables.

Episodic memory task

We calculated mean accuracy and mean response time (RT; ms) for +*APOE4* and −*APOE4* individuals, as well as self-reported males and females, for all possible response types: correct object recognition (recognizing old objects but providing no or incorrect associative spatial context), correct associative spatial context recollection (correctly recalling object-location associations); source misattributions

(incorrectly identifying spatial context of an old object; e.g., saying an object previously seen on the left was initially presented on the right), false alarms (incorrectly identifying new objects as old), misses (incorrectly identifying old objects as new), and correct rejections (correctly identifying new objects). These stimulus-response categories are presented in Table 1. We computed overall accuracy (i.e., hits) using the sum of correct associative spatial context recollection judgments and correct object recognitions, including source misattribution trials. We used d', computed as overall standardized hit rate minus standardized false alarm rate, as a measure of sensitivity, and c, computed by multiplying the average of the standardized hit and false alarm rates by –1, to measure response bias [50]. We further estimated episodic memory performance by measuring the probability of source recall (pSource) and recognition (pRecog), calculated as follows:

$$(1) \quad \text{pSource} = Z_{(\text{source hits})} - Z_{(\text{source misattributions})}$$
$$(2) \quad \text{pRecog} = Z_{(\text{recognition hits})} - Z_{(\text{false alarms})}$$

Similar to d', these scores provide a relative measure of accuracy that takes into account both hits and false alarms while isolating responses based on source recall versus familiarity. We then used multivariate general linear models to evaluate between-group differences on hits, pSource and pRecog scores, and RT on hit, miss, and false alarm trials.

fMRI analyses

We used spatio-temporal PLS to conduct multivariate event-related fMRI analysis using PLSGUI software (https://www.rotman-baycrest.on.ca/index.php?section=84). We selected PLS due to its ability to identify whole-brain spatially and temporally distributed patterns of brain activity that differ across experimental conditions and/or relate to a specific behavioral measure [51; see elaboration of PLS advantages above]. We conducted two types of PLS analyses: 1) mean-centered task PLS (T-PLS) to identify group similarities and differences in event-related activity during successful

object-location associative encoding and retrieval; and 2) behavioral partial least squares (B-PLS) to examine group similarities and differences in the correlations between event-related activity and performance, indexed by pSource and pRecog. Details on PLS have been published elsewhere [52, 53].

For both T-PLS and B-PLS, we averaged the event-related data for each participant across the entire time series and stacked these data by group (i.e., *APOE4*) and based on participants' subsequent memory performance as follows: 1) encoding objects in which participants subsequently remembered object-location source associations (correct source recall; ENC-source); 2) encoding objects in which participants subsequently remembered only the object identified, but failed to recall spatial source information (source failure with object recognition; ENC-recog); 3) retrieval objects for which participants correctly recalled object-location source associations (RET-source); and iv) retrieval objects for which participants correctly recalled only the object identity, but failed to recall spatial source association (RET-recog). The stacked data matrix contained the fMRI data for each event onset (time lag = 0) with seven subsequent time lags, representing a total of 14 s of activation after event onset (TR = 2s * 7 = 14 s) for *successfully encoded* (ENC-source, ENC-recog) and *successfully retrieved* (RET-source and RET-recog) events. All participants analyzed had a minimum of eight correct events per event type. There was no signal at lag 0 because data were baseline corrected to the event onset. Therefore, signal in subsequent lags was expressed as percentage deviation from event onset.

Task PLS (T-PLS)

We mean centered the fMRI data column-wise during the encoding and retrieval phases of the episodic memory task, to evaluate whole-brain similarities and differences between –*APOE4* and +*APOE4* individuals in brain activity related to encoding and retrieval of object-location associations. PLS performs singu-

Table 1
Participant responses and their categorization based on the presented stimuli

Stimulus	Participant Response			
	"Old, Left"	"Old, Right"	"Familiar"	"New"
Old, Left	Source Hit	Source Misattribution	Recognition	Miss
Old, Right	Source Misattribution	Source Hit	Recognition	Miss
New	False Alarm	False Alarm	False Alarm	Correct Rejection

lar value decomposition on the stacked data matrix to express the cross-covariance between the fMRI data and each condition into a set of mutually orthogonal latent variables (LVs). The number of LVs produced is equivalent to the number of event types included in the analysis. Thus, this analysis yielded eight LVs (4 event-types * 2 groups). Each LV comprises: 1) a singular value reflecting the amount of covariance accounted for by the LV; 2) a design salience with a set of contrasts representing the relationship between tasks in each group and the pattern of brain activation; and 3) a singular image representing the numerical weights assigned to each voxel at each TR/time lag (i.e., the "brain salience" representing the contribution of a region at each TR), yielding a spatio-temporal pattern of whole-brain activity for the entire time series. Design saliences and brain weights can be either positive or negative, and indicate whether activity in the associated voxels are positively or negatively associated with the *correlation profile*: positive brain weights (depicted as warm-colored regions in the singular images) are positively correlated to *positive* design saliences, whereas negative brain weights (depicted as cool-colored regions in the singular images) are positively correlated with *negative* design saliences and vice-versa [52, 53]. Thus, the pattern of whole brain activity shown in the singular image is symmetrically associated with the contrast effect identified by the design salience plot.

Behavioral PLS

We used B-PLS to analyze whole-brain similarities and differences in brain activity directly correlated with pSource and pRecog during encoding and retrieval between +*APOE4* and –*APOE4* individuals. We stacked the behavioral vector containing pSource and pRecog in the same order as the fMRI data matrix (i.e., participant within group). As in the T-PLS, B-PLS performed singular value decomposition of the stacked cross-correlation matrix to yield eight LVs. However, rather than design saliences, B-PLS analysis yields: 1) a singular value, reflecting the amount of covariance explained by the LV; 2) a singular image consisting of positive and negative brain saliences (weights), and 3) a correlation profile depicting how participants' retrieval accuracy (pSource or pRecog) correlates with the pattern of brain activity identified in the singular image. The correlation profile and brain saliences represent a symmetrical pairing of brain-behavior correlation patterns for each group

to a pattern of brain activity, respectively. As with the T-PLS analysis, brain saliences can have positive or negative values, and reflect whether activity in a given voxel is positively or negatively associated with the correlation profile depicted. Thus, negative correlations on the correlation plot indicate a negative correlation between performance and *positive* brain weights (depicted as warm-colored regions in the singular image), but a *positive* correlation between performance and negative brain weights (depicted as cool-colored regions in the singular image). Conversely, positive correlations indicate a positive correlation between performance and *positive* brain weights, but a *negative* correlation between performance and negative brain weights.

We assessed the significance of each LV in the T-PLS and B-PLS through 1000 permutations involving resampling without replacement from the data matrix to reassign the order of event types within participant. We determined the stability of the brain saliences using 500 bootstrap samples for the standard errors of voxel saliences for each LV, sampling participants with replacement while maintaining the order of event types for all participants. We considered only voxels with brain saliences ≥ 3.28 times greater than the bootstrap standard error (approximately corresponding to $p = 0.001$) and a minimum spatial extent of 10 contiguous voxels as stable.

We computed temporal brain scores for each significant LV to determine the time lags with the strongest correlation profile. Temporal brain scores reflect how strongly each participant's data reflected the pattern of brain activity expressed in the singular image in relation to its paired correlation profile, at each time lag. We report only peak coordinates from time lags at which the correlation profile was maximally differentiated within the temporal window sampled (lags 2–5; 4–10 s after event onset). We converted these peak coordinates to Talairach space using the icbm2tal transform [54] as implemented in GingerAle 2.3 [55]. Because our acquisition incompletely acquired the cerebellum, peak coordinates from this region are not reported. We used the Talairach and Tournoux atlas [56] to identify the Brodmann area (BA) localizations of significant activation sites.

RESULTS

After removing age outliers (i.e., individuals with age above or below 2SD from the mean), we analyzed

data from 165 participants, including 98 –*APOE4* and 67 +*APOE4* individuals. Participant demographics and mean motion during fMRI are shown in Table 2. Evidence suggests that proximity to the age of AD diagnosis in a parent or sibling may predict the onset of dementia symptomatology [32]. We therefore included estimated years to AD symptom onset (EYO), calculated as the age of AD onset in the earliest affected family member subtracted from the participant's current age, as part of these baseline analyses.

We found that –*APOE4* individuals were significantly older ($t_{163} = 2.15$, $p = 0.033$). We therefore included age as a covariate in our analyses of performance below.

Neuropsychological performance

Participant scores on the neuropsychological tests are presented in Table 3. Although groups were balanced in their sex distributions ($\chi^2 = 0.057$, $p = 0.812$), we found a significant correlation between sex and performance on the MoCA ($r_{pb} = 0.227$, $p = 0.003$) and CDR ($r_{pb} = -0.183$, $p = 0.019$). Thus, we included sex as a factor in our analyses of neuropsychological performance factors, with age as a covariate.

MoCA total score

We found a significant main effect of *APOE4* ($F_{(1,159)} = 10.07$, $p = 0.002$, $\eta_p^2 = 0.06$) and of sex ($F_{(1,159)} = 6.45$, $p = 0.011$, $\eta_p^2 = 0.04$), but no interaction between the two (Fig. 1). Follow up analyses

revealed that +*APOE4* individuals had significantly higher MoCA scores compared to –*APOE4* individuals ($t_{162} = 2.81$, $p = 0.006$), and that women had significantly higher MoCA scores compared to men ($t_{58.11} = 2.66$, $p = 0.01$). Notably, nine –*APOE4* individuals scored below the clinical cutoff of 26 compared to only two +*APOE4* individuals, although this difference was not significant ($\chi^2 = 1.31$, $p = 0.25$). Conversely, the proportion of women who scored below 26 on the MoCA ($5/119 = 4\%$) was significantly lower than the proportion of men ($7/34 = 21\%$; $\chi^2 = 7.77$, $p = 0.005$).

RBANS scores

Multivariate ANOVA on the RBANS subtests revealed no significant effect of *APOE4* (Wilk's $\lambda = 0.971$, $F_{(6,148)} = 0.744$, $p = 0.615$), of sex (Wilk's $\lambda = 0.981$, $F_{(6,148)} = 0.487$, $p = 0.817$), or an interaction between the two (Wilk's $\lambda = 0.933$, $F_{(6,148)} = 1.763$, $p = 0.11$), on RBANS test scores.

AD8 and CDR total scores

We found a main effect of *APOE4* ($F_{(1,160)} = 6.24$, $p = 0.014$, $\eta_p^2 = 0.038$; ns after removing sex as a factor), and an interaction between *APOE4* and sex ($F_{(1,160)} = 4.92$, $p = 0.028$, $\eta_p^2 = 0.030$; ns after correcting for multiple comparisons) on AD8 total score. We also found a main effect of sex on CDR total score ($F_{(1,160)} = 5.21$, $p = 0.024$, $\eta_p^2 = 0.032$). This effect did not remain significant after correcting for multiple comparisons; we therefore performed no follow up analyses on CDR scores.

Table 2
Demographic background and mean fMRI motion (in mm) of participants included in behavioral analyses ($n = 165$) based on *APOE4* group, represented as mean values ± standard deviation

	Years of Age	Age Range	n Women:Men	Years of Education	EYO	Motion
–*APOE4*	63.43 ± 4.51*	55.30–73.14	73 : 25	14.80 ± 3.34	9.93 ± 8.08	0.025 ± 0.067
+*APOE4*	61.98 ± 3.91	55.13–72.62	51 : 16	15.48 ± 3.46	9.19 ± 7.66	0.027 ± 0.066

*$p = 0.033$.

Table 3
Neuropsychological performance by A) *APOE4* and B) sex, represented as mean values ± standard deviation. Data missing from one participant who did not receive the MoCA ($n = 164$) and seven participants who did not receive the RBANS ($n = 158$)

| A)	AD8	CDR	MoCA	Immediate memory	Visuospatial construction	Language	Attention	Delayed memory	RBANS total
–*APOE4*	0.12 ± 0.41	0.015 ± 0.09	27.68** ± 1.62	104.34 ± 10.9	94.76 ± 12.3	98.40 ± 10.19	106.03 ± 15.74	104.41 ± 8.73	101.62 ± 9.36
+*APOE4*	0.24 ± 0.61	0.007 ± 0.06	28.38 ± 1.45	103.73 ± 11.23	94.66 ± 13.12	101.66 ± 8.69	105.41 ± 13.78	103.47 ± 10.95	102.05 ± 10.73
B)									
Women	0.15 ± 0.45	0.004 ± 0.05	28.17* ± 1.45	103.87 ± 11.36	95.53 ± 12.35	99.78 ± 10.09	106.39 ± 15.07	104.36 ± 9.87	102.22 ± 10.14
Men	0.24 ± 0.62	0.037 ± 0.13	27.34 ± 1.81	104.75 ± 9.95	92.30 ± 13.26	99.55 ± 8.63	103.97 ± 14.58	103.08 ± 9.08	100.53 ± 9.20

*$p = 0.011$; **$p = 0.006$.
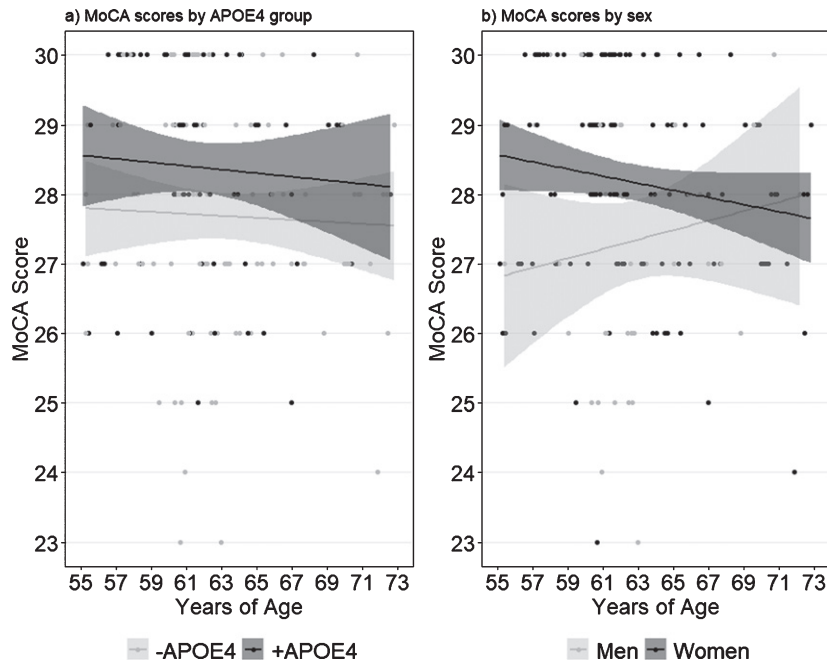
Fig. 1. MoCA scores by (a) *APOE4* carrier status and (b) self-reported sex. Shaded margins indicate 95% confidence intervals.

Table 4
Performance on the episodic memory task (*n* = 165). Errors are standard deviations

A) Mean accuracy metrics by response type and measures of signal detection theory										
	Total hit rate	Source hits	Recognitions	Source misattributions	Misses	False alarms	Correct rejections	d'	pSource	pRecog	c
–*APOE4*	0.84 ± 0.11	0.54 ± 0.15	0.18 ± 0.12	0.13 ± 0.07	0.16 ± 0.11	0.16 ± 0.12	0.84 ± 0.14	–0.12 ± 1.43	–0.05 ± 1.39	–0.14 ± 1.28	–0.09 ± .70
+*APOE4*	0.84 ± 0.13	0.54 ± 0.17	0.18 ± 0.12	0.12 ± 0.06	0.16 ± 0.13	0.12 ± 0.10	0.88 ± 0.10	0.20 ± 1.43	0.15 ± 1.27	0.21 ± 1.29	0.20 ± 1.43

B) RT (s) by response type					
	Source hits	Recognition hits	Source misattributions	Misses	False alarms	Correct rejections
–*APOE4*	1.72 ± 0.30	2.45 ± .59	2.07 ± 0.42	2.04 ± 0.49	2.50 ± .054	1.65 ± 0.34
+*APOE4*	1.73 ± 0.29	2.44 ± .51	2.17 ± 0.39	1.99 ± 0.40	2.41 ± 0.50	1.60 ± 0.25

fMRI: Episodic memory task performance

Behavioral results from the object-location associative memory task are shown in Table 4. Multivariate ANOVA with *APOE* and sex as between subjects factors, and age as a covariate, revealed no significant group differences or interaction effects in measures of task accuracy (Wilk's $\lambda = 0.969$, $F_{(5,156)} = 0.983$, $p = 0.43$) or RT (Wilk's $\lambda = 0.972$, $F_{(7,147)} = 0.607$, $p = 0.749$) at baseline. Similarly, we found no effect of *APOE* (Wilk's $\lambda = 0.990$, $F_{(2,159)} = 0.816$, $p = 0.44$), of sex (Wilk's $\lambda = 0.982$, $F_{(2,159)} = 1.466$, $p = 0.23$), or an interaction between the two (Wilk's $\lambda = 1.0$, $F_{(2,159)} = 0.01$, $p = 0.99$) when examining pSource (i.e., correct associative spatial context recollection) and pRecog (i.e., correct object recognition) as performance outcomes (Fig. 2). Our analyses nevertheless revealed sig-

nificant differences in RT based on response type ($F_{(3.99, 610.8)} = 3.37$, $p = 0.01$, $\eta_p^2 = 0.022$; Fig. 3). In all groups, participants had significantly longer RT for recognition (i.e., source failure) and FA trials compared to source hits, source misattributions, misses, and correct rejections ($t_{164} \geq 6.45$, $p \leq 0.0001$), and significantly faster RT for correct rejections compared to all other trials ($t_{164} \geq 4.00$, $p \leq 0.0001$). Of trials presenting "old" (i.e., previously viewed) objects, participants had the fastest RT for source hits ($t_{159} \geq 8.98$, $p \leq 0.0001$).

fMRI results

T-PLS

The PLS analysis yielded two significant LVs ($p < 0.0001$). The first significant LV accounted for 66.7% of the cross-block covariance and identified
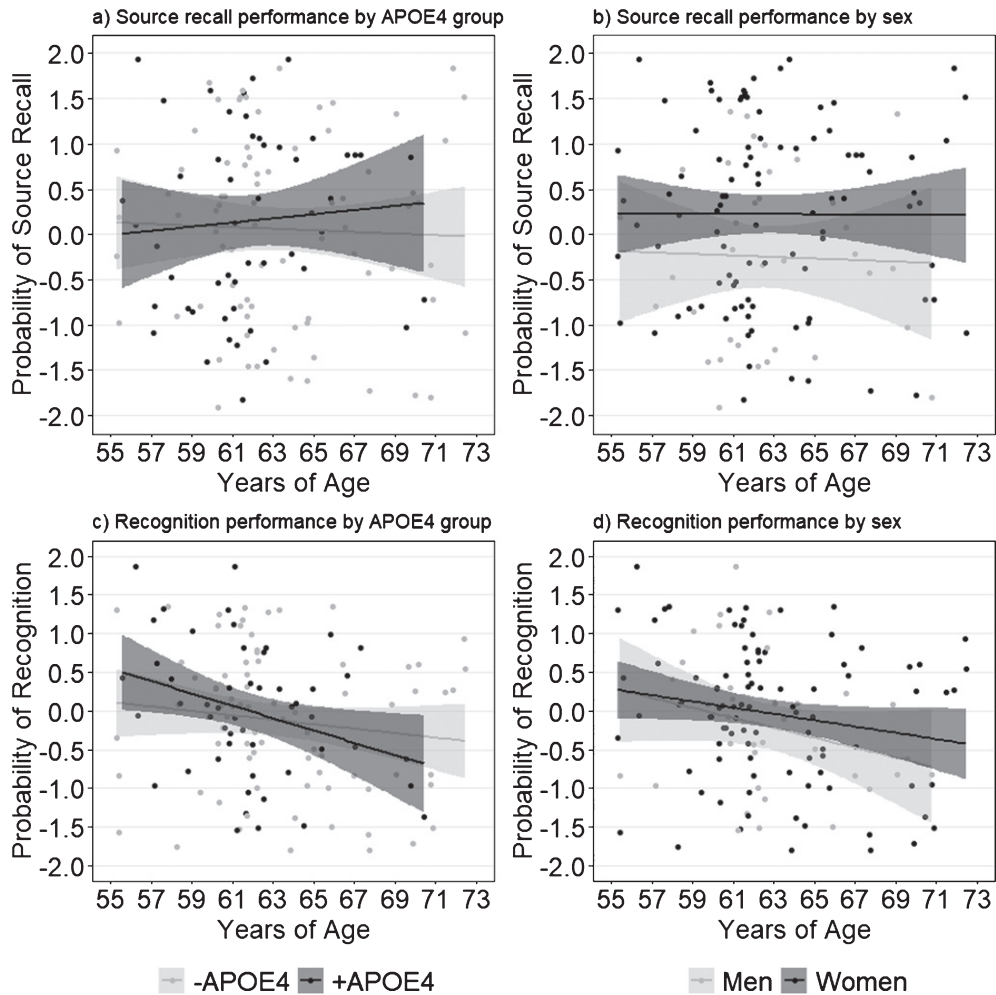
Fig. 2. Performance on the episodic memory task by *APOE4* carrier status (a,c) and self-reported sex (b,d). Probability of source recall represents standardized source misattribution rate subtracted from standardized source hit rate. Probability of recognition represents standardized false alarm rate subtracted from standardized object recognition rate. Shaded margins indicate 95% confidence intervals.

brain regions in which activity significantly differed during encoding, compared to retrieval, in both +*APOE4* and –*APOE4* groups (Fig. 4A). Table 5 lists the local maxima from LV 1. In both *APOE4* groups, positively-weighted brain regions were more active during retrieval, compared to encoding, whereas the negatively-weighted brain regions were more active during encoding, compared to retrieval, across all groups. More activity was detected in the left ventromedial/orbitofrontal/anterior cingulate, and the left lateral middle temporal cortex during encoding, compared to retrieval. Conversely, during retrieval there was more activity in the bilateral claustrum, cingulate gyrus, inferior frontal gyrus, and precuneus, as well as the left middle frontal gyrus, compared to encoding.

LV2 of the T-PLS accounted for 13.78% of the cross-block covariance. The design salience plot and singular image presented in Fig. 4B indicates that this LV identified brain regions that were differentially activated during correct retrieval of object-location associations, compared to objects alone (i.e., source hits versus source misattributions and failures) in both *APOE* groups. The local maxima from this LV are presented in Table 6. This LV identifies mainly negatively-weighted brain regions and indicates that activity was greater in middle occipital, inferior parietal lobule, caudate, and temporal gyri, including the left parahippocampus and right hippocampus, during object-location associative retrieval, compared to object only retrieval. In contrast, activity was greater in the bilateral inferior frontal gyrus, cingulate gyrus,
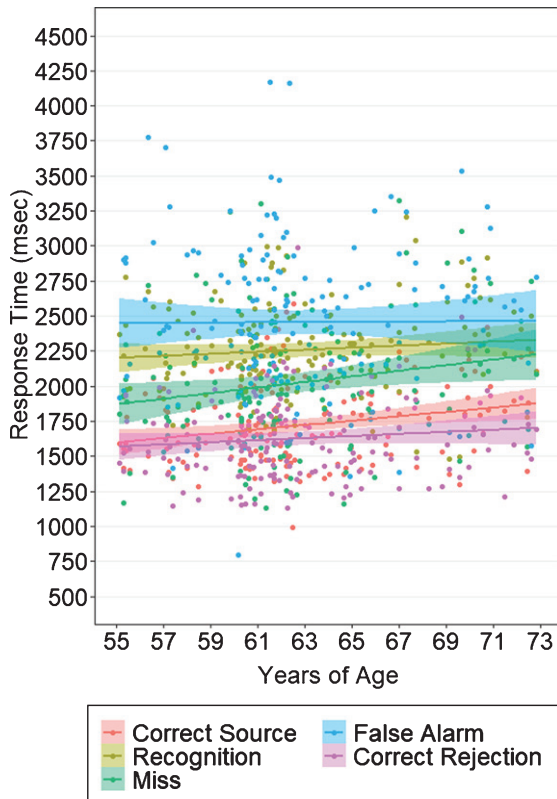
Fig. 3. Response times on the episodic memory task by response category. On average, participants in all groups responded fastest for correct rejections, followed by correct object-location source associations, and slowest for object recognitions and false alarms. Shaded margins indicate 95% confidence intervals.

left middle frontal gyrus, and right inferior parietal lobule during object only retrieval, compared to object-location retrieval.

B-PLS

After removing performance outliers based on pSource and pRecog, we analyzed data from 129 participants (78 –*APOE4* and 51 +*APOE4*). The B-PLS yielded one significant LV ($p = 0.008$), which accounted for 23.82% of the cross-block covariance (Fig. 5). Table 7 lists the local maxima for positively- and negatively-weighted brain regions. This LV identified brain regions with group differences in the correlation between pRecog performance and encoding activity for objects which participants subsequently retrieved only object identity but failed to recall the spatial source information (ENC-recog). In addition, this LV identified brain regions in which activity during object-location source retrieval (RET-source) correlated

with pSource performance in –*APOE4* individuals. Specifically, in these individuals, activity in positively-weighted brain regions during ENC-recog events was negatively correlated with pRecog scores, and activity in these same regions during RET-source events was positively correlated with pSource scores. In addition, in –*APOE4* individuals, activity in negatively-weighted brain regions during ENC-recog events was positively correlated with pRecog scores and activity in these regions during RET-source was negatively correlated with pSource scores. Positively-weighted brain regions included right thalamus, right supramarginal gyrus and left insula (Table 7). Negatively-weighted brain regions included bilateral occipito-temporal cortices, uncus, caudate, and anterior-medial PFC, as well as left parahippocampal gyrus. Therefore, in –*APOE4* individuals, activity in a traditional episodic memory network (negatively-weighted brain regions) during encoding predicted subsequent object-only retrieval (i.e., source failures), and less activation in these regions at retrieval predicted better source performance.

Individuals with +*APOE4* genotype exhibited the opposite pattern of brain activity-behavior correlations to –*APOE4* individuals at encoding, particularly for encoding of subsequently recognized objects, and did not exhibit significant brain-behavior correlations at retrieval. Specifically, in +*APOE4* individuals, activity within right thalamus, right supramarginal gyrus, and left insula during ENC-recog and ENC-source correlated with better subsequent memory for both event types. In contrast, encoding activity in more traditional episodic memory-related areas (negatively-weighted regions) was negatively correlated with subsequent memory in these adults.

Taken together these results indicate that individuals with +*APOE4* versus –*APOE4* genotype engaged distinct patterns of brain activity at encoding to support subsequent memory. In addition, –*APOE4* adults appeared to exhibit an encoding/retrieval flip in the regions supporting memory.

Post-hoc regions of interest (ROI) analyses

We investigated activation profiles for the ROI displaying the highest peaks during encoding in our B-PLS analysis and consistent with our TPLS results (Fig. 6). Multivariate general linear models evaluating group differences in ROI activation, averaged across lags 2–5, indicated no significant group differences during ENC-source or ENC-recog.
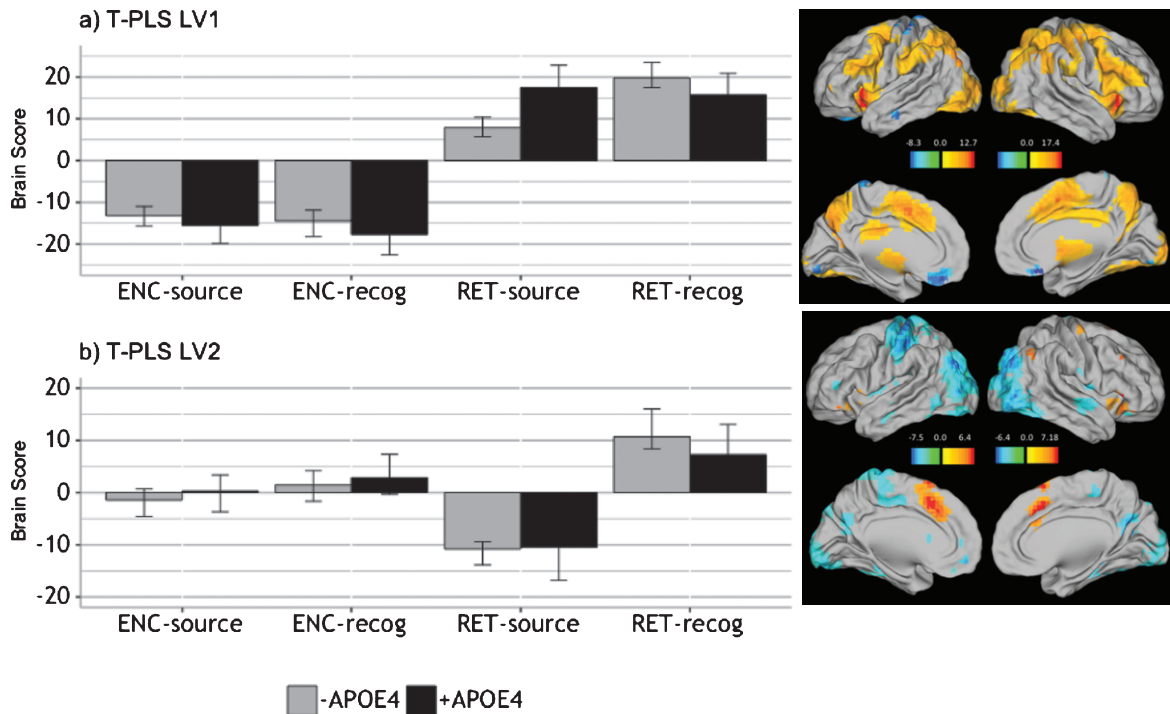
Fig. 4. Design salience plot and singular image representing brain activity patterns by condition for (a) LV1 and (b) LV2, revealed by the T-PLS analysis. LEFT: Error bars on design salience plots represent 95% confidence intervals. Positive brain scores indicate conditions in which activity was greater in positive brain salience regions (shown in red in the singular images) and vice versa. Negative brain scores indicate conditions in which activity was greater in negative brain salience regions (shown in red in the singular images) and vice versa. RIGHT: Singular images were thresholded at a bootstrap ratio of ± 3.5, $p < 0.001$. Red brain regions represent positive brain saliences; blue regions represent negative brain saliences. Activations are presented on template images of the lateral and medial surfaces of the left and right hemispheres of the brain using Caret software (http://brainvis.wustl.edu/wiki/index.php/Caret:Download).

DISCUSSION

The PREVENT-AD study aimed to identify signs of AD pathogenesis in pre-symptomatic older adults with elevated risk of developing late-onset sporadic AD [37]. Because neural changes may occur decades before the onset of clinical AD symptoms [8, 9], PREVENT-AD used sensitive biomarkers such as brain imaging, biochemistry, metabolic, and cognitive measures to explore characteristic changes during disease progression. The PREVENT-AD cohort study directly addressed several shortcomings of previous investigations of prodromal AD [57], including use of sufficiently large sample size, appropriate sample composition (e.g., older adults with family history of AD who may be in an early, pre-symptomatic phase of the disease), longitudinal design, and comprehensive cognitive and biological outcomes. Furthermore, whereas previous studies of AD have often included population samples with mixed family history, here we were able to account

for this potential confound by studying a cohort who all had family history of AD.

Here we drew on baseline data from the PREVENT-AD cohort to examine the potential influence of having an *APOE4* allele on episodic memory function, over and above the influence of family history. Moreover, few studies have assessed the relationship between *APOE4* and brain activity from the whole-brain perspective. Instead studies have often used univariate approaches and focused on specific regions or networks of interest (i.e., the medial temporal lobe system) that are implicated in AD pathology [58–62]. These studies have contributed significantly to our understanding of memory-related dysfunction in preclinical samples with the *APOE4* risk factor for AD. The current study aimed to expand on this extant literature by using a data-driven multivariate approach, PLS, to compare brain activity related to episodic memory encoding and retrieval between –*APOE4* and +*APOE4* individuals with family history of AD. In addition, contrary to previous

Table 5
Local maxima revealed for LV1 of the T-PLS analysis. We report only lags 2–5, and clusters with a spatial threshold of at least 10 continuous voxels

Temporal lag	Bootstrap ratio	Spatial extent (voxels)	Talairach coordinates			Gyral location	Brodmann area
			X	Y	Z		
Positive Salience Regions							
Right Hemisphere							
2,3,4,5	17.42	6781	25	21	3	Claustrum	45
2	10.23	225	13	−56	17	Posterior Cingulate	23
5	9.29	162	2	−74	48	Precuneus	7
4	8.06	63	10	−6	4	Thalamus	
5	7.68	75	39	−59	46	Inferior Parietal Lobule/Precueus	7
4	7.19	33	6	−91	−11	Lingual Gyrus	18
2	7.16	19	6	13	42	Cingulate Gyrus	32
2	7.01	32	35	−83	29	Superior Occipital Gyrus	19
4	6.61	14	29	53	24	Superior Frontal Gyrus	10
Left Hemisphere							
4	12.69	2183	−13	−73	40	Precuneus	7
3	12.20	495	−20	−91	−5	Lingual Gyrus	17
2,4	10.48	253	−9	13	45	Medial Frontal Gyrus	32
2	10.12	94	−39	−79	29	Superior Occipital Gyrus	19
4	10.04	98	−30	18	−2	Claustrum	
2,3,4	8.79	123	−46	14	34	Middle Frontal Gyrus	9
4	8.68	74	−5	−30	27	Posterior Cingulate	23
2	7.64	38	−5	−23	27	Cingulate Gyrus	23
4	7.29	25	−16	−8	−4	Lentiform Nucleus	Medial Globus Pallidus
4	6.98	20	−31	−88	3	Middle Occipital Gyrus	18
3	6.63	9	−1	−24	−41		
Negative Salience Regions							
Right Hemisphere							
5	−7.23	61	21	−92	3	Lingual Gyrus	17
Left Hemisphere							
3,4	−8.27	58	−1	30	−11	Medial Frontal	11
3	−7.91	23	−60	−11	−19	Inferior Temporal Gyrus	20
2,3	−7.67	139	−39	−34	62	Postcentral Gyrus	2
2,5	−7.48	80	−35	−27	66	Precentral Gyrus	4
5	−7.15	28	−4	26	−15	Medial Frontal Gyrus	11
2	−6.73	5	−64	−10	9	Superior Temporal Gyrus	22
5	−6.34	12	−46	−84	−4	Inferior Occipital Gyrus	19

studies focusing primarily on recognition/novelty, we employed a novel episodic memory task distinguishing object-location source association from recognition via a single response.

Few behavioral group differences

Overall, we found that both –*APOE4* and +*APOE4* individuals performed well on neuropsychological tests and the fMRI episodic memory task. This result aligns with previous studies that have shown no significant behavioral differences in cognitive performance on the basis of *APOE4* status in younger [63] and healthy older adults of similar demographic background [64]. These behavioral findings also echo our previous work, in which we found no effect of *APOE4* on episodic memory in middle-aged adults

at risk of AD using a similar task ([29] but see [57, 65] for evidence of *APOE4* effects on memory in mid-adulthood).

Interestingly, we observed a significant group difference in MoCA scores in the current study, with +*APOE4* individuals scoring higher than –*APOE4* individuals, on average. Given the high sensitivity of the MoCA for detecting mild cognitive impairment [66], lower MoCA performance among the –*APOE4* group may support theories suggesting that carrying an *APOE4* allele may paradoxically benefit cognitive function in early and midlife [67]. However, the majority of participants in both groups scored well above the MoCA score cutoff of 26, which is argued by some to be overly conservative even in highly educated older adults [68]. This suggests that most participants in both groups had good cognitive

Table 6
Local maxima revealed for LV2 of the T-PLS analysis. We report only lags 2–5, and clusters with a spatial threshold of at least 10 continuous voxels

Temporal lag	Bootstrap ratio	Spatial extent (voxels)	Talairach coordinates			Gyral location	Brodmann area
			X	Y	Z		
Positive Salience Regions							
Right Hemisphere							
4,5	7.18	306	2	17	42	Cingulate Gyrus	32
4, 5	5.87	127	40	21	0	Inferior Frontal Gyrus	47
5	4.75	39	46	–62	42	Inferior Parietal Lobule	40
4,5	4.55	32	32	–15	61	Precentral Gyrus	6
Left Hemisphere							
3,4	6.39	160	–45	17	2	Inferior Frontal Gyrus	47
5	4.84	113	–45	33	–8	Inferior Frontal Gyrus	47
Negative Salience Regions							
Right Hemisphere							
3,4,5	–6.37	127	14	23	18	Caudate	
2	–5.96	192	28	–77	37	Precuneus	19
2,3,4	–5.37	82	51	–8	–6	Superior Temporal Gyrus	22
2	–5.40	332	43	–69	–2	Inferior Temporal Gyrus	37
2	–4.86	100	47	–3	12	Insula	13
3	–4.79	35	54	–10	44	Postcentral Gyrus	3
4	–4.78	24	32	–35	–6	Hippocampus	
2,5	–4.05	53	29	–30	–20	Parahippocampal Gyrus	36,37
2	–3.91	19	13	–12	36	Cingulate Gyrus	24
Left Hemisphere							
2,3,4	–7.54	953	–35	–30	62	Precentral Gyrus	4
3	–7.34	2294	–31	–79	22	Middle Occipital Gyrus	19
2	–6.62	1747	–39	–32	47	Inferior Parietal Lobule	40
3,5	–6.23	175	–20	24	13	Caudate	
4	–5.99	493	–23	32	3		
3	–5.43	70	–60	–12	–5	Middle Temporal Gyrus	21
5	–5.03	74	21	–44	15		5
5	–4.85	35	–17	–42	65	Postcentral Gyrus	5
2,4,5	–4.79	29	–38	–34	–10	Parahippocampal Gyrus	36
2	–4.50	95	29	32	4		
2	–4.32	16	–16	43	12	Medial Frontal Gyrus	10
2	–4.31	11	–56	–7	–15	Inferior Temporal Gyrus	20
2,5	–4.07	10	–19	–6	–29	Uncus	36
5	–4.01	10	–31	–73	0	Lingual Gyrus	18
2	–3.94	22	–12	–21	13	Thalamus	

performance, at least as indicated by the MoCA. In addition, evidence suggests a greater effect of *APOE4* in women compared to men [69]; this effect may have been masked in the current study, as most of our participants were women. Moreover, both *+APOE4* and *–APOE4* individuals in this study were relatively young compared to other studies of AD, with median ages of 61 and 62 years (sometimes referred to as "young-old"), respectively. Notably, participants were an estimated 9–10 years away from anticipated symptom onset. This stage may therefore have been too early to detect detrimental changes in cognitive performance on the basis of *APOE4*, at least at the group level [70].

We expected comparable episodic memory performance in both groups due to the lack of clinical symptoms in our sample. As predicted, we observed

no significant effect of *+APOE4* on episodic memory performance. Across both groups, participants were more likely to recollect the object-location association (54%) than recognize the object only (i.e., fail to remember the source; 18%). Nevertheless, we observed a non-significant trend whereby *–APOE4* individuals had a greater number of FA and fewer correct rejections, as well as low response discriminability (i.e., negative d', pSource, and pRecog values) and a bias towards selecting "old" (i.e., negative c value); this was not true of the *+APOE4* group. Importantly, our task demanded that participants reflect on their memory of a presented object (or lack thereof) and respond in a single four-choice step. Therefore, during each retrieval trial where participants recognized an object as "old", participants likely attempted to recall the object-location
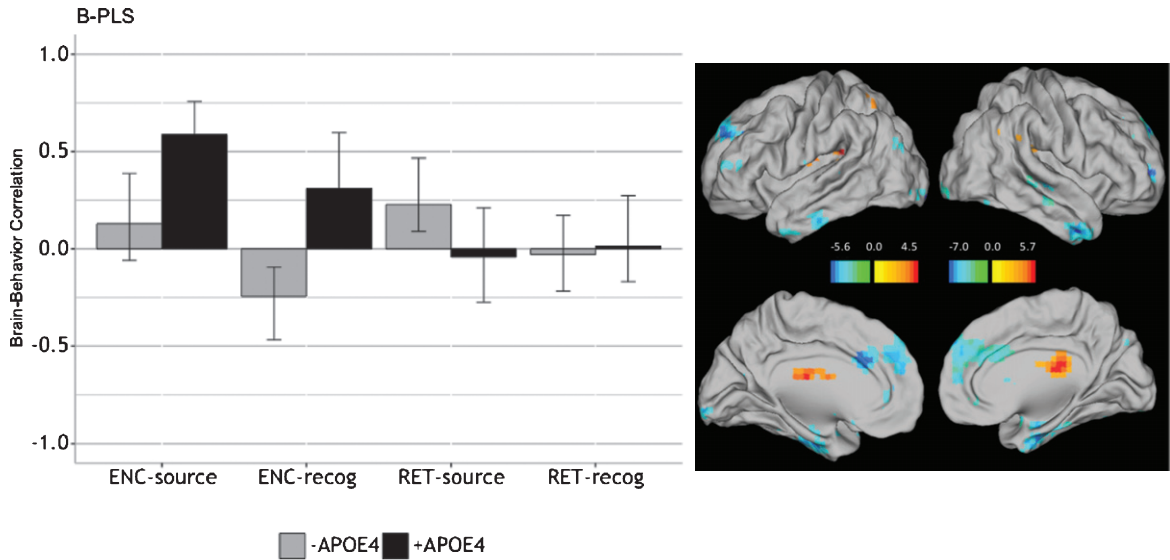
Fig. 5. Correlations between brain activity and task performance by condition, revealed by the B-PLS analysis. LEFT: Bars represent brain-behavior correlations for each group, by condition. Positive correlations indicate conditions in which performance was positively associated with activity in positive brain salience regions (shown in red in the singular images) and vice-versa. Negative correlations indicate conditions in which performance was positively associated with activity in negative brain salience regions (shown in blue in the singular images) and vice-versa. Error bars represent 95% confidence intervals. RIGHT: The singular image thresholded at a bootstrap ratio of ± 3.5, $p < 0.001$. Red brain regions represent positive brain saliences; blue regions represent negative brain saliences. Activations are presented on template images of the lateral and medial surfaces of the left and right hemispheres of the brain using Caret software (http://brainvis.wustl.edu/wiki/index.php/Caret:Download).

Table 7
Local maxima revealed by the B-PLS analysis. We report only lags 2–5, and clusters with a spatial threshold of at least 10 continuous voxels

Temporal lag	Bootstrap ratio	Spatial extent (voxels)	Talairach coordinates			Gyral location	Brodmann area
			X	Y	Z		
Positive Salience Regions							
Right Hemisphere							
3, 5	5.69	63	58	−53	29	Supramarginal Gyrus	39,40
3	5.46	319	6	−26	20	Thalamus	
Left Hemisphere							
3	4.50	17	−38	−33	19	Insula	13
Negative Salience Regions							
Right Hemisphere							
2,3,5	−7.02	442	6	48	38	Medial Frontal Gyrus	6,8,10
2	−5.28	42	44	5	−27	Middle Temporal Gyrus	21
3,4,5	−5.16	155	22	−2	−28	Uncus	28,36, Amygdala
3	−4.96	47	14	17	6	Caudate	Caudate Body
5	−4.84	12	43	−31	−2	Superior Temporal Gyrus	22
5	−4.22	34	21	−87	−11	Middle Occipital Gyrus	18
Left Hemisphere							
3	−5.61	50	−16	13	16	Caudate	Caudate Body
3,5	−5.44	143	−34	−14	−27	Uncus	20,28
2	−4.86	23	−20	25	35	Middle Frontal Gyrus	8
5	−4.71	18	−53	−18	−24	Fusiform Gyrus	20
3	−4.39	14	−9	−90	−12	Lingual Gyrus	18
3	−4.35	64	−23	34	22	Medial Frontal Gyrus	9
3	−4.33	16	−2	15	67	Superior Frontal Gyrus	6
3	−3.97	11	−41	13	−31	Superior Temporal Gyrus	38
3	−3.89	13	43	−39	−2		
2	−3.78	10	−27	−46	−1	Parahippocampal Gyrus	19
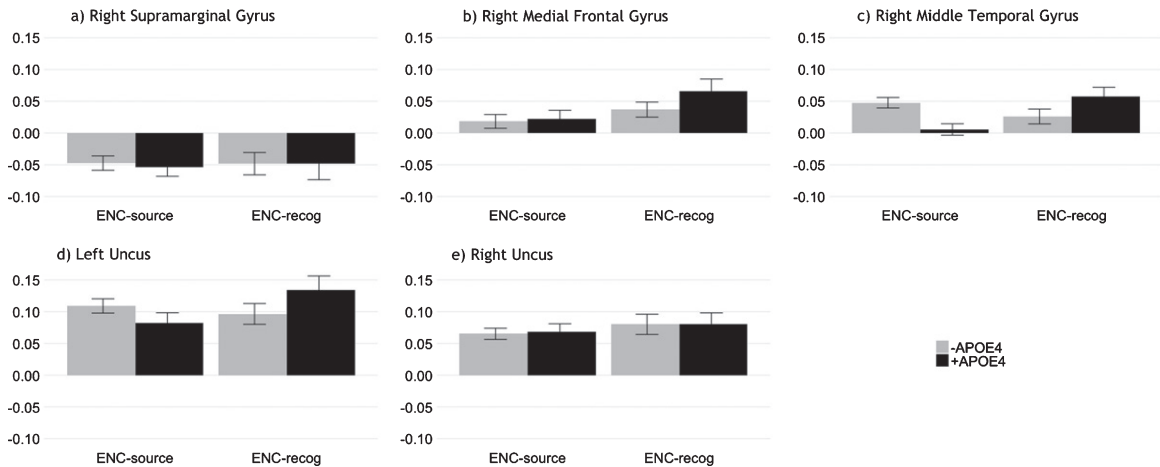
Fig. 6. Mean activation across lags 2–5 at encoding for ROI identified via B-PLS. The plots show similar activation patterns for both *APOE4* groups during episodic encoding, supporting our T-PLS results. Error bars represent 95% confidence intervals.

source association first, selecting that the object was simply familiar only if they failed to recall its contextual information. Supporting this interpretation, participants had longer RT during both trials where participants correctly recognized objects but failed to recall the source and where participants misidentified new objects as old (i.e., FA). Conversely, successfully encoded object-location source associations, as well as correct rejections, were identified much more rapidly. These behavioral patterns suggest that recognition trials in the present task reflect objects for which participants could not retrieve source information (i.e., source failures; see also our discussion of task activation and brain-behavior correlations below), with slightly better discriminability in +*APOE4* individuals.

Few group differences in task activation patterns

Results from our mean-centered T-PLS analysis support the effectiveness of our task in selectively isolating episodic memory encoding versus retrieval (LV1) and object recognition versus source recollection (LV2). Furthermore, counter to our hypothesis, T-PLS revealed group similarities in task-related activation during episodic encoding and retrieval, as well as for object recognition versus source recollection.

Specifically, T-PLS LV1 demonstrated that individuals in both *APOE4* groups activated the ventromedial frontal and temporal cortices more during encoding, compared to retrieval. In contrast, both groups activated the frontal and parietal cor-

tices more during retrieval, compared to encoding. These results align with previous reports of increased activation in left-lateralized medial prefrontal, middle and inferior temporal, as well as primary and secondary sensory cortices (e.g., prefrontal and ventral occipito-temporal areas) for encoding objects and their location; and increased activation in broad bilateral areas including the precuneus, parietal, and medial prefrontal cortices during episodic retrieval in older adults [71, 72]. Prefrontal activity during encoding appears to correlate with successful recall in older adults [71], and may reflect greater strategic elaboration of episodic memories in older age [73].

Similarly, T-PLS LV2 indicated that, in both *APOE4* groups, there was greater activity in the bilateral caudate, precuneus, and temporal cortices, as well as left parahippocampal gyrus and right hippocampus during object-location source retrieval, compared object recognition. This result is consistent with prior studies that have also reported increased activity in similar brain regions during successful encoding of contextual information [71], and overlap with areas of the "core recollection network" [74]. Notably, some studies have observed greater task-related fMRI activity in posterior parahippocampal cortex during familiarity-based retrieval, compared to recollection [75]. Yet, others have noted the importance of the posterior parahippocampal region in the *encoding* of spatial context or source encoding [76]. The current findings suggest that posterior parahippocampal cortex is more active during the retrieval of object-location associations, compared to recog-

nition, and is engaged during the retrieval of spatial contextual details.

We also found greater activity in the bilateral middle and medial prefrontal cortices, angular gyrus, and inferior parietal lobule in both *APOE4* groups during object recognition, compared to spatial source retrieval. This is surprising as fronto-parietal activity is often greater during source retrieval, compared to object retrieval, and thought to reflect the greater engagement of cognitive control processes [28, 77]. However, our findings suggest greater cognitive control demands during object recognition, compared to source retrieval, in the present task. The reversed pattern observed here may reflect the nature of our task design. Because the task required participants to select a single response indexing their memory of a presented object, trials in which participants indicated recognition without object-location associations may have reflected their *failure to recall contextual information*. This may have led to activation of fronto-parietal regions involved in cognitive control processes necessary for memory search, inhibition, and response selection [78], despite failed source recall. Our behavioral results support this interpretation: we observed longer RT during both recognition and FA trials compared to source retrieval. This suggests that participants searched for object-location source association but, in both cases, failed to retrieve the correct information.

Drawing on objective measures of source recall and recognition, our results extend previous findings, which have been largely identified using the traditional "remember versus know" paradigm that often relies on subjective report and may be less sensitive to the effects of age on episodic memory [79]. Our results further indicate partial indices of pathological memory-related brain activity in older adults at higher risk of AD: on the one hand, similar to healthy older adults, participants in the present study demonstrated activation of parahippocampal cortices during encoding of novel stimuli [24]. However, similar to high performing individuals with early dementia [80], our participants demonstrated greater prefrontal and temporal activation during episodic encoding and broad activation in areas affected by AD, including the claustrum, precuneus, inferior parietal, and middle and medial frontal cortices, during retrieval, suggesting possible preclinical indices of pathological aging.

Contrary to our hypothesis, our findings related to performance and task-related activation (i.e., T-PLS) support studies suggesting no measurable distinction in episodic memory performance and underlying brain function based on *APOE4* status. Although *APOE4* is linked with impaired memory, cognition, and functional activity, more rapid cognitive decline, and hippocampal atrophy in clinical populations (e.g., mild cognitive impairment and AD) and preclinical states such as subjective memory decline [81–83], effects in asymptomatic older adults are less clear. Studies have shown an association between *APOE4* and accelerated memory decline later in life [70] as well as altered structure and function in medial temporal lobe circuitry [84, 85]. Moreover, using verbal episodic memory tasks, previous studies have shown greater activation of areas affected in AD (e.g., dorsolateral prefrontal cortex and superior temporal gyrus) during episodic retrieval in young adults with at higher genetic risk of AD [86]. However, although *APOE4* is the strongest genetic risk factor for late-onset AD [87], presence of the allele does not appear to be a significant independent predictor of AD [57, 88]. One possible explanation for this discrepancy is family history, which may mediate *APOE4* effects on memory and related brain activity. Thus, the independent influence of *APOE4* may be moderated when accounting for family history, as we were able to do here. In addition, lifestyle choices (e.g., higher education level, moderate alcohol consumption) may mitigate *APOE4* effects and contribute to discrepant reports of its influence on cognitive aging [64]. Although an investigation of lifestyle factors was beyond the scope of this study, high education among both *APOE4* groups, coupled with our participants' heightened awareness of dementia risk due to their family history and eagerness to engage in stimulating activities such as PREVENT-AD, may at least partly explain our lack of observed group differences in behavior and task-related fMRI.

APOE4-based differences in brain-behavior correlations

In contrast to our performance and T-PLS results, and supporting our hypothesis, our B-PLS analysis indicated group differences in correlations between brain activity at encoding and subsequent memory performance. These differences were most pronounced for subsequently recognized objects, where successful recognition performance correlated with encoding-related activity in bilateral medial and middle frontal cortices, temporal areas, uncus, and caudate, as well as left parahippocampus in *APOE4* non-carriers, compared to right inferior frontal, superior temporal, and supramarginal cortices, as well as

the left precuneus, claustrum, and insula in +*APOE4* individuals. We also found differential reliance on brain activity supporting retrieval of object-location source associations in *APOE4* carriers versus non-carriers. Whereas performance correlated negatively with activity in regions typically associated with source recollection (e.g., bilateral occipito-temporal cortices, uncus, caudate, and anterior-medial PFC, as well as left parahippocampal gyrus) in non-carriers, this correlation was positive in *APOE4* carriers. Notably, we found few group differences in correlations between performance and brain activity during encoding of source memory (ENC-source), or recognition of objects in the absence of source recall (RET-recog).

In summary, we found that, when factoring out family history, +*APOE4* and −*APOE4* individuals exhibit similar brain activity patterns during episodic encoding and retrieval of both source and object information, but draw on different brain regions to perform the task. In particular, our results support our hypothesis that group differences in brain activity would emerge for object recognition and suggest that source recall compared to object recognition may associate with different neural substrates in −*APOE4* versus +*APOE4*.

These patterns may reflect a difference in approach taken by *APOE4* carriers and non-carriers to complete the task. For example, mnemonic strategy training appears to improve performance on face-name associative memory tasks and further correlate with increased frontoparietal activity in older adults with amnesic mild cognitive impairment [89, 90]. We did not assess strategy use in the present study and were therefore unable to test this possibility directly. However, because task instructions did not direct participants to use any particular approach or strategy, and based on the lack of behavioral differences, this seems unlikely to explain the observed findings.

An alternative possibility is that participants here demonstrated a survival effect. Despite comparable levels of education and EYO, and after accounting for age differences, +*APOE4* individuals had comparable or slightly better performance on the neuropsychological tests and episodic memory task. The activation patterns and brain-behavior correlations in +*APOE4* older adults may therefore support, rather than compensate for, memory performance. In this case, our results may indicate that when considering family history, +*APOE4* may lead to altered neural substrates supporting memory performance but, on its own, does not contribute meaningfully to behavioral

deficits. Performance benefits in +*APOE4* individuals were nevertheless small and did not remain when evaluating performance in each group across age.

Given that participants were nearly 10 years away from estimated symptom onset, on average, the observed group differences in performance-related neural substrates may indicate that +*APOE4* individuals were in a transitory period with respect to AD development. Supporting this possibility, we observed a non-significant trend whereby younger *APOE4* carriers tended to recognize objects on the episodic memory task better than younger non-carriers, and a reversed pattern in older participants. Interestingly, we found increased activity in right frontal regions in +*APOE4* individuals, in the absence of behavioral deficits and marginally better episodic memory performance. This may reflect compensatory neural recruitment of frontal regions in response to decreased performance-related activity in medial temporal regions and grey matter volume loss in critical memory areas, i.e., the hippocampus [91, 92]. Indeed, an earlier study of the PREVENT-AD cohort revealed lower hippocampal subfield volumes, extra-hippocampal white matter integrity, and cognitive performance in individuals with high tau and low amyloid-beta levels in the cerebrospinal fluid, of which nearly all were +*APOE4* [31]. Moreover, compared to the −*APOE4* individuals, the +*APOE4* individuals in this study exhibited cerebrospinal fluid biomarker levels consistent with early signs of AD pathology, despite a lack of clinical symptomatology or indices of cognitive decline. Similarly, recent work in a larger sample of older adults who participated in PREVENT-AD suggests morphometric changes in medial prefrontal regions in +*APOE4*, compared to −*APOE4* cohorts [93]. Together these observations are consistent with our interpretation that increased performance-related activity in frontal regions in +*APOE4* individuals may reflect functional compensation.

Limitations and future directions

Despite the relatively large number of older adults who participated in the PREVENT-AD study, we excluded many from the present analyses based on genetic composition, performance, and quality of MRI scans. Thus, different patterns may have emerged with a larger sample. However, our results are largely consistent with the previous literature on cognitive performance and task-related brain activity in −*APOE4* versus +*APOE4* individuals. In addi-

tion, here we focused on task-related activity on successful trials because of an insufficient number of unsuccessful trials (i.e., false alarms and misses). Analyzing such trials, when possible, may provide greater insights into the mechanisms underlying changes in episodic memory function with elevated age and AD risk, as has previously been shown for recognition memory in healthy aging [94]. Such analyses should represent a greater focus in future research. Similarly, the present study aimed to examine brain activation patterns associated with a single encoding and retrieval phase, carried out over a relatively short interval. However, using a comparable paradigm, researchers have identified that activity in distinct areas, including posteromedial areas at encoding and frontal areas at retrieval, supports durable memories that last over the course of weeks [95]. Such time course likely reflects a more representative period over which memories form and consolidate over the long term, and may serve as important regions of interest in future investigations, particularly of pathological aging. Finally, the present results reflect only the baseline data from a longitudinal cohort; our future analyses will integrate these findings with performance and memory-related brain activity from follow-up assessments.

Conclusions

Here we examined the relationship between memory performance and brain activity based on *APOE4* carrier status in older adults with family history of AD. We found different correlations between brain activity and subsequent memory performance in *APOE4* carriers compared to non-carriers, despite similar neuropsychological and episodic memory performance as well as task-related activation during episodic encoding and retrieval for both recognized objects and recalled object-location associations. Consistent with our hypothesis, this difference in brain-behavior relationships was particularly prominent for recognition, compared to source memory. Together, our results suggest that both *APOE4* carriers and non-carriers recruit brain regions expected to be active during encoding and retrieval of object recognition and object-location associations in older adults; however, *APOE4* status may influence the way in which brain regions that subserve episodic memory encoding support recognition performance. Moreover, our activation-related findings, coupled with performance outcomes, highlight the importance of task considerations in interpreting processes under-

lying source recall and suggest that recognition may represent a failure of source retrieval.

Our findings are consistent with our previous work on the influence of *APOE4* on brain activity in middle-aged adults at risk of AD [29] and are the first to identify recognition-related differences in brain-behavior relationships in asymptomatic older adults at risk of AD. These findings add a nuanced perspective to the study of neural processes associated with recollection and familiarity as well as the role of *APOE4* on brain-behavior relationships in asymptomatic older adults with family history of AD, which remains poorly characterized [57]. Future research should further investigate the lifespan effects of *APOE4* on neurocognitive processes and the potential to distinguish risk of AD development based on genetic composure, behavior, and associated patterns of brain activity.

AUTHOR CONTRIBUTIONS

Data creation was a collaborative effort from the PREVENT-AD Research Group, with contributions from MELM and support from JB. SR and MNR

analyzed and interpreted the data with help from SR and SP. SR wrote the manuscript with contributions from EY and MNR. All authors provided feedback and approved the final version of the manuscript.

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