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Family history and APOE4 risk for Alzheimer's Disease impact the neural correlates of episodic memory by early midlife

Running Title: Altered brain activity in middle-aged adults at risk of AD

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Abstract

Episodic memory impairment is a consistent, pronounced deficit in pre-clinical stages of late-onset Alzheimer's disease (AD). Individuals with risk factors for AD exhibit altered brain function several decades prior to the onset of AD-related symptoms. In the current event-related fMRI study of spatial context memory we tested the hypothesis that middle-aged adults (MA; 40-58yrs) with a family history of late onset AD (MA_{+FH}), or a combined +FH and apolipoprotein E ε4 allele risk factors for AD ($MA_{+FH+APOE4}$), will exhibit differences in encoding and retrieval-related brain activity , compared to –FH –APOE4 MA controls. We also hypothesized that the two at-risk MA groups will exhibit distinct patterns of correlation between brain activity and memory performance, compared to controls. To test these hypotheses we conducted multivariate task, and behavior, partial least squares analysis of fMRI data obtained during successful context encoding and retrieval. Our results indicate that even though there were no significant group differences in context memory performance, there were significant differences in brain activity and brain-behavior correlations involving hippocampus, left angular gyrus, cingulate, and precuneus in MA with AD risk factors, compared to controls. In addition, we observed that brain activity and brain-behavior correlations in anterior-medial PFC and in ventral visual cortex differentiated the two MA risk groups from each other, and from $MA_{controls}$. This is the first study to show that there are differences in the brain areas engaged during context memory encoding and retrieval in middle-aged adults with +FH and +APOE-4 risk factors for late onset AD, compared to controls.

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1. Introduction

Aging is associated with episodic memory decline: a reduced ability to encode, store and retrieve information about past events (recognition memory) in rich spatial and temporal contextual detail (context memory)[1-4]. These deficits negatively impact older adults' quality of life [5] and can be an early sign of late-onset Alzheimer's disease (AD)[6-9]. One promising way to support healthy brain aging and memory function into late life and prevent/delay AD onset is early identification of episodic memory decline in adults at risk of developing AD, and early intervention to prevent/delay further decline. To achieve these goals it is important to identify when episodic memory decline arises in adulthood, and determine how known risk factors for AD, e.g. having a family history of AD (+FH) or having an apolipoprotein E □4 allele (+APOE4), alter memory and brain function at this critical time.

Recent studies of healthy adults show that episodic memory decline can be detected by early midlife (40 – 58 yrs) when memory is assessed using spatial context memory tasks [10-12]. In contrast, item recognition memory remains intact in early midlife[13]. This suggests that spatial context memory tasks are sensitive to detecting early episodic memory decline in healthy adults. Spatial context memory tasks require subjects to form item-location associations. As such, they are a type of associative memory task and place greater demands on recollection processes compared to item recognition tasks[14]. Neuroimaging studies of healthy young adults indicate that recollection of spatial contextual details relies on the activation of a distributed network of brain regions that include the medial temporal lobe (MTL), prefrontal cortex (PFC) and inferior parietal cortex (IPC) [15-18]. Recently, we have examined the functional brain differences associated with context memory decline in middle-aged adults[12]. We reported that differences in ventrolateral prefrontal cortex (VLPFC) function at encoding and in ventral occipito-temporal cortex at retrieval negatively impacted memory performance in middle-aged adults, compared to young adults, and may reflect functional decline at midlife. In addition, middle-aged adults (MA) also exhibited increased activity in anterior-lateral PFC

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at retrieval, compared to young adults, which correlated with better memory performance (potentially a mechanism for functional compensation).

Taken together, these findings indicate that associative context memory tasks are more powerful than item recognition tasks at detecting behavioral and brain differences in episodic memory at early midlife. Thus**,** fMRI studies of context memory can help us detect brain differences in *early* MA at risk of AD, compared to controls, which may be indicative of early pathological brain changes within the episodic memory system. Yet, to our knowledge, no fMRI study of associative context memory has been conducted in MA at-risk of AD. However, fMRI studies of item recognition in MA with AD risk factors have reported functional differences in brain regions in the MTL [19-22], inferior parietal cortex [23, 24], prefrontal cortex [25], and posterior midline cortex [21, 26]. However, the results are varied. For example, some of these studies report reduced brain activity in hippocampus and other areas, in at-risk groups vs. controls [19, 27, 28]; others report increased activity [20, 21]. Moreover, it is unclear whether these results were directly linked to altered memory performance in MA with vs. without AD risk factors.

The goal of the current study was to understand the impact of having AD risk factors on the functional neural correlates of spatial context memory encoding and retrieval in early midlife (ages 40 – 58). To this aim, we conducted an event-related fMRI study in which the following middle-aged adult (MA) groups were scanned while performing spatial context encoding and retrieval tasks: 1) -FH, -APOE4 MA ($MA_{controls}$), 2) +FH, -APOE4 MA (MA_{+FH}), and 3) +FH, +APOE4 MA ($MA_{+FH+APOE4}$). We hypothesized that having +FH or combined +FH, +APOE4 risk factors for AD would be related to differences in event-related activity in the hippocampus/parahippocampal gyrus [21, 29], and other brain areas associated with recollection-related processing that are also implicated in the AD, i.e. inferior parietal cortex and PFC. To test these hypotheses we used multivariate "task" partial least squares analysis (T-PLS), a powerful method that allows one to identify whole-brain patterns of activity which maximally account for the co-variance between event-related brain activity and the

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experimental design [30]. We also hypothesized that having +FH and/or combined +FH, +APOE4 risk factors for AD would alter the correlation between brain activity in the aforementioned areas, and behavior. To test this hypothesis we used behavior-PLS. The current study is novel in that it is the first to use a spatial context memory tasks and multivariate PLS methods to assess functional brain differences in recollection-related brain activity at encoding *and* retrieval across at early middle-aged adults with +FH and with combined +FH, +APOE4, compared to controls.

2. Materials and Methods

2.1. Subjects

Fifty-one middle aged adults (MA; age range 41-58 yrs, mean age = 50.69 yrs, 40 females [10 menopausal, 4 on hormone replacement therapy]) were recruited using newspaper and online advertisements in Montreal, Canada. All subjects were healthy at the time of testing and had no history of neurological or psychiatric illness. All subjects were right-handed as measured by the Edinburgh Inventory for Handedness [31]. The study was approved by the Institutional Review Board of the Faculty of Medicine, McGill University, and all subjects provided informed consent to undergo neuropsychological testing, fMRI testing and to have their blood drawn for APOE genotyping.

2.1.1. Neuropsychological assessment and exclusionary criteria

We administered the following battery of neuropsychological tests to screen out individuals suffering from psychiatric symptoms and cognitive impairment, and to obtain measures of memory and language function: Mini Mental Status Exam [MMSE, exclusion cut-off score < 27, [32]] the Beck Depression Inventory (BDI) [inclusion cut-of < 15 [33]], the American National Adult Reading Test (NART) [inclusion cut-off $\leq$ 2.5 SD for age and education [34]]. Additional medical exclusion criteria included having a history of mental health or substance abuse issues, neurological insult resulting a loss of conscious > 5 min, diabetes, having untreated cataracts and glaucoma, smoking > 40 cigarettes a day; and having a current diagnosis of high cholesterol levels and/or high blood pressure left untreated in the past six months. All subjects who participated in the fMRI scanning session met these cut-off

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criteria. In addition, the California Verbal Learning Task (CVLT) was administered to assess item memory.

2.1.2. Definitions of risk factors

Having a family history of late onset sporadic AD (+FH) was defined using the criteria used in the Cache County study [35, 36]: having a first degree relative, living or deceased, with a probable or confirmed diagnosis of AD. Having no family history of AD (–FH) was defined as the absence of first and second degree relatives with AD type dementia[36]. For APOE genotyping, genomic DNA was extracted from whole blood using the FlexiGene DNA kit from Qiagen (Qiagen, Ontario, Canada). Samples were genotyped with Sequenom iPLEX Gold Assay technology at Genome Quebec Innovation Centre (Quebec, Canada, [37]). APOE genotype results were used to stratify participants into three risk groups based on family history and genotype combination: no family history with APOE□□3/3 genotype ($MA_{controls}$), family history with APOE □3/3 (MA_{+FH}), and family history with APOE □3/4 ($MA_{+FH+APOE4}$ 4).

2.2. Experimental Protocol

2.2.1. Cognitive activation task

Subjects performed easy and difficult versions of spatial context memory tasks while undergoing blood-oxygen-level-dependent (BOLD) fMRI scanning. Scans were obtained during encoding and retrieval. E-Prime (Psychology Software Tools, Inc.; Pittsburgh, PA, USA) was used to present memory tasks and collect behavioural data (accuracy and reaction time)

Spatial context encoding

Subjects were shown black and white photographs of human faces, presented one at a time on either the left or right side of a monitor, for 2 sec each, with a variable inter-trial interval (ITI) of 2.2 – 8.8 sec (mean ITI 5.13 sec) . Subjects were instructed to rate whether the face was pleasant/neutral using a button press, and to encode the spatial location (left/right) in which the face was presented. During easy spatial context memory tasks (SE) subjects encoded six face stimuli, and during hard

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spatial context memory asks (SH) subjects encoded 12 face stimuli. Subjects were aware at encoding that their memory for spatial location would be tested following a 1 min break. During the break subjects performed a verbal alphabetizing distractor task to prevent rehearsal of face stimuli, and to ensure retrieval involved long-term, episodic memory processes. There were 12 blocks of SE encoding blocks and 6 blocks of SH encoding tasks. There were 72 encoding stimuli per task.

Spatial context retrieval

Subjects were presented with two previously encoded face stimuli for 6 sec, with variable ITI (as stated above), and were asked to select which face was originally presented on the left (or the right) side of the screen at encoding using a button press, depending on the retrieval cue. Thus, subjects had to recollect the spatial location of the encoded face to perform the task above chance. There were 12 SE retrieval blocks and 6 SH retrieval blocks. There were 36 retrieval stimuli per task.

2.2.2. Behavioral Data Analysis

SPSS for Windows (version 17.0) was used to conduct between group one-way ANOVAs on demographic and neuropsychological variables to ensure groups were matched on age, education, and neuropsychological tests. In addition, 3 (group: $MA_{controls}$; MA_{+FH}; $MA_{+FH+APOE4}$) x 2 (event-type: SE, SH) repeated measures ANOVAs were conducted to examine group main effects, task main effects and group*task interactions in spatial context memory accuracy (% correct) and reaction time (RT; msec) during easy and hard task versions (significance threshold $p < 0.05$). Post-hoc Tukey's tests were conducted on the group variable to clarify any significant group main effects and interaction effects.

2.3. MRI Data Acquisition

Structural and functional magnetic resonance images were acquired using a 3T Siemens Trio scanner, located at the Douglas Brain Imaging Centre. Subjects lay supine in the scanner wearing a standard head coil. T1-weighted structural images were acquired at the beginning of the fMRI session using a 3D gradient echo MPRAGE sequence (acquisition time: 5 min, 3sec; TR=2300 msec TE=2.98 msec, flip angle=9 degrees, 176 1mm saggital slices, 1 x 1 x 1 mm voxels, FOV=256mm2). BOLD

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images were acquired using a single-shot T2*-weighted gradient echo-planar imaging (EPI) pulse sequence (TR=2000ms, TE=30ms, FOV=256mm2, matrix size=64 x 64, in-plane resolution 4 x4 mm, 32 oblique 4mm slices with no slice gap) while participants performed the memory tasks. A mixed rapid event-related design was used with variable ITI (as stated above) to add jitter to the event-related acquisitions.

Visual task stimuli were generated on a computer using E-Prime (described above) and were 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. A fiber-optic 4-button response box was used by subjects to make task-related responses.

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2.4. MRI Data Analysis

2.4.1. Functional MRI Analysis

Preprocessing

Images were reconstructed from raw (k-space), converted to ANALYZE format, and preprocessed using Statistical Parametric Mapping (SPM) version 8 software (http://www.fil.ion.ucl.ac.uk/spm) run with MATLAB (www.mathworks.com) on a Linux platform. Images acquired during the first 10 sec of scanning were removed from analysis to ensure all tissue had reached steady state magnetization. All functional images were realigned to the first image and corrected for movement artifacts using a 6 parameter rigid body spatial transform and a least squares approach. If a subject had more than 4mm movement, they were discarded from analysis. Functional images were then spatially normalized to the MNI EPI-template (available in SPM) at $4mm^3$ voxel resolution, and smoothed using an 8mm full-width half-maximum (FWHM) isotropic Gaussian kernel. ArtRepair toolbox for SPM8 was used to correct for bad slices prior to realignment and for bad volumes after normalization and smoothing (http://cibsr.stanford.edu/ tools/human-brain-project/artrepair-software.html).

Multivariate fMRI Data Analysis

Spatio-temporal Partial Least Squares (PLS) was used to conducted event-related fMRI data analysis using PLSGUI software (https://www.rotman-baycrest.on.ca/index.php?section=84). Mean centered T-PLS was used to examine group similarities and differences in patterns of whole brain activity related to encoding and retrieval during SE and SH tasks [30]. B-PLS was used to examine group similarities and differences in patterns of whole brain activity *that were directly correlated to* SE and SH retrieval accuracy. Details on these methods have been published elsewhere [38, 39]. For both T-PLS and B-PLS analyses, fMRI analysis was restricted to successful context encoding and retrieval events. The event-related fMRI data corresponding to each event-onset (time lag =0) and subsequent seven TRs/time lags (TR = 2 sec * 7 = 14 sec) for successfully encoded (eSE, eSH) and successfully

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retrieved (rSE and rSH) events were stacked by subject within group to create a between group fMRI data matrix. All subjects analyzed had a minimum of 18 correct events per event type (mean # of correct events for SE task = 30 within each group; and for SH task = 29 for $MA_{controls}$ MA_{+FH} and 30 for $MA_{+FH+APOE4}$).

In T-PLS, this fMRI data matrix was mean centered, column-wise, within each event type, and underwent singular value decomposition (svd). SVD yields a set of mutually orthogonal latent variables (LVs) in descending order of the magnitude of covariance explained. The number of LVs produced is equivalent to the number of event/task types included in the analysis * the number of groups; in this analysis there were 12 (4 event-types * 3 groups). Each mean centered T-PLS LV consists of: i) a singular value, reflecting the amount of covariance accounted for by the LV, ii) design salience, representing the event-related contrast effect identified by the LV, and iii) a singular image (s.i.) representing the corresponding pattern of brain saliences, which are numerical weights assigned to each voxel at each TR/time lag included in the data matrix, and identify a pattern of whole brain activity symmetrically related to the design salience. Brain saliences can be negative or positive. Brain regions with positive voxel saliences are positively related to the effect identified by the design salience, and those with negative voxel saliences are negatively related to this effect. Thus the relationship between the singular image and design salience is symmetrical.

In B-PLS, the between group fMRI data matrix was correlated with a behavioral vector containing the mean retrieval accuracy for SE and SH tasks (% correct spatial context retrieval), stacked in the same order as the data matrix (subject within group). SVD of this cross-correlation matrix was conducted to yield a series of LVs. The output is similar to the T-PLS output, but instead of design saliences, the B-PLS analysis yields: i) a singular value, ii) a singular image consisting of positive and negative brain saliences, and iii) *a correlation profile* depicting how subjects' retrieval accuracy correlates with the pattern of whole brain activity identified in the singular image. The correlation profile and voxel saliences represent a symmetrical pairing of i) brain-behavior correlation

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patterns for each group to ii) a pattern of whole 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.

Significance testing of LVs identified from the T-PLS and B-PLS was conducted using permutation tests ($p < 0.05$, 1000 permutations) on the singular values. In addition, the stability of each voxel's contribution to a LV was assessed with bootstrapping (bootstrap ratio = ±3.5, $P < 0.001$, 500 iterations; minimum cluster size = 10). Significant stable peaks that are identified with bootstrapping are presented in the singular image as positive or negative brain saliences reflect regions that are maximally stable and significant across subjects. The bootstrap ratio (BSR) of a significant voxel salience reflects the stability of its activation. In addition, to determine at which time lags the task differences in a given LV were strongest, we also computed temporal brain scores for each task in each significant LV. Temporal brain scores represent the degree to which each subject expresses the pattern of brain activity identified by the s.i., in relation to its paired design salience (T-PLS)/correlation profile (B-PLS), at each time lag. The temporal brain score can be used to indicate at which time lag the LV effect is maximally differentiated within the temporal window sampled (McIntosh et al., 2004). We used this temporal score to identify the subset of time lags which maximally represented the effects of interest, and only report activations from those time lags [40, 41]. In the current analyses the peak time lags were lags 2 – 5 (4 – 10 sec post event-onset). Peak coordinates are only reported from these time lags at which task differences were maximal. These peak coordinates were converted to Talairach space using the icbm2tal transform (Lancaster et al. 2007) as implemented in GingerAle 2.3 (Eickhoff et al. 2009). Since our acquisition incompletely acquired the cerebellum, peak coordinates from this region are not reported. The Talairach and Tournoux atlas (1988) was used to identify the Brodmann area (BA) localizations of significant activations.

3. Results

3.1. Demographics and Behavioral Results

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Of the 51 MA tested, 26 were identified as $MA_{controls}$ (-FH, -APOE4); 14 MA were MA_{+FH} (-APOE4); and 11 were $MA_{+FH+APOE4}$. Table 1 presents the demographic, neuropsychological and behavioral data from the fMRI tasks for each group. There were no significant group differences in any of the demographic or neuropsychological variables. The group (3) x task (2) repeated measures ANOVA for retrieval accuracy (% correct) revealed no significant effects, although there was a trend towards there being a task main effect ($p = 0.10$) due to accuracy on SH tasks being lower than on SE tasks. The group (3) x task (2) repeated measures ANOVA for reaction time (RT, msec) revealed a significant task main effect ($F_{1,48}=12.85$, $p < 0.001$, SH RT slower than SE), but no other main effects or interactions. Therefore, the three groups were matched on task performance, and retrieval performance on SH tasks was worse than retrieval performance on SE tasks.

3.2. FMRI Results

We conducted two multivariate analyses to determine whether there were : 1) group differences in event-related *activity* (Task PLS) and 2) group differences in brain activity-retrieval performance *correlationi* (Behavior PLS). These two analyses are complementary and results from both analyses need to be considered together in order to understand how having specific risk factors for AD impact brain activity in a behaviorally relevant manner. In the following sections we describe the Task and Behavior PLS results separately. In the Discussion we focus on regions consistently identified across PLS methods to help clarify their roles in context memory encoding and retrieval in MA with vs. without AD risk factors.

3.2.1. Task PLS Results

The mean centered T-PLS analysis identified three significant LVs. The first two LVs identified group similarities in task-related brain activity. T-PLS LV1 (accounted for 45.95% cross-block covariance) and identified brain regions that were differentially activated during successful context encoding vs. retrieval in all three groups. Positive salience brain regions were more active during retrieval, compared to encoding, across all groups. Negative salience brain regions were more active

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during encoding, compared to retrieval, across all groups. T-PLS LV2 (accounted for 14.44% cross-block covariance) identified brain regions that were differentially activated during SH encoding, compared to SE encoding in all three groups. Positive salience regions were more active during SH encoding, compared to SE encoding. Negative salience brain regions were more active during SE encoding, compared to SH encoding. The local maxima from these two LVs are presented in Tables 2 and 3.

T-PLS LV3 (accounted for 12.81% cross-block covariance) identified a complex three-way interaction between group*task*phase (encoding/retrieval). This LV was of primary interest in this study, since it identified group differences in brain activity. Figures 1A and 1B present the design salience plot and singular image for this LV. Table 4 presents the local maxima identified by T-PLS LV3. Positive brain salience regions from Table 4 were generally more active during encoding, compared to retrieval, in $MA_{controls}$ and MA_{+FH}. These regions included left angular gyrus, precuneus, and cingulate gyrus. Interestingly, these same regions were more active during SE retrieval, compared to SE encoding, in $MA_{+FH+APOE4}$. Negative brain salience regions reflected the opposite effect. These regions were more active during retrieval, compared to encoding, in $MA_{controls}$ and MA_{+FH}. In contrast these same regions were more active during SE encoding, compared to SE retrieval in $MA_{+FH+APOE4}$. Negative salience brain regions included bilateral fusiform cortices.

3.2.2. B-PLS Results

The B-PLS analysis identified two significant LVs. Figure 2A presents the singular image and the corresponding bar graph depicting the brain activity-behavior correlation profile for B-PLS LV1, which accounted for 32.36% of the cross-block covariance. Table 5 lists the local maxima from this LV. Most of the peaks identified were positive brain saliences. In general, there was a positive correlation between encoding activity in positive salience brain regions and subsequent retrieval accuracy across groups. However in $MA_{controls,}$ this effect was only significant during SH encoding events; in MA_{+FH} subjects this effect was only significant during SE encoding events; and in

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$MA_{+FH+APOE4}$ subjects this was observed for both SE and SH encoding events. At retrieval, activity in these same regions during SE events was positively correlated with memory performance in MA_{+FH}, but activity in these regions during SE and SH retrieval was negatively correlated with memory performance in $MA_{+FH+APOE4}$. Therefore, LV1 identified brain regions in which: i) encoding activity was correlated with better subsequent retrieval in $MA_{controls}$; ii) encoding and retrieval activity during SE memory tasks was positively correlated with memory performance in MA_{+FH}; and iii) there was phase-related difference between activity and memory performance correlations in $MA_{+FH+APOE4}$. Positive salience brain regions identified in this LV included medial precuneus, bilateral inferior parietal cortex, anterior-medial prefrontal cortex and cingulate, and hippocampus.

B-PLS LV 2 accounted for 17.94% of the cross-block covariance and identified group differences in brain activity – behavior correlations between MA_{+FH} vs. $MA_{+FH+APOE4}$ groups. This LV identified the effect of having +APOE4 status within the context of having a family history of AD on brain-behavior correlation. Figure 2B presents the singular image and corresponding bar graph depicting the behavior-brain correlation profile for this LV. Table 6 lists the local maxima from this LV. Positive brain saliences listed in Table 6 represent areas in which there was: i) a positive correlation between encoding and retrieval activity and memory performance in the $MA_{+FH+APOE4}$ group, and ii) a negative correlation between encoding activity and subsequent retrieval accuracy in the MA_{+FH} group. These regions primarily included bilateral occipto-temporal cortices and right ventrolateral prefrontal cortex. Negative brain salience regions represent the inverse effect and were regions in which encoding activity was positively correlated with subsequent retrieval in MA_{+FH} subjects, but in which encoding and retrieval activity was negatively correlated with memory performance in $MA_{+FH+APOE4}$ subjects. These regions included primarily anterior medial prefrontal cortex.

3.2.3. Post-hoc ROI-based analysis of medial temporal lobe regions identified in PLS analyses

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One of our a priori hypotheses was that there would be group differences in hippocampal/parahippocampal activation during spatial context encoding/retrieval. T-PLS LV2 identified two peaks in right hippocampus that were similarly activated during easy > hard encoding across all groups. B-PLS LV1 also identified a region in left hippocampus. To explore if there were between group differences in hippocampal activation we examined group differences in event-related activity within the three hippocampal ROIs identified in T-PLS LV2 and B-PLS LV1 (marked with asterisks in Table 3 and 5). This was done by extracting the mean percent signal difference for a 4mm cubic region surrounding each ROI using the multiple voxel extraction option in PLSGUI, calculating the mean activity for the ROIs for lags 2 – 5, for each ROI within each subject, and then conducting post-hoc group (3) x event-type (2) x phase (2) repeated measures ANOVAs (significance assessed at $p<0.05$, corrected).

The post-hoc analysis indicated there was a significant group x task interaction in activity of the right hippocampal ROI (x=40 mm, y =-15 mm, z = -18 mm; $F_{2,48}=4.73$, p<.05det) identified from T-PLS LV2. Figure 1B presents the adjusted mean % signal differences in right hippocampus across all events, for each group. To clarify this interaction effect, between-group one-way ANOVAs of ROI activity during eSE, eSH, rSE and rSH, respectively, with post-hoc comparisons on the group variable, were conducted. These one-way ANOVAs indicated there were group differences in encoding activity during eSE events, and no other events. $M_{controls}$ activated right hippocampus to lesser degree than $MA_{+FH+APOE4}$ subjects ($p<0.05$). MA_{+FH} subjects' activation of this region fell midway between the two other groups. In addition, we conducted within phase (encoding, retrieval) x task (SE, SH) group repeated measures ANOVAs of this right hippocampal ROI. These ANOVAs indicated that there was no significant task-related, or phase-related, modulation of right hippocampal activity in either $MA_{controls}$ or MA_{+FH} groups. However, in $MA_{+FH+APOE4}$ there was a significant task main effect in right hippocampal activation ($p<0.05$) and a trend towards a significant phase x task interaction ($p =0.09$).

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Therefore, the group x task interaction was driven by a task-related difference in right hippocampal activation during encoding in $MA_{+FH+APOE4}$.

4. Discussion

The goal of this study was to use novel multivariate PLS methods to assess functional brain differences in recollection-related brain activity during the encoding *and* retrieval of spatial contextual details in early middle-aged adults with +FH, and combined +FH, +APOE4, risk factors for late-onset AD, compared to controls. Our behavioral results show there were no significant group differences in spatial context memory ability. However, in a previous study in which we compared spatial context memory in –FH young adults and –FH MA, we found that there were behavioral deficits on these same tasks in MA vs. young adults (Kwon et al., 2016). Therefore, having risk factors for AD did not impact the level of recollection-based spatial context memory decline at midlife, beyond the effect of age.

The fMRI analyses indicate that even though there were no significant group differences in behavioral performance, there were significant group differences in event-related activity, and in brain activity-memory performance correlations. Group differences in activity and brain-behavior correlations were most apparent in hippocampus, inferior parietal cortex, anterior medial prefrontal cortex (PFC) and fusiform cortex. However, despite these differences, there was also considerable overlap in the pattern of brain activity during encoding and retrieval observed across groups. This was highlighted by the group similarities identified by Task PLS LV1 and 2. We will discuss the group similarities and differences in brain activity and brain-behavior correlation in detail in the following sections.

4.1. Group similarities in brain activity

4.1.1. Group similarities at encoding

The T-PLS results indicated that overall, all three MA groups exhibited similar brain activation patterns during recollection-related encoding vs. retrieval (T-PLS LV1), and as a factor of task difficulty during encoding (T-PLS LV2). Successful encoding of spatial contextual details was

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associated with increased activity in a distributed set of brain regions including: bilateral occipito-temporal cortices, left VLPFC, and bilateral anterior-medial PFC in all three groups, compared to successful contextual retrieval. These results are consistent with prior studies of face encoding which have also report increased activity in VLPFC and bilateral occipito-temporal cortices [42-45].

T-PLS LV2 indicated there was increased right hippocampal activation during easy > hard encoding across all groups. We also observed a positive correlation between encoding activity in left hippocampus and subsequent retrieval in all three groups (B-PLS LV1). Therefore, hippocampal activity at encoding was related to successful subsequent retrieval in all three groups. This result is consistent with a large body of literature highlighting the importance of the hippocampus in the episodic memory and in encoding of contextual features [46-49].

Despite this overall group similarity in hippocampal activity, as identified by multivariate PLS; our post-hoc univariate analyses indicated there were subtle group differences in right hippocampal activation. Specifically, $MA_{+FH+APOE4}$ subjects exhibited greater activity in right hippocampus during easy spatial context encoding events compared to other event-types, and the level of activity they exhibited was significantly greater than that observed in $MA_{controls}$. MA subjects with only a +FH risk factor exhibited activation levels in right hippocampus during easy spatial context encoding that were midway between $MA_{controls}$ and $MA_{+FH+APOE4}$ subjects. Therefore, our univariate analysis indicated that MA with risk factors for AD over-activated the hippocampus during easy spatial context encoding, compared to MA controls.

This finding is in contrast to Trivedi et al (2006) who reported MA with +FH and +APOE4 AD risk factors exhibited less activity in hippocampus compared to MA with only the +FH risk factor or neither risk factors (controls). However, Trivedi et al (2006) tested adults who were on average older than our sample [19]. Given that hippocampal activity has been shown to decrease with age during episodic encoding; it is possible that the difference between our current results and Trivedi et al. is due to the differing age of the groups tested. This interpretation is consistent with the observation that our

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findings are more similar to those reported by Filippini et al (2009) and Dennis et al (2010) who reported increased hippocampal activation at encoding in *young* +APOE4 carriers [50, 51]. In fact, Filippini et al (2011) showed that there may be interaction between age and APOE4 impact on hippocampal activity [28]. Thus, testing on average younger (40-58yrs, in this study) vs. older (40-65, Trivedi et al (2006)) MAs may impact the pattern of hippocampal activation observed.

Our current results also indicate that the increased hippocampal activity observed in MA with AD risk factors, compared to controls, supported memory encoding [27, 50, 52, 53]. This interpretation is consistent with the fact that B-PLS LV1 identified a positive correlation between encoding activity in hippocampus and subsequent memory in all three groups, and that all groups performed better on spatial easy vs. spatial hard context memory tasks. These findings support the hypothesis that over-recruitment of hippocampal activity in MA at risk of AD reflects a compensatory response [54-56], possibly to underlying neural inefficiency [57]. In other words, given that: 1) hippocampal activity at encoding was correlated with subsequent memory; and, 2) there were no group differences in memory performance in the current study; suggests that over-recruitment of hippocampus in MA with AD risk factors compared to controls reflected "successful" compensation in the current study.

4.1.2. Group similarities at retrieval

Successful recollection of spatial contextual detail was related to greater activation in bilateral dorsal VLPFC, right DLPFC, left dorsal inferior parietal cortex and bilateral fusiform cortex, compared to encoding. This pattern of retrieval-related activation is consistent with prior studies of episodic retrieval of faces [43, 58, 59]. Retrieval activity in fusiform cortex is consistent with the idea that successful recollection requires the re-activation of stimulus-related brain regions engaged at encoding [60]. Greater activity in left dorsal inferior parietal cortex during successful retrieval, compared to encoding, is consistent with the hypothesis that this region is involved in top-down attentional processing of mnemonic stimuli and retrieval success [61]; and greater right lateral PFC activation at

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retrieval, relative to encoding, is consistent with hemispheric encoding-retrieval asymmetry model [62]. Therefore, the patterns of brain activation related to spatial context encoding and retrieval for face stimuli are consistent with previous studies. Given that these patterns were observed across all three group, this indicates that having +FH or +FH and +APOE4 risk factors for AD at midlife did not impact the overall function of episodic memory encoding and retrieval systems.

4.2. Group differences in brain activity and/or in brain activity-behavior correlations

T-PLS LV3 identified group differences in task-related activity in a variety of brain regions including: inferior parietal cortex, cingulate gyrus, precuneus and ventral fusiform cortices. Importantly, these activations overlapped with areas identified in the B-PLS results. In addition, there were activations identified in the B-PLS results (i.e. medial PFC), which overlapped with activations in T-PLS LV1, which highlight group similarities in encoding vs. retrieval activity. In the following subsections we discuss brain regions than were identified in both T-PLS and B-PLS results in the aim to better understand how AD risk factors impact both activity and brain-behavior associations at midlife.

4.2.1. Overlap in regions identified in T-PLS LV3 and B-PLS LV1

Bilateral inferior parietal cortex, cingulate gyrus and precuneus were positive salience areas from T-PLS LV3. This indicates these regions were more active during encoding, compared to retrieval, in $MA_{controls}$ and MA_{+FH} subjects, and were more active during the SE retrieval, compared to SE encoding, in $MA_{+FH+APOE4}$ subjects. These brain regions were also positive salience areas in B-PLS LV1. Thus, in $MA_{controls}$, greater encoding activity in these brain regions was positively correlated with subsequent recollection, particularly during SH events (see Figure 2a). In MA_{+FH} subjects, encoding activity in these regions was positively correlated with subsequent recollection of SE events, but reduced retrieval activity in these regions, as indicated by the T-PLS results, was negatively correlated with recollection of SE events. Therefore, the pattern of activation observed in this subset of brain regions supported successful encoding, but not successful retrieval for MA_{+FH} subjects.

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In $MA_{+FH+APOE4}$ subjects the pattern of event-related activity observed in bilateral inferior parietal, cingulate gyrus and precuneus was not beneficial to their task performance. Specifically, the B-PLS LV1 correlation profile (Figure 2a) indicates that increased encoding activity and decreased retrieval activity in these areas was positively correlated with memory performance for this group. However, the Task PLS result (Figure 1b) shows that this group exhibited the opposite pattern of activation in these brain regions: increased activity during retrieval, and decreased activity during encoding of SE events. Taken together these results indicate that there may be a progressive difference in brain activity and brain-behavior correlations involving the left angular gyrus, cingulate gyrus, and precuneus going in MA_{+FH} and $MA_{+FH+APOE4}$, compared to controls.

Interestingly, inferior parietal, cingulate gyrus and precuneus are key nodes of the default mode network (DMN), which is a functionally connected set of brain regions found to be more active during baseline vs. task conditions in fMRI studies [63-65]. Several studies have reported differences in DMN activity and functional connectivity in MCI, AD, and in healthy adults with risk factors for AD [66-70]. The fact that we observed memory-related activations in inferior parietal, cingulate and precuneus, is not surprising since previous studies have noted the overlap in brain activation patterns during autobiographical/episodic memory processing and resting state [71-74]. It has been hypothesized that these regions may be involved in the attentional processing and integration of one's experience, which occurs both during rest and episodic memory task performance [61, 74-76]. Although, in the current study we did not observe overt behavioral deficits in MA with AD risk factors, compared to controls; the current B-PLS results suggest that there may be subtle, differences in inferior parietal, cingulate and precuneus function in both MA groups with AD risk factors, compared to controls, which was negatively related to their memory performance. This suggests that having a family history of AD may alter the function of these brain regions at midlife, since this risk factor was common to both MA risk groups.

4.2.2. Overlap in regions identified in T-PLS LV3 and B-PLS LV2

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T-PLS LV3 identified significant group differences in bilateral fusiform cortex activation. More specifically, these regions were more active during retrieval, compared to encoding in $MA_{controls}$ and MA_{+FH} subjects. In contrast, these regions were more active during SE encoding, compared to SE retrieva, in $MA_{+FH+APOE4}$ subjects (see Figure 1). These brain regions were also positive salience areas in B-PLS LV2 (see Figure 2B). Taken together, these results indicate MA_{+FH} adults showed decreased activity in fusiform cortex at encoding compared to retrieval, and this was positively related to subsequent retrieval in this group. $MA_{+FH+APOE4}$ adults showed increased activity in these same regions at encoding compared to retrieval, and this was positively correlated with subsequent retrieval in this group. In contrast, at retrieval, $MA_{+FH+APOE4}$ exhibited decreased fusiform activity, relative to encoding; and this pattern of retrieval activity was negatively correlated to memory performance. MA_{+FH} exhibited increased activity in ventral visual regions at retrieval, compared to encoding, but this was not strongly associated with memory performance.

Overall, the current results show that $MA_{+FH+APOE4}$ differentially activated fusiform cortex and encoding and retrieval compared to MA_{+FH}. However, by combining T-PLS with B-PLS results we see that even though the two MA risk groups displayed distinct activation profiles for these regions, the impact on memory performance was similar across both groups. One speculative interpretation is that these differences in fusiform activity at encoding may reflect the utilization of distinct encoding strategies in each of the two at-risk groups, respectively, to support spatial context encoding. For example, in our prior work on healthy aging using the same paradigm we have reported that successful spatial context memory in young adults was associated with increased activity in fusiform cortex[12, 77]. We interpreted this as reflecting young adults' vivid encoding of perceptual details which supported subsequent memory. Others have also reported that increased ventral visual activity at encoding and retrieval in young adults supported vivid encoding and detailed recollection[78, 79]. This suggests that $MA_{+FH+APOE4}$ adults may be relying on similar perceptual strategies to support spatial context encoding in the current study. In contrast, MA_{+FH} may be using a non-perceptual strategy, i.e.

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socio-affective strategy at encoding – similar to what we have reported in older adults in this same paradigm [12, 77](discussed below). Thus, decreased activity in fusiform cortex at encoding supported their utilization of an non-perceptual strategy. Additional research is needed to determine if altered ventral visual function is consistently observed in adults with both +FH and +APOE4 risk factors and how it relates to memory performance.

4.2.3. Group differences in brain-behavior correlations involving anterior-medial PFC

Anterior-medial PFC was identified as a negative brain salience region in T-PLS LV1 and in B-PLS LV2. T-PLS LV1 identified group similarities in phase-related differences in brain activity at encoding and at retrieval and indicated that all groups exhibited greater activity in anterior-medial PFC at encoding compared to retrieval. B-PLS LV2 indicated that increased encoding activity in anterior-medial PFC was correlated with better subsequent memory performance in MA_{+FH} adults, and poorer subsequent memory performance in $MA_{+FH+APOE4}$ adults. Encoding activity in this region was not significantly correlated with performance in $MA_{controls}$.

Prior fMRI studies of adults with AD risk factors have reported disruptions in the activation and functional connectivity of the anterior-medial PFC [66, 69, 70]. Moreover, generalized increased activity in medial PFC has been observed in AD patients and older adults with mild cognitive impairment compared to controls [52, 80]. The current results indicate that having AD risk factors did not impact the pattern of anterior-medial PFC activity at midlife, but there was an interaction in how +FH and +APOE4 risk factors impacted how anterior-medial PFC activity correlated with memory performance.

In the current study, at encoding, subjects had to make pleasant/neutral judgements for face stimuli while simultaneously encoding the face-location association. Activity in anterior-medial PFC at encoding has been associated with the use of subjective encoding strategies[81, 82]. Thus, our T-PLS results suggest that greater anterior-medial PFC activity at encoding in may reflect subjects' engaging subjective value-based processes to make the pleasantness judgments of face stimuli at

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encoding. Interestingly, our B-PLS results suggest that MA_{+FH} subjects' memory performance benefitted from processing the subjective (pleasantness) aspects of the face stimuli during spatial context encoding. This may reflect a shift in using subjective vs. objective stimulus information to make a retrieval judgment in MA_{+FH}. Similar results have been reported in fMRI studies of episodic memory in healthy older, compared to younger, adults [83-85]. Therefore, MA_{+FH} may be exhibiting this shift in processing preferences at an earlier age, compared to other MA groups; or this may be a group difference in memory processing in general, which is unrelated to aging.

In contrast, $MA_{+FH+APOE4}$ subjects exhibited a negative correlation pattern between anterior-medial PFC activity and memory performance. This correlation pattern is similar to what has been reported in a meta-analysis of subsequent memory effects in healthy young adults [86]. In young adults, activation of anterior-medial PFC during encoding has been associated with poorer subsequent memory when the memory tasks employed required subjects to encode objective stimulus information[86]. This suggests that for MA with both AD risk factors, successful memory performance was related to successful encoding of objective vs. subjective information, similar to what is observed in young adults [83, 84, 87]. This is consistent with the positive correlation observed between ventral visual encoding activity and memory performance in both MA groups with AD risk factors (discussed above).

5. **Conclusions**

The current study identified three key results: 1. There were group differences in activity and brain-behavior correlations in left angular gyrus, cingulate gyrus and precuneus in MA with AD risk factors, compared to controls. This suggests that middle-aged adults with AD risk factors show differences in how these brain regions contribute to spatial context encoding and retrieval, compared to controls. This difference negatively impacted their memory performance. 2. Both MA groups with AD risk factors exhibited greater activation in hippocampus during easy spatial context encoding events compared to $MA_{controls}$, and increased hippocampal activity at encoding was correlated with better subsequent

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memory performance. 3. Activity and brain activity-behavior correlations in anterior-medial PFC and in ventral visual cortex differentiated the two MA risk groups from each other, and from $MA_{controls}$.

Despite the strengths of the current study, there are some caveats to our findings. First, we have relatively small sample sizes for the $MA_{+FH+APOE4}$ risk groups which may affect the generalizability of the current findings. However, the sample size used in the current study is comparable to previously published work [21, 25, 50, 88, 89]. Also, we used multivariate PLS with permutation and bootstrap methods to assess the statistical significance and stability of our fMRI results, which are robust methods that are more amenable for use with smaller sample sizes compared to more traditional univariate fMRI methods [90, 91]. Another caveat is that we did not have a –FH, +APOE4 MA sample, since only a small portion of the general population are +APOE4 [92]. This prevented us from differentiating the unique impacts of +FH vs. +APOE4 risk factors on the neural correlates of spatial context memory further. Nonetheless, the current study advances our understanding of how having +FH only vs combined +FH, +APOE4 AD risk factors alter brain activity and brain-behavior associations at midlife and provides clinically relevant. Our results are of clinical relevance since they APOE4 and FH status interactively impact brain function in anterior-medial PFC and ventral visual cortex; and additively impact brain function in inferior parietal, cingulate, precuneus and hippocampus, at midlife.

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Figure Captions

Figure 1: A) The singular image and B) design salience plot for T-PLS LV3. The singular image is thresholded at a bootstrap ratio of ±3.5, p<0.001. Red brain regions reflect positive brain saliences and blue regions reflect 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). The design salience profile plots the brain scores with 95% confidence intervals (y-axis) for each group for each task-type (x-axis). eSE = encoding, easy spatial context memory tasks; eSH = encoding, hard spatial context memory tasks; rSE = retrieval, easy spatial context memory tasks; rSH = retrieval, hard spatial context memory tasks. The design salience plot for T-PLS LV3 indicates this LV identified a group*task*phase interaction. Positive salience brain regions were more active during encoding > retrieval in MA_{+FH} and $MA_{controls}$; and more activity during easy spatial context retrieval > easy spatial context encoding in $MA_{+FH+APOE4}$. Negative salience brain regions exhibited the inverse pattern of associations. C) ROI Activation Plot for right hippocampus from T-PLS LV2.

Figure 2: A) The singular image at a bootstrap ratio threshold = ±3.5, p<0.001 and the brain-behavior correlation profile with 95% confidence intervals for B-PLS LV1. In the singular image red brain regions reflect positive brain saliences and blue regions reflect 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. The correlation profile indicates that encoding activity in positive salience regions was positively correlated with subsequent retrieval for both task in MA+FH+APOE4 and MAcontrols; and retrieval activity in these same regions was negative correlated with retrieval accuracy on both tasks in $MA_{+FH+APOE4}$. In MA+FH encoding and retrieval activity in positive salience regions during SE tasks was correlated with better performance on this task. Negative salience regions exhibited the inverse pattern of brain-behavior correlations. B) The singular image at a bootstrap ratio threshold = ±3.5, p<0.001 and the brain-behavior correlation profile with 95% confidence intervals for

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B-PLS LV2. The correlation profile indicates that increased encoding and retrieval activity in positive salience regions was positively correlated with memory performance on both tasks in $MA_{+FH+APOE4}$ subjects, and negatively correlated with memory performance on both tasks in MA_{+FH}. Negative salience regions exhibited the inverse pattern of brain-behavior correlations.

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Table 1. Demographics and Behavioral Data

	Middle-aged adults with no family history of dementia (-FH), with APOE e3/3 genotype	Middle-aged adults with a family history of Alzheimer's disease (+FH), with APOE e3/3 genotype	Middle-aged adults with a family history of Alzheimer's disease (+FH), with APOE e3/4 genotype
Sample size (n)	26	14	11
Age (mean ± SE)	49.27 ± 1.13	51.43 ± 1.08	51.91 ± 1.52
Gender (n, [%] female)	21 [81]	10 [71]	9 [82]
Education (years, mean ± SE)	15.46 ± 0.37	15.64 ± 0.43	14.92 ± 0.62
BDI (mean ± SE)	3.85 ± 0.85	4.64 ± 1.33	5.41 ± 1.33
CVLT: delayed free recall (mean ± SE)	12.35 ± 0.46	12.86 ± 0.61	12.64 ± 0.66
CVLT: delayed cued recall (mean ± SE)	13.04 ± 0.41	13.14 ± 0.51	12.73 ± 0.82
CVLT: delayed recognition (mean ± SE)	15.19 ± 0.15	15.07 ± 0.27	14.73 ± 0.56
SE reaction time (msec; mean ± SE)	2467.40 ± 77.36	2485.71 ± 135.01	2566.09 ± 200.67
SH reaction time (msec; mean ± SE)	2578.68 ± 61.55	2649.64 ± 135.36	2672.19 ± 131.08
SE retrieval accuracy (% correct; mean ± SE)	0.86 ± 0.02	0.86 ± 0.03	0.85 ± 0.03
SH retrieval accuracy (% correct; mean ± SE)	0.81 ± 0.03	0.87 ± 0.02	0.83 ± 0.03

Note: This table presents the group means and standard errors (S.E.) for demographic, neuropsychological, and task fMRI behavioral measures. BDI = Beck Depression Inventory; CVLT = California Verbal Learning Task. All CVLT results presented are "hits". There were no significant group differences on these measures.

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Table 2: Task PLS Results - LV 1

Lag	BSR	Spatial Extent	Talairach Coordinates (mm)			Gyral Location	Brodmann Area (BA)
			X	Y	Z		
Positive Saliences: Regions that were more active during retrieval vs. encoding across all groups							
Left Hemisphere							
2,3,4	9.13	76	-31	21	2	Inferior Frontal Gyrus/Insula	BA 47
2,3	5.41	107	-38	-78	14	Middle Occipital Gyrus	BA 19
2	5.23	27	-16	2	8	Putamen	
2	5.09	88	-13	-59	16	Posterior Cingulate	BA 23
3	6.32	806	-5	-10	54	Precentral Gyrus	BA 6
3	5.31	44	-38	11	30	Middle Frontal Gyrus	BA 9/44
3	4.49	14	-12	-1	0	Lentiform Nucleus	
3,4	5.19	69	-31	-80	32	Superior Occipital Gyrus	BA 19
4	5.26	60	-46	-73	0	Inferior Temporal Gyrus	BA 37
4	5.23	32	-38	-52	-16	Fusiform Gyrus	BA 37
4	4.11	32	-42	-35	40	Inferior Parietal Lobule	BA 40
4	4.08	11	-38	-6	10	Insula	
4	4.05	16	-53	-26	19	Postcentral Gyrus	BA 43
Right Hemisphere							
2,3	10.24	114	29	25	0	Insula	
2	5.26	28	14	5	9	Putamen	
2	4.39	57	28	-75	19	Middle Occipital Gyrus	BA 19
3,4	7.48	423	10	-56	21	Posterior Cingulate	BA 30
3	5.41	65	39	10	31	Middle Frontal Gyrus	BA 9/44
4	6.06	143	32	24	4	Inferior Frontal Gyrus	BA 45
5	4.75	59	36	-45	-17	Fusiform Gyrus	BA 37
Negative Saliences: Regions that were more active during encoding vs. retrieval across all groups							
Left Hemisphere							
2	-10.77	925	-27	-99	-2	Cuneus	BA 18
2	-7.99	426	-57	-41	21	Superior Temporal Gyrus	BA 22
2	-6.09	137	-42	22	-5	Inferior Frontal Gyrus	BA 47
2	-5.72	124	-12	48	34	Superior Frontal Gyrus	BA 9
2	-5.49	44	-53	-13	45	Postcentral Gyrus	BA 3
2	-4.24	27	-35	-18	16	Insula	
3,4	-8.02	590	-60	-54	-2	Middle Temporal Gyrus	BA 37
3	-6.97	375	-8	36	4	Anterior Cingulate	BA 24

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3,4,5	-8.22	263	-46	-6	50	Precentral Gyrus	BA 6
4	-4.59	17	-39	17	48	Superior Frontal Gyrus	BA 8
5	-5.15	24	-5	1	51	Medial Frontal Gyrus	BA 6
5	-4.81	36	-31	43	11	Superior Frontal Gyrus	BA 10
Right Hemisphere							
2	-8.45	590	58	-23	25	Postcentral Gyrus	BA 2
2	-6.52	92	51	8	-23	Superior Temporal Gyrus	BA 38
2	-5.44	88	40	45	24	Middle Frontal Gyrus	BA 10
2	-4.06	12	36	-9	-3	Claustrum	
3,4,5	-14.12	1177	3	-87	-8	Lingual Gyrus	BA 17,18
3,4	-7.80	472	55	-23	-8	Middle Temporal Gyrus	BA 21
3,4	-6.23	192	32	20	50	Superior Frontal Gyrus	BA 8
3,4,5	-5.75	18	54	-10	44	Precentral Gyrus	BA 4
3	-4.41	13	40	9	-34	Middle Temporal Gyrus	BA 21,38
4	-6.24	12	50	-48	47	Inferior Parietal Lobule	BA 40
4	-5.28	179	10	32	4	Anterior Cingulate Gyrus	BA 24
5	-5.38	21	25	47	6	Superior Frontal Gyrus	BA 10

Note: Temporal lag represents the time after event onset, when a cluster of voxels exhibited a contrast effect of interest. The bootstrap ratio threshold was set to ±>3.5, and identified dominant and stable activation clusters. The spatial extent refers to the total number of voxels included in the cluster (threshold = 10). Gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988).

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Table 3: Task PLS Results – LV 2

Lag	BSR	Spatial Extent	Talairach Coordinates (mm)			Gyral Location	Brodmann Area (BA)
			X	Y	Z		
Positive Saliences: Regions that were more active during hard vs. easy spatial context encoding							
Left Hemisphere							
3	5.08	33	-53	-60	27	Angular Gyrus	BA 39
5	4.55	13	-12	-81	4	Lingual Gyrus	BA 17
Right Hemisphere							
3	5.04	12	54	-65	31	Angular Gyrus	BA 39
Negative Saliences: Regions that were more active during easy vs. hard spatial context encoding							
Left Hemisphere							
2,3	-10.97	2071	-31	17	5	Inferior Frontal Gyrus	BA 45
2,5	-7.84	463	-9	9	45	Medial Frontal Gyrus	BA 32
2,5	-5.48	68	-31	-50	39	Inferior Parietal Gyrus	BA 40
2,3	-4.98	38	-34	54	16	Superior Frontal Gyrus	BA 10
2	-4.77	13	-35	-85	14	Middle Occipital Gyrus	BA 18
2	-4.09	11	-9	-72	30	Precuneus	BA 31
2	-4.80	33	-1	-34	23	Posterior Cingulate	BA 23
4,5	-5.54	39	-49	-47	3	Middle Temporal Gyrus	BA 21, 37
4	-4.12	14	-9	-17	10	Thalamus	
Right Hemisphere							
2	-5.54	78	13	-60	24	Precuneus	BA 31
2	-4.59	63	36	6	34	Precentral Gyrus	BA 6
2,5	-4.15	11	47	34	26	Middle Frontal Gyrus	BA 46
3	-5.18	30	29	5	-24	Hippocampal Gyrus*	BA 35
3	-4.97	12	40	-15	-18	Hippocampus*	
4	-8.94	4943	6	9	48	Superior Frontal Gyrus	BA 6

Note: Temporal lag represents the time after event onset, when a cluster of voxels exhibited a contrast effect of interest. The bootstrap ratio threshold was set to ±>3.5, and identified dominant and stable activation clusters. The spatial extent refers to the total number of voxels included in the cluster (threshold = 10). Gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988).

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Table 4: Task PLS Results – LV 3

Lag	BSR	Spatial Extent	Talairach Coordinates (mm)			Gyral Location	Brodmann Area (BA)
			X	Y	Z		
Positive Saliences: Regions that were more active during encoding vs. retrieval in MA control and MA+FH groups, but more active during retrieval vs. encoding of SE tasks in MA+FH+APOE4 group							
Left Hemisphere							
2,3, 4	6.33	174	-54	-58	38	Angular Gyrus	BA 40
2	5.26	42	-49	-32	11	Superior Temporal Gyrus	BA 22
2	4.27	21	-9	-23	63	Precentral Gyrus	BA 6
4, 5	4.90	207	-2	-36	48	Precuneus	BA 7
4	4.48	10	-61	-52	20	Superior Temporal Gyrus	BA 22
4,5	4.75	36	-16	10	37	Cingulate Gyrus	BA 24
5	4.66	39	-17	-41	58	Paracentral Lobule	BA 5
Right Hemisphere							
2,3	6.13	56	54	-47	44	Inferior Parietal Lobule	BA 40
2	4.71	20	44	29	-3	Inferior Frontal Gyrus	BA 47
2	4.44	27	20	-25	53	Precentral Gyrus	BA 4
2,3,5	4.64	16	58	-32	2	Middle Temporal Gyrus	BA 21
4	4.24	32	21	-17	43	Cingulate Gyrus	BA 24
5	5.31	112	6	-15	61	Medial Frontal Gyrus	BA 6
5	4.90	19	18	-2	1	Putamen	
5	4.67	35	20	-42	66	Postcentral Gyrus	BA 5
Negative Saliences: Regions that were more active during retrieval vs. encoding in MA controls and MA+FH groups, but more active during encoding vs. retrieval of SE tasks in MA+FH+APOE4 group							
Left Hemisphere							
3	-4.39	18	-42	-75	-14	Fusiform Gyrus	BA 19
4	-4.53	22	-27	-95	-5	Lingual Gyrus	BA 18
Right Hemisphere							
4	-4.77	56	36	-75	-13	Fusiform Gyrus	BA 19

Note: Temporal lag represents the time after event onset, when a cluster of voxels exhibited a contrast effect of interest. The bootstrap ratio threshold was set to ±>3.5, and identified dominant

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and stable activation clusters. The spatial extent refers to the total number of voxels included in the cluster (threshold = 10). Gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988).

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Table 5: Behavior PLS Results – LV 1

Lag	BSR	Spatial Extent	Talairach Coordinates (mm)			Gyral Location	Brodmann Area (BA)
			X	Y	Z		
Positive Saliences: Regions where there was a positive correlation between encoding activity and subsequent memory for all groups, and between retrieval activity during SE and accuracy for MA +FH; and a negative correlation between retrieval activity and retrieval accuracy in MA +FH +APOE4							
Left Hemisphere							
2,3	5.17	54	-13	-17	49	Cingulate Gyrus	BA 24
3	5.48	122	-24	-11	64	Precentral Gyrus	BA 6
3	5.40	14	-45	16	12	Inferior Frontal Gyrus	BA 44
3	4.54	24	-50	-19	27	Postcentral Gyrus	BA 2
3	3.85	11	-35	-48	14	Superior Temporal Gyrus	BA 22
4	5.54	128	-13	-29	55	Medial Frontal Gyrus	BA 6
4	5.43	17	-34	33	0	Inferior Frontal Gyrus	BA 45
4	5.33	44	-42	-47	46	Inferior Parietal Lobule	BA 40
4,5	5.62	29	-57	-56	27	Superior Temporal Gyrus	BA 39
4,5	6.31	1125	-13	-44	47	Precuneus	BA 7
5	5.90	41	-34	-6	-26	Hippocampal Gyrus	BA 35
5	4.52	17	-5	-15	21	Thalamus	
Right Hemisphere							
2	4.89	30	2	-32	41	Cingulate Gyrus	BA 31
3	4.22	10	62	-52	18	Superior Temporal Gyrus	BA 22
3	3.96	22	13	-47	47	Precuneus	BA 7
4	5.75	28	28	-18	53	Precentral Gyrus	BA 4
4	4.56	27	21	20	7	Insula	
4,5	5.12	105	36	-30	24	Inferior Parietal Lobule	BA 40
4,5	4.32	15	58	-50	33	Supramarginal Gyrus	BA 40
5	7.96	93	9	-10	54	Medial Frontal Gyrus	BA 6
5	4.70	35	43	8	17	Inferior Frontal Gyrus	BA 44
5	4.21	11	40	45	24	Middle Frontal Gyrus	BA 10
5	4.02	10	32	25	40	Middle Frontal Gyrus	BA 8
Negative Saliences: Regions where there was a negative correlation between encoding activity and subsequent memory for all groups, and between retrieval activity during SE and accuracy for MA +FH; and a positive correlation between retrieval activity and retrieval accuracy in MA +FH +APOE4							
Left Hemisphere							
3	-5.47	105	-8	14	-5	Caudate	

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5	-6.30	26	-8	45	-10	Medial Frontal Gyrus	BA 10/11
Right Hemisphere							
2	-5.59	10	10	-14	17	Thalamus	

Note: Temporal lag represents the time after event onset, when a cluster of voxels exhibited a contrast effect of interest. The bootstrap ratio threshold was set to ±>3.5, and identified dominant and stable activation clusters. The spatial extent refers to the total number of voxels included in the cluster (threshold = 10). Gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988).

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Table 6: Behavior PLS Results – LV 2

Lag	BSR	Spatial Extent	Talairach Coordinates (mm)			Gyral Location	Brodmann Area (BA)
			X	Y	Z		
Positive Saliences: Regions where there was a positive correlation between encoding and retrieval activity and memory performance in MA +FH +APOE4, and a negative correlation between encoding and retrieval activity and memory performance in MA +FH							
Left Hemisphere							
2	6.60	45	-54	-29	51	Postcentral Gyrus	BA 40
2	5.52	16	-35	-23	66	Precentral Gyrus	BA 6
2	5.23	27	-31	-74	15	Middle Occipital Gyrus	BA 19
2,3,4	5.32	22	-16	-91	-8	Inferior Occipital Gyrus	BA 17
2	4.80	15	-46	-64	-10	Fusiform Gyrus	BA 18/19
2,3	5.03	12	-9	-14	53	Medial Frontal Gyrus	BA 6
3	5.90	66	-54	-32	47	Inferior Parietal Lobule	BA 40
3,5	6.79	75	-49	-49	-12	Fusiform Gyrus	BA 37
3	4.09	13	-31	-11	57	Precentral Gyrus	BA 6
Right Hemisphere							
2,3	6.86	42	43	-61	-4	Middle Occipital Gyrus	BA 19
2,4	5.78	20	28	-85	8	Middle Occipital Gyrus	BA 18,19
2,3	5.73	14	46	-23	61	Postcentral Gyrus	BA 3
3	5.32	25	39	-43	41	Inferior Parietal Lobule	BA 40
3,4	6.80	24	10	-95	-5	Lingual Gyrus	BA 17
3	4.74	11	24	-45	62	Superior Parietal Lobule	BA 7
3	4.11	11	39	2	38	Precentral Gyrus	BA 6
4	5.73	16	29	19	-15	Inferior Frontal Gyrus	BA 47
5	5.67	13	51	-42	-6	Middle Temporal Gyrus	BA 21
Negative Saliences: Regions where there was a negative correlation between encoding and retrieval activity and memory performance in MA +FH +APOE4, and a positive correlation between encoding and retrieval activity and memory performance in MA +FH							
Left Hemisphere							
2	-6.53	31	-31	-39	4	Caudate	
2,3	-5.50	40	-42	-64	26	Middle Temporal/Angular Gyrus	BA 39
3,5	-8.08	354	-9	52	27	Superior Frontal Gyrus	BA 9/10
3	-4.30	11	-9	8	63	Superior Frontal Gyrus	BA 6

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Right Hemisphere

2,5	-6.45	38	10	56	31	Superior Frontal Gyrus	BA 9
3	-6.02	31	44	-2	-31	Middle Temporal Gyrus	BA 21
3	-4.71	15	13	8	59	Superior Frontal Gyrus	BA 6

Note: Temporal lag represents the time after event onset, when a cluster of voxels exhibited a contrast effect of interest. The bootstrap ratio threshold was set to ±>3.5, and identified dominant and stable activation clusters. The spatial extent refers to the total number of voxels included in the cluster (threshold = 10). Gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988).

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Figure 1.

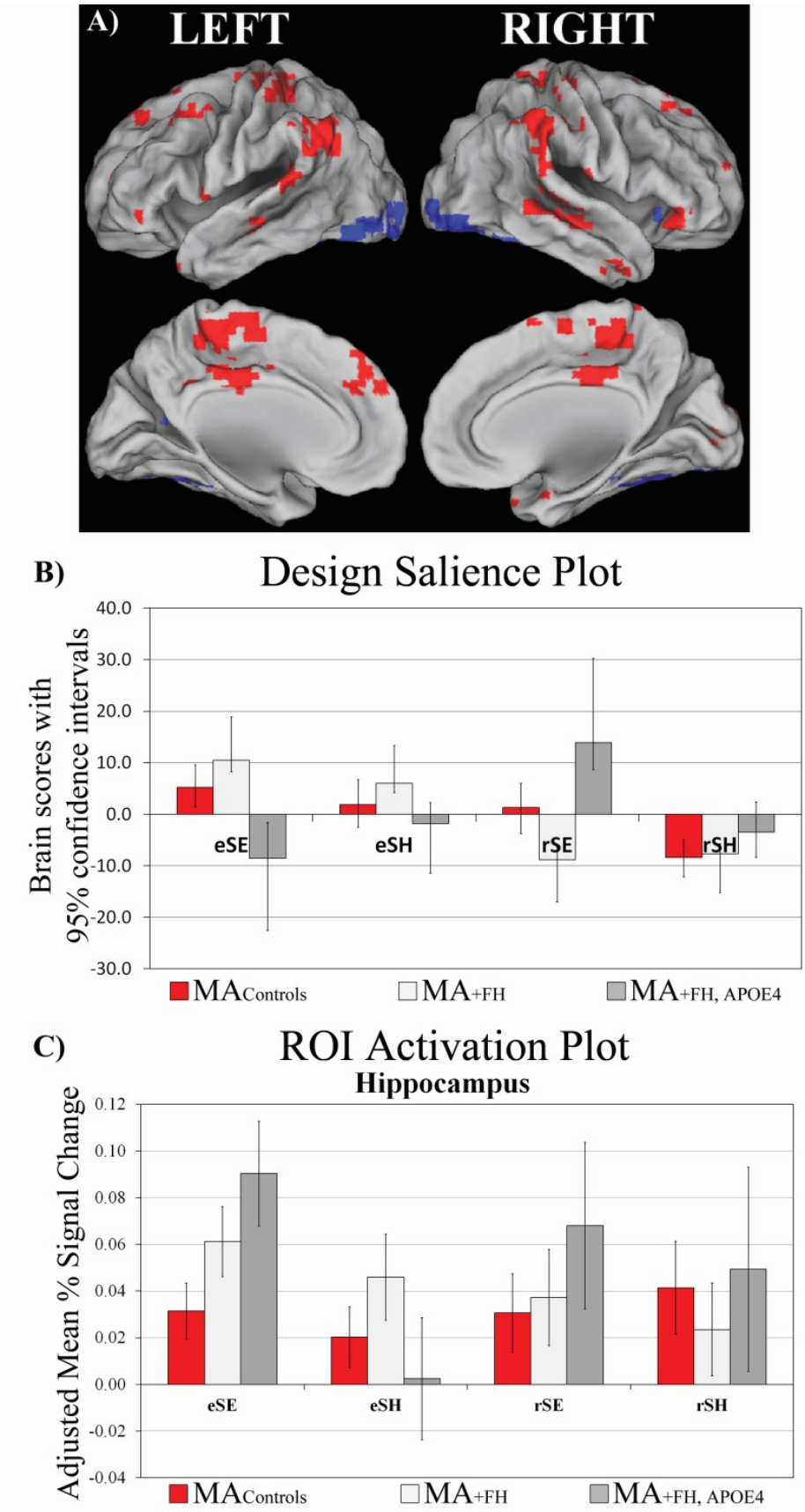
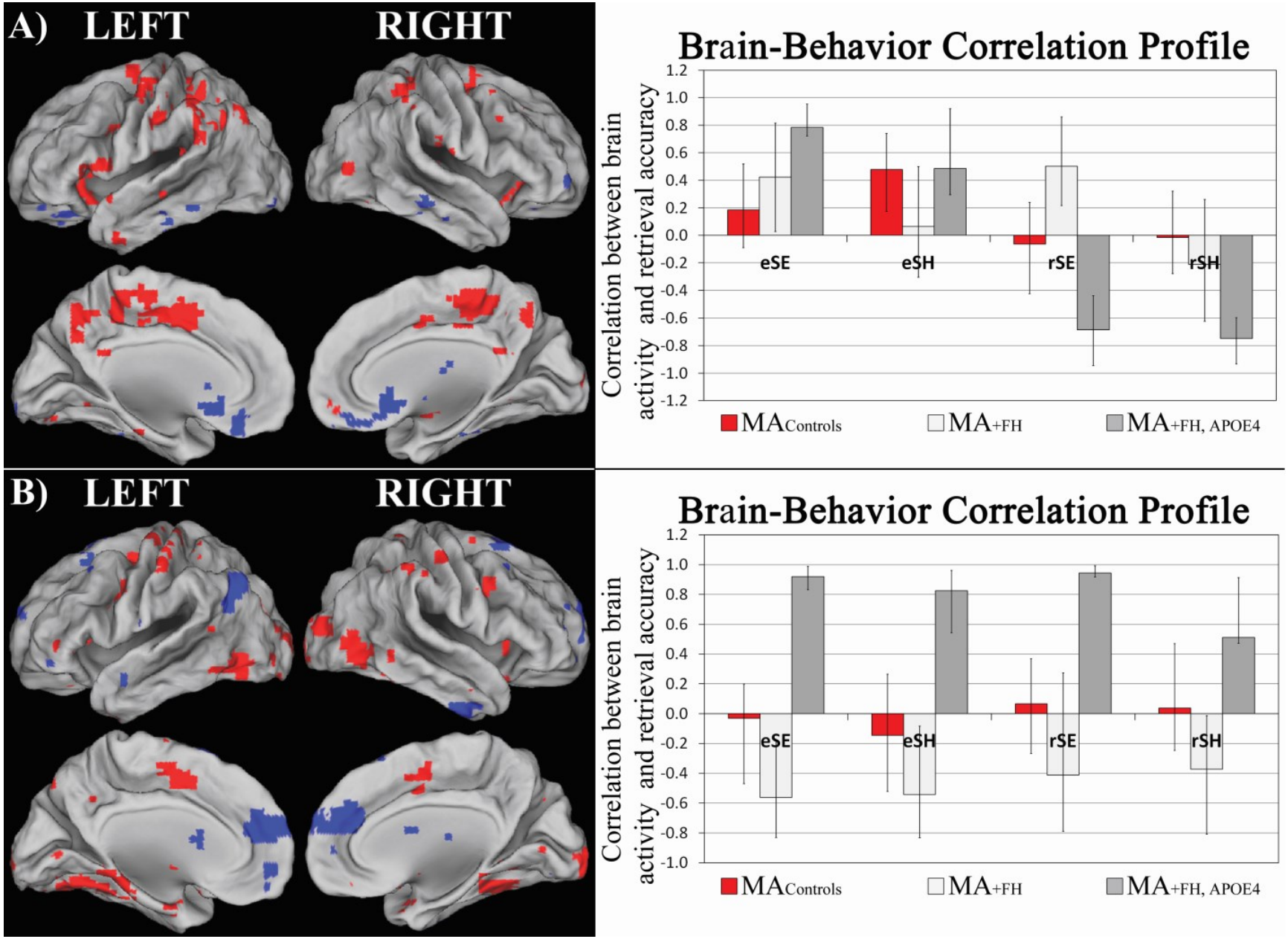


Figure 2.


A) LEFT
RIGHT
Brain-Behavior Correlation Profile
Correlation between brain activity and retrieval accuracy
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
eSE
eSH
rSE
rSH
MAControls
MA+FH
MA+FH, APOE4
B) LEFT
RIGHT
Brain-Behavior Correlation Profile
Correlation between brain activity and retrieval accuracy
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
eSE
eSH
rSE
rSH
MAControls
MA+FH
MA+FH, APOE4