Disturbed temporal dynamics of episodic retrieval activity with preserved spatial activity pattern in amnestic mild cognitive impairment: A simultaneous EEG-fMRI study

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Research

Keywords: Amnestic mild cognitive impairment, Episodic memory, Familiarity, Recollection, Retrieval, Simultaneous EEG-fMRI

Posted Date: September 15th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-71429/v1

Version of Record: A version of this preprint was published at NeuroImage: Clinical on January 1st, 2021.
See the published version at https://doi.org/10.1016/j.nicl.2021.102572.

Abstract

Background

Episodic memory (EM) deficit is the core cognitive dysfunction of amnestic mild cognitive impairment (aMCI). However, the episodic retrieval circuit detected by functional MRI (fMRI) appears preserved in aMCI subjects. To address this discrepancy, this study employed simultaneous electroencephalography (EEG)-fMRI recording to determine whether temporal dynamics of brain episodic retrieval activity were disturbed in patients with aMCI.

Methods

Twenty-six aMCI and 29 healthy control (HC) subjects completed a word-list memory retrieval task during simultaneous EEG-fMRI. The retrieval success activation pattern was detected with fMRI analysis, and the familiarity- and recollection-related components of episodic retrieval activity were identified using event-related potential (ERP) analysis. The fMRI-constrained ERP analysis explored the temporal dynamics of brain activity in the retrieval success pattern, and the ERP-informed fMRI analysis detected fMRI correlates of the ERP components related to familiarity and recollection processes.

Results

The two groups exhibited similar retrieval success patterns in the bilateral posteromedial parietal cortex, the left inferior parietal lobule (IPL), and the left lateral prefrontal cortex (LPFC). The fMRI-constrained ERP analysis showed that the aMCI group did not exhibit old/new effects in the IPL and LPFC that were observed in the HC group. In addition, the aMCI group showed decreased fMRI activity in the precuneus and left hippocampus related to ERP familiarity and recollection components, respectively.

Conclusions

This study identified disturbed temporal dynamics in episodic retrieval activity with a preserved spatial activity pattern in aMCI. Taken together, the simultaneous EEG-fMRI technique demonstrated the potential to identify individuals with a high risk of cognitive deterioration.

Background

Episodic memory (EM) refers to the ability to recall past personal experiences with their associated spatiotemporal contexts. Alzheimer's disease (AD) remains the most common type of dementia in the elderly population. Impairments in EM emerge as the earliest cognitive dysfunction of AD and correlate closely with disease progression (1, 2). EM deficits are associated with abnormalities of established AD biomarkers, including β-amyloid or tau protein deposition in the medial temporal lobe (MTL) (3), reduced

entorhinal volume (4), and cortical hypometabolism (5). Nevertheless, the neural mechanism underlying EM deficits remains unclear, which impedes early identification of individuals who are at high risk of cognitive deterioration.

Successful episodic retrieval acts as a prerequisite for recalling events, as an event recall is comprised of a familiarity process followed by a recollection process; both processes occur on the scale of hundreds of milliseconds (ms) (6). The brain regions associated with successful retrieval have been identified using functional MRI (fMRI) by comparing differences in brain activity during the correct identification of familiar items versus unfamiliar items (7). These regions include the medial parietal cortex, the inferior parietal lobule (IPL), and the lateral prefrontal cortex (LPFC), and have been identified as the retrieval success pattern (8). Intriguingly, the retrieval success pattern is largely preserved in amnestic mild cognitive impairment (aMCI) cohorts, rather than being disrupted along with the behavioral EM impairment (9). One interpretation of this discrepancy is that the preserved activity pattern reflects a compensatory process against pathogenesis in aMCI (10). Another possibility is that the limited temporal resolution of the fMRI technique is insufficient to reflect cognitive processes during episodic retrieval. When compared to fMRI, the electroencephalography (EEG) technique serves as an ideal tool to detect the temporal dynamics of episodic retrieval. Particularly, an event-related potential (ERP) old/new effect, as identified by more positive-going ERPs when correctly identifying old stimuli relative to new stimuli, was applied to characterize psychophysiological processes during episodic retrieval. In general, an early mid-frontal ERP old/new effect, which peaks around 400 ms, is linked to the familiarity process, whereas a late parietal ERP old/new effect, which peaks around 600 ms, is related to the recollection process (11). Given the low spatial resolution of the EEG technique, identifying neural sources of the observed scalp potentials as described above remains a challenge. Therefore, by using the fMRI or the EEG techniques alone, only part of the neural underpinnings of the retrieval success will be revealed, as each tool has limitations when addressing the questions of whether and how changes in brain activity occur when episodic retrieval is impaired in aMCI (12).

Notably, simultaneous EEG-fMRI recording allows for both high-resolution temporal dynamics and spatial localization (13). Relative to obtaining EEG and fMRI data collected separately, simultaneous EEG–fMRI recording unifies data acquisition and behavioral performance. Here, we applied concurrent EEG and fMRI recording during an episodic retrieval task in both aMCI patients and healthy controls. In addition to conventional ERP and fMRI analyses, fMRI-constrained ERPs analysis and single-trial EEG-informed fMRI analysis were conducted. Specifically, conventional fMRI analysis was used to identify the spatial retrieval success pattern. Within these regions, fMRI-constrained ERPs analysis was used to examine the temporal dynamics of the retrieval success pattern. Moreover, conventional ERP analysis was employed to identify familiarity- and recollection-related old/new effects on an episodic retrieval task. In the ERP-informed fMRI analysis, we explored brain regions where the fMRI activities were modulated by these effects. Taken together, in this study, the simultaneous EEG–fMRI recording technique was applied to investigate neural mechanisms underlying episodic retrieval in cognitively normal elderly and aMCI cohorts. This technique will advance the current understanding of EM deficits in aMCI and facilitate identifying individuals who are at high risk of cognitive deterioration.

Materials And Methods

Subjects

A total of sixty-four subjects were recruited from community health screenings. All subjects were right-handed, aged between 50 and 80 years, and underwent a three-step inclusion process (detailed in the **Supplemental Material S1**). Nine subjects were excluded due to excessive motion artifacts (i.e., during the fMRI scan, head motion exceeded either 2 mm of the maximum displacement in any direction or 2° of angular motion) or incomplete data acquisition. The remaining 55 subjects, comprised of 26 aMCI and 29 healthy control (HC) subjects, were included in the final analysis. This study was approved by the Human Participants Ethics Committee of the Affiliated ZhongDa Hospital, Southeast University and Henan Mental Hospital, the Second Affiliated Hospital of Xinxiang Medical University, China. Written informed consent was obtained from all participants.

Clinical Evaluation

Global cognitive function was assessed using the Mini-Mental State Examination (MMSE) and the Mattis Dementia Rating Scale-2 (MDRS-2). Moreover, a neuropsychological battery was used, which covered EM, visuospatial function, information processing speed, and executive function. Details of the neuropsychological tests are provided in **Supplemental Material S1.**

Inclusion Criteria and Exclusion Criteria

The inclusion criteria for aMCI subjects were as follows: 1) subjective memory complaints; 2) objective memory impairment measured at 1.5 standard deviations (SD) below the age-adjusted norms in the Auditory Verbal Learning Test 20-minute delayed recall score; 3) minimal or absent impairments in global cognition or daily activities: MMSE score ≥ 24, MDRS-2 score ≥ 120, and activities of daily living score ≤ 25, and 4) the absence of dementia. All HC subjects presented MMSE scores ≥ 26.

In this study, the following exclusion criteria were applied: 1) any history of neurological or psychiatric diseases; 2) major medical illness or severe visual or hearing loss that interfered with cognitive evaluation; 3) contraindications to the MRI scan, and 4) gross brain structural abnormality as revealed by MRI.

Evaluation Procedure and Stimuli

The episodic retrieval paradigm included a study phase (40 trials, approximately 3.1 minutes), followed by a retrieval phase (80 trials, approximately 7.5 minutes). These two phases were separated by a distracter task in which the subjects were asked to silently repeat the numbers “one, two, three” for approximately two minutes (**Figure 1A**). In the study phase, 40 different nouns, consisting of two Chinese characters were presented, one at a time. These involved nouns that were used with high frequency in speech as defined by the Frequency Dictionary of Modern Chinese. In the retrieval phase, the 40 studied, as well as the 40 unstudied nouns, were presented in a pseudo-randomized order. No significant

difference was observed between the frequencies of the studied and unstudied words presented (t_{78} = -0.075, p = 0.940). The stimuli were displayed in a white color against a black background using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA). All stimuli were presented in the central vision via MR-compatible goggles (Resonance Technology, Inc., Northridge, CA, USA). Example trials are illustrated in **Figure 1B** and in **Supplemental Material S2**.

Simultaneous EEG-fMRI Data Acquisition

In this study, fMRI data were acquired using a Siemens Verio 3.0 Tesla scanner (Siemens, Erlangen, Germany) with a standard 12-channel head coil. A gradient echo planar imaging sequence was used with the following parameters: 34 axial slices, repetition time (TR) = 2700 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view (FoV) = 220 × 220 mm, matrix = 96 × 96, and thickness = 3.4 mm.

EEG data were acquired with an MR-compatible EEG amplifier (BrainAMP MR, Brain Products, Munich, Germany) at a sampling rate of 5,000 Hz, using 64 electrodes in the extended 10-20 montage, plus one extra EEG electrode. An experienced specialist (L.G.) positioned the EEG caps on the subjects. To ensure valid standard positions, the electrode Cz was placed halfway between the nasion and the inion, and was right-left-centered. The reference was set at the mid-frontal position FCz, and the impedances were kept below 10 kΩ. The data were transmitted via fiber optics outside the scanner room. To facilitate the removal of MR-induced artifacts from the EEG data, the sampling clocks of the EEG and MRI systems were synchronized by the Sync box (Brain Products, Munich, Germany).

Data Processing and Analysis

Behavioral Data Analysis

For behavioral data analysis, a total of 4 conditions were identified given each subject's response in the retrieval trials, including hit ("old" response to an old word), miss ("new" response to an old word), correct rejection (CR, "new" response to a new word), and false alarm (FA, "old" response to a new word). Subsequently, a discrimination index, d-prime (d'), was calculated as the Z-score of the hit rate minus the Z-score of the false alarm rate. Independent two-sample t-tests were employed to compare the hit number, CR number, and the d' values between HC and aMCI groups. For the demographic and neuropsychological data, independent two-sample t-tests and Chi-square tests were used to compare quantitative and qualitative variables, respectively. The significance threshold was set at $p < 0.05$.

fMRI Data Preprocessing and Analysis

In this study, fMRI data were preprocessed using the Analysis of Functional NeuroImages (AFNI) software (https://afni.nimh.nih.gov/afni). The preprocessing pipeline included despiking (3dDespike, AFNI), slice timing and motion correction (3dvolreg, AFNI), aligning functional data to structural data and spatial normalization to the Talairach space (3dAline, AFNI), and smoothness with a 6-mm Gaussian kernel (3dmerge, AFNI).

The BOLD functional response to the four conditions was estimated by the general linear model (GLM) (3dDeconvolve, AFNI). The design matrix contained three types of regressors. First, the hemodynamic response to the onset of each condition was modeled by the canonical hemodynamic response function with the first-order time derivative. Second, six motion parameters, including three translational and three rotational movements, and signals from cerebrospinal fluid (CSF) and white matter (WM), were included as regressors of no interest. Third, baseline detrending was conducted at a polynomial degree of 4, given the 496 seconds of scanning time. The contrast maps of hit versus baseline, CR versus baseline, and hit versus CR were created at individual subject levels. Then, the effects of hit, CR, and hit relative to CR were identified by one-sample t-tests in HC and aMCI groups, respectively. The differences in these effects were estimated by two-sample t-tests between groups (3dttest++, AFNI). For group-level analysis, a voxel-wise threshold of $p < 0.005$ with 15 contiguous voxels was used. Thus, the contrast map of hit versus CR represented the retrieval success pattern in this study.

EEG Data Preprocessing and ERP Analysis

EEG data were preprocessed using the BrainVision Analyzer software 2.0 (Brain Products GmbH, Munich, Germany), and the preprocessing pipeline included the following steps: 1) removal of MR-induced artifacts from the raw EEG signal with the *All Scanned Intervals for Average* approach (14); 2) down-sampling the EEG data to 250 Hz; 3) removal of cardioballistic artifacts by restricted infomax independent component analysis (ICA) based correction; 4) visually identifying and spherically interpolating noisy channels; 5) re-referencing to the average of all scalp electrodes; 6) bandpass filtering from 0.5 hertz (Hz) to 30 Hz; 7) ICA-based ocular correction; 8) inspecting raw data for the removal of waveforms with an amplitude greater than +100 μV or less than -100 μV; 9) editing markers to reject trails with incorrect responses, forming epochs from 100 ms of pre-stimulus to 1600 ms of post-stimulus for hit and CR trials, respectively; 10) correcting the baseline using the waveform before the stimulus onset, and 11) averaging waveforms across trials. The “stimulus” at steps 9 and 10 referred to the word shown on the screen but not the button-press response indicating an old or new word.

The components of interest ranged from 350 to 550 ms for the early old/new effect at electrode FCz and from 580 to 750 ms for the late old/new effect at electrodes P2 and P4, which was in accordance with the grand average ERP waveforms, and was consistent with a simultaneous EEG-fMRI study using the word-list retrieval task (15). To determine if the ERP component had a significant effect, repeated-measures analysis of variance (RMANOVA) were used with post hoc simple main effect analysis. Specifically, with regard to the ERP data at FCz, analysis was performed using the stimuli (hit versus CR) as the within-subject factors and the groups (NC versus aMCI) as the between-subject factors. With respect to the ERP data at P2 and P4, analysis was performed using the stimuli (hit versus CR) and electrodes (P2 versus P4) as the within-subject factors, and the groups (NC versus aMCI) as the between-subject factors. Statistical significance was set at $p < 0.05$. As presented in a previous study, no significant early old/new effects were observed among the frontal electrodes. The mean amplitude at electrode FCz was calculated to inform the fMRI analysis, which was consistent with the data presented in a previous study (15). Our data indicated significant late old/new effects at electrodes P2 and P4

among the parietal electrodes. Therefore, the mean amplitudes were used at the two electrodes to inform the fMRI analysis. The mean amplitudes of these components were extracted for the hit and CR conditions, which acted as amplitude modulators in the subsequent single-trial EEG-informed fMRI analysis. In addition, we calculated the signal-to-noise ratio (SNR) to evaluate the ERP signal quality. The method and result are detailed in **Supplemental Material S3**.

fMRI-constrained ERP Analysis

For each group, the fMRI-constrained ERP analysis was performed. In brief, source localization analysis was conducted to calculate the source waveforms across the whole brain using Brainstorm 3.0 software (http://neuroimage.usc.edu/brainstorm). The head model was computed using the OpenMEEG Boundary Element Method on the cortical surface of a standard 3D brain model. Subsequently, for each subject, the noise covariance matrix was calculated on the EEG baseline period (-100 ms to stimulus onset). The cortical current maps were computed from the averaged ERP time series using the weighted minimum norm estimate (wMNE) inverse solution for the hit and CR conditions, respectively. Furthermore, brain regions showing significant BOLD activation in the hit versus the CR contrast, which were informed by fMRI results, were used as the regional sources to obtain the source waveforms for each condition. The group-wise source waveforms for the hit and CR conditions (old/new effect) are presented in **Figure 4**.

Single-trial EEG-informed fMRI Analysis

Single-trial EEG-informed fMRI analysis was performed for the early and late old/new effects. In brief, mean amplitudes of the single-trial EEG data within a 350 to 550 ms time window at electrode FCz were extracted as the early old/new effect, and mean amplitudes of the single-trial EEG data at the P2 and P4 electrodes within the 580 to 750 ms time window were extracted as the late old/new effect. Next, extracted amplitudes from the hit and CR conditions were entered into the GLM as amplitude modulators (AM) with respect to hit and CR regressors. Specifically, the regressors in the GLM included: 1) the hemodynamic response to the onset of hit, miss, CR, and FA, as well as the AM of hit and CR; 2) six motion parameters, including three translational and three rotational movements, and CSF and WM signals, and 3) baseline detrending regressor with a polynomial degree of 4. Then, for each subject, the contrasts (hit AM versus baseline, CR AM versus baseline, and hit AM versus CR AM) were calculated. Finally, one-sample and two-sample *t*-tests were employed to calculate the statistical differences within each group as well as the differences between the groups.

Results

Subjects Characteristics

As illustrated in **Table 1**, the two groups were matched for age and gender distribution, however, significant difference was observed in education years ($t_{53} = 2.98$, $p < 0.01$). As expected, the aMCI group exhibited significantly lower neuropsychological scores in the MMSE, MDRS-2, and EM tests. The two groups showed comparable hit numbers, CR numbers, and *d'* index values in the task during the EEG-fMRI

experimental recordings. Notably, the aMCI group showed a trend toward lower CR numbers when compared to the HC group. This trend should not bias the subsequent fMRI and ERP analyses since these analyses were performed on correct judgments (hits and CRs) during the task.

Brain Activity Patterns During the Task

The fMRI-only analysis showed significant activation for contrasts of hit versus baseline, CR versus baseline, and hit versus CR, in HC and aMCI groups. First, in the HC group within the hit versus baseline contrast, significant activation was observed in the bilateral dorsolateral prefrontal cortex (DLPFC), the bilateral posterior medial frontal cortex (pMFC), the bilateral inferior temporal gyrus, and the IPL (**Figure 2A**). Moreover, in the aMCI group, significant activation was observed in the bilateral pMFC, the left IPL, the right premotor cortex (PMC), and the right insula (**Figure 2D**). Second, in the CR versus baseline contrast, activation primarily occurred in the bilateral pMFC, the left IPL, and the left superior parietal lobule in both HC and aMCI groups (**Figures 2B** and **2E**). Third, in the hit versus the CR contrast, also named the retrieval success pattern, significant activation was observed in the bilateral precuneus/posterior cingulate cortex (Pcu/PCC), the left IPL, and the left PMC in both HC and aMCI groups. In addition, activation was observed in the left DLPFC and the left insula/inferior frontal gyrus (IFG) of subjects in the HC group and in the left LPFC and bilateral medial prefrontal cortex of subjects in the aMCI group (**Figures 2C** and **2F**).

ERP Components in Retrieval-Related Time Windows

The ERP-only analysis was performed to identify ERP components during the retrieval-related time windows (**Figure 3**). No significant main effects of stimuli (hit versus CR) and group (HC versus aMCI) was observed on the mean amplitudes of the early mid-frontal component at FCz [stimuli: $F(1, 53) = 0.295$, $p = 0.589$; group: $F(1, 53) = 4.303$, $p = 0.075$]. In addition, after Bonferroni *post-hoc* analysis, no significant differences were observed between hits and CRs, in either HC or aMCI groups (HC: $p = 0.218$.; aMCI: $p = 0.611$). In contrast, significant main effects of stimuli (hit versus CR) and groups (HC versus aMCI) were observed in mean amplitudes of the late parietal component [stimuli: $F(1, 53) = 7.127$, $p = 0.010$; group: $F(1, 53) = 4.836$, $p = 0.033$]. Bonferroni *post-hoc* analysis identified a significant difference between both hits and CRs (hits greater than CRs) at P2 and P4 in the HC group (P2: $p = 0.028$; P4: $p = 0.011$), whereas no significant differences were observed between the hits and CRs in the aMCI group (P2: $p = 0.573$; P4: $p = 0.112$).

Source Waveforms for Regions with Retrieval Success

Using fMRI-constrained ERP analysis the source waveforms for the hit and CR conditions was estimated in each active region of the retrieval success pattern (**Figure 4** and **Table S1**). Although the two groups exhibited similar retrieval success patterns, our data showed divergent and convergent temporal dynamics between HC and aMCI groups. First, in the left IPL, retrieval success effects were observed in both HC and aMCI groups, and an ERP old/new effect was observed in the time window from 452 to 876 ms in the HC group but not in the aMCI group. Second, in the LPFC, the old/new effect after 800 ms was

evident in the HC group (left DLPFC and left insula/IFG). In the same post-800ms time window, there was an old/new effect in MPFC in the aMCI group. Third, both HC and aMCI groups showed old/new effects with similar time windows in the Pcu and the PMC.

Between-group Differences by ERP-informed fMRI Analyses

In the hit versus CR contrast, the aMCI group showed significantly decreased BOLD activity in the left ventrolateral prefrontal cortex (VLPFC) when compared to the HC group, as demonstrated by the fMRI-only analysis (**Figure 5A** and **Table S2**). Furthermore, the single-trial EEG-informed fMRI analysis demonstrated between-group differences in the fMRI correlates of ERP familiarity and recollection components. In the familiarity component, the aMCI group exhibited a decreased fMRI correlate in the Pcu relative to the HC group (**Figure 5B** and **Table S2**). In the recollection component, the aMCI group showed a decreased fMRI correlate in the left hippocampus (**Figure 5C** and **Table S2**) and an increased fMRI correlate in the bilateral LPFC (**Figures 5D, 5E,** and **Table S2**).

Discussion

To our knowledge, this was the first study in which a simultaneous EEG–fMRI technique was employed to explore the spatiotemporal characterization of brain episodic retrieval activity in control subjects compared to aMCI patients. In our study, the fMRI-only analysis validated the spatial pattern of retrieval success that has been reported in previous studies. Based on this spatial pattern, the fMRI-constrained ERP analysis identified distinct temporal dynamics underlying similar retrieval success patterns between the two groups. In addition, the aMCI group presented reduced activities in the Pcu and left hippocampus which were related to familiarity and recollection processes. Taken together, our findings provide novel insights into changes in the neural circuitry of episodic retrieval in aMCI subjects with a high spatiotemporal resolution.

In our study, fMRI-only analysis identified the retrieval success patterns in the bilateral Pcu/PCC, the left IPL, and the left lateral frontal cortex in both aMCI and HC subjects. In addition, the aMCI group presented a decreased brain activity in the left VLPFC relative to the HC group. These findings were in agreement with prevailing data regarding the neural substrates of episodic retrieval and the alteration thereof in aMCI subjects (9). This validation highlights the quality of our study samples, even though our sample size was relatively small. The identified retrieval success pattern provides a framework to understand the neural mechanism of episodic retrieval. For example, the IPL is assumed to support the recall of item details; the Pcu/PCC is linked to decision-related retrieval processes, and the prefrontal cortex is thought to be involved in the top-down control of memory retrieval, such as post-retrieval monitoring and evaluation (8). Decreased activation in the left lateral prefrontal area indicated deficits in top-down memory retrieval control in aMCI individuals, which has been demonstrated previously (16). Notably, the episodic retrieval pattern identified in this study was mainly located in the left-lateralized brain regions, and was likely attributed to verbal processing. Therefore, our fMRI-only analysis identified a retrieval

success pattern that validates the current literature and provides a spatial basis for fMRI-constrained ERP analysis.

The ERP-only analysis identified a late parietal old/new effect, however, no significant frontal old/new effects were observed. This is not unexpected given the following factors: first, in several studies, it was demonstrated that elderly adults, when compared to young adults, exhibit diminished frontal old/new effect but preserved parietal old/new effect (17, 18). These findings suggested aging as a major factor in reorganizing the ERP correlates of episodic retrieval. Moreover, emerging studies identified a parietal old/new effect in the right electrodes (as was the case in our study), thereby implying that elderly individuals utilized visual stimuli features, rather than conceptual features while performing episodic retrieval (19, 20). Second, education level, in conjunction with age, may impact the ERP correlates of episodic retrieval. Elderly subjects with a low education level failed to exhibit a frontal old/new effect, but instead showed a parietal old/new effect (20). These findings further supported our results, given that the mean education years in our HC group (10.95 years) was far lower when compared to that in most published studies. Third, simultaneous EEG-fMRI acquisition may decrease the signal-to-noise ratio of the EEG data, thereby attenuating the frontal old/new effect. Another study using simultaneous EEG-fMRI acquisition also observed a parietal old/new effect but not a frontal old/new effect, as in our study (15). Thus, the results from our ERP-only analysis appeared consistent with existing studies and provided a temporal basis for the ERP-informed fMRI analysis.

The most notable finding of our study was the identification of temporal dynamics in regions active during retrieval success as identified by the fMRI-constrained ERP analysis. This analysis revealed the roles of these brain regions during episodic retrieval. In the left IPL, an old/new effect around 600 ms was observed in the HC group, thereby indicating that the IPL supported the recollection of contextual details during episodic retrieval. Specifically, the IPL acted as an “output buffer,” temporarily storing EM information transferred from the MTL, thereby influencing the retrieval decision (12, 21). When memory contents are rapidly recollected, the IPL served as a “circuit breaker” to mediate the automatic attentional capture by recollected memory through its function in bottom-up attention (22, 23). Furthermore, in the left DLPFC/insula, the old/new effect after 800 ms was analogous to the ERP late frontal effect, and suggested that the role of these regions in episodic retrieval was related to cognitive control and post-retrieval monitoring or evaluation (24). Intriguingly, the aMCI group showed the old/new effects in neither of the two regions above but exhibited the old/new effect after 800 ms in the MPFC. It indicates that the ERP late frontal effect was relocated to the MPFC in the aMCI group. In contrast, both the HC and aMCI groups showed old/new effects in the Pcu and the PMC. In recent studies, it was demonstrated that the Pcu and PMC were functionally connected to accumulate mnemonic evidence for retrieval decisions (25, 26). The emergences of the old/new effects in both groups suggested that this function was preserved in the aMCI group. Taken together, although the retrieval success patterns were similar between the HC and aMCI groups, the IPL and LPFC showed differing temporal dynamics between the two groups, thereby indicating a diminished contribution of these regions to successful episodic retrieval in the aMCI group.

Single-trial EEG-informed fMRI analysis explores brain regions where fMRI activities correspond to the ERP indices of familiarity or recollection. With regard to familiarity, the Pcu was activated in control subjects but not in aMCI subjects. Current knowledge recognized the Pcu as a neural substrate, underlying the perceived familiarity of a stimulus (27). A greater Pcu activity indicated a stronger familiarity signal to capture the subject's attention (28). Thus, the absence of Pcu activity herein suggested impaired familiarity-related processing in aMCI subjects. With respect to recollection, no within-group activity was observed on the whole brain. However, between-group comparisons identified reduced left hippocampus activity in aMCI subjects. These findings connected a reduced hippocampal activity to the recollection deficit in aMCI subjects. The absence of significant hippocampal activity in HC or aMCI groups may be attributed to susceptibility-related signal loss in part of the hippocampus, thereby limiting the cluster extent that is necessary for a statistical significance. Taken together, single-trial EEG-informed fMRI analysis has the potential to locate changes in brain activity related to familiarity and recollection processes during episodic retrieval, and increases the current temporal resolution available to detect changes in brain EM activity relative to conventional fMRI techniques.

Our study was an exploratory study with several limitations. First, although our study sample was of high quality, the sample size was relatively small, and as such, limiting the statistical power and the signal-to-noise ratio needed to detect brain activity patterns. Future studies with an independent dataset are essential to validate the current findings. Second, the cross-sectional design of this study had limited scope to associate changes in fMRI or ERP with clinical outcomes. We are following-up with these subjects to determine whether the fMRI or ERP changes represented a "state" or "trait" of aMCI. Third, the time windows used in our ERP-informed fMRI analysis were adapted using a visual inspection of the grand average of the "hits" and "correct rejections" with prior knowledge. These time windows need to be further validated, as the ERP components related to episodic retrieval may be different in an elderly population. Fourth, the fMRI-constrained ERP analysis was conducted by first averaging the ERP time series from individual subjects to one group-level ERP time series, and then performing the source localization analysis on the group-level ERP time series. This analysis had a limitation to provide statistical results given that only one averaged ERP time series was employed to compute the source waveform. Thus, additional analysis is required to validate the results of the fMRI-constrained ERP analysis.

Conclusions

. This study showed an integrated EEG-fMRI technique to detect brain episodic retrieval activity changes in aMCI subjects with high spatiotemporal sensitivity. Although aMCI subjects and controls shared similar retrieval success activation patterns, the electrophysiological activities related to the recollection and post-retrieval monitoring processes were significantly diminished in aMCI subjects. In addition, using ERP-informed fMRI analysis, decreased hemodynamic correlates of familiarity and recollection were observed in the Pcu and hippocampus. Therefore, our findings bridge the gap between the electrophysiological and hemodynamic activities related to episodic retrieval, and provide insight into

disruptions in the neural circuitry underlying EM deficits in aMCI, thereby helping to identify individuals who are at high risk of cognitive deterioration at an early stage.

Abbreviations

EM: Episodic memory; AD:Alzheimer's disease; MTL:medial temporal lobe; ms:milliseconds; fMRI:functional MRI; IPL:inferior parietal lobule; LPFC:lateral prefrontal cortex; aMCI:amnestic mild cognitive impairment; EEG:electroencephalography; ERP:event-related potential; HC:healthy control MMSE:Mini-Mental State Examination; MDRS-2:Mattis Dementia Rating Scale-2; SD:standard deviations; TR:repetition time; TE:echo time; FoV:field of view; CR:correct rejection; FA:false alarm; *d'*:d-prime; AFNI:Analysis of Functional NeuroImages; GLM:general linear model; CSF:cerebrospinal fluid; WM:white matter; ICA:independent component analysis; Hz:hertz; RMANOVA:repeated-measures analysis of variance; SNR:signal-to-noise ratio; wMNE:weighted minimum norm estimate; AM:amplitude modulators; DLPFC:dorsolateral prefrontal cortex; pMFC:posterior medial frontal cortex; PMC:premotor cortex; Pcu/PCC:precuneus/posterior cingulate cortex; IFG:inferior frontal gyrus; VLPFC:ventrolateral prefrontal cortex;

Declarations

Ethics approval and consent to participate

This study was approved by the Human Participants Ethics Committee of the Affiliated ZhongDa Hospital, Southeast University and Henan Mental Hospital, the Second Affiliated Hospital of Xinxiang Medical University, China. Written informed consent was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

Funding

This work was supported by the National Natural Science Foundation of China (81420108012, 81671046, 81901108, and 61773092) and The Project of Invigorating Health Care through Science, Technology and Eduation, Jiangsu Provincial Medical Outstanding Talent (JCRCA2016006).

Authors' contributions

Drs. Z.Z., and L.L. designed the study. Drs. Lihua G., Lijuan G., Hongxing Z., and Haisan Z. acquired the data. Drs. H.S., Lihua G., P.Y., Z.X., W.W., M.V.L, and L.L. analyzed and interpreted the data. Drs. H.S., P.Y., W.W., L.L., and Z.Z. wrote the paper.

Acknowledgments

We sincerely thank Dr. Gavin P. Reynolds, Ph.D., for editorial assistance.

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Tables

Table 1. Comparison of Demographic and Cognitive Data Between the HC and aMCI Groups

	HC (n=29)	aMCI (n=26)	*p* value
Demographic information			
Age, mean (SD), years	60.48 (6.22)	62.35 (6.34)	0.27
Male, No. (%)	11 (37.93)	10 (38.46)	0.96
Education, mean (SD), years	10.95 (1.78)	9.58 (1.60)	0.00*
Neuropsychological scores			
MMSE, mean (SD)	28.90 (1.01)	27.38 (1.53)	0.00*
MDRS-2, mean (SD)	139.79 (1.93)	136.50 (3.33)	0.00*
AVLT–20-min DR, mean (SD)	6.72 (1.71)	2.50 (1.03)	0.00*
LMT–20-min DR, mean (SD)	3.07 (1.49)	1.38 (1.17)	0.00*
CFT–20-min DR, mean (SD)	18.78 (5.67)	11.04 (5.57)	0.00*
Composite memory *z*-score, mean (SD)	0.60 (0.51)	-0.69 (0.44)	0.00*
Performances in the verbal memory task			
Hits, mean (SD)	26.83 (6.74)	26.69 (7.21)	0.94
Correct rejection, mean (SD)	29.17 (6.86)	25.50 (8.43)	0.08
d', mean (SD)	0.23 (1.48)	-0.26 (1.43)	0.22

The *p* values were obtained by independent two-sample *t*-tests for quantitative data, or by the chi-squared test for qualitative data. The *d'* was calculated using the Z-score of the hit rate minus the Z-score of the false alarm rate.

* indicates significant differences between groups.

Abbreviations: HC, healthy control; aMCI, amnestic mild cognitive impairment; *d'*, d-prime; SD, standard deviation; No., number; MMSE, Mini-Mental State Examination; MDRS-2, Mattis Dementia Rating Scale-2; AVLT–20-min DR, auditory verbal learning test–20-minute delayed recall; LMT–20-min DR, logical

memory test–20-minute delayed recall; CFT–20-min DR, Rey-Osterrieth Complex Figure test–20-minute delayed recall.

Figures

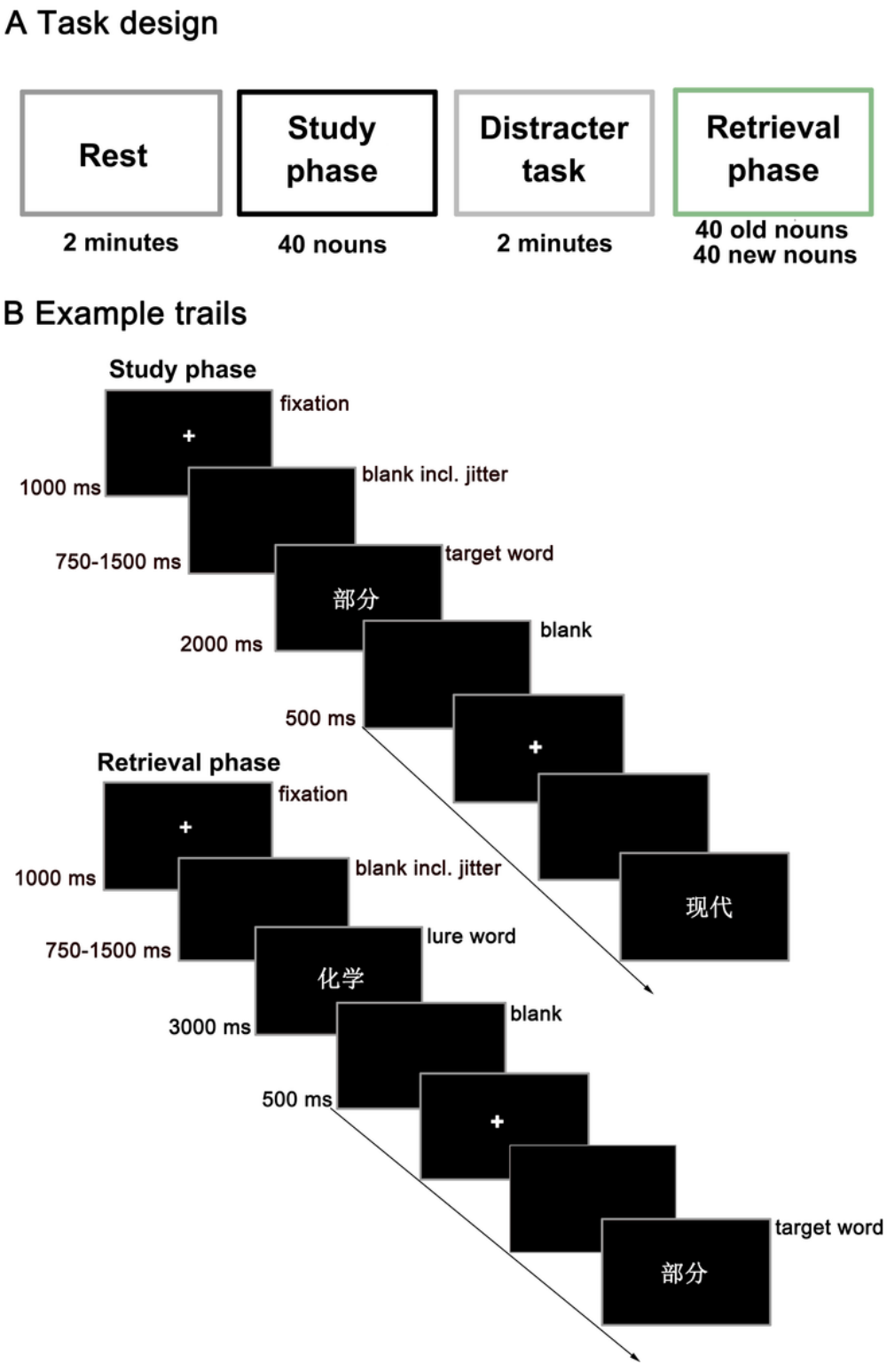

Figure 1

Experimental design of the verbal retrieval task. This task included four phases as listed in (A) in temporal order: a resting phase lasting two minutes, a study phase that included 40 nouns, a distracter task lasting two minutes, and a retrieval phase that included 80 nouns. (B) provides examples of the trials of the study phase (upper row) and retrieval phase (lower row), respectively.

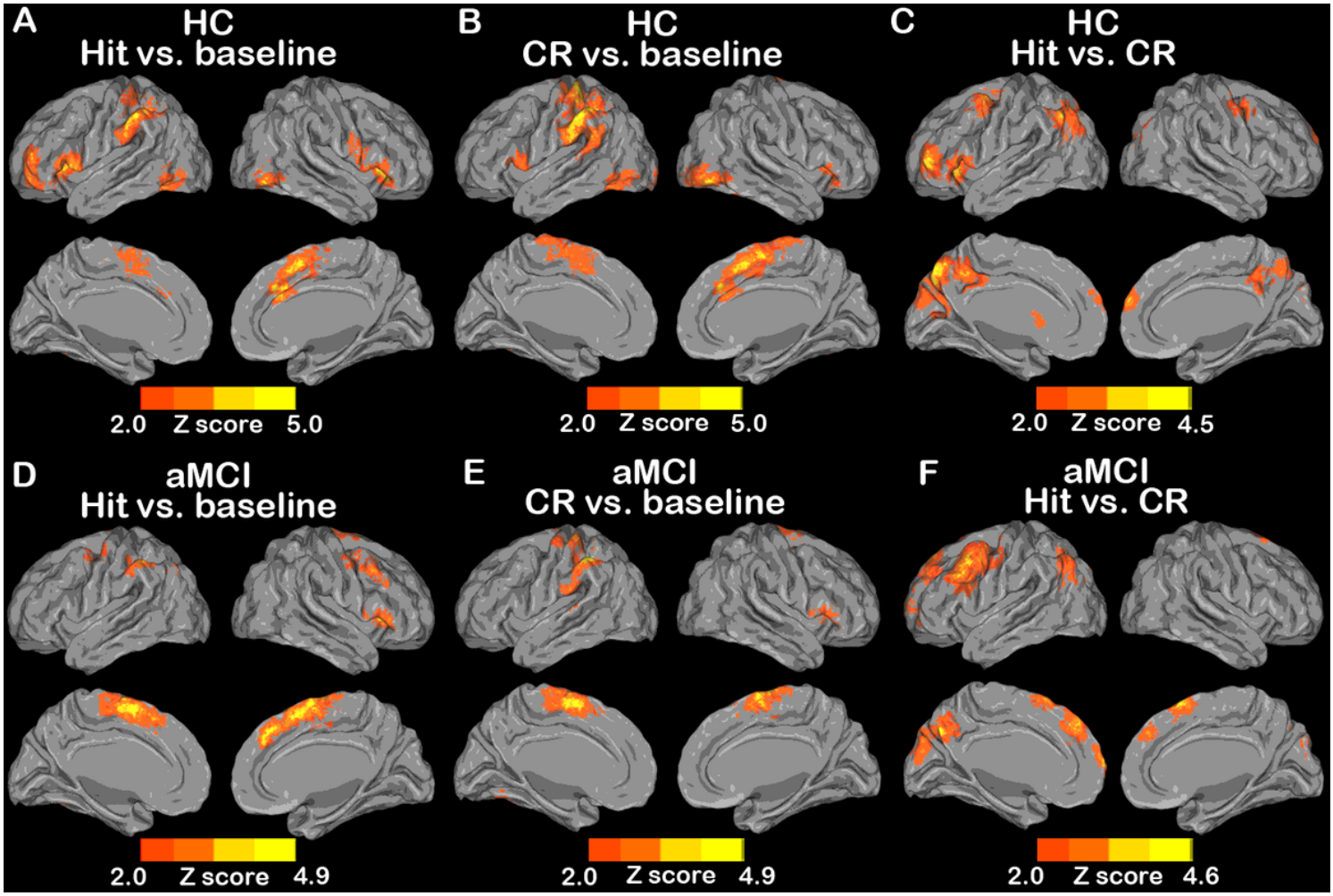

Figure 2

fMRI-only analysis reveals brain activity patterns during the verbal retrieval task in the HC group (A-C) and the aMCI group (D-F). Brain activation patterns for hits relative to the baseline in the HC group (A) and the aMCI group (D). Brain activation patterns for correct rejections relative to the baseline in the HC group (B) and the aMCI group (E). The retrieval success effect as revealed by the contrast hits versus the correct rejections in the HC (C) and the aMCI (F) groups. A warm color indicates brain activity during the task ($p < 0.005$, cluster size > 15 voxels). Abbreviations: fMRI, functional magnetic resonance imaging; HC, healthy control; aMCI, amnestic mild cognitive impairment; CR, correct rejection.

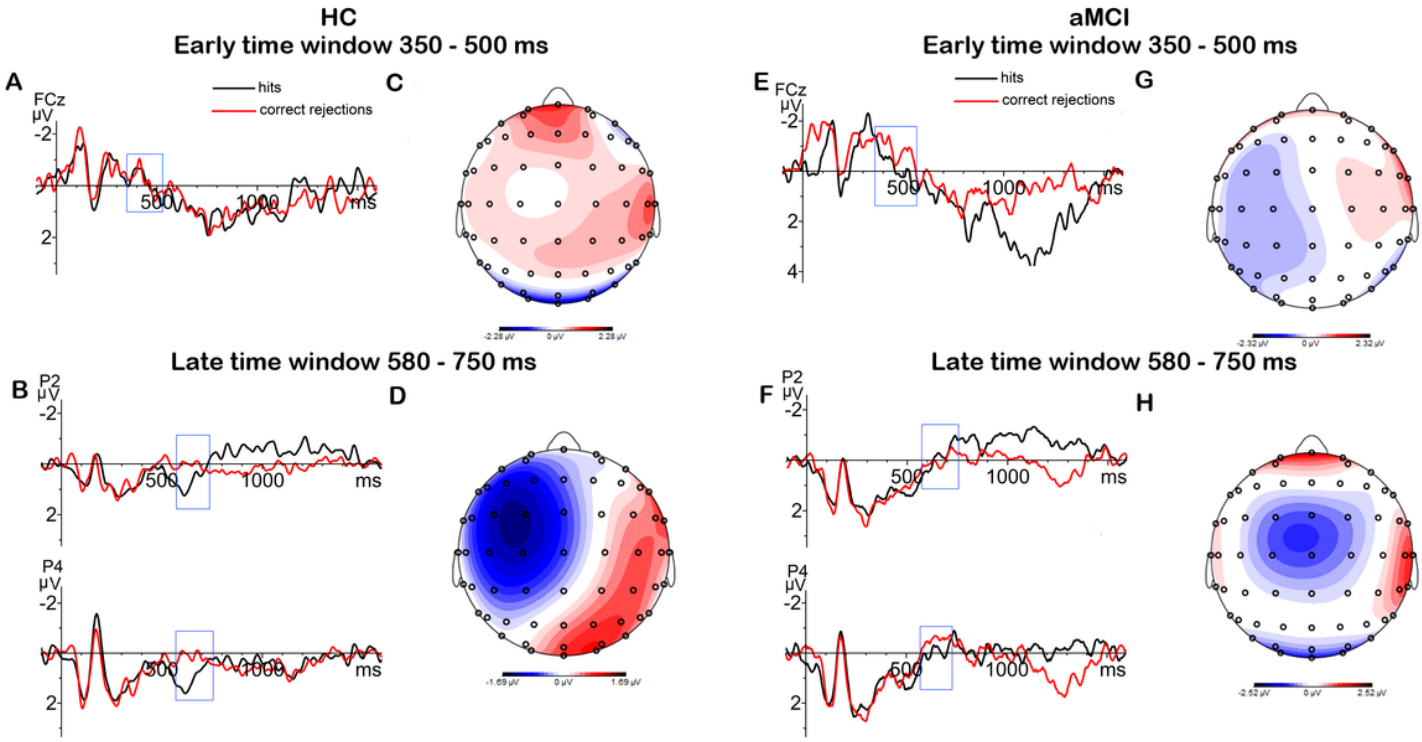

Figure 3

ERP-only analysis reveals ERP waveforms and topographic maps in the hit and correct rejection conditions. The ERP waveforms at electrode FCz were obtained to explore brain activity within an early time window from 350 to 550 ms in the HC group (A) and the aMCI group (E). ERP waveforms at electrodes P2 and P4 were collected to explore brain activities within a late time window from 580 to 750 ms in HC group (B) and aMCI group (F). Topographic maps for the contrast of hits versus correct rejections are depicted for early (C and G) and late (D and H) time windows in the two groups. The time windows correspond to the blue rectangles in the waveforms. Abbreviations: HC, healthy control; aMCI, amnestic mild cognitive impairment; ERP, event-related potential; HC, healthy control; aMCI, amnestic mild cognitive impairment.

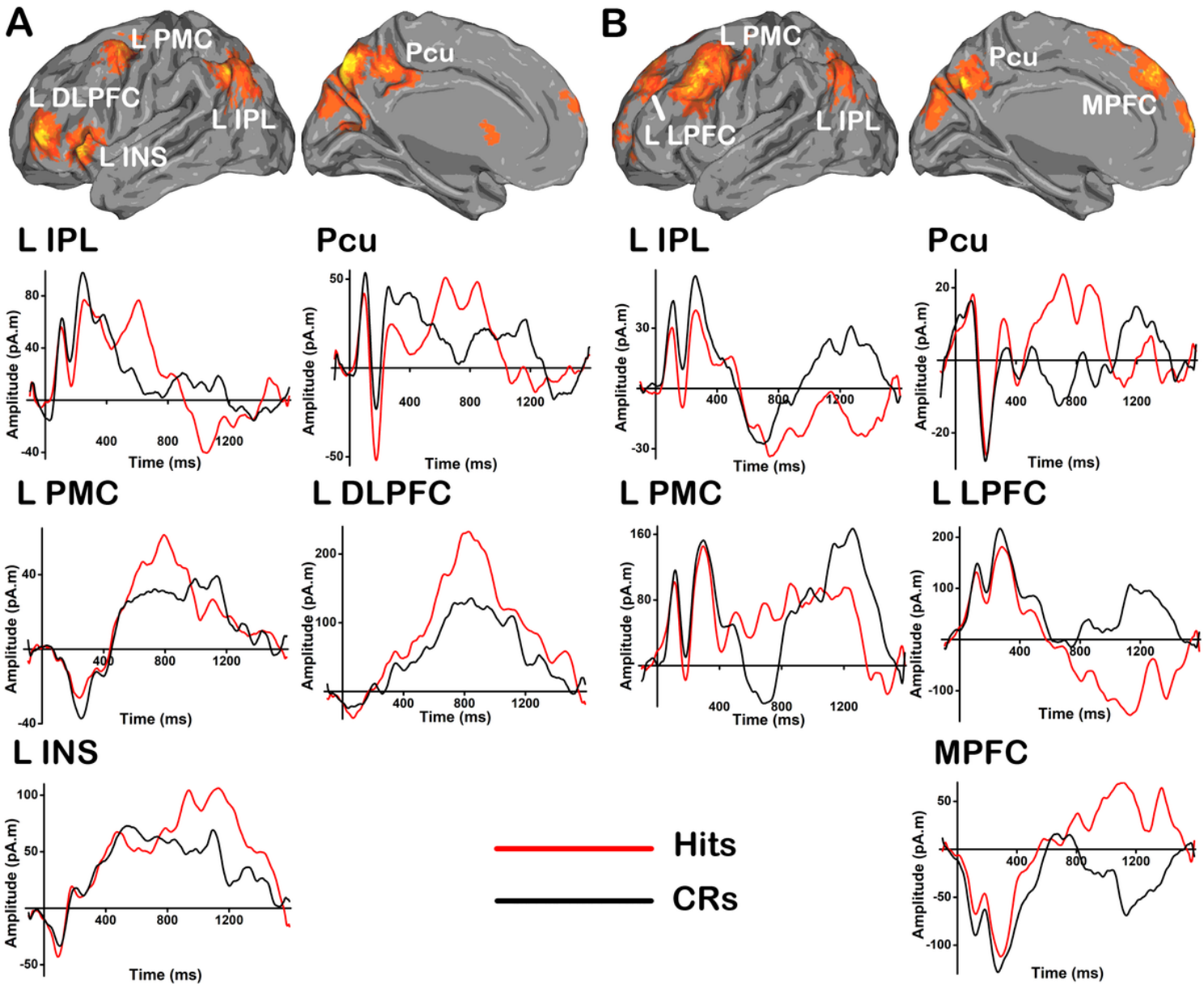

Figure 4

fMRI-constrained ERP analysis identified the source waveforms of the regional sources for retrieval success in the HC group (A) and the aMCI group (B). Although the retrieval success patterns were similar between groups (top row), the regional source waveforms related to the retrieval success pattern were different between groups. Red waveforms indicate hit conditions, while black waveforms indicate correct rejection conditions. Abbreviations: L, left; R, right; IPL, inferior parietal lobule; Pcu, precuneus; PMC, premotor cortex; DLPFC, dorsal lateral prefrontal cortex; LPFC, lateral prefrontal cortex; MPFC, medial prefrontal cortex; INS, insula; CRs, correct rejections.

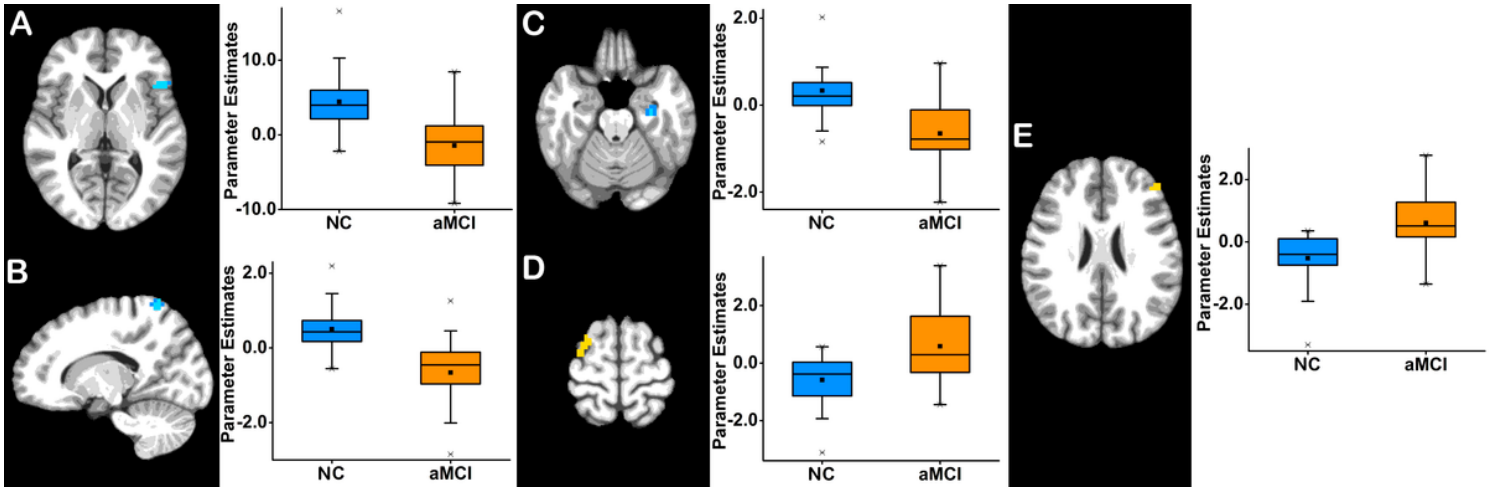

Figure 5

Between-group differences of the contrast hits versus correct rejections obtained by fMRI-only analysis (A) and by single-trial EEG-informed fMRI analysis for familiarity (B) and recollection (C, D, and E) components. (A) shows that in the fMRI-only analysis, the aMCI group showed decreased activity in the left ventrolateral prefrontal cortex when compared to the HC group (voxel-wise $p < 0.005$, cluster size > 15, same below). With regard to the ERP-informed fMRI analysis, the aMCI group showed decreased activity in the Pcu that was related to the ERP familiarity component (B); they exhibited decreased activity in the hippocampus (C), and increased activity in the right (D) and left (E) LPFC related to the ERP recollection component. Abbreviations: fMRI, functional magnetic resonance imaging; HC, healthy control; aMCI, amnestic mild cognitive impairment; Pcu, precuneus; LPFC, lateral prefrontal cortex.

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