Altered Neural Activity during Semantic Object Memory Retrieval in Amnestic Mild Cognitive Impairment as Measured by Event-Related Potentials

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Abstract. Deficits in semantic memory in individuals with amnestic mild cognitive impairment (aMCI) have been previously reported, but the underlying neurobiological mechanisms remain to be clarified. We examined event-related potentials (ERPs) associated with semantic memory retrieval in 16 individuals with aMCI as compared to 17 normal controls using the Semantic Object Retrieval Task (EEG SORT). In this task, subjects judged whether pairs of words (object features) elicited retrieval of an object (retrieval trials) or not (non-retrieval trials). Behavioral findings revealed that aMCI subjects had lower accuracy scores and marginally longer reaction time compared to controls. We used a multivariate analytical technique (STAT-PCA) to investigate similarities and differences in ERPs between aMCI and control groups. STAT-PCA revealed a left fronto-temporal component starting at around 750 ms post-stimulus in both groups. However, unlike controls, aMCI subjects showed an increase in the frontal-parietal scalp potential that distinguished retrieval from non-retrieval trials between 950 and 1050 ms post-stimulus negatively correlated with the performance on the logical memory subtest of the Wechsler Memory Scale-III. Thus, individuals with aMCI were not only impaired in their behavioral performance on SORT relative to controls, but also displayed alteration in the corresponding ERPs. The altered neural activity in aMCI compared to controls suggests a more sustained and effortful search during object memory retrieval, which may be a potential marker indicating disease processes at the pre-dementia stage.

Keywords: Cognition, electroencephalography, event-related potentials, memory, mild cognitive impairment, semantics
INTRODUCTION

The diagnosis of amnestic mild cognitive impairment (aMCI), a clinical entity proposed to be an intermediate state between normal aging and Alzheimer disease (AD), has been widely used to identify subjects at higher risk of progressing to dementia [1, 2]. Current models of AD suggest that biomarkers associated with AD precede clinically recognizable signs by at least 5 to 10 years [3]. In particular, neuropathological evidence of adaptation and dysfunction of synapses in the medial temporal and neocortical regions has been found in AD patients [4] and is indicative of incipient AD [5, 6]. Advanced neuroimaging techniques have recently played a critical role in characterizing the earliest neurobiological changes that occur in AD [7, 8]. Techniques such as event-related potentials (ERPs), which reflect the summation of post-synaptic potentials that are time-locked to certain events of interest, are affected by changes in synaptic integrity, and may hence have the potential to detect early disease processes in the AD brain and to monitor disease progression [9].

Although deficits in episodic memory are considered to be the hallmark symptom of AD [10], growing evidence suggests that semantic memory impairment is another key clinical symptom in MCI and early AD [11–13]. While degradation in the neural underpinnings of semantic memory has been suggested in ERP studies of AD showing delayed or diminished/absent semantic ERP components such as in N400 [14–22], fewer ERP studies have examined semantic memory in individuals who are in the pre-dementia phase, or MCI. Using a semantic congruity task with repetition, Olichney et al. found delayed N400 latency in MCI and diminished repetition effects for both congruous (late positive potentials) and incongruous (N400) trials in those MCI patients who converted to AD within 3 years [23, 24]. An ERP study found reduced N400 effect in MCI compared to controls during lexical ambiguity processing [25]. The majority of these studies have used either verification or priming paradigms in the context of word associations and semantic relations, but the extent to which these paradigms directly examine semantic memory retrieval is debatable. In view of the deficits observed in lexicosemantic recall in MCI during category fluency [26, 27], EEG tasks that involve direct lexicosemantic retrieval may advance our understanding of the neurobiological alterations associated with semantic retrieval deficits in individuals with MCI. The Semantic Object Retrieval Test (SORT) comprises a task that requires recall of a specific concept (e.g., object) upon direct evaluation of semantic feature information [28–30]. In particular, retrieval items (e.g., desert and humps) target active retrieval of objects (e.g., camel) and non-retrieval items (e.g., desert and clock) do not. Semantic memory retrieval dysfunction in SOR will behaviorally manifest as either a retrieval failure (false negative) during the retrieval trials or failure to suppress inappropriate object retrieval (false alarms) during the non-retrieval trials [30, 31]. A previous study using a 32-item SORT showed overall more errors in MCI patients (when errors for both retrieval and non-retrieval items were included). In particular, one-third of the MCI participants performed 2 standard deviations below the normal average [31]. These findings suggest that semantic memory retrieval deficit in MCI on SORT is not homogenously observed and that decrement in SORT performance might be one early predictor of disease progression in some individuals. Given that neural alterations have been found to precede behavioral deficits [3], those MCI subjects who were not evidently impaired based on SORT task performance may have underlying alterations in neural activity during semantic retrieval, which cannot be detected using behavioral paradigms. Thus, objective neuroimaging techniques may help to more fully characterize semantic memory retrieval deficits in individuals with MCI.

Our group developed an EEG version of the SORT (EEG SORT) and has studied neural underpinning related to this task in young and older adults. The first study involving young adults found a left frontotemporal component (beginning at 750 ms and lasting over 1500 ms post-stimulus) differentiating retrieval from non-retrieval trials [32]. When we examined the effects of normal aging using this same paradigm employing a data-driven approach, we replicated the findings of Brier et al. study. We found that in both younger and older adults differences between retrieval and non-retrieval trials occurred between 750 and 1500 ms. Additionally, we observed a frontal ERP effect (800–1000 ms post-stimulus) which differentiated non-retrieval from retrieval trials in older adults, suggesting a prolonged search process prior to judgment in older adults [30]. It is important to note that this later frontal ERP effect observed in older adults was independent (orthogonal) of the effect that was observed between 750–1500 ms. Intriguingly in our SORT ERP studies, we have not detected N400 effects (250–500 ms post-stimulus), which are typically observed in semantic processing studies [33]. Lack of typical N400 effects in the EEG SORT might be attributed to the fact that retrieval and non-retrieval
trials are not analogous to congruous and incongruous trials [also see discussion in 30], which are often carefully and strategically manipulated in paradigms that yield N400 components; thus SORT may involve different and/or additional neural mechanisms [29]. Nevertheless, converging findings from both the young adult study and the aging study show that a left fronto-temporal ERP component corresponds to object memory retrieval in SORT in both young and old. The primary aim of the current study was to use the EEG SORT to examine semantic object memory retrieval in individuals with aMCI as compared to normal aging controls. We hypothesized to identify altered neural activity associated with the SORT task in individuals with aMCI, as compared to controls, as qualitative differences (e.g., changes in topographical distribution or polarity of scalp potentials) and/or quantitative differences (e.g., reduced or delayed effects but with similar topographical distribution and polarity). A secondary aim of the current study was to look for associations between the ERP effects and neuropsychological measures to more fully address potential functional significance of the ERP effects and its implications [34].

MATERIALS AND METHODS

Subjects

We studied 16 aMCI subjects (6F; Mage = 69.7, SD = 7.9 years) and 17 normal control subjects (12F; Mage = 64.9, SD = 6.6 years). Participants (both controls and aMCI) were all Caucasian, 55 years or older, right-handed, and native English speakers. None had a history of learning disability, stroke, major psychiatric illness, alcoholism and substance abuse, uncorrected hearing and vision loss, or elevated depressive symptoms (Beck Depression Inventory-II [35] or Geriatric Depression Scale [36]). Controls did not have any subjective memory or cognitive complaints and performed normally on a battery of neuropsychological evaluation (Table 1). All the aMCI subjects met the standard clinical criteria [2] including the following: (a) memory concerns raised by the patient and/or corroborated by a reliable informant, (b) episodic memory impairments (1.5 SD below normal average) verified by objective measures, (c) grossly intact daily functions, and (d) not demented. aMCI subjects were either evaluated at the Alzheimer’s Disease Center at the University of Texas Southwestern Medical Center or by a behavioral neurologist (J.H.) who special-izes in memory disorders. Twelve met criteria for single-domain aMCI and four were multiple-domain aMCI. The Clinical Dementia Rating (CDR) [37] was used in all MCI subjects (CDR = 0.5, sum of boxes: 1.57 (mean) ± 1.05 (SD)), and full neuropsychological results are listed in Table 1. Three of the aMCI patients were taking cholinesterase inhibitors when tested (two on donepezil and one on rivastigmine, all on stabilized doses for at least 3 months). Informed consent was obtained from all participants in accordance with the protocols approved by the Institutional Review Boards of The University of Texas at Dallas and of The University of Texas Southwestern Medical Center. Procedures involving experiments on human subjects were done in accord with the ethical standards of the Committee on Human Experimentation of these institutions in which

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Controls (n = 17)</th>
<th>aMCI (n = 16)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>69.4 (6.6)</td>
<td>69.7 (7.9)</td>
</tr>
<tr>
<td>Education</td>
<td>17.2 (1.7)</td>
<td>16.1 (2.2)</td>
</tr>
<tr>
<td>Gender</td>
<td>5M/12F</td>
<td>10M/6F</td>
</tr>
<tr>
<td>Neuropsychological measures</td>
<td></td>
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</tr>
<tr>
<td>MMSE</td>
<td>28.4 (0.9)</td>
<td>28.3 (1.3)</td>
</tr>
<tr>
<td>MoCA</td>
<td>28.4 (1.6)</td>
<td>—</td>
</tr>
<tr>
<td>Category fluency</td>
<td>22.5 (3.6)</td>
<td>18.1 (0.5)</td>
</tr>
<tr>
<td>BNT-30 item</td>
<td>29.0 (1.1)</td>
<td>27.8 (1.6)*</td>
</tr>
<tr>
<td>DS forward</td>
<td>7.9 (0.9)</td>
<td>6.8 (1.3)*</td>
</tr>
<tr>
<td>DS backward</td>
<td>6.3 (1.1)</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Similarities</td>
<td>27.8 (2.7)</td>
<td>26.1 (4.6)</td>
</tr>
<tr>
<td>Digit symbol</td>
<td>27.6 (1.3)</td>
<td>42.6 (10.4)*</td>
</tr>
<tr>
<td>TMT-A Time</td>
<td>28.2 (5.9)</td>
<td>38.6 (12.1)*</td>
</tr>
<tr>
<td>TMT-B Time</td>
<td>33.1 (14)</td>
<td>101.1 (44.2)*</td>
</tr>
<tr>
<td>LM immediate</td>
<td>15.8 (1.2)</td>
<td>9.3 (2.3)*</td>
</tr>
<tr>
<td>LM delayed</td>
<td>14.1 (2.8)</td>
<td>7.7 (2.5)*</td>
</tr>
</tbody>
</table>

Each represents group mean (standard deviation). *MMSE, Mini-Mental State Exam [38]; MoCA, Montreal Cognitive Assessment [39]; COWAT, Controlled Oral Word Association Test [40]; Category fluency [41]; BNT, Boston Naming Test-30 items [42]; DS, digit span [43]; TMT, Trail Making Test [44]; LM, logical memory [45]. The numbers in the table are raw test scores. R, retrieval trials; NR, non-retrieval trails. Significance of each test between groups is shown as (p < 0.05 when p < 0.01 in the aMCI column; otherwise the test is not significant. Tests for neuropsychological measures using raw scores were controlled for age and education.
the experiments were done in accord with the Helsinki Declaration of 1975.

**EEG SORT task and procedure**

All participants completed the EEG SORT [30] and the majority performed the EEG task within 1 month of the neuropsychological testing (mean = 41.5 days). The EEG SORT consists of 56 pairs of words in the retrieval condition, with each pair representing features of a particular object. The non-retrieval condition contains 56 pairs derived from the same set of words, but with these words randomly and nonsensically paired. For example, the word pair ‘humps’ and ‘desert’ would facilitate memory retrieval of ‘camel’ (retrieval pair). In contrast, ‘humps’ and ‘monitor’ do not typically lead to memory retrieval of any object (non-retrieval pair). The full sets of retrieval and non-retrieval word pairs were randomly combined into two different sequences, to which subjects were randomly assigned. Word pairs were presented simultaneously for three seconds, with one word above the other. Between each trial, a fixation sign (+) was presented at the center of the screen for three seconds. Participants were asked to push either the ‘yes’ or ‘no’ button under right index or middle finger, respectively, to indicate if a word pair led to object retrieval. The following written instructions were given prior to the EEG task: “You are going to see two words. These represent features that are related to objects. Push the button under your index finger if the two words combine to bring to mind the name of some particular object. If the two words do not combine to bring to mind a particular object, push the button under your middle finger.” In addition, both speed and accuracy were recorded for each trial. Responses made outside the window between 300 and 3500 ms were labeled as incorrect. The EEG epochs were then re-referenced to the common average potential from all electrodes and baseline corrected (average potential of the pre-stimulus period between −200 to 0 ms). In order to still examine the standard ERPs at individual level, we averaged all the preprocessed EEG epochs to ascertain the quantity of the data for each single subject. The trial-by-trial EEG epochs were used for data-driven analysis, i.e., STAT-PCA, a procedure that utilizes statistical inference at each temporal and spatial unit (STAT) followed by a

**Continuous EEG**

Continuous EEG was recorded using a 64-electrode elastic cap (Neuroscan Quickcap) through a Neuroscan SynAmps2 amplifier and using Scan 4.5 software (Compumedics Neuroscan, USA; sampling rate: 1 kHz, DC-200 Hz). Electrode impedances were typically below 10 kΩ. The reference electrode was located at midline between Cz and CPz and vertical electroocculogram (VEOG) was recorded at sites above and below left eye. Data were processed off-line using Neuroscan Edit software (Compumedics Neuroscan). Poorly functioning electrodes were identified by visual inspection of the data, and electrodes that had impedance over 20 kΩ were excluded from analysis. No more than 5% of the electrodes were rejected in any single subject (on average, 1.8 % in controls and 2.5 % in aMCI). The continuous EEG data were high-pass filtered at 0.15 Hz and corrected for eye blinks using the spatial filtering function in the Scan 4.5 software. EEG data were then processed using EEGLAB functions [46] in MATLAB (the MathWorks Inc.). The data were first segmented into multiple trial-by-trial EEG epochs (~200 to 2000 ms) and only correct trials were included for analysis. We applied digital low-pass filtering with a cutoff value of 30 Hz (linear finite impulse response function) to minimize high frequency noise, such as muscle activity. Epochs with peak signal amplitude of more than 75 μV were rejected. Bad epochs were identified by visual inspection and by rejection algorithms in EEGLAB (rejecting improbable and abnormally distributed data lying beyond 5 standard deviations from the mean, using pop_rejprob.m and pop_rejkurt.m EEGLAB algorithms, respectively) and were excluded from further analysis. The average retaining rates (good trials / all correct trials) were 82.4% (41.1 trials) and 83.2% (42.7 trials) in the control group, and 82% (37.8 trials) and 82.9% (38.3 trials) in the aMCI group, for retrieval and non-retrieval trials, respectively. The EEG epochs were then re-referenced (global average potential from all electrodes) and baseline corrected (average potential of the pre-stimulus period between −200 and 0 ms). In order to still examine the standard ERPs at individual level, we averaged all the preprocessed EEG epochs to ascertain the quality of the data for each single subject. The trial-by-trial EEG epochs were used for data-driven analysis, i.e., STAT-PCA, which will be described in the next section.

**Statistical analysis**

A standard general linear model (GLM) was applied to measures of RT and accuracy to assess the effects of group, condition, and group by condition interaction. We analyzed pre-processed EEG epochs using STAT-PCA, a procedure that utilizes statistical inference at each temporal and spatial unit (STAT) followed by a
principal component (factoring) analysis (PCA) to isolate the most salient temporal and spatial properties of the ERPs [47].

In the first step of STAT-PCA, all the trial-by-trial EEG epochs are converted into an overall data matrix, coded by a number of ERP factors and experimental factors (Fig. 1a). ERP factors included a column for coding electrode-time combination (ETC) and two columns for electrode and time window, respectively. For the current study, we had 62 electrodes and 16 time windows (50-ms time windows between 400 and 1200 ms post-stimulus), resulting in $62 \times 16 = 992$ electrode-time combinations in total. In a previous study of SORT ERP [30], we determined that 50-ms time windows maintained an appropriate effective temporal resolution. Smaller fractionated windows (15 to 30 ms) only added to the multiple-testing burden without measurably improving the signal-to-noise ratio or the temporal resolution of mean amplitude data. We focused on the later time windows based on previous findings showing that SORT ERP effects arise later than 400 ms post-stimulus [30, 32]. However, we tested the time window between 0 and 400 ms using the same analysis to examine any potential effects. The experimental factors included columns for group ($i = 2$), condition ($k = 2$), subject ($j = 17$ and 16 in normals and MCIs, respectively), and trials ($l$ varied across individuals and conditions). The dependent variable (D.V.) was the mean amplitude within each 50-ms time window for each combination of the above factors (Fig. 1a).

STAT-PCA retains EEG trial-by-trial information in the data structure, which allows flexible modeling of experimental effects (e.g., within-subject and between-subject effects) by accounting for both intra-subject and inter-subject variance components [47]. In addition, it allows an automatic weighting of subject-level averages because trial numbers retained for analysis

![Fig. 1. Schematic flow chart of the STAT-PCA analysis. STAT-PCA is composed of two main steps: statistical analysis (a) followed by principal component analysis (b). The final results can be represented using both spatial and temporal information (c). Refer to the Methods section for detailed, step-wise descriptions. ETC, electrode-time combination; D.V., dependent variable; GLM, generalized linear modeling.](image)
vary from subjects to subjects due to varied accuracy and data quality among different subjects. To clarify, the STAT-PCA approach performs tests on the means of EEG epochs (hence averaging like ERP) for each level of the experimental factors so in essence the method is still predicated on ERP. The inclusion of subjects as a random variable in the statistical model, rather than in the PCA, makes results less sensitive to the deletion or addition of a single subject and makes the statistical inference generalizable to the population from which the subjects were sampled. We implemented a linear mixed model for each one of the 992 electrode-time combinations

\[ Y_{ijkl} = \mu + \lambda_i + b_{ij} + \Gamma_k + (\lambda \Gamma)_{ik} + e_{ijkl}, \]

to examine the effects of group \((\lambda_i)\), condition \((\Gamma_k)\) and the interaction between group and condition \((\lambda \Gamma)_{ik}\), on the scalp potential (mean amplitude) \(Y_{ijkl}\), where each subscript indexes group, subject, condition and trial, respectively (Fig. 1a). The variances associated with subject variability, \(b_{ij}\), and trial variability, \(e_{ijkl}\), were estimated by default residual maximum likelihood estimation of variance components. The outputs were the statistical results, including estimates, \(\lambda\) and \(\Gamma\) values, as depicted in the data matrix in Fig. 1a. Three such data matrices were generated (one matrix each for the effects of condition, group, and condition x group). In these matrices, only those estimates surviving an alpha threshold of 0.01 were passed on to the PCA step (Fig. 1b). The average potential of each of these three effects (estimates) of interest was retained if the corresponding test \(p\) value was below threshold; otherwise, they were set to zero. We chose this alpha level for the significance mask as a compromise between false positives and statistical power in our specific multiple-testing context. Additionally, this thresholding approach reduced the noise fed to the PCA to isolate only the most salient effects [47]. We were also guided to some extent by \textit{a priori} hypotheses of both timing and spatial location based on knowledge of previous findings using EEG SORT [30, 32].

We then applied PCA on the spatial factor (electrode) to the 3 matrices of thresholded average potentials, and retained the main spatial components by parallel analysis based on eigenvalues [48] (as represented in Fig. 1b). For each retained spatial component, the temporal components were simply the resulting PCA scores. We depicted the retained spatial/temporal components by plotting spatial PCA loadings in topographical distribution across scalp and temporal PCA scores as a time-series (Fig. 1c). The GLMs for both task performance and ERP data were implemented in SAS (Cary, NC), using the mixed model procedure, with the Kenward-Roger degree-of-freedom method to adjust the downward bias in variances when testing for fixed effects in mixed models [47].

In order to examine the relationships between ERP effects and behavioral measures, we performed linear regression analyses (IBM SPSS Statistics 21) combining data from both groups to test how well individual STAT-PCA effect scores would predict task performance (RT and accuracy averaged across retrieval and non-retrieval conditions) and neuropsychological measures (including logical memory immediate and delayed recall, letter fluency, category fluency, BNT, digit span forward and backward, digit symbol, and trail-making tests A & B, controlling for age and education). Assumptions of linearity, normally distributed errors, and uncorrelated errors were checked and met. Each individual STAT-PCA effect score was calculated as the matrix product of the ERP mean amplitude matrix \((16 \times 62\) matrix\), the PCA loading vector \((62 \times 1\) matrix\), and the PCA score vector \((1 \times 16\) matrix\), collapsing both spatial and temporal dimensions and calculating one single effect score \((1 \times 1\) matrix\) for each subject. The ERP mean amplitude matrix was derived from both retrieval and non-retrieval trials, separately, to account for their distinctive contributions to the object memory retrieval process.

RESULTS

EEG SORT task performance

Behavioral measures included RT and accuracy (Table 1). For RT, there was a significant main effect of condition, \(F(1,31) = 49.24, p < 0.001\), showing longer responses for non-retrieval trials \((1817 \pm 423\) ms\) than for retrieval trials \((1496 \pm 295\) ms\), and a trend in the main effect of group, \(F(1,31) = 3.81, p = 0.06\), with aMCI patients \((1771 \pm 411\) ms\) having longer response times than did controls \((1549 \pm 355\) ms\). The interaction between condition and group was not significant \((p=0.35)\). For accuracy, the main effect of group was significant, \(F(1,31) = 13.19, p = 0.001\), showing aMCI subjects \((82.8 \pm 5.7\%)\) performing less well than did controls \((90.3 \pm 5.7\%)\). The main effect of condition was also significant, showing lower accuracy during retrieval trials \((84.4 \pm 6.2\%)\) compared to non-retrieval trials \((90 \pm 10.8\%)\), \(F(1,31) = 5.91, p = 0.021\). The interaction between condition and group was not significant \((p=0.58)\). To examine the relationships between RT
and accuracy, correlation analyses were done combining both groups. Findings showed that during retrieval trials the longer the RT, the less accurate the responses, $R = -0.388$, $p = 0.026$; in contrast, there was no significant association between RT and accuracy in non-retrieval trials ($p > 0.1$, after excluding two extreme MCI outliers in the analysis). When both retrieval and non-retrieval trials were pooled together, no significant correlation was found ($p > 0.1$, after excluding two extreme MCI outliers in the analysis). Also, no significant correlations were found for either condition when the two groups were tested separately ($p > 0.1$).

**STAT-PCA results**

Group ERPs are shown in Figs. 2 and 3; topographical representations of the group ERPs over time (averaged across 100-ms time windows) are shown in Fig. 4. For condition differences (retrieval versus non-retrieval), one spatial PCA factor was detected (77.6% of total variance). The factor was loaded over the left fronto-temporal region (F7, FT7) starting at around 750 ms post-stimulus, with a smaller amplitude component near the right centro-parietal region (CP2, CP4) (Fig. 5a). In the left fronto-temporal region, the retrieval condition was associated with larger negative potentials relative to the non-retrieval condition in both groups (Fig. 5b); conversely, in the right centro-parietal region, the non-retrieval condition was associated with larger negative potentials relative to the retrieval condition (Fig. 5c).

To represent topographical patterns of the group level results based on the temporal PCA scores, we calculated the matrix product of each subject’s mean ERP data matrix (62 x 16 matrix) and the PCA scores (16 x 1 matrix), averaged them within each group, and plotted the weighted data matrix (62 x 1 matrix) overlying the scalp (as shown in Fig. 5d). Both groups showed

![Fig. 2. Group ERPs for the control group.](image-url)
that the left fronto-temporal and right centro-parietal effects were modulated by condition. For group differences (normal versus aMCI), there were no significant effects prior to 1000 ms post-stimulus onset.

For the group by condition interaction, one spatial PCA factor emerged (43.6% of total variance) in the frontal (FP1, F3) and parietal electrodes (Pz, P2), maximal between 950 and 1050 ms post-stimulus (Fig. 6a). This interaction was mostly a result of the condition effect in the aMCI group, with a more positive frontal potential in non-retrieval than retrieval trials (Fig. 6b) and, conversely, a more positive parietal potential in retrieval trials than non-retrieval trials (Fig. 6c). Topographical representations based on the temporal PCA scores for each separate group (Fig. 6d) showed that only aMCI subjects had this fronto-parietal effect modulated by condition, but controls did not. Finally, the same sets of analyses that were performed on the time window between 0 and 400 ms did not reveal any significant results or any PCA components using the same threshold (p < 0.01) in STAT-PCA.

In terms of regression analyses using ERP effects to predict behavioral and neuropsychological measures, the PCA loading and PCA score vectors were derived from the retained PCA factors for condition (Fig. 5a) and group/condition interaction (Fig. 6a). Each subject’s STAT-PCA effect score represents the degree to which each subject’s ERP pattern corresponding to each condition (separately for retrieval and non-retrieval trials) conforms to the STAT-PCA result. The results are shown in Table 2.

The late fronto-parietal ERP effect captured by non-retrieval trials was larger in those subjects with lower scores in logical memory, including both immediate, $R = -0.363, p = 0.045$, and delayed recall, $R = -0.374, p = 0.038$, and letter fluency, $R = -0.4, p = 0.031$ (scat-
Group-level topographical representations of ERP over time. Group level ERPs are illustrated in a topographical fashion for the control (a) and the aMCI group (b) between 200 and 1200 ms post-stimulus. Each scalp map is representative of the mean potentials averaged across each 100-ms time window. R, retrieval trials; NR, non-retrieval trials. NR-R represents the difference ERP.

DISCUSSION

Overall, we found that aMCI patients performed less accurately and more slowly during the EEG SORT compared to controls. While both control and aMCI groups demonstrated a left fronto-temporal ERP component starting around 750 ms post-stimulus, the MCI patients compared to controls, showed greater ERP difference between retrieval and non-retrieval trials occurring at around 950–1050 ms post-stimulus mainly in the fronto-parietal regions.

The lower accuracy in aMCI patients during SORT may be attributed to lexical or semantic processing deficits which have been documented widely using measures such as verbal fluency, BNT, and other tasks probing various aspects of knowledge about objects, famous people, buildings, and events [49–53]. On the other hand, slower RT could be due to slower processing speed in motor and cognitive functions, since aMCI patients performed worse than normal controls in speed-based tasks including trail making tests A & B and digit symbol. Regardless of group differences, RT was longer in non-retrieval trials compared to retrieval trials in both groups. We posit that arriving at a response in non-retrieval trials takes longer and requires more cognitive effort to search for any potential answers. Not until all the possibilities that initially come to mind are dismissed would someone make a negative decision/response. Here RT-accuracy tradeoff is less likely, since our analysis at the group level (including both groups) showed that accuracy was in fact worse when RT was longer in retrieval trials ($R = -0.388$), as opposed to better as would have been if an RT-accuracy tradeoff was a prominent factor.

With regard to the ERP findings, an ERP effect of comparable magnitude was observed in both controls and aMCI patients in the left fronto-temporal region. This ERP component, reflecting a more negative
potential in retrieval than non-retrieval trials starting around 750 ms, was also reported in previous studies on EEG SORT involving young and normal aging adults [30, 32]. This ERP component has been posited to indicate earlier stages of activation of semantic object memory during retrieval process [29]. That both controls and aMCI patients showed this effect suggests that earlier stages in semantic object memory retrieval in aMCI patients may be relatively intact. That is, the activation of object memory representation initially appears to be comparable in aMCI and controls, prior to other delayed differential responses potentially at a later semantic or post-semantic stage that might more substantially impact their performance in retrieving object memory during the SORT.

What differed between aMCI and controls was an increased fronto-parietal scalp potential between 950 and 1050 ms that differentiated retrieval from non-retrieval trials in aMCI patients but not in controls. In Chiang et al. [30], the fronto-parietal effect was found in healthy older adults, but at an earlier time frame between 800 and 1000 ms (but no such effect in young adults) and was posited to relate to a more extensive search during non-retrieval trials. It is plausible that aMCI patients require more effort in searching for a semantic link between the two features above and beyond what is needed by those who are normally aging, which is indexed neurally by this more positive potential in the non-retrieval compared to the retrieval condition in the
frontal electrodes. The disease process appears to affect the neural substrates that are critical for semantic object retrieval [28, 29] and thus leads to the delayed activity in scalp potentials. Other alternative cognitive processes to which this effect may be linked include a late decision making process that could be more demanding later during non-retrieval trials and the updating of working memory, as other late or delayed ERP components have suggested in AD/MCI [19, 23, 54]. Given that the fronto-parietal delayed response (between 950 and 1050 ms) occurred at least 600 ms earlier than the average RT (1588 and 1954 ms for retrieval and non-retrieval trials, respectively) and that there was no correlation between RT and this component, it is unlikely that this reflects prominent differences in motor responses, or lateralized readiness potential (LRP, normally occurs 100–200 ms before a motor response).

The fronto-parietal distribution of the late differential ERP effect indicates significant correlation in time between frontal and parietal potentials though in opposite polarities. At the neural level, it could be

Table 2
Regression analysis between behavioral measures and STAT-PCA effect scores (based on group by condition interaction)

<table>
<thead>
<tr>
<th>Behavior Measure</th>
<th>Retrieval</th>
<th>Non-retrieval</th>
</tr>
</thead>
<tbody>
<tr>
<td>SORT-RT</td>
<td>R = 0.044</td>
<td>R = 0.277</td>
</tr>
<tr>
<td>SORT-accuracy</td>
<td>R = 0.042</td>
<td>R = -0.149</td>
</tr>
<tr>
<td>LM-immediate</td>
<td>R = -0.145</td>
<td>R = -0.36*</td>
</tr>
<tr>
<td>LM-delayed</td>
<td>R = -0.192</td>
<td>R = -0.37*</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>R = 0.113</td>
<td>R = -0.4*</td>
</tr>
</tbody>
</table>

*p < 0.05. Analyses for LM (logical memory) and letter fluency were controlled for age and education.
that in one condition, different cellular populations are being synaptically impinged relative to the other condition. Those different neural impingements could be happening within the same regions of brain, thus causing activation of distinct neural generators projecting to opposite polarities at different sites on the scalp. Alternatively, the activity could be in different brain regions altogether, with consequent opposite-polarity across the scalp. However, it would be overly speculative to propose a detailed mechanism for how this front-parietal distribution on the scalp potential reflects either activity in individual underlying neural generators or the summation of potentials from different generators, given the complexities associated with EEG source identification [55]. The question warrants future studies using EEG source localization methods, or neuroimaging methods such as functional magnetic resonance imaging that afford higher spatial resolution.

The association between the late fronto-parietal effect during semantic object memory retrieval and episodic memory performance further suggests that altered neurophysiological activity on SORt is associated with the hallmark cognitive impairment in AD [10, 12], as we found that the worse a subject performed on logical memory (both immediate and delayed recall), the more the subject demonstrated delayed fronto-parietal ERP effect during non-retrieval trials. Studies have shown that over the course of MCI and AD, semantic memory dysfunction is associated with progressive reduction in brain volume and regional blood flow in a number of brain regions [12]. These brain regions include not only neocortical structures (e.g., inferior frontal gyrus and anterior temporal lobe) that are central to semantic-related functions [51, 56, 57], but also medial temporal lobe structures that normally display signs of neural degeneration and closely associated with episodic memory deficits [58, 59]. More specif-
ically, regions in the frontal and temporal lobes and other subcortical regions (thalamus and caudate) have been associated with SORt performance in a number of neuroimaging and neuropsychological studies [28, 60–62], and these regions could also be susceptible to AD pathology [63–65]. Furthermore, the strong negative correlation between the fronto-parietal effects and letter fluency performance suggests that there is some degree of deficits in output lexical processing that could be related to this late differential activity.

In conclusion, aMCI patients demonstrated worse performance than controls in a semantic object memory retrieval task. Neural responses at the earlier stage of semantic retrieval process show little impact of AD pathology [63–65]. Furthermore, the strong negative correlation between the fronto-parietal effects and letter fluency performance suggests that there is some degree of deficits in output lexical processing that could be related to this late differential activity.

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