Decreased Event-Related Beta Synchronization During Memory Maintenance Marks Early Cognitive Decline in Mild Cognitive Impairment

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Handling Associate Editor: László Vécsei

Abstract. Mild cognitive impairment (MCI) refers to a measurable deficit in cognition in the absence of dementia or impairment in activities of daily living. Working memory impairment is among the earliest signs of MCI. Oscillatory analysis of working memory might be a potential tool for identifying patients at increased risk of developing dementia. Our study aimed to assess the temporospatial pattern of spectral differences during working memory maintenance between MCI patients and healthy controls and to compare the sources of oscillatory activity between the two groups. Event-related spectral perturbation of 17 MCI patients and 21 healthy control participants was studied with 128-channel EEG during the Sternberg working memory task. Source localization was performed by using the eLORETA software. Among the participants, 13 MCI and 15 control participants underwent a structural brain MRI examination. Event-related synchronization (ERS) in the alpha and beta frequency band was significantly lower in MCI patients compared to healthy control participants during retention. Both study groups showed significant memory load-related enhancement in both frequency band. In the MCI group, source localization revealed significantly attenuated beta oscillatory activity in the inferior and middle temporal gyrus, in the fusiform gyrus, and in the cuneus. Beta ERS correlated significantly with the size of the hippocampus, entorhinal cortex, and parahippocampal gyrus. During the retention period, MCI is characterized by decreased alpha and beta ERS compared to controls indicating early impairment in neural networks serving working memory maintenance. The assessment of electrophysiological changes in the beta frequency range may provide a useful diagnostic tool for the early detection of cognitive impairment.

Keywords: Alpha rhythm, beta rhythm, electroencephalography, memory, mild cognitive impairment, short-term

INTRODUCTION

Mild cognitive impairment (MCI) refers to a measurable deficit in cognition in the absence of dementia

or impairment in activities of daily living [1]. MCI patients have an increased risk of developing dementia compared to the average elderly population. However, it could also be a stable or reverse condition without further progression [2]. Identifying patients with high risk of conversion has gained considerable interest, as these individuals are the best applicants for therapeutic intervention.

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This study is a continuation of our previously published works about structural and neuropsychological differences in MCI [3, 4], focusing on the spectral dynamics assessed with EEG and source localization of electrophysiological activity estimated by exact low-resolution brain electromagnetic tomography analysis (eLORETA) on the same population of subjects.

Working memory tasks are widely used paradigms in EEG studies of MCI [5–10], as working memory impairment is among the earliest signs of MCI [11–15] and it has been identified as a reliable predictor of Alzheimer's disease [11, 13, 16].

Previous analyses of event-related potentials (ERPs) were able to identify potential electrophysiological biomarkers of MCI [17]. Nevertheless, oscillatory analysis (event-related spectral perturbation, ERSP) brings important insights to memory deficits in MCI compared to conventional ERP analysis, since ERSP also captures the induced activity, which is not represented in ERPs. ERSP measures relative changes from the spectral power baseline, allowing the analysis of the time course of the EEG signal energy in specific frequency bands [18]. To gain a full insight into the electrophysiological activity linked to working memory, evoked and induced activity were analyzed by calculating the ERSP during the Sternberg working memory task.

Oscillatory activity in the alpha and beta frequency range plays an essential role in working memory. During the retention period of working memory tasks increased alpha [19–23] and beta power [24, 25] have been found consistently. Furthermore, memory load-related enhancement has been observed in both frequency bands [19, 20, 26, 27]. However, despite the similar dynamics, the two frequency bands might have different roles: alpha oscillation reflects a top-down mechanism of active suppression of irrelevant information [19, 22, 28, 29] and the top-down modulation of attention [21, 30], while beta oscillation is important in the active maintenance of new information for further task requirements [24, 26, 31].

In MCI, only a few studies examined alpha and beta event-related oscillatory activity during a working memory task. Decreased beta event-related synchronization (ERS) has been revealed in progressive MCI and Alzheimer's disease compared to stable MCI and healthy controls during a two-back task [8]. Decreased alpha/beta (10–20 Hz) activity was found in MCI compared to healthy controls in an auditory Sternberg memory task [7].

Most of the previous time-frequency analyses used the n-back task paradigm [5, 6, 8, 32]. The main advantage of the Sternberg task is the opportunity to separate the encoding, retention and retrieval conditions temporally. Therefore, we applied this paradigm in the present research. Furthermore, former studies did not investigate the effect of task difficulty on modulation of alpha and beta activity in MCI.

For the source localization, the low-resolution electromagnetic tomography approach was applied, which has been previously successfully used for the analysis of ERPs in MCI patients [33, 34]. However, to our knowledge, this is the first study examining the sources of induced time-varying oscillations in MCI.

Our study aimed to assess the temporospatial pattern of spectral differences between MCI patients and healthy controls in working memory processes as revealed by ERSP and to analyze the differences in the cortical projections of the time-varying cross-spectral density between the two study groups. The main goal of this study was to find electrophysiological biomarkers that mark deteriorated retention in MCI.

Based on the previous research, we assumed a modulation of alpha and beta oscillations by memory load, and decreased alpha and beta ERS of the temporal lobe in MCI patients compared to controls, reflecting the early impairment of working memory network. Furthermore, we hypothesized a correlation between alpha and beta ERS and other early markers of cognitive decline such as neuropsychological tests and the volume and cortical thickness of medial temporal lobe structures measured by MRI.

MATERIALS AND METHODS

Participants and clinical measures

The study was carried out in the Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary. Altogether 17 MCI patients and 21 healthy control participants were enrolled in the study. Among them, 13 MCI patients and 15 healthy control participants underwent a structural brain MRI examination (others refused participation). Demographic and neuropsychological data are summarized in Table 1.

Selection criteria were no history of head injury, stroke, mental retardation, epileptic seizure, acute psychiatric disorder or substance dependence. Subjects with dementia were excluded according to

Table 1
Demographic data and results of basic neuropsychological tests

	control ($n = 21$)	MCI ($n = 17$)	p value
Age (Mean (SD))	64.9 (5.2)	69.2 (7)	$p = 0.04$
Education[a]	19%/19%/62%	18%/18%/65%	n.s.*
Gender (Female)	66,70%	47%	n.s.*
RAVLT 1–5 sum[b]	54.3 (6.4)	40.4 (10.8)	$p < 0.0001$
RAVLT delayed recall[c] (MCI: $n = 14$)	10.9 (2.4)	7 (4.3)	$p = 0.002$
ACE Total Score[d]	94.5 (2.9)	87 (7.7)	$p = 0.0002$
ACE VL/OM-ratio[e]	2.6 (0.4)	2.7 (0.5)	n.s.*
MMSE Total Score[f]	29 (1.2)	28.1 (1.2)	$p = 0.04$
TMT Part A[g]	34.4 (8.5)	70.2 (52.8)	$p < 0.0001$
TMT Part B[g] (MCI: $n = 16$)	63.1 (16)	142.5 (68.4)	$p < 0.0001$
GDS Score[h] (control: $n = 20$)	4.4 (3.2)	4.2 (3.5)	n.s.*
STAI Score[i]	40.8 (11.4)	35.9 (9.4)	n.s.*
Sternberg test[j]	91.7% (8.5)	82.3% (19.7)	$p = 0.049$

MCI, mild cognitive impairment, ACE, Addenbrooke's Cognitive Examination; STAI, State-Trait Anxiety Inventory; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trail Making Test. [a]Participants were categorized into three education groups: 1 = less than 12 years; 2 = high school graduation (12 years education); 3 = more than 12 years of education. [b]Sum of all words in the first five trials. The maximum score is 75. [c]The maximum score is 15. [d]The maximum score is 100. [e]VL/OM: verbal fluency and language points/orientation and delayed recall ratio can be defined based on ACE. Result below 2.2 indicate frontotemporal dementia and result over 3.2 indicate Alzheimer's disease. [f]The maximum score is 30. [g]Time needed for completing the task in seconds. [h]The maximum score is 15. [i]The maximum score is 80. [j]Response accuracy in the Sternberg task. *n.s. (not significant) = $p > 0.05$.

the Mini-Mental State Examination (MMSE) scores standardized for age and education [35].

Participants had subjective memory complaints and applied to take part in a cognitive training program announced among general practitioners and in a Retirement Home (The study is registered at Clinical-Trials.gov, the identifier is 'NCT02310620'). Every participant underwent a regular psychiatric assessment to evaluate possible excluding comorbidity. After that, cognitive functions were assessed with neuropsychological tests to specify the diagnosis.

Diagnostic procedure of MCI was based on the Petersen criteria [1], including subjective memory complaint corroborated by an informant, preserved everyday activities, memory impairment based on a standard neuropsychological test, preserved global cognitive functions and the exclusion of dementia. For the detailed assessment of memory impairment, we applied the Rey Auditory Verbal Learning Test (RAVLT). Attention, executive functions, and cognitive flexibility were examined with the Trail Making Test (TMT) Part A and Part B, global cognitive performance was estimated with the Addenbrooke's Cognitive Examination (ACE). For the differentiation between MCI and healthy controls, we applied a cut-off score of 1 SD under population mean standardized for age and gender/education in these neuropsychological tests. Participants, who scored under the

cut-off value in the delayed recall subscore or the total score of RAVLT or the TMT Part B or the ACE, were put into the MCI group. The results of the neuropsychological tests are summarized in Table 1.

EEG stimuli and procedures

During EEG examination, participants were seated in a dimly lit, sound-attenuated room. White digits, Arial font, point size 60 were presented as stimuli on a computer screen at approximately 50 cm with Presentation 13.0 software (Neurobehavioral Systems, Inc.; Albany, CA). All participants had normal or corrected-to-normal vision.

During EEG recording subjects performed the Sternberg task [36], an extensively used test of working memory [7, 22].

At the onset of each trial, three, four or five randomly selected one-digit number appeared sequentially in the middle of the screen for 2000 ms, separated by a fixation cross for 450–500 ms. The length of the sequence was counterbalanced across 126 trials. An exclamation mark showed for 500 ms indicated the end of the learning sequence. For the retention period, a fixation cross appeared for 3900–4000 ms. In the retrieval condition, two probe numbers were presented for 2000 ms separated by fixation cross presented for 450–500 ms (Fig. 1).
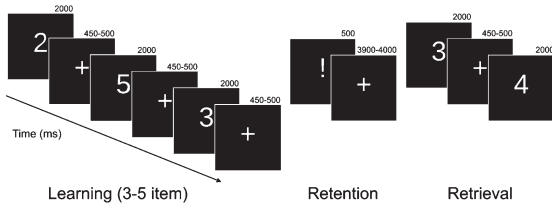
Fig. 1. The Sternberg working memory task.

Participants were instructed to indicate by clicking with the mouse (yes-right/no-left) whether the probe number was part of the presented sequence. Response assignment was counterbalanced across trials. Efficiency was measured by response accuracy.

We ascertained that the participants are alert and understand the instructions, and we monitored them during the completion of the task to bypass the possible distorting effect of extended eye closure on the EEG activity, especially in the alpha frequency range [37]. For the same purpose, participants completed the task in six equal parts separated by a 3-min rest period.

EEG recording and processing

EEG was recorded from DC with a low-pass filter at 100 Hz using a high-density 128-channel BioSemi ActiveTwo amplifier [38]. Electrode caps had an equidistant-layout and covered the whole head. Eye movements were monitored with EOG electrodes placed below the left and above the right external canthi. Data were digitized at a sampling rate of 1024 Hz. Built-in and self-developed functions as well as the freeware EEGLAB toolbox [39] in the Matlab (MathWorks, Natick, MA) development environment was used for subsequent off-line data analyses. EEG was re-referenced to the common average potential and filtered off-line between 0.5 and 45 Hz using zero-phase shift forward, and reverse IIR Butterworth filter.

Epochs from 500 ms pre-stimulus to 2000 ms post-stimulus for the learning and 3500 ms post-stimulus for the retention period were extracted from the continuous EEG and corrected for the pre-stimulus baseline. Removal of muscle, blinking, and eye movement artifacts (detected by EOG) were performed by ADJUST [40], an ICA (Independent Component Analysis) based automatic artifact detector. Furthermore, epochs with a voltage exceeding ± 100 μ V on any channel were rejected from the analysis.

After artifact rejection, the average number of trials in the control group and MCI group were 478.1 (SD = 40.2), 414.6 (SD = 66.8) for the learning condition and 119.4 (SD = 13.3), 103.8 (SD = 19.2) for the retention condition, respectively

We divided the 128 channels into 11 scalp regions (three frontal, three central, three parieto-occipital and two temporal).

EEG data analysis

Stimulus-related alpha (7–14 Hz) and beta (14–25 Hz) activity changes were measured by the ERSP, providing a 2-D representation of the mean change in spectral power (in dB) from baseline [41]. Beyond conventional event-related analytical approach, ERSP is able to capture event-related as well as induced oscillatory activity. Unlike evoked responses, induced activity is not phase-locked to the stimulus, and if a brain response to an event is not phase-locked across trials precisely enough, the potentially important induced activity will be averaged out from the ERPs, and therefore poorly represented in, or completely absent from the time-domain features of the ERP.

To compute the ERSP, baseline spectra are calculated from the EEG immediately preceding each event. The epoch is divided into brief, overlapping data windows, and a moving average of the amplitude spectra is created. Each of these spectral transforms of individual response epochs is then normalized by dividing by their respective mean baseline spectra. Normalized response transforms for many trials are then averaged to produce the average ERSP, plotted as relative spectral log amplitude on a time-by-frequency plane [41] (see details in the Supplementary Material).

The analysis was performed on epochs extending from 500 ms before to 2000 ms and 3500 ms after stimulus onset in learning and retention condition, respectively in the 1.5–30 Hz frequency range. The sliding window was 400 ms wide, and it was applied 200 times with an average step size of 6 ms. No zero padding was applied. The analyzed time interval lasted from 300 ms before to 1800 ms and 3300 after stimulus onset in learning and retention condition, respectively. The ERSP time-frequency matrices were baseline corrected by the average power calculated from the 500 to 200 ms pre-stimulus period. Dynamical changes in oscillatory activity were studied by computing ERSPs for each trial, then averaging them separately for learning and retention condition

[42, 43]. Mean ERSP values were calculated by averaging across electrodes within scalp regions to further attenuate noise.

Based on a prior study [8] and adjusted to the end of desynchronization, we selected the 800–1500 ms (alpha band) and the 800–1700 ms (beta band) time windows in learning condition for further analysis. Epochs of retention were sorted into low and high memory load condition, according to the length of the learning sequence (three-item vs. four and five-item), to assess memory load-related spectral modulation. In retention condition, the analysis was performed on the 600–1000 ms time window (alpha and beta band).

Source localization

Based on the scalp-recorded electric potential distribution, the exact low-resolution brain electromagnetic tomography (eLORETA) software (free academic software at http://www.uzh.ch/keyinst/loreta. htm) was used to compute the cortical three-dimensional distribution of current density. The eLORETA method is a discrete, three-dimensional (3D) distributed, linear, weighted minimum norm inverse solution, where the intracerebral volume is partitioned in 6239 voxels at 5 mm spatial resolution. Description of the method together with the proof of its exact zero-error localization property, are in [44, 45].

For source localization, the artifact-corrected EEG was down-sampled to 256 Hz. Time-varying cross-spectra of epochs were calculated using a Hamming window of 400 ms width. Subsequently, current source density of alpha and beta oscillations was estimated in eLORETA for voxels as a function of time.

MR image acquisition and processing

Participants underwent a routine brain MR examination, producing high-resolution anatomical images used for analysis. Image acquisitions were made at the MR Research Center, Semmelweis University, Budapest on a 3 Tesla Philips Achieva clinical MRI scanner equipped with an 8-channel SENSE head-coil. High resolution, whole brain anatomical images were obtained using a T1 weighted 3-dimensional spoiled gradient echo (T1W 3D TFE) sequence (see details in the Supplementary Material).

Statistical analysis

The different effects on ERSP in learning condition were tested by two-way analyses of covariance (ANCOVA) of the study group (HC versus MCI) × region. To test the effect of memory load on ERSP three-way ANCOVA of study group × region × memory load (three- vs. four and five-item) was applied for the analysis in retention period. All the main effects including age and gender, two- way and three-way interactions for the second model were included into the ANCOVA models.

Post-hoc pairwise contrasts were conducted to investigate the interactions. Since between-group comparisons were evaluated over eleven regions, Hochberg correction for multiple comparisons was applied to the *post-hoc* contrasts [46, 47].

Group differences were characterized by Cohen's d. Associations between neuropsychological test scores, size of medial temporal lobe structures and ERSP in regions of large [48] between-group difference in learning (Cohen's d > 0.8) and regions of large load-related difference in retention condition (Cohen's d > 1.0) were assessed. For the analysis, Pearson correlation was applied adjusted for age. For variables, deviating largely from the normal distribution Spearman correlation was used adjusted for age. Structural MRI results were derived from previous, former published part of our study, as the size of medial temporal lobe structures could most effectively distinguish MCI patients from healthy controls [3, 4].

In eLORETA, voxel-by-voxel comparisons were estimated for learning condition and retention period for the previously defined time windows between the subject-wise corrected control and MCI groups by using independent *t*-test (Baseline Corrected Control vs. Baseline Corrected MCI). Statistical significance was assessed with a nonparametric randomization test ($n = 5000$) that corrects for multiple comparisons [49].

RESULTS

Behavioral results

The MCI group (mean score = 82.3%, SD = 19.7) showed a significantly decreased memory performance (U = 111, $p = 0.049$) compared to the control group (mean score = 91.7%, SD = 8.5) in the Sternberg task.
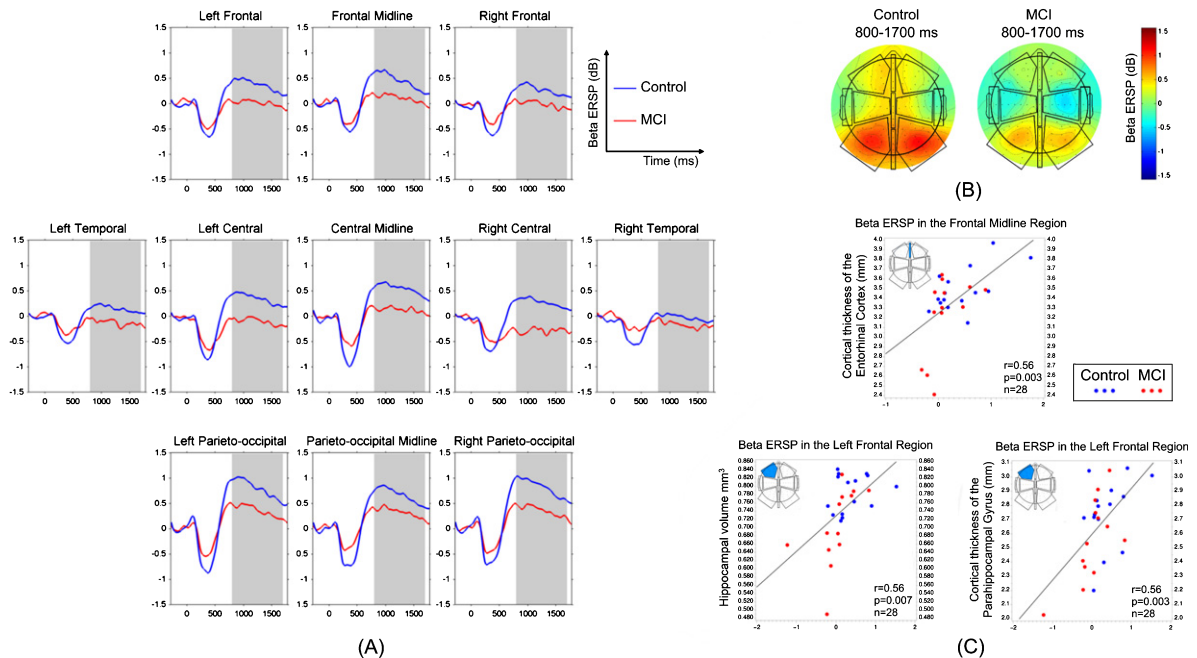
Fig. 2. Late learning/early retention condition. A) Beta event-related spectral perturbation (ERSP) in study groups (800–1700 ms time-window highlighted). B) Scalp topography of the beta ERSP in study groups in the 800–1700 ms time window. C) Correlation of beta ERSP with the size of medial temporal lobe structures in the 800–1700 ms time window.

Alpha synchronization in late learning/early retention

During learning condition in the 800–1500 ms time window control subjects showed a significant event-related synchronization (ERS) in the alpha frequency band in all scalp regions (i.e., differences from zero were significant at a corrected level of $p < 0.05$), while in the MCI group alpha no similar ERS was observable (corrected $p > 0.05$).

A significantly decreased alpha ERS $(F(1,34) = 4.44, p = 0.04)$ was detected in the MCI group relative to controls. The main effect of age and gender on alpha ERSP were not significant $(p > 0.05)$, while the interaction of region and group had a significant effect $(F(10,34) = 4.75, p = 0.0003)$. Post hoc analyses of this interaction revealed large between-group differences in the right central and left temporal regions (Cohen's d = 1.1 and 0.9). The between-group difference in the right central region $(t = 3.47, df = 34, p = 0.001)$ remained significant after correction for multiple comparisons.

Beta synchronization in late learning/early retention

Control subjects showed significant beta ERS in all frontal, midline and parieto-occipital scalp regions

in the late 800–1700 ms time window for learning condition. While in the MCI group beta ERS was only observable in the left parieto-occipital and midline parieto-occipital regions in the same time window (corrected $p < 0.05$) (Fig. 2A, B).

A significantly decreased beta ERS $(F(1,34) = 6.69, p = 0.01)$ was detected in the MCI group relative to the control group. The main effect of age and gender were not significant $(p > 0.05)$, while region and group had a significant interaction effect $(F(10,34) = 3.13, p = 0.006)$. Between-group differences were large in terms of Cohen's d in midline (frontal: 0.9, central: 1.0, parieto-occipital: 0.9), pariteo-occipital (left: 1.0, right: 0.9) and left frontal (0.9) regions. The between-group difference in the central midline region $(t = 3.04, df = 34, p = 0.0045)$ remained significant after correction for multiple comparisons.

Correlational analysis of alpha and beta synchronization in late learning/early retention

Significant negative correlations were found between the time needed for participants to complete TMT Part A and Part B and alpha ERS in right central (A: Spearman $r = -0.49, p = 0.002$, B: Spearman $r = -0.52, p = 0.001$) and left temporal regions

(A: Spearman $r = -0.45$, $p = 0.005$. B: Spearman $r = -0.50$, $p = 0.002$). Alpha ERS did not correlate significantly with the size of medial temporal lobe structures.

Beta ERS in early retention showed significant correlations with the ACE total score, TMT Part A, and Part B results, RAVLT delayed recall and with response accuracy in the Sternberg task. Additionally, beta ERS correlated significantly with the cortical thickness of the entorhinal cortex and parahippocampal gyrus and the volume of the hippocampus (Fig. 2C, Table 2).

Source localization of alpha and beta synchronization in late learning/early retention

Group comparison revealed a significantly (corrected non-parametric $p < 0.05$) lower beta activity in MCI group in temporal, occipital and frontal lobe relative to controls. In the beta band, the most expanded clusters with voxels of significant between-group differences were localized in inferior temporal gyrus, middle temporal gyrus, and fusiform gyrus (Fig. 3, Table 3).

In the alpha frequency band, tendency level (corrected non-parametric $p < 0.1$) differences were observed between groups in frontal and parietal lobe structures.

Alpha and beta synchronization in late retention with varying memory load

During retention, in the 600–1000 ms time window, both groups showed increased alpha activity in high memory load (four- and five-item learning sequence) condition compared to low memory load (three-item learning sequence) (F(1,34) = 42.9, $p < 0.0001$). However, the alpha band did not show significant between-group difference.

Contrary to that in beta frequency band significantly lower beta ERS (F(1,34) = 6.26, $p = 0.02$) was observable in MCI participants relative to controls (Fig. 4A, B). Beta ERS increased significantly with memory load (F(1,34) = 45.97, $p < 0.0001$) in both groups similarly, as the three-way interaction of group, load, and the region was not significant ($p > 0.05$).

The modulation in the beta band was large (Cohen's d > 0.8) in all regions and reached its maximum in the right central region (Cohen's d = 1.2). Interestingly, this region showed the largest between-group differences both in low and high memory load conditions (Cohen's d = 0.94 and 0.73).

Correlational analysis of beta synchronization in late retention

Correlational analysis was performed for the beta frequency range, as alpha activity did not show significant between-group difference.

Mean beta ERS of late retention condition correlated significantly with the RAVLT immediate recall and the TMT Part A and Part B scores. Furthermore, beta ERS showed a significant correlation with the cortical thickness of the entorhinal cortex and the volume of the hippocampus (Fih. 4C, Table 2).

Source localization of beta synchronization in late retention

A tendency level (corrected non-parametric $p < 0.1$) between-group difference was observed in the beta activity of the precentral gyrus (Table 3).

DISCUSSION

In this study, the electrophysiological correlates of working memory maintenance were examined in MCI patients and healthy controls.

Retention of information is deteriorated in MCI [50] and neuropsychological tests, assessing the efficacy of the maintenance of newly learned information are considered as sensitive instruments of early detection of MCI [51, 52].

Previous studies found that alpha and beta oscillations are linked to working memory maintenance [20, 22]. Therefore we specifically examined changes in these frequency bands applying the neural synchrony approach. For the assessment, we used the Sternberg memory paradigm allowing temporal separation of encoding, retention, and retrieval.

During the learning condition, various cognitive processes can be distinguished: encoding of new stimulus, adding to the pool of memory contents and maintenance of the newly acquired information. A late time window was applied similarly to a previous study [8] assuming, that oscillatory changes during this late time window reflect neural activity related to the early period of retention rather than encoding. Our assumption is corroborated by the observed dominance of alpha and beta synchronization during this time window [19, 24, 31] in contrast

Table 2
Correlations between the neuropsychological test results, temporal lobe structures and the Beta Event-Related Synchronization (ERS) across the entire sample

| | Beta ERS | | | | | | | | | |
| | Early retention | | | | | Late retention | | | | |
	Midline	Left Parieto-occipital	Frontal Midline	Right Parieto-occipital	Left Frontal	Parieto-occipital Midline	Right Central	Left Central	Right Frontal	Right Temporal
Neuropsychological test										
ACE Total Score ($n=38$) *Spearman r (p-value)*	0.32 (0.06)	0.29 (0.09)	0.18 (0.3)	0.26 (0.1)	0.32 (0.05)	**0.36 (0.03)**	0.18 (0.3)	0.12 (0.5)	0.12 (0.5)	0.27 (0.1)
RAVLT items 1–5 sum ($n=38$) *Pearson r (p-value)*	0.27 (0.1)	0.17 (0.3)	0.16 (0.3)	0.13 (0.4)	0.21 (0.2)	0.19 (0.3)	**0.35 (0.03)**	0.07 (0.7)	0.22 (0.2)	0.26 (0.1)
RAVLT delayed recall ($n=35$) *Pearson r (p-value)*	**0.39 (0.02)**	0.15 (0.4)	0.23 (0.2)	0.13 (0.5)	0.14 (0.4)	0.23 (0.2)	0.25 (0.1)	–0.004 (1.0)	0.16 (0.4)	0.26 (0.1)
TMT part A ($n=38$) *Spearman r (p-value)*	**–0.55 (0.0004)**	**–0.42 (0.01)**	–0.30 (0.07)	**–0.47 (0.003)**	**–0.41 (0.01)**	**–0.37 (0.03)**	**–0.37 (0.02)**	–0.30 (0.07)	–0.22 (0.2)	–0.25 (0.1)
TMT part B ($n=37$) *Spearman r (p-value)*	**–0.53 (0.0008)**	**–0.47 (0.004)**	**–0.38 (0.02)**	**–0.45 (0.006)**	**–0.48 (0.003)**	**–0.49 (0.002)**	**–0.38 (0.02)**	–0.21 (0.2)	–0.32 (0.06)	–0.21 (0.2)
Sternberg task ($n=38$) *Spearman r (p-value)*	0.27 (0.1)	0.25 (0.1)	0.10 (0.54)	**0.34 (0.04)**	0.21 (0.2)	**0.33 (0.0495)**	–0.01 (0.9)	–0.12 (0.5)	0.16 (0.4)	0.17 (0.3)
Cortical thickness (mm)										
Entorhinal cortex ($n=28$) *Pearson r (p-value)*	**0.45 (0.02)**	**0.46 (0.02)**	**0.56 (0.003)**	**0.4 (0.04)**	**0.47 (0.01)**	**0.46 (0.02)**	**0.55 (0.003)**	**0.54 (0.004)**	**0.46 (0.02)**	**0.45 (0.02)**
Parahippocampal gyrus ($n=28$) *Pearson r (p-value)*	**0.48 (0.01)**	**0.55 (0.003)**	**0.39 (0.04)**	**0.46 (0.02)**	**0.56 (0.003)**	**0.41 (0.03)**	0.18 (0.4)	0.06 (0.8)	0.10 (0.6)	0.09 (0.6)
Volume (mm^3)										
Hippocampus ($n=28$) *Pearson r (p-value)*	0.32 (0.1)	**0.44 (0.02)**	0.37 (0.06)	**0.46 (0.02)**	**0.51 (0.007)**	**0.40 (0.04)**	**0.40 (0.04)**	**0.39 (0.046)**	0.26 (0.2)	0.39 (0.45)
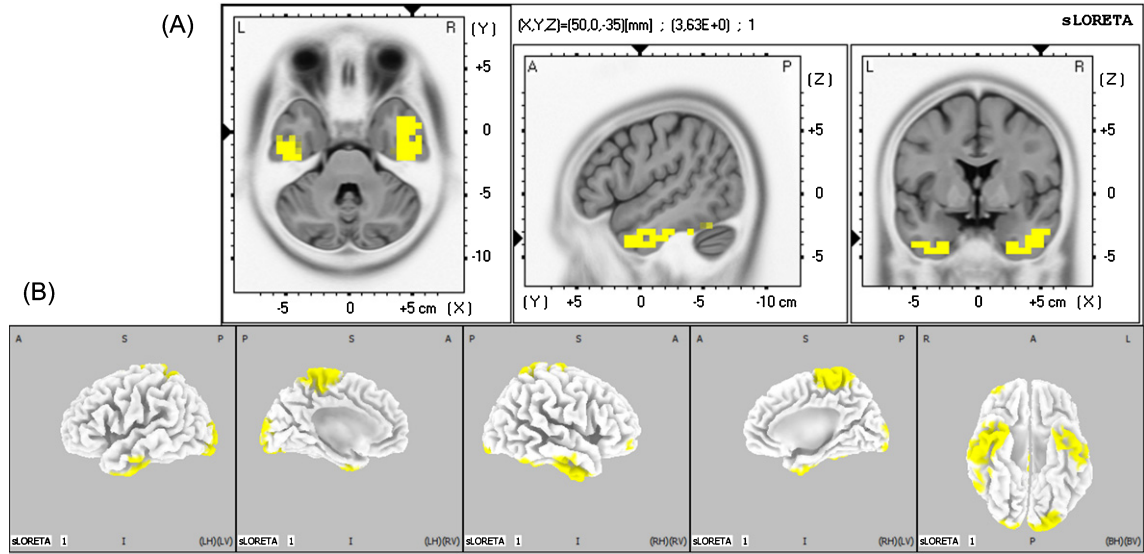
Fig. 3. Source localization of beta oscillatory activity in late learning/early retention condition. A) Largest cluster with voxels of significant ($p < 0.05$) between-group difference in the inferior temporal gyrus. B) The result of the source localization in late learning/early retention condition. Highlighting indicates significant ($p < 0.05$) group differences in beta activity (Control > MCI) in the 800–1700 ms time window.

to desynchronization, which characterizes encoding [53]. Therefore, we refer to this late time window as an early period of retention.

Beta frequency band

During early and late retention beta ERS in MCI group appeared only in the posterior regions, while the control group showed significant beta ERS in almost all scalp regions.

Converging evidence suggests that beta oscillation is an essential contributor for the sufficient functioning of working memory. Previous studies found beta activity enhancement during the retention period in various memory tasks [24, 25], that has been suggested to reflect the process of active maintenance of newly acquired information for further task requirements [8, 24, 26, 31].

We observed diminished beta ERS during early and late retention in the MCI group relative to controls, which is consistent with the results of previous studies [7, 8].

Significant correlation of beta ERS with response accuracy in Sternberg task and TMT results further supports the role of beta oscillations in active maintenance of information, as TMT Part B specifically reflects the ability to maintain two tracks of thought simultaneously [35].

The active role of beta oscillations is also corroborated by its observed enhancement according to

increasing task demands in line with previous results of healthy individuals [20, 26]. Our results show that in MCI this adaptive modulation is preserved.

While the differences of beta ERS between the two groups were significant in both condition, the reduction of beta oscillation in the MCI group did not have a region-specific distribution, indicated by similar effect sizes across scalp regions. In order to gain insight into the source of diminished beta activity in MCI, we used eLORETA for source localization. The results showed that the decreased beta ERS in the MCI group during early retention is linked to attenuated beta activity in the inferior and middle temporal gyrus, in the fusiform gyrus, and in the cuneus. These cortical areas play an important role in processing and encoding visual information. Our finding fit to the framework suggesting that sustained activity of the cortical regions involved in processing the representations of information may contribute to the neural process of maintenance in working memory [54, 55]. Attenuated beta activity in task-related areas in the MCI group might reflect the disturbance of the cortical network supporting retention of information during memory task.

Furthermore, beta ERS during early and late retention showed significant positive correlation with the volume of the entorhinal cortex, the parahippocampal gyrus, and the hippocampus. Working memory maintenance stands on the complementary functions of the prefrontal cortex, medial temporal lobe and

Table 3
Results of the source localization by eLORETA

Condition	Frequency band	Time-window	Areas	Brodmann Areas	MNI coordinates at t_{max}			cluster size	volume
					X	Y	Z	(voxel)	(cm^3)
Early retention	Alpha	800–1500 ms	Postcentral Gyrus(*)	3,4,5,7	–20	–35	70	24	3
			Medial Frontal Gyrus(*)	6	–10	–15	70	21	2.625
			Precuneus(*)	7	–5	–65	60	19	2.375
			Paracentral Lobule(*)	4,5,6	10	–50	65	13	1.625
			Precentral Gyrus(*)	4,6	–15	–30	70	11	1.375
			Superior Frontal Gyrus(*)	6	–15	–15	70	8	1
			Superior Parietal Lobule(*)	7	15	–60	65	7	0.875
	Beta	800–1700 ms	Inferior Temporal Gyrus*	20,21,37	50	0	–35	71	8.875
			Middle Temporal Gyrus*	21,38	50	10	–40	33	4.125
			Fusiform Gyrus*	18,19,20,36,37	–25	–85	–20	31	3.875
			Cuneus*	17,18,19	–25	–95	–5	29	3.625
			Postcentral Gyrus*	3,4,5,7	10	–35	70	29	3.625
			Paracentral Lobule**	4,5,6	0	–35	65	24	3
			Medial Frontal Gyrus**	6	5	–30	70	21	2.625
			Uncus*	20,36,38	30	0	–45	21	2.625
			Middle Occipital Gyrus*	18,19	–25	–85	–15	16	2
			Lingual Gyrus**	17,18	–25	–95	–10	12	1.5
			Superior Temporal Gyrus*	38	35	15	–45	9	1.125
			Inferior Occipital Gyrus**	17,18	–25	–90	–15	8	1
			Precentral Gyrus**	4,6	20	–20	70	7	0.875
			Superior Frontal Gyrus**	6	10	–20	70	7	0.875
			Middle Frontal Gyrus*	10,11	45	55	–5	4	0.5
			Superior Parietal Lobule*	7	–25	–60	65	3	0.375
			Temporopolar Area*	38	25	10	–45	1	0.125
Late retention	Beta	600–1000 ms	Precentral Gyrus(*)	6	20	–20	70	2	0.25

(*)$p < 0.1$, two-tailed, *$p < 0.05$, two-tailed, **$p < 0.01$, two-tailed.

cortical regions responsible for processing the representations [56]. In this network, the medial temporal lobe modulates the activity of task-specific posterior areas [57]. The beta oscillatory activity might be a candidate for mediating this connection, as memory load-related enhancement of beta phase synchronization was observed between the medial temporal lobe and the inferior temporal cortex [58]. Therefore, decreased beta activity of task-relevant cortical regions in MCI might reflect deteriorated regulatory function of the medial temporal lobe and might be an indirect marker of subtle functional impairment.

Our results complement previous studies referring decreased beta ERD during encoding [59] and recognition [7, 60]. and decreased beta ERS during retention [8] in MCI, leading us to the conclusion that reduced beta reactivity in working memory tasks could be a sensitive marker of early, subtle cognitive deterioration [7, 61].

Alpha frequency band

In line with the result of former studies we observed memory load-related enhancement of alpha activity [22, 23, 27] in both study groups and decreased alpha ERS in the MCI group relative to controls during early retention [7].

Oscillatory changes in the alpha frequency range are often explained in the context of the active inhi-
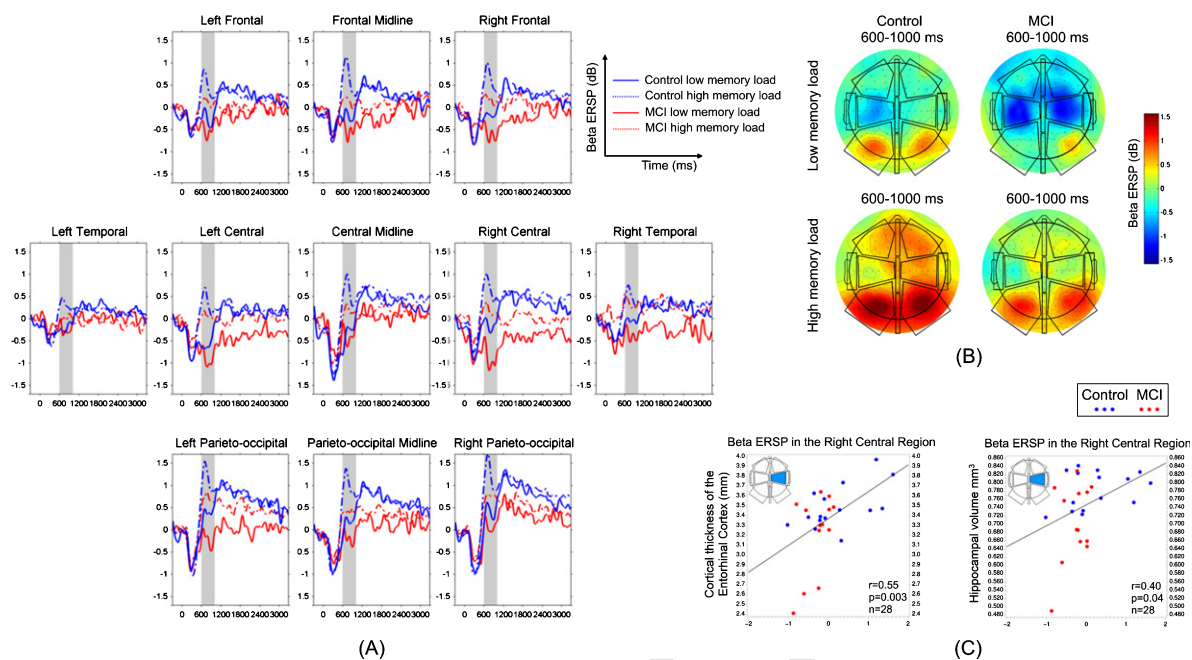
Fig. 4. Late retention condition. A) Beta event-related spectral perturbation (ERSP) in study groups (600–1000 ms time window highlighted). B) Scalp topography of the beta ERSP in study groups in the 600–1000 ms time window. C) Correlation of mean beta ERSP with the size of medial temporal lobe structures in the 600–1000 ms time window.

bition theory. According to this theory, increased alpha amplitude arising in cortical regions, that are not involved in stimulus processing protects the task-relevant information from interference [62]. Therefore decreased alpha ERS in MCI group might reflect deteriorated gating of task-irrelevant external information.

Correlation of alpha ERS with TMT results further support this assumption, as successful completion of TMT demands the effective filtering of interfering stimuli.

In late retention, alpha ERS did not show significant between-group difference. A potential reason for that might be that working memory retention is characterized by enhanced and attenuated alpha activity in different cortical regions simultaneously [21, 63, 64], and therefore during averaging these spectral changes might be smoothed out.

Limitation

The present study was limited by a slight age difference between groups, although statistical tests were corrected for age and gender as covariates and none of them had a significant effect in either condition. MRI data was not accessible for every subject as ten attendees refused participation. The study focused on

the early diagnosis of cognitive impairment; however, involving patients with Alzheimer's disease or other type of dementia could paint a more detailed picture and expand the possible clinical application of the results. In this study, we did not apply a control task, which is a further limitation. Finally, follow-up data is not yet available to examine the predictive value of spectral perturbation in the conversion rate to dementia. However, our study provides a cross-sectional view of the electrophysiological changes during working memory maintenance in MCI.

Conclusion

Working memory maintenance is accompanied by decreased alpha and beta ERS in MCI. While diminished ERS in the alpha frequency range during early retention might reflect deteriorated gating of external information in MCI patients, decreased beta ERS during early and late retention could mark the impairment of active information maintenance. In MCI, attenuated beta oscillatory activity in working memory maintenance network is observable during the early period of retention, primarily in the temporal lobe.

The assessment of electrophysiological changes especially in the beta frequency range may provide a useful diagnostic tool for the early detection of cog-

nitive impairment, although further studies applying similar paradigms are required to verify our results.

ACKNOWLEDGMENTS

AVAILABILITY OF DATA AND MATERIAL

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

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The National Scientific and Ethical Committee, Budapest, Hungary approved the research. Participants gave their written informed consent before the procedures.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-171079.

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