Reduced Visual Event-Related Delta Oscillatory Responses in Amnestic Mild Cognitive Impairment

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Abstract: Mild cognitive impairment (MCI) is considered as a prodromal stage for Alzheimer’s disease (AD) in the majority of cases. Event-related oscillations might be used for detection of cognitive deficits. Our group’s earlier results showed diminished delta visual and auditory target oscillatory responses in AD, and we investigated whether this prevails for MCI. Eighteen MCI subjects and 18 age-matched healthy elderly controls were investigated. The maximum peak-to-peak amplitudes of oscillatory responses for each subject’s averaged oscillatory target responses in delta, theta, and alpha frequency bands upon application of visual oddball paradigm were measured. Repeated measures of ANOVA was used to analyze four locations (frontal, central, parietal, occipital), at three coronal (left, midline, right) sites. Independent t tests were applied for post-hoc analyses. The oddball target delta response (0.5–3.0 Hz) was 26–32% lower in MCI than healthy controls over fronto-central-parietal regions [F(1.34) = 4.562, p = 0.04]. Without a group effect, theta oscillatory responses (4–7 Hz) showed significant differences in coronal electrodes indicating highest values over mid-electrode sites, and a anteriorposterior x coronal effect, being maximum at mid-central. Alpha frequency band analyses indicated no statistical differences. Peak-to-peak amplitudes of visual target delta oscillatory responses were lower in fronto-central-parietal regions in MCI than in healthy controls. This supports our earlier findings in AD, showing hypoactive delta fronto-central-parietal regions during cognitive tasks. These results indicate that event-related oscillations may detect early changes of brain dynamics in MCI, and deserves to be investigated as a candidate biomarker in further studies using multimodal techniques.

Keywords: Biomarker, early diagnosis of Alzheimer’s disease, electroencephalographic rhythms, event-related potentials, mild cognitive impairment, oscillations

INTRODUCTION

Mild cognitive impairment (MCI) is one of the most investigated neurological topics in recent years. Persons with MCI commonly have mild problems performing complex functional activities such as managing finances or shopping. Even though these functions are achieved less efficiently, MCI subjects need minimal assistance for their functionality or do not lose their independence. This stage is generally considered as a symptomatic predementia phase of Alzheimer’s disease (AD) [1], as the conversion rate of clinical MCI to dementia is about 10–15% each year [2, 3]. Early intervention strategies at the predementia stage are important in reducing the conversion rate, which affects public welfare. The full potential of electrophysiological methods in helping to predict [4–6], to diagnose [7–11], and to monitor either treatment or progress [12, 13] in AD/MCI patients has
subjects with the diagnosis of amnestic MCI (mean study included 18 consecutive, community-dwelling subjects. The disease process and the occurrence of MCI group's VERO (visual event-related oscillation) in the pre-dementia phase of AD. The deviation of controls, as most of the subjects are considered to be especially over fronto-central-parietal regions than would show lower event-related oscillatory responses, [28, 29] in AD. Coherence in alpha, theta, and delta frequency ranges decreased in visual and auditory oddball paradigms, along with decreased event-related coherence of AD subjects in visual and auditory sensory modalities. The term “event-related” is used for a potential elicited after an event including cognitive task [23].

Oscillatory brain activity as a hallmark of neuronal network function can accurately index normal and abnormal brain functions. Brain oscillatory responses provide non-invasive analysis of cortico-cortical connectivity, local neuronal synchronization of firing, and coherence of rhythmic oscillations at various frequencies [20]. Event-related oscillations (ERO) provide a powerful technique, with high temporal resolution, which can be used as a tool for detecting subtle abnormalities of cognitive processes [21, 22]. In our previous work, we explored ERO, evoked oscillations, and evoked or event-related coherence of AD subjects in visual and auditory sensory modalities. The term “event-related” is used for a potential elicited after an event including cognitive task [23].

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Our group [24, 25] and others [26, 27] reported decreased delta ERO in either visual or auditory oddball paradigms, along with decreased event-related coherence in alpha, theta, and delta frequency ranges [28, 29] in AD.

We hypothesized that amnestic MCI subjects would show lower event-related oscillatory responses, especially over fronto-central-parietal regions than controls, as most of the subjects are considered to be in the pre-dementia phase of AD. The deviation of MCI group’s VERO (visual event-related oscillation) responses from the responses of healthy controls was mainly observed in the delta frequency in our earlier studies.

MATERIAL AND METHODS

Subjects

We conducted a prospective open study. The study included 18 consecutive, community-dwelling subjects with the diagnosis of amnestic MCI (mean age 70.5 years, age range 60–76 years) according to the Petersen criteria [30]. Eighteen age- and education-matched normal elderly controls (mean age 68.2 years, age range 60–78 years) were recruited from various community sources. None of the healthy controls were consanguineous to the patients. Mean education level was 10.7 years in the MCI group and 10.3 years in the control group (p = 0.91). There were nine females in the control group and eleven in the MCI group. All MCI subjects underwent an extensive cognitive testing and a complete neurological, neuro-imaging (MRI), and laboratory examination including blood glucose, electrolytes, liver and kidney function tests, full blood count, erythrocyte sedimentation rate, thyroid hormone, vitamin B12, HIV, and VDRL. The cognitive testing included episodic memory (Oktem verbal memory processes test, [31]), non-verbal memory (Wechsler's visual reproduction test), attention (WMS-R digit span test), orientation, executive functions (Stroop test, clock drawing test, verbal fluency test), language (Boston naming test), and the Mini-Mental State Examination (MMSE). A score of Clinical Dementia Rating (CDR) of 0.5, not reaching dementia criteria, was obtained from the subjects (Table 1). The participants diagnosed with MCI had subjective memory complaints, which were verified by a relative and by a memory test score 1–1.5 standard deviations below the mean norm for their age, and all but four were followed one more year and their neuropsychological tests were repeated. Depressive co-morbidity was excluded on the basis of a geriatric depression scale score higher than 11 (GDS, [32]). At one year follow-up of neuropsychological tests, four subjects out of 18 did not answer to our follow-up calls. Out of 14 MCI subjects, eleven progressed. Out of these 11 progressive MCI subjects, four converted to AD and seven showed lower cognitive test scores. Only three MCI subjects remained stable. The groups’ characteristics are shown in Table 1. Subjects with abnormal laboratory results, indicating other causes of memory disorder, and those with vascular lesions in their MRI were excluded from the

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Controls (n = 18)</td>
</tr>
<tr>
<td>Age (SD) (year)</td>
</tr>
<tr>
<td>Education (SD) (year)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
</tr>
<tr>
<td>MMSE (SD)</td>
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</table>

SD: Standard deviation, M, male; F, female, MMSE, Mini-Mental State Examination, *independent sample t-test, χ²-test.
All participants had normal vision, and none reported a history of head injury, or any other neurological or psychiatric disorders. All participants with regular use of anti-dementia drugs, antidepressants, neuroleptics, anti-epileptic medications, stimulants, opioids, or beta-blockers were excluded from the present study. Informed consent was obtained from all subjects or their relatives. The study was approved by the local ethical committee.

Stimuli and paradigms

A classical visual oddball paradigm was used in the experiments. Two types of stimuli were used: the standards and the deviants. The probability of the deviant stimuli was 40/120 and that of standard stimuli 80/120. As stimulation, we used a white screen with a luminance of 40 cd/cm² for standard signals. The luminance of the deviant stimuli was 10 cd/cm². In all the paradigms, the deviant stimuli were embedded randomly within a series of standard stimuli. The task required was mental counting of the target stimuli. These stimulation signals were applied randomly and inter-stimulus interval varied from 3 to 7 seconds.

During the elicitation period of event-related oscillations, all subjects had displayed sufficient accuracy of mental count of target stimuli, being slightly worse in the MCI group than the controls.

Electrophysiological recording

The EEG was recorded from F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, O2, and Oz locations according to the international 10–20 system, with 30 Ag-AgCl electrodes mounted on an elastic cap (Easy-cap). Additionally, two linked Ag-AgCl earlobe electrodes (A1+ A2) served as references. The electrooculography (EOG) from the medial upper and lateral orbital rim of the right eye was also registered. All electrode impedances were less than 10 kΩ. The EEG was amplified by means of a BrainAmp 32-channel DC amplifier with band limits of 0.01–250 Hz. The EEG was digitized on-line with a sampling rate of 500 Hz. Subjects’ averages and grand-averages were calculated for each electrode site and experimental condition.

Computation of Visual Event-Related Oscillations (VERO)

Before the averaging procedure, epochs containing artifacts were rejected by an off-line technique, i.e., single sweep EOG recordings were visually studied, and trials with eye-movement or blink artifacts were rejected. Subject averages and grand-averages were calculated for each electrode site and experimental condition.

As oscillatory responses, we measured the peak-to-peak amplitudes of each subject’s averaged responses filtered in the delta, theta, and alpha frequency ranges [24–26, 33]. We measured the peak-to-peak amplitude of each subject’s averaged target responses, which were digitally filtered for delta band (0.5–3.0 Hz) in 0–800 ms, for theta (4–7 Hz) in 0–500 ms, for alpha (8–13 Hz) in 0–300 ms poststimulus time window in both groups. According to the literature on brain oscillations and basic principles of systems theory, the range of oscillatory signals was chosen in correlation to the frequency signal studied [34].

Statistical analysis

The SPSS (version 19 for Windows, IBM) was used for statistical analysis. Maximum peak-to-peak amplitude oscillatory responses were analyzed separately for each frequency band by means of repeated measures ANOVA, including the between-subjects factor as groups (healthy aged controls, MCI) and the within-subject factors for 3 coronal (left, medial, right) × 4 anterior-posterior (frontal, central, parietal, occipital), and Greenhouse–Geisser corrected p-values were taken into consideration. Post-hoc analyses were conducted using independent t test.

RESULTS

Visual event-related oscillations

Delta frequency band

In the present study, we found that the MCI group had 25–37% lower values for the maximum peak-to-peak amplitudes of delta oscillatory responses compared with healthy elderly controls over frontal, central, and parietal locations [F1.34 = 4.562, p = 0.04]. Figure 1A presents all significant results on a topological map. The delta response was larger in healthy controls than in MCI. The reduction of the delta response in MCI was 29% over F3 and C3, and 32% over P3. Post-hoc comparisons using the independent sample t-test revealed that the peak-to-peak delta oscillatory response was significantly larger for healthy controls than for MCI over the electrode sites F3, F4, C3, C4, P3, and P4 (p < 0.05) (Table 2, Fig. 1). The repeated measures of ANOVA revealed a significant effect for anterior-posterior × group [F1.10 = 4.894,
Fig. 1. A) Grand-averages of maximum peak-to-peak delta amplitudes for visual oddball target in healthy elderly controls (shown as black) and subjects with mild cognitive impairment (shown as red). The difference between groups is prominent over frontal, central, and parietal regions. B) Maximum peak-to-peak delta amplitudes of visual oddball target in healthy elderly controls (shown as black) and subjects with mild cognitive impairment (shown as red) differ in frontal, central, and parietal regions. The '*' symbol indicates the significance levels of \( p < 0.05; \) and '**' \( p < 0.01. \)

\[ p < 0.009 \) indicating lower values over fronto-central-parietal regions in MCI compared to healthy controls.

Regardless of group effects, significant results for coronal \( (F_{3,68} = 11.813, \ p < 0.0001) \), indicating increased delta responses, were observed over left- and mid recording sites; and for anterior-posterior \( (F_{3,102} = 12.448, \ p < 0.0001) \), indicating higher delta response, were observed over frontal and central sites, compared to parietal and occipital sites. Parietal electrodes displayed higher amplitudes than those on occipital locations. In the results for coronal × anterior-posterior, midline fronto-central electrodes showed higher values than left or right corresponding electrode sites.

The mean peak-to-peak oscillatory responses amplitudes of the control group were 8.36 (3.50), 7.96 (2.85), and 7.46 (3.00) \( \mu V \) at F3, C3, and P3 locations, respectively. MCI subjects had smaller amplitudes of

| Table 2 |
| Difference in maximum peak-to-peak delta (0.5–3.0 Hz) amplitudes between mild cognitive impairment (MCI) and healthy elderly controls (visual oddball paradigm, target responses) |

<table>
<thead>
<tr>
<th></th>
<th>Controls ( n=18 ) ( \mu V )</th>
<th>MCI ( n=18 ) ( \mu V )</th>
<th>Change ( % )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3</td>
<td>8.36 (3.50)</td>
<td>5.91 (2.04)</td>
<td>-29</td>
<td>&lt;0.05</td>
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<tr>
<td>Fz</td>
<td>9.31 (4.22)</td>
<td>6.89 (7.72)</td>
<td>-26</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>F4</td>
<td>8.10 (3.47)</td>
<td>5.93 (2.30)</td>
<td>-27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>C3</td>
<td>7.96 (2.85)</td>
<td>5.68 (2.11)</td>
<td>-29</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cz</td>
<td>8.81 (3.87)</td>
<td>6.37 (2.97)</td>
<td>-28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>C4</td>
<td>7.99 (3.21)</td>
<td>5.78 (2.64)</td>
<td>-27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P3</td>
<td>7.46 (3.00)</td>
<td>5.08 (2.56)</td>
<td>-32</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pz</td>
<td>7.74 (3.08)</td>
<td>5.31 (2.70)</td>
<td>-29</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P4</td>
<td>6.97 (2.53)</td>
<td>5.32 (2.51)</td>
<td>-24</td>
<td>NS</td>
</tr>
<tr>
<td>O1</td>
<td>4.91 (2.38)</td>
<td>5.15 (1.87)</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>O2</td>
<td>4.75 (2.11)</td>
<td>5.26 (3.33)</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>O3</td>
<td>4.64 (2.00)</td>
<td>5.25 (1.94)</td>
<td>13</td>
<td>NS</td>
</tr>
</tbody>
</table>

5.91 (2.04), 5.65 (2.11), and 5.08 (2.58), respectively, at corresponding electrode sites (Table 2, Fig. 1).
The occipital locations did not show any variation in peak-to-peak oscillatory responses amplitude between MCI subjects and controls.

Theta frequency band (4–7 Hz)

Regardless of group effects, significant results for coronal ($F_{2,63} = 11.19, p < 0.0001$) sites, indicating highest theta responses, were observed over mid-electrode sites ($p < 0.001$); and right sided electrodes were higher than left sided electrodes ($p < 0.003$). For anteriorposterior X coronal ($F_{6,304} = 3.49, p < 0.008$) analysis, mid-central electrode (Cz) was found to have the highest peak-to-peak amplitude in comparison to other electrode sites ($p < 0.001$) (Table 3).

Alpha frequency band

Alpha frequency band did not show any significant differences regarding group, coronal, or anteriorposterior effect in target peak-to-peak amplitude analysis (Table 3).

DISCUSSION

Brain oscillatory activity has the potential to be useful as a measuring tool for cognitive dysfunction. In the present study, we analyzed VERO responses in MCI in comparison to healthy elderly controls. Decreased delta VERO responses were found over fronto-central-parietal regions in MCI, in line with our expectations. Our group’s earlier findings on mild AD subjects indicated decreased delta responses most prominently over fronto-central and parietal regions utilizing either visual or auditory oddball paradigm [24, 25]. Other groups also emphasized the importance of delta ERO responses in AD [26, 27].

Brain oscillatory activity as a hallmark of cognitive dysfunction

Neural plasticity of brain networks helps the maintenance of healthy brain activity in the daily life of elderly people. Oscillatory brain activity can indicate whether neuronal network function is normal or abnormal; and provide non-invasive analysis of cortico-cortical connectivity, and neuronal synchronization and coherence of rhythmic oscillations at various frequencies [20]. These approaches hypothesize that the EEG consists of the activity of an ensemble of generators producing oscillatory activity in several frequency ranges. These oscillators are usually active in a random way. However, by application of cognitive stimulation, these generators couple and act together coherently. Evoked potentials, representing ensembles of neural population responses, were considered to be a result of transition from a disordered to an ordered state [35]. Oscillations in the delta frequency range are related to “focused attention”, “signal detection”, “recognition”, and “decision making” [36–38]. As the major shape determining oscillatory activity of P300, delta responses are related to basic information processing mechanisms of attention allocation and immediate memory [39]. The amplitude of delta responses increases during oddball paradigms, and may be related to signal detection and decision making [40]. Brain oscillations at lower frequencies are proposed to play a role in mediating long-range interactions [41]. In agreement with this, simulation studies have indicated that lower frequencies, such as delta or theta oscillations, are better suited to sustain long-range synchronization [42]. Not only thalamic neurons, but also cortical neurons may discharge in the slow frequency range such as delta [43]. Since memory and complex attention functions are reduced in MCI [44], our results are in accordance with cognitive deficits from the psycho-physiological point of view.

The electrophysiological continuum of MCI and AD

In the present report, peak amplitudes of delta oscillatory responses upon application of visual oddball paradigm are reduced in amnestic MCI subjects, similarly to AD. The earlier data comparing AD and MCI subjects in our laboratory are illustrated in Fig. 2. This figure shows a continuum of delta oscillatory responses among healthy controls, MCI, and AD subjects. In our earlier studies using classical visual or auditory oddball paradigm, we observed reduced delta oscillatory response in frontal, central, and parietal regions of AD subjects [24, 25]. Moreover, visual event-related coherences were found to be decreased between frontal and almost all other parts of the brain in AD [29], indicating a widespread cortico-cortical disconnection in this disease [28].

Among the earlier reports of event-related brain oscillations in MCI/mild AD, the neuro-physiological deviation from controls was mostly a decrease in the slow frequency ranges (delta and theta) [10, 24–29, 45–50]; and less prominent changes were reported in high frequency ranges [13, 49, 51, 52].

Functional role of delta oscillatory responses

Delta oscillatory responses have a functional role in brain dynamics. We used the classical visual oddball paradigm, since it is known that MCI subjects
are cognitively impaired. By means of application of oddball paradigm, increased attention, learning and working memory, and perception can be investigated. The studies show that the delta response is related to decision making. Parnefjord and Başar [53] and Demiralp et al. [54] reported that, after application of stimuli with decreasing intensities, the oscillatory responses consist of nearly pure delta responses when stimuli approach the subjective hearing threshold. At the threshold intensity, stimulation poses the subjects into focused attention. In this context, the lower delta oscillatory responses over fronto-central-parietal regions in MCI/mild AD subjects upon either visual or auditory oddball paradigm are quite understandable, as individuals with MCI tend to show decreased focused attention or decision making [55].

**Topographical differences between MCI and healthy elderly**

We found the expected diminished fronto-central-parietal activity upon a cognitive task in MCI. Occipital locations did not show any difference between the subject groups. Also, a complex time course and configuration consisting of a double peak (one within 0–300 ms time window, and a second peak within 300–800 ms time window) were observed in MCI, but only a later peak appeared in the late time-window of healthy elderly controls.

Our earlier reports on AD strongly suggest hypo-responsive fronto-central-parietal areas in response to cognitive tasks [20, 21, 46, 47]. In addition, decreased connectivity measures between frontal and almost all other parts of the cortex were shown by event-related coherence studies in AD [28, 56] and further studies on event-related coherence analyses in MCI are needed to observe whether a similar pattern exists in amnestic MCI subjects.

**Concluding remarks**

The present paper opens a new conjecture for investigating a new type of physiological intervention to
explore the observed reduction in delta responses in MCI. In particular, delta frequency band showed prominent reduction in MCI. The cognitive dysfunction in MCI and its relation to brain oscillations cannot be answered by this study alone, but remains to be investigated. Our findings of VERO in MCI subjects present several conclusions and remarks: 1) Amplitudes of delta oscillatory responses are lower in MCI; 2) the electrophysiological differences between MCI and healthy subjects are similar to, and possibly less prominent than, that seen between mild AD and healthy subjects (Fig. 2); and 3) the present results also suggest that delta VERO responses may be an important parameter for differentiating MCI from healthy controls in further studies.

Our results lead us to believe that, in clinical situations such as MCI/AD where the cognitive impairments are more evident than sensory impairments, electrophysiological methods using cognitive stimulation may have an advantage over the electrophysiological measurements of spontaneous activity or simple sensory stimulation. Moreover, comparison of cognitive task responses with spontaneous EEG activity or sensory-evoked responses may elicit the dynamic changes seen in different circuits activated in certain conditions (i.e., resting, sensory, or cognitive). Further methods using coherence, phase-locking or prestimulus/poststimulus response analysis can provide additional information regarding changes in brain dynamics in MCI.

One of the major limitations of the present study is the small group size. However, it can be assumed that, with a greater number of subjects and by using multimodal methods, that the introduced ensemble of parameters may lead to the possibility to use them as biomarkers. This electrophysiological ensemble of parameters allows analysis of brain dynamics during the immediate post-stimulus time window, thus serving as a dynamic indicator that is impossible to reach by any other functional neuroimaging methods with a lower time resolution, such as fMRI. Further studies should aim not only to distinguish physiological and pathological states of brain at the group level, but also at the individual level. Applying more widely used biological markers together with neurophysiological techniques may facilitate the development of inexpensive and non-invasive methods of screening for brain pathological conditions.

Briefly, gathered from the present study and from our earlier studies, the most important parameters in the search for neurophysiological markers in MCI/AD seem to be: 1) peak-to-peak amplitudes of oscillations.


