The visual cognitive network, but not the visual sensory network, is affected in amnestic mild cognitive impairment: A study of brain oscillatory responses

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ABSTRACT

Mild Cognitive Impairment (MCI) is considered in many as prodromal stage of Alzheimer’s disease (AD). Event-related oscillations (ERO) reflect cognitive responses of brain whereas sensory-evoked oscillations (SEO) inform about sensory responses. For this study, we compared visual SEO and ERO responses in MCI to explore brain dynamics (Background). Forty-three patients with MCI (mean age = 74.0 year) and 41 age- and education-matched healthy-elderly controls (HC) (mean age = 71.1 year) participated in the study. The maximum peak-to-peak amplitudes for each subject’s averaged delta response (0.5–3.0 Hz) were measured from two conditions (simple visual stimulation and classical visual oddball paradigm target stimulation) (Method). Overall, amplitudes of target ERO responses were higher than SEO amplitudes. The preferential location for maximum amplitude values was frontal lobe for ERO and occipital lobe for SEO. The ANOVA for delta responses showed significant results for the group X paradigm. Post-hoc tests indicated that (1) the difference between groups was significant for target delta responses, but not for SEO, (2) ERO elicited higher responses for HC than MCI patients, and (3) females had higher target ERO than males and this difference was pronounced in the control group (Results). Overall, cognitive responses display almost double the amplitudes of sensory responses over frontal regions. The topography of oscillatory responses differs depending on stimuli: visualsensory responses...
are highest over occipitals and cognitive responses over frontal regions. A group effect is observed in MCI indicating that visual sensory and cognitive circuits behave differently indicating preserved visual sensory responses, but decreased cognitive responses (Conclusion).

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1. Introduction

Recently, the increasing prevalence of Alzheimer’s disease (AD) has caused an increase in the amount of investigators researching conditions of pre-dementia. The majority of patients with amnestic mild cognitive impairment (MCI) are believed to be in the symptomatic pre-dementia phase of AD. Individuals with MCI often have mild problems performing complex functional activities, but they do not lose their independence in daily life (Albert et al., 2011).

For many years, isolated brain regions were considered to be related to certain cognitive domains. However, the latest evidence indicates that the dynamic interactions of several widely distributed brain areas operating in large-scale networks results in cognition (Bressler and Menon, 2010). These networks can be assessed in several ways, including neurophysiological methods, which have an advantage of having higher resolution time (Büyükşar, 2011). The brain consists of functional network dynamics and connectivity, both of which are crucial for normal functioning. Recent research on functional network disruption, which was assessed with electroencephalography or related methods, has shown that network abnormalities are somewhat specific to pre-dementia conditions (Pievani et al., 2011; Yener and Başar, 2013a). Oscillatory brain activity is a hallmark of neuronal network function and can accurately determine normal and abnormal brain functions. Brain oscillatory responses provide non-invasive analyses of cortico-cortical connectivity, local neuronal synchronization of firing, and coherence of rhythmic oscillations at various frequencies (Rossini et al., 2013a, 2013b). Event-related potentials (Papaliagkas et al., 2011) and oscillations (ERO) can be used as tools for detecting subtle abnormalities in cognitive processes, especially in dementia or related disorders. Here, the expression “event-related” is used to describe a potential elicited upon the application of a classical visual oddball paradigm. The term “sensory-evoked” is used when the potential is elicited by simple visual sensory stimulation, such as a simple light. Oscillatory responses transmit rhythms over distinct time durations, and they are elicited following Fourier transformation in post-stimulus time domain (Büyükşar, 1983). In our previous work, we studied the ERO of AD (Yener et al., 2007; 2008; 2012) and MCI subjects (Yener et al., 2013; Güntekin et al., 2013). In addition, we also studied the sensory-evoked oscillations (SEO) (Yener et al., 2009) and evoked- and event-related coherences of AD (Güntekin et al., 2008, Yener and Başar, 2013b). Results of these previous studies indicate that group differences in paradigms using cognitive tasks (ERO or ER coherences) were much more prominent and widespread over the cortex than were those seen in SEO or SEO-coherences in patients with AD (Büyükşar et al., 2010). In addition to diminished frontal theta (Yener et al., 2007, Caravaglios et al., 2010), we also reported reduced central, frontal and parietal delta responses upon cognitive stimulation (Polikar et al., 2007; Caravaglios et al., 2008; Yener et al., 2008; 2012) in AD. On the contrary, simple visual sensory stimulation evoked increased theta parieto-occipital oscillatory responses (Yener and Başar, 2010) in AD patients. We believe that these results indicate that there are fewer reactive heteromodal associations between cortices during cognitive processes and that there are possibly disinhibited visual cortices during simple sensory processes in AD patients (Yener and Başar, 2013a). Results of our previous studies supported the notion that sensory and cognitive circuits are activated differentially in AD patients. Comparing two paradigms in the same group of subjects can be used to determine the separation of sensory and cognition-related neural circuits. Our recently published studies focused on the reduced frontal-central-parietal target delta oscillatory responses (Yener et al., 2013) and diminished beta event-related power spectra in amnestic MCI patients (Güntekin et al., 2013). In the present study, we aimed to explore the behavior of neural networks related to cognitive and sensory processes by comparing visual target ERO and SEO responses in patients with MCI. To our knowledge, this is the first report comparing SEO and ERO responses in patients with MCI. Previous studies imply that connectivity between heteromodal cortices is disrupted (Pievani et al., 2010) and sensory cortices are spared at the clinical stage of MCI (Kantarci et al., 2010). These results indicate that electro-physiological investigations may provide insight into the basic fundamentals of visual sensory and cognitive networks. Such analyses could provide useful information related to the existence and separation of sensory and cognitive neural networks in patients with MCI.

2. Results

The ANOVA on the delta responses revealed that there were no direct differences between the groups. However, the group x paradigm was significantly different between the groups [F(1,79) = 5.046; p < 0.03]. Post-hoc analysis indicated that there were significant differences between groups for delta responses upon presentation of the target stimulation, but not for the visual sensory stimulation. Post-hoc analysis indicated that the target stimulation elicited a higher delta response for the healthy subjects than it did for the MCI patients (p < 0.00001). ANOVA for delta responses revealed significant results for paradigm [F(1,81) = 62.98; p < 0.00001], which indicated higher delta responses upon presentation of the target stimulation in comparison with the presentation of visual sensory stimulation (p < 0.00001) (Fig. 1). Furthermore, significant differences were found for the following: anteriorposterior [F(3,243) = 3.776; p < 0.02]; coronal [F(2,162) = 24.792; p < 0.00001]; anteriorposterior × coronal [F(6,486) =
5.767; \( p < 0.00008 \); paradigm \( x \) anteriorposterior \( [F(3.243) = \] 30.389; \( p < 0.00001 \) and paradigm \( x \) anteriorposterior \( x \) coronal sites \( [F(6.486) = 2.79; p < 0.02 \). Post-hoc comparisons showed that frontal electrode sites gave higher delta responses than did the occipital electrode sites \( (p < 0.01) \) and that mid recording sites gave higher delta responses than did the left \( (p < 0.00001) \) and right \( (p < 0.00001) \) recording sites. Post-hoc comparisons also showed that the frontal midline electrode \( (F_z) \) had the highest delta responses when compared to all of the other recording sites \( (p \) values between \( p < 0.01 \)–\( 0.00001 \). Furthermore, post-hoc comparisons showed that the difference between target stimulation and sensory visual stimulation was most pronounced for the frontal electrode sites \( (p < 0.00001) \) and especially for the midline electrode site \( (F_z) \); paradigm \( x \) anterior-posterior \( x \) coronal effect; \( p < 0.02) \). Target stimulation elicited higher delta responses from the \( F_z \) electrode than did sensory visual stimulation \( (p < 0.00001) \). Pearson correlation analysis showed that MMSE scores were positively correlated with \( C_4 \) \( (p < 0.05) \) and \( P_3 \) \( (p < 0.02) \) delta response amplitudes.

Fig. 1. – (a) The grand-averages of maximum peak-to-peak amplitudes of visual sensory evoked oscillations (SEO) and visual oddball target delta oscillations (ERO) in healthy elderly controls (HC) and subjects with mild cognitive impairment (MCI). SEO responses occur early at maximum amplitude over occipitals whereas cognitive responses appear later with maximum amplitudes over frontal regions; (b) The group difference between MCI and HC is prominent in ERO and not in SEO indicating cognitive network is affected in MCI.

Fig. 2. – The difference between the topography of visual SEO and target ERO responses from both groups together. The amplitudes of ERO responses are much higher than that of visual SEO. Maximum amplitudes were observed over occipital lobes in SEO whereas over frontal regions in target ERO.
2.1. Comparison of visual sensory oscillations (SEO) to visual event-related oscillations (ERO)

In our previous study, which investigated the ERO of 21 MCI patients, we found that the maximum peak-to-peak amplitudes of delta target oscillatory responses were 20–37% lower in the MCI group when compared to those of healthy elderly controls (Yener et al., 2013). In the current study, which included 43 MCI subjects, this decrease was between 11–25%.

The grand-averages of visual SEO and ERO over the midline electrodes of MCI and HC subjects are presented in Fig. 1. Over the electrode sites F3, F4, C3, Cz, C4, P3, Pz, and P4, the target delta response was larger in healthy controls than in MCI patients. The reduction in the target delta response in MCI patients was 19% over F3, 21% over Cz, and 25% over P3. However, there were no significant differences found between the visual SEO for the MCI patients and the healthy controls. The sensory responses appeared early and were maximal over the occipital electrodes, whereas the cognitive responses appeared approximately 100–200 ms later, with their maximum amplitudes being over the frontal regions.

2.2. The statistical results of gender difference

The number of female and male subjects were not equal in the MCI patient (16 female /26 male) and control groups (25 female/16 male). Since it was not easy to recruit MCI patients and healthy volunteers for this study, we did not reduce the number of subjects, and we did not equalize the number of females and males in both groups. Rather, we used data from all subjects in the analysis. In order to determine the effects of this gender inequality, we added “gender” as a covariance factor, and found that the p value, which was $p<0.03$, changed to group $\times$ stimulation $p<0.06$ with the inclusion of “gender”. Further, we observed that including “gender” had effects on delta responses. Adding the gender as a between-subjects factor showed that there were significant gender $[F(1,79) = 4.37; p<0.05]$ and gender $\times$ group $[F(1,79) = 4.98; p<0.03]$ differences. The post-hoc comparisons using t tests showed that females had higher delta responses than did males ($p<0.001$) and this difference was mostly pronounced in the control group. The MCI patients did not have a gender difference in delta responses.

In order to see the effect of gender on the groups and on stimulation, we also ran separate ANOVAs for females and males. The ANOVA for female subjects showed a significant group effect, and the post-hoc comparisons showed that healthy females had higher delta responses than did MCI females. On the other hand, the ANOVA for male subjects did not indicate that there were any group differences. The effects of within-subject factors for both ANOVAs were very similar to the ANOVA of the whole group, which was described in Section 3. For this reason, we did not describe these factors in detail here.

3. Discussion

In previous studies, the peak-to-peak amplitudes of visual target delta oscillatory responses were shown to be reduced in amnestic MCI patients when compared to healthy controls. However, these previous studies also showed that there were no differences between groups in response to simple visual light stimulation. In the present study, a stimulation paradigm, which evokes cognitive networks, seems to gain more informative results in MCI patients than simple visual sensory stimulation, which evokes only sensory circuits.

In classical neurological essays, single isolated brain regions were considered to be related to certain cognitive domains. However, in later years, it has been accepted that cognition results from the dynamic interactions of widely distributed brain areas operating in large-scale networks (Bressler and Menon, 2010; Mesulam, 1990). Neurophysiological methods can assess the integrity, dynamics, and connectivity of neural networks with the advantage of having a higher time resolution ( Başar, 2011). A better definition of network disruption in AD/MCI patients might help to elucidate the bridge between symptoms and pathological changes (Pievani et al., 2011). From a structural point of view, underlying structural changes affect the entorhinal and hippocampal regions, and cause functional changes to the inferior parietal lobules and precuneus in early AD. Atrophy in the entorhinal area/hippocampus and hypometabolism/hypoperfusion in the inferior parietal lobules is the most reliable predictor of the progression from amnestic MCI to AD (Schorer et al., 2009). Our earlier findings on AD indicated that both the sensory and cognitive circuits of visual modality were affected (Yener et al., 2008, 2009). However, our present study indicates a dysfunction in cognitive circuits, with no involvement of visual sensory networks, in MCI patients. In subjects with early AD, lesions that are limited to the medial temporal lobe alter the plasticity of the low event-related potential (ERP) components, but the earlier components of sensory ERP are spared (Olichney et al., 2011). These findings are similar to those of the present study. Therefore, we can speculate that in MCI patients, while the visual sensory network that is modulated by the inferior parietal lobules and the precuneus appears to function well, visual sensory responses increase in AD patients (Yener et al., 2009), possibly due to decreased inhibition from the anterior parts of brain (Vincent et al., 2008).

As shown in previous reports, cognitive tasks often enhance electroencephalography (EEG) related abnormalities in MCI patients (Van der Hiele et al., 2007; Missonnier et al., 2007). In addition, studying brain oscillations in various cognitive disorders while performing cognitive tasks provides more informative results than does spontaneous (resting) EEG (Başar and Güntekin, 2008; Yener et al., 2009; Jackson and Snyder 2008; Papaliagkas et al., 2011; Sanchez-Alavez et al., 2014). Further, some ERP cognitive task paradigms may be more precise for certain types of MCI (Bennys et al., 2011; Cid-Fernández et al., 2014). The present study also indicates that cognitive paradigms enhance the subtle differentiation between physiological conditions and pathological states in which cognitive circuits are affected.

3.1. Anatomical correlates of EEG that show different dynamics during resting state and cognitive tasks

EEG dynamics vary depending on whether spontaneous (resting) EEG is used, or if it is performed while performing cognitive tasks, such as ERO. Increased slow frequency ranges
and decreased fast frequencies are characteristic of AD or MCI during spontaneous EEG (Moretti et al., 2009; Yener et al., 1996; Babiloni et al., 2006; Jelic et al., 2002). However, increasing delta target ERO amplitudes upon application of a cognitive task are indicative of a better cognitive response. Cognitive tasks elicit greater delta ERO responses in healthy elderly controls than in MCI/AD subjects. The values of target ERO amplitudes that are observed in MCI patients are often in between those of AD subjects and healthy controls (Yener and Başar, 2013b).

Visual impairments in patients with AD and MCI are mainly caused by higher-level parallel visual pathway dysfunction. In particular, a deficit in ventro-dorsal stream function, which is related to optic flow perception, is responsible for the earliest and most prominent visual symptoms in MCI (Yamasaki, et al., 2012). However, primary sensory and motor cortices are spared (Kantarci et al., 2010) and appear to have more of a reaction in early AD. Some electrophysiological changes have been reported in accordance with these anatomical findings. Our results indicated that there were increased visual SEO responses over the posterior parts of the hemispheres in AD patients (Yener et al., 2009). Several other reports also stated that there were increased motor evoked responses (Ferreri et al., 2011; Rossini et al., 2013a, 2013b), increased auditory evoked magnetoencephalography (MEG) responses (Osiyova et al., 2006), and increased somatosensory responses in MCI/AD (Stephen, et al., 2010).

3.2. Differences between cognitive and sensory responses

In this report, two different paradigms of visual stimuli were presented to the same subjects. These paradigms elicited totally different characteristics of oscillatory responses. The differences between sensory and cognitive responses can be discussed under four topics as follows:

1- Amplitude: cognitive responses (ERO) display higher amplitude values than do sensory responses (SEO). This may be because complex neural network interactions caused by cognitive stimuli activate a wider range of neural networks (Fig. 3). These structures are interwoven and activate reverberating circuits, which give rise to rhythmic oscillations in various frequency ranges. Among those, the delta frequency band appears to be the most prominent frequency band for differentiating AD/MCI from healthy controls (Yener and Başar, 2013b). In our previous report, we showed that event-related coherences are almost double that of sensory-evoked coherences (Yener and Başar, 2010), indicating higher connectivity prevails for cognitive tasks than simple sensory stimulation. An earlier report comparing the amplitudes of auditory delta SEO responses with those of target ERO responses indicated that ERO had much greater amplitudes than did auditory SEO (Başar-Eroğlu et al., 1992). In line with these findings, the present report shows that visual cognitive response amplitudes were much higher than those from visual sensory responses.

2- Location: upon simple light presentation, where sensory circuits are most likely to be highly activated, the elicited visual SEO responses show greater amplitudes over the occipital locations than in the rest of brain, while the visual ERO responses are largest over the frontal regions. These location preferences are in line with the results of earlier event-related (Polich, 2007) and evoked potential (Celesia et al., 1993) findings, which indicated that differential circuits are activated in the paradigms described above.

3- Gender: our results confirmed those of earlier studies, which showed higher target or emotional ERO responses in females (Güntekin and Başar 2007) than in males. Furthermore, we also observed that the target delta ERO response group difference was prominent in females, but not in males.

4- Group differences: post-hoc comparisons showed that there were no differences between the groups in terms of SEO responses. However, upon application of a cognitive task, the topology of ERO responses shifted to the fronto-central regions, and there was a reduction in delta target responses in the MCI group when compared to healthy controls (Figs. 1,2). It is plausible to hypothesize that this group difference appears when cognition-related circuits are activated in addition to sensory circuits. During ERO, the brain becomes more alert, attention, memory and decision making mechanisms become involved, and frontal regions become the most active. It is a well-known fact that MCI subjects do not show prominent anatomical changes in their visual sensory cortex. However, the earliest changes are observed in heteromodal association areas, including frontal regions (Braak and Braak, 1996).

5- The characteristics of visual responses elicited over occipital regions where an overlap occurs in SEO and ERO: the occipital lobe is involved in both visual sensory and cognitive responses. The unique situation in this region can be determined by means of superimposed SEO and ERO responses. In Fig. 1, it is clear that the cognitive response shows a double peak, with the first appearing in the SEO time era and the second appearing in the ERO time era in MCI patients. However, in healthy control subjects, the first ERO peak, which is in the SEO time...
era, is almost abolished, and a greater and earlier cognitive response is seen in ERO. From this diagram, it can be hypothesized that MCI subjects cannot inhibit visual sensory responses during cognitive processes. Our earlier report also indicated that theta SEO responses over occipital regions increased in AD patients. A possible mechanism for this finding might be the lack of inhibition of the posterior parts of the hemispheres by the anterior parts of the brain (Vincent et al., 2008), or it could be due to the decreased connectivity between the frontal and occipital regions, as shown by decreased coherence values in AD (Güntekin et al., 2008).

As reported in several recent publications, target delta ERO responses elicited by means of classical oddball paradigm are significantly decreased in various diseases (schizophrenia, AD, MCI). Accordingly, the delta ERO response appears to be an important marker in diseases with deficits in working memory, focused attention, and learning. ERO may be a new biomarker candidate for the evaluation of MCI and AD, since it may also predict disease progression (Yener and Başar, 2013b).

In conclusion, we believe that electrophysiological methods that use cognitive stimulation may be more advantageous than spontaneous activity- or sensory-evoked stimulation for the diagnosis of MCI/AD. However, further investigations using individualistic analysis may be helpful in determining the validity of these methods in routine clinical practice. Moreover, to better understand underlying brain dynamics, cognitive task responses must be compared with sensory-evoked responses, which may elicit the changes present in differential neural circuits that are activated in certain conditions, i.e. sensory or cognitive.

4. Experimental procedure

4.1. Subjects

This was a prospective and open study that included 43 consecutive, community-dwelling subjects with amnestic MCI [mean age 74.0 (SD: 6.8) years], which was diagnosed according to the Petersen criteria (Petersen et al., 2006), and 41 age-and education-matched normal elderly controls [mean age 71.1 (SD: 8.1) years] who were recruited from various community sources. Some of the subjects in this study also participated in our previous study on visual ERO (Yener et al., 2013). None of the healthy controls were consanguineous to the patients. The mean education level in the MCI group was 8.5 years and was 10.7 years in the control group. There was no significant difference in the ages or education levels between groups. There were 25 females in the control group and 17 in the MCI group. We performed complete neurological, neuro-imaging (magnetic resonance imaging) and laboratory examinations on each patient, 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 (Öktem, 2003), non-verbal memory (Weschler 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). Those diagnosed with MCI had subjective memory complaints, which were verified by a relative and by a memory test (score 1.5 standard deviations below the mean norm for their age), and a Clinical Dementia Rating (CDR) score of 0.5, which did not reach dementia criteria (Table 1). Depressive co-morbidity was excluded if the patient had a geriatric depression scale score higher than 10 (Yesavage et al., 1982–1983).

The characteristics of each group are shown in Table 1. Subjects were excluded from the study if they had abnormal laboratory results, which indicated other causes of memory disorder, and/or if they had vascular lesions in their MRI. All participants had normal vision, and none reported a history of head injury or any other neurological or psychiatric disorders. Patients were also excluded from the study if they regularly used anti-dementia drugs, antidepressants, neuroleptics, anti-epileptic medications, stimulants, opioids and/or beta-blockers. There was no difference between the groups regarding alcohol and tobacco use. Informed consent was obtained.

<table>
<thead>
<tr>
<th>Location</th>
<th>HC SEO (n=41)</th>
<th>MCI SEO (n=43)</th>
<th>HC ERO (n=41)</th>
<th>MCI ERO (n=43)</th>
<th>Decrease of ERO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3</td>
<td>4.26 (1.84)</td>
<td>4.04 (1.63)</td>
<td>8.07 (3.11)</td>
<td>6.51 (2.34)</td>
<td>19</td>
</tr>
<tr>
<td>Fz</td>
<td>4.70 (2.15)</td>
<td>4.45 (2.01)</td>
<td>8.57 (3.37)</td>
<td>7.21 (2.64)</td>
<td>16</td>
</tr>
<tr>
<td>F4</td>
<td>4.34 (2.14)</td>
<td>4.12 (1.86)</td>
<td>7.93 (2.72)</td>
<td>6.57 (2.49)</td>
<td>17</td>
</tr>
<tr>
<td>C3</td>
<td>4.2 (1.89)</td>
<td>4.00 (1.87)</td>
<td>7.73 (2.81)</td>
<td>6.09 (2.57)</td>
<td>21</td>
</tr>
<tr>
<td>Cz</td>
<td>4.91 (2.17)</td>
<td>4.75 (2.47)</td>
<td>8.09 (3.15)</td>
<td>6.75 (2.86)</td>
<td>17</td>
</tr>
<tr>
<td>C4</td>
<td>4.22 (2.01)</td>
<td>4.00 (2.33)</td>
<td>7.67 (2.66)</td>
<td>6.31 (2.72)</td>
<td>18</td>
</tr>
<tr>
<td>P3</td>
<td>4.33 (1.79)</td>
<td>4.16 (1.77)</td>
<td>7.21 (2.91)</td>
<td>5.44 (2.58)</td>
<td>25</td>
</tr>
<tr>
<td>P2</td>
<td>5.01 (2.02)</td>
<td>5.16 (2.40)</td>
<td>7.28 (3.09)</td>
<td>6.13 (2.77)</td>
<td>16</td>
</tr>
<tr>
<td>P4</td>
<td>4.47 (2.15)</td>
<td>4.57 (2.16)</td>
<td>6.91 (2.74)</td>
<td>5.85 (2.99)</td>
<td>15</td>
</tr>
<tr>
<td>O1</td>
<td>4.92 (2.30)</td>
<td>5.20 (2.20)</td>
<td>5.97 (2.94)</td>
<td>5.03 (2.00)</td>
<td>16</td>
</tr>
<tr>
<td>O2</td>
<td>5.20 (2.44)</td>
<td>5.40 (2.41)</td>
<td>5.86 (2.92)</td>
<td>5.12 (2.27)</td>
<td>13</td>
</tr>
<tr>
<td>O2</td>
<td>5.07 (2.63)</td>
<td>5.17 (2.44)</td>
<td>5.78 (2.93)</td>
<td>5.12 (2.11)</td>
<td>11</td>
</tr>
</tbody>
</table>

HC: healthy controls, MCI: mild cognitive impairment. Decrease of ERO in MCI in comparison to healthy controls in percentage is calculated as (HC-MCI)/HC.
obtained from all of the subjects or their relatives. The study was approved by the local ethical committee Table 2.

4.2. Stimuli and paradigms

4.2.1. Visual sensory-evoked oscillatory responses
A visual sensory paradigm was used for these experiments. A white screen with 40 cd/cm² luminance was used as the stimulus. Sixty stimulation signals were applied randomly, and the inter-stimulus intervals were varied between 3 and 7 s.

4.2.2. Visual event-related oscillatory responses
A classical visual oddball paradigm was used for these experiments. The probability of the deviant stimuli was 40/120 and that of the standard stimuli was 80/120. A white screen with a 40 cd/cm² luminance was used as the stimulus for standard signals. The luminance of the deviant stimuli was 10 cd/cm². In all of the paradigms, the deviant stimuli were embedded randomly within a series of standard stimuli. Patients were required to mentally count the target stimuli, which were applied randomly. The inter-stimulus interval varied between 3 and 7 s. All of the subjects had sufficient accuracy in their mental count of target stimuli, although the MCI group fared worse than the controls. The mean number of errors in the target count was 0.95 (SD: 2.02) for the controls and 2.23 (SD: 3.17) for the MCI patients.

4.3. Electrophysiological recording

Recordings were made from the F3, F4, Fz, C3, Cz, C4, P3, Pz, P4, Oz, O1, O2 and O3 locations according to the International 10–20 system using 30 Ag–AgCl electrodes mounted on an elastic cap (Easy-cap). Two additional linked Ag–AgCl earlobe electrodes (A1–A2) served as references. The EOG was registered from the medial upper and lateral orbital rim of the right eye. All electrode impedances were less than 10 kΩ. The EEG was amplified with a BrainAmp 32-channel DC amplifier with band limits of 0.01–250 Hz. A sampling rate of 500 Hz was used. Averages and grand-averages were calculated for each experimental condition and electrode site.

4.4. Computation of sensory-evoked (SEO) and event-related oscillations (ERO) in visual modality

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

For visual oscillatory responses, we defined the peak-to-peak maximum amplitude for both groups as an oscillatory component of SEO or ERO potential in the delta frequency range (0.5–3.0 Hz) during the post-stimulus 0–800 ms time window.

4.5. Statistical analysis

Statistica software was used for statistical analysis. Maximum peak-to-peak amplitude responses were analyzed separately for each frequency band by a repeated measures ANOVA. The between-subjects factors were the individual groups (healthy aged controls, MCI), the within-subject factors were the 3 coronal (left, medial, right) × 4 anterior-posterior (frontal, central, parietal, occipital) × 2 paradigms (SEO and ERO), and the Greenhouse-Geisser corrected p-values were taken into consideration. Post-hoc analyses were conducted using Bonferroni tests.

Since the number of the females and males in each group were not equal, we ran a separate ANOVA with the “gender” factor as a covariance. After observing that the healthy females had higher delta responses than did the healthy males and the MCI females, we repeated the ANOVA for males and females separately, including the between-subjects and within-subjects factors as above.

The correlation between the MMSE scores and the delta mean amplitudes were analyzed by a Pearson correlation test.

REFERENCES


