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# Frontal delta event-related oscillations relate to frontal volume in mild cognitive impairment and healthy controls

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ABSTRACT

Amnesic mild cognitive impairment (MCI) represents a risk of developing Alzheimer's disease (AD), but not all MCI subjects progress to dementia of AD type. Magnetic resonance imaging (MRI) of cortical and hippocampal atrophy supports early diagnosis of AD in MCI subjects, while frontal event-related oscillations (EROs) at delta frequencies (<4 Hz) are appealing markers for this purpose, as they are both cost-effective and largely available. The present study tested the hypothesis that these EROs reflect cortical frontal neurodegeneration in the continuum between normal and amnesic MCI subjects.

EROs and volumetric MRI data were recorded in 28 amnesic MCI and in 28 healthy elderly controls (HCs). EROs were collected during a standard visual oddball paradigm including frequent (66.6%) and rare (33.3%; targets to be mentally counted) stimuli. Peak-to-peak amplitude of delta target EROs (<4 Hz) was measured. Volume of the frontal cortex was estimated from MRIs.

Frontal volume was lower in MCI compared to the HC group. Furthermore, widespread delta target EROs were lower in amplitude in the former than in the latter group. Finally, there was a positive correlation between frontal volume and frontal delta target EROs in MCI and HC subjects as a whole group. These results suggest that frontal delta EROs reflect frontal neurodegeneration in the continuum between normal and amnesic MCI subjects.



## 1. Introduction

Alzheimer's disease (AD) is due to a brain neurodegeneration starting several years before the prodromal condition of amnesic mild cognitive impairment (MCI; Petersen et al., 1999; Gauthier et al., 2006; Albert et al., 2011) and more than 10 years before the clinical manifestation of dementia (Lanctôt et al., 2003; Jack et al., 2010). Unfortunately, no single instrumental non-invasive and cost-effective marker is available to be repeated several times for diagnostic, predictive, prognostic, and/or disease and therapy monitoring purposes. Rather, several procedures are available for the instrumental in-vivo assessment of some neurobiological processes related to AD (Dubois et al., 2007; Albert et al., 2011; Jack et al., 2010; McKhann et al., 2011; Sperling et al., 2011). The current model of the typical (i.e. more frequent) presentation of AD assumes that first abnormal neurobiological changes are reflected by brain amyloidosis biomarkers such as abnormal tracer retention on amyloid PET imaging and low Aβ42 concentration in cerebrospinal fluid (CSF). These initial changes are subsequently followed by massive neuronal loss reflected by FDG-positron emission tomography (PET) markers of cortical hypometabolism and structural magnetic resonance imaging (MRI) markers of cortical and hippocampal atrophy (Ingelsson et al., 2004; Jack et al., 2009, 2010, 2012; Prestia et al., 2013; Frisoni et al., 2010; Petersen et al., 2010).

The mentioned CSF, MRI and PET markers provide useful information for clinical decision making, although they are expensive and/or invasive and cannot be systematically used for screening across long periods of time (e.g. years) of large populations of subjects with subjective memory complaints and amnesic MCI. Among other candidates, recording of electroencephalographic (EEG) activity provides optimal features, as it is cost effective, diffuse and not affected by learning or repetition effects (Başar et al., 2013a, 2014 in this issue, for further references see Güntekin and Başar and Emek-Savaş et al., 2015-in this

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issue). A popular EEG methodology is the extraction of spectral markers of resting state EEG rhythms. Compared to normal control subjects, amnesic MCI and AD patients were characterized by an increase of delta (1–4 Hz) rhythms and a decrement of posterior alpha (8–12 Hz) rhythms (Dierks et al., 1993, 2000; Huang et al., 2000; Ponomareva et al., 2003; Jeong, 2004; Prichep et al., 2006). These EEG abnormalities were associated with altered regional cerebral blood flow/metabolism and with impaired global cognitive function as evaluated by the Mini-mental state examination (MMSE) (Sloan et al., 1995; Rodriguez et al., 1998, 1999a,b; Jeong, 2004). In the same vein, MCI subjects showed a decrease of alpha rhythms compared to normal elderly subjects (Zappoli et al., 1995; Elmståhl and Rosén, 1997; Huang et al., 2000; Jelic et al., 2000; Koenig et al., 2005). Of note, these EEG markers were found to be related to MRI markers indexing brain atrophy as revealed by hippocampus (Babiloni et al., 2009), normalized volume of cortical gray matter (Babiloni et al., 2013), and cortical gray matter density (Babiloni et al. in press). Noteworthy, compared to HCs, AD patients showed abnormal frontal delta rhythms related to reduced volume of frontal white matter density as a sign of a relation between functional oscillatory and structural abnormalities of the frontal lobe (Babiloni et al., 2006).

Another promising EEG methodology is the extraction of spectral markers of event-related oscillations (ERO) unveiling brain neural synchronization mechanisms associated with cognitive and sensorimotor processes (Başar, 1980). Previous studies have shown EROs in MCI and AD patients during a standard visual oddball paradigm including frequent stimuli (66.6%) and rare targets (33.3%) to be detected and mentally counted (Yener and Başar, 2013). Earlier studies of Başar and Stampfer (1985), Stampfer and Başar (1985) and Başar et al. (1984) showed that delta ERO activity reflected cognitive activity. Peak-to-peak amplitude of post-target delta EROs (<4 Hz) was dominant in frontal areas in both healthy elderly controls (HCs) and MCI/AD patients. Compared to HCs, MCI and AD showed decreased ERO responses in both slow frequency bands including delta (<4 Hz) and theta (4–7 Hz) frequencies and beta (15–30 Hz) bands (Başar et al., 2013a, b; Yener et al., 2008; Yener et al., 2013; Kurt et al., 2014; Güntekin et al., 2013; Caravaglios et al., 2008). Furthermore, there was a recovery in both theta event-related phase-locking and in alpha event-related coherence upon application of cholinergic medication (Yener et al., 2007; Yener et al., 2009). Finally, event-related coherence measurements reflecting functional brain connectivity showed decreased values in alpha, theta and delta frequency bands of AD subjects in comparison to HCs (Başar et al., 2010; Güntekin et al., 2008).

In summary, MCI represents a risk of AD, but not all MCI subjects progress to dementia of AD type. MRI of cortical and hippocampal atrophy enhances an early diagnosis of AD in MCI subjects, while frontal EROs at delta frequencies (<4 Hz) are appealing markers for this purpose as cost-effective and largely available technique (Yener and Başar, 2013; Güntekin, 2015-in this issue). The present study tested the hypothesis that these EROs reflect cortical frontal neurodegeneration in the continuum between normal and amnesic MCI subjects towards future clinical application for the screening of large populations of elderly subjects at risk for AD.

## 2. Methods

An open prospective study was conducted. Twenty-eight subjects with MCI and 28 age- and education-matched healthy elderly voluntary control subjects were examined by means of MRI and EROs.

### 2.1. Subjects

For the present study, 28 community dwelled subjects with amnestic MCI [mean age 72.29 (SD: 5.73) years] were recruited from the memory outpatient clinic of Dokuz Eylul University Neurology Department, Izmir, Turkey; and 28 age- and education-matched healthy elderly subjects [mean age 69.57 (SD: 6.15) years] volunteered for the study. Some of the subjects participated in our previous study on visual ERO (Yener et al., 2013). A complete neurological, neuro-imaging (MRI) and laboratory examination including blood glucose, electrolytes, liver and kidney function tests, erythrocyte sedimentation rate, full blood count, vitamin B12, thyroid hormone, VDRL and HIV were applied. Extensive cognitive testing was performed on all subjects and included episodic memory (Öktem, 1992), executive functions (Stroop Test, Clock Drawing Test, Verbal Fluency Test), attention (WMS-R Digit Span Test), orientation, language (Boston Naming Test), and the Mini Mental State Examination (MMSE) (Table 1). Patients with a depressive comorbidity were excluded on the basis of a geriatric depression scale score higher than 10 (Yesavage et al., 1983). All participants had normal vision. All experimental protocols were approved by the local ethics committee. Informed consent was obtained from all subjects. Group characteristics are presented in Table 1. There were no statistical differences in gender, age, education and handedness between the groups.

### 2.2. Diagnostic criteria

Patients were selected on the basis of inclusion and exclusion criteria for amnestic MCI that were reported on previous reports (Petersen et al., 1999; Dubois et al., 2007). The inclusion criteria were as follows: a) objective memory impairment on verbal and visual memory tests out of an extensive neuropsychological test battery, b) normal activities of daily living documented by history and their relatives, and c) clinical dementia rating score was 0.5. All subjects underwent MRI and laboratory tests to rule out other causes of cognitive impairment. Exclusion criteria were chosen as follows: a) history of depression or psychosis, b) history or signs of major stroke, c) any other psychiatric diseases, drug addiction, alcohol abuse, dementia, epilepsy, d) use of psychotropic drugs including cholinesterase inhibitors or other nootropics enhancing brain activity, e) uncontrolled systemic diseases, and f) traumatic brain injury.

### 2.3. Event-related oscillatory responses (ERO)

A classical visual oddball paradigm was used in the experiments. The probability of the deviant stimuli was 40/120 and that of standard stimuli 80/120. We selected a ratio of 1/3 for rare stimuli, as MCI subjects are more prone to dismiss the target stimuli due to attention and memory deficits. A white screen with a luminance of 40 cd/cm$^2$ for standard

**Table 1**
Groups' demographical and clinical characteristics.

| | HC (N = 28) | MCI (N = 28) | p |
|---|---|---|---|
| Age | 69.57 (6.15) | 72.29 (5.73) | 0.093[a] |
| Gender (M/F) | 11/17 | 18/10 | 0.061[b] |
| Education (year) | 9.54 (5.53) | 9.39 (4.64) | 0.917[a] |
| Handedness (L) | 1/28 | 0/28 | 0.500[b] |
| Number of mentally counted target stimuli | 39.79 (1.87)/40 | 39.50 (4.13)/40 | 0.741[a] |
| MMSE | 29.18 (0.98) | 26.00 (2.95) | 0.000[a*] |
| Memory | | | |
| Öktem's VMLT | 110.43 (11.74) | 65.86 (21.85) | 0.000[a*] |
| Language | | | |
| Phonemic fluency | 44.20 (17.33) | 26.27 (10.69) | 0.004[a*] |
| Categorical fluency | 21.93 (4.71) | 16.8 (4.04) | 0.000[a*] |
| Boston naming | 14.60 (0.60) | 13.92 (1.78) | 0.083[a] |
| Attention and executive | | | |
| Stroop | 47.29 (12.52) | 80.24 (45.83) | 0.002[a*] |
| Digit span fw | 4.96 (0.96) | 4.96 (0.99) | 1.000[a] |
| Digit span bw | 3.93 (1.36) | 3.41 (0.84) | 0.095[a] |

The sign "*" indicates statistical significance of $p < 0.05$, a: Mann–Whitney *U* test, b: Chi Square Test, MMSE: Mini Mental State Examination, VMLT: Verbal Memory Learning Test, fw: forward, bw: backward.

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