Increased long distance event-related gamma band connectivity in Alzheimer's disease

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ABSTRACT

Background: Brain oscillatory responses can be used for non-invasive analyses of cortico-cortical connectivity, local neuronal synchronization, and coherence of oscillations in many neuropsychiatric conditions including Alzheimer's disease (AD). In the present paper, we examine sensory-evoked and event-related gamma coherences elicited by visual stimuli in three sub-gamma bands in two sub-groups of patients with AD (i.e., acetylcholinesterase-inhibitor treated and untreated) and healthy controls.
Methods: We studied a total of 39 patients with probable mild AD (according to NINCDS-ADRDA criteria) who had been sub-divided into untreated ($n = 21$) and treated ($n = 18$) (patients either on cholinergic monotherapy or combined therapy with memantine) AD groups, and 21 age-, gender-, and education-matched healthy elderly controls. A simple flash visual paradigm was applied for the acquisition of sensory-evoked coherences. Event-related coherences were elicited using a classical visual oddball paradigm. Both sensory-evoked and event-related gamma coherences were calculated for long-distance intrahemispheric pairs for three frequency ranges: 25–30 Hz, 30–35 Hz, and 40–48 Hz in post-stimulus 0–800 ms duration. The long-distance intrahemispheric pairs from both sides were fronto-parietal, fronto-temporal, fronto-temporoparietal, fronto-occipital, centro-occipital and parieto-occipital.
Results: The sensory-evoked or event-related gamma coherences revealed that both treated and untreated AD patients had significantly increased values compared to healthy controls in all three sub-gamma bands. Moreover, the treated AD patients demonstrated significantly higher fronto-parietal gamma coherences during both sensory stimulation and oddball paradigm and lower occipito-parietal coherences during oddball paradigm in comparison to untreated AD patients.
Conclusion: The present study demonstrated that an increase of gamma coherences was present in response to both visual sensory and cognitive stimulation in AD patients in all gamma sub-bands. Therefore, gamma oscillatory activity seems to be fundamental in brain functions at both the sensory and cognitive levels. The increase of gamma coherence values was not due to cholinergic treatment to any significant extent, as both treated and untreated AD patients had increased gamma coherence values compared to healthy controls. The use of coherence values reflecting brain connectivity holds potential for neuroimaging of AD and understanding brain dynamics related to the effects of medication.

1. Introduction

Alzheimer's disease (AD) is one of the most devastating illnesses that threatens public health.

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It is characterized by progressive synaptic failure and brain atrophy related to neurodegeneration (Jack et al., 2010). The investigation of candidate biomarkers for the early detection of mild cognitive impairment (MCI) and/or AD by using several neuroimaging techniques has recently been a hot topic (Jack et al., 2010; Yener and Başar, 2013; Başar, 2013; Babiloni et al., 2016; Rossini et al., 2006; Frisoni et al., 2011).

Brain oscillatory responses can be used for non-invasive analyses of cortico-cortical connectivity, local neuronal synchronization, and

coherence of oscillations (Rossini et al., 2007). Event-related oscillations (EROs), used as a powerful technique with high temporal resolution, can be elicited upon application of cognitive stimuli. It is a useful tool for detecting subtle abnormalities in cognitive processes (Başar, 1980, 2004).

Our research group has published reports on the analyses of EROs and electrophysiological connectivity measurements in AD/MCI over the last decade. In addition to EROs, we have explored sensory-evoked oscillations (SEOs), and the evoked- or event-related coherences of AD/MCI patients using visual and/or auditory sensory and cognitive stimulation (Yener et al., 2008, 2009, 2012; Güntekin et al., 2008; Başar et al., 2010; Yener and Başar, 2010). The term "event-related" is used for a potential that is elicited after a cognitive task, while the term "sensory-evoked" is used for a potential that is elicited after a simple sensory stimulus of auditory or visual modality (Başar et al., 1997).

In our previous studies, frontal delta EROs were found to be associated with frontal volume in patients with MCI and healthy elderly controls (Yener et al., 2016), indicating that EROs can be used as a biomarker candidate in diagnosis. The use of electrophysiological measures in diagnosis and monitoring of treatment responses is important. In the present paper, we aim to explore evoked- and event-related gamma coherences in AD.

Although the history of gamma activity began in the 1940s (Adrian, 1942), it was discovered in later years by Freeman (1975) and Başar et al. (1975a, 1975b, 1975c) that gamma oscillatory activity reflects a wide variety of cognitive functions. In 1973, the terminology "gamma response" was introduced by Başar and Ungan (1973) to describe hippocampal gamma band activity elicited by stimuli in cats. Galambos (1981) later indicated that there are sensory and cognitive correlates of gamma responses in human participants. Gamma oscillatory responses do not appear to have a specific function in the nervous system, even though they are selectively distributed in widespread brain regions including the cortex, hippocampus, thalamus, and reticular formations in both animal and human brains (Başar, 2013). Thus, it can be speculated that gamma synchronization is a fundamental process for all brain functions (Başar et al., 1999, 2013; Başar-Eroglu et al., 1996a). Furthermore, gamma oscillatory activity is related to proper functioning of inhibitory interneurons which mostly consists of GABAergic neurons (Palop and Mucke, 2016).

As gamma oscillatory responses have a fundamental role in many cognitive and sensory processes, they are reported to play a role in attention, perception, object recognition, memory processes, face recognition, and emotional paradigms (Güntekin and Başar, 2014; Keil et al., 1999; Busch et al., 2004, 2006; Tallon-Baudry et al., 1998; Gruber et al., 2004; Herrmann et al., 2004a; Müller and Keil, 2004; Senkowski and Herrmann, 2002). (For further information on gamma responses, please see reviews from Başar, 2013; Başar-Eroglu et al., 1996b; Herrmann et al., 2004b; Singer, 1999; Tallon-Baudry and Bertrand, 1999.)

The limited literature that exists on gamma responses in AD is highly controversial. Ribary et al. (1991) showed by magnetic field tomography that the cortical component of the thalamocortical coherence of 40 Hz oscillations was reduced in AD patients. Van Deursen et al. (2008) reported significantly higher gamma band power in AD patients as compared with healthy controls in all resting state, music listening, story listening and visual stimulation conditions. The authors stated that both groups showed increased gamma band power during tasks in comparison to resting state (van Deursen et al., 2008). Moreover, both magnetoencephalography (MEG) and EEG studies demonstrated increased 40 Hz steady-state responses in AD patients compared to healthy controls (Osipova et al., 2006; van Deursen et al., 2011). Koenig et al. (2005) reported decreased gamma global field synchronization (GSF) values in AD patients compared to controls and stated that the inter-individual variance of gamma GSF values was much larger than the other frequency bands. Stam et al. (2002) showed decreased gamma band synchronization in AD patients compared to controls but no differences on gamma coherence were found between groups. However, Stam et al. (2006) later reported increased functional connectivity

in the occipito-parietal regions (measured by resting state coherence) in the gamma band in AD patients. Rossini et al. (2006) demonstrated that higher resting state gamma coherence (fronto-parietal regions) is associated with faster conversion of MCI to AD. The discrepancies between these studies likely involve methodological differences regarding the recording condition (i.e., task versus resting state), gamma band frequency range, measurement techniques (i.e., power, coherence, synchronization, etc.) and the medication status of the AD patients. To the best of our knowledge, there is no study investigating gamma coherence in treated versus untreated AD patients using an event-related design. Moreover, previous studies included either only psychoactive drug naïve AD patients (Osipova et al., 2006; van Deursen et al., 2008, 2011; Koenig et al., 2005; Rossini et al., 2006) or mixed groups involving both treated and untreated AD patients (Stam et al., 2002, 2006).

Güntekin et al. (2008) reported a study on electrophysiological connectivity measurement, i.e., coherence, upon oddball paradigm in AD. A later comprehensive article by Başar et al. (2010) covered coherence measurements of low frequency ranges and the gamma window in the same group of participants. However, these reports did not thoroughly analyze the gamma coherences by separating the sub-gamma windows. Başar et al. (2015) showed that a more comprehensive gamma response analysis includes division of the gamma window into three sub-gamma bands (25–30, 30–35 and 40–48 Hz). A detailed analysis of gamma sub-bands in many time-windows indicated that the AD group showed a delayed gamma response, most likely due to a delay in reverberating memory circuits. The present study now introduces the analysis of connectivity by means of coherence measurement in the three sub-gamma groups.

In the literature, it is standard that analyses of gamma responses include a single frequency and time window. Our previous study in healthy control participants emphasized the importance of analyzing the gamma responses in multiple frequencies and time windows (Başar et al., 2015). Başar et al.'s (2015) study demonstrated that during a cognitive paradigm (e.g., oddball), at least 3–4 phase/time-locked gamma responses between 25 and 45 Hz occur in multiple time-windows (between 0 and 800 ms). In our recent study on AD, we investigated sensory and cognitive gamma responses in three frequency ranges (25–30, 30–35, 40–48 Hz) over four time windows (0–200, 200–400, 400–600, 600–800 ms) and found that AD patients show decreased early sensory gamma responses and delayed cognitive gamma responses compared to healthy controls (Başar et al., 2016a). Overall, the cognitive gamma responses were delayed about 100 ms in AD patients, and this delay was probably related to delays in propagation, reverberation of signals, or recurrent excitation.

The present study aims to investigate the sensory-evoked and event-related gamma coherences in both treated and untreated AD patients in comparison to healthy controls using visual sensory stimulation and a visual oddball paradigm. To the best of our knowledge, this is the first study that explores evoked and/or event-related gamma coherence in AD patients as well as drug effects. AD animal models suggest disrupted inhibitory interneuron activity causes gamma abnormalities (Verret et al., 2012; Palop and Mucke, 2016). We expect abnormalities in the gamma networks of AD patients. We hypothesized that the evoked and event-related gamma networks and the evoked/event-related gamma coherence would be abnormal in AD patients as AD patients had increased late gamma responses in our previous study (Başar et al., 2016a). These compensatory late gamma responses could also be represented in the long-distance gamma networks.

2. Materials and methods

2.1. Participants

A total of 39 patients with probable mild AD who were diagnosed according to DSM-IV and NINCDS-ADRDA criteria and 21 age-, gender-, and education-matched healthy elderly controls took part in the

study. AD patients were divided into two groups—treated and untreated AD; the treated AD group consisted of 18 patients who were either taking cholinergic monotherapy (n = 12) or combined cholinergic treatment with memantine (n = 6), and the untreated AD group consisted of 21 patients. All AD patients were within the first year of their diagnosis.

The mean age was 69.00 years (SD 7.11) for the healthy controls, 75.09 years (SD 8.23) for the untreated AD patients, and 72.72 years (SD 6.38) for the treated AD patients. The mean number of educational years was 7.61 years (SD 4.30) for the healthy controls, 5.58 years (SD 2.64) for the untreated AD patients, and 9.11 years (SD 4.31) for the treated AD patients. There were 13 women in the control group, 11 women in the untreated AD group, and 7 women in the treated AD group. The mean of mini-mental state examination (MMSE) scores was 28.85 (SD 1.03) for the control group, 22.55 (SD 3.88) for the untreated AD patients, and 23.52 (SD 3.89) for the treated AD patients, out of a possible 30 points. The general demographic and clinical characteristics of the groups are shown in Table 1. The local ethical committee approved the study, and all participants and/or their relatives provided informed consent.

2.2. Paradigms

2.2.1. Visual sensory stimulation

A visual sensory paradigm was applied to all participants for the acquisition of sensory-evoked coherences. A white screen with 40 cd/cm^2 luminance was used for the stimulation, and the duration of stimuli was 1000 ms. Sixty stimulation signals were applied, and the inter-stimulus interval varied randomly between 3 and 7 s.

2.2.2. Visual event-related stimulation

Event-related coherences were elicited using a classical visual oddball paradigm. A total of 120 stimulation signals were used, and there were 40 target and 80 standard stimuli. A white screen with a 10 cd/cm^2 luminance was used for the standard stimuli, and 40 cd/cm^2 was used for the target stimuli. The duration of stimuli was 1000 ms. The target stimuli were embedded randomly within a series of standard stimuli, and the inter-stimulus interval varied randomly between 3 and 7 s. The participants were required to count the target stimuli in the oddball paradigm, and only the individuals who demonstrated sufficient accuracy in their mental count of target stimuli were included in the study. There was no significant difference between groups in terms of counting the target stimuli (p = 0.162).

2.3. Electrophysiological recording

EEGs were recorded from 30 Ag-AgCl electrodes mounted in an elastic cap (Easy-cap), according to the International 10–20 system. Two additional linked Ag-AgCl earlobe electrodes (A1 + A2) were used as references. The electrooculogram (EOG) was registered from both the medial upper and the 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 system with band limits of 0.01–250 Hz, and a sampling rate of 500 Hz was used.

Artifact-containing epochs were manually rejected prior to averaging the data (i.e., single sweep EOG recordings were visually studied, and trials with eye movement or blink artifacts were rejected). Sweep numbers were randomly equalized between the event-related target and simple visual stimulation conditions. A notch filter of 50 Hz was applied to the EEG data.

2.4. Data analysis

BrainVision Analyzer Software was used for signal analysis, evaluation of oscillatory dynamics, and sensory-evoked and event-related coherence analyses. First, the Fast Fourier Transform (FFT) of each epoch (0–800 ms duration) was performed, and then sensory-evoked and event-related gamma coherences were calculated for long-distance intrahemispheric pairs for three frequency ranges: 25–30 Hz, 30–35 Hz, 40–48 Hz. The long distance intrahemispheric pairs were F_3–T_7, F_3–TP_7, F_3–P_3, F_3–O_1, C_3–O_1 and P_3–O_1 on the left side and F_4–T_8, F_4–TP_8, F_4–P_4, F_4–O_2, C_4–O_2 and P_4–O_2 on the right side. The method used was cross-spectrum/autospectrum, and the mathematical relations are described in the following:

$$Coh(c_1, c_2)(f) = |CS(c_1, c_2)(f)|^2 / (|CS(c_1, c_1)(f)||CS(c_2, c_2)(f)|),$$

in conjunction with

$$CS(c_1, c_2)(f) = \Sigma \, c_{1,i}(f) \, c_{2,i}(f)^*.$$

Fisher's Z transformation was then used to normalize the distribution of average coherence values. The peak with the maximum coherence Z score within this frequency range for each person was included for the statistical analysis.

2.5. Statistical analysis

Statistical analyses were performed with Statistica Software. Repeated measures ANOVA was used for statistical analysis. Age was taken as a covariate as it was significantly different between groups (p = 0.007). Repeated measures ANOVAs were run separately for sensory-evoked and event-related coherences for three different gamma frequency ranges (25–30 Hz, 30–35 Hz, 40–48 Hz). The repeated measures ANOVA included Group (three levels: untreated AD patients, treated AD patients, and healthy controls) as the between-participant factor, and Region (six levels: fronto-parietal, fronto-temporal, fronto-temporoparietal, fronto-occipital, centro-occipital, parieto-occipital) and Hemisphere (two levels: left, right) as within-participant factors. Greenhouse–Geisser corrected p-values are reported. Post hoc analyses were performed using the Bonferroni test. Significance level was p < 0.05 for all comparisons.

3. Results

3.1. Visual sensory-evoked gamma coherences at three frequency ranges

Fig. 1 illustrates the grand averages of coherence analysis in the 25–48 Hz frequency band upon application of visual sensory stimulation over F_3-P_3 and F_4-P_4 electrode pairs. Green line represents the healthy controls, red line represents the untreated AD patients, and blue line represents the treated AD patients. As can be seen in the figure, average gamma coherence values upon presentation of visual sensory stimulation are higher in AD patients in comparison to healthy controls. Treated AD patients had the highest coherence value.

Table 1
General demographic and clinical features of participants.

	Healthy controls (n = 21)	Untreated AD patients (n = 21)	Treated AD patients (n = 18)	p
Age (SD)	69.00 ± 7.11	76.19 ± 7.64	72.72 ± 6.39	0.007[a]
Education (SD)	10.48 ± 4.95	7.76 ± 4.27	9.11 ± 4.43	0.165[a]
Gender (M/F)	8/13	10/11	11/7	0.357[b]
MMSE (SD)	28.81 ± 1.03	22.85 ± 3.83	23.53 ± 3.89	0.000[a]

SD: standard deviation, M: male, F: female, AD: Alzheimer's disease, MMSE: Mini-Mental State Examination.
[a] One-way ANOVA.
[b] Chi-square.

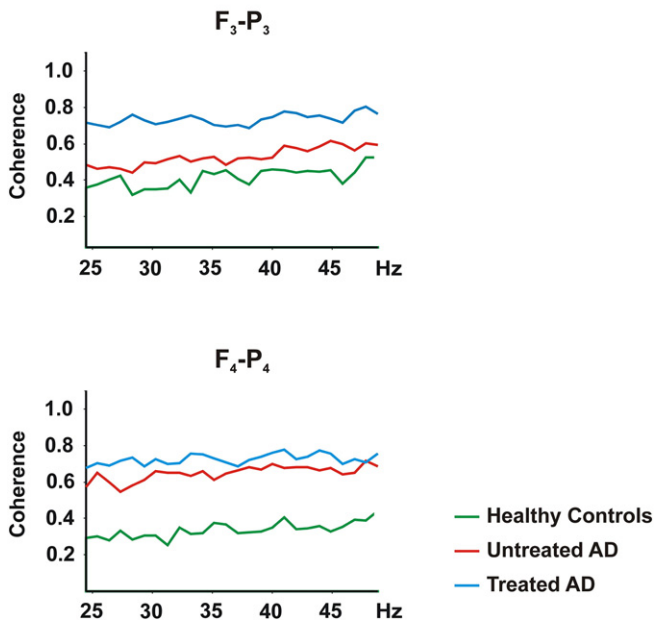## Visual Sensory-Evoked Coherence Gamma (25-48 Hz) Band

F_3-P_3

F_4-P_4

— Healthy Controls
— Untreated AD
— Treated AD

Fig. 1. Grand averages of visual sensory-evoked gamma (25–48 Hz) coherences for a) F_3-P_3 and b) F_4-P_4 electrode pairs. Green line refers healthy controls, red line refers untreated AD patients, and blue line refers treated AD patients.

3.1.1. Visual sensory-evoked gamma coherences in the 25–30 Hz frequency range

There was no main GROUP effect on visual sensory-evoked gamma coherences in the 25–30 Hz frequency range. However, there was an interaction effect for REGION × GROUP [$F_{10.280}$ = 5.284; p < 0.001], indicating the visual sensory-evoked coherence values in the 25–30 Hz frequency range were significantly different in the fronto-parietal (p < 0.001), fronto-temporoparietal (p = 0.002), and fronto-occipital (p = 0.002) regions between groups. Post hoc analysis revealed that both treated and untreated AD patients had significantly increased sensory-evoked coherences compared with healthy controls in the fronto-parietal, fronto-temporoparietal, and fronto-occipital regions (all, p < 0.03). Moreover, treated AD patients had significantly higher coherences than untreated AD patients in the fronto-parietal region (p = 0.021), (Fig. 2, Fig. 3).

Visual Sensory-Evoked Coherence Gamma (25-30 Hz) Band

Fig. 3. Visual sensory-evoked coherences in the 25–30 Hz frequency range were significantly different between groups in the fronto-parietal, fronto-temporoparietal, and fronto-occipital regions. "*" indicates that untreated AD patients had significantly higher sensory-evoked coherences than healthy controls; "†" indicates that treated AD patients had significantly higher sensory-evoked coherences than healthy controls; "‡" indicates that treated AD patients had significantly higher sensory-evoked coherences than untreated AD patients; "§" indicates untreated AD patients had significantly higher sensory-evoked coherences than treated AD patients. Error bars indicate standard errors of the mean.

3.1.2. Visual sensory-evoked gamma coherences in the 30–35 Hz frequency range

Repeated measures ANOVA yielded a main GROUP effect on visual sensory-evoked gamma coherence values in the 30–35 Hz frequency range [$F_{2.56}$ = 3.646; p = 0.032]. Post hoc comparisons showed that the treated AD patients had higher sensory-evoked coherences than healthy controls in the F_3-P_3 (p < 0.001), F_4-P_4 (p = 0.002), F_3-O_1 (p = 0.001), and F_4-O_2 (p = 0.021) electrode pairs; the untreated AD patients had higher sensory-evoked coherences than healthy controls in the F_4-P_4 (p = 0.049) electrode pair, and the treated AD patients had higher sensory-evoked coherences than the untreated AD patients in the F_3-P_3 (p = 0.021) electrode pair (Fig. 4).

There was also an interaction effect for REGION × GROUP [$F_{10.280}$ = 5.260; p = 0.001], indicating the visual sensory-evoked coherence values in the 30–35 Hz frequency range were significantly different in the fronto-parietal (p < 0.001), fronto-temporoparietal (p = 0.008), fronto-occipital (p < 0.001), and centro-occipital (p = 0.045) regions between groups. Post hoc analysis revealed that both treated and untreated AD patients had significantly higher sensory-evoked coherences than healthy controls in the fronto-parietal, fronto-temporoparietal, and fronto-occipital regions (all, p < 0.03). Moreover, treated AD patients had significantly higher coherences than untreated AD patients in the fronto-parietal region (p = 0.021) (Fig. 5).

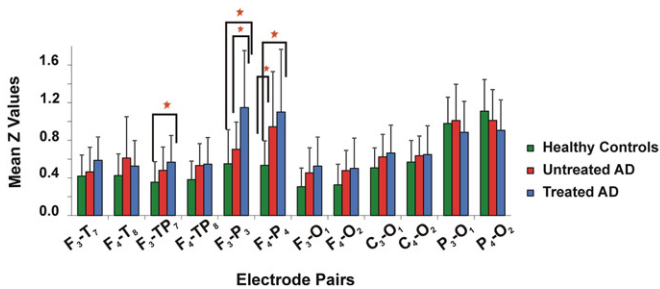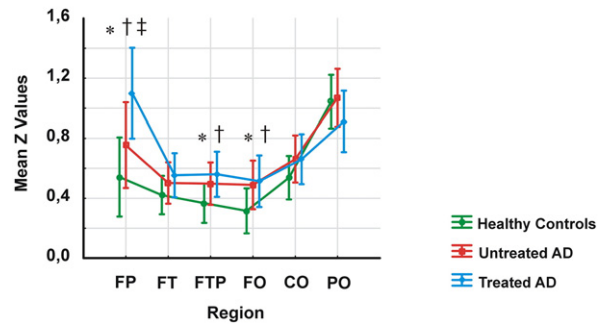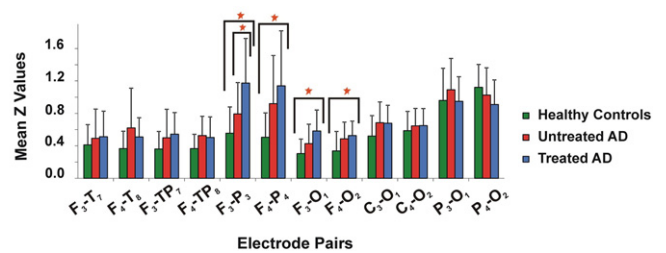### Visual Sensory-Evoked Intrahemispheric Coherence (25-30 Hz)

Fig. 2. Mean Z values with standard deviation of healthy controls, treated AD patients, and untreated AD patients for visual sensory-evoked coherences in the 25–30 Hz frequency range upon simple light stimulation ("*" represents p < 0.05).

Visual Sensory-Evoked Intrahemispheric Coherence (30-35 Hz)

Fig. 4. Mean Z values with standard deviation of healthy controls, treated AD patients, and untreated AD patients for visual sensory-evoked coherences in the 30–35 Hz frequency range upon simple light stimulation ("*" represents p < 0.05).

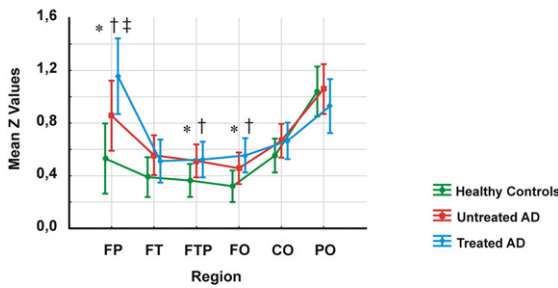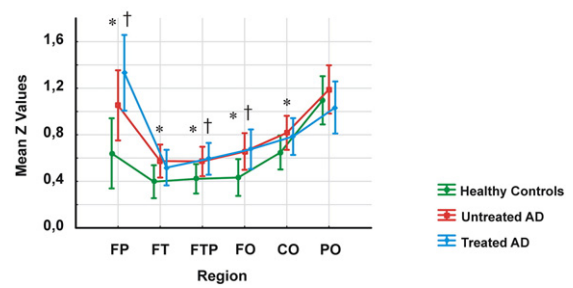## Visual Sensory-Evoked Coherence Gamma (30-35 Hz) Band

Fig. 5. Visual sensory-evoked coherences in the 30–35 Hz frequency range were significantly different between groups in the fronto-parietal, fronto-temporoparietal, fronto-occipital, and centro-occipital regions. "*" indicates that untreated AD patients had significantly higher sensory-evoked coherences than healthy controls; "†" indicates that treated AD patients had significantly higher sensory-evoked coherences than healthy controls; "‡" indicates that treated AD patients had significantly higher sensory-evoked coherences than untreated AD patients; "§" indicates untreated AD patients had significantly higher sensory-evoked coherences than treated AD patients. Error bars indicate standard errors of the mean.

3.1.3. Visual sensory-evoked gamma coherences in the 40–48 Hz frequency range

Repeated measures ANOVA showed a main GROUP effect on visual sensory-evoked gamma coherence values in the 40–48 Hz frequency range [$F_{2.56} = 4.142$; $p = 0.021$]. Post hoc comparisons revealed that the treated AD patients had higher sensory-evoked coherences than healthy controls in the F_3-P_3 ($p = 0.001$), F_4-P_4 ($p = 0.001$), F_3-O_1 ($p = 0.045$) and F_4-O_2 ($p = 0.02$) electrode pairs, and the untreated AD patients had higher coherences than healthy controls in the F_4-P_4 ($p = 0.023$), F_3-O_1 ($p = 0.036$), and C_4-O_2 ($p = 0.046$) electrode pairs (Fig. 6).

A significant interaction effect for REGION × GROUP [$F_{10.280} = 5.488$; $p = 0.001$] was also observed, indicating the visual sensory-evoked coherences in the 40–48 Hz frequency range were significantly different in the fronto-parietal ($p < 0.001$), fronto-temporal ($p = 0.021$), fronto-temporoparietal ($p = 0.005$), fronto-occipital ($p < 0.001$), and centro-occipital ($p = 0.007$) regions between groups. Post hoc analysis showed that both treated and untreated AD patients had significantly higher sensory-evoked coherences than healthy controls in the fronto-parietal, fronto-temporoparietal, and fronto-occipital regions (all, $p < 0.03$). Moreover, untreated AD patients had significantly higher coherences than healthy controls in the fronto-temporal and centro-occipital locations (all, $p < 0.02$) (Fig. 7).

3.2. Visual event-related gamma coherences in three frequency ranges

Fig. 8 illustrates the grand averages of coherence analysis in the 25–48 Hz frequency band upon application of target stimulation (oddball

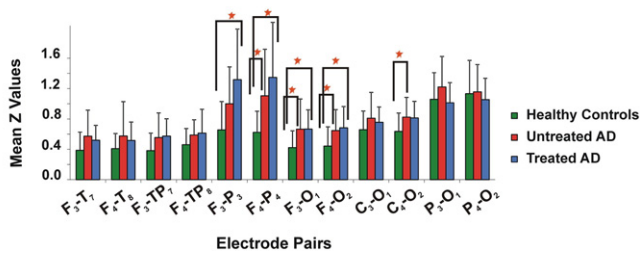## Visual Sensory-Evoked Intrahemispheric Coherence (40-48 Hz)

Fig. 6. Mean Z values with standard deviation of healthy controls, treated AD patients, and untreated AD patients for visual sensory-evoked coherences in the 40–48 Hz frequency range upon simple light stimulation ("*" represents p < 0.05).

Visual Sensory-Evoked Coherence Gamma (40-48 Hz) Band

Fig. 7. Visual sensory-evoked coherences in the 40–48 Hz frequency range were significantly different between groups in the fronto-parietal, fronto-temporal, fronto-temporoparietal, fronto-occipital, and centro-occipital regions. "*" indicates that untreated AD patients had significantly higher sensory-evoked coherences than healthy controls; "†" indicates that treated AD patients had significantly higher sensory-evoked coherences than healthy controls; "‡" indicates that treated AD patients had significantly higher sensory-evoked coherences than untreated AD patients; "§" indicates untreated AD patients had significantly higher sensory-evoked coherences than treated AD patients. Error bars indicate standard errors of the mean.

paradigm) over F_3-P_3 and F_4-P_4 electrode pairs. Green line represents the healthy controls, red line represents the untreated AD patients, and blue line represents the treated AD patients. As can be seen in the figure, average gamma coherence values upon presentation of target stimulation are higher in AD patients in comparison to healthy controls. Treated AD patients had the highest coherence values.

3.2.1. Visual event-related gamma coherences in the 25–30 Hz frequency range

Repeated measures ANOVA revealed a main GROUP effect on visual event-related gamma coherence values in the 25–30 Hz frequency range [$F_{2.56} = 3.491$; $p = 0.037$]. Post hoc comparisons showed that the treated AD patients had higher event-related coherences than healthy controls in the F_3-P_3 ($p = 0.002$), F_4-P_4 ($p = 0.001$), F_3-TP_7 ($p = 0.035$), F_4-TP_8 ($p = 0.024$) and F_4-O_2 ($p = 0.012$) electrode

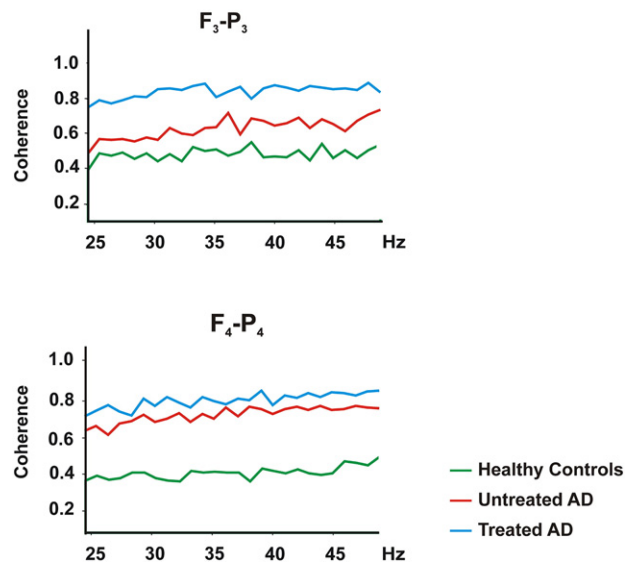## Visual Event-Related Coherence Gamma (25-48 Hz) Band

Fig. 8. Grand averages of visual event-related gamma (25–48 Hz) coherences for a) F_3-P_3 and b) F_4-P_4 electrode pairs. Green line refers healthy controls, red line refers untreated AD patients, and blue line refers treated AD patients.

Fig. 9. Mean Z values with standard deviation of healthy controls, treated AD patients, and untreated AD patients for visual event-related coherences in the 25–30 Hz frequency range upon application of target stimuli ("*" represents p < 0.05).
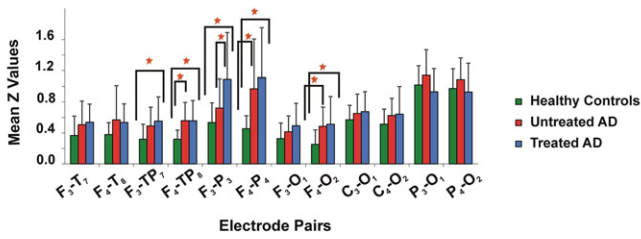

Fig. 11. Mean Z values with standard deviation of healthy controls, treated AD patients, and untreated AD patients for visual event-related coherences in the 30–35 Hz frequency range upon application of target stimuli ("*" represents p < 0.05).

pairs; the untreated AD patients had higher coherences than healthy controls in the F_4-P_4 (p = 0.011), F_4-TP_8 (p = 0.017), and F_4-O_2 (p = 0.021) electrode pairs, and the treated AD patients had higher coherences than the untreated AD patients in the F_3-P_3 (p = 0.03) electrode pair (Fig. 9).

There was also an interaction effect for REGION × GROUP [$F_{10.280}$ = 4.837; p = 0.001], indicating the visual event-related coherence values in the 25–30 Hz frequency range were significantly different in the fronto-parietal (p < 0.001), fronto-temporal (p = 0.04), fronto-temporoparietal (p < 0.001), fronto-occipital (p = 0.001), centro-occipital (p = 0.013), and parieto-occipital (p = 0.02) regions between groups. Post hoc comparisons indicated that both treated and untreated AD patients had significantly higher event-related coherences than healthy controls in the fronto-parietal, fronto-temporoparietal and fronto-occipital regions (all, p < 0.02). Moreover, untreated AD patients had higher coherences than healthy controls in the centro-occipital region (p = 0.015), and untreated AD patients showed significantly higher coherences than treated AD patients in the parieto-occipital region (p = 0.019) (Fig. 10).

3.2.2. Visual event-related gamma coherences in the 30–35 Hz frequency range

There was a main GROUP effect on visual event-related gamma coherence values in the 30–35 Hz frequency range [$F_{2.56}$ = 4.419; p = 0.017]. Post hoc analysis revealed that the treated AD patients had higher event-related coherences than healthy controls in the F_3-P_3 (p < 0.001), F_4-P_4 (p < 0.001), F_3-TP_7 (p = 0.035), F_4-TP_8 (p = 0.031),

F_3-O_1 (p = 0.004), and F_4-O_2 (p = 0.006) electrode pairs; the untreated AD patients had higher coherences than healthy controls in the F_4-P_4 (p = 0.004) and F_4-O_2 (p = 0.017) electrode pairs, and the treated AD patients had higher coherences than the untreated AD patients in the F_3-P_3 (p = 0.005) and F_4-O_2 (p = 0.023) electrode pairs (Fig. 11).

A significant interaction effect for REGION x GROUP [$F_{10.280}$ = 7.593; p < 0.001] was also found, indicating the visual event-related coherence values in the 30–35 Hz frequency range were significantly different in the fronto-parietal (p < 0.001), fronto-temporoparietal (p = 0.001), fronto-occipital (p < 0.001), centro-occipital (p = 0.013), and parieto-occipital (p = 0.003) regions between groups. Post hoc analysis showed that both treated and untreated AD patients had significantly higher event-related coherences than healthy controls in the fronto-parietal, fronto-temporoparietal, and fronto-occipital regions (all, p < 0.02). Moreover, untreated AD patients had significantly higher coherences than healthy controls in the centro-occipital region (p = 0.015). Furthermore, treated AD patients demonstrated higher coherences in the fronto-parietal (p = 0.015) region and lower coherences in the parieto-occipital (p = 0.002) region than untreated AD patients (Fig. 12).

3.2.3. Visual event-related gamma coherences in the 40–48 Hz frequency range

There was a main GROUP effect on visual event-related gamma coherence values in the 40–48 Hz frequency range [$F_{2.56}$ = 9.489; p < 0.001]. Post hoc analysis yielded that the treated AD patients had higher event-related coherences than healthy controls in the F_3-P_3
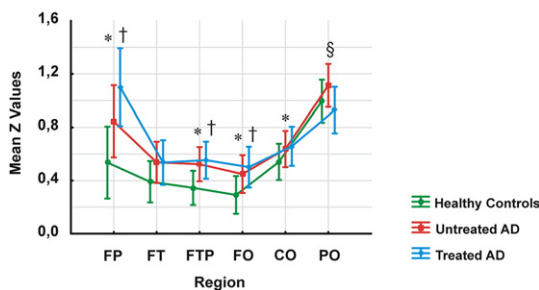

Fig. 10. Visual event-related coherences in the 25–30 Hz frequency range were significantly different between groups in the fronto-parietal, fronto-temporal, fronto-temporoparietal, fronto-occipital, centro-occipital, and parieto-occipital regions. "*" indicates that untreated AD patients had significantly higher event-related coherences than healthy controls; "†" indicates that treated AD patients had significantly higher event-related coherences than healthy controls; "‡" indicates that treated AD patients had significantly higher event-related coherences than untreated AD patients; "§" indicates untreated AD patients had significantly higher event-related coherences than treated AD patients. Error bars indicate standard errors of the mean.

Fig. 12. Visual event-related coherences in the 30–35 Hz frequency range were significantly different between groups in the fronto-parietal, fronto-temporoparietal, fronto-occipital, centro-occipital, and parieto-occipital regions. "*" indicates that untreated AD patients had significantly higher event-related coherences than healthy controls; "†" indicates that treated AD patients had significantly higher event-related coherences than healthy controls; "‡" indicates that treated AD patients had significantly higher event-related coherences than untreated AD patients; "§" indicates untreated AD patients had significantly higher event-related coherences than treated AD patients. Error bars indicate standard errors of the mean.

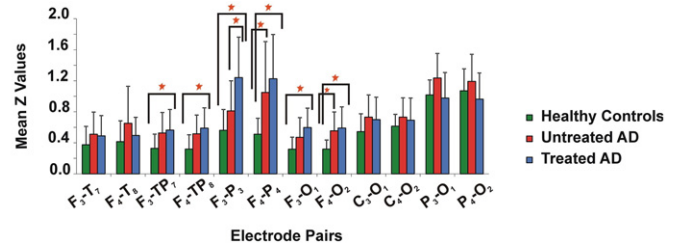## Visual Event-Related Target Intrahemispheric Coherence (40-48 Hz)

Fig. 13. Mean Z values with standard deviation of healthy controls, treated AD patients, and untreated AD patients for visual event-related coherences in the 40–48 Hz frequency range upon application of target stimuli ("*" represents p < 0.05).

($p < 0.001$), F_4-P_4 ($p < 0.001$), F_3-T_7 ($p = 0.027$), F_3-TP_7 ($p = 0.013$), F_4-TP_8 ($p = 0.005$), F_3-O_1 ($p = 0.005$), and F_4-O_2 ($p < 0.001$) electrode pairs; the untreated AD patients had higher coherences than healthy controls in the F_4-P_4 ($p = 0.002$), F_4-T_8 ($p = 0.004$), F_4-TP_8 (0.005), F_3-O_1 ($p = 0.002$), F_4-O_2 ($p < 0.001$), C_3-O_1 ($p = 0.006$), C_4-O_2 ($p = 0.006$), and P_3-O_1 ($p = 0.043$) electrode pairs, and the treated AD patients had higher coherences than the untreated AD patients in the F_3-P_3 ($p = 0.01$) electrode pair and lower coherences in the P_3-O_1 ($p = 0.048$) electrode pair (Fig. 13).

There was also an interaction effect for REGION x GROUP [$F_{10.280} = 7.211$; $p < 0.001$], indicating the visual event-related coherence values in the 40–48 Hz frequency range were significantly different in the fronto-parietal ($p < 0.001$), fronto-temporal ($p = 0.002$), fronto-temporoparietal ($p < 0.001$), fronto-occipital ($p < 0.001$), centro-occipital ($p < 0.001$), and parieto-occipital ($p = 0.003$) regions between groups. Post hoc comparisons showed that both treated and untreated AD patients had significantly higher coherences than healthy controls in the fronto-parietal, fronto-temporal, fronto-temporoparietal, fronto-occipital, and centro-occipital regions (all, $p < 0.008$). Moreover, untreated AD patients had higher coherences than healthy controls in the parieto-occipital region ($p = 0.025$). Furthermore, treated AD patients demonstrated higher coherences in the fronto-parietal ($p = 0.016$) region and lower coherences in the parieto-occipital ($p = 0.005$) region compared to untreated AD patients (Fig. 14).

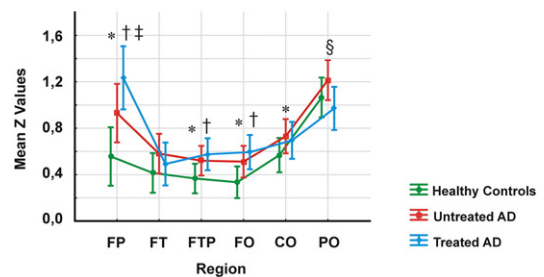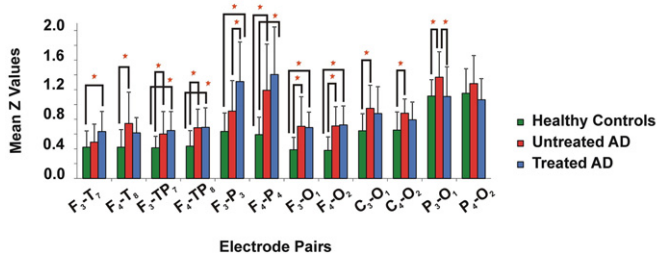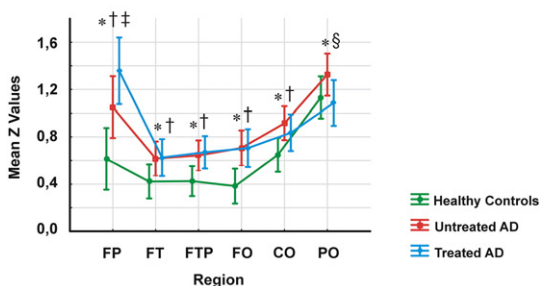## Visual Event-Related Coherence Gamma (40-48 Hz) Band

Fig. 14. Visual event-related coherences in the 40–48 Hz frequency range were significantly different between groups in the fronto-parietal, fronto-temporal, fronto-temporoparietal, fronto-occipital and centro-occipital regions. "*" indicates that untreated AD patients had significantly higher event-related coherences than healthy controls; "†" indicates that treated AD patients had significantly higher event-related coherences than healthy controls; "‡" indicates that treated AD patients had significantly higher event-related coherences than untreated AD patients; "§" indicates untreated AD patients had significantly higher event-related coherences than treated AD patients. Error bars indicate standard errors of the mean.

4. Discussion

4.1. Increase of gamma coherence: unusual or strong finding?

The results of the present study showed that AD patients had increased sensory-evoked and event-related gamma coherence values compared to healthy controls. Both treated and untreated AD patients had higher coherence values than healthy controls in all three gamma frequency sub-bands (25–30 Hz, 30–35 Hz, 40–48 Hz). In our previous study, we presented our preliminary findings on event-related gamma coherences in twelve untreated AD patients and twelve healthy controls (Başar et al., 2016b). An increase of gamma coherence values in three different frequency ranges was reported during a visual oddball paradigm. The present study, with the addition of a treated AD group of participants, further showed that the increase in gamma coherence values was not affected by drug therapy. Both treated and untreated AD patients had increased gamma coherence values compared to healthy controls. Furthermore, the present study demonstrated that this abnormal increase of gamma coherences in AD existed both during sensory visual stimulation as well as during target stimulation of the visual oddball paradigm. In the current study, the treated AD patients demonstrated significantly higher fronto-parietal gamma coherences during both sensory stimulation and oddball paradigm and lower occipito-parietal coherences compared to untreated AD patients in response to the target stimulation of the oddball paradigm.

Previous studies on gamma oscillations in AD presented mixed results. Some authors reported decreased gamma band synchronization in AD patients (Koenig et al., 2005; Stam et al., 2002), while others indicated increased gamma band power (van Deursen et al., 2008) and/or steady-state gamma responses in AD patients (Osipova et al., 2006; van Deursen et al., 2011). Likewise, gamma coherence was found to be similar to healthy controls (Stam et al., 2002), higher in AD patients in the occipito-parietal regions (Stam et al., 2006), and higher in MCI patients with faster conversion rates to AD in the fronto-parietal regions (Rossini et al., 2006). The finding of higher gamma coherence in the occipito-parietal regions was explained by impaired long distance cortico-cortical connections, which in turn may cause compensatory increases in local connections in AD (Stam et al., 2006; van Deursen et al., 2008). In a MEG study, Bajo et al. (2010) demonstrated that during a memory task MCI patients had higher posterior inter-hemispheric synchronization in the gamma band; on the other hand, healthy controls showed higher gamma synchronization than MCI patients between central-posterior and frontal-posterior channels. According to these results, the authors concluded that increased inter-hemispheric connectivity could be due to a compensatory mechanism for the lack of efficiency of the memory networks in MCI patients (Bajo et al., 2010). Moreover, compared to healthy controls MCI patients showed a hypersynchronization in the gamma band during an internal mental calculation task, which was related to a poorer cognitive performance (López et al., 2014).

In other neuropsychiatric conditions, our group has reported that bipolar disorder patients had decreased gamma coherence values both in manic (Özerdem et al., 2010) and euthymic stages (Özerdem et al., 2011). Özerdem et al. (2010) analyzed the event-related coherence of drug-free manic patients and healthy controls upon application of a visual oddball paradigm. Drug-free manic patients had lower gamma coherence values than healthy controls in the first recordings; after six weeks of valproate monotherapy there were no significant differences between groups. Moreover, Özerdem et al. (2011) showed that euthymic bipolar disorder patients had reduced event-related gamma coherence values compared to healthy controls both in target and non-target stimulation. However, there were no significant differences between patients and healthy controls during simple sensory visual stimulation. Özerdem et al. (2010, 2011) discussed that the reason for reduced gamma coherence in bipolar disorder patients could be related to application of cognitive stimulation but not sensory stimulation. The

authors concluded that there was an inadequate connectivity in the brain of bipolar disorder patients during cognitive load but not during sensory stimulation. These findings were explained in conjunction with the results of cognitive dysfunction in bipolar disorder patients (Martínez-Arán et al., 2004).

4.2. Possible mechanisms for increased sensory-evoked and event-related gamma coherences in AD

There are many possible mechanisms related to the increase of sensory-evoked and event-related gamma oscillations and coherence in AD. These include, (1) the different dynamics of resting state EEG and evoked and/or event-related oscillations upon application of a sensory or cognitive task (i.e., oddball paradigm) (Başar, 1980; Başar et al., 2016b); (2) inhibitory interneuron impairment in AD; (3) disrupted Ca^{2+} signaling; (4) drug effects (i.e., cholinergic and glutamatergic modulation).

Previous studies using animal models reported abnormal gamma oscillations; the authors mostly demonstrated reduced gamma oscillations in AD models (Verret et al., 2012). However, these results are mostly performed under resting conditions; during exploratory behaviors, gamma oscillations were increased both in healthy mice and AD models (Verret et al., 2012). The studies of gamma oscillations in human participants have contradictory results. Some authors reported decreased gamma band synchronization in AD (Koenig et al., 2005; Stam et al., 2002; Herrmann and Demiralp, 2005), while others presented increased gamma activity (Osipova et al., 2006; Stam et al., 2006; van Deursen et al., 2008, 2011). In our previous study, we have found that healthy controls had higher gamma responses than AD subjects in early time windows during cognitive paradigms (Başar et al., 2016a). Furthermore, we have indicated that AD subjects had higher gamma responses in late time windows than healthy controls.

The controversies between animal studies and human studies could be due to several factors: (1) The animal studies were mostly conducted during resting conditions; the dynamics of spontaneous gamma activity could be different than the evoked/event-related gamma responses elicited during cognitive paradigms. The animal studies also showed that the resting animal and behaving animal have different gamma activity (Verret et al., 2012). (2) The analysis of local dynamics and long-range dynamics could be different. Analysis of evoked power with single electrodes could present different results than analysis of evoked coherence between different electrode pairs. (3) The network properties of animals could be different than humans. The AD models mostly performed with mice or rats, the human brain network properties could be more complicated than the network properties of mice or rats. (4) Although gamma oscillations were defined mostly between 25 and 100 Hz, there could be more than one gamma band. Most likely in the near future, researchers will define gamma oscillations with multiple sub-bands. A recent study by Başar et al. (2015) showed that during cognitive load, three different gamma bands were differentiated in four different time windows.

There is an important relationship between gamma oscillations and inhibitory GABAergic interneurons (Gray and McCormick, 1996). In earlier publications, the neurotransmitters that affect the gamma frequency band have been identified as GABA, GABA/glutamate and dopamine respectively (Whittington et al., 1995; Muthukumaraswamy et al., 2009; Gray and McCormick, 1996; Kömek et al., 2012). Combinations of many transmitters play a role in even the simplest cognitive responses. As reported earlier, the synchrony of gamma oscillations is essential for integration of distributed sets of neurons and cortico-cortical interaction (Rodriguez et al., 1999).

The abnormalities of gamma coherence in AD patients during sensory and cognitive stimulation could be due to interneuron impairment in AD patients. Inhibitory interneurons produce gamma activity; impairment in these inhibitory interneurons should cause a decrease of gamma activity (Verret et al., 2012; Palop and Mucke, 2016). Decreased

GABAergic inhibition was demonstrated in a mice model of AD and was associated with hyperactivity of cortical neurons (Busche et al., 2008). Decreased activity of high-frequency oscillations in AD patients may be associated with this decreased inhibition (Nimmrich et al., 2015). However, these results mostly come from spontaneous EEG studies as reviewed by Herrmann and Demiralp (2005). More recent studies presented increased gamma responses in AD patients (Stam et al., 2006; Osipova et al., 2006; van Deursen et al., 2008, 2011; Başar et al., 2016a). In the present study, we report increased gamma coherence in AD after both sensory and cognitive stimulation. It is not possible elucidate the exact reason for the increase of evoked gamma coherence with the current studies in the literature. There is no previous research in AD models in which gamma responses were investigated with coherence analysis (the connectivity in multiple brain areas) during cognitive load. Further research is needed to understand how the gamma networks change during cognitive load in animal models. Application of similar methodologies to both animal models and AD patients could clarify the results on gamma activity, evoked gamma responses and evoked gamma coherence.

Moreover, gamma band activity was found to be related with Ca^{2+} channels (Luster et al., 2015); modulation of gamma oscillations in the pedunculopontine nucleus by neural calcium sensor protein was reported by D'onofrio et al. (2015). Berridge (2013) reported recently that there was an increase of Ca^{2+} signaling in AD. The author further stated that "Ca^{2+} has two diametrically opposed actions: it can both form and erase memories, and alternation in Ca^{2+} signaling will contribute to apoptosis resulting in the neurodegeneration". In bipolar disorder, Ca^{2+} signaling is also increased, which causes membrane excitability rather than apoptosis and memory loss (Berridge, 2013). According to the present manuscript and according to the results of Özerdem et al. (2010, 2011), there were inverse results between bipolar disorder and AD. The complex signaling patterns of Ca^{2+} and the complex relationship between different neurotransmitters could result in this differentiation. Both bipolar disorder patients and AD patients had abnormalities in Ca^{2+} signaling; Ca^{2+} signaling was found to be related to gamma oscillations. The abnormal gamma coherence values in both diseases could be related to Ca^{2+} signaling abnormalities.

Cholinergic modulation causes augmentation of long-distance thalamo-cortical tracts, while diminishing short cortico-cortical connections in the neocortex (Hasselmo and Sarter, 2011). This in turn results in attentional increase in experimental animals.

For an investigation of drug effects, we compared treated and untreated AD patients in the present study. We observed increased evoked and event-related long distance gamma connectivity and decreased short distance event-related coherence in treated AD patients compared to untreated AD patients. These findings may share similar mechanisms with the observed increase in long-distance connectivity in addition to the decrease of short-distance connectivity. Moreover, GABAergic interneurons coexpress alpha7 nicotinic receptors (Voytenko et al., 2015). Therefore, cholinergic treatment can increase GABA activity, resulting in increased gamma responses.

Memantine, a drug used widely in AD, is a glutamatergic NMDA receptor antagonist that modulates calcium influx. It helps in restoration of the signal-to-noise ratio in excited neurons (Chen et al., 1992). As some of our treated AD patients had taken memantine in addition to cholinergic treatment, the effect of memantine on event-related gamma coherence increase should be investigated in future studies. However, the increase of event-related gamma coherence in AD cannot be solely explained by drug effects, as untreated AD patients also showed increased event-related gamma coherences in comparison to healthy controls.

4.3. Synthesis of all results on event-related α, β, γ, θ, δ oscillations

For the first time in the literature, the present manuscript demonstrated that AD patients had increased abnormal gamma coherences

during both simple sensory and cognitive stimulation. Previously, our group and other groups in the literature reported event-related EEG biomarkers for AD in different frequency bands with different methodologies. A decrease of the delta response in AD patients in comparison to healthy controls during both visual and auditory cognitive paradigms was reported (Caravaglios et al., 2008; Yener et al., 2008, 2012). Decrease of delta responses upon application of cognitive paradigms was also found for patients with MCI (Yener et al., 2013; Kurt et al., 2014). Furthermore, the decrease of delta responses in frontal areas was correlated with the decrease of frontal volume in MCI patients (Yener et al., 2016). Frontal theta phase-locking was also impaired in AD patients. AD patients without any medication had decreased frontal theta phase-locking in comparison to healthy controls. On the other hand, cholinesterase inhibitors had positive effects on theta phase-locking; increased frontal theta phase-locking was reported for AD patients treated with cholinesterase inhibitors (Yener et al., 2007). Caravaglios et al. (2010) reported decreased poststimulus theta power in AD patients in comparison to healthy controls during auditory oddball paradigm. Increased gamma activity during steady-state stimulation was reported by Osipova et al. (2006) and by van Deursen et al. (2008, 2011). (Please see Table 2 for a short review of results; please see review article by Yener and Başar, 2013 for detailed information.)

Event-related coherence analysis in AD patients was performed by Başar et al. (2010) and by Güntekin et al. (2008). Decreases of delta, theta, and alpha coherence values were reported upon application of cognitive paradigms (Başar et al., 2010; Güntekin et al., 2008). There were no differences in the coherence values between healthy controls and AD patients upon application of simple visual paradigm (Başar et al., 2010). Başar et al. (2010) also performed event-related coherence analysis in the gamma frequency band and reported that there was an increase in gamma coherence values in AD patients in comparison to healthy controls but in very few electrode pairs. Başar et al. (2010) analyzed the event-related coherence values in the 28–48 Hz frequency range. Başar et al. (2015) showed that analyzing gamma frequency in different sub-bands was necessary and brought out important results. The present manuscript analyzed event-related gamma coherences in three different frequency sub-bands (25–30 Hz, 30–35 Hz, 40–48 Hz). Analysis of event-related gamma coherences in three sub-bands indicated more significant results in comparison to analysis of gamma coherence in one broad range (28–48 Hz, as performed in Başar et al., 2010). Gamma coherence values were overall higher in AD patients in comparison to healthy controls, but most significantly for the 40–48 Hz frequency band (Fig. 14). (Please see Table 3 for a short review of results; please see review article by Yener and Başar, 2013 for detailed information).

Table 2
Event-related oscillatory responses.

●	AD	References
Delta	▼ Decreased in cognitive paradigms ▲ Increased in occipital areas during visual sensory stimulation	Yener et al. (2008, 2009, 2012, 2013) Kurt et al. (2014)
Theta	▼Decreased frontal phase-locking in untreated AD patients ▲Cholinesterase inhibitors had positive effects on frontal theta phase-locking	Yener et al. (2007) Cummins et al. (2008) Caravaglios et al. (2010)
Alpha	▼Decreased event-related desynchronization (ERD) in AD ▼Decreased alpha activity in AD	Karrasch et al. (2006) Zervakis et al. (2011)
Beta	▼ Decreased in cognitive paradigms	Güntekin et al. (2013) Missonnier et al. (2007)
Gamma	▼Decreased in the first 200 ms during cognitive load ▲Delay of gamma responses, increased in the late time windows during cognitive load ▲ Increased during auditory steady-state stimulation	Başar et al. (2016a) Osipova et al. (2006) van Deursen et al. (2008, 2011) Haupt et al. (2008)

Table 3
Event-related coherence analysis.

●━●	AD	References
Delta	▼ Decreased in cognitive paradigms ►Does not change in sensory paradigms	Başar et al. (2010) Güntekin et al. (2008)
Theta	▼ Decreased in cognitive paradigms ► Does not change in sensory paradigms	Başar et al. (2010) Güntekin et al. (2008)
Alpha	▼ Decreased in cognitive paradigms ► Does not change in sensory paradigms ▼ Decreased in visual photic stimulation	Başar et al. (2010) Hogan et al. (2003), Güntekin et al. (2008) Kikuchi et al. (2002) Jiang (2005)
Beta	▲ Trend towards increase for both sensory and cognitive paradigms	Başar et al. (2010)
Gamma	▲ Increased in both sensory and cognitive paradigms	Present manuscript

5. Conclusions

The present study showed that the increase of gamma coherence values was not due to AD treatment to any great extent, as both treated and untreated AD patients had increased gamma coherence values compared to healthy controls. Furthermore, the present study showed that this abnormal increase of gamma coherences was present in response to both visual sensory and cognitive stimulation. The treated AD patients had significantly higher fronto-parietal gamma coherences during both sensory stimulation and oddball paradigm; and lower occipito-parietal coherences during the oddball paradigm compared to untreated AD patients. Whether this is a general result of the impairment of the inhibitory interneurons in AD or a compensatory effect related to the cholinergic modulation is unclear. Future studies on animal models and human participants are needed to clarify this issue.

There are several limitations of the present study. We did not compare the prestimulus and/or spontaneous EEG coherence with evoked and/or event-related coherence. To the best of our knowledge, there are only two studies in the literature investigating spontaneous EEG gamma coherence in MCI or AD. Rossini et al. (2006) reported that increased gamma coherence values were associated with higher rates of conversion from MCI to AD. Stam et al. (2006) found that AD patients had increased functional connectivity in the gamma band in the occipito-parietal regions as compared with healthy controls. Despite this, we interpreted the increased gamma coherences in AD as related to dysfunctional sensory and/or cognitive processing; it could be argued that the observed effect might be related to more basic neuro-compensation processes also present during resting or non-sensory or cognitive processing. Further studies should compare the spontaneous, evoked and event-related gamma coherences.

Other well-studied biomarkers of AD or other patient groups were not included in the present study. Previous studies demonstrated correlations of EEG findings with well-defined AD biomarkers such as CSF (Papaliagkas et al., 2010), PET (Dierks et al., 2000) and MRI (Babiloni et al., 2015; Moretti, 2015; Vecchio et al., 2016; Yener et al., 2016) in MCI/AD. Future studies using multimodal biomarkers including MRI, PET and CSF and comparing AD patients with different patient groups would potentiate the use of electrophysiological techniques as biomarkers and strengthen differential diagnosis. The relationship of well-defined AD biomarkers to oscillatory responses in various frequency bands awaits exploration in future studies. Using some of the most discriminating frequency bands over certain brain regions may give rise to a model of oscillatory responses (Başar et al., 2015) in diagnostics of neuropsychiatric conditions in future studies.

had no involvement in the conduct of the research or preparation of the article.

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