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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. 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

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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