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Delay of cognitive gamma responses in Alzheimer's disease

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ABSTRACT

Event-related oscillations (EROs) reflect cognitive brain dynamics, while sensory-evoked oscillations (SEOs) reflect sensory activities. Previous reports from our lab have shown that those with Alzheimer's disease (AD) or mild cognitive impairment (MCI) have decreased activity and/or coherence in delta, theta, alpha and beta cognitive responses. In the current study, we investigated gamma responses in visual SEO and ERO in 15 patients with AD and in 15 age-, gender- and education-matched healthy controls. The following parameters were analyzed over the parietal-occipital regions in both groups: (i) latency of the maximum gamma response over a 0–800 ms time window; (ii) the maximum peak-to-peak amplitudes for each participant's averaged SEO and ERO gamma responses in 3 frequency ranges (25–30, 30–35, 40–48 Hz); and (iii) the maximum peak-to-peak amplitudes for each participant's averaged SEO and ERO gamma responses over a 0–800 ms time block containing four divided time windows (0–200, 200–400, 400–600, and 600–800 ms). There were main group effects in terms of both latency and peak-to-peak amplitudes of gamma ERO. However, peak-to-peak gamma ERO amplitude differences became noticeable only when the time block was divided into four time windows. SEO amplitudes in the 25–30 Hz frequency range of the 0–200 ms time window over the left hemisphere were greater in the healthy controls than in those with AD. Gamma target ERO latency was delayed up to 138 ms in AD patients when compared to healthy controls. This finding may be an effect of lagged neural signaling in cognitive circuits, which is reflected by the delayed gamma responses in those with AD. Based on the results of this study, we propose that gamma responses should be examined in a more detailed fashion using multiple frequency and time windows.

1. Introduction

Alzheimer's disease (AD) is the most common dementing illness. In the majority of cases, mild cognitive impairment (MCI) is considered to be prodromal AD (Petersen et al., 2001; Rasquin et al., 2005; Alexopoulos et al., 2006). Current diagnostic methods are heavily weighted by the amyloid and tau levels in the cerebrospinal fluid (CSF) and by volumetric magnetic resonance imaging (MRI) measurements. The full potential of electrophysiological methods for use in predicting (Cichocki et al., 2005; Babiloni et al., 2006a; Rossini et al., 2006), diagnosing (Yener et al., 1996; Polich and Herbst, 2000; Jeong, 2004; Babiloni et al., 2006b; Karrasch et al., 2006), and monitoring treatment or progress (Jelic et al., 2000; Dauwels et al., 2010) in AD/MCI patients has not been fully examined in routine clinical practice.

Brain oscillatory responses can be used for the non-invasive analysis of local neuronal synchronization, cortico-cortical connectivity, and coherence of oscillations (Rossini et al., 2007). Cognitive stimuli can elicit event-related oscillations (EROs), which is a powerful technique with high temporal resolution. ERO has been described as a useful tool for detecting subtle abnormalities of cognitive processes (Basar, 1980, 2004).

In our previous work, we explored ERO, sensory-evoked oscillations (SEOs), and the evoked or event-related coherence of AD/MCI patients using visual and auditory sensory modalities (Yener et al., 2008, 2009, 2012; Güntekin et al., 2008; Basar 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 sensory stimulus (Başar et al., 1997).

The history of gamma activity began in the 1940s (Adrian, 1942). In subsequent years, Freeman (1975) and Başar et al. (1975a, 1975b, 1975c) indicated that gamma oscillatory responses reflect a wide variety of functions. In 1972, Başar and Özesmi introduced the terminology "gamma response" to describe hippocampal gamma band activity elicited by external stimuli in cats. In human studies, Galambos (1981) later

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indicated that there are sensory and cognitive correlates of gamma responses. Gamma oscillatory responses are selectively distributed in the brain, but they do not appear to reflect a specific function in the nervous system. Gamma activity has been related to both sensory and cognitive responses from the cortex, hippocampus, thalamus, and reticular formations in both animal and human brains (Başar, 2013). Thus, it can be hypothesized that gamma-band synchronization is most likely a fundamental process in all brain functions [see Başar et al. (1999, 2013) and Başar-Eroglu et al. (1996a)].

In the last decade, there have been several studies published on gamma activity in cognitive impairment, especially in schizophrenia. Most of the results related to these functions indicate a decrease in gamma responses. It is important to note that studies on healthy participants and participants with cognitive impairment have contradictory results and interpretations. Gamma oscillatory responses have been found to play role in perception, attention and memory processes, object recognition, 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 Başar, 2013; Başar-Eroglu et al., 1996b; Herrmann et al., 2004b; Jensen et al., 2007; Singer, 1999; Tallon-Baudry and Bertrand, 1999). In the literature, gamma responses have mostly been analyzed in single frequency and single time windows. There are few studies analyzing gamma responses in multiple frequency and time windows. However, our recent study (Başar et al., 2015) showed that analyzing the gamma responses in multiple frequency and time windows is extremely important. Başar et al. (2015) showed that, especially during cognitive paradigm, there are at least 3–4 phase/time-locked gamma responses in the 25–45 Hz frequency windows that occur in multiple time windows (between 0 and 800 ms). In most cases cognitive responses are late (200–400 ms, 400–600 ms), and they depict higher frequencies. Since there were many differences in the gamma responses in multiple frequency and time domains, this manuscript aims to analyze gamma responses in multiple time and frequency windows.

The literature regarding gamma responses in AD or MCI indicates that auditory steady state gamma responses with amplitudes of 40 Hz are increased in AD (Osipova et al., 2006) and MCI (van Deursen et al., 2011) patients when compared to controls. Another study comparing gamma activity during the N-back paradigm in stable and progressive MCI patients indicates that the progressive MCI group has lower average changes in gamma values (Missonnier et al., 2010). In the present study, we aimed to analyze gamma responses elicited by sensory or cognitive stimulation in AD patients using multiple frequency bands and many time windows. A new strategy was used that involved the analysis of three gamma frequency bands within four time windows. We hypothesized that cognitive gamma responses would be delayed in AD due to lagged neural signals in cognitive circuits.

2. Materials and methods

2.1. Participants

A total of 15 probable mild AD patients who were diagnosed according to DSM-IV and NINCDS-ADRDA criteria and 15 age-, gender-, and education-matched healthy controls were consented to participate in the study. All AD patients were within the first year of their diagnosis, and six of these patients were taking a cholinesterase inhibitor (donepezil, rivastigmine). The mean age of the healthy controls was 67.47 years (SD 4.14), while the mean age of the AD patients was 67.53 years (SD 6.48). The mean educational years was 8.73 (SD 6.03) for the healthy controls and 8.67 (SD 4.75) for the AD patients. There were 7 females and 8 males in each group. The mini-mental state examination (MMSE) scores ranged between 28 and 30 for the healthy controls and 16–27 for the AD patients, out of a possible 30 points. The general demographic and clinical features of both groups are shown in Table 1. All participants and/or their relatives provided informed consent for the study, which was approved by the local ethical committee.

2.2. Acquisition of visual sensory-evoked oscillations (SEOs) and visual event-related oscillations (EROs)

2.2.1. Sensory-evoked oscillations (SEOs)

A visual sensory paradigm was administered to each participant. A white screen with 40 cd/cm^2 luminance was used as the stimulus. The duration of the stimulation was 1000 ms. Sixty stimulation signals were applied, and the inter-stimulus intervals varied randomly between 3 and 7 s.

2.2.2. Event-related oscillations (EROs)

A classical visual oddball paradigm was administered to all participants. There were 40 target and 80 standard stimulations. The probability of the target stimuli was 0.33. A white screen with a 10 cd/cm^2 luminance was used for standard signal stimulation and 40 cd/cm^2 was used for the target signals. The duration of the stimulation was 1000 ms. The light appeared at full size on a 22-inch computer monitor with a refresh rate of 75 Hz. The target stimuli were embedded randomly within a series of standard stimuli in all of the paradigms. The task required the target stimuli to be counted, and the inter-stimulus interval varied randomly between 3 and 7 s.

Ten of the healthy controls counted 40 target stimulations; three of the healthy controls made one mistake while counting the target stimulation; and two made more than one mistake. Eight of the AD patients counted 40 target stimulations; two of the AD patients made one mistake; and five of them made more than one mistake. There was no significant difference between groups in terms of counting the target stimulation ($p = 0.389$).

2.3. Electrophysiological recording

EEGs were recorded according to the International 10–20 system using 30 Ag-AgCl electrodes mounted in an elastic cap (Easy-cap). 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.

Prior to 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). Sweep numbers were randomly equalized between the target and simple visual stimulation.

2.4. Measurements

Gamma SEO and ERO responses were digitally filtered in three gamma ranges measured from P_3, P_z, P_4, O_1, O_z and O_2 locations and using filter limits of 25–30, 30–35, and 40–48 Hz. The slope of the

Table 1
General demographic and clinical features of participants.

	Healthy controls (N = 15)	AD patients (N = 15)	p
Age (SD)	67.47 (4.14)	67.53 (6.48)	0.973[a]
Education (SD)	8.73 (6.03)	8.67 (4.75)	0.973[a]
Gender (M/F)	8/7	8/7	1.000[b]
MMSE (SD)	28.73 (2.02)	21.85 (3.46)	0.000[a]

SD: standard deviation, M: male, F: female, AD: Alzheimer's disease, MMSE: mini-mental state examination
[a] Independent sample t-test.
[b] Chi-square.