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Decrease of event-related delta oscillations in euthymic patients with bipolar disorder

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ABSTRACT

Decreased delta oscillation upon cognitive load is common in patients with Alzheimer's disease, mild cognitive impairment, and schizophrenia. However, there is no previous study analyzing the delta responses in euthymic medication-free patients with bipolar disorder. Participants comprised of 22 euthymic medication-free patients with DSM-IV diagnoses of bipolar disorder and 21 healthy controls who were matched to the patients for sex, age, and education. Electroencephalographic activity was recorded at 30 electrode sites using an application of an auditory oddball paradigm. The maximum peak-to-peak amplitudes for each subject's averaged delta response (0.5–3.5 Hz) were measured. There was a significant inter-group difference in evoked and event-related delta (0.5–3.5 Hz) responses. Post-hoc comparisons revealed that the event-related delta oscillatory responses of the bipolar patient group were significantly lower than those of the healthy control group over the temporo-parietal and occipital electrode sites. Euthymic bipolar patients showed reduced event-related delta oscillatory responses in comparison to healthy subjects under cognitive load. The decrease of delta oscillations may be a common phenomenon that can be observed in different neuropsychiatric disorders with cognitive dysfunction.

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1. Introduction

Although bipolar disorder (BD) is characterized by manic and depressive episodes, patients also suffer from cognitive dysfunctions that cannot be explained only by mood episodes (Bora et al., 2009). Cognitive task-based neuroimaging methods including electroencephalography (EEG) may provide valuable information that will aid in understanding the pathophysiology of neuropsychiatric diseases. The EEG is an inexpensive, noninvasive method with high temporal resolution that may provide a unique opportunity to observe cognitive processes over longer periods of time than feasible with other neuroimaging techniques. The hemodynamic response is an indirect indicator of neuronal activity; whereas the EEG can measure the bioelectrical activity of neuron populations. Poor spatial resolution is the major disadvantage of the EEG.

Some studies of the event-related potential in bipolar disorder have identified reduced P300 amplitudes (Muir et al., 1991; Salisbury et al., 1998, 1999; El-Badri et al., 2001; O'Donnell et al., 2004a, 2004b; Fridberg et al., 2009), whereas other studies have reported no difference between healthy controls and patients with bipolar disorder (Souza et al., 1995; Strik et al., 1998; Hall et al., 2007; Kaya et al., 2007; Schulze et al., 2007, 2008). Furthermore, three studies reported prolonged P300 latency (O'Donnell et al., 2004b; Turetsky et al., 2007; Schulze et al., 2008), whereas Salisbury et al. (1999) did not detect any delay in P300 latency in bipolar disorder. These divergent results may be related to the variable nature of bipolar disorder. Many confounders (e.g., clinical state, history of psychotic episodes, family history, and medication status) may have influenced the reported results.

The global P300 activity of the brain is the superimposition of multiple oscillations in delta (0.5–3.5 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (18–30 Hz) and gamma (30–70 Hz) frequencies, which are selectively distributed in various parts of the brain (Başar, 1998). Delta oscillations are the major component of P300 responses (Stampfer and Başar, 1985). All brain functions are controlled by the complex integration of various parts of the brain via these oscillatory activities (Başar et al., 2001). Disturbed sensory or cognitive processing might have reflections in various frequency responses, and connectivity deficits between the implicated brain regions might influence a certain frequency response (Başar, 2006).

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Oscillatory brain responses are widely studied in schizophrenia and dementias, but studies of bipolar disorder are less common (Başar and Güntekin, 2008; Başar et al., 2012). The most consistent findings regarding bipolar disorder have been obtained with auditory paradigms. For example, three studies reported decreased evoked power upon auditory steady state stimulation (O'Donnell et al., 2004a; Spencer et al., 2008; Oda et al., 2012). Euthymic patients with bipolar disorder showed reduced mean trial power and phase-locking factor (PLF) upon auditory steady-state stimulation (Rass et al., 2010). Medication-free euthymic patients with bipolar disorder showed decreased amplitude in slow (4–6 Hz) and fast (6–8 Hz) theta frequency bands in an auditory oddball paradigm (Atagün et al., 2013). Reite et al. (2009) detected abnormal lateralization of auditory cortices in auditory steady state responses in euthymia. Furthermore, the authors indicated that medicated patients showed decreased PLF in comparison to medication-free subjects. With an auditory dual-click paradigm, Hall et al. (2011) showed that the power of the gamma response was reduced in euthymic and depressed patients with bipolar disorder. Compared with healthy subjects or patients with schizophrenia, euthymic patients with bipolar disorder had higher (20–45 Hz) responses to speech sounds (Oribe et al., 2010). Another recent study reported significant differences between schizophrenia and bipolar disorder in an auditory oddball paradigm (Ethridge et al., 2012). The authors indicated that N200 responses to target stimuli differentiated patients with bipolar disorder and schizophrenia from healthy subjects; late beta response power to auditory target and standard stimuli differentiated bipolar patients from schizophrenia and healthy controls. Hamm et al. (2012) showed that N100 differentiated the group with schizophrenia from bipolar and healthy control groups; and late beta responses differentiated the bipolar patient group from schizophrenia and healthy control groups.

To our knowledge, only one study reported that 'medicated' euthymic patients with bipolar disorder ($n=10$) had increased delta (2–4 Hz) synchronization at frontal sites (Chen et al., 2008). Many excellent pharmaco-EEG studies have examined the effects of medications on brain bioelectrical activity. Our research group previously showed that oscillatory responses can be influenced by mood stabilizers such as valproate (Özerdem et al., 2008). It has also been shown that cholinergic treatment affects oscillatory brain responses in patients with Alzheimer's disease (Yener et al., 2007). This study examines oscillatory delta responses in medication-free euthymic patients with bipolar disorder. It is hypothesized that, upon application of auditory simple and oddball paradigms, oscillatory delta responses may be altered in patients with bipolar disorder.

2. Methods

2.1. Subjects

The study enrolled 22 euthymic, medication-free patients with bipolar disorder (19 Bipolar I, 3 Bipolar II disorder) and 21 healthy control participants matched for age, education and gender (Table 1). Diagnoses were confirmed using the Structured Clinical Interview (SCID) (First et al., 1996); and clinical evaluation tools for bipolar patients were the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). Inclusion criteria for the patient group were as follows: to have been diagnosed with bipolar disorder, euthymic for at least 8 weeks and unmedicated for at least 2 weeks. Good medical health, as confirmed by a physical examination and routine laboratory tests, was required for participation. Exclusion criteria were the following: pregnancy, lactation, consumption of alcohol or substances 2 weeks before the recordings, axis I and II psychiatric co-morbidity, and neurological conditions such as neurodegenerative diseases, epilepsy, or brain surgery. Volunteers who proved to have no present or past psychiatric condition as assessed by the SCID-I and who were found to be medically healthy on physical examination were enrolled in the control group. All participants were right-handed. The participants were asked to avoid sleep deprivation before the experiments, which were all performed at the same time of day (1 pm to 5 pm). The study design was reviewed and approved by the ethical committee, and informed consent was obtained from the participants after the nature of the procedures had been clearly explained.

Table 1
Sociodemographic and clinical characteristics of the groups.

	Patients with bipolar disorder ($n=22$)	Healthy controls ($n=21$)	p
Age[c]	30.82 ± 6.46	29.10 ± 7.87	0.436[a]
Education[c]	11.77 ± 3.61	13.41 ± 2.69	0.097[a]
Gender (females/males)	16/6	16/5	0.795[b]
Age at disorder onset[c]	21.86 ± 6.30		
Duration of euthymia[d]	48.64 ± 37.71		
Duration of the disorder[c]	10.05 ± 4.96		
Duration of the last episode[e]	35.95 ± 34.91		
Type of the last episode (depression/mania)	5/17		
Lifetime hospitalization	1.20 ± 1.06		
History of any psychotic episode	13 (59.09%)		
History of any episode with mixed features	7 (31.82%)		
Young Mania Rating Scale	0.67 ± 1.28		
Hamilton Depression Rating Scale	2.43 ± 2.27		
Total number of			
Episodes	3.91 ± 3.13		
Mania	1.77 ± 1.54		
Depression	1.14 ± 1.08		

Means ± standard deviations are reported.
[a] t test.
[b] Chi-square test ($\chi^2=0.068$).
[c] Years.
[d] Months.
[e] Days.

2.2. Stimuli and procedures

The tests were conducted in a dimly lit isolated room. Two types of auditory stimuli—simple and oddball paradigm—were presented to the subjects via two loud-speakers positioned 50 cm in front of the subject. The auditory stimuli were 1000 ms in duration. One type of stimulus (80 dB, 1600 Hz tone) was presented in the simple paradigm, and no instructions were given to the subjects. Subsequently, the classical auditory oddball paradigm consisting of 40 task-relevant target tones (80 dB, 1600 Hz) and 80 task-irrelevant non-target (80 dB, 1500 Hz) stimuli were presented in a random sequence. The interval between tones varied randomly between 3 and 7 s. Participants were asked to discriminate and mentally count the number of target stimuli.

2.3. EEG recording

EEG was recorded using an elastic cap (easy-cap), containing 30 Ag–AgCl electrodes, according to the international 10–20 system. Two linked earlobe electrodes (A_1–A_2) were used for references, and another pair of electrodes to measure electrooculographic (EOG) activity was placed on the medial upper and lateral orbital rim of the right eye. All electrode impedances were less than 10 kΩ. The EEG was amplified by means of a BrainAmp 32-channel DC device (Brain Products, Gilching, Germany) with band limits of 0.01–250 Hz. The EEG was digitized on-line at a sampling rate of 500 Hz. The recording sites were prepared using an abrasive cleaning paste "TEN20" (The Weaver and Company, Aurora, CO, USA), and electrodes were carefully filled with electrode gel "ABRALYT" (Easycap, Herrsching, Germany).

2.4. Data analyses

Data analyses were performed with BrainVision Analyzer 2 software (Brain Products, Gilching, Germany). Artifacts in the EOG recordings were eliminated by manual off-line selective averaging. The epochs (between −500 and 1000 ms) of each subject were averaged and then digital Fast Fourier Transform (FFT)-based power spectrum analysis was performed (Fig. 1; 10% Hanning windowing function) to calculate the oscillatory delta frequency peak.

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