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

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A B S T R A C T

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).
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) responses to speech sounds (Oribe et al., 2010). Another disorder. Compared with healthy subjects or patients with schizophrenia and bipolar disorder. Hall et al. (2011) showed that the power of the gamma response in medication-free euthymic patients with bipolar disorder. It is hypothesized that, upon application of auditory simple and oddball paradigms, 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 patient groups 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.

2.2. Stimuli and procedures

The tests were conducted in a dimly lit isolated room. Two types of auditory stimuli—simple and oddball paradigms—were presented to the subjects via two loud-speakers positioned 50 cm in front of the subject. The auditory 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 (Fig. 1). Two linked earlobe electrodes (A1–A2) 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 “TENZO” (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 EEG 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.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sociodemographic and clinical characteristics of the groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with bipolar disorder (n=22)</td>
<td>Healthy controls (n=21)</td>
</tr>
<tr>
<td>Agec</td>
<td>30.82 ± 6.46</td>
</tr>
<tr>
<td>Educationd</td>
<td>11.77 ± 3.61</td>
</tr>
<tr>
<td>Gender (females/male)</td>
<td>16/6</td>
</tr>
<tr>
<td>Age at disorder onset</td>
<td>21.86 ± 6.30</td>
</tr>
<tr>
<td>Duration of euthymia</td>
<td>48.64 ± 37.71</td>
</tr>
<tr>
<td>Duration of the disorder</td>
<td>10.05 ± 4.96</td>
</tr>
<tr>
<td>Duration of the last episode</td>
<td>35.95 ± 34.91</td>
</tr>
<tr>
<td>Type of the last episode</td>
<td>3/17</td>
</tr>
<tr>
<td>Depression (mania)</td>
<td></td>
</tr>
<tr>
<td>Lifetime hospitalization</td>
<td>1.20 ± 1.06</td>
</tr>
<tr>
<td>History of any psychotic episode</td>
<td>13 (59.09%)</td>
</tr>
<tr>
<td>History of any episode with mixed features</td>
<td>7 (31.82%)</td>
</tr>
<tr>
<td>Young Mania Rating Scale</td>
<td>0.67 ± 1.28</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale</td>
<td>2.43 ± 2.27</td>
</tr>
<tr>
<td>Total number of Episodes</td>
<td>3.91 ± 3.13</td>
</tr>
<tr>
<td>Mania</td>
<td>1.77 ± 1.54</td>
</tr>
<tr>
<td>Depression</td>
<td>1.14 ± 1.08</td>
</tr>
</tbody>
</table>

Means ± standard deviations are reported.

a t test.
b Chi-square test (χ² = 0.068).
c Years.
d Months.
e Days.
Subject averages and grand averages were calculated for each electrode site and experimental condition. Averaged evoked and event-related potentials were filtered in 0.5–3.5 Hz ranges. The event-related oscillatory delta responses to the target auditory stimuli were analyzed and compared. The maximum peak-to-peak amplitudes of oscillatory delta responses were calculated. Delta frequency is a slow frequency that lasts for 400–500 ms; therefore the window was determined as 0–600 ms.

2.5. Statistical analyses

Statistical analyses were performed using Statistica 10.0 software (StatSoft Inc., Tulsa, OK, USA). Repeated measures analysis of variance (ANOVA) was used to identify significant group differences in oscillatory delta responses for different conditions, different locations, and between the bipolar patient and healthy control groups. Mean values and standard deviations are reported. Repeated measures ANOVA included the bipolar patient and the healthy control groups as the between-subject factor. Stimulus types (simple, target and non-target) at three levels, locations (frontal (F3–F4), central (C3–C4), temporal (T7–T8), temporoparietal (T7–T8), parietal (P3–P4) and occipital (O1–O2)) at six sites and two hemispheres (left–right) were included as within-subject factors. Greenhouse–Geisser corrected p-values were reported, and significance level was set at 0.05. Bonferroni corrections were applied for post-hoc comparisons. Planned comparisons were performed to analyze the differences between groups for six different locations upon application of target stimulation and to identify the most significantly affected electrode site. Bonferroni corrections were also performed while comparing locations between different groups during target stimulation. The number of errors made by each subject was noted and, due to extreme values, logarithmic transformation was applied; the log-transformed numbers of errors were compared by t-test. Subjects were grouped as error-positive or error-negative and compared via the chi-square test. Spearman’s correlation test was conducted for each group to detect any correlation between clinical and behavioral parameters and mean amplitude values in evoked and event-related responses.

3. Results

Groups were matched for age, gender, and education (Table 1).

There was a significant inter-group difference in evoked and event-related delta (0.5–3.5 Hz) responses (p = 0.002). Post-hoc comparisons revealed that event-related delta oscillatory responses of the bipolar patient group were significantly lower than those of the healthy control group over the temporoparietal and occipital electrode sites. Repeated measures ANOVA revealed a significant stimulus type interaction [F(2,82) = 63.26, p < 0.001]. Post-hoc comparisons showed that oscillatory delta responses to auditory target stimuli (8.71 ± 3.99) were significantly higher than those of both simple stimuli (4.93 ± 2.19) [p < 0.00001] and non-target stimuli (4.78 ± 2.26) [p < 0.00001]. ANOVA revealed significant results for location [F(5,205) = 50.86, p < 0.001]. Post-hoc comparisons showed that amplitudes of frontal, central and parietal locations were significantly higher than amplitudes of temporal, temporoparietal, and occipital locations. ANOVA revealed significant results for the stimulus × location interaction [F(5,205) = 11.51, p < 0.001] interaction. Post-hoc comparisons showed that the difference between target stimulation versus simple stimuli (p < 0.00001) and versus non-target stimuli (p < 0.00001) were most prominent at the parietal location.

The ANOVA revealed a stimulus × Laterality difference [F(2,82) = 4.36, p = 0.016]. Post-hoc comparisons showed that amplitude values of right hemisphere responses to auditory target stimuli were significantly greater than left hemisphere responses (p = 0.002).

Delta oscillatory responses differed significantly between the bipolar patient and healthy control groups [F(1,41) = 11.17, p = 0.002]. The stimulus × group × location or group × location interactions were not significant, thus showing that the observed differences between groups were found in overall electrode sites. However, we have also observed that this difference could be more prominent in some of the electrode sites, especially upon target stimulation. Accordingly, we ran planned comparisons in which we analyzed delta oscillatory responses only for target stimulation and for frontal, central, temporal, temporoparietal and occipital locations. After Bonferroni correction, the significance level for p values was set at p = 0.008. The planned comparisons showed that healthy subjects had higher delta responses than bipolar disorder patients over central (p = 0.04), temporal (p = 0.01), temporoparietal (p = 0.006), parietal (p = 0.03) and occipital (p = 0.008) locations. After Bonferroni correction, it was seen that healthy subjects had higher delta responses than bipolar patients only for...
temporo-parietal (p=0.006) and occipital (p=0.008) locations upon target stimulation. Fig. 2 presents the between-group differences.

Analysis of behavioral data showed that 18 out of 22 patients with bipolar disorder made errors, whereas 9 out of 21 healthy controls made errors (χ²=6.19, p = 0.013). The number of errors (log-transformed) differed significantly between groups (Z = -2.85, p = 0.004). No correlation was identified between the number of errors and the amplitudes of target responses.

Correlation analysis showed that age and age at the onset of disorder significantly correlated with the amplitude of target responses in the bipolar group (Table 2). Young Mania Rating Scale scores correlated with amplitude at the right temporo-parietal (r=0.45, p < 0.05) and occipital (r=0.45, p < 0.05) locations. Education negatively correlated with the number of errors in target detection (r = -0.48, p < 0.05). Duration of bipolar disorder correlated with number of errors in target detection (r = -0.51, p < 0.05). However, these significant correlations were not significant after Bonferroni correction. Other variables (education, HAM-D scores, duration of disease, duration of euthymia and number of total/manic/depressive episodes) did not show any correlation with mean amplitude values.

### 4. Discussion

The findings show that evoked and event-related delta oscillations in patients with bipolar disorder are significantly lower than those in healthy controls at central, parietal, temporal, temporo-parietal, and occipital regions. Oscillatory delta responses in cognitive tasks have also been reported to be significantly decreased in other diagnostic groups such as schizophrenia (Ergen et al., 2008; Ford et al., 2008; Bates et al., 2009; Başar-Eroğlu et al., 2009; Doege et al., 2010), and Alzheimer’s disease (Güntekin et al., 2008; Yener et al., 2008; Başar et al., 2010; Yener et al., 2012) as well as in elderly healthy subjects (Schmidt-Fehr and Başar-Eroğlu, 2011). These findings suggest that delta oscillations might play a critical role in cognition, which might be commonly influenced by neuropathology of various neuropsychiatric disorders, as proposed by Başar and Güntekin (2013).

Delta oscillations are related to focused attention, signal detection, recognition, and decision-making (Başar-Eroğlu et al., 1992; Başar et al., 1998, 1999, 2001; Schürmann et al., 2001). Delta oscillations are also involved in cortical communication over long distances (Bruns and Eckhorn, 2004). Yener and colleagues (Yener and Başar, 2010; Yener et al., 2012) suggested that there were two different networks activated in delta frequency in response to different stimulus modalities, according to the stimulation characteristics and requirements (i.e., sensory or cognitive demands). Although the groups differed in event-related delta oscillations, there was no difference between healthy controls and patients with Alzheimer’s disease in their evoked responses (Yener et al., 2012). Evoked oscillations do not include cognition-related components whereas event-related oscillations include cognitive task-related responses.

Independent of the group (n = 43), event-related delta oscillations were higher in frontal, central, and parietal locations compared with temporal and occipital locations. This pattern may indicate that operations with delta oscillations spread to fronto-parietal regions in response to the cognitive demands of the oddball paradigm (Schürmann et al., 1995; Başar, 1998, 1999; Ishii et al., 2009; Mathes et al., 2012). Notwithstanding the general trend, however, the between-group difference in delta oscillations in the oddball paradigm was not significant at frontal locations.

Dysfunction of certain networks might have several sub-cellular, cellular or tissue level explanations (e.g., synaptic transmission, axonal transfer, myelination) that could cause disrupted connectivity (Tkachev et al., 2003; Uranova et al., 2004), and therefore synchronization deficits in various neuropsychiatric diseases (Güntekin et al., 2008; Özerdem et al., 2010, 2011; Schmidt-Fehr and Başar-Eroğlu, 2011; Başar-Eroğlu et al., 2008; Başar and Güntekin, 2008; Uhlhaas and Singer, 2006). Although these neuropsychiatric diseases have common characteristics in their physiopathology, the spatial distribution and temporal dynamics of connectivity deficits may determine the clinical course of the disorder.

The major limitation of the present study is the relatively small sample size. The number of female subjects in the groups was higher than the number of male participants (n = 43, female/male: 32/11). The study included three patients with bipolar disorder II, and it is still not clear whether there is a difference between bipolar I and bipolar II disorders in terms of oscillatory brain responses. Most of the patients were mild cases and therefore were unmedicated. On the other hand, medication-free patients can be seen as the major strength of the study because such patients offer the possibility of understanding the de novo neurophysiology of bipolar disorder. In addition, all patients were euthymic, and none of the patients had sub-threshold depressive or manic symptoms.

### 5. Conclusion

It can be suggested that delta oscillations are critically important in cognitive functions, and that diminished oscillatory delta responses may be a common characteristic of cognitive dysfunction in neuropsychiatric disorders (Başar, 2011; Başar and Güntekin, 2013).

Abnormalities of brain oscillations may have specific profiles in neuropsychiatric disorders, and those profiles may potentially distinguish between different disorders. These profiles can only be detected by studies that have eliminated confounders such as medications. As summarized in Table 3, to date we have detected increased event-related beta and decreased event-related alpha responses in mania (Özerdem et al., 2008), reduced gamma coherence in mania (Özerdem et al., 2010) and euthymia
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References


Table 3

Brain oscillations studies by our group in medication-free patients with bipolar disorder.

<table>
<thead>
<tr>
<th>Study (chronological order)</th>
<th>Clinical state</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Özerdem et al. (2008)</td>
<td>Mania</td>
<td>Increased visual event-related beta (18–30 Hz) and reduced event-related alpha (8–13 Hz) responses</td>
</tr>
<tr>
<td>Özerdem et al. (2010)</td>
<td>Mania</td>
<td>Reduced gamma (28–48 Hz) coherence</td>
</tr>
<tr>
<td>Özerdem et al. (2011)</td>
<td>Euthymia</td>
<td>Reduced gamma (28–48 Hz) coherence</td>
</tr>
<tr>
<td>Başar et al. (2012)</td>
<td>Euthymia</td>
<td>Decreased spontaneous alpha (8–13 Hz) activity and visual-evoked alpha (8–13 Hz) responses</td>
</tr>
<tr>
<td>Atagün et al. (2013)</td>
<td>Euthymia</td>
<td>Decreased evoked and event-related slow (4–6 Hz) theta and decreased event-related fast (6–8 Hz) theta responses. Fast theta (6–8 Hz) was more responsive to cognitive components of the task</td>
</tr>
<tr>
<td>This study</td>
<td>Euthymia</td>
<td>Decreased auditory-evoked and event-related delta (0.5–3.5 Hz) responses</td>
</tr>
</tbody>
</table>

(Özerdem et al., 2011), decreased spontaneous EEG alpha activity and evoked visual alpha response in euthymia (Başar et al., 2012), decreased evoked and event-related slow theta (4–6 Hz) and event-related fast theta (6–8 Hz) responses in euthymia (Atagün et al., 2013), and the present study reveals that auditory-evoked and event-related delta responses are decreased in euthymic medication-free patients with bipolar disorder. Further studies should focus on brain oscillations in different clinical states for bipolar disorder. Comparing bipolar disorder with schizophrenia and schizoaffective disorder may help to identify differences and allow us to investigate whether there are any biological correlates of clinical differences between these psychotic spectrum disorders.