Increased Beta Frequency (15-30 Hz) Oscillatory Responses in Euthymic Bipolar Patients Under Lithium Monotherapy

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Abstract
The effect of lithium on neurocognition is not still fully explored. Brain oscillatory activity is altered in bipolar disorder. We aimed to assess the oscillatory responses of euthymic bipolar patients and how they are affected by lithium monotherapy. Event-related oscillations in response to visual target stimulus during an oddball paradigm in 16 euthymic drug-free and 13 euthymic lithium-treated bipolar patients were compared with 16 healthy controls. The maximum peak-to-peak amplitudes were measured for each subject’s averaged beta (15-30 Hz) responses in the 0- to 300-ms time window over frontal (F3, Fz, F4), central (C3, Cz, C4), temporal (T7, T8), tempo-parietal (TP7, TP8), parietal (P3, Pz, P4), and occipital (O1, Oz, O2) areas. Patients under lithium monotherapy had significantly higher beta responses to visual target stimuli than healthy controls (P = .017) and drug-free patients (P = .015). The increase in beta response was observed at all electrode locations, however, the difference was statistically significant for the left (T7; P = .016) and right (T8; P = .031) temporal beta responses. Increased beta responses in drug-free patients and further significant increase in lithium-treated patients may be indicative of a core pathophysiological process of bipolar disorder and how it is affected by lithium. Whether the finding corresponds to lithium’s corrective effect on the underlying pathology or to its neurocognitive side effect remains to be further explored. In either case, the finding is a sign that the oscillatory activity may be useful in tracking medication effect in bipolar disorder.

Keywords
bipolar disorder, euthymia, lithium, brain oscillations, beta response

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Introduction
Bipolar disorder is one of the most debilitating illnesses worldwide.¹ It follows a chronic, relapsing and remitting course, with unpredictable manic or depressive relapses. Neurocognition is largely disturbed in bipolar disorder across depressed and manic phases as well as during euthymia, the well-being state of the illness. Cognitive deficits in euthymia involve response inhibition, set-shifting, executive function, verbal memory, sustained attention, processing speed, visual memory, and verbal fluency.² Brain imaging data points at a disruption in frontal connections³ along with a possible inability to activate appropriate brain regions in preventing impulsive response⁴⁵ leads to dysregulation of fronto-limbic networks and eventually to the evident cognitive dysfunction and emotional dysregulation in bipolar disorder. Neural circuits, receiving projections that connect prefrontal to striatal structures with further projections to thalamic nuclei are suggested to be involved in the wide range of cognitive problems in bipolar disorder.⁶

The relationship between cognitive pathology, different neurotransmitter systems and brain oscillations is well defined in a multidimensional model of electrical signals.⁷ Previous assessments of brain oscillatory activity in bipolar disorders indicated a high potential for an alternative functional imaging method.⁸¹⁴ In some studies, reduced P300 amplitudes have been reported in bipolar disorder.⁹¹⁵⁻²⁰ However, some studies identified no difference between healthy controls and patients

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with bipolar disorder.\textsuperscript{21-26} A prolonged P300 latency have been detected in 3 studies\textsuperscript{19,26,27} but another study did not find any delay in P300 latency in bipolar disorder.\textsuperscript{17} These discrete findings may be result from the variable nature of bipolar disorder.

The superposition principle indicates synergy between alpha, beta, gamma, theta, and delta oscillations during the performance of sensory cognitive tasks. Integrative brain function operates through the combined action of multiple oscillations.\textsuperscript{28} Low amplitude fast (beta and gamma) oscillations ranging between 15 and 80 Hz have been associated with synchronous communication between brain regions.\textsuperscript{29,30} Previous studies showed reduced resting state long-range synchrony in manic patients compared with healthy controls in all frequency bands\textsuperscript{8} increased delta and decreased beta synchronization in the frontal region in euthymic medicated patients,\textsuperscript{10} deficits in auditory EEG synchronization in beta and gamma range activity during click entrainment paradigm in the manic or mixed state.\textsuperscript{9,11,31}

To date, we have reported increased beta, decreased alpha response to visual target stimuli\textsuperscript{32} and significantly decreased fronto-temporal gamma band coherence in drug-free manic patients,\textsuperscript{33} decreased evoked and event-related slow theta (4-6 Hz) and event-related fast theta (6-8 Hz) responses in euthymia,\textsuperscript{34} and decreased auditory-evoked and event-related delta responses in euthymic medication-free patients with bipolar disorder.\textsuperscript{35} Drug-free euthymic patients also showed decreased fronto-temporal gamma coherence.\textsuperscript{36} Our group recently showed that the subjects treated with lithium had higher event related beta responses than healthy controls and medication-free euthymic bipolar patients during auditory oddball paradigm.\textsuperscript{37} Evidence also indicates a possible medication effect in electrophysiology\textsuperscript{32,33} and in other imaging findings\textsuperscript{38} in bipolar disorder.

The aim of the present study was to assess the oscillatory responses of euthymic bipolar patients who were under lithium monotherapy in comparison to drug-free euthymic bipolar patients and healthy controls to further corroborate particularly the role of beta responses in euthymia with and without lithium, the gold standard treatment option for bipolar disorder. To our knowledge, this is the leading study using event-related oscillatory assessment as a tool to trace the effects of lithium in euthymic bipolar patients during visual oddball paradigm.

**Material and Method**

The study was approved by the local Ethics Committee of Maltepe University, Faculty of Medicine.

**Participants**

Sixteen *DSM-IV (Diagnostic and Statistical Manual of Psychiatric Disorders, fourth edition)*\textsuperscript{39} euthymic drug-free (DF) bipolar I (n = 14) and bipolar II (n = 2) patients (10 females, 6 males; mean age 32.94 ± 6.02 years; range 26-44 years), 13 euthymic lithium-treated (LT) bipolar I (n = 13) patients (8 females, 5 males; mean age 33.77 ± 9.55 years; range 21-60 years), and 16 healthy controls (HC; 7 females, 9 males; mean age 29.56 ± 8.85 years; range 20-48 years) were enrolled in the study. Lithium was given as monotherapy to the LT patients. All participants provided written informed consent. Diagnoses were confirmed with the Turkish version of the SCID-I (Structured Interview for DSM-IV).\textsuperscript{30,41}

Both DF and LT patients were required to be euthymic for at least six months; to score 7 or less on the reliable and validated Turkish versions of the Young Mania Rating Scale (YMRS)\textsuperscript{42}, the Hamilton Depression Rating Scale (HAM-D 21),\textsuperscript{43} to have no comorbid axis I diagnosis, and to be medically healthy as shown through physical examination and routine laboratory tests. DF patients were psychotropic-free for at least 2 weeks prior to the study enrollment. Patients under lithium monotherapy had received this treatment for a minimum of 6 weeks. Serum lithium levels were monitored on the day of EEG recording. All patients were off short-acting benzodiazepines with half-lives of 6 to 11 hours for at least 24 hours before the EEG recording. All previously used benzodiazepines were short-acting with half lives of 6 to 11 hours. Two patients were enrolled in EEG recording both before and after lithium therapy as euthymic DF and LT patients, respectively.

Clinical data (age of illness onset, duration of illness, total number of past episodes, duration of euthymia) were collected from patients’ charts.

**Experimental Procedure and Stimuli**

The participants sat in a dimly lit, isolated room during recordings. A classical visual oddball paradigm\textsuperscript{44} was applied by using a simple 35 cd/m\textsuperscript{2} luminance light as the standard and 20% lower luminance as the target stimuli, which were sent to the recording room by a monitor switch. The light appeared at full size on a 17 cm × 17 cm monitor screen. The duration of the stimulation was 1000 ms. The probability of the deviant stimuli was .20 and, in all paradigms, they were embedded randomly within a series of standard stimuli. These stimulation signals were applied randomly, with interstimulus intervals varying between 3 and 7 seconds. To assess focused attention and working memory, the task required mental counting of the target stimuli.

**Electroencephalogram Recording**

Electroencephalogram was recorded with 30 Ag–AgCl electrodes mounted in an elastic cap (Easy-cap) according to the international 10-20 system. Additionally, 2 linked earlobe electrodes (A1 + A2) served as references. The EOG from the medial upper and lateral orbital rim of the right eye was also registered. For the reference electrodes and EOG recordings, Ag–AgCl electrodes were used. All electrode impedances were less than 10 kohm. The EEG was amplified by means of a BrainAmp 32-channel DC amplifier with band limits of 0.01 to 250 Hz. The EEG was digitized online with a sampling rate of 500 Hz. All epochs contaminated with ocular, muscular, or other non-EEG activity were excluded by manual off-line checks. Subject
Electroencephalography Analysis

Filtering produces visual displays of the time courses of oscillatory components within the frequency limits of the used filters. Digital filters are advantageous because they do not produce the phase shifts that are a characteristic of electronic filters. Digital filtering was employed in the present study for the digital pass-band filtering of the event-related potentials (ERPs) and thus to demonstrate peak amplitude values of the event-related oscillations (EROs) in the beta frequency band (15-30 Hz). The rationale for choosing the beta response as the focus of attention in this study was based on our previous finding of significantly increased beta response to visual target stimulus in DF manic patients and the dramatic decrease in response after treatment in the same patient population. The maximum peak-to-peak amplitudes were measured for each subject’s averaged beta responses (15-30 Hz) in the 0 and 300 ms time window over frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), temporal (T7, T8), temporo-parietal (TP7, TP8), and occipital (O1, Oz, O2) areas.

Statistical Analysis

The Statistical Package for Social Studies (SPSS, version 15) was used for statistical analysis. Electrophysiological and clinical data were log transformed due to failing normal distribution (Wilks–Shapiro test; \( P < .05 \) for all variables) before statistical analysis.

Maximum peak-to-peak amplitude beta responses to visual target stimulus in the 0- to 300-ms time window were analyzed by means of repeated-measures analysis of variance (ANOVA). Electrode locations at 6 levels (frontal, central, temporal, temporo-parietal, parietal, and occipital) and lateralization at 2 levels (right and left) were included as the within-subject factors; participant groups (DF euthymic patients, ILT euthymic patients, and HC) were included as between-subject factors. To control for the effect of level of education on the findings, the number of years of education was included as a covariate in a second analysis.

Table 1. Demographic and Clinical Characteristics of the Participants.

<table>
<thead>
<tr>
<th></th>
<th>Drug-Free Patients</th>
<th>Lithium-Treated Patients</th>
<th>Healthy Controls</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.94 ± 6.02</td>
<td>33.77 ± 9.55</td>
<td>29.56 ± 8.85</td>
<td>NS</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.25 ± 4.04</td>
<td>11.31 ± 4.48</td>
<td>15.13 ± 1.71</td>
<td>.019</td>
</tr>
<tr>
<td>Age at illness onset (years)</td>
<td>23.56 ± 7.63</td>
<td>21.38 ± 4.89</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Duration of euthymia (months)</td>
<td>43.75 ± 35.61</td>
<td>38.84 ± 51.86</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (months)</td>
<td>117.00 ± 59.84</td>
<td>153.85 ± 85.73</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Total number of past episodes</td>
<td>4.13 ± 3.69</td>
<td>7.31 ± 7.38</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Serum lithium level (mmol/L)</td>
<td>0.81 ± 0.11</td>
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</table>

Abbreviation: NS, nonsignificant

*Data are expressed as mean ± standard deviation.

Results

Clinical Features

There was no significant age difference between the 3 groups. However, the groups differed significantly with regard to the years of education (\( F = 4.359; \ df = 2; P = .019 \)). Post hoc Bonferroni comparison showed that HCs had the longest duration of education (15.13 ± 1.71 years), which was significantly greater than that of LT patients (11.31 ± 4.48 years; \( P = .037 \)). The difference between the LT and DF patients (11.25 ± 4.04 years) was nonsignificant (Table 1).

Patients in the DF and LT groups did not differ significantly with regard to duration of euthymia, total number of past episodes, age of illness onset, and duration of illness. The mean serum lithium level was within the therapeutic range in the LT group (0.81 ± 0.11 mmol/L; range 0.69-1.08 mmol/L; Table 1).

Electrophysiology Data

Repeated measures ANOVA revealed a significant location effect—\( F(5, 210) = 29.806, P < .001 \)—and a significant group difference (\( P = .007 \)). Post hoc Bonferroni test showed that LT patients had significantly higher beta responses to visual target stimuli than HCs (\( P = .017 \)) and DF patients (\( P = .015 \)). After including years of education as a covariate, location by hemisphere interaction was significant (\( P = .017 \)) and the group difference was still significant (\( P = .013 \)). ANOVA showed no significant interaction between years of education and electrode locations, hemispheres, or groups.
Figure 1. Beta response to target stimuli during visual oddball paradigm at different electrode locations. Lithium treated patients show increased beta response compared to healthy controls at all electrode locations. The difference reaches significance level at the right and left temporal locations. It is of note that the drug-free euthymic patients already has higher beta responses than healthy controls in the frontal, central, temporal, and temporo-parietal locations where lithium treatment patients show further increase in the beta range response.

Figure 1 depicts the beta response to target stimuli at different electrode locations and Figure 2 depicts grand averages of event-related beta responses in left (F3), center (Fz), and right (F4) frontal electrode sites in HCs, DF, and LT patients.

Pairwise comparisons across the whole group (n = 45) between different electrode locations showed that frontal beta responses were significantly higher than temporal and temporo-parietal beta responses (P < .001); central beta responses were significantly higher than temporal and temporo-parietal beta responses (P < .001); temporal beta responses were significantly smaller than parietal (P = .003) and occipital beta responses (P < .001); temporo-parietal beta responses were significantly smaller than parietal (P < .001) and occipital beta responses (P < .001).

Across the whole group (n = 45), there was a significant negative correlation between years of education and left frontal (F3; r = −0.452; P = .002), right frontal (F4; r = −0.393; P = .008), right central (C4; r = −0.379; P = .011), left temporal (T7; r = −0.528; P < .001), left temporo-parietal (TP7; r = −0.328; P = .028), and right parietal (P4; r = −0.434; P = .003) beta responses. In other words, as the level of education increased, the amplitude of beta response decreased. However, there was no interaction with the level of education in the ANOVA comparisons, as presented above.

In the DF group, the total number of past episodes was significantly positively correlated with F3 (r = 0.724, P = .002), F4 (r = 0.784, P < .001), and C3 electrode beta values (r = 0.570, P = .021). Duration of illness was also positively correlated with the F3 (r = 0.531, P = .021) and F4 (r = 0.626, P = .009) electrode responses. These correlations were not observed in the LT group; instead, duration of euthymia showed significant positive correlations with beta responses at F3 (r = 0.664, P = .013) and TP8 (r = 0.712, P = .006) locations.

Discussion

The main finding of the present report is significantly higher beta range oscillatory response to visual target stimuli in LT euthymic bipolar patients compared with DF patients as well as HCs. The significantly increased beta response in the LT patients may be directly associated with lithium use, as the response is independent of any clinical or demographic characteristics of the patients. The intriguing feature of the finding is that beta activity shows further increase in LT patients compared with DF patients whose beta responses are already higher than HCs. The increased beta response to visual target stimuli in euthymic DF patients compared with HCs is in line with the previously reported significantly increased beta response in DF manic patients. Increased beta response in both euthymic and manic DF patients appears to be a core electrophysiological feature of bipolar disorder. A further increase in beta response in lithium-responsive patients may be a double featured phenomenon. First, it may be an enhancement of a previously suggested compensatory mechanism operating through beta oscillatory activity toward restoration of impairment in the brain’s integrative functioning in bipolar disorder. A second feature would be related to lithium’s disputed role in cognition, indicating an adverse effect of such therapy. Both features are discussed in the following sections.

Beta activity was shown to be related to various functions such as visual attention, movement-related changes, excitation-inhibition, sensory memory, facial recognition and differentiation of familiar and unfamiliar faces. In an emotion-recognition task, negative emotions were found to be related to increased beta responses in humans, independent of stimulus types. Possible involvement of beta activity in the core pathophysiology of bipolar disorder seems reasonable with regard to the wide range of cognitive deficits in bipolar disorder.
in attentional, memory, and emotional processing domains. It is important to note that in the DF patients, beta responses are significantly correlated with a more morbid course of illness (i.e., the higher the number of past episodes or the longer the duration of illness, the higher the beta response becomes). This suggests that increase in beta response may be a reflection of loss or dysfunction at the cellular level or at the neural circuitry level. The loss of such correlation in lithium treatment and the appearance of a positive correlation between duration of euthymia and beta responses can be interpreted as the dominance of lithium’s effect on the beta responses, as the duration of euthymia in LT patients can be considered as an indirect sign of duration of lithium use. In addition, it is suggested that the neuropsychological impairment may be an expression of the disease phenotype but not bear any relationship with other illness characteristics such as severity of the illness or polypharmacy.

In our previous work, manic patients showed increased beta and alpha oscillations on a visual oddball paradigm, and treatment of the episode with valproate reduced the responses. It is suggested that breakdown of alpha activity can be considered as a biomarker for euthymic bipolar disorders. Some studies showed that late beta response power to auditory target and standard stimuli was increased in bipolar disorder group. That late beta response differentiated psychotic bipolar patients from schizophrenia and healthy control groups. Also, in bipolar disorder group, increase in the beta frequency were correlated with depression scores. That suggests a relationship between emotional dysregulation and increased beta responses in the bipolar disorder group.

Our group subsequently presented evidence for significantly decreased long-range gamma coherence presenting a synchronization deficit in both DF euthymic and manic patients. This was in support of our previous finding of altered beta response given the suggested interplay between beta and gamma oscillations. In the manic patients, we also observed a significant decrease (normalization) of the beta response after 6 weeks of valproate monotherapy when the patients were not as severely manic as before. Based on this finding, one would expect a decreased (normalized) beta response in LT patients compared with DF patients. Following this line of thought, we would argue that the further-increased beta response in LT patients may be a reflection of lithium’s adverse effect on cognitive functions rather than being associated with its treatment effect on the illness itself.

Figure 2. Grand averages of event-related beta responses in left (F3), center (Fz), and right (F4) frontal electrode sites in (from top to bottom) healthy controls, untreated euthymic patients, and patients under lithium monotherapy.
Some cognitive deficits may occur at least by the time of initial diagnosis of bipolar disorder\textsuperscript{59,60} although most of these studies have all been conducted in multiple-episode patients with bipolar disorder. Cognitive performance may be impaired in euthymic patients with bipolar disorder,\textsuperscript{52,61-63} and that cognitive deficits predict poor functional outcome in bipolar disorder.\textsuperscript{64-66} With some exception,\textsuperscript{67} attention/processing speed, verbal memory, and executive functioning are found to be significant predictors of quality of life in addition to mood symptoms in nonelderly euthymic bipolar patients.\textsuperscript{52,64,68-72} A study also showed an illness-related prefrontal cortex dysfunction in bipolar disorder.\textsuperscript{73} Therefore, cognitive impairment in patients with bipolar disorder probably persists throughout remission and may be related to executive dysfunction.\textsuperscript{72}

Recent findings support the preclinical literature on lithium’s neurotrophic effects\textsuperscript{74,75} and suggest that long-term lithium treatment is associated with preservation of memory function, increased hippocampal size in vivo, and increased gray matter.\textsuperscript{76-78} It is assumed that regular and extended lithium intake over time might produce positive changes in cognition.\textsuperscript{79,80} The lack of verbal memory impairment may point to the neuroprotective properties of lithium.\textsuperscript{81} However, there is no evidence that lithium enhances cognitive function. On the contrary, studies in both healthy volunteers and euthymic patients with bipolar disorder showed an association between lithium and slowed motor speed, impaired short- and long-term memory, slowed reaction time, and diminished verbal or associative fluency.\textsuperscript{52,81} No adverse effect on attention or sustained attention was detected under lithium use. The negative cognitive effects of lithium were found to be independent of moderating factors such as duration of illness or lifetime number of episodes.\textsuperscript{82} A study performed with functional magnetic resonance imaging, tapping into the cognitive impairment of euthymic bipolar patients treated with lithium and with a specific focus on working memory suggested that the neuropsychological deficit might be related to the failure in engaging fronto-executive areas of the brain.\textsuperscript{84} Lithium was also shown to cause some mild disturbances in motor functions.\textsuperscript{85,86} In summary, data on lithium’s deteriorating effect on neurocognition is contradictory.\textsuperscript{83,85,87} Then, it should be questioned whether these excessively increased amplitudes relate to an effect or a cognitive side effect of lithium. Because of the cross-sectional nature of the present study, the link between good lithium response and increased beta oscillations is equivocal. Despite lithium’s well-known neuroprotective and neurotrophic effects,\textsuperscript{88} excessively enhanced beta oscillations may be representing an adverse effect from the perspective of the neurotoxicity hypothesis of lithium.\textsuperscript{79}

Together with the evidence on an interrelationship between gamma and beta oscillations in humans, both gamma and beta oscillatory activity are suggested to be involved in processes associated with encoding into sensory memory, both at the cellular level (synaptic potentiation) and at the cognitive level as shown by event-related potentials to mismatch negativity task.\textsuperscript{89} As the previously reported reduction in fronto-temporal gamma coherence in DF euthymic state\textsuperscript{90} includes patients of this study, increased beta response to a cognitive load as presented during an oddball task in the presence of long-distance gamma coherence reduction can be interpreted as a sign of cognitive deficit. In this case, a further and significant increase in the beta response in LT patients may be associated with lithium’s disruptive effect on cognition.

The relatively small sample size constitutes the major limitation of the present study, leading to nonsignificance in increased beta response in the DF group. Although 2 patients were enrolled in recording both before and after medication use, it is considered to have nonsignificant effect on results because the smaller size of LT patients than DF patients had statistically significant impact on beta response. The main strength of the study is the presence of well-defined homogeneous groups of patients with regard to mood state (euthymia), and to medication use (either drug free or under lithium monotherapy). The patient groups were also similar in terms of clinical features. Changes in the state of the brain and fluctuations in mood state between mania, depression, and euthymia present a major challenge for research in bipolar disorder. Interference from medication use constitutes a further challenge while studying the underlying mechanisms in bipolar disorder. Therefore, the findings on beta range oscillatory responses reported here can be regarded as reflections of a core pathophysiological process of bipolar disorder and how it is affected by lithium use. However, whether the finding corresponds to lithium’s corrective effect on the underlying pathology or its neurocognitive side effect remains to be further explored as there is a need to determine whether observed neurotrophic effects of lithium that are suggested to be associated with increase cerebral volume are associated with functional changes in cognitive performance.\textsuperscript{82} The finding also points to the need for better understanding of possible dosing relationship between lithium’s neuroprotective versus neurotoxic effects. As our findings are coming from a cross-sectional design, to better understand the role of lithium use on the beta responses, we suggest a repeated measure longitudinal study on a larger sample of euthymic patients before and after lithium use.

**Author Contributions**

DT designed the study, wrote the protocol, did the psychiatric interviews of the participants, collected the clinical data, assisted EEG recordings, participated in the EEG data acquisition and ran the beta response analysis, wrote the first draft of the manuscript. AÖ designed the study, supervised ET in writing the protocol, supervised psychiatric and clinical evaluation of the subjects, and was in charge of statistical analysis and writing the article. BG assisted in designing the study, coordinated and controlled EEG recordings and analysis, participated in editing the article. MIA assisted in writing the protocol, managed the laboratory infrastructure for the EEG recordings and EEG analysis; she also contributed to the EEG recordings. FK participated in patient and volunteer recruitment. EB supervised the whole laboratory process, designing the protocol process, worked on the accuracy of the EEG data; screen all recordings, worked together with AÖ and ET in writing the manuscript.

All authors contributed to and have approved the final manuscript.
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