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Research report

# Lithium excessively enhances event related beta oscillations in patients with bipolar disorder

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ABSTRACT

*Background:* Previous resting-state electroencephalography studies have consistently shown that lithium enhances delta and theta oscillations in default mode networks. Cognitive task based networks differ from resting-state networks and this is the first study to investigate effects of lithium on evoked and event-related beta oscillatory responses of patients with bipolar disorder.
*Methods:* The study included 16 euthymic patients with bipolar disorder on lithium monotherapy, 22 euthymic medication-free patients with bipolar disorder and 21 healthy participants. The maximum peak-to-peak amplitudes were measured for each subject's averaged beta responses (14–28 Hz) in the 0–300 ms time window. Auditory simple and oddball paradigm were presented to obtain evoked and event-related beta oscillatory responses.
*Results:* There were significant differences in beta oscillatory responses between groups ($p=0.010$). Repeated measures ANOVA revealed location ($p=0.007$), laterality X group ($p=0.043$) and stimulus X location ($p=0.013$) type effects. Serum lithium levels were correlated with beta responses.
*Limitations:* The lithium group had higher number of previous episodes, suggesting that patients of the lithium were more severe cases than patients of the medication-free group.
*Discussion:* Lithium stimulates neuroplastic cascades and beta oscillations become prominent during neuroplastic changes. Excessively enhanced beta oscillatory responses in the lithium-treated patients may be indicative of excessive activation of the neuron groups of the certain cognitive networks and dysfunctional GABAergic modulation during cognitive activity.



## 1. Introduction

Lithium has several neurotrophic and neuroplastic effects that may trigger long-term changes on synaptic plasticity and networking functions (Kim and Thayer, 2009). Increasing volume and density of gray matter (Bearden et al., 2007; Moore et al., 2000a), improving white matter connectivity (Benedetti et al., 2013) and increasing brain levels of N-acetyl-aspartate, a marker of neuronal function and viability (Moore et al., 2000b) are some instances of lithium's beneficial effects on neuronal integrity.

Electroencephalography (EEG) is an electrophysiological method with a high temporal resolution that may provide valuable advantages for research areas that focus on cognitive networks (Başar, 2010). Either cognitive or sensory, all brain activities are operated in a specific oscillatory activity, thus all brain activities are governed by specific brain oscillations (Başar, 1998, 1999; Başar et al., 2001). Although dysfunction in sensory or cognitive processes cannot be explained by a frequency, connectivity characteristics may cause differences in a frequency response (Başar, 2006). Within the last two decades, brain oscillatory analyses have been applied to clinical pathologies, including bipolar disorder (Başar et al., 2013; Başar and Güntekin, 2008, 2013).

Despite the wealth of electroencephalography and magnetoencephalography studies in bipolar disorder, very limited studies reported beta frequency abnormalities (O'Donnell et al., 2004; Rass et al., 2010; Özerdem et al., 2008; Hamm et al., 2012; Ethridge et al., 2012; Lee et al., 2010). Patients with bipolar disorder in either manic or mixed mood state showed deficits in responses of beta and gamma frequency ranges upon auditory steady-state stimulation (O'Donnell et al., 2004; Rass et al., 2010). Manic patients showed increased beta and alpha oscillations upon a visual oddball paradigm, and treatment of the episode with valproate reduced the responses (Özerdem et al., 2008).

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Late beta response power to auditory target and standard stimuli was increased in bipolar disorder group and this finding differentiated psychotic bipolar patients from schizophrenia and healthy control groups (Hamm et al., 2012; Ethridge et al., 2012). Ethridge et al. (2012) also reported that depression scores were correlated with the beta frequency increase in bipolar disorder group, which suggest a relationship between emotional dysregulation and increased beta responses in the bipolar disorder group. Similarly, in comparison to major depression or healthy control groups, bipolar disorder group had increased alpha and beta oscillatory responses upon an emotional task (Lee et al., 2010). Most of these studies had mixed samples and medicated patients. However, both medications and clinical state may substantially alter neurophysiology, particularly beta oscillations are more vulnerable to neurochemical changes in particular Gamma-Amino-Butyric-Acid (GABA) and n-Methyl-d-Aspartate (NMDA) receptor activities (Arai and Natsume, 2006; Traub et al., 2004).

Previous studies by our group with medication-free patients with bipolar disorder also showed that in euthymia evoked and event related theta (Atagün et al., 2013b) and delta oscillations (Atagün et al., 2014) decreased upon auditory oddball paradigm. Resting state alpha activity and evoked alpha responses decreased (Başar et al., 2012). Gamma coherence is reduced in mania (Özerdem et al., 2010) and euthymia (Özerdem et al., 2011). It can be concluded that medication-free patients with bipolar disorder have a reduction in neural activation energy and reduced coherence values, which may mean a loss of functional connectivity and activation deficits.

The most consistent finding of previous lithium resting state EEG studies is increased power of resting state delta and theta activity in patients with bipolar disorder (Schulz et al., 2000; Zakowska-Dabrowska and Rybakowski, 1973; Hyun et al., 2011) or in healthy volunteers (Karniol et al., 1978; Thau et al., 1989). Ulrich et al. (1987) and Ulrich et al. (1990) detected enhanced alpha power in healthy male volunteers. Most of the abovementioned lithium-EEG studies were with mixed samples; patients were also taking various additional psychotropic medications.

However, it has recently been shown that task based networks differ from default-mode networks (Moussa et al., 2011; Kirschner et al., 2012). Accordingly, cognitive tasks may trigger activities that require the brain to reorganize and establish distinct networks with distinct characteristics. For instance, fast frequencies are related to cognitive activity in local networks (Başar et al., 2013), whereas slow frequencies—either in rest and activity—are related with activities of longer distances and larger amounts of neurons (Bruns and Eckhorn, 2004). There has not yet been a study that evaluates whether lithium has any different effect on cognition based networks. The effects of external manipulations (like medications) may become observable in responses to stimuli of either a bottom-up or a top-down task (Kenemans and Kähkönen, 2011).

Although it needs to be translated into human neuroscience, neuroplasticity drives networks to oscillate with beta frequency, instead of gamma frequency in animal studies (Whittington et al., 2000). As mood stabilizers induce neuroplastic cascades (Kim and Thayer, 2009; Soeiro-de-Souza et al., 2012), and since beta oscillations are related to neuroplastic changes (Whittington et al., 2000), it could be expected that lithium may alter beta responses in cognitive networks. In addition to neuroplasticity cascades, lithium also reduces excitatory neurotransmission (dopamine or glutamate) and increases inhibitory neurotransmission (GABA) (Malhi et al., 2013). Given the fact that EEG signal consists of excitatory-end-synaptic potentials, then it would be quite possible that psychotropic medications may alter the EEG signal. Cognitive processes demand broader range of oscillations that may include fast frequencies as well as slow frequencies, thus beta oscillatory responses could be investigated under cognitive tasks.

## 2. Methods

### 2.1. Subjects

All patients were euthymic for at least 6 months. 22 patients were medication-free (19 Bipolar I, three Bipolar II disorder) and 16 patients were on lithium monotherapy. 21 healthy participants were enrolled to the control group (Table 1). Diagnoses were confirmed with the Structured Clinical Interview According to DSM-IV (SCID) (First et al., 1996). The Young Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) were the clinical evaluation tools. All subjects were right handed. Clinical data and previous history of the disorder were assessed by the psychiatrist, taking into account available charts and case notes. Patients enrolled into the lithium group were required to be on lithium monotherapy for at least 8 weeks (average = 114.87 ± 208.06 weeks, range: 8–832 weeks), and on effective serum lithium levels (average = 0.80 ± 0.12 mEq/dl, range: 0.59–1.08 mEq/dl). Exclusion criteria were: comorbid axis I diagnosis, mental retardation, pregnancy, lactation, consumption of alcohol or substances 2 weeks prior to the recordings,

**Table 1**
Clinical and socio-demographic characteristics of the groups.

| | | Lithium group ($n=16$) | Euthymic drug-free ($n=22$) | Healthy controls ($n=21$) | $F/z/\chi^2$ | $p$ |
|---|---|---|---|---|---|---|
| **Age** | | 34.75 ± 9.90 | 30.82 ± 6.46 | 29.10 ± 7.87 | 2.33 | 0.107 |
| **Education**[a] | | 9.88 ± 4.44 | 11.77 ± 3.61 | 14.67 ± 2.22 | **9.13** | **< 0.001**** |
| **Gender (f/m)** | | 6/10 | 7/15 | 5/16 | 0.83 | 0.660 |
| **HDRS** | | 0.88 ± 1.09 | 2.45 ± 2.22 | | **2.62** | **0.013** |
| **YMRS** | | 0.56 ± 0.96 | 0.73 ± 1.28 | | 0.43 | 0.668 |
| **Age at disease onset**[a] | | 21.75 ± 7.45 | 21.86 ± 6.30 | | 0.51 | 0.960 |
| **Duration of the disorder**[a] | | 13.36 ± 6.02 | 10.05 ± 4.96 | | −1.81 | 0.073 |
| **Duration of euthymia**[b] | | 37.75 ± 45.69 | 48.64 ± 37.71 | | 0.80 | 0.427 |
| | **Total** | 7.31 ± 6.49 | 3.91 ± 3.13 | | **−2.15** | **0.039** |
| | **Manic** | 3.25 ± 2.70 | 1.82 ± 1.56 | | **−2.07** | **0.046** |
| **Number of previous episodes** | **Depressive** | 2.94 ± 2.89 | 1.09 ± 1.11 | | **−2.75** | **0.009** |
| | **Hypomanic** | 0.81 ± 1.17 | 0.77 ± 1.19 | | −0.10 | 0.919 |
| | **Mixed** | 0.38 ± 1.26 | 0.23 ± 0.53 | | −0.49 | 0.623 |
| **Serum lithium levels (mEq/lt)** | | 0.80 ± 0.12 | | | | |

One-way ANOVA, $t$ test, Mann–Whitney $U$ test and $\chi^2$ tests were used. f/m: female/male *Mann–Whitney $U$ test

** Posthoc Bonferroni test, healthy controls > drug-free patients, $p=0.022$, healthy controls > lithium group, $p<0.001$.

[a] Years.

[b] Months.