Event related oscillations in euthymic patients with bipolar disorder

Ayşegül Özerdem, Sibel Kocaaslan, Zeliha Tunca, Erol Başar

Department of Psychiatry, Dokuz Eylül University Medical School, Narlıdere, 35340, Izmir, Turkey
Department of Neurosciences, Dokuz Eylül University Health Sciences Institute, Narlıdere, 35340, Izmir, Turkey
Brain Dynamics Research Center, Dokuz Eylül University, Narlıdere, 35340, Izmir, Turkey
Department of Biophysics, Dokuz Eylül University Medical School, Izmir, Turkey
Istanbul Kultur University, Brain Dynamics, Cognition and Complex Systems Research Unit, Faculty of Science and Letters, Istanbul, Turkey

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ABSTRACT

Bipolar disorder involves dysfunction in gamma amino butyric acid (GABA)/glutamatergic systems and neural circuits that regulate cognitive processing. Valproate, a mood stabilizing anticonvulsant, modulates GABA/glutamate and shows neuroprotective effect. Electroencephalographic oscillatory activity assessment is an alternative brain imaging technique with high time resolution. It presents integrative brain functioning. We aimed to assess the oscillatory responses of patients with bipolar disorder in euthymic state of bipolar disorder and the changes after treatment with valproate. Event related potentials to visual odd-ball paradigm in 10 euthymic medication free, bipolar patients were measured before and after 6 weeks of valproate monotherapy and compared with sex- and age-matched healthy controls. Delta frequency bands, as representative of signal detection and decision-making, were obtained by digital filtering. At baseline, patients showed higher delta responses to target stimuli in the left frontal and bilateral anterior temporal areas frequency electrical activity which was prominent in the left frontal location in euthymic patients with bipolar disorder. Reduction of the electrical activity of the left frontal and bilateral anterior temporal areas with treatment may be through modulation of glutamatergic and GABAergic mechanisms and indicative of valproate’s neuroprotective effect.

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Bipolar disorder is a chronic mental illness with a relapsing and remitting course. Relapses are manic or depressive in nature. Patients suffer from a wide range of cognitive deficits [26, 14, 41] even when they are euthymic. Functional brain imaging data point to dysfunction of neural circuits which connect prefrontal/frontal regions to limbic structures and serve in modulation of cognitive functions and emotional processing [40]. Post-mortem histopathological studies also point to neuronal and glial loss and neurochemical changes in the abovementioned regions [33]. Gamma amino butyric acid (GABA) spreads in neural networks which are involved in cognitive and emotional processing and modulates noradrenergic, dopaminergic and serotonergic local neural circuitry [11]. GABA activity had been shown to be low in bipolar disorder [6, 7, 22, 20, 21, 8]. It was suggested to be a genetically determined vulnerability to the development of either mania or depression [31]. Among different types of psychotrops that are used in bipolar disorder, valproate is an anticonvulsant with a GABA/glutamate modulatory effect and proposed neuroprotective properties [25, 42]. It is an effective antimanic agent and is relatively efficacious in maintenance treatment of bipolar disorder [10].

Transmission of information in the nervous system is provided by electrical impulses between neurons. Oscillatory electrical activity is the most obvious observable type of electrical activity in the brain. It is now possible to achieve measurements, via scalp electrodes, of human subjects under various states of behavior and learning, sensory or cognitive events. Early experimental studies on large scale brain activity in animals and humans showed superposition of multiple oscillations in delta (0.5–3.5 Hz), theta (3.5–7 Hz), alpha (8–13 Hz), beta (18–30 Hz), gamma (30–70 Hz) and higher frequencies as the 300 Hz component in various parts of the brain [3]. These oscillatory systems are selectively distributed in the brain. They control the integrative brain functions at all sensory and cognitive levels [4].
There have been a relatively limited number of earlier electrophysiology studies in bipolar disorder, both in symptomatic and euthymic states [12,28,37,34,35,30]. Despite different stimulus modalities, mostly being auditory, the common finding was prolonged P300 latency and reduced P300 amplitude which was equivocal and mostly found to be related to psychosis and suggested to have an association with an underlying frontal lobe pathology [35]. More recent studies showed disturbed resting EEG activity in euthymic bipolars [16] and abnormal high frequency synchronization in response to auditory stimuli [29] in symptomatic bipolar patients.

With its high time resolution, electrophysiological assessment of oscillations can be a useful functional imaging tool. Assessment of the brain’s responsivity without any potential symptom or medication-related confounding effect in unmedicated euthymic bipolar patients is a major challenge to understanding the underlying pathophysiology. Taken together, this study aimed to assess oscillatory event related (visual target stimuli) responses of unmedicated euthymic patients with bipolar disorder in comparison to healthy controls and the impact of valproate monotherapy on the oscillatory activity. To our knowledge, this is the first study using event related oscillatory assessment as a tool to trace medication effects in drug-free euthymic bipolar patients.

Ten DSM-IV (Diagnostic and Statistical Manual of Psychiatric Disorders, fourth edition) [15] euthymic bipolar I (n = 5) or II (n = 5) patients (six female, four male), aged between 18–65 years (mean age ± S.D.: 37.60 ± 12.16) and 10 sex, age and educationally matched healthy controls were enrolled in the study. All subjects were interviewed with SCID-I (Structured Interview for DSM-IV) [17]. The study was approved by the local Ethics Committee for Drug Trials of Dokuz Eylul University Medical School, Turkey. All participants provided written informed consent. Patients needed to be euthymic at least for 4 weeks and psychotrop free for at least 2 weeks; to score 7 or less on the reliable and validated Turkish versions of the Young Mania Rating Scale (YMRS) [23], Hamilton Depression Rating Scale (HAM-D 21) [11], having no co-morbid axis I diagnosis, and be medically healthy as shown through physical examination and routine laboratory tests.

All patients underwent electrophysiological recording first at baseline, then after 6 weeks of valproate monotherapy. Healthy controls were also assessed twice with a 6-week time difference.

Patients were clinically assessed at weeks 0 through 6. Serum valproate levels and liver function tests were monitored at weeks baseline, then after 6 weeks of valproate monotherapy. Healthy laboratory tests. A total of 10 patients and 10 controls at baseline compared to healthy controls and the within-subject factors location (frontal (F3–F4), central (C3–C4), temporal (T3–T4), parietal (P3–P4), occipital (O1–O2)) and hemisphere (left (F3, C3, T3, T5, P3, O1), right (F4, C4, T4, T6, P4, O2)).

**Electrophysiological assessment:** Visual odd-ball paradigm was applied by using 35 cd/m2 luminance simple 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. Subjects were asked to count and report the number of target stimuli. The number of errors was calculated for each subject and comparisons between means of each group were done. EEG was recorded with Nihon Kohden 10 channel Analogue EEG and 32 channel digital EEG devices which were simultaneously and directly connected to Brain Data EEG-ERP system. Ag/AgCl electrodes were connected according to international Jasper 10/20 system through a EEG-CAP. Electrode positions were F3, F4, Cz, C3, C4, P3, P4, T3, T4, T5, T6, O1, O2. Derivations were against a left earlobe reference. Electrooculography (EOG) and MATLAB trigger channels were applied as main schemes. The EEG settings were 2000 sample/s, 1024 point/sweep and the stimulus point was 512. Electrode impedance was kept below 5 kΩ, 50 Hz a notch filter was applied. Recorded EEG was evaluated for ERP analysis as off line to determine pre- and post-stimulus 1000 ms recordings, then digitally filtered by using Brain Data (version 3.25) and MATLAB (version 6.5) programs. Amplitude frequency characteristics (AFC) in both patient and control groups were computed by transforming the averaged ERP to the frequency domain from the electrode locations mentioned above.

The numerical evaluation of the frequency characteristics was accomplished using a Fast Fourier Transform (FFT) of the following form: let $X_n$ be a discrete time series ($X_n = x(nT)$, $T = (N-1)Dt$). Then the Fourier Transform of $X_n$ is:

$$Y_k = Y(\omega_k) = \sum_{n=0}^{N-1} X_n \exp(-i2\pi n T^{-1}) \omega_k = 2\pi k T^{-1}$$

where $Y_k = a_k + ib_k$ are the complex Fourier coefficients whose geometric mean is the amplitude spectrum. The digitally filtered frequencies were assessed according to the results of the AFC and the delta-band (0.5–3.5 Hz) responses to visual target stimuli were selected as the frequency of interest for analysis as the most prominently presenting component among all frequencies; grand averages of AFCs in both the patient and control groups for each location were computed, based on single subject averages. Peak-to-peak maximum amplitude was defined as the oscillatory response for the chosen frequency range.

**Statistical analysis:** Maximum peak-to-peak amplitude delta responses in 0–1000 ms time window for non–medicated and medicated conditions were analyzed separately by means of repeated measures ANOVA, including the between-subjects factor grouping (patient, healthy control) and the within-subject factors location (frontal (F3–F4), central (C3–C4), temporal (T3–T4), parietal (P3–P4), occipital (O1–O2)) and hemisphere (left (F3, C3, T3, T5, P3, O1), right (F4, C4, T4, T6, P4, O2)).

The mean number of previous episodes was 11.10 (range 1–45). The mean serum level of valproate stayed within the therapeutic range of the controls after valproate monotherapy (Fig. 1, Fig. 2). Central posterior temporal (T5) delta responses also decreased significantly after treatment in comparison to baseline (Fig. 1, Fig. 3). Healthy controls did not differ between the two assessments.
Fig. 1. Baseline delta amplitudes were higher in unmedicated patients compared to normal controls in all electrodes but significantly in the left frontal (F3) location. After 6 weeks of valproate, patients showed significantly lower delta responses to target stimuli in left frontal (F3), central frontal (Fz), left and right anterior temporal (T3, T4), and left posterior temporal (T5) areas in comparison to baseline.

Fig. 2. Delta wave (0.5–3.5 Hz) amplitude of patients vs their sex and age matched healthy controls before and after valproate treatment in left frontal (F3) electrode. Thin lines represent averages (mean values) of all sweeps of each patient and the thick line represents the grand average (mean) of averages of all subjects. The grand average of patients is significantly higher than that of the controls ($p: 0.032$). It reduces significantly ($p: 0.027$) compared to the baseline after 6 weeks of valproate treatment.
The mean number of errors was persistently higher in the patient group both before (2.25 ± 2.96) and after valproate (2.44 ± 2.50) in comparison to first (0.5 ± 1.27) and second assessment (0.22 ± 0.44) of the control group. As the controls recorded a lower number of mistakes at the second assessment, the difference between the two groups became significant (z: −2.368; p: 0.035).

This study shows diffuse but most prominently left sided frontal event-related high amplitude delta response in euthymic, drug free bipolar patients compared to normal controls. The high delta response decreased significantly in fronto-temporal regions after 6 weeks of treatment with valproate. Delta response is thought to be related to signal detection and decision-making. It is considerably increased during odd-ball experiments. The largest response appears in the parietal locations [5]. High delta response to target stimuli is most probably a reflection of disinhibition in the focused attention and decision-making properties of patients, leading to impulsive responses even when they are well, and may be representing a trait rather than a state-dependent finding. Impulsive response bias during a cognitive task and cortical hyper-arousal were shown to exist in euthymic bipolar patients by using functional magnetic resonance imaging [39], and resting EEG [16]. Previously, kindling and behavioral sensitization models also suggested an increase in cerebral excitability in bipolar disorder [32]. The greater number of errors made by the patients while counting the target stimuli in comparison to healthy controls is supportive of this assumption. The statistical non-significance between the groups at baseline is most probably due to the small sample size and high standard deviation of the mean delta amplitude. However, the difference became significant at the second assessment, as the controls recorded a lower number of errors, which may be due to learning, while the patients’ score was unchanged. Improvement in learning in the patients may be taking longer than the change in the brain’s responsivity. Longer periods of medication may be necessary for a clinically evident cognitive improvement.

The high delta response may appear to contradict the previously shown reduced P300 amplitude [35]. Delta response is a part of the component P300. However, it dominates the P300 response with auditory measurements. It is dependent on the P300 task [2]. Previous P300 findings were obtained with auditory stimulus. Patients were symptomatic and medicated. Taking these methodological differences together, it is not possible to compare studies and make any inferences with regard to the relationship between delta and P300 amplitudes.

Existing data can explain the significant increase in left sided delta response. Bipolar disorder was shown to be associated with a trait abnormality in the activation of the left ventral prefrontal cortex [9] which serves in inhibition of impulsive responses [38]. Levels of glutamate/glutamine – the major excitatory neurotransmitter – were found to be elevated in the left dorsolateral prefrontal cortex [27].

Reduction in the high delta oscillation after valproate may be linked to the medication’s regulatory effect on the excitatory and inhibitory neurotransmission [43] and modulation of glutamatergic receptor subtypes [18]. Anticonvulsant mood stabilizing drugs

![Graphs of delta responses before and after valproate treatment.](image-url)
might be working through attenuation of glutamate release or membrane depolarization subserving to reduction in postsynaptic excitability [24]. Valproate has a significant modulation effect on the activity of excitatory amino acid at mPFC pyramidal neurons [19]. It also attenuates NMDA glutamate receptor mediated neural excitation and has a direct action on excitable membranes [42,10]. These may explain the significant delta response reduction observed in the left frontal and temporal regions after valproate. However, it would be too simplistic to link valproate’s effect only to its GABAergic properties. Its effect on dopaminergic and serotonergic systems might also be contributing to the demonstrated regulatory effect of the medication.

Both trophic and neurochemical support seem to be necessary for an optimal treatment in bipolar disorder when the structural alterations in critical neuronal circuits [41,40] are taken into consideration. Reestablishing and maintaining normal synaptic connectivity will allow a healthy chemical trafficking and eventually cognitive as well as affective regulation in related neural circuits. Normalized delta response after valproate in our patients may be a sign of the medication’s corrective effect on the neuronal function through its neuroprotective properties. Besides inducing neuroprotective gene bcl-2 [13], valproate can attenuate the amyloid beta-peptide or glutamate elicited intracellular free calcium elevation and thus can block amyloid beta-peptide neurotoxicity [10]. Valproate was assumed to have unique actions with possible implications on neuronal function. This assumption was based on previous data revealing that valproate at therapeutic concentrations can block amyloid beta-peptide neurotoxicity and thus can block amyloid beta-peptide neurotoxicity [10]. Valproate was assumed to have unique actions with possible implications on neuronal function.

It has been suggested that the functional alterations of dynamic neural networks involved in mood and cognition are neurodevelopmental, possibly genetic in origin, but plastic changes, associated with a mood-driven disturbance of attention that may adversely affect cognition in acute states of the illness [36]. However, cognitive deficits seem to persist during the euthymic state [26,41]. Based on this, assessment of neurocognitive functioning and its footprints during the euthymic state may provide us with valuable biological markers for bipolar disorder.

In conclusion, our results show the importance of oscillatory dynamics in complicated cognitive pathologies such as bipolar disorder. It has been possible to detect the increased delta response to visual target stimuli in comparison to healthy controls and valproate’s corrective effect by this non-invasive technique even in such a small group of patients. Our results point to a definite need for further exploratory and comparative studies of a larger number of euthymic drug free patients by using different antiepileptic medications to validate and expand our findings and explore the underlying mechanisms.

References


