Research Report

Brain oscillatory responses in patients with bipolar disorder manic episode before and after valproate treatment

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Background: GABA/Glutamatergic dysfunction and neural circuits which regulate cognitive processing are involved in the underlying pathology of bipolar disorder. Event related oscillatory neuroelectrical activity reflects integrative brain functioning, different frequency bands representing different cognitive functions. Methods: Event Related Potentials to visual odd-ball paradigm in ten manic/hypomanic medication free, DSM-IV bipolar patients were measured before and after six weeks of valproate monotherapy in comparison to ten sex and age matched healthy controls. Different frequency band responses were obtained by digital filtration of ERPs. Young mania rating scale (YMRS) was used to assess clinical response. Repeated measures ANOVA, Wilcoxon and Mann Whitney U tests were used for statistical analysis. Results: Patients showed significantly higher baseline occipital beta (18–30 Hz) response than healthy controls. They were devoid of the occipito-frontal alpha (8–13 Hz) dominance presented by the control group. Occipital beta response reduced significantly and became similar to controls after treatment. Post-treatment alpha responses were significantly lower than baseline in anterior temporal (p: 0.038) and occipital (p: 0.027) locations. Healthy controls displayed a significantly increased frontal alpha response at the second assessment but the patients did not. Mean YMRS score reduced significantly compared to baseline at the end of six weeks (p: 0.004). Conclusions: Alpha response is the universal operator in the brain. Increased occipital beta response in mania may be compensatory to the dysfunctional alpha operation. Its reduction after valproate may be through modulation of glutamatergic and GABAergic mechanisms and indicate medication’s corrective effect on the underlying pathogenesis.

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1. Introduction

Bipolar disorder is a chronic illness with a relapsing and remitting course. Mania is the core feature of the illness which gives rise to the definite diagnosis (DSM-IV, 1994). Manic state is characterized by increased energy and motor activity, decreased need for sleep, distractibility with a strong involvement of pleasure seeking and impulsive behavior. Manic
patients also display signs of dysfunction in attentional measures, complex processing and memory as well as emotional processing. Having an acute episode of mania or depression is suggested to give way to damage to learning and memory systems (Bearden et al., 2001). Pathology has been shown to involve decreases in cortical thickness in multiple cortical areas which are associated with sensory function as well as emotional and cognitive processing such as left cingulat cortex, left middle frontal cortex, left middle occipital cortex, right fusiform cortex and bilateral postcentral cortices (Lyoo et al., 2006).

Among a wide range of neurotransmitters that are involved in bipolar disorder, Gamma amino butyric acid (GABA) plays an important role. It spreads in neural networks that are involved in cognitive and emotional processing and modulates noradrenergic, dopaminergic and serotonergic local neural circuitry (Brambilla et al., 2003). GABAergic interneurons which are the core component of cortico-limbic circuitry were found to be defective in cerebral cortex of bipolar patients (Benes and Berretta, 2001). Findings pointing to disrupted cortical GABA related inhibitory neurotransmission (Levinson et al., 2007) Several studies revealed low plasma (Berettini et al., 1983; Kiiya et al., 1982) or cortical (Bhagwagar et al., 2007) GABA activity or altered genetic expression of GABA (Guidotti et al., 2000; Heckers et al., 2002) in bipolar disorder. Low GABA activity was thought to be a genetically determined trait creating a vulnerability to development of either mania or depression with contribution of environmental factors and suggested to return to baseline levels with remission (Petty, 1995). GABAergic activity is reciprocally regulated by dopamine, hyperactivity of which also plays a role in mania (Yatham et al., 2002). Alterations in modulation of the dopamine system may trigger the appearance of a defective GABA system (Benes and Berretta, 2001).

Valproate is an effective antimanic agent (Bowden, 2003). Evidence supports a GABA potentiating mechanism of action of valproate (O’Donnell et al., 2003). Valproate was shown to augment the ability of atypical antipsychotic medications to increase dopamine (DA) and acetylcholine (ACh) efflux in the rat hippocampus and medial prefrontal cortex (Huang et al., 2006). It was also shown to lead to a significant reduction in presynaptic dopamine function in manic patients. This was thought to be related to improvement in manic symptoms (Yatham et al., 2002). It regulates cell survival pathways such as cAMP-responsive element binding protein (CREB), Brain Derived Neurotrophic Factor (BDNF), bcl-2 and mitogen-activated protein kinases (MAP) which may underlie its neuro-protective and neurotrophic effects (Xiaohua et al., 2002; Löscher, 2002).

Oscillations constitute the most obvious observable type of electrical activity in the brain in response to well-defined sensory or cognitive events. Event related oscillations are either “evoked” (phase locked) or “induced” (temporally related) to the event and can be easily recorded from the scalp. After off-line eradication of any interference –vascular or muscular in origin– remaining EEG sweeps can be digitally filtered and oscillations are classified according to the natural frequencies of the brain such as delta (0.5–3.5Hz), theta (3.5–7 Hz), alpha (8–13 Hz), beta (18–30 Hz) and gamma (30–70 Hz) ( Başar et al., 1999). In a more simple way, the oscillatory activity occurring in different frequencies can be defined as the building blocks of the P300 response. They provide new evidence to be real signals of the CNS. Oscillations are selectively distributed, controlling the integrative brain functions at all sensory and cognitive levels ( Başar et al., 2001; Mountcastle, 1992). This suggests a paradigm change in neuroscience. It is now possible to achieve measurements on scalp electrodes of human subjects under various states of behavior and learning. Early experimental studies on large scale brain activity showed superposition of multiple oscillations in delta, theta, alpha, beta, gamma in various parts of the brain. This raised the necessity to use brain’s multiple oscillatory activities for the analysis of all brain functions in both animals and humans ( Başar, 1980; Başar et al., 1975). Generation of P300 to visual target stimuli involves frontal brain structures such as orbito-frontal cortex, anterior cingulate cortex as well as deeper brain structures such as hippocampus/parahippocampal areas, the insula, the temporal lobe and thalamus (Herrmann and Knight, 2001), the anatomic structures that constitute the mostly affected neural circuitry in bipolar disorder as shown by imaging studies (Soares and Mann 1997; Strakowski et al., 2005). As to the neurotransmitter involvement, GABAergic interneurons and pyramidal cells were found to build and maintain complex interconnections which lead to large scale network oscillations, such as theta, gamma (40–100 Hz), and ultrafast (200 Hz) frequency bands (Benes and Berretta, 2001).

There has been limited number of earlier electrophysiology studies in symptomatic bipolar patients. A prolonged P300 latency and reduced P300 amplitude was found to be equivocal and most probably related to psychosis (Salisbury et al., 1999). It was once suggested to have an association with an underlying frontal lobe pathology as previously shown by different neurocognitive and imaging studies (Salisbury et al., 1999). A more recent study showed abnormal high frequency synchronization in response to auditory stimulus (O’Donnell et al., 2004) in manic bipolar patients.

The aim of this study was to assess oscillatory brain activity in manic phase of bipolar disorder before and after treatment with valproate as monotherapy in comparison to healthy controls. We hypothesized that the patients would show hyper-responsive low frequency oscillatory activity before treatment and valproate monotherapy would lead to reduction in the oscillatory responses. To our knowledge, this is the first study assessing oscillatory brain activity in a prospective and controlled design.

2. Results

2.1. Clinical data

Clinical characteristics of the patient group are summarized in Table 1. These were moderate to severely ill chronic patients who had had relatively high number of previous episodes (4.67 ± 2.69; range 1–10). Mean duration of present episode was 64.67 ± 53.96 days (range 15–190 days) and mean YMRS score at the time of enrollment was 24.40 ± 8.90 (range: 15–43). Two
patients were drug naïve. Mean drug free time for the other eight patients was 159.63±270.19 weeks (range: 2.50–804.00 weeks). Nine out of ten patients completed the six week valproate monotherapy. One patient withdrew consent at week three. Mean daily valproate dose over the six week study period reached 84.08±15.08 mg and the mean valproate serum level for the same period was 1029.13±131.82 mg (range: 875.00–1375.00 mg). Repeated measures ANOVA revealed a significant reduction in YMRS scores (n=10, LOCF; F: 7.78; p: 0.003) over the six week period, beginning from week one (mean YMRS: 20.10±10.54) in comparison to baseline (24.40±8.90) (z: −2.81; p: 0.005). This held until the end of study period and the difference between the mean baseline and end of study YMRS scores (n=10, LOCF; 11.10±13.18) revealed statistical significance (z: −2.60; p: 0.009) (Fig. 1). Eight patients out of nine completers met the remission criteria (YMRS ≤8) at the end of the study.

Behavioral data defines the reported number of mistaken target stimuli which is the difference between real number and the number counted by the subject. The target stimulus which is the difference between real number and the number counted by the subject. The number of mistaken targets decreased significantly after treatment (1.67±0.56) compared to baseline (p: 0.033). This was similar to the number of mistakes normal controls presented at second assessment (1.78±2.68). Symptom severity was not correlated with the number of mistakes in the patient group before medication. Similarly, number of mistaken targets did not show any correlation with alpha or beta responses either before, or after valproate treatment.

### Table 1 – Summary of the clinical features of the patient group. VPA: Valproate

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Episode</th>
<th>N</th>
<th>Sex</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar I</td>
<td>7</td>
<td>Mania</td>
<td>6</td>
<td>Female</td>
<td>4</td>
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<tr>
<td>Bipolar II</td>
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<td>Hypomania</td>
<td>4</td>
<td>Male</td>
<td>6</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td></td>
<td>Maximum</td>
<td></td>
<td>Mean±SD</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>24</td>
<td>60</td>
<td></td>
<td>37.80±14.05</td>
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</tr>
<tr>
<td>Age of onset of illness</td>
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<td>60.00</td>
<td></td>
<td>30.30±13.54</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>0.17</td>
<td>26.00</td>
<td></td>
<td>7.49±7.56</td>
<td></td>
</tr>
<tr>
<td>Total number of prior episodes</td>
<td>1.00</td>
<td>10.00</td>
<td></td>
<td>4.67±2.69</td>
<td></td>
</tr>
<tr>
<td>Duration of last episode (days)</td>
<td>15.00</td>
<td>190.00</td>
<td></td>
<td>64.67±53.96</td>
<td></td>
</tr>
<tr>
<td>Mean VPA dose throughout study (mg/day)</td>
<td>875.00</td>
<td>1375.00</td>
<td></td>
<td>1029.13±131.82</td>
<td></td>
</tr>
<tr>
<td>Mean VPA serum level throughout study (µg/ml)</td>
<td>59.40</td>
<td>107.15</td>
<td></td>
<td>84.08±15.08</td>
<td></td>
</tr>
</tbody>
</table>

2.2. Oscillatory responses in general

Maximum peak-to-peak amplitude beta responses in 0–300ms and alpha responses in 0–500ms 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 frequency (alpha, beta), location [frontal (F3–F4), central (C3–C4), temporal (T4–T5), parietal (P3–P4), occipital (O1–O2)] and hemisphere [left (F3, C3, T3, T5, P3, O1), right (F4, C4, T4, T6, P4, O2)]. Greenhouse-Geisser corrected p-values are reported. For post-hoc analysis, Wilcoxon and Mann Whitney U tests were used for within and between group comparisons of alpha and beta responses respectively.

In the non-medicated condition, repeated measures ANOVA revealed significant location (F: 5.52; p: 0.003) and frequency was also significant (Frequency x Location: F: 5.69; p: 0.006). Group (patients vs controls) effect over location and frequency was also significant (Frequency x Location x Group: F: 3.67; p: 0.031). Latter significance disappeared after six weeks of treatment although frequency (p: 0.001), location (p: 0.049) and frequency by group effect (p: 0.021) sustained.

2.3. Alpha (8–13 Hz) results

Post-hoc pair-wise comparisons (Wilcoxon; p≤0.008 after correction for multiple comparisons) revealed that in the control group alpha responses were significantly larger in the posterior temporal, parietal and occipital locations over frontal and anterior temporal locations (Respective p values for F3–4 vs T5–6, P3–4 and O1,2: 0.000, 0.000, 0.000; respective p values for T3–4 vs P3–4 and O1,2: 0.005, 0.001). In the patient

![Fig. 1](image-url) – Young Mania Rating Scale (YMRS) scores over the six week treatment period. The scores reduced significantly beginning from week one until the end of study period (repeated measures ANOVA p: 0.003). †: p: 0.005; ‡: p: 0.009.
group, alpha responses did not show any significant fronto-occipital difference due to lower occipital alpha response (4.28±1.64 μV) compared to controls (5.32±2.47 μV) despite similar frontal alpha activity (F 3–4 patients vs controls: 2.93±1.38 vs 2.36±0.84 μV) (Fig. 2). However, the difference in the occipital responses did not reach statistical significance. Similar to the controls, patients had a significantly smaller anterior temporal compared to posterior temporal, parietal and occipital alpha responses (p values for T3–4 vs T5–6, P3–4 and O1–2: 0.004, and 0.000 and 0.007).

After six weeks of valporate monotherapy, patients showed either unchanged or reduced alpha responses in general whereas controls tended to increase alpha responses in all but the occipital locations at their second assessment. This increase reached statistical significance in the frontal (F3–4 first vs second assessment: 2.36±0.84 vs 4.01±1.48 μV; p: 0.000) and central regions (C3–4 first vs second assessment: 3.39±1.21 vs 4.23±1.68 μV; p: 0.048) whereas frontal and central alpha responses did not differ before and after medication in the patient group. However, after medication, patients showed a significantly lower occipital alpha response (3.06±1.42 μV) compared to their baseline value (4.28±1.64 μV) (p: 0.027) (Fig. 3). This was significantly lower also than the mean occipital alpha response of the controls at second assessment (4.15±1.36 μV) (p: 0.022) who did not differ between two recordings. In the patient group anterior temporal alpha response (1.96±0.72 μV) also reduced significantly after treatment compared to its own baseline value (2.62±1.08 μV) (p: 0.038) and that of the control group at second

Fig. 2 – Alpha (8–13 Hz) responses to visual target stimuli at different locations in the manic patients before treatment (red line), after treatment (green line), healthy controls at first recording (dark blue line) and second recording (bright blue line). Locations depicted here represent both right and left hemispheres. Baseline posterior alpha responses were lower in the patient group than the controls whereas frontal alpha activity in both groups were similar. After treatment, occipital alpha response was further decreased in the patients. It was significantly lower in the temporal electrodes as well. Healthy controls were able to increase frontal alpha response at second recording whereas the patients generated an unchanged alpha response after treatment.

Fig. 3 – Right occipital (O2) alpha (8–13 Hz) response in the manic patients before (A) and after (B) treatment with valproate. Graph A represents the grand average of the averages from 10, graph B from 9 patients. Post-treatment occipital alpha response is significantly lower than the unmedicated condition.
assessment (3.13±1.27 μV) (p: 0.003). Patients also showed a significantly lower posterior temporal alpha response (T5–6: 2.98±1.68 μV) compared to controls (4.90±3.90 μV) (p: 0.047). The difference was caused by a non-significant increase in the control, and decrease in the patient group’s T5–6 alpha responses at second assessment (Fig. 2). Change in YMRS scores did not show a correlation with change in occipital alpha responses.

2.4. Beta (18–30 Hz) responses

At baseline patients showed a bimodal large beta responses at frontal (F3–4: 3.47±1.67 μV) and occipital (O1–2: 3.82±2.47 μV) locations whereas controls had a homogeneously distributed beta responses over all locations (Fig. 3). The mean baseline occipital beta response of the patients (3.82±2.47 μV) was significantly higher compared to healthy controls (2.21±1.31 μV) (p: 0.014) (Fig. 4). It reduced significantly after medication to a mean of 2.67±1.13 μV (p: 0.009) and became similar to the second assessment occipital beta response of the controls (2.59±0.62 μV) who did not differ between two recordings (Figs. 4 and 5). Anterior temporal beta responses (T3–4) also reduced significantly from the pretreatment mean value of 2.83±1.56 μV to 1.90±0.57 μV after medication in the patient group (p: 0.038). A minimal non-significant reduction in the controls’ mean frontal beta response at second assessment elicited a significant difference between controls and medicated patients (F3–4 beta response patients vs controls: 3.31±1.05 vs 2.44±0.90 μV; p: 0.010). Change in YMRS scores did not show and correlation with change in occipital beta responses.

Baseline occipital alpha to beta ratio was lower in the patient group (α/βpatient: 1.12) compared to that of healthy controls (α/βcontrol: 2.40) largely due to significantly higher occipital beta response of the patients compared to controls. The ratio stayed the same in the patient group after medication (α/βpatient: 1.14) owing to significant decreases both in alpha and beta responses whereas it reduced in the controls (α/βcontrol: 1.60) due to non-significant decrease in alpha but increase in beta activity.

In the patient group there was no significant correlation between changes in occipital and anterior temporal alpha and beta responses and change in YMRS scores after treatment.

3. Discussion

3.1. Baseline oscillatory responses

The results of the present study indicate that drug free patients with bipolar disorder in the manic or hypomanic phase of the illness show altered alpha (8–13 Hz) and beta (18–30 Hz) oscillatory responses to visual target stimuli of the oddball paradigm compared to healthy controls. Patients had a significantly high occipital beta response compared to
controls. They were devoid of the occipito-frontal alpha dominance presented by the control group.

This is the first study assessing event related low frequency oscillatory activity in drug free patients with bipolar disorder in manic phase of the illness. Previous studies on event related responses used auditory stimulation (Olincy and Martin, 2005; Souza et al., 1995, Salisbury et al., 1998, Salisbury et al., 1999) and measured either P50 suppression (Olincy and Martin, 2005) or P300 amplitude or latency (Souza et al., 1995, Salisbury et al., 1998, 1999). Experiments on humans testing auditory and visually evoked oscillatory responses showed that evoked potential responses are topography and stimulus modality dependant and that neural structures with different resonance properties may be involved in processing of the auditory and visual stimuli (Bazar, E., Schürman, 1998). Occipito-frontal dominance in the alpha responses in our healthy controls is in line with these findings. However, manic patients seem to have lost this expected response pattern specifically in the occipital region. This is a very important finding which addresses a possible disruption in brain’s integrative working mechanisms in manic state of bipolar disorder. Based on experimental study findings, Bazar (1998) hypothesized that the 10 Hz processes may facilitate overall association mechanisms in the brain and that alpha can be interpreted as a universal code or universal operator in the brain. It is a strong possibility that the diminished occipital alpha response elicited by the cognitive input we applied is an indicator of an inefficient communication between different structures of the brain in mania.

Occipital origin of the altered alpha response may be due to low occipital GABA activity as shown previously (Bhagwagar et al., 2007). There is also evidence for cortical thinning in parietal and occipital cortices in patients with bipolar disorder. The finding was associated with impairments in visual spatial neuropsychologic functions (Lyoo et al., 2006). However, a type II error due to a small sample size (n = 10) on each arm may be the reason for statistical non-significance between occipital alpha responses of the patients and the controls. The difference may be shown more evidently by enrolling higher number of patients and controls in a future study.

Healthy controls showed a significant increase in the frontal and central alpha responses at the second testing which was six weeks apart from the first one. This is large is due to learning since alpha activity strongly correlates with working memory and probably with long-term memory engrams (Bazar et al., 2001). However, the patients were not able show a similar increase their alpha responses. This will be further discussed in relation to treatment effect in following parts of this section.

3.2. Alpha responses

Loss of occipito-frontal alpha dominance in the patient group is most probably due to non-significant but still lower occipital alpha response compared to healthy controls.

Auditory and visual stimulations elicit alpha responses and cognitive targets significantly influence the alpha responses in P300 (Bazar et al., 2001). Previous experimental studies showed that resonant alpha generators are distributed selectively throughout the brain and elicited the possibility that the number of alpha generators is greater or they are densely distributed in occipital cortex in comparison to other structures (Bazar and Quiroga, 1998). Occipito-frontal dominance in the alpha responses in our healthy controls is in line with these findings. However, manic patients seem to have lost this expected response pattern specifically in the occipital region. This is a very important finding which addresses a possible disruption in brain’s integrative working mechanisms in manic state of bipolar disorder. Based on experimental study findings, Bazar (1998) hypothesized that the 10 Hz processes may facilitate overall association mechanisms in the brain and that alpha can be interpreted as a universal code or universal operator in the brain. It is a strong possibility that the diminished occipital alpha response elicited by the cognitive input we applied is an indicator of an inefficient communication between different structures of the brain in mania.

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3.3. Beta responses

Significantly increased occipital beta activity in the patient group may be compensatory to the presumed disrupted connectivity in brain’s integrative functioning. Low amplitude fast oscillations such as beta and gamma (15–80 Hz) were shown to be specifically related to brain’s effort to screen and establish synchronous communication between brain regions (Munk et al., 1996). Switching from gamma to beta activity during different modes of response formation in the brain potentates excitatory synaptic activity which is further mediated by the activation of recurrent excitatory connections between projection neurons. Thus, generation of beta oscillations by the gamma induced synchrony represents established synchronous communication within the brain (Whittington et al., 2000). A reciprocal and compensatory relationship between alpha and beta responses was explicitly presented in the control group. They revealed an inverse response pattern at the second assessment. For instance, in the frontal region beta response decreased as the alpha increased whereas in the occipital region beta increased as alpha decreased. However, this was not the case in the patients. The finding will be discussed later in relation to treatment effect.

3.4. Post-treatment findings

After six weeks of valproate treatment, occipital beta response came down to normal levels whereas occipital alpha response further reduced in the patient group and became significantly lower than before and that of normal controls. Both alpha and beta responses in the anterior temporal and only alpha response in the posterior temporal region reduced significantly after treatment with no change in frontal alpha responses. This calming effect may be resulting from reduction in the severity of mania as eight out of nine completers showed more than 50% reduction in YMRS scores, or even remission in some patients. However it is a weak possibility since there was no correlation between reduction in YMRS scores and changes in alpha and beta responses. Thus, it is plausible to consider medication effect on the findings. On the other hand, it is not really possible to rule out the possibility that patients who improve spontaneously, without medication might also have seen EEG changes. However, it is not possible to run such a study for ethical reasons.

Fig. 6 – (A) Delta wave (0.5–3.5 Hz) amplitude of patients vs sex and age matched healthy controls before and after valproate treatment in left frontal 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 higher than that of the normal controls. It reduces significantly (p: 0.028) compared to baseline after six weeks of valproate treatment; (Published in: Biol Psychiatry 61: 226S, 2007). (B) Delta response in left anterior temporal electrode. The delta amplitude declines significantly after valproate treatment in the patient group compared to baseline (p: 0.011) and compared to controls (p: 0.023).
AVERAGE AND GRAND AVERAGE OF DELTA RESPONSES TO VISUAL STIMULI AT LEFT FRONTAL (F3) AREA

Patient group

(N = 10)
before valproate

(N = 9)
after valproate

Healthy controls

(N = 10)
first recording

(N = 9)
second recording

AVERAGE AND GRAND AVERAGE OF DELTA RESPONSES TO VISUAL STIMULI AT LEFT ANTERIOR TEMPORAL (T3) AREA

Patient group

(N = 10)
before valproate

(N = 9)
after valproate

Healthy controls

(N = 10)
first recording

(N = 9)
second recording
also found to be weak (Spencer et al., 2003). It is interesting that one recent study showed reduced visually evoked gamma phase locking in the occipital region in chronic, medicated patients with schizophrenia (Spencer et al., 2007). However, this still does not allow to make any inferences with regard to similarities or differences between these two mental disorders.

There was no correlation between behavioral data and alpha-beta responses either before, or after treatment despite a significant post-treatment improvement in the number of correct answers in the patient group. This and the similar abovementioned discordance between the change in YMRS scores and oscillatory responses may represent a dissociation between clinical and cognitive improvement and a true healing at the cellular level. Longer periods of medication use may be necessary for an integrated clinical and cellular recovery.

The major limitation of the present study is the small sample size. Although findings are quite robust, a replication of this study with larger number of patients and with different medications seems to be necessary. With regard to data analysis, studying coherence would also allow us explore the level of disturbance in the integrative brain functioning especially in mania.

3.5. Conclusion

Findings of the present study on drug free patients point to a preliminary finding of occipitally located pathology most probably due to deficient GABA activity and cortical disruption in manic phase of bipolar disorder as shown by disrupted occipito-frontal alpha activity and significantly increased occipital beta activity which may be representing a widely disturbed connectivity function of the brain. Valproate proves to be clinically effective on the manic symptoms and be able to reduce the occipital beta activity to normal levels while causing further decrease in alpha responses.

4. Experimental procedures

4.1. Subjects

Ten (6 male, 4 female) bipolar I (n = 7) and II (n = 3) patients either in manic (n = 6) or hypomanic (n = 4) state according to DSM-IV (Diagnostic and Statistical Manual of Psychiatric Disorders-fourth edition, 1994) and 10 sex, age and education-wise matched healthy controls were enrolled in the study. The diagnosis was confirmed by SCID-I (Structured Interview for DSM-IV) (First et al., 1996) interview. Patients aged between 24–60 years (mean age ± SD: 37.80 ± 14.05). All subjects provided written informed consent. The study was approved by the local Ethics Committee for Drug Trials of Dokuz Eylül University Medical School. Patients needed to be psychototropic free at least for 2 weeks except for benzodiazepines prior to study enrollment; score 15 or more on the validated and reliable Turkish version of Young Mania Rating Scale (YMRS) (Karadağ et al., 2002; Young et al., 1978) and score 7 or less on the validated and reliable Turkish version of 21 item Hamilton Depression Rating Scale (HAM-D 21) (Aydemir and Artuner, 2003; Hamilton, 1960); be medically healthy as shown with physical examination, routine biochemical, hematological and endocrinologic laboratory tests and electrocardiogram at screening. Females who were already pregnant or planning to become pregnant or lactating, patients with known hypersensitivity to valproate, active drug or alcohol use during last 2 weeks, alcohol or drug dependency during one month prior to study and those with mixed episode, any co-morbid axis I disorder, any unstable renal, hepatic, thyroid, cardiac or hematomal condition, neurodegenerative disease, epilepsy and history of brain surgery were excluded. Volunteers who proved to have no present or past psychiatric condition on SCID-I interview and to be medically healthy on physical examination were enrolled as the control group.

4.2. Study procedures

All subjects underwent electrophysiological assessment twice. After first (baseline) assessment on day zero, the patients were started on valproate monotherapy. Six weeks later the same electrophysiological testing was done in both patient and control groups. Patients were seen at weeks 0, 4 and 6 for clinical assessments. Serum valproate levels and liver function tests were monitored at weeks 1, 3 and 6. The main clinical outcome measures were the YMRS, and HAMD-21 scores. Response for manic/hypomaniac patients was defined as at least 50% reduction in YMRS score and remission as a score no greater than 8 on YMRS during trial.

Switching into depression according to DSM-IV with clinical interview and scoring 15 or higher on HAM-D, increase in baseline YMRS score by 25% or more or valproate intolerance were reasons to terminate the study.

4.3. 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. Subjects were asked to focus on and report the number of target stimuli at the end of the recording session. Later on, number of errors either above or below the given number of target stimuli was calculated for each subject.

EEG was recorded with Nihon Kohden 10 channel Analogue EEG and Nihon Kohden 32 channel digital EEG devices which were simultaneously and directly connected to Brain Data EEG-ERP system. Ag/Ag Cl electrodes were connected according to international Jasper 10/20 system through an 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 was digitized on-line with a sampling rate of 512 Hz and a total recording time of 2000 ms, 1000 ms of which served as the pre-stimulus baseline. Electrode impedance was kept below 5 kΩ, 50 Hz a notch filter was applied.

The epochs containing artifacts such as eye-movement or blink artifacts were rejected by an off-line technique before the averaging procedure. Subject averages and grand averages
for the target stimuli were calculated for each electrode site. The data were digitally filtered according to determined frequency bands of interest.

### 4.4 Amplitude frequency characteristics and digital filtering

Filtering produces visual displays of time courses of oscillatory components within the frequency limits of the utilized filters. The digital filters are advantageous because they do not produce phase shift characteristics as the electronic filters do.

First, 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 \( X_n = X(nD_t) \), \( T = ((N – 1) D_t) \). Then the Fourier Transform of \( Y_k \) of \( X_n \) is:

\[
Y_k = Y(\omega_k) = \sum_{n=0}^{N-1} X_n \exp(-i2\pi n k / N), \quad \omega_k = 2\pi k T^{-1}
\]

where \( Y_k = a_k + ib_k \) are the complex Fourier coefficients whose geometric mean is the amplitude spectrum. The frequencies of interest were determined and the frequency ranges for the digital filtering process were defined by studying the amplitude frequency characteristics (AFC). The filter limits were chosen according to cut off frequency of several frequency windows. Further, AFCs of averaged ERPs were used for the determination of the frequencies that were selectively distributed along the scalp during visual target stimuli. Since alpha and beta responses presented the most remarkable changes in the AFCs of this dataset, they were chosen as the theme of this paper. For the frequency ranges, grand averages were computed based on single subjects' averages of the AFCs for each location. Peak to peak maximum amplitude was defined as the oscillatory response for the chosen frequency ranges and subsequently measured for each subject. Peak to peak maximum amplitude was computed based on single subjects' averages of the AFCs averaged of the AFCs. For the target stimuli, the peak to peak maximum amplitude was defined as the oscillatory response for the chosen frequency range and subsequently measured for each subject.

### 4.5 Statistical analysis

SPSS was used for statistical analysis. Repeated measures ANOVA was used to determine the statistical significance of differential alpha and beta responses over different locations and between patients and controls. The model that was used is given before presentation of the oscillatory responses in the results section of this paper. The change in YMRS scores of the patients over the six week period was calculated using repeated measures ANOVA, including weeks as the within group factor. Difference between each week's YMRS scores was assessed using Wilcoxon test. Last observation carried forward (LOCF) procedure was used for the missing data. Spearman correlation test was used to determine the relationship between the change in electrophysiological parameters in the patients and change in YMRS scores after treatment as well as baseline and post-treatment number of mistakes made by the patients.

The difference in the number of mistakes made in determining the target stimuli (behavioral data) by the patient and control groups at first and second assessments were compared by using one-way-ANOVA. Post-hoc, LSD analysis results are reported.

### References


