Disturbance in long distance gamma coherence in bipolar disorder

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1. Introduction

Mania is the core feature of bipolar disorder. Besides symptoms related to mood, behavior, energy and sleep–wake cycle, mania involves disordered thought, disturbance in attentional measures, complex processing, memory and emotional processing (Quraishi and Frangou, 2002).

We have previously reported abnormally increased left frontal delta in euthymic states (Özerdem et al., 2008b) and increased occipital beta activity in manic states (Özerdem et al., 2008a) in response to visual oddball paradigm. The latter finding (Özerdem et al., 2008a) was suggested to be compensatory to a presumed disrupted connectivity in the brain's integrative functioning. Generation of beta oscillations requires involvement of gamma-induced synchrony (Whittington et al., 2000). Patients in the manic or mixed state were shown to have deficits in auditory EEG synchronization in beta (20 Hz) and gamma (30, 40, and 50 Hz) range activity during click entrainment paradigm (O'Donnell et al., 2004). The degree of resting state long-range synchrony was found to be significantly reduced in manic patients compared to healthy controls in all frequency bands (Bhattacharya, 2001), whereas euthymic medicated patients displayed increased delta and decreased beta synchronization in the frontal region (Chen et al., 2008).

For almost a decade, the concept and methods of the emerging field of “oscillatory brain dynamics” have increased rapidly (Başar Ergülo et al., 2008; Güntekin et al., 2008; Yener et al., 2008), as summarized in a recent review of brain oscillations in pathology conditions (Başar and Güntekin, 2008). As one of the assessment models of oscillatory activity EEG coherence describes the coupling of or relationship between signals in a given frequency band. Varying degrees of spatial coherence occur over long distances as parallel processing (Başar, 1980; Miltner et al., 1999; Schürmann and Eimer, 2000). EEG coherence is considered an important large-scale measure of functional relationships or synchronized functioning between pairs of cortical regions, and therefore, the

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Abbreviations: ANOVA, Analysis of variance; Cx(f), The magnitude-squared coherence, as a function of the frequency; DSM-IV, Diagnostic and Statistical Manual of Psychiatric Disorders-fourth edition; EOG, Electro-occulography; EEG, Electro-encephalography; f, Frequency; GABA, Gamma amino butyric acid; HAM-D, 21, 21-item Hamilton Depression Rating Scale; LOCT, Last observation carried forward; P300, Power spectral density; SCID-I, Structured Interview for DSM-IV-SD, Standard deviation; SPSS, The Statistical Package for Social Studies; YMRS, Young Mania Rating Scale.

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brain's functional connectivity (Nunez et al., 1997; Lopes da Silva et al., 1980; Petsche and Etlinger, 1998; Rappelsberger et al., 1982). At this point, it is vital to emphasize that there are important functional differences between “EEG coherence”, “Evoked Coherence” and “Cognitive Response Coherence”. In the EEG analysis, only sporadically occurring coherences from hidden sources can be measured. Sensory Evoked Coherences reflect the property of sensory networks activated by a sensory stimulation. Event-Related (or cognitive) Coherences manifest coherent activity of sensory and cognitive networks triggered by a cognitive task. Accordingly, the cognitive response coherences comprise activation of a greater number of neural networks that are most possibly not activated, or less activated, in the EEG and during sensory evoked responses. Within the context of cognitive processing, event-related coherence merits special attention.

Human studies reported stimulus specific gamma or gamma/beta synchronization over several centimeters during attentional and memory tasks (Tallon-Baudry et al., 2001). Gamma oscillations originate within networks of inhibitory GABAergic interneurons (Gray and McCormick, 1996) and cause a membrane-potential oscillation in long-axoned projection neurons such as pyramidal cells in the neocortex, hippocampus and thalamocortical neurons to provide communication between spatially separate sites and control brain function. According to Whittington et al. (2000) GABAergic modulation is required for synchronization of glutamatergic firing. Such network inhibitory postsynaptic potential oscillations as 40 Hz oscillations were proposed to be driven by metabotropic glutamate receptor activation (Whittington et al., 1995). Coupled together, the findings point to the role of interplay between GABA/glutamate system and the gamma oscillations. The relationship between cognitive pathology, different neurotransmitter systems and brain oscillations is well defined in a multidimensional model of electrical signals (Başar and Güntekin, 2008). Therefore, any such disruption in normal neuronal synchronization as the type caused by dysfunctional GABA/glutamate system may contribute to deficits in cognitive and affective integration. Bipolar disorder is known to have low GABA activity (Pett, 1995; Bhagwagar et al., 2007), abnormalities affecting GABA related inhibitory neurotransmission (Levinson et al., 2007; Benes and Berretta, 2001), and also cognitive dysfunction in several domains throughout ill and remitted states (Martínez-Arán et al., 2004).

The aim of this study was to assess event-related gamma response coherence in drug-free manic patients before and after treatment with valproate, a mood-stabilizing agent with well-known antimanic activity (Petty, 1995; Bhagwagar et al., 2007), abnormalities affecting GABA related inhibitory neurotransmission (Levinson et al., 2007; Benes and Berretta, 2001), and also cognitive dysfunction in several domains throughout ill and remitted states (Martínez-Arán et al., 2004). The participants sat in a dimly-lit, isolated room during recordings. A classical visual oddball paradigm was applied by using a simple 35 cd/m² 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 × 17 cm monitor screen. The duration of the stimulation was 1000 ms. The probability of the deviant stimuli was 0.20 and, in all paradigms, they were embedded randomly within a series of standard stimuli. These stimulation signals were applied randomly, with inter-stimulus intervals varying between 3 and 7 s. In order to assess focused attention and working memory, the task required mental counting of the target stimuli.

EEG was recorded with Nihon Kohden 32-channel digital EEG devices, which were simultaneously and directly connected to a Brain Data EEG–ERP system, which was used for signal analysis and evaluation of oscillatory dynamics. Electrode positions were Fp1, Fp2, C3, C4, P3, P4, T3, T4, T5, T6, O1, and O2. Derivations were against A1 and A2 earlobe reference. Electro-occulography (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. The post-stimulus 1000 ms was evaluated for coherence analysis. Electro-impedance was kept below 5 kΩ; a 50 Hz notch filter was applied. All epochs contaminated with ocular, muscle or other non-EEG activity were excluded by manual off-line.

Traditional EEG spectral analysis was performed using magnitude-squared coherence. The magnitude-squared coherence $C_{xy}(f)$, as a function of the frequency f, was defined for every pair of channels as the square of the modulus of the cross power spectral density (PSD) normalized to the product of the mean auto PSDs. The coherence between two channel wave-forms x and y was calculated as:

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}$$

where $P_{xy}(f)$ is the cross PSD estimate of x and y, $P_{xx}(f)$ and $P_{yy}(f)$ are the PSD estimates of x and y, respectively. In the calculation, each signal is divided into sections of 650 ms length with a 50% overlap; each section is windowed with a Haning window. The Matlab program was used for coherence analysis by using 10–14 artifact free epochs for each subject. The sweep numbers were equalized randomly between the target and non-target stimulation conditions. Coherence was calculated for the target and non-target stimuli for long-range intra-hemispheric and inter-hemispheric pairs for gamma
frequency band (28–48 Hz). The long-range intra-hemispheric pairs were F3–P3, F7–T5, F3–O1, C3–O1, Fz–Pz, Fz–T6, Fz–O2 and Cz–O2; the inter-hemispheric pairs were Fz–F4, Cz–C4, T3–T4, T5–T6, P3–P4, and O1–O2.

Distribution of coherence values was normalized using Fisher's Z transformation.

2.2. Statistical analysis

The Statistical Package for Social Studies (SPSS) was used for statistical analysis. The differences within the intra-hemispheric locations (Fz–Pz, F7–T5, F3–O1, and C3–O1 vs. Fz–Pz, F7–T5, F3–O2, and C3–O2) and inter-hemispheric locations (Fz–F4, Cz–C4, T3–T4, T5–T6, P3–P4, and O1–O2) for the gamma frequency band coherence values were assessed by means of a repeated measure analysis of variance (ANOVA). For the pre-treatment condition, to assess intra-hemispheric coherence differences, electrode locations at four levels (fronto-parietal, fronto-temporal, fronto-occipital, and centro-occipital), lateralization at two levels (right and left hemispheres) and signal specification at two levels (target and non-target) were taken as the within-subject factors, whereas, patient and control groups were included as the between-subjects factor. For inter-hemispheric comparisons, electrode locations at six levels (F3–F4, C3–C4, T3–T4, T5–T6, P3–P4, and O1–O2), signal specification at two levels (target and non-target) were taken as within, patient and controls as between-subject factors. To assess the difference in the intra and inter-hemispheric gamma response coherence between pre and post-treatment conditions, repeated measures ANOVA was performed only on the patient group. Time at two levels (pre-treatment and post-treatment), electrode locations at four levels (fronto-parietal, fronto-temporal, fronto-occipital, and centro-occipital), lateralization at two levels (right and left hemispheres) and signal specification at two levels (target and non-target) were taken as the within-subject factors. Greenhouse–Geisser corrected p-values are reported. For the independent group comparisons t test was used. Cohen's d was calculated to determine the effect size of the increase in coherence after treatment.

YMRS scores over six weeks were calculated using repeated measures ANOVA, including weeks as the within-group factor. The last observation carried forward (LOCF) procedure (Streiner, 2002) was used for missing data. The difference between the accurate number of given stimuli and the number reported by the participant at the end of the recording session was considered as the "error". In the patient group, the significance of the difference between pre and post-treatment errors was assessed with a Wilcoxon test. Baseline errors between controls and patients were compared using a Mann–Whitney U test. Spearman's correlation test was used to assess the correlation between coherence, YMRS scores and the errors in the patient group at both baseline and post-treatment recordings. All reported p-values are two-tailed.

3. Results

Clinical characteristics of the patients are presented in Table 1. Two patients were drug-naive, eight were drug-free. One patient withdrew consent at week three. Repeated measures ANOVA revealed a significant reduction in mean YMRS scores (n = 10, LOCF; F: 7.78; p: 0.003) over six weeks, beginning from week one (20.10 ± 10.54) in comparison to baseline values (24.40 ± 8.90) (z: −2.81; p: 0.005). The difference between the mean baseline and end of study YMRS (n = 10, LOCF; 11.10 ± 13.18) was statistically significant (z: −2.60; p: 0.009). At baseline, patients made significantly higher errors (9.22 ± 8.378) on the number of target stimuli compared to controls (0.70 ± 1.89) (p: 0.011). After treatment, errors in the patient group decreased to 1.50 ± 1.77. The difference between pre and post-treatment values was statistically significant (p: 0.042). There was no correlation between coherence scores and errors, or YMRS scores, in either pre or post-treatment conditions. Similarly, change in errors or YMRS scores was not correlated with change in coherence scores at any of the locations.

3.1. Intra-hemispheric pre-treatment assessment results

Patients showed lower pre-treatment right and left hemispheric gamma coherence values for both target and non-target signals in all locations compared to healthy controls. Repeated measures ANOVA revealed a significant difference between groups (F: 6.803, df: 1, p: 0.018). The effect for electrode location (F = 18.056, p = 0.001) was also significant. Post-hoc comparisons revealed that fronto-parietal and centro-occipital coherence values were higher than the fronto-temporal and fronto-occipital coherence values in all comparisons (p<0.001). None of the permutations of location, lateralization, signal, group interaction on the repeated measures ANOVA was significant. Despite this non-significance, based on varying statistical approaches and the merit in describing the significantly differing locations between groups as an additional information (Güntekin and Başar, 2007), we followed up on the significant group difference, and performed t test on the coherence values of all electrode pairs between the patient and control groups for both target and non-target conditions. Results revealed that for the target stimuli, the mean baseline right-fronto-temporal (F4–T6) gamma coherence Z value of the patients (0.321 ± 0.058) was significantly (35.41%) lower compared to that of controls (0.497 ± 0.146) (p: 0.004) (Fig. 1). Also for the non-target stimuli, patients had significantly lower mean baseline gamma coherence Z values of the right fronto-temporal (F4–T6; 0.326 ± 0.061; 28.51% decrease), right fronto-occipital (F4–O2; 0.325 ± 0.082; 23.71%, decrease) and right centro-occipital (C6–O2; 0.486 ± 0.087; 25.69% decrease) locations compared to healthy controls (F4–T6; 0.456 ± 0.102; F4–O2; 0.426 ± 0.094; C6–O2; 0.654 ± 0.195) (respective p-values for F4–T6, F4–O2, and C6–O2 are, 0.004, 0.024 and 0.029).

3.2. Intra-hemispheric post-treatment assessment results

In the repeated measures ANOVA for the pre and post-treatment conditions, target and non-target coherence Z values of the patients showed no statistically significant time by electrode location or lateralization interaction.

3.3. Inter-hemispheric assessment results

Repeated measures ANOVA showed no significant difference between either groups or locations in both pre and post-treatment conditions in inter-hemispheric coherence values.

4. Discussion

The main finding of this study was diminished long distance gamma response coherence values to the target and non-target visual stimuli in drug-free manic patients, compared to healthy controls. The decrease in the gamma response coherence for the target stimuli reached statistical significance at the right fronto-temporal location,

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where it was 35.41% less than that of the controls. For the non-target stimuli the gamma coherence decrease was significant at the right fronto-temporal fronto-occipital and right centro-occipital locations by 28.51%, 23.71%, and 25.69% respectively. The coherence decrease in response to both target and non-target stimuli points to an inadequate connectivity between different parts of the brain under cognitive load. The higher decrease in the coherence in response to target stimuli may be due to the fact that target stimuli are “attend” signals by definition. Therefore they represent higher cognitive load compared to non-target stimuli. Accordingly, any deficiency in functional connectivity would be more intensely precipitated by the target stimuli in the oddball paradigm. It is also self revealing that non-target stimuli also require a type of attention but this is much less than target stimuli. The difference in the strength of connectivity reduction as shown in our findings is in accordance with the underlying psychophysiological mechanisms.

Synchronous neural gamma oscillations are critical for cortico-cortical communication and the large-scale integration of distributed sets of neurons for integrated cognitive functioning (Rodriguez et al., 1999). The baseline finding is in line with previous brain imaging studies supporting structural abnormalities in the prefrontal cortex, medial temporal lobe and subcortical structures in bipolar disorder, and a model of bipolar disorder where prefrontal modulation of subcortical and medial temporal structures within the anterior limbic network (e.g., amygdala, anterior striatum and thalamus) is diminished (Strakowski et al., 2005). In a study by our group assessing the structural changes in the corticolimbic circuitry in untreated bipolar patients, voxel based morphometric (VBM) measurements revealed greater white matter (WM) volume in the right superior frontal gyrus of the patient group (n = 24) compared to healthy volunteers (n = 19). The study included all of the patients of the present report (Gür Yağış et al., 2008). White matter comprises of fiber tracts interconnecting cortical and subcortical gray matter and connective wiring of the brain. Contradictory findings on the WM alterations have been reported in detail in a recent and extensive review by Mahon et al. (2010) where it was stated that alterations in WM tissue would likely have significant implications for the functioning of the brain as a whole, as it is the WM which serves as the circuitry.

Although it is too early to couple our electrophysiologic findings to the imaging findings, we find it inspirational to consider the two findings together in the light of brain’s functional connectivity.

The total absence of cross-talk within and between different cortical regions in the gamma range was suggested to correlate with brain states characterized by continuous cognitive disruptions, with important deficits in attention, memory and perceptive functions, and an inability to create a global awareness of the world or the self, as seen in both REM and slow wave sleep (Cantero et al., 2004). On the other hand, gamma oscillations were suggested to have a gating effect on the incoming information within the temporal domain, thus facilitating the synchronization of spatially separate brain regions and leading to long-term changes in the strength of synaptic connectivity between areas (Whittington et al., 2000). Taken together, disruption in the “long-range gamma coherence” in our untreated manic patients may represent the underlying mechanism of the well-documented neurocognitive dysfunction in bipolar illness (Martínez-Arán et al., 2004).

According to Whittington et al. (2000), for an agent to manipulate fast oscillations, a population of interconnected inhibitory cells and sufficient postsynaptic GABAergic response are necessary. It has also been proposed that generation and maintenance of gamma band oscillation depend on the presence of sufficient GABA (Traub et al., 2003). Disruption in the right fronto-temporal gamma coherence in mania may be indicative of insufficent GABA transmission; improvement with valproate, an agent with well-known GABAergic effects confirms this suggestion to be applicable in bipolar disorder.

The lack of correlation between the gamma coherence scores and the behavioral parameters used in this study does not necessarily represent an absence of a link between the two measurements. To date, there is no established behavioral parameter or task that directly reflects such finely tuned and instantaneous changes in the brain’s responsiveness as detected by oscillatory analysis.

The robustness of gamma coherence disruption, despite a small sample size, which is the major limitation of this study, is a fundamental finding. However, a larger sample size would be more beneficial to alleviate any potential type II error in detecting medication effect on the electrophysiologic findings.

5. Conclusions

Electrophysiological assessment of the brain’s functions in bipolar disorder using different evaluation approaches (such as power spectra, coherence analysis etc.) reveals state, task and treatment-dependent changes in a complex network of different neurons that are topographically distributed over the brain. Determining the nature of these neural interactions may help to improve our understanding of underlying pathology and medication effects.

The results of this study show that:

1. There is clear disruption of right sided long distance gamma band coherence in manic patients, compared to healthy controls. This may correspond to a functional long distance connectivity problem in bipolar disorder.
2. Moreover, our findings point to the possibility that processing at the neuronal level can be used in clinical applications, mainly due to the robust finding of decreased gamma coherence in the patient group; the finding confirms and extends our previous finding of altered beta and alpha oscillatory response pattern in mania (Özerdem et al., 2008a).

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