Reduced long distance gamma (28–48 Hz) coherence in euthymic patients with bipolar disorder

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1. Introduction

The utilization of the concept and methods of oscillatory brain dynamics in neuropsychiatric disorders has increased rapidly during the last decade (Başar and Güntekin, 2008; Uhlhaas et al., 2008; Herrmann et al., 2010; O’Donnell et al., 2004; Spencer et al., 2008). The aim of the present study was to explore long distance gamma coherence in euthymic drug-free patients with bipolar disorder. The research objective was informed by recent findings by our group, pointing to long distance connectivity dysfunction in mania (Özerdem et al., 2008; Özerdem et al., 2010).

Bipolar disorder is a chronic illness with a relapsing and remitting course. Relapses are manic or depressive in nature. It is one of the most debilitating illnesses worldwide (Murray and
oscillatory responses in drug-free euthymic bipolar patients pathophysiology of the illness, we have previously studied transmission in bipolar disorder. In search of the underlying findings were considered to involve insuffi-

Both disrupted connectivity in the brain’s integrative functioning. Abnormal neuronal synchronization may contribute to de- and reported abnormally increased left frontal delta in response to visual odd-ball paradigm, which reduced after six weeks of valproate monotherapy (Özerdem et al., 2008).

In one of the very few studies addressing neural synchron-ization in bipolar disorder, 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). Spencer et al. (2008) reported significantly reduced phase locking and reduced evoked power at 30 and 40 Hz stimulation as well as at 40-Hz harmonic of the 20-Hz auditory steady-state responses in first episode schizophrenia and affective psychosis patients compared to healthy controls.

Finally, a recent study reported gamma oscillation decreases in the frontal regions of a mixed population of depressed and euthymic medicated patients with bipolar disorder in response to negative emotion context (Lee et al., 2010). Despite as-sessment of heterogeneous patient populations in different states of illness and different tasks and analysis methods applied in these studies, synchronization deficits in bipolar disorder seem to localize in the frontal and temporal regions and to be dominated by gamma and beta band deficits. The corresponding neurotransmitter disturbance was thought to be GABAergic (O'Donnell et al., 2004). Taken together, these findings can be accounted for the neurocognitive deficits in bipolar disorder.

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 pro-cessing (Başar, 1980; Mittner et al., 1999; Schürmann, et al., 2000). EEG coherence is considered to be an important large scale measure of functional relationships or synchronized functioning between pairs of cortical regions, and therefore represents the brain’s functional connectivity (Nunez, 1997; Lopes da Silva et al., 1980; Petsche and Etlinger, 1998; Rappelsberger et al., 1982). 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).

Human studies reported stimulus specific gamma or gamma/ beta synchronization over several centimeters during atten-tional and memory tasks (Tallon-Baudry et al., 2001). Coherence analysis has seldom been studied in neuropsychiatric disorders, nevertheless, presenting key findings in relation to the underlying functional pathophysiology in both bipolar disorder and Alzheimer’s disease (Özerdem et al., 2010; Güntekin et al., 2008; Başar et al., 2010).

Since synchronous neural gamma oscillatory responses are required for integrative functioning of the brain, and as abnormal neuronal synchronization may contribute to deficits in cognitive and affective integration, such pathology as bipolar disorder with deficits in neurocognition and mood regulation might be expected to present disruption in gamma coherence especially between frontal and other intra-hemispheric structures. Assessment of unmedicated patients in euthymic state can provide a good opportunity to explore the under-lying pathology of bipolar disorder since the condition is not
confounded by any mood or behavioral symptoms and the previously shown possible medication effect on oscillatory responses (Özerdem et al., 2008, 2010), is eliminated. No study up to date has assessed long distance gamma coherence in such a homogeneous group of patients with bipolar disorder. It is also worth mentioning that assessment of both sensory evoked and event related (cognitive) coherence is important given the difference between the two measurements. The evoked coherence mostly reflects the augmentation or strengthening of links between various neural networks upon application of pure sensory signals, whereas the event related coherence reflects the strengthening of links (or neural connections) of neural networks upon stimulation by a sensory signal loaded with a cognitive task. Accordingly, upon application of a signal loaded with cognitive task (in this case the odd-ball paradigm) most possibly extended neural assemblies are activated; in turn, a recorded increase of coherence in a given frequency channel reflects the strengthening of links and amplification of electrical signal flow between the brain areas under examination.

Based on previous findings, the present study had two inter-related exploratory goals: 1. how can evoked and event related coherences serve in finding physiological and/or functional changes in the brain in bipolar disorder; 2. as gamma oscillations are thought to be linked to GABA/glutamate system (Gray and McCormick, 1996; Whittington et al., 1995), can the results open a new avenue to understand the interplay between neurotransmitters and oscillations, and thus future understanding of the basic mechanisms underlying the dysfunctional cognitive networks in bipolar disorder?

2. Methods

2.1. Participants

20 (6 male, and 14 female) DSM-IV (Diagnostic and Statistical Manual of Psychiatric Disorders-fourth edition) (American Psychiatric Association, 1994), bipolar I (n = 18) and II (n = 2) drug-free euthymic patients and 20 sex-matched, healthy controls were enrolled in the study. The study was approved by the local Ethics Committee for Clinical Trials at Bakirkoy Research and Training Hospital for Psychiatry and Neurology, Istanbul, Turkey. All participants provided written informed consent. Patients and controls were interviewed using SCID-I (Structured Interview for DSM-IV) (First et al., 1996). Patients needed to be euthymic for at least 6 months, psychotropic-free (except for benzodiazepines) for at least two weeks prior to study enrollment and off benzodiazepines for at least 24 h before the EEG recording; score 7 or less on the validated and reliable Turkish version of the Young Mania Rating Scale (YMRS) (Karadağ et al., 2002) and score 7 or less on the validated and reliable Turkish version of the 21-item Hamilton Depression Rating Scale (HAM-D 21) (Aydemir and Deveci, 2003), having no comorbid axis I diagnosis; be medically healthy, as shown via physical examination and routine laboratory tests. Volunteers who proved to have no present or past psychiatric condition and to be medically healthy on physical examination were enrolled as the control group.

2.2. Electrophysiological recording

EEG was recorded by using the BrainAmp EEG amplifier, Brain Vision Recorder software (Brainproducts, Munich, Germany), and the BrainCap electrode cap at 30 positions, in accordance with the international 10–20 system. The EEG was amplified by means of a BrainAmp with band limits of 0.01–250 Hz. Two 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. Ag–AgCl electrodes were used for the reference electrodes and EOG recordings. All electrode impedances were kept below 10 kΩ. The EEG was digitized on-line with a sampling rate of 500 Hz.

The participants sat in a dimly lit, isolated room during recordings. Two types of stimuli were presented: simple visual stimuli for analyzing visual evoked coherence; and visual oddball paradigm for analyzing visual event related coherence. First, simple visual stimuli were presented in the form of a light (10 cd/m² luminance) with inter-stimulus intervals varying between 3 and 7 s. Then, a classical visual oddball paradigm was applied by using the simple 10 cd/m² luminance light as the standard and 40 cd/m² luminance light as the target stimuli. A monitor switch was used to send the stimuli to the recording room. The light appeared at full size on a 19-inch computer monitor with a refresh rate of 60 Hz. The duration of the stimulation was 1000 ms. The probability of the deviant stimuli was 0.33 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.

Artifacts were eliminated by manual off-line selective averaging, taking into consideration the EOG recorded from the right eye. The sweep numbers were equalized randomly between the target, non-target and simple visual stimulation conditions.

2.3. Coherence

Brainvision Analyzer Software was used for signal analysis, evaluation of oscillatory dynamics and coherence analysis. After calculation of fast Fourier transform for each epoch with 0–1000 ms duration, coherence analysis was performed with a 1.25 Hz resolution. The method used was the cross-spectrum/autospectrum. The mathematical relations are described in the following:

\[
\text{Coh}(c_1, c_2) = \frac{|\text{CS}(c_1, c_2)(f)|^2}{|\text{CS}(c_1, c_1)(f)||\text{CS}(c_2, c_2)(f)|},
\]

in conjunction with

\[
\text{CS}(c_1, c_2) = \sum c_1\cdot c_2^*.
\]

Coherence was calculated for the target, non-target and simple visual stimuli for long-distance intrahemispheric pairs for the gamma band (28–48 Hz). Fisher’s Z transformation was used to normalize the distribution of average coherence values.

The peak with the maximum coherence Z score within this frequency range for each person was included for the
statistical analysis. The long distance intrahemispheric pairs were F3-T3, F3-TP7, and F3-P3, F3-O1 on the left side and F4-T4, F4-TP8, F4-P4, F4-O2 on the right side.

2.4. Statistics

The Statistical Package for Social Studies (SPSS) was used for statistical analysis. For both the sensory evoked coherence (EC) and event related coherence (ERC) values, the differences within the left fronto-temporal, fronto-temporoparietal, fronto-parietal and fronto-occipital (F3-T3, F3-TP7, F3-P3, F3-O1 respectively); and right fronto-temporal, fronto-temporoparietal, fronto-parietal and fronto-occipital (F4-T4, F4-TP8, F4-P4, F4-O2 respectively) intra-hemispheric electrode pairs for the gamma frequency band coherence Z scores were assessed by means of a repeated measure analysis of variance (ANOVA). For the EC, electrode pairs at four levels (fronto-temporal, fronto-temporoparietal, fronto-parietal and fronto-occipital) and lateralization at two levels (right and left hemispheres) were included as the within-subject factors; patient and control groups were included as the between-subjects factor. Age and years of education were included as covariates in the analysis. For the ERC, in addition to the electrode pairs and lateralization, signal specifications at two levels (target and non-target) were included as the within-subject factors, patient and control groups were included as the between-subjects factor, and age and years of education were included as covariates. Greenhouse–Geisser corrected p-values are reported. A t-test was used for the post-hoc independent group comparisons. All reported p-values are two-tailed. Significance level was $p < 0.05$ for all comparisons.

Behavioral data consisted of the number of target stimuli reported by the participants. The difference between the actual number of stimuli given and the number reported by the participant at the end of the recording session was considered as the “errors”. To explore the corresponding functional outcome of the coherence values, Pearson’s correlation test was used to assess the correlation between event related and evoked coherence values and clinical and behavioral data in the patients.

3. Results

3.1. Clinical characteristics

A summary of the clinical characteristics can be found in Table 1. Female and male participants were equally distributed in both patient and control groups (female/ male: 14/6). Patients had a significantly higher mean age (32.15 ± 5.74; range: 24.00–44.00 years) compared to healthy controls (27.60 ± 7.54; range: 20.00–41.00 years) ($t = 2.147$; $p = 0.038$). Mean years of education in the patient group (12.00 ± 3.45 range: 5.00–17.00 years) was significantly lower than that of the controls (14.35 ± 2.01; range: 11.00–17.00 years) ($t = -2.634$; $p = 0.012$). Patients had been ill for 10.60 ± 4.74 years (range: 1.00–22.00 years) and in euthymic state for 57.55 ± 37.31 months (range: 5.00–108.00 months). Mean age at onset of illness was 22.20 ± 6.26 years (range: 14–38 years), and mean number of past episodes was 3.35 ± 1.95 (range: 1.00–8.00).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of the patients.</th>
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<tbody>
<tr>
<td>Patients (n = 20)</td>
<td>Minimum</td>
</tr>
<tr>
<td>Age</td>
<td>24</td>
</tr>
<tr>
<td>Mean years of education</td>
<td>5</td>
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<tr>
<td>Age at onset of illness</td>
<td>14</td>
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<tr>
<td>Duration of illness (years)</td>
<td>1</td>
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<tr>
<td>Duration of euthymia (months)</td>
<td>5</td>
</tr>
<tr>
<td>Total number of prior episodes</td>
<td>1</td>
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</tbody>
</table>

3.2. Event related coherence (ERC)

Repeated measures ANOVA revealed that the signal (target vs. non-target) effect ($F = 4.386; df: 1.36; p: 0.043$) was statistically significant indicating larger coherence values for target stimuli in both groups. Furthermore patients showed lower right and left hemispheric gamma (28–48 Hz) coherence values for both target and non-target signals at all electrode pairs compared to healthy controls (Fig. 1a and b). There was also a significant group by electrode pair interaction ($F = 4.118; df: 3.108; p: 0.019$).

Pair-wise comparison of the coherence values for the target stimuli in patients and controls showed that patients had significantly lower values between left fronto and temporal regions ($F_{3T7}: 0.46 ± 0.29; 40.50\%$ decrease; $p_{\text{F3T7}:0.012}$) as well as between right fronto and temporal regions ($F_{4T8}: 0.59 ± 0.30; 28.85\%$ decrease; $p_{\text{F4T8:0.034}}$) compared to healthy controls ($F_{3T7}: 0.78 ± 0.45; F_{4T8}: 0.83 ± 0.38$) (Figs. 1a and 2). Likewise, coherence values between fronto and temporo-parietal regions on both left ($F_{3TP8}: 0.49 ± 0.21; 34.69\%$ decrease; $p_{\text{F3TP8:0.007}}$) and right sides ($F_{4TP8}: 0.59 ± 0.34; 32.41\%$ decrease; $p_{\text{F4TP8:0.016}}$) were significantly lower in the patients than in the healthy controls ($F_{3TP8}: 0.75 ± 0.35; F_{4TP8}: 0.76 ± 0.27$) (Fig. 1a).

Coherence values for the non-target stimuli differed significantly between patients and controls only for the right fronto and temporal electrode pairs ($F_{3T8}$ patients: 0.33 ± 0.22; controls: 0.58 ± 0.28; 43.10\% decrease; $p: 0.004$) and for the left fronto and temporo-parietal electrode pairs ($F_{4TP}$ patients: 0.30 ± 0.18; controls: 0.54 ± 0.31; 44.44\% decrease; $p: 0.004$) (Fig. 1b).

3.3. Sensory evoked coherence (EC)

The between group difference for the EC values was non-significant, although the patient group had lower EC responses compared to healthy controls at all electrode locations (Fig. 1c). However, there was a significant lateralization by electrode pair interaction on EC values in the whole group ($n = 40$; $F = 6.557; df: 3.11; p: 0.001$). Comparing EC values from all right and left electrode pairs in the whole group ($n = 40$) showed that there was no significant lateralization between mirroring electrode pairs (i.e. between $F3-T7$ and $F4-T8$, $F3-TP7$ and $F4-TP8$, $F3-P3$ and $F4-P4$, $F3-O1$ and $F4-O2$). However, fronto-parietal electrode pairs on both left and right sides ($F3-P3 = 0.677 ± 0.475$ and $F3-TP8, 0.6056 ± 0.331$ respectively) had the highest EC values compared to all other electrode pairs. The results show that lateralization by electrode pair effect originates from the significant difference between EC values of fronto-parietal electrode pair on one
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3.4. Correlations between clinical and behavioral variables and coherence values

Neither age nor years of education showed significant correlation with the event related or evoked coherence values of any of the electrode pairs in either patient or control groups.

In the patient group, the mean number of past episodes (3.35±1.95) showed a significant negative correlation with non-target F4T8 (Pearson correlation: −0.488, p: 0.029), F4P4 (Pearson correlation: −0.56, p: 0.010), and F4O2 (Pearson correlation: −0.532, p: 0.016) coherence values. Mean illness duration (10.60±4.74 years) was significantly and negatively correlated with non-target F4O2 coherence (Pearson correlation: −0.460, p: 0.041). The number of past episodes, illness duration, age at onset of illness and duration of the illness showed no significant correlation with the event related or evoked coherence values of any of the electrode pairs.

Side and fronto-temporoparietal and fronto-occipital electrode pairs of the counter-lateral side: Left fronto-parietal electrode pair (F3-P3) had significantly higher EC values than right fronto-temporoparietal (F4-TP8: 0.4837±0.32077; t: 2.137, p: 0.036) and right fronto-occipital (F4-O2: 0.4163±0.23204; t: 3.125, p: 0.002) electrode pairs (Fig. 1c). Likewise, right fronto-parietal (F4-P4) EC value was significantly higher than the left fronto-temporoparietal (F3-TP7: 0.4580±0.30183; t: 2.082, p: 0.041) and left fronto-occipital (F3-O1: 0.4352±0.28079; t: 2.480, p: 0.015).

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euthymia showed no significant correlation with either target ER or sensory evoked coherence values.

The mean number of errors made by the patients during odd-ball task (1.35±2.39) was not correlated with either event related or evoked coherence values at any of the assessed electrode pairs.

4. Discussion

4.1. What does the coherence change mean?

The present study examined the cortico-cortical connectivity in response to visual odd-ball paradigm in a group of drug-free euthymic patients with bipolar disorder in comparison to healthy controls, by measuring sensory and event related coherence by means of sensory visual stimulation and a visual odd-ball paradigm. The patients showed bilaterally diminished long distance gamma coherence between frontal and temporal as well as frontal and tempo-parietal regions compared to healthy controls. However, no significant sensory evoked coherence reduction was recorded in the patient group compared to the healthy controls. The decrease in event related coherence differed topographically and ranged between 28.85% and 44.4%. Oscillatory responses to both target and non-target stimuli are manifestations of working memory processes. Therefore, the coherence decrease in response to both stimuli points to an inadequate connectivity between different parts of the brain under cognitive load. The occurrence of large coherence decrease only under cognitive load, but not in response to simple sensory stimuli in the present report is a major finding with regard to the well-documented cognitive dysfunction across all states of bipolar disorder (Martinez-Aran et al., 2004).

Based on previous magnetic resonance imaging studies, where structural abnormalities were displayed in the pre-frontal cortex, medial temporal lobe and sub-cortical structures in bipolar disorder, Strakowski et al. (2005) suggested a diminished prefrontal modulation of subcortical and medial temporal structures within the anterior limbic network (e.g., amygdala, anterior striatum and thalamus) for bipolar disorder. Supportive of this is a more recent study (Chepenik et al., 2010) showing reduced negative correlation between ventral prefrontal cortex (vPFC) and amygdala in bipolar patients compared to healthy controls. Additionally, previously shown decreased gamma coherence addressing functional fronto-temporal connectivity disturbance in mania (Özerdem et al., 2010) is in line with the abovementioned imaging findings pointing at importance of fronto-temporal circuits in bipolar disorder. The findings of the present report provide new input to the connectivity reduction between frontal and temporal/temporo-parietal regions. Due to the fact that this study involves only medication free euthymic patients, findings can be exclusively representative of the underlying core neurobiological mechanisms in bipolar disorder.

4.2. The association between gamma oscillations and GABA/glutamate neurotransmission

Synchronous neural gamma oscillations are critical for cortico-cortical communication and the large-scale integration of distributed sets of neurons for integrated cognitive func-
tioning (Rodriguez et al., 1999). Gamma oscillations originate within networks of inhibitory GABAergic interneurons (Gray and McCormick, 1996) that cause a membrane-potential oscillation in long-axoned projection neurons such as pyramidal cells in the neocortex, hippocampus and thalamo-cortical neurons to provide communication between spatially separate sites and also control brain function. Gamma oscillations are known to have a network inhibitory effect and were proposed to be driven by metabotropic glutamate receptor activation (Whittington et al., 1995). GABAergic modulation is required for synchronization of glutamatergic firing (Whittington et al., 2000). Taken together, there is an interplay between the GABA/glutamate system and the gamma oscillations. Bipolar disorder is known to include low GABA activity (Petty, 1995) and abnormalities affecting GABA related inhibitory neurotransmission (Levinson et al., 2007; Benes and Berretta, 2001). In a multidimensional model of electrical signals by Başar and Güntekin (2008) the interplay between a given neuropathology and different neurotransmitter systems can be displayed in oscillatory activity by application of several different input modalities such as visual, auditory, somatosensory, cognitive and emotional. In accordance with this model, any dysfunction in neuronal synchronization caused by any such dysfunctional neurotransmitter system as the GABA/glutamate system may be related to cognitive and affective integration deficits, such as those seen in bipolar disorder. We have previously reported increase in fronto-temporal coherence and decrease in error rates while reporting target stimuli during odd-ball paradigm after six weeks of valproate treatment in patients suffering from mania (Özerdem et al., 2010). Given that valproate is a GABA/glutamate modulating mood stabilizer, findings of this study coupled with those reported previously seem to be indicative of an association between gamma oscillations and GABA/glutamate neurotransmission.

4.3. Specificity of reduced gamma coherence to bipolar disorder

Gamma responses to various stimulus modalities have been extensively studied in different pathologies. Previous investigators reported altered gamma activity in schizophrenia (Gallinat et al., 2004; Light et al., 2006; Basar-Eroglu et al., 2007; Yeragani et al., 2006; Ford and Mathalon, 2008). It is of note that Basar-Eroglu et al. (2007) recorded increased gamma activity during a working memory task. In a comparative study by Spencer et al. (2008), gamma band auditory steady-state responses (ASSR) were found to be impaired in both first episode psychosis patients with schizophrenia and affective disorder (most of whom had bipolar disorder) compared to healthy controls. The impairment had different patterns of expression in schizophrenia and affective disorder patients. The findings were attributed to the possibility that both conditions were sharing some common neural circuits and different aspects of psychosis were common denominators of both conditions. Another recent study by Reite et al. (2009) tested the activation pattern of the primary auditory cortex in response to steady state (SS) gamma band eliciting stimuli in euthymic bipolar patients. The results showed diminished left-right hemisphere asymmetry of the primary, but not the secondary auditory cortex, in bipolar disorder. Overall, the results indicated shared and non-shared features of auditory cortical disruption between the schizophrenia and bipolar
disorder and functional disorganization that help explain previously reported decreases in amplitude and phase synchrony of SS gamma band responses in bipolar subjects. Our findings from drug-free patients in euthymia that we are reporting here as well as previously reported findings from patients in mania (Özerdem et al., 2010) provide clear evidence of a gamma response dysfunction in bipolar disorder, in response to visual stimuli. Despite existing data, the question of whether gamma response alteration is specific to bipolar disorder still remains to be answered. Comparative studies are needed that include both patient groups with bipolar disorder and schizophrenia in the absence of psychotic symptoms.

4.4. Clinical relevance of the coherence reduction

The negative correlation between the event related coherence and such clinical features as the mean total number of episodes and mean illness duration may have a clinical relevance. This may be a sign that, as the duration and severity of illness increase, the long distance connectivity of the brain reduces in bipolar disorder. However, generality of the finding is questionable given that the significant negative correlations occur only for non-target ERC not for either target ERC or EC values.

4.5. Concluding remarks

1. The observed reduction of up to 44.44% in coherence values is a robust finding, indicating a marked disruption of a functional fronto-temporal coupling in bipolar disorder.
2. The disruption observed under unmedicated conditions in euthymic patients as reported here and in patients in manic state as reported previously (Özerdem et al., 2010) suggests a core pathophysiological process of the illness.
3. Regardless of its specificity to bipolar disorder, the reported coherence change can be considered as a functional imaging correlate of cognitive impairment in the illness, because it is more heavily accentuated under cognitive load than during sensory stimulation. In other words, event related stimulation (cognitive loading) triggers a pathway that responds differently than the sensory pathway.
4. The findings also raise the question of whether gamma coherence reduction can be a candidate biomarker for bipolar disorder. To answer this, further studies are needed with larger sample size and which include patients in different states of illness (i.e. depressed, manic, and euthymic) as well as unaffected first degree relatives of bipolar patients. In addition, it is imperative to show reversal of this functional disruption by medication use in euthymic state.

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References


