Distinct neuronal oscillatory responses between patients with bipolar and unipolar disorders: a magnetoencephalographic study

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ABSTRACT

Background: Bipolar disorder (BD) and major depressive disorder (MDD) have distinct pathophysiologies but similar depressive appearances. The present study aimed at the differentiation of the brain responses between BD and MDD patients. We hypothesized that different affective disorder patients may have distinct patterns of oscillatory cortical activities in response to negative emotional stimuli.

Methods: Twenty BD patients, twenty MDD patients, and twenty age- and gender-matched healthy normal subjects were recruited. We adopted an implicit emotional task with facial image stimuli. The acquired event-related magnetoencephalographic signals were processed by the time-frquency analysis and beamformer-based source imaging techniques followed by statistical inference.

Results: We found that there were gamma oscillation decreases in the frontal regions of both BD and MDD patients, gamma oscillation increases in the bilateral temporal regions of MDD, and alpha-beta rhythm increases in BD patients. Relative to the cortical activation in the control group, the BD patients displayed more widely increased oscillatory activities over the fronto-parieto-occipital regions than MDD patients.

Conclusions: Our results demonstrate the distinct neuropathological patterns of emotional responses in BD and MDD patients. The findings suggest that the dysfunction of emotion regulation in BD may result from the increased sensitivity to emotionally salient information, implicating the potential cause of the emotion lability. The present study also suggests that the implicit emotional task is an effective approach to differentiate bipolar from unipolar disorders and their distinct neuropathological patterns to emotional stimuli may provide objective and quantitative measures for potential diagnostic significance.

INTRODUCTION

Early intervention in affective disorders can minimize the delay in diagnosis and initiation of appropriate therapy (Berk et al., 2009; Evans, 2000). Current diagnoses are determined mainly according to structured clinical assessment based on Diagnostic and Statistical Manual (DSM) of Mental Disorders-IV, with a symptom-based rather than an etiology-based approach. However, misdiagnosis would be made by failure of patient's self-report of past history or depressive appearance in bipolar patients (Hirschfeld et al., 2003). Hence an effective classification for differentiating bipolar from depressive disorders is a need for improving the treatments and functional outcomes of patients with bipolar disorder (BD), which has been emphasized in the research agenda for DAM-V (Phillips and Frank, 2006).

Numerous neuroimaging studies have provided evidences that bipolar and unipolar disorders displayed distinct patterns of functional and structural abnormalities in neural systems critical for emotion regulation (Almeida et al., 2009; Lawrence et al., 2004; Phillips et al., 2003b). A newly functional neuroimaging study indicated that, in response to positive stimuli, patients with major depressive disorder (MDD) exhibited abnormal left-sided top-down effective connectivity from orbitomedial prefrontal cortex to amygdala, whereas a right-sided bottom-up connectivity abnormality from amygdala to orbitomedial prefrontal cortex was found in BD patients (Almeida et al., 2009). Furthermore, depressed patients had less activation in response to negative stimuli in the anterior cingulate cortex (Davidson et al., 2003) and dorsolateral prefrontal cortex (Baxter et al., 1989). Another BD study showed reduced activities in mid to lower ventral prefrontal cortex on both sides and heightened activities in the left amygdala in response to negative facial stimuli (Lawrence et al., 2004).

Brain oscillations at different frequency bands have been shown to be associated with a variety of cognitive functions and emotional processing (Guntekin and Basar, 2007; Knyazev, 2007; Schnitzler and Gross, 2005). A previous study reported that MDD patients showed right frontal asymmetry and impaired functional connectivity at alpha and theta frequency bands (Fingelkurts et al., 2007). Özerdem et al. (Özerdem et al., 2008) proposed that the significantly increased occipital beta activity in the manic state might be compensatory to the presumed disrupted connectivity in the brain's integrative functioning as indicated by the decreased alpha activity in BD patients. Among multiple neuroimaging modalities, magnetoencephalography (MEG) offers a potentially promising way to examine neural synchrony across brain regions by taking advantage of its high temporal resolution. The present study aimed to

differentiate the brain responses between BD and MDD patients by analyzing the MEG signals in an implicit emotional task with time-frequency and source imaging techniques. We hypothesized that different affective disorder patients may have distinct patterns of oscillatory cortical activities in response to negative emotional stimuli.

METHODS

Subjects

Twenty MDD patients (11 females; age range: 20–58 years) and twenty BD patients (13 females; 10 BD I; 10 BD II; age range: 20–58 years) were recruited from the outpatients of psychiatric department of Taipei Veterans General Hospital. All patients underwent structured clinical interview by two independent psychiatrists according to DSM-IV-TR. Exclusion criteria included a history of neurological trauma, current neurological disorder, current comorbid Axis I disorder, and drug abuse. All patients were on a range of medications, including lithium, anticonvulsants, antidepressant, and antipsychotics, who were euthymic (HAMD17$\leqq$8: 13 BD, 11 MDD) or depression (7 BD, 9 MDD) at the time of study. Twenty gender- and age-matched healthy normal controls (NC) (12 females; age range: 20-58 years) with no history of any psychiatric disorder, neurological disorder, or head injury resulting in a loss of consciousness were recruited by advertisement from the local community. All the normal controls underwent Mini International Neuropsychiatric Interview before the experiments to exclude the possible morbidity of major psychiatric illness. All subjects provided written informed consent to participate in the experiment according to the guidelines approved by the Institutional Review Board of Taipei Veterans General Hospital.

Paradigm

We adopted an implicit emotional task with image stimuli containing four kinds of facial expressions, including happy, angry, sad, and neutral. There were 72 images for each expression. These face-only images were gray-colored and were presented in a pseudorandom order. Each image was displayed for 1500 milliseconds followed by a 700-millisecond blank image with a plus in the middle. Then a response visual cue, a question mark, was presented for 1200 milliseconds. Each subject was instructed to judge the gender of the face image with index finger lifting movement, left for male and right for female, once the subject saw the response cue.

Data acquisition

Event-related neuromagnetic signals were measured at a sampling rate of 1000 Hz by a whole-head magnetometer with a sensor array of 306 channels (Vectorview, Elekta Neuromag, Finland) and were bandpass filtered at 0.03-330 Hz. The vertical and horizontal electrooculogram (EOG) were recorded to obtain the EOG-free epochs which were not contaminated by eye movements and/or blinks. Around 70 EOG-free epochs were acquired for each facial expression. Four head-position-indicator (HPI) coils attached on subject's head, two on the forehead and two behind the ears, were used to locate the head of the subject relative to the sensor array before data recordings. A magnetic resonance (MR) T1-weighted image for each participant was acquired by a GE Signa EXCITE 1.5T system (3D-FSPGR, TR = 8.67 ms, TE = 1.86 ms, matrix size = 256×256×124, voxel size = 1.02×1.02×1.5 mm^3). The coordinate systems between the MR image and MEG device were co-registered by means of locating three landmarks (nasion and bilateral pre-auricular points) in both systems.

Data analysis

Only responses to angry expression were compared in this study because of its emotional salience and high arousal scores. For each participant, the event-related MEG signals were analyzed by the Morlet wavelet approach with parameter σ=7 to obtain the time-frequency map of time interval from 0 to 400 milliseconds after stimulus onset and of frequency band from 2 to 50 Hz. For each sensor, non-parametric statistical analysis (Wilcoxon rank-sum test) was applied to compare the time-frequency components between each pair of the three involved independent groups, such as NC vs. BD, NC vs. MDD, and BD vs. MDD, in order to determine the most discriminative bands among all sensors for further source analysis.

Once the frequency band with significant difference was determined, the event-related MEG signals were filtered in this frequency band. Then the F-statistic map of oscillatory neuronal activities in the specified active and control states was calculated by a beamformer-based source imaging technique (Chen et al., 2006). In this study, the active and control states were set as the durations from 50 ms to 300 ms after the onset and from 200 ms to 100 ms before the onset, respectively. Finally, a voxel-wise two-sample t-test was applied to locate the cortical regions with significant difference of oscillatory activities between groups.

RESULTS

Demographic features of the three subject groups and the corresponding statistical results are presented in Table 1. Only significant differences of YMRS

(p=0.041) and episodes (p=0.026) between BD and MDD were found. The pair-wise comparison results of time-frequency maps are shown in Figure 1. Compared with the NC group, the BD and MDD groups had similar patterns of the decreased gamma activities in the frontal and parietal regions (p<0.125), where BD had slightly decreased gamma oscillations in the fronto-central region than MDD and MDD displayed increased gamma activities in the bilateral temporal regions than BD. The BD had increased alpha-beta activities in the bilateral temporal and occipital regions (p<0.125), particularly higher in the right hemisphere, compared with NC; whereas no particular changes of alpha-beta activity were found in MDD comparing with NC group. Thus alpha power changes were found to be the most discriminative pattern between BD and MDD groups. We therefore selected the alpha band (8-12 Hz) as frequency of interest for further analysis.

Figure 2 illustrates the voxel-wise statistical results of alpha oscillatory activity comparison between each pair of the three groups with a threshold of p<0.01. BD exhibited significantly increased cortical activation than NC in the right inferior/middle frontal gyrus, left insula, left middle cingulate gyrus, right middle occipital gyrus, left cuneus, and right inferior parietal gyrus (Fig. 2a). Compared with the NC group, MDD showed significantly decreased activation in the left parahippocampal gyrus and right middle temporal gyrus, and increased activations in the left superior temporal gyrus, left cuneus, and right precentral gyrus (Fig. 2b). Comparing the BD and MDD groups, BD showed hyperactivation in the regions of right supplementary motor area, right precuneus, left parahippocampal gyrus, and right caudate; whereas BD had hypoactivation than MDD in the right inferior/superior temporal, left middle occipital, and right precentral gyri (Fig. 2c).

DISCUSSION

This study demonstrates that BD and MDD patients exhibit different patterns of oscillatory activities in terms of cortical activation distribution and frequency spectrum, in response to negative emotion context. The present study also indicates that the implicit emotional task is an effective approach to differentiate bipolar from unipolar disorders. The findings suggest that the distinct neuropathological patterns of emotional responses in these two affective disorders may provide objective and quantitative measures for potential diagnostic significance.

Different brain oscillations have been suggested as various mechanisms for cerebral integration underlying cognitive functions (Basar and Guntekin, 2008; Knyazev, 2007). Alpha oscillation is involved in long-range communication and participates in inhibitory process with attention and memory; whereas beta rhythm plays an important role in visual attention, movement-related changes, and sensory

memory (Klimesch, 1999). Gamma synchrony, mainly contributing to short-range synchronization, is considered as binding features for encoding, retention, and retrieval of information which is independent of sensory modality (Herrmann and Demiralp, 2005). This study focused on differentiating the spectrum of brain oscillations between patients with bipolar and major depressive disorders. We found that there were gamma oscillation decreases in the frontal regions of both BD and MDD patients, implicating their impaired top-down inhibitory control systems in emotion regulation (Savitz and Drevets, 2009). Furthermore, the larger gamma activation in the bilateral temporal regions of MDD patients implicated that their bottom-up appraisal functions over-activated and may be associated with dysfunction of emotion generation and perception in   (Phillips et al., 2003b). Higher alpha-beta rhythm found in BD patients was in line with the report in (Phillips et al., 2003b), which implicated high sensitivity of emotional context and may be associated with increased vulnerability in bipolar disease model (Basar and Guntekin, 2008).

Relative to the cortical activation in the NC group, the BD patients displayed more widely increased oscillatory activities over the fronto-parieto-occipital regions than MDD patients. The increased activities in the occipito-parietal regions were found in BD group, including middle occipital, superior parietal, and inferior parietal gyri. These regions belong to the dorsal visual stream specialized for processing location and biological motion information (LaBar et al., 2003) and were found to be impaired in schizophrenia (Doniger et al., 2002) and hypomania (Malhi et al., 2004). Furthermore, we found that the BD patients exhibited increased activities in the regions related to affective evaluation, including the right inferior frontal gyrus which was reported as a role in coping with emotional detection (Wang et al., 2008), the insula involved in target detection (Nakata et al., 2008), the middle cingulate gyrus involved in planning-based regulation of emotional behavior (Heimer and Van Hoesen, 2006; Phillips et al., 2003a), and the caudate associated with the monitoring, learning, and memory of reward system (Kringelbach, 2005). These results implicated that BD patients tend to be more sensitive to negative valence and were engaged in more visual information processing, comparing with MDD patients. These findings suggest that the dysfunction of emotion regulation in BD may result from the increased sensitivity to emotionally salient information, implicating the potential cause of the emotion lability. The limitation of the present study would be that our patients used a wide range of medications, such as anticonvulsant, antipsychotics, lithium, and antidepressant which could be a discernible confound. Further studies are needed to clarify the pharmacological effects on the oscillatory activity in patients with different affective disorders

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Table 1

Table 1. Demographic features

	BD n=20	MDD n=20	NC n=20
Mean Age (years) [n]	32.1 (±8.33)	35.6 (±9.97)	38.4 (±12.06)
Gender (male/female) [n]	7/13	9/11	8/12
HAMD-17 [n]	7 (±3.97)	8.6 (±7.92)	-
YMRS*	1.8 (±2.16)	0.59 (±1.22)	-
Duration of illness (years) [n]	6.9 (±4.52)	8.7 (±7.57)	-
Episode*	7.3 (±4.16)	4.3 (±3.74)	-

HAMD: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale.

BD: bipolar disorder; MDD: Major depressive disorder; NC: normal controls.

Mean (±standard deviation)

*: $P < .05$;   [n]: non-significance
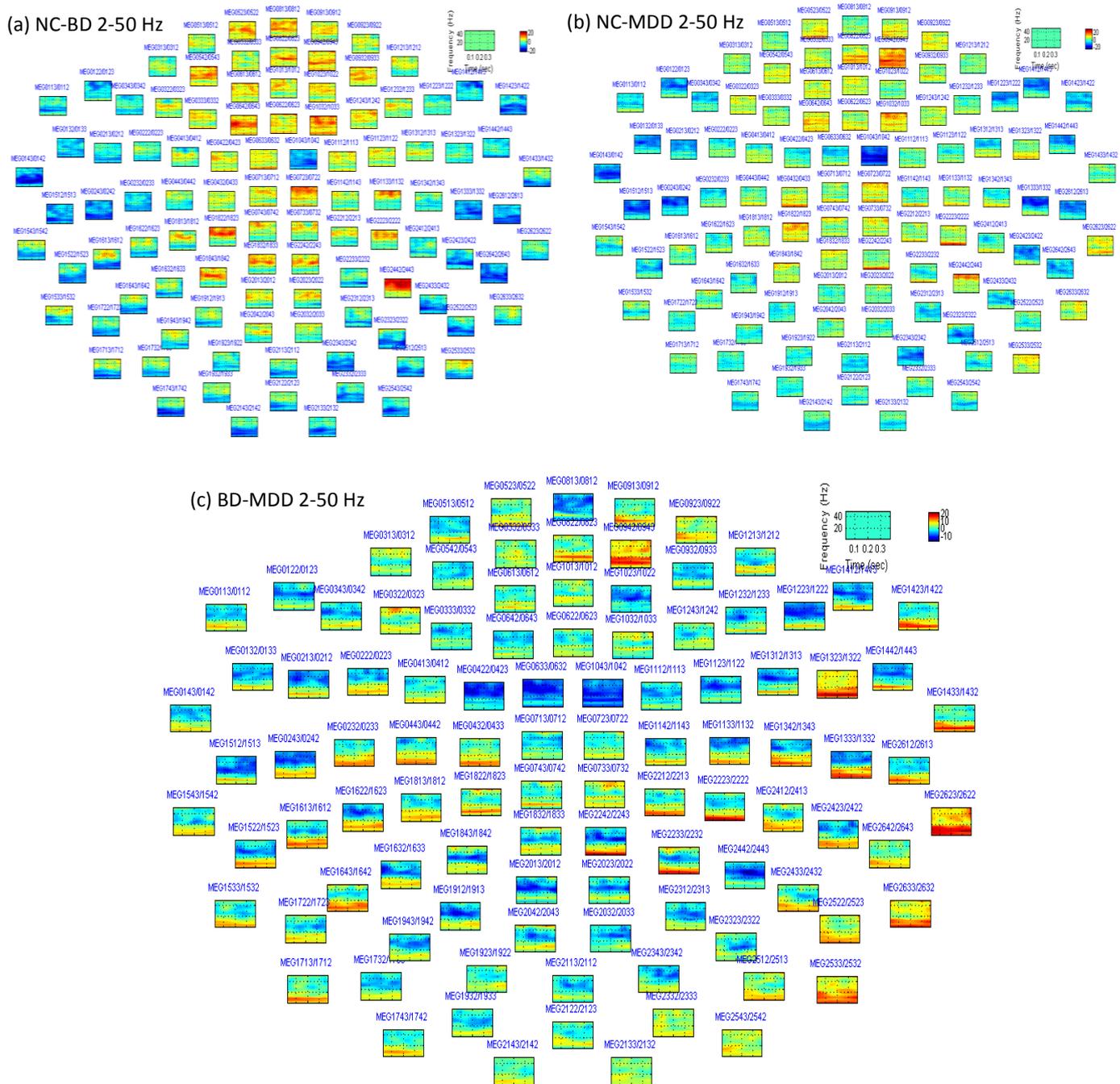
Figure 1

Figure 1. Illustration of the Wilcoxon rank-sum test results of time-frequency components within 2-50 Hz (colorbar:χ^2 statistics) between (a) NC vs. BD, (b) NC vs. MDD, and (c) BD vs. MDD groups, where NC is for normal controls, BD for bipolar disorder, and MDD for major depressive disorder.

Figure 2

(a)   NC>BD   NC<BD   (b)   NC > MDD   NC < MDD

(c)   BD > MDD   BD < MDD
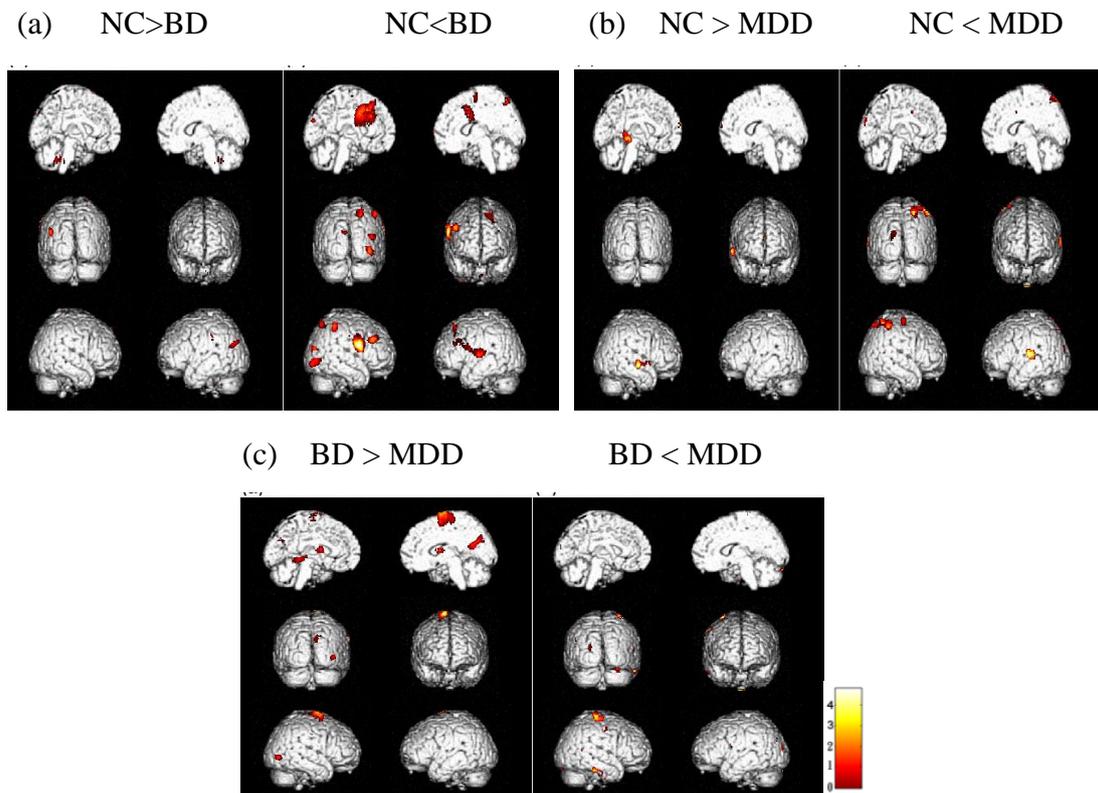
Figure 2. Voxel-wise statistical results (color map: two-sample t statistics, $P < 0.01$) of comparing alpha-band cortical activity between (a) NC vs. BD, (b) NC vs. MDD, and (c) BD vs. MDD groups, where NC is for normal controls, BD for bipolar disorder patients, and MDD for major depressive disorder patients.