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Different patterns of abnormal gamma oscillatory activity in unipolar and bipolar disorder patients during an implicit emotion task

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ABSTRACT

This study investigates the distinct patterns of local and long-range gamma oscillations between patients with bipolar disorder (BD) and major depressive disorder (MDD). Twenty BD patients, twenty MDD patients, and twenty normal controls participated in this study. For each participant, the event-related magnetoencephalographic responses while performing an implicit emotional task were recorded and processed with time-frequency analysis. Compared to normal controls, the BD patients exhibited the gamma power decease at the right frontal and prefrontal regions and yet gamma power increase at the right posterior temporal region. The abnormal long-range gamma oscillation between the right frontal and parietal-occipital region was also found. These results indicate that the BD patients may have hyperactivity in perceptual binding of emotional features and tend to be oversensitive to facial features. On the other hand, MDD patients displayed increased early gamma activity at the left anterior temporal region, which may imply their hyperactivated binding process of emotional features at corticolimbic regions. The distinct alterations of gamma patterns between the BD and MDD patients implicate that their impairments of binding processes are located at different regions. Gamma activity in the parietal and left posterior temporal regions may be a potential index to differentiate BD patients from MDD patients.

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1. Introduction

Bipolar disorder (BD) and major depressive disorder (MDD), the two major categories of mood disorders with a lifetime prevalence estimate of 20.8% (Kessler et al., 2005), are characterized by pervasive changes in mood. According to DSM-IV criteria, the manic/hypomanic episodes are the key features that differentiate BD from MDD. However, BD patients during depression may be misdiagnosed as unipolar disorder (Muzina, Kemp, & McIntyre, 2007; Phillips & Vieta, 2007). Neuroimaging studies have reported abnormal brain regions and functional connectivity of emotion processing in BD and MDD patients, suggesting that dysfunction of emotion perception is one of their core deficits (Almeida et al., 2009; Lawrence et al., 2004; Phillips, Drevets, Rauch, & Lane, 2003). Quantitative measurements of neural communication of emotion perception in human brains would assist clinical diagnosis of BD patients for better treatment outcomes.

Processing of facial expression is rapid and essential for social communication and understanding in humans. Perception of emotional faces involves detection and integration of various features, including changeable (e.g. expression) and unchangeable (e.g. identity) features of faces (Haxby, Hoffman, & Gobbini, 2000), which requires effective coordination among brain regions (Vuilleumier & Pourtois, 2007). Gamma oscillation has been proposed as a key mechanism of perceptual binding in neural networks, reflecting integration of various features of an object (Rodriguez et al., 1999; Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998). Critically, a prior electroencephalography (EEG) study reported interaction between hemispheric gamma power and emotional valence, which suggested that the spatial distribution of gamma power might correlate with neural substrates of emotional responses, including limbic, temporal, and frontal structures (Müller, Keil, Gruber, &

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Elbert, 1999). Hence spectral gamma power would be a potential index for investigating perceptual binding of emotional faces and providing valuable measures for neurophysiological assessment of emotion processing in affective disorders.

Implicit emotional paradigms, which require participants to judge nonemotional facial cues (e.g. gender) are considered an effective way to investigate neural substrates of emotional processing within corticolimbic regions (Critchley et al., 2000; Scheuerecker et al., 2007). A previous functional MRI study indicated that implicit emotional processing of faces elicited increased subcortical and ventral prefrontal cortical responses in BD patients but diminished brain responses in MDD patients (Lawrence et al., 2004). This finding raises the question whether the difference of brain responses in these patients originated from their impaired perceptual processes of emotional features, effects of emotion modulation on task-related processing, or both.

To address this question, the present study adopted an implicit emotional paradigm and utilized gamma band power measured by magnetoencephalography (MEG) to investigate early perceptual processing of emotional faces and late task-related processing in BD and MDD patients, compared with healthy controls. An EEG study indicated that early gamma activity (around 100 ms) reflected perceptual binding of multisensory input in the occipital and medial-frontal regions (Senkowski, Talsma, Grigutsch, Herrmann, & Woldorff, 2007). The late induced gamma activity (above 200 ms) was linked specifically to task-related signals (Tallon-Baudry & Bertrand, 1999). Measurements of early and late gamma activity evoked by faces in an implicit emotional task could thus provide a possibility for delineating the neural processing of perceptual binding and task-related function. We hypothesized that BD and MDD patients would exhibit distinct neuronal alterations in perceptual binding of emotional features, reflected by the spatial pattern of gamma power could be a biological index for distinguishing these two affective diseases.

2. Material and methods

2.1. Subjects

The subjects in this study consisted of twenty BD patients (mean age 34.75 ± 11.04, female 12), twenty MDD patients (mean age 33.50 ± 9.38, female 12), and twenty normal controls (NC, mean age 34.05 ± 11.40, female 12). The three groups were matched for age and gender, and all subjects were right-handed except one in the MDD group. The demographic variables (Table 1) for the three groups showed no significant differences ($p > 0.05$). All patients met the DSM-IV criteria for clinical diagnosis, which was made by two independent psychiatrists. The NC subjects underwent the Mini International Neuropsychiatric Interview before the experiments to confirm the absence of psychiatric illness. All subjects signed written consent forms approved by the Institutional Review Board at Taipei Veterans General Hospital. Before data acquisition, mood symptoms of the BD and MDD patients were evaluated according to the Young Mania Rating Scale (YMRS) and the 17-item Hamilton Rating Scale for Depression (HAMD). For the BD patients, the YMRS and

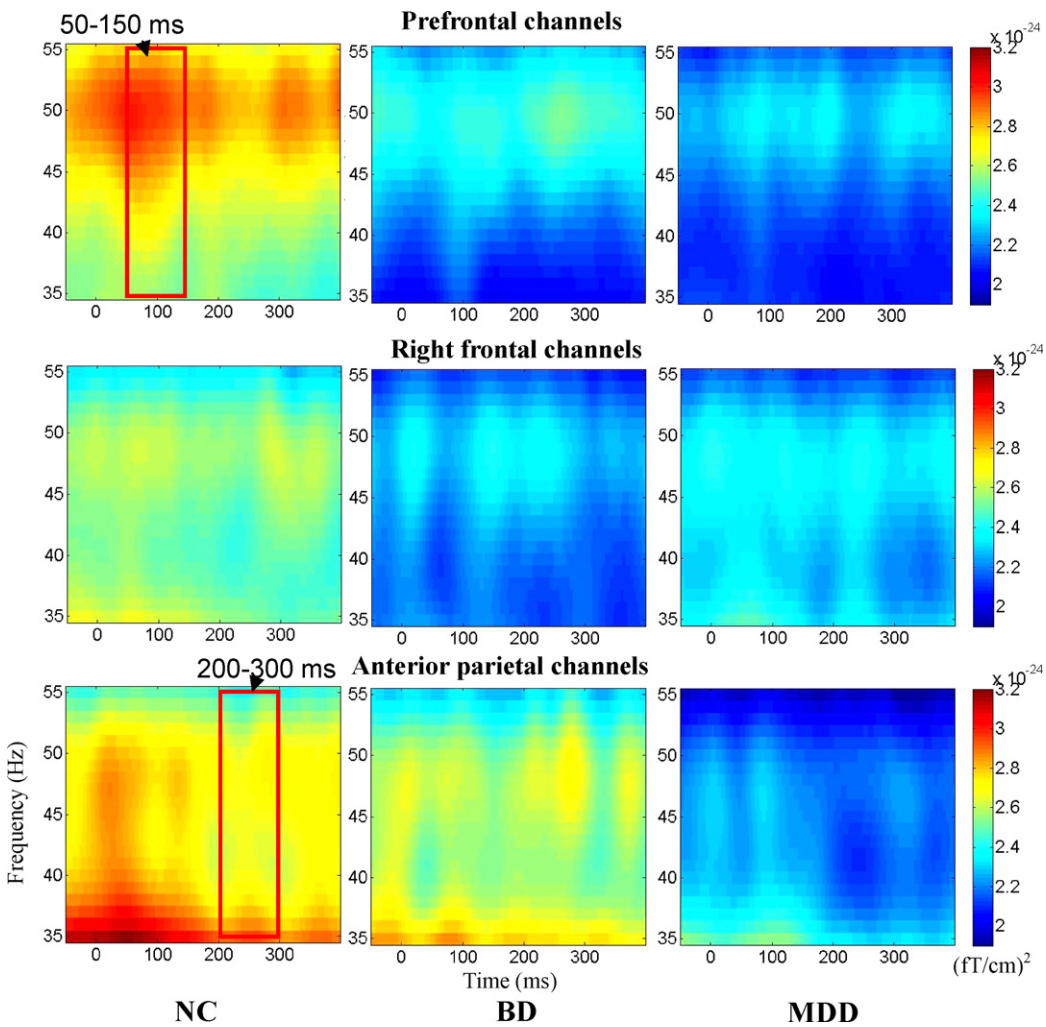

Fig. 1. Time-frequency maps for three groups. The left column is for normal control (NC); the middle one is for bipolar disorder (BD); and the right one is for major depressive disorder (MDD). Two time windows of interest (50–150 ms; 200–300 ms) are marked in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 1
Demographic variables for the bipolar, major depression and control groups.

	BD	MDD	NC
Gender (male:female)	8:12	8:12	8:12
Age	34.75 (11.04)	33.50 (9.38)	34.05 (11.40)
Age of onset	26.50 (8.64)	25.25 (9.39)	–
Duration of illness (years)	7.85 (6.64)	8.30 (7.03)	–
Number of manic episodes	2.95 (2.01)	–	–
Number of depressive episodes	3.55 (1.79)	4.15 (3.60)	–
Number of major depressive episodes	3.05 (1.00)	2.60 (1.09)	–
Young Mania Rating Scale	1.60 (2.16)	0.55 (1.15)	–
Hamilton Depression Rating Scale	6.70 (4.69)	7.85 (6.51)	–
Divided attention (visual)	950.00 (157.86)**	886.05 (90.31)*	821.22 (100.82)
Face recognition (retention)	96.18 (11.12)	93.16 (8.71)	99.50 (6.52)

Except for the gender variable, all other variables are presented as mean (SD).
* Statistically significant differences at the level of $p < 0.05$ compared with NC group.
** Statistically significant differences at the level of $p < 0.01$ compared with NC group.

HAMD-17 scores were 1.60 ± 2.16 and 6.70 ± 4.69, and the scores for MDD patients were 0.55 ± 1.15 and 7.85 ± 6.51, respectively.

2.2. Behavioral data recording

Before MEG recordings, all participants underwent two behavioral tests, including an attention test and a face memory test in order to examine potential confounds of behavioral difference among patient and normal groups. The Test for Attention Performance (TAP; version 1.5) was used to assess visual attention ability. In the visual attention task, subjects had to detect whether the crosses that appear in a random configuration in a 4×4 matrix formed the corners of a square. The overall time spent was measured as performance index of visual attention function.

For the face memory task, the three-stage procedure is described as follows. In the first (acquisition) stage, each subject was instructed to memorize 24 target faces that each was shown once with a duration of around 2 s. In the second (immediate recognition) stage, each subject was instructed to recognize the target faces from 48 faces, comprised of 24 target faces previously displayed in the first stage and another 24 new faces. The subject was asked to orally reply "yes" if a target face was displayed and "no" otherwise. In the third (delayed recognition) stage, after a 30-min interval, the subject was asked to recognize the target faces again from another set of 48 faces, comprised of 24 target faces previously displayed in the first stage and 24 new faces (different from those shown in the second stage). The number of successfully recognized target faces was used as a face recognition score for both the immediate and delayed recognition stages. Face retention ability was defined as a ratio of the face recognition score in the third stage divided by that in the second stage.

2.3. Paradigm

Grayscale face-only visual stimuli containing four kinds of expressions (neutral, angry, sad, and happy) were randomly presented using STIM2 (Neuroscan Inc.; VA, USA). There were 72 trials for each expression and the inter-stimulus interval was approximately 3 s. Each trial started with a face image for 1.5 s, followed by a blank image (700 ms) and a response cue of 1.2 s. Subjects were asked to lift their fingers to identify gender of the face (right index finger for female and left for male) when the response cue was presented. All subjects practiced the test before their MEG signals were recorded. Some of the data in this study have been published previously (Lee, Chen, Hsieh, Su, & Chen, 2010).

2.4. MEG acquisition

For each subject, event-related MEG signals with a sampling rate of 1000 Hz were recorded using a whole-head 306-channel neuromagnetometer (Vectorview; Elekta-Neuromag, Helsinki, Finland). Trials contaminated with ocular movements or containing deflections exceeding 9000 fT/cm were rejected. Three anatomical landmarks (nasion and left/right preauricular points) were specified for co-registration of the MEG and structural MRI data. The subjects' heads were attached with four head position indicator coils to provide similar alignment of head positions among subjects during MEG recording.

2.5. Data analysis

After signal space projection and offline artifact rejection, time-frequency analysis with Morlet wavelet (Kronland-Martinet, Morlet, & Grossmann, 1987) was performed to calculate the trial-by-trial amplitude of the induced gamma oscillatory activity for each MEG sensor (Fig. 1). For each of the 162 planar gradiometers, the mean induced gamma activity in the early time window (50–150 ms) and the late time window (200–300 ms) after stimulus onset was calculated for each frequency band (35–45 Hz, 35–55 Hz, and 45–55 Hz).

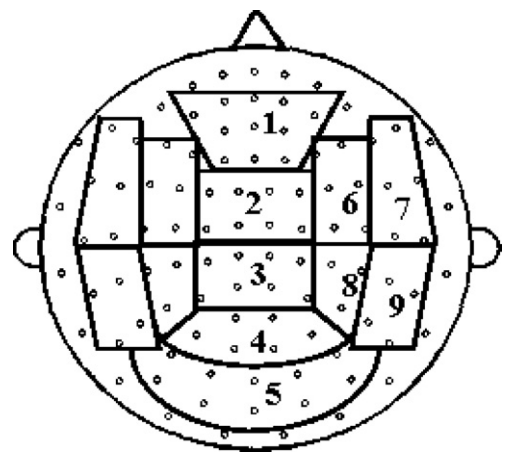

Fig. 2. Illustration of recording-site parcellation. There are 13 parceled regions for statistical analysis. 1, prefrontal region; 2, central region; 3, anterior medial parietal region; 4, parietal-occipital region; 5, occipital region; 6, right frontal region; 7, right anterior temporal region; 8, right temporal-parietal region; and 9, right posterior temporal region.

The relative mean gamma activity was calculated by dividing the mean activity of all regions (162 planar gradiometers in total) for each frequency band. The 162 planar gradiometers were separated into 13 cortical regions, containing 22 prefrontal, 12 right frontal, 6 right temporal-parietal, 12 right anterior temporal, 8 right posterior temporal, 16 central, 16 anterior medial parietal, 20 occipital, 12 occipital-parietal, 12 left frontal, 6 left temporal-parietal, 12 left anterior temporal, and 8 left posterior temporal planar gradiometers (Fig. 2). After averaging the relative mean gamma activity in each region, we calculated the regional relative mean gamma activity (RRMGA) (Osipova, Ahveninen, Jensen, Ylikoski, & Pekkonen, 2005). The mean of the RRMGAs of the four facial expressions, represented as mRRMGAs, in the early and late time windows were referred as early and late gamma activity, respectively, in this study.

2.6. Statistical analysis

To determine whether the overall gamma activity in the whole brain was different between groups, we averaged the $\log_{10}$ absolute gamma power values of the whole brain and performed a one-way ANOVA test. Because the scale of the absolute gamma power was as small as 10^{-24} $(\text{fT/cm})^2$, $\log_{10}$ function was applied to avoid numerical rounding error as well as to adjust data toward a normal distribution (Gasser, Bacher, & Mocks, 1982). The ranges of RRMGA and mRRMGA were from zero to two and hence were not adjusted. This study focused on relative gamma power that was used in the following statistic analysis. For each gamma band in each time window, the data were analyzed by a three-way ANOVA with group (BD, MDD, and NC) as between-subject factor, emotional facial expression (neutral, angry, sad, and happy) and region (13 areas) as within-subject factors. Because no main effect or interaction of the facial expression was found in the results, a two-way ANOVA with group and region as factors was then performed with planned comparisons followed by Bonferroni correction ($p < 0.0167$). Given a seed region, this study used Spearman correlation with Bonferroni correction to measure correlations between gamma activity in the seed and the other twelve regions ($|r| = >0.608$, $p < 0.0042$).

Demographic and symptomatic data between groups were examined using t-test and behavioral data (attention and face retention) between groups were tested

using one-way ANOVA. This study also used Spearman correlation coefficients to test the associations between mRRMGAs and behavioral data in each group. All reported p values were two-sided.

3. Results

A main effect of attention performance was found ($F(2,54) = 5.353$, $p = 0.008$), where the BD group was worse than the NC group ($t(36) = 2.96$, $p = 0.006$). No significant difference of face retention capability among three groups was found ($F(2,54) = 2.246$, $p = 0.116$).

The whole-brain mean induced gamma activity and the relative mean gamma activity showed no significant difference among the three groups ($F(2,57) < 0.001$, $p > 0.9971$). A three-way ANOVA for the RRMGAs showed a main effect of region ($F(12,2964) > 19.92$, $p < 0.0001$) and significant interaction between group and region ($F(24,2964) > 1.69$, $p < 0.02$) for both time windows and the three frequency bands. There was no main effect of group or facial expression nor an interaction between these two factors. In two-way ANOVA tests, a main effect of region ($F(12,741) > 29.90$, $p < 0.0001$) and an interaction between group and region ($F(24,741) > 2.39$, $p < 0.001$) were also found for the two time windows and the three frequency bands.

3.1. Patterns in the time and frequency factors

Comparing the BD patient group with the NC group, the right frontal mRRMGAs were significantly decreased at 35–45 Hz in the two time windows and at 35–55 Hz in the early time window (Fig. 3A, $p < 0.0167$). The prefrontal gamma activity was significantly decreased at 45–55 Hz and 35–55 Hz in the late time windows. By contrast, in the right posterior temporal region, the mRRMGA was found to be significantly increased at 35–45 Hz and 35–55 Hz in the early time window (Fig. 3A, $p < 0.0167$).

Comparing the MDD patient group with the NC group, the anterior medial parietal, right temporal-parietal, and prefrontal mRRMGAs for the three frequency bands were significantly

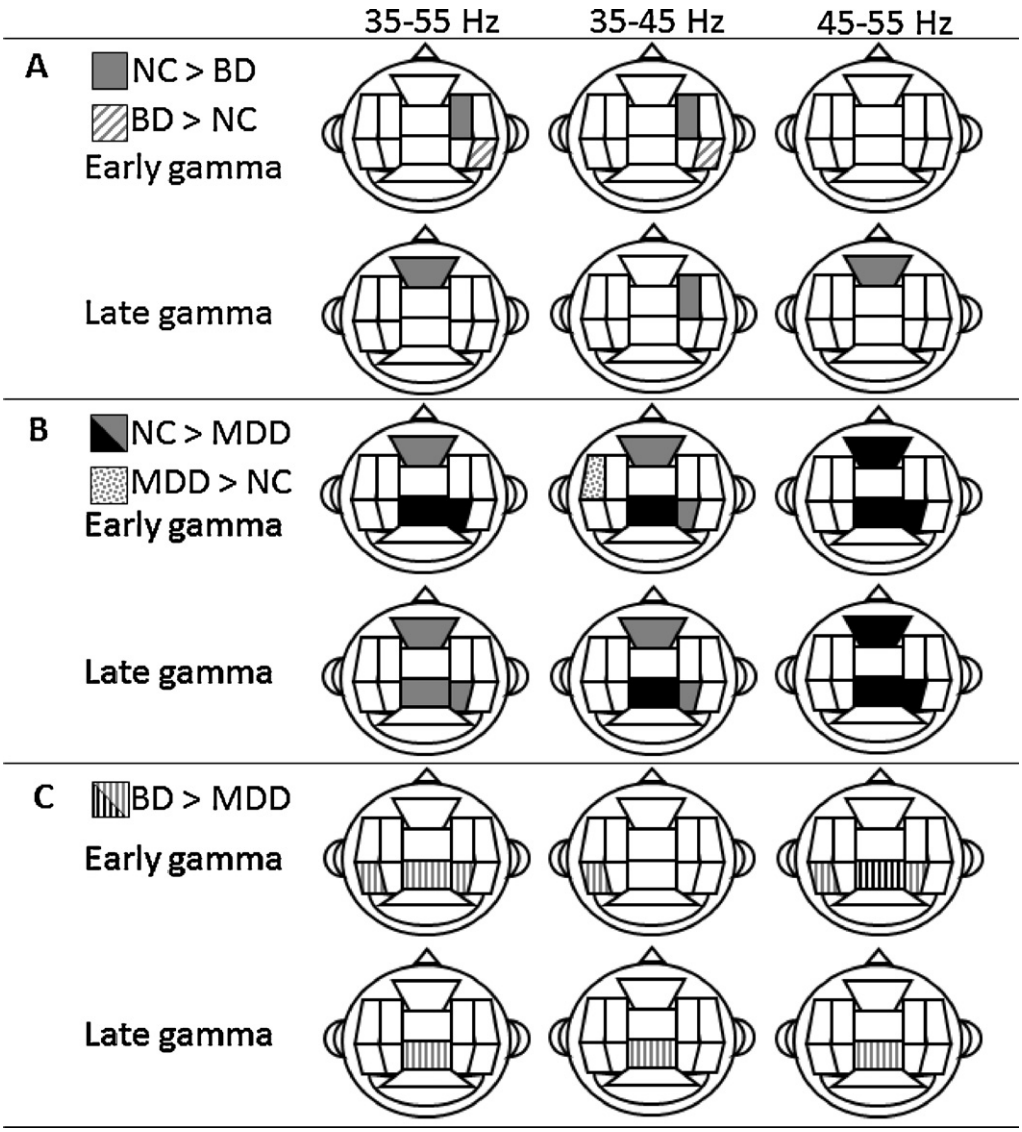

Fig. 3. Comparison results of mRRMGAs between each pair of the three groups for two time windows and three gamma frequency bands. (A) Compared to the NC group, the BD patients displayed decreased gamma activity in the right frontal and prefrontal regions (filled) and increased gamma activity in the right posterior temporal regions (diagonal stripes). (B) Compared to the NC group, the MDD patients showed decreased gamma activity in the prefrontal, anterior medial parietal, and right temporal-parietal regions (filled) and increased gamma activity in the left anterior temporal region (dots). (C) Compared to the MDD patients, the BD patients had larger gamma activity in the left posterior temporal, anterior medial parietal, and right temporal-parietal regions (vertical stripes). Gray color: $p < 0.0167$; black color: $p < 0.0034$ (both p-values with Bonferroni correction). mRRMGA, mean of regional relative mean gamma activity; BD, bipolar disorder; MDD, major depressive disorder, and NC, normal control.

decreased in the two time windows (Fig. 3B, $p < 0.0167$ for gray color and $p < 0.0034$ for black color). The increase of mRRMGA in the left anterior temporal region at 35–45 Hz in the early time window was significant (Fig. 3B, $p < 0.0167$).

Comparing the BD patient group with the MDD patient group, there were significantly larger mRRMGAs for the BD group at the anterior medial parietal, right temporal-parietal, and left posterior temporal regions (Fig. 3C, $p < 0.0167$ for gray color and $p < 0.0034$ for black color). No significantly larger gamma activity for the MDD group was found.

3.2. Cross-region correlations at 35–55 Hz

The three different regions (prefrontal, right frontal, and right posterior temporal regions) were selected at 35–55 Hz in the early and late gamma for comparison between the BD and NC groups and four different regions (prefrontal, anterior medial parietal, right temporal-parietal, and left anterior temporal regions) for comparison between the MDD and NC groups. Each of these selected regions was used as a seed region for correlation analysis with each of the twelve other regions.

For the BD patient group, the right frontal and parietal-occipital mRRMGAs were negatively correlated in the early time window (Fig. 4A). More inter-region correlations were found in the MDD group (Fig. 4B). In the early time window, the positive correlations were found between the anterior medial parietal and occipital regions as well as between the left anterior temporal and left frontal regions. The left anterior temporal region was also negatively correlated to the left parietal-occipital and occipital regions. In the late time window, the pattern in the left hemisphere was the same as that in the early time window, whereas a negative correlation in the right hemisphere was found between the anterior medial parietal and anterior temporal regions.

3.3. Correlation between mRRMGA and behavioral performance

Attention ability, as assessed by the divided attention task, in the BD group showed a significant correlation with regional gamma activity, but no significant correlations with regional gamma activity in the MDD and NC groups in the two time windows at 35–55 Hz. The scores for divided attention were negatively correlated to the early and late left posterior temporal mRRMGAs ($r = -0.57$, $p < 0.01$; $r = -0.48$, $p < 0.05$, respectively) in the BD patient group. The larger gamma activity of the BD patients in the left posterior temporal was associated with better attention performance.

Memory maintenance, as assessed by retention of face recognition between immediate and delayed task phases, in the MDD patient group and the NC group showed significant correlations with regional gamma activity, but no significant correlations with regional gamma activity in the BD group in the two time windows at 35–55 Hz. For the MDD group, the face retention score was positively correlated with anterior medial parietal late gamma activity ($r = 0.47$, $p < 0.05$). The better memory maintenance in MDD patients was associated with higher late gamma activity in the anterior medial parietal region. In the NC group, the face retention score was positively correlated with the early and late right frontal gamma activity ($r = 0.61$, $p < 0.01$; $r = 0.49$, $p < 0.05$, respectively), but negatively correlated with the early parietal-occipital gamma activity ($r = -0.56$, $p < 0.05$).

3.4. Correlation between mRRMGA and symptomatic data

The symptom indices, including YMRS and HAMD, were tested for correlations with regional gamma activity of the BD and MDD groups in the two time windows at 35–55 Hz. No significant correlation between symptomatic indices and regional gamma activity was found.

4. Discussion

This study demonstrates that gamma oscillatory power could be an effective index for differentiating BD and MDD regarding distinct alterations of neuronal coordination, which may be considered central to the pathophysiology of neuropsychiatric diseases (Wilson et al., 2008). BD patients showed decreased gamma activity in the right frontal and medial prefrontal regions, and increased activity in the right posterior temporal visual region. On the other hand, the MDD patients showed decreased gamma activity in the prefrontal and parietal regions, and increased activity in the left temporal emotion-related region. Gamma activity in the parietal and left posterior temporal regions may distinguish BD patients from MDD patients.

In the BD patient group, increased and decreased early gamma activity was found at the right posterior temporal and frontal regions, respectively. A previous electrocorticogram (ECoG) study showed that ventral occipitotemporal gamma oscillations were sensitive to face perception and could be modulated by attention (Engell & McCarthy, 2010, 2011). Another ECoG study also demonstrated that visual perception of faces activated gamma band responses in occipitotemporal regions followed by parietal regions (Lachaux et al., 2005). Our finding of the increased early gamma activity in the posterior temporal regions suggests hyperactivity in perceptual binding of emotional features in BD patients. The cognitive deficit in the BD patients was reflected by abnormal gamma synchronization in the frontal region, which was in line with the results in (O'Donnell et al., 2004) and decreased activity in the dorsal ventral prefrontal cortex of the BD group compared to that of the NC group while performing attention tasks. Impaired sustained attention was a specific marker of the BD patients (Clark, Iversen, & Goodwin, 2002; Harmer, Clark, Grayson, & Goodwin, 2002; Maalouf et al., 2010). We speculate that decreased right frontal and prefrontal gamma activity could be related to attention deficits in BD patients.

Among BD patients in this study, early gamma activity in the right frontal regions was negatively related to early parietal-occipital gamma activity, reflecting abnormal fronto-occipital integration. Our results are in line with the findings in (Özerdem, Guntekin, Saatci, Tunca, & Basar, 2010), which reported disturbance between the right frontal and occipital region in gamma coherence exhibited in the mania of bipolar patients. According to the model presented in (Ochsner & Gross, 2007), emotion regulates the interaction between bottom-up and top-down processing. BD patients may not adequately regulate their emotions because of impaired interaction between bottom-up processing and top-down processing (Almeida et al., 2009). The finding of abnormal local and long-range gamma activity in the BD patients may indicate abnormal regional functions and inter-cortical integration, which may relate to both bottom-up processing (visual processing in the right posterior temporal region) and top-down processing (attention function in the right frontal and prefrontal regions).

In the MDD patient group, the finding of increased early gamma activity in the left anterior temporal region may imply a hyperactivated binding process of emotional features in corticolimbic regions. The decreased early and late gamma activity at both of the parietal and prefrontal regions may indicate impaired attention function in depressive patients. The anterior temporal pole was reported abnormal and correlated with impaired emotional self-regulation in major depression (Beauregard, Paquette, & Levesque, 2006; Takahashi et al., 2010). The finding of increased anterior temporal activity in this study is consistent with a previous imaging

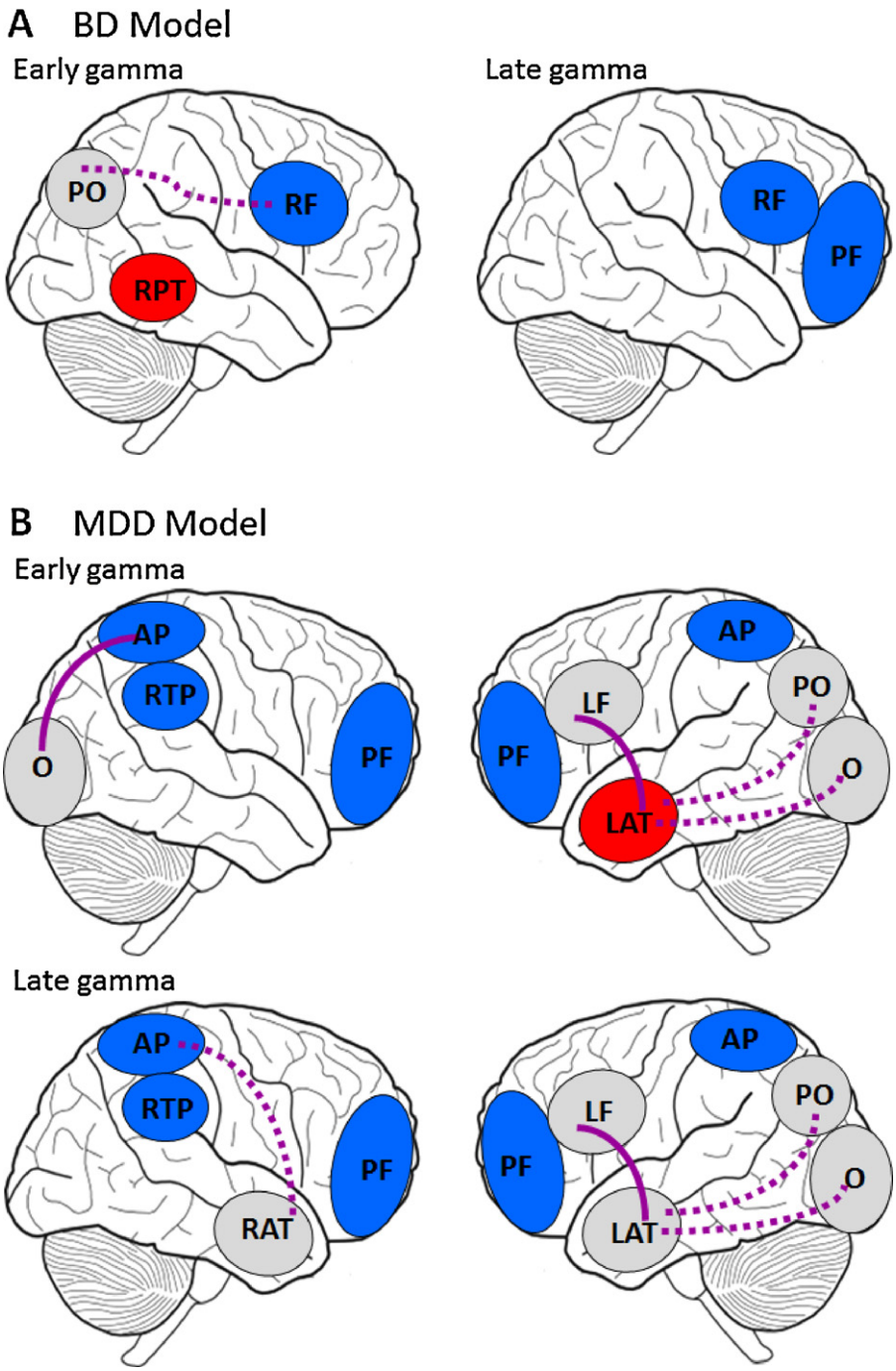

Fig. 4. Distinct patterns of inter-region correlations with the increased (red), decreased (blue), or non-altered (gray) gamma activity for the BD (A) and MDD (B) patients. Solid line, positive correlation; dash line, negative correlation. RF, right frontal area; RPT, right posterior temporal area; PO, parietal-occipital area; PF, prefrontal area; AP, anterior medial parietal area; RTP, right temporal-parietal areas; O, occipital area; LAT, left anterior temporal area; LF, left frontal area; and RAT, right anterior temporal area. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

study (Ebmeier, Rose, & Steele, 2006), which found increased activity in the emotion-related regions among MDD patients. The gamma coherence between frontal and parietal cortex increased while salient stimuli drew attention automatically (Buschman & Miller, 2007). Our findings may suggest that the MDD patients adopt an unbalanced resource allocation strategy between bottom-up hyperactive emotional processing and top-down hypoactive attention function.

In this study, the parietal and left posterior temporal gamma activity may be a potential index to differentiate MDD patients from BD patients. Our data also showed that the better retention scores of the MDD patients were related to higher anterior medial parietal late gamma activity. The impaired memory function in the depressive patients may be reflected by less gamma power in the parietal region. In the present study, the better attention performance in the BD patients was related to higher gamma activity in the left posterior temporal region, but not in the MDD patients. This may suggest that the left posterior temporal gamma activity could be a potential biological indicator of differentiation. The patients in this study were not drug-naïve or drug-free, which could have a confounding

effect on the brain signals. The small number of patients using each type of medication increases the difficulty of drug effect analysis. The abnormal patterns of gamma activity may reflect a trait-like marker of BD and MDD, because thirteen of the twenty BD and fifteen of the twenty MDD patients were in remission.

In summary, the abnormal pattern in the BD patients showing decrease in the right anterior frontal region and increase in the right posterior temporal region as well as abnormal gamma synchronization of fronto-occipital regions may indicate impaired regional functions and inter-cortical integration. These findings suggest that the BD patients tend to be oversensitive to facial features, which might contribute to their prominent mood swings and emotional liability. The findings in the MDD patients suggest that the anterior temporal region is heavily engaged in feature binding of emotional information and the decreased parietal and prefrontal gamma activity may reflect functional impairment of attention, suggesting that MDD may display insufficient attentional disengagement and task-related maintenance due to the distraction of salience emotional context. The distinct alterations of gamma patterns between the BD and MDD patients suggest that their impairments of binding processes are located in different regions. Gamma activity in the parietal and left posterior temporal regions may be a potential index to differentiate BD patients from MDD patients.

Acknowledgments

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