The altered cortical connectivity during spatial search for facial expressions in major depressive disorder

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To characterize the altered directed connectivity within a distributed cortical network, as is associated with the impaired attention modulation involved in the manifestation of mood disorder in depression, short-window partial directed coherence (PDC) combining with the event-related brain potentials (ERPs) was applied in this study. ERPs were recorded from 13 normal subjects and 12 depressed patients during visual search for facial expressions. The evoked N2 component of ERPs by responding to all neutral faces showed no significant between-group effect (F(1,22) = 5.11, P = 0.05) and the positive face was reduced in the depressed patients as compared to the normal subjects (F(1,22) = 5.71, P < 0.05), while the evoked N2 component by detecting the negative face showed no significant between-group effect (F(1,22) = 2.10, P = 0.16). The reduced N2 amplitude reflected deficits in effortful attentional modulation in depression. Obtained PDC values within the N2 time-window (150–300 ms post stimulus) showed weaker intra-frontal and intra-central directed interactions and enhanced occipital information output when responding to all neutral faces in depression relative to those in the normal group. Few decreased intra-frontal directed interactions were observed when detecting the emotional facial emotion in depression. The altered cortical directed connectivity contributed to the impairment occurring in the effortful attention modulation in depression. Our findings supported that the impaired attention modulation processing in depression was associated with the altered cortical connectivity.

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1. Introduction

Various investigations have found deficits in attention modulation in depression (Clark et al., 2009; Phillips et al., 2003a; Suslow et al., 2004), which contributed to the manifestation of mood disorder (Clark et al., 2009). Neuroimaging investigations demonstrated that the attention modulation implicated a distributed cortical network consisting of several cortical and subcortical structures (Davidson, 1998; Davidson et al., 2002; Phillips et al., 2003b; a; Marchand et al., 2007). Decreased activity in the dorsal prefrontal cortex (dPFC) and the dorsal regions of anterior cingulated cortex (ACC) were observed, which might result in the reduced capacity for executive control and effortful regulation of attention in depression (Clark et al., 2009; Davidson et al., 2002; Liotti and Mayberg, 2001; Phillips et al., 2003a, 2003b; Taylor and Liberzon, 2007; Thayer and Lane, 2000). Reduced volume and increased activity within the amygdala and increased activity within the insula in major depression were related to a negative bias in directing attention to emotional information (Phillips et al., 2003b). These findings reflected that the impaired attention modulation in depression was associated with the alterations in the cortical circuit consisting of multiple structures. Thus it led to the assumption that impaired attention modulation in depressed patients might be due to the altered directed connectivity within the cortical network, rather than the independent alterations in each structure (Sun et al., 2008). Investigations on the directed interactions between cortical regions are greatly desired, so they will enable a more comprehensive understanding of impairments in attention modulation in depression.

Multi-channel event related brain potentials (ERPs) analysis has demonstrated that a distinct ERPs component, termed “N2”, seemed to be indicative of the timing of effortful attention modulation (Carreté et al., 2001; Feng et al., 2008; Huang and Luo, 2006). Anterior N2 was sensitive to novel stimuli and attributed to the orienting of visual attention (Folstein and Van Petten, 2008). Enhanced N2 amplitude was...
evolved by rare targets than frequent non-targets (Breton et al., 1988). Larger N2 amplitude was observed when task-relevant features didn’t match and reflected the mismatch effect (Wang et al., 2004). The non-targets which shared features with targets elicited larger N2, which was located in medial frontal cortex (Azizian et al., 2006). These investigations provided the evidence that N2 indexed the attentional manipulation in the processes of cognitive control (Folstein and Van Petten, 2008). In mood disorder, altered N2 activity was also demonstrated and was related to cognitive deficits (Debener et al., 2000; Levin et al., 2007; Liotti and Mayberg, 2001; Vuilleumier and Pourtois, 2007). Decreased N2 over the right posterior in response to facial stimuli showed face processing anomaly in depression (Deldin et al., 2000). N2b enhancement was involved in the selective attentional deficit in patients with major depression (Levin et al., 2007). Therefore, the altered N2 amplitudes in depression met the assumption that abnormal neural activity within the N2 time-windows might contribute to the diminished capacity of attentional modulation in depression. With this consideration, our interest was confined to the process during the N2 time-window. The altered directed cortical connectivity in depression was assessed within N2 time-windows in particular.

Various quantitative electroencephalography (qEEG) methods have been proposed to study the cortical interaction (Pereda et al., 2005). Compared with traditional coherence analysis and mutual synchronicity, partial directed coherence (PDC) analysis evaluated causality in terms of directional influence between multi-channel electrophysiological time series (Ding et al., 2000; Sun et al., 2008; Supp et al., 2005). PDC approach was based on a multivariate autoregressive (MVAR) model (Baccalá and Sameshima, 2001; Ding et al., 2000) and was a genuine multi-channel method (Pereda et al., 2005). It could help to reveal where the information flow is derived from, transmitted to, or feedback among separated cortical regions (Supp et al., 2005, 2007). More attention has been paid for this method in recent years, due to its success in revealing the multi-channel directed cortical interactions (Pereda et al., 2005; Sun et al., 2008; Supp et al., 2005; Supp et al., 2007; Zhang et al., 2009). Further, a short-window PDC approach was offered to meet temporal requirement (Ding et al., 2000). Since the measured ERP trials to attain the N2 component were reasonably assumed as different realizations of the same process, the final covariance matrix for the MVAR model of the observed signal could be obtained by averaging across all the realizations, even though the duration of each realization was short (Ding et al., 2000; Supp et al., 2005; Zhang et al., 2009). In this paper, we evaluated the cortical directed connectivity within the specified N2 time-window, so as to estimate the temporospatial patterns of the cortical directed connectivity with high temporal resolution.

In this study, a visual search task for emotional facial expressions was performed by both the depressed subjects and the normal control ones. The visual search paradigm was effective to demonstrate the visual search strategy for emotionally biased expressions in multi-face stimuli (Ohman et al., 2001a,b; Pegna et al., 2008; Suslow et al., 2004; Tang et al., 2009; Williams et al., 2008). Attention modulation played an important role in enhancing the visual information relevant to the target and inhibiting the irrelevant one when performing a visual search task (Lorenzo-Lopez et al., 2008). We applied the paradigm to explore the diminished capacity in attentional modulation in depression. With short-window PDC analysis, we measured the changes of the cortical directed connectivity within the cortical network in depressed patients as compared to normal controls. We hypothesized that: (1) The ERPs component N2 would demonstrate whether the capacity of attention modulation was impaired in depression; (2) The PDC values would demonstrate the patterns of altered cortical directed connectivity which might contribute to the impairments of attentional modulation in depression. A well-recognized model of visual attention consisted of a bottom-up component for image-based saliency processing across the posterior visual cortex and a top-down component for task-dependent modulation mainly at prefrontal and frontal cortex (Itti and Koch, 2001). In the normal subjects, the forward bottom-up pathway transferred the visual perceptual saliency from the occipital cortex to the frontal cortex for high-level processing. Then the feedback top-down pathway transferred the high-level cognitive control from anterior or central cortex to the sensory cortex. We assumed that the balance between these two components was disrupted in depression, the decreased feedback regulation in conjunction with increased forward input, contributed to the dysfunction of attention modulation in depression (Fig. 1).

To further explore whether the alteration in directed connectivity within the network in depression was due to the same node which ceased to fire independently or to a collective phenomenon, twice PDC analysis were performed basing on two different MVAR modeling.

2. Materials and methods

2.1. Subjects

A total of 25 subjects participated in this study: (1) the normal control group included thirteen right-handed normal subjects (male/female = 7/6, 39.54 ± 9.65 years) with no personal history of neurological or psychiatric illness, no drug or alcohol abuse, no current medication, and normal or corrected-to-normal vision; (2) the depressed group: twelve right-handed depressed outpatients (male/female = 8/4, 31.67 ± 13.55 years) were recruited in Shanghai Mental Health Center (SMHC). All depressed subjects had no history of manic episode, and fulfilled ICD-10 (the tenth revision of International Classification of Diseases) diagnosis criteria of major depressive disorder (current episode of depression). Nine patients were first-episode and three patients were recurrent. Nine patients were unmedicated and hadn’t taken medicine for at least one month. Three depressed patients had taken antidepressants for less than 2 weeks. Two patients had taken paroxetine with a dosage of 20 mg/day, and another patient had taken fluoxetine with a dosage of 20 mg/day. All subjects including healthy controls had no history of any substance or alcohol abuse. Each subject has normal or corrected-to-normal vision. Informed consent was obtained from each participant before the experiments. The experimental protocol was approved by the SMHC Ethics Committee in compliance with the Helsinki Declaration.

After taking part in the experimental testing session, all subjects participated in an interview in which HAMD (Hamilton Rating Scale for Depression) was administered. SAS (Self-rating Anxiety Scale) and SDS (Self-rating Depression Scale) were self-rated. The scores of the normal group were in the normal range showing no mood disorder (see Table 1).

2.2. Materials and procedure

The face-in-the-crowd task was constructed according to the experiments of Thomas Suslow et al. (White, 1995; Suslow et al., 2004). Schematic faces were used. Stimuli consisted of three types of pictures (Fig. 2): 16 pictures with four neutral faces, namely “condition without target” hereafter; 8 pictures were with one positive face among three neutral faces, namely “condition with positive target” hereafter; and another 8 pictures were with one negative face among three neutral faces, namely “condition with negative target” hereafter. The faces randomly located at the eight cardinal compass points of an imaginary circle. Therefore, there were 16 + 8 + 8 = 32 independent stimuli in total in one block. The block repeated five times.
times in the experiment. In each block, each stimulus was displayed randomly for 1500 ms with a gray background and presented with an inter-stimulus interval (ISI) of 1000 ms. The procedure is similar to our previous study (Tang et al., 2009).

Participants were seated at 1-m distance from the screen in a sound-attenuating, electrically shielded chamber with dim illumination. They were instructed to sit quietly and focus on the center of the screen. The subjects were asked to distinguish via a button press whether they found the same expression within a single trial as soon and correctly as possible after the onset of each stimulus. They would press the button labeled “1” if the faces were all neutral ones, and they would press the button labeled “5” if there was a target face (with either a positive or a negative face among neutral ones). The stimuli were presented with a rest period of 1 min in between blocks.

2.3. EEG recording and data preprocessing

The electroencephalogram (EEG) was recorded from 64-channel surface electrodes mounted in an elastic cap (QuickCapTM, Brain Products Inc., Bavaria, Germany) including two pairs of vertical and horizontal surface electrodes mounted in an elastic cap (QuickCapTM, Brain Products Inc., Bavaria, Germany) (Miller et al., 1988). The artifact-free data was band-pass filtered between 0.01 Hz and 40 Hz using a zero phase-shift IIR filter (24 dB/Oct). EEG was segmented separately from 200 ms before the stimulus onset to 1500 ms post-stimulus. All the segmentations were baseline corrected to the first 200 ms of the epoch. Segmentations with artifacts (>±100 μV) or leading to incorrect answers were excluded. Considering the amount of calculation, this study focused on the 12 typical electrodes which covered nearly the whole cortex: Fp1, Fp2, Fz, F5 and F6 in the prefrontal and frontal cortex, C5, C6 and Cz in the central cortex, and Pz, P07, P08 and O2 in the occipito-parietal cortex.

2.4. ERP data

For the selected electrodes, individual EEG segmentations were averaged separately for each category of stimuli at each electrode. Grand averages were smoothed with a 0.5–30 Hz bandpass filter. Individual peak amplitude (mean over a 10 ms time-window around the peak) and peak latency was obtained from each category at the N2 time-window: between 150 ms and 300 ms. The N2 peak was a local maximum at the N2 time-window and could not occur at the boundary of the time-window. These values were submitted to statistical analysis.

2.5. PDC analysis

Artifact-free EEG segmentations from 200 ms pre-stimulus to 1500 ms post-stimulus at 12 selected electrodes were obtained as described in Section 2.3. The EEG segmentations within the N2 time-window (150–300 ms post-stimulus, according to grand average waves) were selected. These selected segmentations were detrended by subtracting the ensemble mean and then normalized with their standard deviations (Ding et al., 2000) before multivariate autoregressive (MVAR) modeling. The PDC, proposed by Baccala and Sameshima in 2001 (Baccalá and Sameshima, 2001), is derived from the estimation of a MVAR model. The M-channel EEG vector was represented as $X(t) = [X(1,t), X(2,t), ..., X(M,t)]^T$, where $X(i,t)(i = 1, 2, ..., M)$ stood for the $i$th

Table 1

<table>
<thead>
<tr>
<th>Demographic and affective characteristics of depressed patients and normal subjects (mean ± S.D.).</th>
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<tr>
<td>Normal controls</td>
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* Indicates the difference is statistically significant (the significant value is P < 0.05).
The channel of EEG signals at the time instance $t$ and $M = 12$ since EEG signals were selected from 12 electrodes in this study. The MVAR model was a mathematical modeling of EEG time serials, as described by Eq. (1)

$$X(t) = \sum_{r=1}^{p} A(r)X(t-r) + E(t).$$

The matrix $A(r)$ indicated $M \times M$ coefficient matrices of the model up to an order $p$, $E(t)$ was the vector of residual error, which would be uncorrelated noise when the MVAR model gave a good description to the EEG signals. To estimate $A(r)$, several steps were required. Firstly, Eq. (1) could be multiplied on the right by $X'(t-k), (k = 1, 2, \ldots, p)$ so as to obtain the Yule–Walker equations

$$\sum_{r=1}^{p} R(-k + r)A(r) = 0,$$

where $R(n) = \langle X(t)X'(t+n) \rangle$ was $X'(t)$'s covariance matrix of lag $n$. With the multiple realizations of the same process, the covariance matrix of each realization was first estimated separately and the final covariance matrix of the process could be obtained by averaging all the covariance matrices of the realizations. Then the Levinson–Wiggins–Robinson (LWR) algorithm was used to get a solution of $A(r)$ (Ding et al., 2000). The order $p$ of the MVAR model was determined by the Akaike information criterion (Kaminski and Blinowska, 1991).

The coefficient matrices $A(r)$ were transformed into the frequency domain

$$A(f) = \sum_{r=1}^{p} A(r)e^{-j2\pi f r}.$$  

The transfer function $\tilde{A}(f) = 1 - A(f) = [\tilde{a}_1(f), \tilde{a}_2(f), \ldots, \tilde{a}_p(f)]$ yielded a $M \times M$ matrix $\tilde{A}(f)$ for each frequency $f$. The PDC value from the $j$th channel to the $i$th one at the frequency $f$ was obtained according to

$$PDC_{i \rightarrow j}(f) = \frac{\tilde{A}_{ij}(f)}{\sqrt{\tilde{A}_{ii}(f)\tilde{A}_{jj}(f)}}.$$  

where $\tilde{A}_{ij}(f)$ was the $i$th-row and the $j$th-column element of $\tilde{A}(f)$. We averaged PDC values over the frequency band $\Delta f$ of 1–30 Hz as the average directed interaction from electrode $j$ to electrode $i$, $PDC_{i \rightarrow j}(f) = \sum_{f=1}^{\Delta f} PDC_{i \rightarrow j}(f)/\Delta f$ (Zhang et al., 2009). In the context below, we submitted the average PDC values to statistical analysis and referred to PDC values for short.

Let us further explain how it can differentiate between coherence from A electrode to B electrode and coherence from B to A. For instance, we got the directed coherences of $Cz \rightarrow Pz$ and $Pz \rightarrow Cz$ by PDC analysis, respectively. According to Eq. (4), the PDC value of $Cz \rightarrow Pz$ represented the relative coupling strength of the interaction of a given source $Cz$, with regard to the electrode $Pz$, as compared to all of $Cz$'s connections to other 11 electrodes (Pereda et al., 2005). On the other hand, the PDC value of $Pz \rightarrow Cz$ was calculated by considering $Pz$ as a given source, and represented the relative coupling strength of the interaction of $Pz$ with regard to $Cz$, as compared to all of $Pz$'s connections to other 11 electrodes. Thus, PDC values of $Cz \rightarrow Pz$ and $Pz \rightarrow Cz$ differed from each other and reflected the directed interactions between electrodes $Pz$ and $Cz$.

In order to demonstrate that the alteration of directed connectivity in depression was due to the local changes, i.e. $Fz$ where the N2 activity was significantly altered, another PDC analysis was performed. The other 11 electrodes excluding $Fz$ were selected to establish MVAR model as described above. Then PDC values were obtained for each directed interaction between every two electrodes.

### 2.6. Statistical analysis

As described in Section 2.2, two conditions, the condition with positive/negative target (with one emotional face among three neutral faces) and the condition without target (with all neutral faces), were involved in the face-in-the-crowd task. Considering that there were more trials in the condition without target than that with target and the “neutral” trials and the “positive/negative” trials could represent different underlying processing, therefore, we separately analyze the results in the two conditions.

In the condition with positive/negative target, the behavioral reaction times (RTs) and accuracy, the individual N2 amplitude and latency at the electrode $Fz$ were statistically analyzed with repeated measures ANOVA (using Greenhouse–Geisser correction) for within-group factor Expression (positive and negative), between-group factor Group (the depressed group and the normal) and covariate factor Gender (male and female). To test the significant changes of PDC values, M-ANOVA was performed for all directed interactions between selected electrodes. Different PDC values obtained from different electrode pairs were considered as dependent variables when a within-group factor Expression (positive and negative) and a between-group factor Group (the depressed group and the normal) were considered as fixed factors, and the potential confounding factor Gender as a
covariate variable. When there was a significant interaction of Group and Expression, additional univariate analysis (ANCOVA) was used to test differences between two groups at each level of the factor Expression with the covariate variable Gender.

In the condition without target, only the effect of the between-group factor Group was measured. The behavioral RTs and accuracy, the individual N2 amplitude and latency at the electrode Fz were statistically analyzed using ANCOVA for the between-group factor Group and the covariate factor Gender. M-ANOVA with the between-group factor Group and the covariate factor Gender was performed to the PDC values for all directed interaction between selected electrodes.

3. Results

Significant Group effect was observed on the behavioral responses, N2 amplitude and latency, and PDC values, which differed between the depressed subjects and the normal ones. Comparisons of behavioral RT and accuracy, N2 amplitude and latency, and PDC values were performed using analysis of covariance controlling for potential confounding variable Gender. No significant Gender effect was observed in the following results.

3.1. Behavioral results

In the condition without target, the accuracy of the depressed group was significantly lower than that of the normal (F(1,22) = 4.21, P < 0.05). The reaction times (RTs) showed no significant Group effect (F(1,22) = 2.28, P = 0.15).

In the condition with positive/negative target, the accuracy of the depressed group tended to be lower than that of the normal (F(1,22) = 3.54, P = 0.07). The factor Expression showed no significant main effect on the accuracy (F(1,22) = 2.62, P = 0.12). The Group effect tended to be significant for the RTs (F(1,22) = 2.85, P = 0.1). The following ANCOVA test for each expression showed that the RTs in the depressed group were longer than those in the normal group when detecting the negative face (F(1,22) = 4.23, P < 0.05). The main effect of the factor Expression was significant on the RTs (F(1,22) = 8.66, P < 0.01). The RTs of detecting the negative face were significantly shorter than that of detecting the positive one for both groups (Fig. 3).

3.2. ERPs results

Significant Group effect on the N2 component was only observed at the electrode Fz, so ERPs results at the electrode Fz were shown alone. In the condition without target, significant Group effect on the N2 amplitude was observed at the electrode Fz (F(1,22) = 5.51, P < 0.05) (Fig. 4). Reduced N2 amplitude was found in the depressed subjects as compared to the normal when responding to all neutral faces. Significant Group effect on the N2 latency was also observed at Fz (F(1,22) = 4.24, P < 0.05). The latency of N2 in response to all neutral faces in the depressed subjects (279 ± 11 ms) was later than that in the normal ones (248 ± 10 ms).

In the condition with positive/negative target, Group effect on the N2 amplitude tended to be significant (F(1,22) = 3.88, P = 0.06). The following test found that: (1) when detecting the positive face, the evoked N2 amplitude in the depressed group was significantly lower than that in the normal one (F(1,22) = 5.71, P < 0.05); (2) when detecting the negative face, the evoked N2 amplitude showed no significant differences between two groups (F(1,22) = 2.10, P = 0.16). There was no significant Group effect on the N2 latency (F(1,22) = 0.00, P = 0.99). No significant Expression effect was found on either the amplitude or latency of N2 (F(1,22) = 0.43, P = 0.52 and F(1,22) = 0.00, P = 0.95, respectively).

The N2 results verified that impaired attention modulation in depression. Thus, the following PDC analysis was confined to the N2 time-window to explore the dysfunctional mechanism.

3.3. PDC results

PDC values of the EEG segments between the selected electrodes were calculated in the N2 time-window, 150–300 ms post-stimulus. In the condition without target, the PDC values revealed quantitative and topographical differences of information transfer in the cortical network during attentional modulation between the depressed group and the normal one. Our results showed a significant main effect of the factor Group on the directed interaction between the selected sites. Information flow derived from the parieto-occipital regions was stronger in the depressed subjects as compared to the normal ones, while that derived from central sites and over intra-frontal regions was weaker (Table 2). PDC values across the cortex were performed for the following three types of coherence increase in the depressed group as compared to the normal (Fig. 5(a)):

1. Occipital → centro-parietal interactions, i.e., Oz → Cz (F(1,22) = 10.52, P = 0.01); PO8 → Cz (F(1,22) = 19.20, P < 0.01); Pz → PO8 (F(1,22) = 9.42, P < 0.01); and PO8 → Pz (F(1,22) = 4.77, P < 0.05);
2. Occipital → frontal interactions, i.e., PO8 → F6 (F(1,22) = 6.23, P < 0.05) and PO8 → Fz (F(1,22) = 8.91, P < 0.01);
3. Frontal information output, i.e., Fz → PO8 (F(1,22) = 5.09, P < 0.05); F6 → Pz (F(1,22) = 3.90, P < 0.05) and F6 → PO8 (F(1,22) = 11.30, P < 0.01).

Fig. 3. Mean reaction time (ms) and accuracy of the behavioral responses in the face-in-a-crowd task (mean ± S.E.). In the condition without target, the Group effect was significant for accuracy. In the condition with target, the Group effect tended to be significant for the RTs and accuracy; and the significant Expression effect was significant on RTs. * tends to be statistically significant (P < 0.1); ** means statistically significant (P < 0.05) and *** means statistically extreme significant (P < 0.01).
On the other hand, lower PDC values in the depressed group appeared between the following sites as compared to the normal (Fig. 5(b)):

1. Intra-frontal interactions, i.e., Fz → Fp1 (F(1,22) = 5.10, P < 0.05), Fz → Fp2 (F(1,22) = 7.11, P < 0.05), Fz → F5 (F(1,22) = 5.00, P < 0.05), Fp2 → Fp1 (F(1,22) = 4.86, P < 0.05) and Fp2 → F6 (F(1,22) = 5.74, P < 0.05);

2. Central information output, i.e., Cz → Fp2 (F(1,22) = 6.38, P < 0.05), Cz → C5 (F(1,22) = 9.72, P < 0.01), Cz → Pz (F(1,22) = 10.11, P < 0.01) and Cz → PO7 (F(1,22) = 7.21, P < 0.05).

In the condition with positive/negative target, significant Group effect was observed on a few directed interactions (Fig. 5(c), (d)). Enhanced directed interactions as following were observed in the depressed group as compared to the normal: PO7 → Cz (F(1,22) = 11.59, P < 0.01), Oz → Cz (F(1,22) = 8.79, P < 0.01), Oz → Pz (F(1,22) = 5.39, P < 0.05), Pz → Cz (F(1,22) = 5.87, P < 0.05), F6 → PO7 (F(1,22) = 18.74, P < 0.01), Oz → Fz (F(1,22) = 5.08, P < 0.05) and Oz → F6 (F(1,22) = 4.40, P < 0.05). On the other hand, weaker central outputs were observed, e.g., Cz → CS (F(1,22) = 12.18, P < 0.01), Cz → CS (F(1,22) = 5.80, P < 0.05), Cz → Fz (F(1,22) = 15.18, P < 0.01) in the depressed subjects relative to the normal ones. Weaker directed interactions of Fz → F6 (F(1,22) = 5.87, P < 0.05), F5 → Oz (F(1,22) = 4.40, P < 0.05) were observed in the depressed subjects. Significant interaction of Expression and Group was found in F6 → Fp1 (F(1,22) = 4.38, P < 0.05), F5 → F6 (F(1,22) = 4.66, P < 0.05), Cz → PO7 (F(1,22) = 7.23, P < 0.05), F5 → PO8 (F(1,22) = 4.96, P < 0.05), and Cz → Fz (F(1,22) = 5.99, P < 0.05). F5 → PO8 and F5 → F6 interdependencies were lower when detecting the positive face in depression as compared to that in the normal subjects, while F6 → Fp1, Cz → PO7 and Cz → Fz interdependencies were lower when detecting the negative one in depression.

To explore whether the alteration of the directed connectivity within the network was due to the changes of the local node, i.e.,
the electrode Fz, we further did the PDC analysis on the basis of 11 electrodes (excluding the electrode Fz). Our results showed a significant main effect of the factor Group on the directed interaction between the selected sites. Similar topographic patterns were observed in the alteration of directed connectivity in depression (Fig. 6). Both in the conditions without target and with target, enhanced occipito-parietal outputs were observed in depression as compared to those in the normal group. And the central outputs were significantly weaker in depression as compared to those in the normal group. After removing the electrode Fz, fewer weaker intra-frontal interactions were observed in the condition without target.

4. Discussion

Converging results of investigations in depression have shown various impairments of executive function such as attention, memory, executive control, affective processing and problem-solving (Clark et al., 2009; Levin et al., 2007; Phillips et al., 2003a). The present study was performed to examine the hypothesis that specific topographic patterns of altered cortical directed connectivity might play an important role in the impairments of attentional modulation in major depressive disorder. The behavioral responses and ERPs results showed cognitive deficits during attention modulation in depression. Furthermore, PDC results revealed the weaker central outputs and intra-frontal interactions, and the enhanced occipito-parietal outputs, which might contribute to the impaired effortful attention modulation in depression.

In the condition without target, previous converging evidence suggested that the response to trials on which all faces were neutral was a controlled, serial processing with the consumption of attentional resources (Hammar et al., 2003; Ito and Cacioppo, 2000; Suslow et al., 2004; Tang et al., 2009). Lower behavioral accuracy was observed in the depressed patients than that in the normal subjects. Apparent between-group differences were also observed on the N2 amplitude and latency in response to the neutral faces. The depressed group had reduced N2 amplitude and longer N2 latency as compared to the normal controls. Since anterior N2 amplitude was related to the orientation of visual attention and cognitive control (Folstein and Van Petten, 2008; Oddy and Barry, 2009; Vuilleumier and Pourtois, 2007), reduced anterior N2 amplitude in response to the neutral faces reflected the deficits in effortful attention modulation in depression (Mao et al., 2006; Oddy and Barry, 2009; Vuilleumier and Pourtois, 2007).

In the condition with positive/negative target, detecting the emotional face among neutral distractors was an automatic, parallel processing in the absence of consciousness (Hammar et al., 2003; Ito and Cacioppo, 2000; Suslow et al., 2001, 2004; Tang et al., 2009). Our previous investigations further demonstrated that the process of detecting positive faces was different from that of detecting negative ones. The former process was not fully automatic, but partially controlled and serial (Tang et al., 2009). Consist with this view, the behavioral RT when detecting the positive face was significantly longer than that when detecting the negative one in both groups. The evoked N2 amplitude when detecting the positive face was attenuated in depression, whereas the evoked N2 amplitude when detecting the negative face shown no significant between-group effect. The possible reason might be the absence of consciousness and the negligible consumption of attentional resources when detecting the
negative face (Ashley et al., 2004; Huang and Luo, 2006; Suslow et al., 2004; Williams et al., 2006, 2008). The results supported the impairment occurred in the effortless attentional process, instead of the automatic process, in the depressed subjects (Suslow et al., 2004).

The further PDC analysis within the N2 time-window uncovered the altered cortical directed connectivity within the network during attentional modulation in depression. The obtained PDC values reflected several topographical patterns of the directed interdependencies between electrode pairs in depression as compared to normal subjects in the condition without target. (1) Larger PDC values derived from the parieto-occipital electrodes towards the frontal electrodes appeared in depression. The enhanced parieto-occipital information output in depressed patients reflected an active visual perceptual processing of faces. (2) Intra-central and intra-frontal PDC values appeared to be lower in depression, which suggested a relatively weak connectivity and information transfer within these areas in depression. The central cortex was associated with the category of the stimuli and processing demands (Polich, 2007). The hypoactivity over this region might influence decision making and the subsequent behavioral responses in depression (Phillips et al., 2003a, 2003b). The frontal cortex was related to the interaction of both recognition and spatial deployment of attention (Bremner et al., 2000; Itti and Koch, 2001). PFC maintained the representation of goals and the means to achieve them (Davidson et al., 2002). The observed intra-frontal hypoactivity fitted well with the abnormalities in executive function in depression (Leppanen, 2006; Levin et al., 2007).

(3) Larger PDC values of F6 → PO8 and F6 → Pz within the N2 time-window revealed enhanced directed interaction between this electrode pair in depression. The stronger right-frontal information output showed a modulation of the attention by the frontal cortex towards the occipital one (Carretié et al., 2001). The attentional regulation might try to improve the perceptual processing in depressed patients. Therefore, the tempo-spatial patterns of altered directed interactions within the cortical network showed that more resources were engaged in visual perception of stimulus, while fewer resources were allocated for the sequential recognition and estimation of stimulus in depression. The weaker output from the frontal and central cortex contributed to the diminished capacity of cognitive control in effortful processes in depression to a certain degree (Bremner et al., 2000; Itti and Koch, 2001; Phillips et al., 2003a, 2003b; Polich, 2007).

To explore whether the alteration of directed connectivity within the network in depression was derived from the local changes or not, such as from the activity at Fz where we found the attenuated N2 activity, further PDC analysis was performed by removing Fz from the network. Similar topographic patterns of the alteration of directed connectivity, the weaker central outputs and the enhanced occipito-parietal outputs, were observed in patients. These results reflected global changes of directed interdependencies within the network instead of local changes in depression, which consistent with findings in neuroimaging investigations that a circuit consisting of different cortical and sub-cortical structures was related to the depression (Davidson, 1998; Davidson et al., 2002; Phillips et al., 2003b, a; Marchand et al., 2007). Meanwhile, fewer intra-frontal interactions were discovered in the condition without target with the analysis by removing Fz than those by including Fz. We therefore inferred that the local changes around Fz also played an important role in effortful attentional modulation in depression (Leppanen, 2006; Levin et al., 2007).

The present PDC results might supplement the evidence for the frontal hemisphere asymmetry in depression, which has been taken as a trait marker for depression according to the previous investigations (Bruder et al., 1997; Carvalho et al., 2011; Davidson, 1998; Gotlib, 1998; Harmon-Jones et al., 2010; Henriques and Davidson, 1990; Henriques and Davidson, 1991; Jacobs and Snyder, 1996; Mathersul et al., 2008). Larger PDC values in the N2 time-window appeared in the couplings of the right frontal electrodes and the occipital and central electrodes in depression, i.e., F6 → Pz, F6 → PO8, and PO8 → F6 (Fig. 5(a)). Results reflected an enhanced information input and output over the right frontal region. On the other hand, the left-frontal electrodes input, i.e., Fp2 → Fp1, Fz → Fp1, Fz → F5, was weaker in depression as compared to that in the normal subjects (Fig. 5(b)). These results reflected the left-frontal hypoactivity and the right-frontal hyperactivity. The hypoactivity in the left-frontal lobe, which was biased towards positive-valence stimuli, might be the reason that depressed patients were less sensitive to the positive stimuli than normal controls (Debener et al., 2000). The hyperactivity in the right-frontal lobe, which played a role in withdrawal processes, might contribute to the negative bias in depression (Davidson, 1998; Davidson et al., 2002).

The interaction of factors Group and Expression was also found on the directed coherence in the network. An attentional bias towards the negative stimuli has been extensively reported by investigations on emotion processing in depression (Henriques and Davidson, 1990; Phillips et al., 2003a, 2003b). In this study, the PDC values of F5 → F6, F5 → PO8 in the N2 time-window were significantly lower only when detecting the positive face in depression relative to the normal group. These results showed an attenuated information output of the left-frontal region. Depressed subjects might have mild deficits in attentional modulation in the left-frontal regions during detecting the positive face. Nevertheless, no significant attentional deficits appeared in the frontal cortex when detecting the negative face, which was less controlled and absence of consciousness (Ito...
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Conflict of interest

None.

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