Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 1891–1900

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

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

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ARTICLE INFO

Article history:
Received 23 April 2011
Received in revised form 28 July 2011
Accepted 9 August 2011
Available online 23 August 2011

Keywords:
Attention modulation
Cortical directed connectivity
Depression
Event-related brain potentials
Partial directed coherence

ABSTRACT

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 ($F(1,22)=5.51$, $P<0.05$) 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 face 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.

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 (Carretié 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

Abbreviations: ACC, anterior cingulate cortex; CCMD-3, the third editions of the Chinese diagnostic manual; Dep, depressed patients; dPFC, dorsal prefrontal cortex; EEG, electroencephalogram; ERPs, event-related brain potentials; HAMD, Hamilton Rating Scale for Depression; ICD-10, the tenth revision of International Classification of Diseases; ISI, inter-stimulus interval; Nor, normal controls; PDC, partial directed coherence; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale.

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doi:10.1016/j.pnpbp.2011.08.006

evoked 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 temporo-spatial patterns of the cortical directed connectivity with high temporal resolution in depression.

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 some node which ceased to fire independently or to a collective phenomenon, twice PDC analysis were performed basing on two different MVAR modeling. The first modeling was established using all nodes within the network while the second modeling was based on nodes excluding the node where N2 activity has significant changes in depression. This step should help to understand the pathophysiological dysfunction of attention modulation in depression.

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