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Research paper

Prefrontal activation during a working memory task differs between patients with unipolar and bipolar depression: A preliminary exploratory study

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ABSTRACT

Background: To identify bipolar disorder during the initial stages of a depressive episode has always been a great clinical challenge. Patterns of functional brain activity may underlie the differences in the neural mechanisms of bipolar depression (BD) and unipolar depression (UD). This study aimed to investigate the differences in neural activity between BD and UD patients during executive task.

Methods: We performed a 52-channel near-infrared spectroscopy (NIRS) scan in 39 patients with BD, 35 patients with UD, and 36 healthy controls (HCs). The relative concentration changes in oxygenated hemoglobin ([oxy-Hb]) and deoxygenated hemoglobin ([deoxy-Hb]) during a 1-back working memory task were measured for each channel. Clinical characteristics including current mood were evaluated within one week prior to NIRS examination.

Results: Compared to HCs, BD (CH34: $Z = -2.354$, $P = 0.019$) and UD patients (CH18: $Z = -2.358$, $P = 0.018$; CH30: $Z = -2.174$, $P = 0.030$; CH34: $Z = -1.990$, $P = 0.047$) showed reduced activation of [oxy-Hb] in the inferior prefrontal region. Compared to patients with UD, patients with BD showed less decreased [oxy-Hb] changes in the left frontopolar cortex (FPC) (CH18: $Z = -2.366$, $P = 0.018$), left pars opercularis and pars triangularis (POPE/PTRI) regions (Broca's area) (CH30: $Z = -2.333$, $P = 0.020$). No correlation existed between clinical characteristics and NIRS measurements.

Limitations: The effect of medication could not be excluded, and behavioral data was not systematically collected.

Conclusion: The results from this preliminary exploratory study suggest distinct prefrontal activation patterns underlie BD and UD, especially in the left frontopolar region and Broca's area. The NIRS-based prefrontal activation measurement may serve as a potential marker to aid in differentiating bipolar from unipolar depression.

1. Introduction

The early and accurate diagnosis of mood disorders is critical for subsequent treatment and prognosis. However, the similar psychopathologies of depressive episodes pose a great challenge for the differentiation of bipolar from unipolar depression (or major depressive disorder) during the depressed phase (Judd et al., 2003, 2002; Zimmermann et al., 2009). Bipolar patients with depressive episodes are often misdiagnosed and initially treated as unipolar (Akiskal et al., 1995; Goldberg et al., 2001), which leads to the delay of appropriate

Abbreviations: BD, Bipolar depression; UD, Unipolar depression; HCs, Healthy controls; NIRS, Near-infrared spectroscopy; [oxy-Hb], Oxygenated hemoglobin; [deoxy-Hb], Deoxygenated hemoglobin; CH, Channel; FPC, Frontopolar cortex; POPE/PTRI, Pars opercularis and Pars triangularis

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treatment, poorer outcome, and higher health care costs (Dudek et al., 2013; Hirschfeld et al., 2003a, 2003b; Perlis, 2005). The key clinical question is how to identify bipolar disorder among depressed individuals, which will subsequently improve the outcome for patients with bipolar disorder.

Several strategies including clinical, neurocognitive and neuroimaging methods have been applied to make a differential diagnosis during a depressive episode. While clinical assessments such as rating scales and questionnaires might identify unrecognized subthreshold hypomanic symptoms, they are unable to provide a distinction between bipolar and unipolar depression at the first depressive episode (de Almeida and Phillips, 2013). Previous neurocognitive work so far has demonstrated inconsistent findings. Although most studies (Borkowska and Rybakowski, 2001; Gruber et al., 2007; Maalouf et al., 2010) reported poorer cognitive function in bipolar depression (BD), others (Daniel et al., 2013; Godard et al., 2012; Scott et al., 2013) indicated an unspecific deficiency that did not allow differentiating between BD and recurrent unipolar depression (UD). Our research team observed negative results as well, finding quite similar patterns of cognitive deficiency exist in BD and UD (Zhu et al., 2013). Brain imaging has also been used to help improve the understanding of the pathophysiological processes involved in mood disorders. Different patterns of brain functional activities have been found in bipolar versus unipolar individuals during resting-state (Liang et al., 2013) or task-based (Almeida et al., 2010; Cerullo et al., 2014; Chase et al., 2013; Diler et al., 2013) functional magnetic resonance imaging (fMRI) studies. However, poor accessibility and the high cost of fMRI testing limit its routine clinical use. Moreover, disadvantages such as restraint position, noise and the long duration of examination are especially intolerable for psychiatric patients. Functional near-infrared spectroscopy (fNIRS) is a recently developed, functional neuroimaging method allowing noninvasive detection of superficial brain activity by measuring the absorption of near-infrared light (Boas et al., 2004; Strangman et al., 2002). NIRS enables real-time monitoring of changes in the concentration of oxygenated hemoglobin ([oxy-Hb]) and deoxygenated hemoglobin ([deoxy-Hb]) in the micro-blood vessels of surface brain tissue , which are indicators of regional cortical activity (Hoshi et al., 2001; Obrig and Villringer, 2003; Strangman et al., 2002). Additionally, NIRS-Hb signals reflect the regional cerebral blood flow (rCBF) changes (Hock et al., 1997; Ohmae et al., 2006; Villringer et al., 1997) and are also comparable to the blood-oxygenation-level-dependent (BOLD) signals in gray matter (Sato et al., 2013). Because its performance is convenient and economical, NIRS could serve as a bedside technique and is well tolerated by psychiatric patients.

A growing number of studies have used NIRS with an executive function task to investigate brain functional activity in unipolar (Koseki et al., 2013; Noda et al., 2012; Pu et al., 2012b, 2011) or bipolar individuals (Kameyama et al., 2006; Matsuo et al., 2007; Nishimura et al., 2015a), but only a few (Matsubara et al., 2014; Ohtani et al., 2015; Schecklmann et al., 2011; Takei et al., 2014) have compared the difference in brain activation patterns between the two disorders. Working memory (WM) is one process of executive function that is impaired by both unipolar and bipolar depression (Cremaschi et al., 2013; Harvey et al., 2004; Rose and Ebmeier, 2006), and it refers to the system or systems that are assumed to be necessary to keep things in mind while performing complex tasks (Baddeley, 2010). A quantitative meta-analysis (Owen et al., 2005) suggested that the prefrontal cortex and frontopolar regions were robustly activated during n-back WM paradigm variants. To our knowledge, no NIRS study has applied the n-back task to investigate brain activity in unipolar and bipolar individuals. The only NIRS study (Schecklmann et al., 2011) that has been conducted showed unspecific deficits in BD and UD using a visual WM task, and indicated that this paradigm was probably too difficult. Our previous work (Zhu et al., 2013) also demonstrated similar WM performance with no significant difference in BD and UD. Thus, we performed the present study to examine whether there could be some differences in regional functional activity between BD and UD, while no difference exists in WM behavioral performance.

We hypothesized that patients with BD exhibited significantly decreased prefrontal activation compared to healthy controls, and a less deactivation compared to UD in response to the WM task. The aim of the present study was to test our hypothesis and examine whether prefrontal activation patterns can distinguish BD from UD. Furthermore, we will discuss the association between prefrontal activation and depression severity.

2. Materials and methods

Written informed consent was obtained from all participants after providing comprehensive information about the study. The study procedures were approved by the Research Ethics Committee of Peking University Sixth Hospital (Beijing, China) and were in accordance with the Helsinki Declaration as revised 1989. Each individual in the study was compensated for their time and participation with a 50-yuan gift.

2.1. Subjects

Thirty-nine patients with bipolar depression (BD) and thirty-five with recurrent unipolar depression (UD) were recruited from inpatient units of Peking University Sixth Hospital between October 2013 and May 2014. All research participants aged between 18 and 60 years and were right-handed. With the Mini International Neuropsychiatric Interview (M.I.N.I., Chinese version; Si et al., 2009), diagnosis of UD and BD with a current major depressive episode (296.5X, 296.89 or 296.3X) was made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th. ed. (DSM-IV-TR) (APA, 2000). All subjects scored $>=14$ on the 17-item Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1967). Since bipolar depression is frequently misdiagnosed as unipolar depression during the initial stages of a depressive episode (Hirschfeld et al., 2003a, 2003b), in the present study, the illness duration of UD should be no less than five years to maintain the relative diagnostic stability (Morselli and Elgie, 2003). In addition, thirty-six healthy controls (HCs) participated, having no history of major psychiatric or neurological illness and no prescription of psychotropic medication.

In order to decrease the heterogeneity of a depressive phase, those who manifest subthreshold bipolarity (score of Young Mania Rating Scale >5) were excluded (Angst et al., 2003; YMRS, Young et al., 1978; Zimmermann et al., 2009) in order to decrease the heterogeneity within a diagnostic group. The exclusion criteria also included: having current and previous substance dependence or abuse, having a history of electroconvulsive therapy within 6 months, having any physical or mental illness that may affect neurocognitive assessment or NIRS examination, and being unable to perform the cognitive task.

To obtain detailed information on psychiatric symptoms, the participants were interviewed by two experienced psychiatrists (Y. Zhu and W. Quan) using MINI. Affective symptom severities were evaluated by well-trained psychiatrists using the Chinese version of the HAMD-17, YMRS and clinical global impression-bipolar version (CGI-BP; Spearing et al., 1997) within one week prior to each NIRS examination.

2.2. Activation task

We used a 1-back version of the n-back working memory (WM) task to activate brain regions, which was aimed at enabling most patients to manage the task even with the cognitive impairment and decreased self-confidence that is associated with depression. The paradigm consisted of a 30 s pre-task baseline period, a 70 s task period and a 50 s post-task baseline period (Pu et al., 2012b, 2011). During the pre-task and post-task baseline condition, participants were instructed to fix their gaze on a cross at the center of a screen. The activation condition comprised 29 stimuli (14 targets, stimulus duration 0.5 s, stimulus