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Research paper

Biochemical abnormalities in basal ganglia and executive dysfunction in acute- and euthymic-episode patients with bipolar disorder: A proton magnetic resonance spectroscopy study

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ABSTRACT

Background: Recent studies found abnormal biochemical metabolism and executive cognitive deficits in acute bipolar disorder (BD). However, the evidence concerning in euthymic BD is limited. Thus, a comparison between acute and euthymic BD is conductive to better understanding the association between cognition and the outcome of neuroimaging. This study sought to investigate the relationship between the executive function and the biochemical metabolism in acute- and euthymic-episode BD patients and delineate the prominent endophenotype of BD.

Methods: Three groups of participants were recruited in this study: 30 BD patients with an acute depressive episode, 22 euthymic BD patients, and 31 healthy controls. All participants were interviewed using the Structured Clinical Interview for DSM-IV, and underwent two-dimensional multivoxel proton magnetic resonance spectroscopy (1H-MRS) to obtain the bilateral metabolite levels in the lenticular nucleus of basal ganglia (BG). The ratios of N-acetylaspartate (NAA)/creatine (Cr) and Choline-containing compounds (Cho) /Cr ratios were calculated. Executive function was assessed by using the Wisconsin Card Sorting Test (WCST) and Trail Making Test, Part-B(TMT-B).

Results: The comparison of biochemical changes showed that the NAA/Cr ratios in bilateral lenticular nucleus in both acute and euthymic BD patients was significantly lower than that in healthy controls at a confidence level of $p < 0.05$. In the comparison of executive function, both acute and euthymic BD patients showed significantly decreased numbers of categories completed, and increased numbers of total errors, perseverative and non-perseverative errors, and TMT-B uptake compared to the healthy controls at a confidence level of $p < 0.05$. There were no significant differences between the acute BD and euthymic BD groups in the biochemical metabolite ratios and executive function. We found that the NAA/Cr ratio in the left in BG in the acute -episode BD patients was positively correlated with the number of categories completed, whereas it was negatively correlated with the total errors and TMT-B uptake. There was no correlation between the NAA/Cr and Cho/Cr ratios in the bilateral BG and the scores of SWCT and TMT-B in euthymic-episode BD patients.

Limitation: The sample size was relatively small and not all the euthymic-episode patients are the ones with an acute episode.

Conclusions: Our findings suggest that biochemical abnormalities in the lenticular nucleus and the executive dysfunction may occur early in the course of BD, and persist during remission, and are the most likely markers of endophenotypes of BD. The dysfunction of the neuronal function in the lenticular nucleus may be correlated with the cold dysfunction in patients with acute BD.

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1. Introduction

Bipolar disorder (BD) is characterized by episodic pathological mood alterations that can be manic, depressive, or mixed (Nenadic et al., 2015). The depressive phase is the most prevalent component of BD. Patients with BD experiencing a depressive episode have a high rate of morbidity and risk of suicide, which are highly heritable and difficult to treat. Moreover, depressed BD patients are often misdiagnosed with unipolar depressive disorder, which leads to mistreatment and poor clinical outcomes for many BD patients. However, the precise underlying pathophysiology of BD remains unclear.

Considerable interest has been focused on the determination of the possible pathogenesis of BD by neuroimaging studies. Several studies in patients with BD (Arnone et al., 2009; Hallahan et al., 2011; Selvaraj et al., 2012) using magnetic resonance imaging (MRI) have identified structural abnormalities in regions, including amygdala, the subgenual prefrontal cortex, the thalamus, and the basal ganglia(BG) (Emsell et al., 2013). The results of a previous examination show that basal ganglia regional is affected in patients with bipolar disorder which is known to be involved in learning and memory, contextual fear conditioning, and neuroendocrine regulation. Some evidence further suggested that subtle neuroanatomical abnormalities are present in the BG in depressed BD patients (Strakowski et al., 2005). Meanwhile, putamen is an important part of the BG. In volumetric studies, individuals with BD had a larger striatum and right putamen or bilateral pallidum than healthy controls (Arnone et al., 2009; Bonelli et al., 2006; Hallahan et al., 2011). *In vivo* tissue biochemistry proton magnetic resonance spectroscopy (^{1}H-MRS) is a unique non-invasive and non-radioactive approach capable of measuring the levels of important metabolites in specific brain regions. Its results can provied more detailed information about the neuronal abnormalities at the cellular and metabolic levels than relatively gross volumetric estimates. Previous investigations have found morphometrical changes and abnormalities in the BG in patients with acute BD, including decreased N-acetylaspartate levels (Kraguljac et al., 2012), In contrast, increased NAA levels in the bilateral caudate nucleus and the left lentiform nucleus (Port et al., 2008), as well as higher choline-containing compounds (Cho)/Creatine (Cr) ratio were established in the BG of euthymic BD patients (Yildiz-Yesiloglu and Ankerst, 2006). A decrease in the activation of the right putamen in remitted BD patients was also reported (Foland-Ross et al., 2012). All above findings suggest that metabolic alterations in the BG may be related to the neuropathology of BD. However, most prominently evidence in the neurometabolites may partly focus on the acute-episode BD and lack of the consistency in patients with BD in euthymic-episode. Additionally, a comparison of the neurometabolites in the putamen between in acute- and euthymic-episode BD patients has not yet been conducted.

Cognitive deficits have been recognized as a core feature of the clinical expression and have also been suggested as an important source of psychosocial and functional burden of BD (Lopes and Fernandes, 2012). In both acute and euthymic phases, the domains affected include verbal learning, executive function, working memory, attention, and psychomotor functioning (Kurtz and Gerraty, 2009; Martinez-Aran et al., 2004b), Recent reports have documented that approximately 60% of the BD patients in remission fail to regain full state (Cardoso et al., 2015), which may be partly attributed to cognitive impairment (Robinson et al., 2006). These neuropsychological deficits contribute to an impairment of functional recovery. In fact, the impairment of the executive function plays an important role in cognitive dysfunction in BD and may as an independent predictor of functional recovery (Burdick et al., 2010; Robinson et al., 2006). Thus, research findings on the executive function in euthymic- episode patients with BD have been consistently reported. However, few studies that compare the executive function between acute-episode and euthymic-episode BD patients. Thus, further comparative studies are needed. Therefore, in this present study, the executive function in acute-episode and euthymic-episode BD patients was observed by Wisconsin Card Sort Test and the Trail-Making Test, part-B. On the other hand, the pathological mechanism of BDD's cognitive impairment is still unknow. Previous neuroimaging studies found the presence of an abnormal brain structure and aberrant biochemical metabolism in BD that may significantly associated with cognitive dysfunction (Zhong et al., 2014). As is well known, BG, plays an important role in the emotional and cognitive functions, widely involved in emotion, learning, memory, thought, executive cognitive functions, speech and other advanced nerve function activities. Nevertheless, the relationship between biochemical changes and the executive function in acute- and euthymic-episode BD patients is still unclear, although in a few studies such abnormalities were observed to be accompanied by cognitive deficits in BD. Therefore, more specific neuropsychological tests and functional imaging studies are needed.

In this study, a semi-quantitative analysis was performed to quantify the concentrations of NAA, Cho and Cr in the bilateral lenticular nucleus in acute- and euthymic-episode patients with BD. The executive function was assessed by using the WCST and TMT-B task. By comparing the biochemical metabolism ratios and executive function scores among acute-episode BD patients, euthymic-episode BD patients and healthy controls, we aimed to explore the changes of neurometabolites levels and the outcome of executive function in acute- and euthymic-episode BD patients. Moreover, we computed the correlations between the biochemical metabolism ratios and the executive function scores and hypothesized that the abnormalities in the levels of biochemical parameters, such as the ratios of NAA/Cr and Cho/Cr, and bad performance in WCST and TMT-B task can be found in both acute- and euthymic-episode BD patients. Meanwhile, these deficits of executive function may correlate with the biochemical metabolism of the lenticular nucleus.

2. Methods

2.1. Participants

A total of 30 drug-naïve acute depressive episode BD patients, 22 euthymic episode BD patients whose clinical symptoms had disappeared at least six months were recruited at the Department of the psychiatry in the First Affiliated Hospital of Jinan University, Guangzhou, China. The age of all participants was restricted to 18–45 years to diminish the interference of aging and vascular disease.

All patients diagnosed by two experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID). Clinical state was assessed by the 24-item Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS). All scales were finished in 2 days after the MRI.

We selected acute depressed patients with BD had a 24-item HDRS total score > 21, and a YMRS total score < 7. Exclusion criteria included the presence of (1) other Axis I psychiatric disorders and symptoms, (2) a history of the use of any psychotropic medication, psychotherapy or electroconvulsive therapy, (3) a history of neurological or organic brain disorder, (4) alcohol/substance abuse, (5) any physical illness demonstrated by personal history or clinical or laboratory examinations, pregnancy and postpartum depression.

Euthymic BD patients were also selected whose clinical symptoms had disappeared at least six months, with a 24-item HDRS total score < 8, and a YMRS total score < 7.

31 age- and gender-matched healthy controls (fifteen males) were studied. Healthy controls were carefully screened through a diagnostic interview, the Structured Clinical Interview for DSM-IV Nonpatient Edition (SCID-NP), to rule out the presence of current or past history of substance abuse/dependence or any psychiatric illness in self or in first-degree relatives.

All participants were right-handed and were submitted to MRI scanning within 48 h of initial contact. The study was approved by the Ethics Committee of First Affiliated Hospital of Jinan University, China.