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Research report

Combined analyses of gray matter voxel-based morphometry and white matter tract-based spatial statistics in pediatric bipolar mania

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ABSTRACT

Background: Ample evidence has suggested the presence of gray matter (GM) and white matter (WM) abnormalities in bipolar disorder (BD) patients, including pediatric bipolar disorder (PBD). However, little research has been done in PBD patients that carefully classify the mood states. The aim of the present study is to investigate the brain structural changes in PBD-mania children and adolescents.
Methods: Eighteen children and adolescents with bipolar mania (male/female, 6/12) aged 10–18 years old and 18 age- and sex-matched healthy controls were included in the present study. The 3D T1-weighted magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) data were obtained on a Siemens 3.0 T scanner. Voxel-based morphometry (VBM) analysis and tract-based spatial statistics (TBSS) analysis were conducted to compare the gray matter volume and white matter fractional anisotropy (FA) value between patients and controls. Correlations of the MRI data of each survived area with clinical characteristics in PBD patients were further analyzed.
Results: As compared with the control group, PBD-mania children showed decreased gray matter volume in the left hippocampus. Meanwhile, significant lower FA value was detected in the right anterior cingulate (AC) in the patient group. No region of increased gray matter volume or FA value was observed in PBD-mania. The hippocampal volume was negatively associated with the Young Mania Rating Scale (YMRS) score when controlling for clinical characteristics in PBD-mania patients, however, there was no significant correlation of FA value of the survived area with illness duration, the onset age, number of episodes, or the YMRS score in PBD-mania patients.
Limitation: The present outcomes require replication in larger samples and verification in medication free subjects.
Conclusions: Our findings highlighted that extensive brain structural lesions (including GM and WM) were existed in PBD-mania. The widespread occurrence of structural abnormalities mainly located in the anterior limbic network (ALN) which suggested that this network might contribute to emotional and cognitive dysregulations in PBD.

1. Introduction

Pediatric bipolar disorder (PBD), which is one of the most frequent mental problems in childhood or early adolescence, has drawn more and more attentions (Washburn et al., 2011). A survey abroad reported that nearly 1% of adolescents met the diagnosis of bipolar disorder (BD) while this rate would go up to 6% if children with sub-symptoms were included (Goldstein and Birmaher, 2012). A recent meta-analysis showed that about 2% of community children and adolescents received the diagnosis of bipolar spectrum disorder (Van Meter et al., 2011). As compared with adult BD, PBD is characterized by more atypical symptoms and comorbidities, longer disease durations, harder to complete remission and more recurrences (Goldstein and Birmaher, 2012; Perlis et al., 2009). All these may lead patients to more severe functional impairments and poorer prognosis. During the last two decades, plenty of studies have tried to elucidate the pathophysiology underlying PBD, however, it remains unclear. Neuroimaging studies have provided approaches to discover minor brain structural and functional changes and consequently being used to investigate the pathophysiology of mental diseases. Of

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note, magnetic resonance imaging (MRI) studies have documented a range of morphometric differences in widespread brain regions as well in PBD (Adleman et al., 2004; Frazier et al., 2005a; Mahon et al., 2010).

The pathophysiology of PBD was always elucidated by the structural changes in gray matter (GM). Accumulating evidence suggested that diffuse GM deficits could be detected in PBD patients, and most studies indicated that a pattern of volumetric changes in the anterior limbic network (ALN), including prefrontal regions, subcortical structures (such as thalamus, striatum, amygdala, and hippocampal complex), and the midline cerebellum, might be crucial to the origin of PBD (Adler et al., 2006b). However, results were always inconsistent and this dissonance could be due to heterogeneous of sample characteristics, e.g., gender, illness duration, severity of symptoms or episode state (depression/mania/remission) (Foland-Ross et al., 2012; Lu et al., 2012; Najt et al., 2007). In a recent meta-analysis of the volumetric MRI studies for BD, the whole brain and prefrontal lobe volume reductions and increased volume in the globus pallidus and lateral ventricles were corroborated (Arnone et al., 2009). Some specific regions of the PFC were also reported to show decreased GM volume, such as the left dorsolateral prefrontal cortex (DLPFC) (Dickstein et al., 2005) and the orbitofrontal cortex (OFC) (Najt et al., 2007). With respect to amygdala, decreased volume in PBD was the most repeated finding in previous research (Chang et al., 2005; Frazier et al., 2005a). A meta-analysis documented that the bilateral amygdala volume reductions were found in the PBD patients, however this trend was less obvious in adult BD patients (Usher et al., 2010). In terms of hippocampal volume, findings were sometimes discordant. Most MRI studies for PBD reported a trend toward a reduction in hippocampal volume (Bearden et al., 2008a; Frazier et al., 2005a), while no difference of hippocampal volume was also observed when comparing with healthy children (Chang et al., 2005). Studies on alterations of thalamus volume also reflected heterogeneous results, showing normal (Chang et al., 2005; Karchemskiy et al., 2011; Scherk et al., 2008), or enlarged volume (Adler et al., 2007; Chen et al., 2012; Wilke et al., 2004) in this region.

Emerging evidence suggests that disruption of the white matter (WM) integrity may also play a vital role in the development of BD. Diffusion tensor imaging (DTI), an extension of MRI which measures the anisotropic diffusion of water molecules in brain tissues in vivo, allows us to detect the microstructural changes in WM before macrostructural changes are apparent. In DTI studies, the most commonly used parameter is fractional anisotropy (FA) value, which is considered to be a marker of the white matter integrity by measuring the tendency of the water molecules diffusion parallel to the main fiber orientation compared with all other directions. FA value ranges from 0 (standing for completely isotropic diffusion) to 1 (standing for completely anisotropic diffusion). Decreased FA value was often associated with demyelization, edema, gliosis or inflammation in tissues (Assaf and Pasternak, 2008; Xekardaki et al., 2011). Comparing to the conventional T1-weighted MRI, the DTI can better reflect the integrity of WM. To date, most studies have focused on the loss of WM network connectivity in BD patients, further placing the emphasis on the networks connecting the frontal regions (especially the prefrontal cortex) with other non-frontal lobes and subcortical regions (the Limbic System, LS). Therefore alterations of WM integrity in BD patients were frequently reported in frontal regions, especially the prefrontal region (Adler et al., 2006a; Frazier et al., 2007; Liu et al., 2010), and non-frontal lobes, including inferior and middle temporal regions, middle occipital lobe (Bruno et al., 2008), bilateral parietal lobes and occipital corona radiata (Barnea-Goraly et al., 2009) in prior studies. Anterior cingulate (AC), the main WM pathway connecting the LS to the frontal region, also has been reported to be involved in the pathogenesis of BD (Frazier et al., 2007; Wang et al., 2008a). Moreover, the corpus callosum, which plays a key role in the interhemispheric communication pathway, has also showed WM abnormalities not only in adult patients but also in pediatric patients (Saxena et al., 2012; Wang et al., 2008b; Yurgelun-Todd et al., 2007).

Although generous studies have focused on brain changes in BD patients, most studies have investigated adult BD, relatively less research on PBD has been published and the results have been hard to replicate and even contradictory (Wegbreit and Pavuluri, 2012). Moreover, there has been a vital limitation that most previous studies recruited patients with BD as a whole without considering the effect of the different episode states (mania, depression, or remission) on brain structural changes(Chepenik et al., 2012; Wang et al., 2008b). One thing to be noted is that limited studies which carefully classify the episode states of BD have provided evidence to prove that different mood episodes may cause different microstructural abnormalities of brain (Foland-Ross et al., 2012; Nery et al., 2009; Zanetti et al., 2009). To more clearly understand the brain structural changes of PBD-mania patients, we present here a combined analysis of the GM and WM changes of the whole brain in PBD during mania episode. Based on the prior findings of the GM and WM changes in pediatric and adult BD, we hypothesized that children with BD would have unique structural abnormalities at the point of mania episode.

2. Method

2.1. Participants

Eighteen children and adolescents meeting DSM-IV diagnostic criteria for BD with current mania episode were recruited from the child and adolescent psychiatric clinic of the Second Xiangya Hospital of Central South University, Changsha, Hunan, PR China from January to July, 2012. Simultaneously, eighteen age- and gender-matched healthy controls (HC) were recruited through advertisements in public schools. The general inclusion criteria for all participants were as follows: (1) aged between 10 and 18 years, (2) right-handedness, (3) the Han ethnicity, and (4) could follow the instructions to keep still during the MRI scan. Exclusion criteria for all subjects included: (1) the presence of major sensorimotor handicaps, (2) full-scale intelligence quotient (IQ) < 80, (3) contraindications to MRI scan, including metallic implants, retractors or braces, and claustrophobia, (4) with other mental disorders, such as schizophrenia, anorexia or bulimia nervosa, and learning disabilities, (5) alcohol or drug dependence or abuse, (6) active medical or neurological disease, and (7) histories of electroconvulsive therapy (ECT). All subjects and at least one parent or legal guardian signed the assent and informed consent forms. The present study was approved by the ethic committee of the Second Xiangya Hospital of Central South University.

2.2. Procedure

2.2.1. Demographic and clinical assessment

All the participants and at least one of their parents underwent a diagnostic semi-structured interview using Schedule for Affective Disorders and Schizophrenia for School-aged Children-Present and Lifetime Versions (K-SADS-PL) (Kaufman et al., 1997). The diagnoses were made independently by two experienced psychiatrists (Su and Gao). The inter-rater reliability of the KSADS has been tested and yielded satisfactory agreement (kappa $= 0.85$). All the PBD patients belonged to the narrow phenotype BD which defined as at least one distinct manic or hypomanic episode with elevated or expansive mood. The demographic and clinical data was collected using a