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Increased prefrontal and parietal cortical thickness does not correlate with anhedonia in patients with untreated first-episode major depressive disorders

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ABSTRACT

Cerebral morphological abnormalities in major depressive disorder (MDD) may be modulated by antidepressant treatment and course of illness in chronic medicated patients. The present study examined cortical thickness in patients with untreated first-episode MDD to elucidate the early pathophysiology of this illness. Here, we examined cortical thickness in patients with first-episode MDD ($N=27$) and healthy controls ($N=27$) using an automated surface-based method (in FreeSurfer). By assessing the correlation between caudate volume and cortical thickness at each vertex on the cortical surface, a caudate–cortical network was obtained for each group. Subsequent analysis was performed to assess the effect of anhedonia by the Temporal Experience of Pleasure Scale. We observed increased cortical thickness at the right orbital frontal cortex and the left inferior parietal gyrus in MDD patients compared with healthy controls. Furthermore, morphometric correlational analysis using cortical thickness measurement revealed increased caudate–cortical connectivity in the bilateral superior parietal gyrus in MDD patients. All changes were not related to anhedonia. These preliminary findings may reflect disorder manifestation close to illness onset and may provide insight into the early neurobiology of MDD.

1. Introduction

The neurobiological basis of major depressive disorder (MDD) is not fully understood. Extensive previous structural neuroimaging studies had reported volumetric changes in chronic medicated MDD patients at the anterior cingulate cortex (ACC) (Arnone et al., 2012; Du et al., 2012), the thalamus (Kempton et al., 2011; Arnone et al., 2012), the dorsolateral prefrontal cortex (DLPFC) (Bora et al., 2012) and the orbitofrontal cortex (OFC) (Kempton et al., 2011; Arnone et al., 2012). However, these studies usually recruited depressive subjects taking antidepressant medication, and the findings might be confounded by medication effects. Studies with unmedicated patients could better elucidate brain abnormalities independent from these potential confounds.

Several methods are available to measure morphological changes in the brain, including the manual volumetric region-of-interest (ROI) method and the automated voxel-based morphometry (VBM) method (Ashburner and Friston, 2000; Ridgway et al., 2008). Novel methodology has been developed to measure cortical thickness by calculating the distance between gray and white matter surfaces across the entire cortical mantle (Fischl and Dale, 2000). The surface-based estimates serve as more accurate indicators of the integrity of cortical cytoarchitecture, which is sensitive to neurodevelopmental and pathological changes and could reflect the size, density and arrangement of cells (Sowell et al., 2004). However, few studies have examined cortical thickness in patients with MDD and the results are inconsistent. Some studies reported reduced cortical thickness in the prefrontal regions (including the DLPFC and the OFC), the cingulate cortex, the temporal cortex, the parahippocampal regions and the insula in chronic medicated patients such as patients with diabetes and

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major depression (Ajilore et al., 2010), non-remitters (Jarnum et al., 2011) and elderly depressed patients (Lim et al., 2012). In contrast, other studies found significantly increased cortical thickness in the temporal pole (van Eijndhoven et al., 2013), the caudal anterior and posterior cingulate cortex (van Eijndhoven et al., 2013), prefrontal and parietal cortex (Qiu et al., 2014) in first episode medication-free MDD patients and in depressed youths (Fallucca et al., 2011; Reynolds et al., 2014). Recently, two longitudinal studies reported thinner posterior cingulate cortex in depressed non-remitters than in remitters at baseline and at follow-up scan (Jarnum et al., 2011) and increased cortical thickness in the left inferior frontal in patients MDD (Papmeyer et al., 2014). These findings raise the possibility that the increased cortical thickness at illness onset might represent a compensatory response to factors related to inflammation, and cortical thinning might be related to illness chronicity and poor clinical outcome in depressed patients. However, the existing evidence in early-course medication-naïve MDD patients is limited.

To further delineate the regional cortical thickness deficits of the cortex and their relationship, this study used morphometric correlational analysis to measure cortical thickness across the brain to provide information about changes in brain circuitry. This measure has been proposed as an alternative means of studying structural connectivity patterns between cerebral regions (Bullmore et al., 1998; McAlonan et al., 2005). Morphometric correlational analysis relies on the assumption that positive correlations indicate connectivity, as axonally connected regions are believed to have common trophic and maturational influences (Bernhardt et al., 2008). Indeed, previous studies reported that such correlational analyses reveal a similar pattern with white matter connections from diffusion tensor imaging studies (Lerch et al., 2006; He et al., 2007; Bernhardt et al., 2008) and thus this approach allows to assessment localization of alterations of brain networks in a diseased population. To date, only one study has used correlational analysis to examine cortical thickness in MDD. A broad coherent effect across several areas of the association cortex was found in first-episode MDD patients (Qiu et al., 2014). However, their measurements were restricted to the cortical mantle and did not assess cortico–subcortical circuits. Striatal–cortical connectivity has been implicated in the pathophysiology of MDD (Kober et al., 2008; Price and Drevets, 2010). Previous studies have generally focused on characterizing disruptions of ventral ("affective") striatal–prefrontal circuitry supporting emotional processes. Recent evidence, however, has emerged to suggest the presence of primary functional connectivity alterations of dorsal "cognitive" cortico–striatal circuits in depressed populations (Furman et al., 2011; Gabbay et al., 2013; Kerestes et al., 2015). The caudate, the main subregion of the dorsal striatum, mediates reward behaviors and pleasurable experience by dopaminergic neural pathways in MDD (Koob, 1996; Haruno et al., 2004). Neuroimaging studies have reported reduced caudate volume (Harvey et al., 2007; Kim et al., 2008; Pizzagalli et al., 2009), diminished response at the bilateral caudate during reward-related tasks (Pizzagalli et al., 2009; Smoski et al., 2009), as well as increased functional connectivity of the caudate with the cortex in MDD patients (Furman et al., 2011; Zhang et al., 2011; Liu et al., 2014). In our previous work, we also found that weaker caudate nucleus responses are associated with cost-benefit decision-making dysfunction in first-episode MDD patients (Yang et al.,in press). It is possible that the structural deficit of the caudate may be related to clinical symptoms such as anhedonia observed in MDD.

In the present study, we investigated cortical thickness, subcortical volumes and caudate–cortical correlations in untreated first-episode MDD patients to examine the brain abnormalities at the early stage of the illness. First, we compared whole brain morphometric measures including cortical thickness and volume of subcortical structures between MDD patients and healthy controls. Then, we took the caudate as a seed region to evaluate patterns of anatomical correlation between caudate volume and cortical thickness. Finally, we investigated the association between anhedonia and brain abnormalities. Based on the previous studies of prefrontal dysfunction in patients with MDD (Liu et al., 2014), we hypothesized that patients with first episode MDD would exhibit increased cortical thickness in the orbitofrontal cortex compared with healthy controls and these alterations are related to anhedonia as assessed by the Temporal Experience of Pleasure Scale. Given that extensive reciprocal connections exist between the caudate and the cerebral cortex, we also hypothesized that MDD patients would exhibit disrupted caudate–cortical connectivity involving the prefrontal and parietal regions.

2. Materials and methods

2.1. Participants

Twenty-seven first-episode, drug-naïve patients with MDD were recruited from the outpatient clinic of the Second Xiangya Hospital in Central South University. All the patients met the diagnostic criteria for MDD according to the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (APA, 2000). Inclusion criteria were (1) DSM-IV first-episode MDD with no history of drug treatment; (2) currently experiencing an episode of depression with HAMD total score ≥ 20 on the 24-item Hamilton Rating Scale for Depression (HAMD) (Williams, 1988); and (3) a duration of illness of not more than 60 weeks. Exclusion criteria included (1) any history of psychotropic medication or psychotherapy; (2) current or history of MDD with psychotic symptoms; and (3) the presence of other Axis I diagnoses (including lifetime substance dependence and any substance use disorder in the past year), except anxiety disorders.

Twenty-seven healthy controls were also recruited from the community through advertisement. Healthy controls were free from any medical or neurological illness, and were screened using the Structured Clinical Interview for DSM-IV (SCID) (First, 2012) to ascertain the absence of psychiatric disorders. All participants were right-handed as assessed by the Annett Handedness Scale (Annett, 1970). The Central South University Institutional Review Board approved all procedures. A complete description of the study was provided to all participants, who gave written informed consent before the commencement of the study.

2.2. Clinical assessments

The Beck Depression Inventory (BDI) (Beck et al., 1961) is a 21-item scale that evaluates the severity of depression. The Chinese version used for the present study has been validated in Chinese samples (Wang et al., 1999). The internal consistency coefficient in the current sample was 0.83.

Anhedonia was assessed by the Chinese versions of the Snaith–Hamilton Pleasure Scale (SHAPS) (Liu et al., 2012) and the Temporal Experience of Pleasure Scale (TEPS) (Chan et al., 2010, 2012). The SHAPS was used to measure the state of anhedonia, whereas the TEPS was used to measure anticipatory and consummatory pleasure experience. The Chinese version of these scales has also been shown to possess adequate reliability in a previous study (Chan et al., 2012).

2.3. Data acquisition and preprocessing

Structural images from all participants were acquired on a 3-Tesla scanner (TrioTim, Siemens). The scanning parameters of