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VOXEL-BASED MORPHOMETRY STUDY OF THE INSULAR CORTEX IN FEMALE PATIENTS WITH CURRENT AND REMITTED DEPRESSION

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Abstract—*Objective:* Women are more prone to major depressive disorders (MDDs) and the incidence of MDD in women is almost twice that of men. Insular cortex abnormalities are a common finding in neuroanatomical studies of patients with MDD. However, it remains largely unclear whether female MDD patients at different clinical stages show morphologic changes in a specific subregion of the insular cortex. Additionally, it is not understood if any subregion changes can be used as a state or trait marker of MDD, and whether the diagnostic performance of any marker is sufficient to identify MDD.

***Methods:* Nineteen right-handed current MDD (cMDD) female patients and 19 remitted MDD (rMDD) patients, as well as 19 healthy controls matched for age and educational level, were recruited into the study. By means of voxel-based morphometry (VBM), we investigated gray matter volume abnormalities in insular subregions among the three groups and further conducted region-of-interest (ROI)-based receiver operating characteristic (ROC) analyses. The data from these investigations were correlated with clinical data to confirm the effectiveness of the identified changes in the subregions in differentiating the three groups.**

***Results:* Both the cMDD and rMDD groups showed significantly decreased gray matter volumes in the left dorsal anterior insula compared to the healthy controls. The cMDD groups also showed decreased gray matter volumes in the right dorsal anterior insula relative to healthy controls. Further ROC comparisons demonstrated that the left dorsal anterior insula can effectively differentiate cMDD and rMDD groups from healthy controls.**

***Conclusions:* Our findings suggest that the volume changes in the left dorsal anterior insular cortex may be a trait-related marker of vulnerability to MDD and that the right dorsal anterior insular cortex may involve pathological changes of MDD.** © **2014 Published by Elsevier Ltd. on behalf of IBRO.**

Key words: voxel-based morphometry, insular cortex, magnetic resonance imaging, major depressive disorder.

INTRODUCTION

Major depressive disorder (MDD) is the greatest disease burden for women worldwide with a lifetime prevalence twice as often as men (Murray et al., 1996; Leibenluft, 1999; Kessler, 2003; Kim et al., 2007; Nam et al., 2011). Even worse, the risk of suicide or serious suicide attempts are two to three times more common in female patients with MDD than in similar male patients (Stranieri and Carabetta, 2012). However, many researchers have paid less attention to women's mental health problems than men's (Artazcoz et al., 2007). These facts highlight the need for deeper insight into the neurobiological basis of MDD in order to perform appropriate medical interventions (Fagiolini and Kupfer, 2003) and help female patients lead symptom-free lives.

Numerous studies on structural and functional brain changes of MDD patients have reported alterations in the frontal-limbic system (Lorenzetti et al., 2009; Diener et al., 2012; Hamilton et al., 2012), which plays a critical role in emotion cognition and regulation. As one of the core regions in the limbic system, the insular cortex is highly relevant to the etiology of MDD. According to cytoarchitectural, functional, and fiber tract tracing studies, the insular cortex has three distinct subregions

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Abbreviations: AAL, automated anatomical labeling; ANOVA, analysis of variance; BA, Brodmann area; cMDD, current major depressive disorder; DARTEL, diffeomorphic anatomical registration through exponentiated Lie algebra; HAMD, Hamilton Depression Rating Scale; MDD, major depressive disorder; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; rMDD, remitted major depressive disorder; ROC, receiver operating characteristic; ROI, region-of-interest; VBM, voxel-based morphometry.

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(Mesulam and Mufson, 1982a,b; Mufson and Mesulam, 1982; Deen et al., 2011) and abnormalities within each of the insular subdivisions are thought to have related, but functionally distinct, roles in the neurobiological basis of depression (Savitz and Drevets, 2009a,b). The insula also exhibits extensive functional connectivity with the orbitofrontal cortex, anterior cingulate cortex and hippocampus (Cauda et al., 2011). Recent structural studies have reported gray matter loss in the bilateral posterior (Sprengelmeyer et al., 2011), bilateral anterior (Peng et al., 2011), and left posterior (Soriano-Mas et al., 2011) insular cortex in MDD patients. There have been two studies in which structural magnetic resonance imaging (MRI) was used to explore the gray matter changes in currently-depressed participants and currently-remitted participants with MDD (Takahashi et al., 2010; Salvadore et al., 2011). The results of the two studies were quite different. In the study by Takahashi et al. (2010), the left anterior insular cortex showed volume reductions in both the 29 current MDD (cMDD) patients (22 females, seven males) and in the 27 remitted MDD (rMDD) patients (18 females, nine males) using manually delineated analyses. However, Salvadore and colleagues demonstrated no gray matter volume changes in the bilateral insula in either the 58 cMDD patients (37 females, 21 males) or the 27 rMDD patients (21 females, six males) using voxel-based morphometry (VBM) analysis across the whole brain with a statistical threshold set to $p < 0.001$ (uncorrected). Instead, they found that illness duration was inversely correlated with gray matter density in the bilateral insula in the rMDD group. The differences between Takahashi et al. (2010) and Salvadore et al. (2011) may be caused by sex, age at onset of disease, the size of the subject sample, and data processing method. The above research on cMDD and rMDD patients remains unclear which kind of volume difference (increases or decreases) exists in which specific subregions of the insula for female cMDD and rMDD patients.

Clinical markers are usually useful in gaining a deeper insight into the neurobiological basis of MDD (Fagiolini and Kupfer, 2003). State markers of MDD, present only during the acute stage, may reflect pathophysiologic processes of the illness which may in turn act as treatment response markers to guide treatment choice (Maalouf et al., 2011). By contrast, trait markers of MDD, persistent during all stages, may describe vulnerability to long-term secondary effects of the illness, and consequently may be useless in predicting treatment response to the illness (Lorenzetti et al., 2010). It is still unclear whether morphological alterations of the insular cortex constitute a state characteristic of the disorder that is present only during the course of the illness, or a trait marker that underlies a neurobiological vulnerability to the illness that is present even during periods of wellness. Investigating remitted individuals with a history of MDD and those currently experiencing MDD who meet the criteria for MDD may be a particularly useful approach to shed light on this issue or to provide a necessary step toward identifying disease traits (Caetano et al., 2004; Lorenzetti et al., 2009).

The insular cortex is involved in a wide range of cognitive, motor, emotional and somatosensory activity (Craig, 2009; Cloutman et al., 2012), all of which are implicated in MDD and are mediated by the three subdivisions of the insula, which differ in their functional connectivities and anatomical features (Deen et al., 2011). The ventral anterior insula consists of agranular cells with indistinct laminar structure and links to the limbic regions, e.g. the hippocampus and amygdala. Functionally, the ventral anterior insula is believed to be involved in the processing of the emotional component of perceptions (e.g. hunger) (Critchley et al., 2002; Craig, 2003), and in the evaluation and assessment of emotional stimuli (e.g. positive (reward), negative (threat), self protection, or affiliation) (Kong et al., 2006; Lovero et al., 2009). The dorsal anterior insula is composed of dysgranular cells with incomplete laminar structure. Its borders on the ventral anterior insula and its interposition with the frontal operculum suggest that it may be critical for translating undifferentiated motivational states into specific associated actions and may be involved in appraisal and expression of negative emotion (Miller, 2000). The posterior insula encompasses the granular (and the adjacent part of the dysgranular) region (Wylie and Tregellas, 2010) and links to the premotor, sensorimotor, supplementary motor and middle posterior cingulate cortex (Etkin et al., 2011; Cauda et al., 2012). Functionally, the posterior insula is specialized for processing somatosensory stimuli with affective or motivational significance (Augustine, 1996; Craig, 2002, 2009), and interoceptive input from the body (Craig, 2011), parietal cortex and thalamic relay nuclei (Augustine, 1996; Craig, 2003). The subregional differences of the insula (functional and anatomic) may be related to the pathogenesis of emotional, behavioral, cognitive, and endocrine changes in depression (Savitz and Drevets, 2009a,b).

Structural MRI studies, because they are paradigm free, are potentially able to make comparisons containing fewer biases between MDD patients, who may be remitted or currently depressed, and healthy controls (Lai, 2013). Initial morphometric studies relied primarily on manually delineated methods, which are associated with potential biases. Furthermore, the manual tracing method is time-consuming to use to delineate brain regions which are a priori defined and it requires rigorous training to ensure rater reliability (Giuliani et al., 2005). However, the advent of the fully automated VBM method shows comparable accuracy to the manually traced volume method (Uchida et al., 2008; Davies et al., 2009) and can provide a powerful and unbiased measure. However, from a statistical viewpoint, the VBM method is usually limited by an accompanying risk of false-positive errors and the issue of false-positive errors could potentially be avoided by focusing on the regions that are of interest in MDD – the insular cortex in this study (Aickin and Gensler, 1996; Benjamini, 2010). Indeed, the VBM method has successfully been applied to detect neuromorphometric

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