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Enhanced default mode network connectivity with ventral striatum in subthreshold depression individuals

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ABSTRACT

Subthreshold depression (StD) is a highly prevalent condition associated with increased service utilization and social morbidity. Nevertheless, due to limitations in current diagnostic systems that set the boundary for major depressive disorder (MDD), very few brain imaging studies on the neurobiology of StD have been carried out, and its underlying neurobiological mechanism remains unclear. In recent years, accumulating evidence suggests that the disruption of the default mode network (DMN), a network involved in self-referential processing, affective cognition, and emotion regulation, is involved in major depressive disorder. Using independent component analysis, we investigated resting-state default mode network (DMN) functional connectivity (FC) changes in two cohorts of StD patients with different age ranges (young and middle-aged, n = 57) as well as matched controls (n = 79). We found significant FC increase between the DMN and ventral striatum (key region in the reward network), in both cohorts of StD patients in comparison with controls. In addition, we also found the FC between the DMN and ventral striatum was positively and significantly associated with scores on the Center for Epidemiologic Studies Depression Scale (CES-D), a measurement of depressive symptomatology. We speculate that this enhanced FC between the DMN and the ventral striatum may reflect a self-compensation to ameliorate the lowered reward function.

1. Introduction

Subthreshold depression (StD) refers to clinically relevant depressive symptoms without meeting the criteria for full-blown major depressive disorder (MDD) (Rodriguez et al., 2012). Previous studies have suggested that StD is a highly prevalent condition (Horwath et al., 1992) associated with increased service utilization and social morbidity. Thus, although the symptoms of StD are less severe than symptoms of major depressive disorder (MDD), they may be associated with a greater service burden and impairment compared with MDD or dysthymia on a population basis (Johnson et al., 1992). In addition, studies also suggested that StD is an important risk factor for MDD (de Graaf et al., 2010; Horwath et al., 1992; Wesselhoeft et al., 2013). Individuals with StD have an odds ratio of more than 5 for having a first lifetime episode of MDD (Fogel et al., 2006).

Despite its high prevalence and significant social and economic impacts, the neurobiology of StD remains unclear. This is mainly due to a limitation of the current diagnostic systems that set the boundary for the disorder based on the presence of a certain number of symptoms. As a result, individuals that fall below the threshold are not recognized in primary care settings or community

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surveys and are often not included in biological (imaging and genetic) studies (Rodriguez et al., 2012). Intensive investigation of the neuropathology of StD is important because it will not only provide crucial information on brain response during the initial medication-free stage of the depressive symptom onset, but it will also help us elucidate a dynamic course of MDD brain function/connectivity changes, which is crucial for developing tailored treatments for patients at different stages of the disorder.

In the last few decades, with the aid of powerful brain imaging tools, our understanding of MDD has been significantly enhanced. We now know that MDD is associated with structural and functional abnormalities in brain circuits involved in emotional processing, self-representation, reward, and external stimulus (stress, distress) interactions (Davidson et al., 2002; Hasler and Northoff, 2011; Northoff et al., 2011; Pizzagalli, 2011). These brain regions include the ventromedial prefrontal cortex, dorsal medial prefrontal cortex, anterior cingulate cortex, hippocampus, and amygdala. Interestingly, most of these brain regions also fall within the default mode network (DMN) (Andrews-Hanna et al., 2010; Buckner et al., 2008), a network believed to be involved in self-referential processing, affective cognition, and emotion regulation (Berman et al., 2011; Buckner et al., 2009; Connolly et al., 2013; Etkin et al., 2011; Nejad et al., 2013).

Previous studies (Bluhm et al., 2009; Greicius et al., 2007; Hamilton et al., 2013; Ho et al., 2014; Li et al., 2013; Liston et al., 2014; Posner et al., 2013; Wang et al., 2012; Wu et al., 2013; Zhu et al., 2012) have found disrupted DMN functional connectivity (FC) in MDD patients, and these changes are associated with psychiatric measurements such as rumination score in MDD patients. Yet one question that remains unanswered is whether DMN FC changes can be observed in StD patients. The answer to this question will provide us with a complete picture of the association between FC changes in the brain and clinical depressive symptoms, further enhance our understanding of the development of depression, and provide a biological basis for diagnosis of depression.

A core characteristic of depressed patients is anhedonia, the loss of interest in pleasurable activities, and limitations in multiple dimensions of well-being (Bogdan et al., 2013; Hasler and Northoff, 2011; Naranjo et al., 2001; Russo and Nestler, 2013). Previous studies (Rodriguez et al., 2012) also suggested that the most common symptoms of StD patients are depressed mood and loss of interest. Thus, the reward system (Naranjo et al., 2001; Pizzagalli et al., 2009) may play an important role in the pathophysiology of StD.

One challenge in performing brain imaging studies of depression is considerable variation in the nature of the findings across studies (Leibenluft and Pine, 2013). Clearer conclusions might emerge more rapidly if two separate cohorts of patients can be investigated and compared in the same experiment. Thus, in this study, we investigated DMN FC changes in two separate cohorts of StD subjects (young and middle age) and corresponding healthy controls. We hypothesize that there is a dysfunction of MDD FC with a key region in reward network, the ventral striatum in StD subjects. We believe that the two cohorts of StD subjects (young and middle age) will show similar DMN FC differences as compared to healthy controls.

2. Method

We briefly describe the experimental procedures below. Please also see a previously published study for more details on the experimental procedure (Hwang et al., 2015). The data has been used in a previous study to investigate the functional connectivity of bilateral dorsal lateral prefrontal cortex changes between individuals with StD and healthy control. In this study, we used ICA to investigate the DMN FC difference between individuals with StD and controls. These results have not been reported before.

Participants

We screened 981 subjects from three universities (young cohort) and 383 subjects from twelve Beijing residence community centers (middle aged cohort) through advertisements and flyers. All participants received a health lecture from investigators followed by a survey using the Center for Epidemiologic Studies depression scale (CES-D, Chinese version) (Radloff, 1977). The surveys were evaluated by a trained clinician. Potentially depressed participants were further assessed by a licensed psychiatrist using a 17-item Hamilton rating of depression scale (HAMD) to confirm study qualifications.

Inclusion criteria for StD participants included: (1) age between 18 and 60 years; (2) CES-D score $\geq$ 16; (3) 17-item HAMD score between 7 and 17. Exclusion criteria included: (1) abnormal or impaired judgment abilities (Wechsler Adult Intelligence Scale (WAIS) score $\geq$ 90); (2) diagnosis of severe depression based on ICD-10 (first-episode; (3) prior use of psychiatric medications; (4) any suicidal tendencies posing immediate threat to the subject's life; (5) history of addictive disorders such as substance abuse and dependence and alcoholism; and (5) any fMRI exclusion criteria including any major medical, neurological or psychological disorders, pregnancy or intent to become pregnant, and history of head trauma.

Healthy control (HC) participants were recruited from the same sources as StD participants based on the age and gender status of selected StD participants. All HC participants have a CES-D score of less than 16, and satisfied the same exclusion criteria as StD participants. All participants were given a description of the study and provided with written informed consent forms. All subjects signed the consent forms before the fMRI scans. The study was approved by the Committee on the Use of Human Subjects in Research at Beijing University of Chinese Medicine.

MRI data acquisition

Images were acquired on a 3-axis gradient head coil in a 3-T Siemens MRI system equipped for echo planar imaging (EPI) at the Research Institute of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University. T1-weighted sagittal localizing (T1) structures sequence was followed by an 8-min resting state scan. The T1 scanning parameters included TR of 2000 ms, echo time of 3.39 ms, flip angle of 70°, slices thickness of 1.33 mm and a field of view of 256 mm^2. For the resting state, the scan acquisition included 32 slices with a thickness of 4.8 mm, a TR of 2000 ms, a TE of 30 ms, flip angle of 90°, field of view of 240 mm^2 and a 3 $\times$ 3 mm in-plane spatial resolution. During Resting-State (RS) fMRI data acquisition, participants were instructed to remain still with their eyes closed and let their minds wander freely. After every scan, we asked the subjects whether they had fallen asleep during the scan and we received no positive responses.

Independent component analysis for resting state fMRI data

We analyzed the resting-state data of StD patients and healthy control subjects using Independent Component Analysis in the FMRIB Software Library (FSL) (Smith et al., 2004), following similar processing steps as those described in previous studies (Biswal et al., 2010; Fang et al., 2015; Kong et al., 2013). We first applied a band pass filter between 0.01 and 0.1 Hz to the functional time