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Research paper

Imbalanced spontaneous brain activity in orbitofrontal-insular circuits in individuals with cognitive vulnerability to depression

Xiaocui Zhang [a], Xin Di [b], Hui Lei [c], Juan Yang [d], Jing Xiao [e], Xiang Wang [a], Shuqiao Yao [a,*], Hengyi Rao [f,g]

[a] The Medical Psychological Institute of the Second Xiangya Hospital, Central South University, Changsha, Hunan, China
[b] Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ, USA
[c] College of Education, Hunan Agriculture University, Changsha, Hunan, China
[d] Department of Psychology, Hainan Medical College, Haikou, Hainan, China
[e] Beijing Key Laboratory of Learning and Cognition and Department of Psychology, Capital Normal University, Beijing, China
[f] Laboratory of Applied Brain and Cognitive Sciences, Shanghai International Studies University, Shanghai, China
[g] Center for Functional Neuroimaging, Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

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ABSTRACT

Background: The hopelessness theory of depression posits that individuals with negative cognitive styles are at risk of developing depression following negative life events. The purpose of this work was to examine whether individuals with cognitive vulnerability to depression (CVD) exhibit similar spontaneous brain activity patterns as compared to patients with major depressive disorder (MDD).
Methods: Subjects with CVD (N=32), drug-naïve first-episode patients with major depressive disorder (N=32), and sex-, age- and education-matched healthy controls (HCs; N=35) were subjected to resting state functional magnetic resonance imaging (RS-fMRI) and amplitudes of low-frequency fluctuation (ALFF) was compared between the groups. Pearson correlation analysis was performed between regional ALFFs and psychometric scores, namely the Cognitive Style Questionnaire (CSQ) and the Center for Epidemiologic Studies Depression (CES-D) scale scores.
Results: Significant group differences in ALFF values were observed bilaterally in the orbitofrontal cortex (OFC) and insular cortex (IC), and in the left fusiform gyrus (FFG). Compared to HCs, CVD subjects had reduced ALFFs in the bilateral OFC and increased ALFF in the bilateral IC and the left FFG, which were similar to the differences observed between the HCs and MDD patients. Compared to MDD patients, CVD subjects showed significant reduced ALFF values in right IC. Additionally, CSQ scores for the CVD group correlated with ALFF values in the left IC.
Limitations: We did not conduct a longitudinal study. Our findings were limited in cross-sectional analysis.
Conclusions: A hypoactive OFC and hyperactive IC in a resting-state may underlie an imbalance in the spontaneous brain activity in orbitofrontal-insular circuits, and these differences may represent a trait-related marker of vulnerability to depression.

1. Introduction

Depression is associated with heightened mortality risk across one's lifespan and its pervasiveness is on the rise internationally (Marcus et al., 2012). Increasing prevalence rates of depression have brought attention to the possibility of identifying vulnerabilities to depression. The well-developed cognitive vulnerability-stress model of depression, which posits that certain cognitive responses to stressful events can put individuals at increased risk for depression, has borne the notion of cognitive vulnerability to depression (CVD) as an important psychological factor (Beck, 1987). CVD has spurred a great deal of research which has led to elaborate theories of depression, such as hopelessness theory (Abramson, 1989).

Hopelessness theory, framed formally as a cognitive diathesis-stress theory, suggests that vulnerability to depression is related to a negative cognitive style wherein a depressogenic inference style about the self, consequences, and causes puts one at risk for the onset of depression following stressful events (Abramson, 1989). According to hopelessness theory, depression-vulnerable individuals tend to attribute stressful and negative events selectively

* Corresponding author.
E-mail address: shuqiaoyao@163.com (S. Yao).

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to internal, stable and global circumstances, that is, causes beyond their control. This cognitive style leads one to expect negative consequences and make inferences that denigrate their self-worth, thereby putting one at increased risk for depression following stressful life events. Within the framework of hopelessness theory, the weakest link hypothesis posits that a person's most prominent vulnerability factor is the best predictor of a person's risk of depression (Abela and Sarin, 2002). The weakest link approach has been demonstrated to be a good predictor of depression and has been proved to be applicable to Chinese university students (Xiao et al., 2014).

Although there is strong evidence from behavioral data supporting the notion that CVD may play an important causative role in the pathophysiology of depression (Abramson et al., 2002; Alloy et al., 2006; Iacoviello et al., 2006), the model needs to be further confirmed in experiments employing physiological dependent variables. Research examining the brain mechanisms underlying CVD is needed to elucidate the etiological factors of CVD and depression. A better understanding of the brain mechanisms of cognitive-affective processing both in patients with major depressive disorder (MDD) and in individuals with CVD may aid in depression prevention and treatment planning.

Previous structural and functional magnetic resonance imaging (fMRI) studies have demonstrated CVD-related brain abnormalities, including reduced gray matter volume in the left precentral gyrus and right fusiform gyrus (FFG) (Zhang et al., 2012), abnormal fractional anisotropy in subcortical regions (Xiao et al., 2015), increased activity in the amygdala bilaterally, and decreased activity in the dorsolateral prefrontal cortex (DLPFC) bilaterally (Zhong et al., 2011). Additionally, an electroencephalographic study revealed that CVD was associated with low relative left-frontal activity at rest (Nusslock et al., 2011). However, there is no published resting-state functional magnetic resonance imaging (RS-fMRI) studies on CVD.

RS-fMRI is a novel neuroimaging technique used to evaluate brain function while human (or animal model) subjects are in a resting state, in the absence of external tasks. Using RS-fMRI, Biswal et al. first reported that spontaneous low frequency (0.01–0.08 Hz) fluctuations (LFF) of the blood oxygen level dependent (BOLD) signal during rest were highly synchronous among motor cortices in healthy subjects, concluding that the LFF was closely related to the spontaneous neural activities (Biswal et al., 1995). Both animal and human studies indicate that the regional amplitude of low-frequency fluctuations (ALFF) (0.01–0.08 Hz) are physiologically meaningful and reflective of spontaneous neural activity (Goncalves et al., 2006; Shmuel and Leopold, 2008; Zang et al., 2007). Abnormal spontaneous brain activity in the PFC, temporal lobe and subcortical system, and cerebellum has been observed in MDD patients. For instance, Jiao et al. (2011) observed increased activity in the right dorsolateral prefrontal cortex, bilateral triangular inferior frontal gyrus, and orbital inferior gyrus in adolescents with MDD compared with healthy controls. In contrast, first-episode, treatment-naive patients with MDD showed decreased activity in the left dorsolateral prefrontal cortex and bilateral medial orbitofrontal cortex (Wang et al., 2012). Similarly, reduced ALFF were found in bilateral OFC, while increased ALFF in the bilateral temporal lobe extending to the insular and left fusiform cortices in MDD patients compared to healthy controls (Zhang et al., 2014). In addition, decreased regional homogeneity in insular and cerebellum were reported in patients with major depression and normal subjects at high risk for major depression (Liu et al., 2010). The decreased activity bilaterally in the dorsal mid-insular cortex was also reported in unmedicated MDD subjects during interoception (Avery et al., 2014).These findings indicate abnormal spontaneous brain activity in cortical-subcortical circuits in MDD patients. It is unknown whether individuals with CVD show spontaneous brain activity abnormalities that precede the occurrence or development of depression, and whether there are similar changes in spontaneous brain activity between individuals with CVD and patients with MDD. This issue is an important area for future research, particularly because abnormal spontaneous brain activity may represent vulnerability markers for MDD, which could thus identify individuals at greater risk for depression.

In the current study, we utilized RS-fMRI to investigate spontaneous brain activity, as reflected by ALFFs, in individuals with CVD and in drug-naive first-episode MDD patients, and compared to matched healthy controls (HCs). We hypothesized that ALFFs in the CVD group would differ from ALFFs observed in HCs, and that these differences would be similar to the differences observed between patients with MDD and HCs. If our hypothesis is supported, abnormal ALFFs in CVD individuals may be a valid indicator of their risk for developing MDD.

2. Methods

2.1. Participants

Psychometric and RS-fMRI results were compared across three groups: CVD, drug-naïve first-episode patients with MDD, and sex-, age- and education-matched HC subjects (see Table 1). To ensure homogeneity across the three groups, inclusion criteria of all subjects included right handedness, current undergraduate student status, age within the range of 18–24 years, and Han ethnicity. The purpose of this study was explained to all of the participants, and each of them gave written informed consent. The research protocol was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, China.

2.1.1. CVD and HC subjects

CVD and HC subjects were recruited from the undergraduate student populations at two local universities' in Changsha, China based on their Cognitive Style Questionnaire (CSQ) (Abramson and Metalsky, 1986) scores. The mean weakest-link score on the CSQ for the pool of potential participants screened (N=595) was 0.42

Table 1
Demographics and clinical characteristics for groups of individuals with cognitive vulnerability to depression (CVD), patients with major depressive disorders (MDD), and healthy controls (HCs).

Characteristic	CVD (n=32)	MDD (n=32)	HC (n=35)	F/χ^2	*p*
Gender (male/female)	13/19	14/18	18/17	χ^2 (2)=0.092	.656
Age (years)	20.72 ± 1.02	20.53 ± 1.78	20.97 ± 1.29	$F_{2,96}$=0.704	.435
Education (years)	13.75 ± 0.84	13.88 ± 0.87	13.97 ± 0.86	$F_{2,96}$=0.503	.607
CES-D score	18.28 ± 6.27	38.03 ± 6.68	16.20 ± 6.69	$F_{2,96}$=110.206	< .001
Weakest-link score	2.16 ± 0.33	1.03 ± 0.73	0.22 ± 0.60	$F_{2,96}$=95.374	< .001

Note: CVD=individuals with cognitive vulnerability to depression; MDD=patients with major depressive disorders; HC=healthy controls; CES-D=Center for Epidemiological Studies Depression.