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Research paper

Resting-state functional MRI of abnormal baseline brain activity in young depressed patients with and without suicidal behavior

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ABSTRACT

Background: Suicide among youth is a major public health challenge, attracting increasing attention. However, the neurobiological mechanisms and the pathophysiology underlying suicidal behavior in depressed youths are still unclear. The fMRI enables a better understanding of functional changes in the brains of young suicide attempters with depressive disorder through detecting spontaneous neural activity. The purpose of this study was to identify the relationship between abnormalities involving local brain function and suicidal attempts in depressed youths using resting-state fMRI (RS-fMRI).

Method: Thirty-five depressed youths aged between 15 and 29 years with a history of suicidal attempts (SU group), 18 patients without suicidal attempts (NSU group) and 47 gender-, age- and education-matched healthy controls (HC) underwent psychological assessment and R-fMRI. The differences in fractional amplitude of low-frequency fluctuation (ALFF) among the three groups were compared. The clinical factors correlated with *z*-score ALFF in the regions displaying significant group differences were investigated. The ROC method was used to evaluate these clusters as markers to screen patients with suicidal behavior.

Results: Compared with the NSU and HC groups, the SU group showed increased zALFF in the right superior temporal gyrus (r-STG), left middle temporal gyrus (L-MTG) and left middle occipital gyrus (L-MOG). Additionally, significantly decreased zALFF values in the L-SFG and L-MFG were found in the SU group compared with the NSU group, which were negatively correlated with BIS scores in the SU group. Further ROC analysis revealed that the mean zALFF values in these two regions (sensitivity=83.3% and specificity=71.4%) served as markers to differentiate the two patient subtypes.

Conclusion: The SU group had abnormal spontaneous neural activity during the resting state, and decreased activity in L-SFG and L-MFG was associated with increased impulsivity in SU group. Our results suggested that abnormal neural activity in these brain regions may represent a potential neurobiological diathesis or predisposition to suicidal behavior in youth depression.

1. Introduction

According to the World Health Organization, approximately one million people worldwide commit suicide each year (Bertolote and Fleischmann, 2015; Cáceda et al., 2012). In China, suicide is the leading cause of death among individuals aged between 15 and 24 years (Li et al., 2008; Phillips et al., 2002), with an estimated 49,000 suicides committed annually, accounting for 17% of all suicides in the country (Phillips et al., 2002). Suicide among youth is a major public health challenge, attracting increasing attention. Adolescence and early adulthood is a period of high risk for suicidal behavior. Intervention and treatment may have the greatest impact because of structural changes in the brain and significant psychosocial development. Epidemiological and clinical studies established that previous history of suicidal attempts is one of the strongest predictors of future risk for suicide (Coryell and Young, 2005; Joiner et al., 2003; Nordstrom et al., 1995; Ribeiro et al., 2015). Thus, suicidal attempts represent an important point of intervention for prevention efforts.

Epidemiological studies suggest that suicidal behavior is strongly linked to depression (Angst et al., 1999; Rihmer, 2007). The estimated lifetime risk for suicide among individuals with major depressive disorder (MDD) is 2–12% (Barga, 2013; Borges et al., 2010; Kessler et al., 1999). A large-scale, follow-up study

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suggested that 4.2% of patients with major depression died from suicide (Coryell and Young, 2005). Despite the identification of risk factors and protection against suicidal behavior, the neurobiological mechanisms and the pathophysiology underlying suicidal behavior in depression are still unclear. The factors triggering suicidal crisis in an individual are not fully understood. Therefore, determination of the neurobiological correlates of suicidal behavior in depressive disorder and the biomarkers for suicidal risk may provide insight into the pathogenesis of the condition.

Evidence supporting the neurobiological basis of vulnerability to suicidal behavior is increasing (Costanza et al., 2014; van Heeringen and Mann, 2014). Several reviews of neuroimaging studies involving suicidal behavior have been published recently (Desmyter et al., 2013, 2011; Jollant et al., 2011; Lippard et al., 2014; Van Heeringen et al., 2011), reporting widely varying results without focusing on suicide in depression. In addition, most previous neuroimaging studies on suicidal behavior were conducted in adults. So far, few studies have explored the underlying neurobiological substrates of suicidal behavior in youth. Youth is a crucial phase of brain maturation and psychosocial development. Developmental changes may contribute to increased risk of suicide during this time, while the developing brain may also provide a potential window into the risk for suicidal behavior and allow earlier intervention. These factors underscore the importance of investigating into the neurobiology of suicidal behavior in youth depression.

Functional magnetic resonance imaging (fMRI) is a non-invasive method to measure the brain function in vivo by estimating the regional blood flow and identifying the unique neural activation patterns associated with specific cognitive processes and disease states. The fMRI enables a better understanding of the underlying brain mechanisms of suicidal behavior in youth depression. And fMRI studies have yielded potential markers of risk for suicidal behavior in young adults by identifying the neurobiological underpinnings of pathophysiology that are not apparent at the behavioral level, and also provide targets for future interventions (Martin et al., 2015). The identification of potential markers of risk in youth with a history of attempted suicide is a first step toward understanding the pathophysiology underlying suicidal behavior. Previous studies indicate that brain abnormalities in young adults with a history of suicide attempt varied from those in general adults. Therefore, we sought to identify abnormal baseline brain activity, which may yield potential markers of risk for suicidal behavior in young adults with depressive disorder.

Resting state fMRI (RS-fMRI) is a functional imaging technique to detect spontaneous neural activity indirectly via fMRI blood oxygen level-dependent (BOLD) signals elicited by neural activity in subjects resting quietly in the scanner. RS-fMRI has been increasingly used to investigate the spatial and temporal patterns of neural activity and the integration of neural networks in resting state. However, most studies of abnormal neural activity in suicide attempters were conducted using task-based BOLD fMRI (Jollant et al., 2008, 2010; Olie et al., 2015). Until now, only two RS-fMRI studies were performed in individuals attempting suicide (Cao et al., 2015; Fan et al., 2013). RS-fMRI supplementary data provided by task-based imaging, offer several critical advantages for imaging applications in contrast to conventional task-based fMRI. First, task-independent fMRI reveals unexpected changes in functional connectivity by imaging resting activity in multiple spatially distributed and functionally heterogeneous circuits simultaneously (i.e., circuits not engaged by specific tasks). Second, RS-fMRI avoids potential performance confounders associated with cognitive activation paradigms in task-based fMRI, and is relatively easy to implement in clinical studies with minimal patient compliance. Third, RS-fMRI is most appropriate for examination of the so-called default circuit (Buckner et al., 2008; Whitfield-Gabrieli and Ford, 2012). Fourth, individual variation in subject performance is obviated by RS-fMRI.

The amplitude of low-frequency fluctuation (ALFF), in which the square root of the power spectrum is integrated in a low frequency range (0.01–0.08 Hz) is an important approach to RS-fMRI analysis. The ALFF in the BOLD signal represents the intensity of low frequency oscillations (LFOs). It is a proven and index directly reflecting the intensity of spontaneous neural activity at the baseline (Logothetis et al., 2001). The low-frequency (0.01–0.08 Hz) fluctuations of the BOLD signal in the resting state are considered physiologically meaningful and related to spontaneous neural activity. ALFF was higher in gray matter than in white matter (Biswal et al., 1995). In addition, the visual cortex activation by low-frequency fluctuations at about 0.034 Hz using the power spectrum method, indicate that ALFF may be associated with spontaneous neuronal activity in the region (Kiviniemi et al., 2000). Previous studies confirmed that the ALFF approach was effective in assessing disease-related local brain activity based on the regional intensity of spontaneous fluctuations in BOLD signal in resting state (Yu-Feng et al., 2007). It has been successfully used to detect changes in the local synchronization of spontaneous neural activity in multiple neuropsychiatric diseases, such as attention-deficit/hyperactivity disorder (Yu-Feng et al., 2007), Alzheimer's disease (He et al., 2007), epilepsy (Zhang et al., 2008), Parkinson's disease (Skidmore et al., 2013), and schizophrenia (Guo et al., 2014). Therefore, we used the ALFF method to detect synchronous alterations in regional cerebral activity in suicide attempters to advance our understanding of suicidal brain and the neural mechanism underlying suicidal behavior in depressed youths.

Impulsivity is also a characteristic of patients with affective disorders that contributes to the risk for suicidal behavior. Patients with depressive disorder have a high prevalence of suicide, and their suicidal ideas and behaviors are associated with impulsivity. The relationship between impulsivity and suicidal behavior has been investigated directly in patients with depressive disorder. The impulsivity trait has been discussed as a promising endophenotype for suicide (Brent, 2009; Jimenez-Trevino et al., 2011), which may be particularly relevant for individuals attempting suicides impulsively. The impulsivity predicted suicidal acts in depressive disorder (Oquendo et al., 2004). Clinically suicide attempters are characterized by impulsivity, and patients with a history of suicidal attempts exhibit higher impulsivity compared with healthy subjects. Impulsivity distinguished suicidal from non-suicidal inpatients and control subjects (Horesh, 2001), and suicidal from non-suicidal depressed inpatients (Corruble et al., 1999). Among suicide attempters, impulsivity predicted eventual suicide more than 12 months later (Maser et al., 2002). These studies suggested that impulsivity increased suicide risk when combined with depression.

Although the association between suicidal behavior and impulsivity is widely recognized, the underlying pathophysiology of brain is unknown. Lesional and functional neuroimaging studies indicate that the ventromedial prefrontal region (VMPFC), including the orbitofrontal cortex (OFC), anterior cingulated cortex (ACC) and medial prefrontal cortex, and the amygdala may modulate impulsivity. Researchers used fMRI to investigate the relationship between trait impulsivity and BOLD response and found that impulsivity was associated with greater activation in orbitofrontal cortex during response inhibition (Horn et al., 2003). Meanwhile, morphometry also indicated that small OFC volume was related to high impulsivity and VMPFC was involved in the circuit modulating impulsivity. Further, neuroimaging studies suggested that the OFC and ACC play a crucial role in impulsive, risky, and suicidal behaviors. Matsuo et al. (2010) demonstrated a significant negative correlation between the anterior genu of the

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