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Resting-state functional connectivity of the amygdala in suicide attempters with major depressive disorder

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ABSTRACT

In this study, we investigated the difference in resting-state functional connectivity (RSFC) of the amygdala between suicide attempters and non-suicide attempters with major depressive disorder (MDD) using functional magnetic resonance imaging (fMRI). This study included 19 suicide attempters with MDD and 19 non-suicide attempters with MDD. RSFC was compared between the two groups and the regression analyses were conducted to identify the correlation between RSFC and Scale for Suicide Ideation (SSI) scores in the suicide attempt group. Statistical significance was set at p-value (uncorrected) < 0.005 with $k \geq 28$ voxels. Compared with non-suicide attempters, suicide attempters showed significantly increased RSFC of the left amygdala with the right insula and left superior orbitofrontal area, and increased RSFC of the right amygdala with the left middle temporal area. The regression analysis showed a significant correlation between the SSI total score and RSFC of the right amygdala with the right parahippocampal area in the suicide attempt group. The present RSFC findings provide evidence of a functional neural basis and will help reveal the pathophysiology underlying suicidality in subjects with MDD.

1. Introduction

Suicide is one of the most common causes of death (Lozano et al., 2012), and the suicide rate in South Korea is the highest among the Organization for Economic Cooperation and Development countries. Although the social impact, sequelae, and societal costs of suicidal behavior are devastating, physicians unfortunately cannot predict suicide attempts ahead of time. Depressive disorder is one of the leading causes of suicide (Cavanagh et al., 2003; Lesage et al., 1994). Because suicidal ideation and suicide attempts are serious and important symptoms associated with major depressive disorder (MDD), these symptoms are included as part of the diagnostic criteria for MDD in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) (American Psychiatric Association, 2013). However, the majority of individuals with depressive disorders do not commit suicide, although they suffer from suicidal ideation (Coryell and Young, 2005; Sokero et al., 2005), and the severity of depression does not necessarily predict suicide attempts (Campos et al., 2016). For these reasons, many researchers insist that suicidal behavior should be a separate nosological entity from psychiatric disorders.

To determine the neurobiological etiology of suicidal behavior of depression, and to prevent and intervene in such behavior, neuroimaging researches have attempted to discover the underlying mechanisms of suicide in subjects with MDD by investigating structural and functional abnormalities in the brain of suicide attempters with MDD. Structural brain imaging studies have shown that suicide attempters exhibit structural brain alterations in the orbitofrontal cortex, amygdala (Monkul et al., 2007), fronto-limbic network (Wagner et al., 2011), temporal-parietal-limbic networks (Peng et al., 2014), putamen (Dombrovski et al., 2012), left angular gyrus, and right cerebellum (Lee et al., 2016). Additionally, a meta-analysis revealed that a history of suicidal behavior is associated with these types of structural deficits as well as functional overactivation in some brain areas (e.g., the anterior and posterior cingulate cortices) (van Heeringen et al., 2014).

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That study also indicated that vulnerability to suicidal behavior may be related to decreased motivational control over intentional behavioral reactions to negative stimuli (van Heeringen et al., 2014). Task-based fMRI studies have contributed to the concept of an emotional and cognitive intermediate phenotype associated with suicide (Jollant et al., 2008; Jollant et al., 2010; Pan et al., 2013a, 2013b, 2011). However, due to its nature of these studies, the results depend on the subjects' cooperation (Serafini et al., 2016).

The resting-state fMRI (rs-fMRI) is a non-invasive neuroimaging technique that measures the activity of the default brain circuit. Although it could be an excellent method to probe the neural network of suicidality in subjects with MDD, few rs-fMRI studies have been performed. This neuroimaging modality measures the resting-state functional connectivity (RSFC) and identifies relationships between brain regions using a blood oxygen level-dependent signal. Positive correlations among brain areas reflect synchrony of those regions in the same direction, and negative correlations indicate the synchrony of two regions in the opposite direction.

Although rs-fMRI studies and the RSFC method have numerous advantages, to the best of our knowledge, few efforts have been made to examine the RSFC of suicidal behavior using this imaging modality. Previous rs-fMRI studies used the amplitude of low-frequency fluctuation (ALFF) method or regional homogeneity (ReHo) analysis to explore abnormal resting-state brain activity or RSFC in suicide attempters, and they reported diverse and inconsistent brain areas associated with resting-state functional abnormality (Cao et al., 2015; Cao et al., 2016; Fan et al., 2013). Cao et al. (2015) reported that suicide attempters without a psychiatric disorder exhibited significantly different ReHo in the several brain regions relative to non-suicide attempters. Additionally, Cao et al. (2016) and Fan et al. (2013) reported differences in ALFF in several brain regions in depressed subjects with a history of suicide attempts compared with those without a history of suicide attempts and healthy controls.

The amygdala is part of the limbic system and is located in the medial temporal lobe. It plays critical roles in emotional reaction, decision making, memory processing, and, based on a number of studies, in suicide and mood disturbance (Drevets, 2003; Kekesi et al., 2012; Monkul et al., 2007; Spoletini et al., 2011). A proteomic study conducted on post mortem brains of suicide victims to identify protein changes and functional networks found nine proteins that changed in both the amygdala and the prefrontal cortex, and suggested that these two brain areas might be suitable for functional neuroimaging studies on suicide (Kekesi et al., 2012).

To investigate the association between RSFC and suicide attempts, in this study, we focused on the amygdala as the seed region, which is associated with emotional reaction and impulsivity, and assumed that brain regions showing higher or lower RSFC with the amygdala in suicidal attempters compared with non-suicide attempters were significantly associated with suicidal behavior. In this study, we determined the brain areas that differed in their RSFC with the amygdala between suicide attempters and non-suicide attempters with MDD and the brain areas whose relationships with RSFC of the amygdala were correlated with scores on a scale of suicidal ideation.

2. Methods

2.1. Subjects

The participants in this study were MDD patients (18–65 years of age) who visited the Department of Psychiatry at Gachon University Gil Medical Center between September 2012 and August 2014. The structured clinical interview for DSM-IV axis-I disorders (SCID-I) (First et al., 1995) was administered by board-certified psychiatrists to determine whether the participants met the diagnostic criteria for MDD. The exclusion criteria included any history of severe medical problems, current medical or neurological illnesses, other comorbid DSM-IV axis I major psychiatric disorders (e.g., schizophrenia and psychotic disorders, bipolar disorders, major anxiety disorders, dementia, and substance-related disorders), comorbid borderline personality disorder or antisocial personality disorder, an intellectual disability, pregnancy, and/or contraindications for MRI scans (e.g., claustrophobia or pacemaker in the body).

The eligible MDD participants were divided into two groups (suicide attempters and non-suicide attempters). Among eligible participants, 19 had a personal history of suicide attempt (suicide attempters) and 19 had none (non-suicide attempters). In the present study, suicide attempts were defined as self-destructive behavior with the intent to end one's life. The lifetime history of suicide attempts for a subject was confirmed based on the documentation of suicide attempts in their medical records or a history of visits to the hospital emergency department after attempting suicide. To assess the lethality of suicide attempts for the current or most recent attempt, board-certified psychiatrists administered the Risk-Rescue Rating (RRR) scale to the suicide attempters (Weisman and Worden, 1972). To evaluate the severity of suicidal ideation, the participants were asked to complete a self-report version of the Scale for Suicide Ideation (SSI) on the day of the scan (Beck et al., 1988). The participants were interviewed using the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) by board-certified psychiatrists. The participants were also questioned regarding the use of psychotropic medications.

The participants received a thorough description of the study and provided their written informed consent prior to participating in the study, which was approved by the Institutional Review Board of the Gachon University Gil Medical Center.

2.2. rs-fMRI acquisition

We obtained a series of MRI scans using a 1.5-Tesla MR scanner (Magnetom Avanto; Siemens, Erlangen, Germany) of all participants with a 12-element matrix head coil. For the resting-state measurement, T2*-weighted echo planar imaging was obtained with the following parameters: repetition time (TR) = 3000 ms; echo time (TE) = 40 ms; flip angle = 90°; matrix size = 64 × 64; number of slices = 35; pixel size = 2 × 2 mm^2; thickness = 4 mm; field of view = 256 × 256 mm^2; number of frames = 150; total acquisition time = 450 s. The participants were instructed to remain relaxed and awake during the image acquisition.

High-resolution transaxial T1-weighted structural images were obtained using 3D-MPRAGE with the following parameters: repetition time (TR) = 1200 ms; echo time (TE) = 5.02 ms; inversion time (TI) = 600 ms; flip angle = 15°; matrix size = 256 × 256; number of slices = 176; pixel size = 0.45 × 0.45 mm^2; thickness = 0.9 mm; field of view = 230 × 230 mm^2; total acquisition time = 308 s.

2.3. Image processing of rs-fMRI

Before the image processing, board-certified neuroradiologists reviewed the structural MR images to determine the presence of any structural abnormality in the participants' brains. The rs-fMRI data processing was performed using Statistical Parametric Mapping (SPM8) and Data Processing Assistant for Resting-State fMRI (DPARSF) software. The first 10 frames of fMRI data were discarded for signal equilibrium, and the remaining images were realigned to the first volume. Head movement parameters for translation and rotation were estimated for each volume. After motion correction, each individual structural image was co-registered to the mean of the realigned images. The transformed structural images were then segmented into gray matter, white matter, and cerebrospinal fluid. Motion-corrected functional volumes were spatially normalized to Montreal Neurological Institute (MNI) space and resampled to 3-mm isotropic voxels using the normalization parameters. The normalized data were smoothed using a 6-mm FWHM Gaussian low-pass filter. The linear trend removal and 0.01–0.08 Hz band-pass filter were applied to the time series data.