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Research report

White matter alterations are associated with suicide attempt in patients with panic disorder

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ABSTRACT

Background: Panic disorder (PD) is associated with an increased risk of suicide attempt (SA). However, no study has examined the neural correlates of SA in PD. The goal of this study was to evaluate alterations in white matter (WM) and gray matter (GM) in patients with PD with and without a history of SA.
Methods: Twelve patients with PD and a history of SA (PD+SA) and 24 patients with PD and no history of SA (PD−SA) underwent magnetic resonance imaging (MRI). All patients completed the Scale for Suicide Ideation (SSI), the Panic Disorder Severity Scale (PDSS), and the Beck Depression Inventory (BDI). The groups were matched for age, sex, and BDI and PDSS scores. Voxel-based morphometry and tract-based spatial statistics were used for the imaging analysis.
Results: Although no GM or WM volume differences were observed, increased fractional anisotropy (FA) values were found in the WM tracts of the PD+SA group compared with the PD–SA group. The regions with increased FA included the internal capsule, splenium of the corpus callosum, superior and posterior corona radiata, thalamic radiations, sagittal stratum, and superior longitudinal fasciculus. The FA values for the internal capsule and thalamic radiations were significantly correlated with the SSI scores in the PD+SA group.
Limitations: The results should be considered preliminary due to the relatively small sample size.
Conclusions: Our data suggest that the aberrant WM integrity of the internal capsule and thalamic radiations may be the significant neural correlate of SA in patients with PD.

1. Introduction

Suicide is a serious public health issue worldwide. Suicide attempt (SA), which is defined as an act of self-harm with an intent to die (Oquendo et al., 2004), is a powerful predictor of completed suicide (Suominen et al., 2004). Thus, SA may be an important intervention point for predicting and preventing suicide.

Panic disorder (PD) is associated with an increased SA risk (Weissman et al., 1989). The National Epidemiologic Survey on Alcohol and Related Conditions reported an overall adjusted odds ratio of 1.77–2.50 for SA in patients with PD (Nock et al., 2010). A significant number of reports suggest that PD is associated with suicidality. However, some studies have suggested that comorbid major depressive disorder (MDD) may account for the increased suicidality identified in this population (Diaconu and Turecki, 2007; Warshaw et al., 2000). Although the association between PD and SA remains controversial, several factors that link PD with SA have been proposed. For example, a previous study identified the fear of dying during a panic attack as an independent risk factor for SA in patients with PD after controlling for comorbid psychiatric conditions and pertinent demographic factors (Yaseen et al., 2013). Other studies have shown that catastrophic cognitions and symptoms of alpha-adrenergic activation (i.e., sweating and shortness of breath) may be independent risk factors for SA in PD (Katz et al., 2011; Rappaport et al., 2013). Schmidt et al. (2001) reported that anticipatory anxiety and the avoidance of physical sensations were significantly associated with SA in patients with

Abbreviations: BDI, Beck Depression Inventory; CSF, cerebrospinal fluid; EPI, echo planar imaging; DTI, diffusion-tensor image; FA, fractional anisotropy; FOV, field of view; GM, gray matter; ICV, intracranial volume; MDD, major depressive disorder; PD, panic disorder; PDSS, Panic Disorder Severity Scale; PD+SA, Panic disorder with a history of suicide attempt; PD−SA, Panic disorder without a history of suicide attempt; SA, suicide attempt; SSI, Scale for Suicide Ideation; SSRI, selective serotonin re-uptake inhibitor; TBSS, Tract-based spatial statistics; TE, echo time; TFCE, threshold-free cluster enhancement; TR, repetition time; VBM, Voxel-based morphometry; WM, white matter

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PD. In addition, suicidality in PD has been proposed to be related to helplessness, demoralization, separation, and loss in connection with heightened anxiety (Noyes, 1991). Suicide in patients with PD may be characterized as an escape from an intolerable subjective experience.

Numerous studies have attempted to find a relationship between brain characteristics and suicidal behaviors in mental illnesses such as MDD and bipolar disorder. The brains of patients with MDD and a high risk of suicide exhibited decreased gray matter (GM) density in the fronto-striato-limbic network (Wagner et al., 2011). The analysis of white matter (WM) integrity revealed a decrease in the fractional anisotropy (FA) values in the internal capsule (Jia et al., 2013) of patients with MDD and a history of SA. In addition, patients with bipolar disorder and a history of SA exhibited lower WM connectivity in the orbito-frontal cortex (Mahon et al., 2012). Pompili et al. (2008) have suggested that periventricular WM hyperintensities may serve as predictors of SA in bipolar disorder and unipolar depression. Taken together, these previous findings examining the neural correlates of suicidal behaviors in mental illnesses suggest that suicidality might be related to alterations in the fronto-limbic circuit.

No study has reported the possible neural correlates of SA in PD. The goal of this study was to evaluate specific neural correlates of SA in PD, because some characteristics of SA in PD may be distinguishable from those in other mental illnesses such as MDD. This study was designed to examine the structural differences in GM and WM between PD patients with and without a history of SA. We hypothesized that structural differences in the fronto-limbic area may be associated with SA in PD. To examine the neural correlates of SA independent from depressive symptoms and panic severity, patients with PD and no history of SA (control group) were matched to patients with PD and a history of SA for scores on two clinical symptom measures, the Panic Disorder Severity Scale (PDSS) and the Beck Depression Inventory (BDI). In addition, we investigated the relationship between structural alterations in the brain and the severity of clinical symptoms and suicidal ideation in patients with PD.

2. Materials and methods

2.1. Subjects and clinical assessments

Eighty-one patients with PD were screened for our analysis. All patients were recruited from the Department of Psychiatry at CHA Bundang Medical Center between January 2011 and August 2013. Patients aged 18–60 years who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for PD—as diagnosed by experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) Axis I disorders—were included in the study (First et al., 1996). All patients were right-handed and of Korean descent.

Only patients with primary PD were included in the study; patients with secondary lifetime diagnoses of psychiatric conditions such as mood disorders which are frequently comorbid with PD, were eligible provided the symptoms from their secondary diagnoses were clinically less severe than their PD symptoms. The exclusion criteria included a history of schizophrenia; bipolar I disorder; alcohol and substance abuse or dependence; comorbid Axis II disorders, such as personality disorders and mental retardation; and current or past serious medical or neurological disorders.

SA was defined as one or more self-injurious behaviors (e.g., drug overdose, carbon monoxide poisoning, cutting oneself with a sharp instrument, placing oneself in the path of a fast-moving vehicle, hanging oneself, jumping from a great height, or hitting one's head on a hard object) with some intent to die (Oquendo et al., 2004). Two experienced psychiatrists (BK and SHL) conducted a clinical interview to determine whether the patient had a history of SA. The interviewers used the question "Have you ever attempted suicide for any reason in your lifetime?"

Twelve patients with a history of SA (PD+SA) and 24 patients with no history of SA (PD−SA) were included in the study. These two groups were matched for age, sex, and BDI and PDSS scores. Prior to enrollment in this study, a majority of the patients were treated with a selective serotonin re-uptake inhibitor (SSRI) such as paroxetine or escitalopram ($n=32$) and benzodiazepines such as alprazolam or clonazepam ($n=34$) as anxiolytics. These treatments were taken for less than one month before enrollment (mean $\pm$ SD, 6.02 ± 8.3 days).

The Scale for Suicide Ideation (SSI) (Beck et al., 1979) with a predictive value for completed suicide (Brown et al., 2000) was used to assess the seriousness of the suicide intention in each patient. The severity of panic and depressive symptoms was assessed in each patient using the PDSS (Lim et al., 2007; Shear et al., 1997) and BDI (Beck et al., 1961), respectively. The scores on all three scales were determined within 3 days before or after the magnetic resonance imaging (MRI).

All study procedures were approved by the CHA Bundang Medical Center Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent was obtained from all patients.

2.2. MRI acquisition

All scans were performed in the same Signa HDxt 3.0 T scanner (GE Healthcare, Milwaukee, WI, USA) equipped with an 8-channel phased array head coil at CHA Bundang Medical Center, CHA University. The parameters for the three-dimensional T1-weighted fast spoiled gradient-recalled-echo (3D T1-FSPGR) images were as follows: repetition time (TR) 16 ms, echo time (TE) 4.3 ms, flip angle 10°, slice thickness 1.0 mm, field of view (FOV) 25.6 cm, 256×256 matrix, isotropic voxel size $1 \times 1 \times 1$ mm^3. Diffusion-weighted images were acquired using an echo planar imaging (EPI) sequence with the following parameters: TR 17,000 ms, TE 108 ms, FOV 24 cm, 144×144 matrix, slice thickness 1.7 mm, voxel size $1.67 \times 1.67 \times 1.7$ mm^3. A double echo option was used to reduce eddy-current-related distortions. To reduce the impact of EPI spatial distortions, an 8-channel coil and an array spatial sensitivity encoding technique (ASSET, GE Healthcare) with a sensitivity encoding (SENSE) speed-up factor of 2 was used. Seventy axial slices parallel to the anterior commissure–posterior commissure line covering the whole brain were acquired in 51 directions with $b=900$ s/mm^2. Eight baseline scans with $b=0$ s/mm^2 were also acquired. Diffusion-tensor images (DTIs) were estimated from the diffusion-weighted images using the least-squares method.

2.3. Image processing and analyses

2.3.1. Voxel-based morphometry (VBM) analysis of the GM and WM volumes

The image processing for the GM volume analysis was performed on Statistical Parametric Mapping version 5 software (SPM5, Wellcome Trust Centre for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm) using the VBM 5 toolbox (http://vbm.neuro.uni-jena.de/vbm) in MATLAB version 7.9 (The MathWorks, Natick, MA, USA). The two-dimensional DICOM files of each brain were organized into volumetric three-dimensional files in NIFTI-1 (http://nifti.nimh.nih.gov) format using the MRIcron software package (http://www.sph.sc.edu/comd/rorden/mricron). For the VBM preprocessing, the converted files of the T1 images were segmented into GM, WM, and cerebrospinal fluid (CSF) compartments and normalized using the unified model