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White matter alterations associated with suicide in patients with schizophrenia or schizophreniform disorder

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ABSTRACT

The risk of suicide is disproportionately high among people diagnosed with schizophrenia or schizophreniform disorder. Brain imaging studies have shown a few relationships between neuroanatomy and suicide. This study examines the relationship between alterations in brain white matter (WM) and suicidal behavior in people with schizophrenia or schizophreniform disorder. The study participants were 56 patients with schizophrenia or schizophreniform disorder, with ($n=15$) and without ($n=41$) a history of suicide attempts. Fractional anisotropy (FA) values were compared between suicide attempters and non-attempters using Tract-Based Spatial Statistics (TBSS). Attempters showed significantly higher FA values than non-attempters in the left corona radiata, the superior longitudinal fasciculus, the posterior limb and retrolenticular part of the internal capsule, the external capsule, the insula, the posterior thalamic radiation, the cerebral peduncle, the sagittal stratum, and temporal lobe WM. Scores of the picture arrangement test showed a significant positive correlation with FA values of the right corona radiata, the right superior longitudinal fasciculus, the body of the corpus callosum, and the left corona radiata in attempters but not in non-attempters. These findings suggest that fronto-temporo-limbic circuits can be associated mainly with suicidal behavior in people with schizophrenia or schizophreniform disorder.

1. Introduction

Suicide is one of the leading causes of death worldwide and suicide rates for young adults remain remarkably high. One of the risk factors for young adults is psychiatric illness, such as schizophrenia (Pitman et al., 2012). Many studies have sought to understand suicide in psychosis, identifying several clinical risk factors for suicide in patients with psychosis. Such risk factors include being younger, being male, having a greater insight into illness, having achieved a higher level of education, having a history of prior suicide attempts, suffering from depression, experiencing impulsivity, demonstrating prominent positive symptoms, and having a low level of negative symptoms (Hor and Taylor, 2010). Brain imaging studies have shown the possibility of identifying underlying biological mechanisms in establishing the neuroanatomical correlates of suicide in psychosis.

A neuroimaging study using magnetic resonance imaging (MRI) investigated structural abnormalities in schizophrenia patients with suicidal behaviors and compared them to MRIs of non-suicidal patients (Aguilar et al., 2008). This study reported that gray matter density was significantly reduced in the left superior temporal lobe and left orbitofrontal cortex in suicidal patients. Another study used functional MRI to demonstrate that task-specific suppression decreased more significantly in the left medial prefrontal cortex and left posterior cingulate cortex in schizophrenia patients with suicide risk compared to healthy controls (Zhang et al., 2013). A recent study using MRI indicated that, compared to non-attempters, attempters had significantly less gray matter volume in the bilateral inferior and superior temporal cortices, the left superior parietal, the thalamus and supramarginal regions, the right insula, and the superior, rostral middle frontal regions. The regions in which the differences were reported are part of the neural circuitries that modulate impulse control and emotion regulation (Giakoumatos et al., 2013). Based on previous studies, we could predict that the neuronal integrity of fronto-temporo-limbic circuits is important for suicidal behavior in schizophrenic patients, yet there has been no investigation of the abnormality of white matter (WM) reflecting the neuronal

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integrity in the brain.

Diffusion tensor imaging (DTI) is a useful imaging modality that measures the directional coherence of diffusion within axonal bundles and reflects structural integrity. DTI has been used to investigate the alteration of WM integrity in patients with major depressive disorder (Zou et al., 2008). Voxel-based analysis (VBA) offers several advantages for analyzing anatomical abnormality on DTI measuring fractional anisotropy (FA) and mean diffusivity (MD), although the limitations of VBA include alignment difficulty and the smoothing of problems that impeded the investigation of specific axonal or myelin abnormalities. Tract-Based Spatial Statistics (TBSS) can resolve such misalignment and smoothing issues. TBSS also compares abnormal distributions of FA in certain brain regions (Smith et al., 2006). Therefore, we conducted DTI with TBSS, using multiple measures, such as FA, MD, axial diffusivity (AD) and radial diffusivity (RD), in patients with schizophrenia or schizophreniform disorder. We included these patients in a group as they have similar psychopathology (Barrett et al., 2011). The results indicated that 60% to 80% of patients with schizophreniform disorder will progress to schizophrenia and their suicidality is very high—similar to that of schizophrenic patients (Fenton et al., 1997; Sadock and Sadock, 2007). Given these considerations, we hypothesized that patients with schizophrenia or schizophreniform disorder would show altered integrity of WM tracts in the fronto-temporo-limbic circuits between groups with and without a history of suicide attempts. We also investigated the relationship between structural alterations in the brain and neurocognitive functions and clinical symptoms in these patients.

2. Methods

2.1. Subjects

The study sample consisted of 56 patients with schizophrenia ($n=46$) and schizophreniform disorder ($n=10$) [41 women and 15 men; age, 33.02 ± 13.13 (Mean ± SD) years]. The subjects were recruited at the CHA Bundang Medical Center through advertisements between January 2011 and May 2013. All subjects were 18 to 65 years old, Korean, and right-hand dominant.

Patients met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR) criteria for schizophrenia or schizophreniform disorder, as diagnosed by experienced psychiatrists using Structured Clinical Interviews to assess DSM-IV-TR (SCID) Axis I disorders. Exclusion criteria for all subjects included any history of mood disorder, alcohol and substance abuse or dependence, mental retardation, current or past serious medical or neurological disorders, pregnancy, and contraindications to brain MRI scanning, including metal implants.

Patients were categorized as either suicide attempters (with a history of any suicide attempts, defined as a self-destructive behavior with intent or ideation to die) or non-attempters (with no such history) after onset of schizophrenia or schizophreniform disorder based on SCID (Barrett et al., 2011; Jia et al., 2010). Suicide attempters ($n=15$) had a history of 1.47 ± 0.74 attempts by drug intoxication, wrist cutting, hanging, or falling. Every recent suicide attempt was made within the year (4.47 ± 2.42 months, Mean ± SD ago) preceding the MRI scan. Medications provided to the patients were atypical antipsychotics, including aripiprazole, olanzapine, risperidone, and quetiapine and benzodiazepines as anxiolytics, including lorazepam, alprazolam and clonazepam. Antipsychotic doses at the time of the scan were calculated by the dose equivalent to chlorpromazine (Leucht et al., 2014). The benzodiazepine dosage was limited to a once-a-day 1 mg dose equivalent to lorazepam and the mean dosage at the time of scan was 0.68 mg/day (SD=0.42). Patients were assessed for severity of clinical symptoms using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989), the total score of Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989), the total score of Scale for the Assessment of Positive Symptoms (SAPS) (Minas et al., 1992), the Clinical Global Impression Severity Scale (CGI-S) (Haro et al., 2003), and the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960). Intelligence Quotient (IQ) was estimated from the Wechsler Adult Intelligence Scale (K-WAIS) (Wechsler, 1981). Only the attempters were assessed for suicide intent by the Suicide Intent Scale (SIS) (Pierce, 1981). We assessed neurocognitive function of the patients by means of Korean standardized neurocognitive tests including the picture arrangement test, by a trained clinical psychologist (see Supplementary Text).

All study procedures complied with the CHA Bundang Medical Center Institutional Review Board regulations, the Declaration of Helsinki, and the principles of good clinical practice. After a complete description of the study was given to the subjects, their written informed consent was obtained.

2.2. MRI acquisition and image processing

Diffusion data were acquired on a 3 T GE Signa HDxt scanner (GE Healthcare, Milwaukee, WI, USA). Diffusion-weighted images were acquired using an echo planar imaging (EPI) sequence, with the following parameters: repetition time (TR) 17000 ms, echo time (TE) 108 ms, field of view (FOV) 24 cm, 144×144 matrix, 1.7 mm slice thickness, and 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 of spatial sensitivity encoding techniques (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 (AC-PC) 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 were estimated from the diffusion-weighted images using the least-squares method (approximate scan time=17 min).

Voxel-wise statistical analysis of the fractional anisotropy (FA) data was performed using TBSS version 1.2, implemented in the FMRIB Software Library (FSL version 4.1, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl) according to the standard procedure (Smith et al., 2006). First, DTI preprocessing, including skull stripping using the Brain Extraction Tool (BET) and eddy current correction, were performed using the FSL. FA images were created by fitting a tensor model to the raw diffusion data (Smith, 2002). All subjects' FA data were then aligned into the standard space (Montreal Neurologic Institute 152 standard) using the FMRIB's Nonlinear Image Registration Tool (FNIRT). All transformed FA images were combined and applied to the original FA map, resulting in a standard-space version FA map. All transformed FA images were averaged to create a mean FA image, which was then thinned (skeletonized) to create a mean FA skeleton, taking only the centers of WM tracts. The skeleton was thresholded by FA > 0.2 (TBSS default) to include only major fiber bundles.

Three-dimensional individual FA skeletons were extracted from all 4D-skeletonized images. Then, mean FAs of the difference in the two groups of brain FA skeleton, as well as its components were calculated using 3D-slicer (v3.6.3, http://www.slicer.org). All extracted skeletons were overlaid with the Johns Hopkins University (JHU) DTI-based probabilistic tractography atlas, which contains 50 WM tracts/regions (Hua et al., 2008; Mori et al., 2005; Wakana et al., 2007). The averaged DTI indices were then calculated for each atlas region.

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