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A diffusion tensor imaging study of suicide attempters

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ABSTRACT

Background: Few studies have examined white matter abnormalities in suicide attempters using diffusion tensor imaging (DTI). This study sought to identify white matter regions altered in individuals with a prior suicide attempt.
Methods: DTI scans were acquired in 13 suicide attempters with major depressive disorder (MDD), 39 non-attempters with MDD, and 46 healthy participants (HP). Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were determined in the brain using two methods: region of interest (ROI) and tract-based spatial statistics (TBSS). ROIs were limited *a priori* to white matter adjacent to the caudal anterior cingulate cortex, rostral anterior cingulate cortex, dorsomedial prefrontal cortex, and medial orbitofrontal cortex.
Results: Using the ROI approach, suicide attempters had lower FA than MDD non-attempters and HP in the dorsomedial prefrontal cortex. Uncorrected TBSS results confirmed a significant cluster within the right dorsomedial prefrontal cortex indicating lower FA in suicide attempters compared to non-attempters. There were no differences in ADC when comparing suicide attempters, non-attempters and HP groups using ROI or TBSS methods.
Conclusions: Low FA in the dorsomedial prefrontal cortex was associated with a suicide attempt history. Converging findings from other imaging modalities support this finding, making this region of potential interest in determining the diathesis for suicidal behavior.

1. Introduction

Suicide is the eleventh leading cause of death in the United States with over 30,000 individuals dying by suicide annually (Centers for Disease Control and Prevention, 2010). About 90% of suicide attempters have an Axis I diagnosis, and 55–70% have a mood disorder (Kessler et al., 2005). Thus, individuals with mood disorders represent a high-risk population, with 16% of individuals with major depressive disorder (MDD) reporting at least one lifetime suicide attempt (Chen and Dilsaver, 1996). Prospective studies of suicide are difficult partly because of its low base rate (Hawton and van Heeringen, 2009), therefore identifying unique biomarkers associated with nonfatal suicidal behavior, which is more common, may improve our ability to determine suicide risk in MDD. Moreover, since the pathophysiology of suicidal behavior is poorly understood, identification of abnormalities in underlying neural circuitry may help delineate the neurobiological basis for suicide risk.

Deep white matter hyperintensities (DWMH) are reported in mood disordered individuals with a past suicide attempt compared to mood disordered non-attempters (Ahearn et al., 2001; Ehrlich et al., 2004, 2005; Pompili et al., 2008). Such deficits can be studied with diffusion tensor imaging (DTI), which characterizes water movement in white matter fibers using two diffusivity measures, fractional anisotropy (FA) and apparent diffusion coefficient (ADC). FA measures the directionality of water diffusion, i.e. to what extent white matter fibers have the same direction and are intact, whereas

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ADC measures the amount of diffusion in a given voxel, regardless of direction. Only one DTI study has examined the effect of past suicide attempt in MDD (Jia et al., 2010). A whole brain voxel-based analysis found low FA in the left anterior limb of the internal capsule in depressed suicide attempters compared to both depressed non-attempters and healthy participants (HPs), and low FA in the right lentiform nucleus in depressed suicide attempters compared to depressed non-attempters. Although these findings are of significant interest, whole brain voxel-based analysis is sensitive to poor registration (Bookstein, 2001) and is not limited to white matter tissue. Other studies have examined FA in suicide attempters with traumatic brain injury (TBI), showing a non-significant increase in FA in the anterior thalamic radiation of individuals with past suicidal behavior (Lopez-Larson et al., 2013) and a positive correlation between current suicidal ideation and FA in the cingulate (Yurgelun-Todd et al., 2011).

In this study, we determined FA and ADC using a region of interest (ROI) analysis and tract-based spatial statistics (TBSS) in depressed individuals with and without a history of suicide attempt, and HPs. TBSS is a method that overcomes registration issues associated with whole brain voxel-based analyses by performing a non-linear registration to a white matter skeleton that represents the center of the main fiber bundles (Smith et al., 2006). The following bilateral ROIs were chosen *a priori* based on reported white matter deficits in suicide attempters in frontal cortical regions in the literature: medial orbitofrontal cortex (MOFC; Mahon et al., 2012; Oquendo et al., 2003), dorsomedial prefrontal cortex (DMPFC; Amen et al., 2009; Jollant et al., 2008; Oquendo et al., 2003; Willeumier et al., 2011), rostral anterior cingulate cortex (rACC; Willeumier et al., 2011) and caudal anterior cingulate cortex (cACC; Amen et al., 2009; Oquendo et al., 2003). We hypothesized that suicide attempters would have lower FA in white matter adjacent to midline frontal cortex regions compared to both non-attempters and HPs. Given the lack of research on ADC in suicide attempters, the ADC analysis was exploratory without a specific hypothesis.

2. Methods

2.1. Subjects

Participants were recruited through the Molecular Imaging and Neuropathology Division (MIND) Clinic at Columbia University (New York, NY, USA). Fifty-two MDD subjects who met DSM-IV (DSM-IV; American Psychiatric Association, 1994) criteria for a current major depressive episode (MDE) and 46 HPs were included. MDD participants were classified as suicide attempters ($N = 13$, with at least one past suicide attempt) and non-attempters ($N = 39$). Inclusion criteria were assessed through history, chart review, clinical interview, review of systems, physical examination, routine blood tests, pregnancy test, urine toxicology and EKG. Criteria for MDD participants included: 1) age 18–65 years; 2) meet DSM-IV criteria for current MDE; 3) Hamilton Depression Rating Scale (17-item) minimum score of 16; 4) capacity to consent; and *absence of*: 5) psychotropic medications for at least 2 weeks; 6) lifetime alcohol or substance abuse or dependence; 7) lifetime exposure to 3,4-methylenedioxymethamphetamine; 8) significant medical conditions; 9) pregnancy; and 10) psychosis, bipolar disorder, or schizophrenia. Criteria for HPs were similar except for the required absence of psychiatric history and any history of a mood or psychotic disorder or suicidal behavior in a first-degree relative. The Institutional Review Board of the New York State Psychiatric Institute approved the protocol, and subjects gave written informed consent.

2.2. Clinical measures

Diagnoses were based on the Structured Clinical Interview for DSM-IV (SCID I; First et al., 1995). The Beck Depression Inventory (BDI; Beck et al., 1961) and the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) assessed self- and clinician-rated depression severity, respectively. Hopelessness was assessed with the Beck Hopelessness Scale (BHS; Beck and Steer, 1988). Medical damage consequent to the suicide attempt was measured by the Beck Medical Lethality Scale (Beck et al., 1975), which scores medical damage from 0 (no injury) to 8 (fatal). The Beck Scale for Suicidal Ideation (SSI; Beck et al., 1979) measured current suicidal ideation and the Suicide Intent Scale (SIS; Beck et al., 1974) retrospectively measured intent at the time of the most lethal attempt. Patients on antidepressant treatment underwent a two-week medication washout prior to neuroimaging (6 weeks for fluoxetine). For symptomatic relief, one subject (attempter) was on a benzodiazepine until five days prior to scanning and another (non-attempter) on a hypnotic until eight days prior to scanning.

2.3. Image acquisition

All participants underwent a magnetic resonance imaging (MRI) scan. Images were acquired on a 3.0T GE MR scanner. Anatomical T1-3D was acquired with the following parameters: echo time (TE)=2.8 ms, repetition time (TR) = 7.1 ms, field of view (FOV) = 256×256 mm^2, voxel size = $1 \times 1 \times 1$ mm^3, number of slices = 178, with an acquisition time of about 5 min. Diffusion images were acquired using a single-shot EPI (echo planar imaging) sequence. Scan parameters were as follows: TR = 14,000 ms, TE = 82 ms, Flip Angle 90°, slice thickness = 3 mm, FOV (field of view)= 240×240 mm^2, voxel dimensions $0.95 \times 0.95 \times 3$ mm, acquisition matrix = 256×256, b value = 1000 s/mm^2, and 25 collinear directions with 5 non-weighted images. DTI scan time was approximately 11 min.

2.4. Image processing

2.4.1. Diffusion tensor imaging (DTI)

Each DTI image was run through a series of quality assurance tests for common artifacts, including ghosting, ringing, slice-wise intensity, venetian blind, and gradient-wise motion artifacts (Liu et al., 2010). Diffusion images were then corrected for distortion induced by gradient coils and simple head motion using the eddy current correction routine within FSL (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/). FSL's Brain Extraction Tool (BET) was used to remove non-brain tissue from the image. Following this, Camino's dtfit [http://web4.cs.ucl.ac.uk/research/medic/camino/pmwiki/pmwiki.php] was used to estimate maps of scalar measures (FA and ADC). The algorithm computes the least-squares-fit diffusion tensor with non-linear optimization using a Levenberg–Marquardt algorithm, constrained to be positive by fitting its Cholesky decomposition.

2.4.2. Region of interest (ROI) determinations

To obtain ROIs for analysis, original anatomical T1 images were preprocessed over the entire Freesurfer (http://surfer.nmr.mgh.harvard.edu/) cortical thickness pipeline. ROIs were created using the cortical parcellation algorithm based on the Desikan Killiany atlas in Freesurfer and each white matter voxel was labeled based on the closest cortical voxel (Salat et al., 2009). The following bilateral labels were used in the ROI analysis: rACC, cACC, MOFC, and superior frontal cortex. We renamed the superior frontal cortex label "DMPFC" to be consistent with the literature and provide a more descriptive name for the region.