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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) was determined in the brain using two methods: region of interest (ROI) and tract-based spatial statistics (TBSS). ROIs were limited *a priori* to

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Contributors

Doreen M. Olvet performed image processing, undertook the statistical analysis and wrote the manuscript. Denis Peruzzo developed the image processing steps for diffusion tensor imaging (DTI) processing. Binod Thapa-Chhetry performed image processing. M. Elizabeth Sublette, Gregory M. Sullivan, Maria A. Oquendo, J. John Mann, and Ramin V. Parsey designed the study. All authors contributed to and have approved the final manuscript.

Conflict of Interest

D.M.O., D.P., B.T., and R.V.P. have no conflicts to declare. M.A.O. receives royalties for the use of the Columbia Suicide Severity Rating Scale and received financial compensation from Pfizer for the safety evaluation of a clinical facility, unrelated to the current manuscript. She was the recipient of a grant from Eli Lilly to support a year's salary for the Lilly Suicide Scholar, Enrique Baca-Garcia, MD, PhD. She has received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuka, Pfizer, Sanofi-Aventis, and Shire. Her family owns stock in Bristol Myers Squibb. J.J.M. received grants from GlaxoSmithKline and Novartis. M.E.S. is the recipient of a grant for nutritional supplements from Unicity, International, unrelated to the current manuscript.

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.

Keywords

Suicide attempt; major depressive disorder; white matter; diffusion tensor imaging; tract-based spatial statistics; dorsomedial prefrontal cortex

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 to 70% have a mood disorder (Kessler, Berglund, Borges, Nock, & Wang, 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 & Dilsaver, 1996). Prospective studies of suicide are difficult partly because of its low base rate (Hawton & 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., 2005; Ehrlich et al., 2004; 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 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, Burdick, Wu, Ardekani, & Szeszko, 2012; Oquendo et al., 2003), dorsomedial prefrontal cortex (DMPFC; Amen, Prunella, Fallon, Amen, & Hanks, 2009; Jollant et al., 2008; Oquendo et al., 2003; Willeumier, Taylor, & Amen, 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.

Methods

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 to 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) life-time 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.

Clinical measures

Diagnoses were based on the Structured Clinical Interview for DSM IV (SCID I; First, Spitzer, Gibbon, & Williams, 1995). The Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 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 & Steer, 1988). Medical damage consequent to the suicide attempt was measured by the Beck Medical Lethality Scale (Beck, Beck, & Kovacs, 1975), which scores medical damage from 0 (no injury) to 8 (fatal). The Beck Scale for Suicidal Ideation (SSI; Beck, Kovacs, & Weissman, 1979) and the Suicide Intent Scale (SIS; Beck, Schuyler, & Herman, 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.

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)=2.8ms, repetition time (TR)=7.1 ms, field of view (FOV)=256×256 mm², voxel size=1×1×1 mm³, number of slices=178, with an acquisition time of about 5 minutes. Diffusion images were acquired using a single-shot EPI (echo planar imaging) sequence. Scan parameters were as follows: TR=14000 ms, TE=82 ms, Flip Angle 90 degrees, slice thickness=3 mm, FOV (field of view)=240×240 mm², voxel dimensions 0.95×0.95×3 mm, acquisition matrix=256×256, b value = 1000 s/mm², and 25 collinear directions with 5 non-weighted images. DTI scan time was approximately 11 minutes.

Image processing

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 Levenburg-Marquardt algorithm, constrained to be positive by fitting its Cholesky decomposition.

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.

Coregistration of DTI and T1 Images—The cropped T1 from Freesurfer was subpar for registration to the DTI image. Therefore, the T1 images were cropped and corrected for image non-uniformity using the Bias Field Corrector in Advanced Normalization Tools's atropos (ANTS; <http://www.picsl.upenn.edu/ANTS/>). After processing both the DTI and anatomical T1 scans, the DTI image was co-registered to the cropped T1 image using ANTS, which has been shown to be superior to other image registration techniques (Klein et al., 2009; Klein et al., 2010; Murphy et al., 2011). The inverse transformation was applied to the cortical map in order to place ROIs into DTI space for analysis. Finally, mean FA and ADC values were calculated in each ROI using Camino's dtfit (see DTI processing section above). Cortical thickness in each ROI was calculated using Freesurfer (Fischl & Dale, 2000; Fischl, Sereno, & Dale, 1999).

Tract-Based Spatial Statistics (TBSS) analysis—TBSS analysis (Smith et al., 2006) of the FA and ADC diffusion maps included several steps. Individual FA maps were non-linearly aligned to a common FMRIB58 FA template. Aligned FA maps were averaged to obtain a study mean FA map and a white matter skeleton was computed on the mean FA map. The white matter skeleton was then thresholded (FA ≥ 0.2) to exclude gray matter voxels. Each individual FA map was projected onto the common FA skeleton to obtain the individual FA skeleton, on which a voxel-wise analysis was performed to examine differences between the two populations. The white matter skeleton derived from the FA maps was applied to the ADC maps to perform voxel-wise analysis on ADC data.

Statistical analysis

Data were statistically evaluated using IBM SPSS Statistics (SPSS Inc., Chicago, Illinois, USA, Version 19.0). Comparisons of demographic and clinical variables were performed with a univariate analysis of variance (ANOVA) for continuous variables and chi-square analyses for categorical variables with group (HP vs. attempter vs. non-attempter) as the between-subjects factor. *Post-hoc* comparisons were corrected for multiple comparisons using the Bonferroni method ($p < 0.05$, corrected). Non-parametric tests (Mann-Whitney U) were performed for non-normally distributed variables (number of MDEs, length of current depressive episode and days off antidepressants). Covariates were added where there were significant group differences on demographic or clinical variables and included in the analysis as indicated. Correlations between clinical and diffusion measures were performed in the MDD group only using Spearman's Rho.

For the ROI analyses, a univariate analysis of covariance (ANCOVA) was used to compare attempters, non-attempters, and HPs with age as a covariate. To determine whether differences identified in the omnibus ANCOVA were specific to suicide history status, we performed a follow-up ANCOVA comparing attempters and non-attempters controlling for age, number of MDEs, length of current MDE, and BDI score.

For the TBSS analyses, we used the general linear model (GLM) method with the permutation-based non-parametric testing included in the FSL tools. Significance threshold was set to $p < 0.05$ corrected for family-wise error (FWE) using the Threshold-Free Cluster Enhancement (TFCE) method in FSL's randomise tool. The TBSS analysis was performed for FA and ADC maps: HP vs. attempter vs. non-attempter groups adjusted for (mean centered) age, BDI score, number of MDEs, and length of current MDE episode. Only clusters with a minimum of 50 voxels were considered significant (see Chuang, Wu, Huang, Weng, & Yang, 2013; Guo et al., 2012a; Guo et al., 2012b; Osoba et al., 2013; Rae et al., 2012). Mean FA values for significant clusters were extracted to examine correlations between clusters and clinical variables.

Comparisons between the HP and MDD groups are provided in the online Supplementary Material.

Results

Demographics and Clinical Measures

Demographic and clinical data are in Table 1. There were no differences with respect to sex ($\chi^2(2) = 2.14, p = 0.34$), race ($\chi^2(2) = 0.19, p = 0.91$), or handedness ($\chi^2(4) = 5.71, p = 0.22$) distributions among HP, attempter and non-attempter groups. However, the groups differed on age ($F(2,95) = 4.17, p = 0.02$). *Post-hoc* analysis indicated that HPs were 7 years younger on average than the non-attempter group ($p = 0.01$), but there were no age differences between HP and attempter groups ($p = 1.00$) or between attempter and non-attempter groups ($p = 0.85$).

Attempters had more depressive episodes than non-attempters (Mann-Whitney $U = 157.5, p = 0.046$); however, current episode length was about 6 months shorter in the attempter than the non-attempter group (Mann-Whitney $U = 98.0, p = 0.017$). Attempter and non-attempter groups were comparable on clinician-evaluated depression severity (HDRS: $t(50) = -0.82, p = 0.42$), previous antidepressant use ($\chi^2(1) = 1.17, p = 0.28$) and days off antidepressants (Mann-Whitney $U = 20.5, p = 0.79$). However, the attempter group reported greater current suicidal ideation (SSI: $t(50) = -2.80, p = 0.01$), greater current self-reported depression severity (BDI: $t(50) = -2.14, p = 0.04$), and a trend toward greater hopelessness (BHI: $t(41) = -2.01, p = 0.051$).

Table 2 characterizes suicide attempt history in the attempter group and Table 3 shows individual subject data regarding the most recent attempt and the FA values in the bilateral DMPFC. The average number of lifetime suicide attempts was 2.1 (SD=1.8), with half the subjects attempting once (N=7). The median time since the most recent attempt was 5.9 years, and the average age at this attempt was 20.5 years (SD=8.6). Lethality scores for the most recent attempt were generally low, averaging a 2.2 (SD=1.9), with drug overdose and cutting the two most commonly used methods. The most lethal suicide attempt was also the most recent suicide attempt in all but one case.

DTI in Suicide Attempters Compared with Non-attempters and HP

ROI analysis—Table 4 lists FA values for HP, suicide attempters and non-attempters in each of the four bilateral ROIs investigated. Omnibus ANCOVA analyses indicated that the three groups differed in all ROIs, with the exception of the right rACC. The only region that differentiated suicide attempters and non-attempters was the DMPFC (Table 4, right: $p=0.02$, Cohen's $d=0.50$; left: $p=0.03$, Cohen's $d=0.50$). In magnitude, FA values in the attempter group for this region were 2.13% (right DMPFC) and 2.08% (left DMPFC) lower than in the non-attempter group.

Supplementary Table 1 lists ADC values for suicide attempters and non-attempters in each of the four bilateral ROIs investigated. There were no group differences in ADC in any ROI.

TBSS analysis—Table 5 lists the location, cluster extent and p -value for the significant TBSS clusters with corresponding TBSS maps in Figure 1 and mean and standard deviation values in Table 6. In the TBSS analysis, six clusters were lower in the non-attempter group than the HP group. These clusters had a signal peak in the left body of the corpus callosum (Cluster 1, Cohen's $d=1.00$), the left anterior thalamic radiation (Cluster 2, Cohen's $d=0.80$), the left inferior fronto-occipital fasciculus (Cluster 3, Cohen's $d=0.80$), the right medial forebrain bundle (Cluster 4, Cohen's $d=1.00$), the right inferior longitudinal fasciculus (Cluster 5, Cohen's $d=0.80$) and the right anterior thalamic radiation (Cluster 6, Cohen's $d=0.80$). These clusters essentially overlap with those identified in the HP vs. MDD comparison (see Supplementary Material). No clusters differentiated the attempter group from either the non-attempters or the HP group.

We also examined differences between the attempter and non-attempter groups using the TBSS map uncorrected for multiple comparisons. Restricting our analysis to clusters with a minimum of 50 voxels and a p -value < 0.01 , one cluster identified low FA in the attempter compared to the non-attempter group, with a signal peak in the right DMPFC (Figure 1; Cohen's $d=1.20$). There was a small cluster identified in the left DMPFC (26 voxels, $p=0.014$), but this did not meet our cluster threshold. There were no clusters indicating lower FA in non-attempters than the attempter groups.

No clusters identified in the TBSS analysis of ADC data differentiated the three groups.

Correlations between DTI and Clinical Measures

In the entire MDD sample, there were no significant correlations between FA or ADC and clinical measures after correcting for multiple comparisons. In the attempter group, there were no significant correlations between FA or ADC and measures of suicidal behavior.

Exploratory Analyses

We also explored variables that may have an impact on diffusion measures. Cortical thickness in the ROIs investigated were comparable in the three groups (all p -values > 0.05), therefore this variable was not included as a covariate. Fourteen MDD participants had previous antidepressant use (9 attempters and 5 non-attempters). After removing these subjects, the FA ROI results were unchanged: FA in the DMPFC differentiated the

attempters and non-attempters (right: $p=0.047$, Cohen's $d=0.91$; left: $p=0.043$, Cohen's $d=0.93$). In order to rule out bias due to parametric testing with unequal sample sizes, we performed the ROI analysis on a randomly selected subsample (13 attempters and 13 non-attempters) matched on age, sex, length of current episode, total number of episodes, previous antidepressant use, days off antidepressants, HAM-D and BDI scores. The only ROI that differentiated these groups was the DMPFC (right: $p=0.008$, Cohen's $d=1.14$; left: $p=0.02$, Cohen's $d=1.01$).

We divided the attempter group based on suicide attempt method (drugs vs. other) and by the number of attempts (one vs. multiple); however, there were no differences in FA or ADC when comparing these groups.

Discussion

The current study assessed suicide attempters using a 25-direction DTI protocol using two different analytic approaches, ROI and TBSS. Suicide attempters had low FA compared to non-attempters or HP in white matter adjacent to the DMPFC. This finding was reproduced by an uncorrected TBSS analysis comparing suicide attempters and non-attempters. The identified cluster was located in a short association bundle within right DMPFC. Support for abnormal functioning in the DMPFC of suicide attempters exists in the literature. A positron emission tomography (PET) study showed that high lethality suicide attempters had reduced cerebral glucose metabolism in the DMPFC compared to low lethality attempters (Oquendo et al., 2003) and decreased cerebral glucose metabolism in the DMPFC was also reported in two single-photon emission computed tomography (SPECT) studies comparing suicide attempters and HPs (Amen et al., 2009; Willeumier et al., 2011). Finally, a functional magnetic resonance imaging (fMRI) study reported decreased activation in the DMPFC of remitted MDD suicide attempters vs. non-attempters (Jollant et al., 2008). Our finding suggests that functional abnormalities in the DMPFC of suicide attempters may be related to white matter deficits.

Deficits in the DMPFC of suicide attempters are intriguing due to the prominent role of this region in the brain's default mode network (Raichle et al., 2001). The default mode network consists of the DMPFC, anterior medial frontal cortex, ventral medial prefrontal cortex, posterior cingulate cortex, medial temporal lobe, inferior parietal lobe, and the temporo-parietal junction. These regions are functionally correlated when individuals are at rest (Greicius, Krasnow, Reiss, & Menon, 2003), deactivate when actively performing a task (Buckner, Andrews-Hanna, & Schacter, 2008), and are connected by white matter tracts (Greicius, Supekar, Menon, & Dougherty, 2009). Of particular interest, the DMPFC is thought to play an important role in self-referential processing (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Lemogne, Delaveau, Freton, Guionnet, & Fossati, 2012). Self-focus has been an integral part of major cognitive theories of depression (Clark & Beck, 1999) and it has been hypothesized that suicidal behavior is an attempt to escape from negative self-awareness resulting from perceived failure (Baumeister, 1990). Therefore, white matter deficits in DMPFC of suicide attempters may relate to maladaptive self-referential processing.

The implication of the DMPFC finding extends beyond understanding the pathophysiology of suicidal behavior and provides a link to clinical treatment options that may benefit those considering a suicidal act. Cognitive therapy that focuses on self-awareness, such as Mindfulness-Based Cognitive Therapy (MBCT; Hayes, Follette, & Linehan, 2004), could potentially reduce the amount of self-focus at the height of the suicidal thoughts buying clinicians time to intervene. There is some evidence that cognitive behavioral therapy reduced medial prefrontal cortex activation in response to self-referential processing of negative stimuli in individuals with MDD (Yoshimura et al., 2013). This finding appears to be specific to cognitive behavioral therapy, as antidepressant treatment did not alter DMPFC activity during self-referential processing (Lemogne et al., 2010). The relationship between the DMPFC and self-focus in individuals at-risk for suicidal behavior may be leveraged to develop treatment targeting these thought patterns.

Only one other study used DTI to study depressed suicide attempters. Using a voxel-based analysis, Jia and colleagues (Jia et al., 2010) reported low FA in the left anterior limb of the internal capsule and the right lentiform nucleus in depressed suicide attempters compared to depressed non-attempters. We did not use whole brain voxel-based techniques (Bookstein, 2001; Melonakos et al., 2011), which may explain why our results are not consistent with that study. Furthermore, there is some evidence that voxel-based analysis may not reliably register white matter tracts (Melonakos et al., 2011). Additionally, our analysis excluded gray matter regions because it is unclear how to interpret diffusion differences in subcortical gray matter. Therefore, we cannot replicate their findings in the lentiform nucleus. Furthermore, Jia and colleagues (Jia et al., 2010) did not report clinical characteristics of the suicide attempts, and therefore we cannot determine how closely their suicide attempter sample compares to ours.

We did not find any group differences in ADC when comparing attempters, non-attempters and HPs. The few studies of ADC in depression show mixed findings. Two studies reported higher ADC in MDD (Abe et al., 2010; Wu et al., 2011), and two reported no difference in MDD participants compared to HPs (Korgaonkar et al., 2011; Murphy et al., 2012). Thus, the studies concerning ADC and depression or suicide risk are inconclusive. However, ADC is a relatively nonspecific marker of diffusivity. Future investigations performed with higher resolution diffusion scans and comprehensively assessing multiple measures of diffusivity could clarify the role of diffusivity in suicidal behavior.

We did not find differences in cortical thickness when comparing depressed suicide attempters, non-attempters and HP subjects. This result differs from that of Wagner and colleagues who found decreased cortical thickness in the dorsal ACC (extending into the DMPFC) in a high-risk group comprised of depressed suicide attempters and depressed first-degree relatives of suicide attempters, compared to both depressed non-attempters and healthy participants (Wagner et al., 2012). Additional studies are needed to clarify this discrepancy.

Study Limitations

Firstly, we studied only 13 depressed suicide attempters. Regardless, we were able to detect differences in FA between the attempter and non-attempters groups using ROI and

uncorrected TBSS methods with a moderate to large effect size. Other key characteristics of suicidal behavior, such as attempt method, lethality, and number of suicide attempts, may impact brain-imaging findings (Boisseau et al., 2013; Oquendo et al., 2003). We explored whether these variables related to FA or ADC, and found no significant associations, but we urge caution in interpreting this data due to the small sample size. Secondly, our HP group was younger than the non-attempter group, although we did control for age in group comparisons. Thirdly, the most recent suicide attempt ranged from 19 days to 39 years before the DTI scan. Optimally, one would obtain DTI scans before a suicide attempt or on recent suicide attempters; however, there is evidence that suicide risk is still measurable up to 37 years after the initial attempt (Angst, Angst, Gerber-Werder, & Gamma, 2005; Bradvik, Mattisson, Bogren, & Nettelbladt, 2008; Dahlgren, 1977; Mutzell, 1997; Suominen et al., 2004). Furthermore, attempters in our study continued to have increased suicidal ideation compared to non-attempters, indicating a long-term risk for suicidal behavior. Fourthly, 14 MDD participants were not antidepressant naive. It is possible that antidepressants impact measures of white matter integrity; however, follow-up analyses did not support this conclusion. Finally, although our results using ROI and TBSS analyses were comparable, there are limitations with each method. FA derived from the ROI analysis was averaged over large regions, therefore the exact location where white matter tracts differ among the groups is impossible to determine. TBSS performs comparisons only on a white matter skeleton template, which does not include the entire extent of the white matter tracts throughout the brain. Additionally, we did not find significant group differences using the strict FWE correction, the gold standard method.

Our finding of low FA in the DMPFC in suicide attempters suggests that white matter abnormalities may contribute to functional deficits previously observed in this important brain region associated with suicidal behavior. Future research should follow-up on this finding using higher resolution DTI scans in order to examine diffusion measures using fibre tractography. Clarifying the significance of this finding will bring us closer to understanding the pathophysiology of suicidal behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Abe O, Yamasue H, Kasai K, Yamada H, Aoki S, Inoue H, Takei K, Suga M, Matsuo K, Kato T, Masutani Y, Ohtomo K. Voxel-based analyses of gray/white matter volume and diffusion tensor data in major depression. *Psychiatry Res.* 2010; 181:64–70. [PubMed: 19959342]
- Ahearn EP, Jamison KR, Steffens DC, Cassidy F, Provenzale JM, Lehman A, Weisler RH, Carroll BJ, Krishnan KR. MRI correlates of suicide attempt history in unipolar depression. *Biol Psychiatry.* 2001; 50:266–270. [PubMed: 11522261]
- Amen DG, Prunella JR, Fallon JH, Amen B, Hanks C. A comparative analysis of completed suicide using high resolution brain SPECT imaging. *J Neuropsychiatry Clin Neurosci.* 2009; 21:430–439. [PubMed: 19996252]
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition): DSM-IV. American Psychiatric Association; Washington, DC: 1994.
- Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain's default network. *Neuron.* 2010; 65:550–562. [PubMed: 20188659]
- Angst J, Angst F, Gerber-Werder R, Gamma A. Suicide in 406 mood-disordered patients with and without long-term medication: a 40 to 44 years' follow-up. *Archives of Suicide Research.* 2005; 9:279–300. [PubMed: 16020171]
- Baumeister RF. Suicide as escape from self. *Psychol Rev.* 1990; 97:90–113. [PubMed: 2408091]
- Beck AT, Beck R, Kovacs M. Classification of suicidal behaviors: I. Quantifying intent and medical lethality. *Am J Psychiatry.* 1975; 132:285–287. [PubMed: 1115273]
- Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol.* 1979; 47:343–352. [PubMed: 469082]
- Beck, AT.; Schuyler, D.; Herman, I. Development of suicidal intent scales.. In: Beck, AT.; Resnik, HLP.; Lettieri, DJ., editors. *The prediction of suicide.* Charles Press; Bowie, MD: 1974.
- Beck, AT.; Steer, RA. *Manual for the Beck depression inventory.* Psychological Corporation; San Antonio: 1988.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961; 4:561–571. [PubMed: 13688369]
- Boisseau CL, Yen S, Markowitz JC, Grilo CM, Sanislow CA, Shea MT, Zanarini MC, Skodol AE, Gunderson JG, Morey LC, McGlashan TH. Individuals with single versus multiple suicide attempts over 10years of prospective follow-up. *Compr Psychiatry.* 2013; 54:238–242. [PubMed: 22995448]
- Bookstein FL. “Voxel-based morphometry” should not be used with imperfectly registered images. *Neuroimage.* 2001; 14:1454–1462. [PubMed: 11707101]
- Bradvik L, Mattisson C, Bogren M, Nettelbladt P. Long-term suicide risk of depression in the Lundby cohort 1947-1997--severity and gender. *Acta Psychiatr Scand.* 2008; 117:185–191. [PubMed: 18190676]
- Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci.* 2008; 1124:1–38. [PubMed: 18400922]
- Centers for Disease Control and Prevention. National Center for Injury Prevention and Control, Web-based Injury Statistics Query and Reporting System (WISQARS). 2010
- Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. *Biol Psychiatry.* 1996; 39:896–899. [PubMed: 8860192]
- Chuang TC, Wu MT, Huang SP, Weng MJ, Yang P. Diffusion tensor imaging study of white matter fiber tracts in adolescent attention-deficit/hyperactivity disorder. *Psychiatry Res.* 2013; 211:186–187. [PubMed: 23394679]
- Clark, DA.; Beck, AT. *Scientific Foundations of Cognitive Theory and Therapy of Depression.* John Wiley & Sons; New York: 1999.
- Dahlgren KG. Attempted suicides-35 years afterward. *Suicide Life Threat Behav.* 1977; 7:75–79. [PubMed: 613505]

- Ehrlich S, Breeze JL, Hesdorffer DC, Noam GG, Hong X, Alban RL, Davis SE, Renshaw PF. White matter hyperintensities and their association with suicidality in depressed young adults. *J Affect Disord.* 2005; 86:281–287. [PubMed: 15935248]
- Ehrlich S, Noam GG, Lyoo IK, Kwon BJ, Clark MA, Renshaw PF. White matter hyperintensities and their associations with suicidality in psychiatrically hospitalized children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 2004; 43:770–776. [PubMed: 15167094]
- First, M.; Spitzer, R.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P, Version 2.0). Biometrics Research Department, New York State Psychiatric Institute; New York: 1995.
- Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A.* 2000; 97:11050–11055. [PubMed: 10984517]
- Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage.* 1999; 9:195–207. [PubMed: 9931269]
- Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A.* 2003; 100:253–258. [PubMed: 12506194]
- Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb Cortex.* 2009; 19:72–78. [PubMed: 18403396]
- Guo WB, Liu F, Chen JD, Xu XJ, Wu RR, Ma CQ, Gao K, Tan CL, Sun XL, Xiao CQ, Chen HF, Zhao JP. Altered white matter integrity of forebrain in treatment-resistant depression: A diffusion tensor imaging study with tract-based spatial statistics. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012a
- Guo WB, Liu F, Xue ZM, Gao K, Wu RR, Ma CQ, Liu ZN, Xiao CQ, Chen HF, Zhao JP. Altered white matter integrity in young adults with first-episode, treatment-naïve, and treatment-responsive depression. *Neurosci Lett.* 2012b
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960; 23:56–62. [PubMed: 14399272]
- Hawton K, van Heeringen K. Suicide. *Lancet.* 2009; 373:1372–1381. [PubMed: 19376453]
- Hayes, SC.; Follette, VM.; Linehan, MM. Mindfulness and acceptance: expanding the cognitive behavioral tradition. The Guilford Press; New York: 2004.
- Jia Z, Huang X, Wu Q, Zhang T, Lui S, Zhang J, Amatya N, Kuang W, Chan RC, Kemp GJ, Mechelli A, Gong Q. High-field magnetic resonance imaging of suicidality in patients with major depressive disorder. *Am J Psychiatry.* 2010; 167:1381–1390. [PubMed: 20843871]
- Jollant F, Lawrence NS, Giampietro V, Brammer MJ, Fullana MA, Drapier D, Courtet P, Phillips ML. Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. *Am J Psychiatry.* 2008; 165:740–748. [PubMed: 18346998]
- Kessler RC, Berglund P, Borges G, Nock M, Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. *JAMA.* 2005; 293:2487–2495. [PubMed: 15914749]
- Klein A, Andersson J, Ardekani BA, Ashburner J, Avants B, Chiang MC, Christensen GE, Collins DL, Gee J, Hellier P, Song JH, Jenkinson M, Lepage C, Rueckert D, Thompson P, Vercauteren T, Woods RP, Mann JJ, Parsey RV. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage.* 2009; 46:786–802. [PubMed: 19195496]
- Klein A, Ghosh SS, Avants B, Yeo BT, Fischl B, Ardekani B, Gee JC, Mann JJ, Parsey RV. Evaluation of volume-based and surface-based brain image registration methods. *Neuroimage.* 2010; 51:214–220. [PubMed: 20123029]
- Korgaonkar MS, Grieve SM, Koslow SH, Gabrieli JD, Gordon E, Williams LM. Loss of white matter integrity in major depressive disorder: evidence using tract-based spatial statistical analysis of diffusion tensor imaging. *Hum Brain Mapp.* 2011; 32:2161–2171. [PubMed: 21170955]
- Lemogne C, Delaveau P, Freton M, Guionnet S, Fossati P. Medial prefrontal cortex and the self in major depression. *J Affect Disord.* 2012; 136:e1–e11. [PubMed: 21185083]

- Lemogne C, Mayberg H, Bergouignan L, Volle E, Delaveau P, Lehericy S, Allilaire JF, Fossati P. Self-referential processing and the prefrontal cortex over the course of depression: a pilot study. *J Affect Disord.* 2010; 124:196–201. [PubMed: 19945172]
- Liu Z, Wang Y, Gerig G, Gouttard S, Tao R, Fletcher T, Styner M, Liu BJ, Boonn WW. Quality control of diffusion weighted images. *SPIE Medical Imaging.* 2010:86280J–76280J-86289.
- Lopez-Larson M, King JB, McGlade E, Bueler E, Stoeckel A, Epstein DJ, Yurgelun-Todd D. Enlarged thalamic volumes and increased fractional anisotropy in the thalamic radiations in veterans with suicide behaviors. *Front Psychiatry.* 2013; 4:83. [PubMed: 23964245]
- Mahon K, Burdick KE, Wu J, Ardekani BA, Szeszko PR. Relationship between suicidality and impulsivity in bipolar I disorder: a diffusion tensor imaging study. *Bipolar Disord.* 2012; 14:80–89. [PubMed: 22329475]
- Melonakos ED, Shenton ME, Rath Y, Terry DP, Bouix S, Kubicki M. Voxel-based morphometry (VBM) studies in schizophrenia-can white matter changes be reliably detected with VBM? *Psychiatry Res.* 2011; 193:65–70. [PubMed: 21684124]
- Murphy K, van Ginneken B, Reinhardt JM, Kabus S, Ding K, Deng X, Cao K, Du K, Christensen GE, Garcia V, Vercauteren T, Ayache N, Commowick O, Malandain G, Glocker B, Paragios N, Navab N, Gorbunova V, Sporring J, de Bruijne M, Han X, Heinrich MP, Schnabel JA, Jenkinson M, Lorenz C, Modat M, McClelland JR, Ourselin S, Muenzing SE, Viergever MA, De Nigris D, Collins DL, Arbel T, Peroni M, Li R, Sharp GC, Schmidt-Richberg A, Ehrhardt J, Werner R, Smeets D, Loeckx D, Song G, Tustison N, Avants B, Gee JC, Staring M, Klein S, Stool BC, Urschler M, Werlberger M, Vandemeulebroucke J, Rit S, Sarrut D, Pluim JP. Evaluation of registration methods on thoracic CT: the EMPIRE10 challenge. *IEEE Trans Med Imaging.* 2011; 30:1901–1920. [PubMed: 21632295]
- Murphy ML, Carballedo A, Fagan AJ, Morris D, Fahey C, Meaney J, Frodl T. Neurotrophic tyrosine kinase polymorphism impacts white matter connections in patients with major depressive disorder. *Biol Psychiatry.* 2012; 72:663–670. [PubMed: 22609366]
- Mutzell S. Survival after attempted suicide in Sweden. A follow-up after 20 years. *International Journal of Adolescence and Youth.* 1997; 6:315–328.
- Oquendo MA, Placidi GP, Malone KM, Campbell C, Keilp J, Brodsky B, Kegeles LS, Cooper TB, Parsey RV, van Heertum RL, Mann JJ. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. *Arch Gen Psychiatry.* 2003; 60:14–22. [PubMed: 12511168]
- Osoba A, Hanggi J, Li M, Horn DI, Metzger C, Eckert U, Kaufmann J, Zierhut K, Steiner J, Schiltz K, Heinze HJ, Bogerts B, Walter M. Disease severity is correlated to tract specific changes of fractional anisotropy in MD and CM thalamus--a DTI study in major depressive disorder. *J Affect Disord.* 2013; 149:116–128. [PubMed: 23489404]
- Pompili M, Innamorati M, Mann JJ, Oquendo MA, Lester D, Del Casale A, Serafini G, Rigucci S, Romano A, Tamburello A, Manfredi G, De Pisa E, Ehrlich S, Giupponi G, Amore M, Tatarelli R, Girardi P. Periventricular white matter hyperintensities as predictors of suicide attempts in bipolar disorders and unipolar depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008; 32:1501–1507. [PubMed: 18572296]
- Rae CL, Correia MM, Altena E, Hughes LE, Barker RA, Rowe JB. White matter pathology in Parkinson's disease: the effect of imaging protocol differences and relevance to executive function. *Neuroimage.* 2012; 62:1675–1684. [PubMed: 22713671]
- Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A.* 2001; 98:676–682. [PubMed: 11209064]
- Salat DH, Greve DN, Pacheco JL, Quinn BT, Helmer KG, Buckner RL, Fischl B. Regional white matter volume differences in nondemented aging and Alzheimer's disease. *Neuroimage.* 2009; 44:1247–1258. [PubMed: 19027860]
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage.* 2006; 31:1487–1505. [PubMed: 16624579]
- Suominen K, Isometsa E, Suokas J, Haukka J, Achte K, Lonnqvist J. Completed suicide after a suicide attempt: a 37-year follow-up study. *Am J Psychiatry.* 2004; 161:562–563. [PubMed: 14992984]

- Wagner G, Schultz CC, Koch K, Schachtzabel C, Sauer H, Schlosser RG. Prefrontal cortical thickness in depressed patients with high-risk for suicidal behavior. *J Psychiatr Res.* 2012; 46:1449–1455. [PubMed: 22868048]
- Willeumier K, Taylor DV, Amen DG. Decreased cerebral blood flow in the limbic and prefrontal cortex using SPECT imaging in a cohort of completed suicides. *Transl Psychiatry.* 2011; 1:e28. [PubMed: 22832602]
- Wu F, Tang Y, Xu K, Kong L, Sun W, Wang F, Kong D, Li Y, Liu Y. White matter abnormalities in medication-naïve subjects with a single short-duration episode of major depressive disorder. *Psychiatry Res.* 2011; 191:80–83. [PubMed: 21145709]
- Yoshimura S, Okamoto Y, Onoda K, Matsunaga M, Okada G, Kunisato Y, Yoshino A, Ueda K, Suzuki SI, Yamawaki S. Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. *Soc Cogn Affect Neurosci.* 2013
- Yurgelun-Todd DA, Bueler CE, McGlade EC, Churchwell JC, Brenner LA, Lopez-Larson MP. Neuroimaging correlates of traumatic brain injury and suicidal behavior. *J Head Trauma Rehabil.* 2011; 26:276–289. [PubMed: 21734511]

Figure 1.

Coronal, sagittal, and axial view of the TBSS FA clusters (in red) superimposed on the FA skeleton (in green) and the MNI 152 template. All cluster ROIs present a significantly reduced FA ($p < 0.05$ after FWE correction unless otherwise indicated). Abbreviations: FWE=family-wise error, FA=fractional anisotropy, HP=healthy participant, MDD=major depressive disorder, MNI=Montreal Neurological Institute, ROI=region of interest, TBSS=tract-based spatial statistics.

Table 1

Demographic and Clinical Variables. Data are presented as mean $\pm$ standard deviation unless otherwise specified.

	Healthy Participant (N=46)	Suicide Attempters (N=13)	Non-Attempters (N=39)
Demographic Variables			
Sex, N (%) Male	25 (54.3)	6 (46.2)	15 (38.5)
Age, years	30.3 $\pm$ 9.3	33.4 $\pm$ 13.3	37.1 $\pm$ 11.4 ^{**}
Race, N (%) Caucasian	22 (47.8)	7 (53.8)	20 (51.3)
Handedness, N (%) Right	44 (95.7)	9 (75.0)	33 (89.2)
Clinical Variables			
Prior antidepressant use, N (%)	0 (0)	5 (38.5)	9 (23.1)
Number of days off antidepressants	-	36.8 $\pm$ 24.8	38.1 $\pm$ 23.7
Number of MDEs, median	-	4 [†]	2
Length of Current Episode, weeks	-	171.7 $\pm$ 320.4 [†]	339.2 $\pm$ 380.1
Hamilton Depression Rating Scale 17-Item Score	1.6 $\pm$ 1.8	19.9 $\pm$ 4.8	18.7 $\pm$ 4.7
Beck Depression Inventory	0.4 $\pm$ 0.8	29.2 $\pm$ 9.5 [†]	22.7 $\pm$ 9.4
Beck Hopelessness Scale	1.3 $\pm$ 1.1	13.9 $\pm$ 4.5	10.3 $\pm$ 5.6
Scale for Suicide Ideation, Current Score	0	9.2 $\pm$ 8.0 ^{††}	2.5 $\pm$ 4.8

Abbreviations: MDE=major depressive episode.

^{**}
 $p < 0.01$ vs. Healthy Participants

[†]
 $p < 0.05$

^{††}
 $p < 0.01$ indicates differences comparing attempter and non-attempter groups.

Table 2

Clinical characterization of suicide attempt history of both first and most recent suicide attempt. Data are presented as mean $\pm$ standard deviation unless otherwise specified.

Suicide Attempters (N=13)	
Number of suicide attempts	2.1 $\pm$ 1.8
First Suicide Attempt	
Age, years	16.5 $\pm$ 5.5
Time since attempt, median, years	10.3
Beck Medical Lethality Score	1.5 $\pm$ 1.6
Most Recent Attempt	
Age, years	20.5 $\pm$ 8.6
Time since attempt, median, years	5.9
Beck Medical Lethality Score	2.2 $\pm$ 1.9
Suicide Intent Scale score	17.3 $\pm$ 3.8
Most Recent Attempt Method [†]	
Drug Overdose, N	8
Cutting, N	4
Jumping, N	1
Immolation, N	1

[†] One subject reported both drug overdose and cutting.

Table 3

Individual subject data for the most recent suicide attempt, including time since attempt, method, and mean FA values in the DMPFC. Highlighted rows indicate suicide attempts that involved drug overdose.

Subject	Time since most recent attempt	Method	R DMPFC FA	L DMPFC FA
1	19 days	Non-sedative drug overdose	0.47	0.48
2	1 month	Sedative drug overdose	0.46	0.46
3	11 months	Sedative drug overdose, cutting	0.49	0.50
4	4 years	Cutting	0.45	0.46
5	4 years	Non-sedative drug overdose	0.46	0.47
6	6 years	Non-sedative drug overdose	0.49	0.49
7	6 years	Cutting	0.44	0.45
8	8 years	Immolation	0.47	0.48
9	19 years	Jumping	0.44	0.47
10	21 years	Non-sedative drug overdose	0.49	0.49
11	27 years	Cutting	0.46	0.48
12	32 years	Non-sedative drug overdose	0.47	0.48
13	39 years	Sedative drug overdose	0.45	0.46

FA in white matter parcellated ROIs using the Desikan Killiany atlas in FreeSurfer. Data are presented as mean $\pm$ standard deviation. ANCOVA was performed for each ROI with age as a covariate for group comparisons. *Post-hoc* ANCOVAs were performed to compare MDD suicide attempters and non-attempters, controlling for age, BDI score, length of current episode, and number of MDE episodes.

Table 4

	R/L	Healthy Participants (N=46)	Suicide Attempters (N=13)	Non-Attempters (N=39)	Omnibus ANCOVA		Post-hoc	
					F-score	p	A vs. NA	p
cACC	R	0.62 $\pm$ 0.05	0.60 $\pm$ 0.05	0.59 $\pm$ 0.04	3.28	0.04		p=0.60
	L	0.62 $\pm$ 0.04	0.60 $\pm$ 0.04	0.59 $\pm$ 0.04	4.99	0.009		p=0.11
rACC	R	0.60 $\pm$ 0.04	0.58 $\pm$ 0.03	0.58 $\pm$ 0.04	1.34	0.27		-
	L	0.58 $\pm$ 0.03	0.56 $\pm$ 0.03	0.55 $\pm$ 0.03	4.45	0.01		p=0.38
MOFC	R	0.46 $\pm$ 0.02	0.44 $\pm$ 0.03	0.45 $\pm$ 0.03	3.96	0.02		p=0.06
	L	0.45 $\pm$ 0.03	0.43 $\pm$ 0.04	0.43 $\pm$ 0.02	4.34	0.02		p=0.96
DMPFC	R	0.49 $\pm$ 0.02	0.47 $\pm$ 0.02	0.48 $\pm$ 0.02	5.17	0.01		p=0.02
	L	0.49 $\pm$ 0.02	0.48 $\pm$ 0.01	0.49 $\pm$ 0.02	5.62	0.01		p=0.03

Abbreviations: A=attempter, ANCOVA=analysis of covariance, BDI=Beck Depression Inventory; cACC=caudal anterior cingulate cortex, DMPFC=dorsomedial prefrontal cortex, FA=fractional anisotropy, HP=healthy participant, L=left, MDD=major depressive disorder, MDE=major depressive episode, MOFC=medial orbitofrontal cortex, NA=non-attempter, R=right, rACC=rostral anterior cingulate cortex. ROIs=regions of interest, SA= suicide attempters.

Table 5

Significant FA clusters obtained from the TBSS analysis. All clusters showed a reduced FA in attempter and non-attempter groups compared to the healthy participant group ($p < 0.05$, after FWE correction).

Comparisons	Cluster	p-value	Cluster extent (voxels)	Cluster maxima	MNI Coordinates
HP > NA	1	0.005	8953	Left body of the corpus callosum	-8, 12, 23
	2	0.04	2360	Left anterior thalamic radiation	-12, 9, 1
	3	0.04	1697	Left inferior fronto-occipital fasciculus	-37, -13, -12
	4	0.045	803	Right medial forebrain bundle	9, -12, -1
	5	0.045	560	Right inferior longitudinal fasciculus	30, -31, 1
	6	0.048	178	Right anterior thalamic radiation	11, 5, -7
NA > A [†]	1	0.004	52	Right dorsomedial prefrontal cortex	21, 21, 52

Abbreviations: A=attempter, FA=fractional anisotropy, FWE=family-wise error, HP=healthy participants, MNI=Montreal Neurological Institute, NA=non-attempter, TBSS=tract-based spatial statistics.

[†]Uncorrected, $p < 0.01$.

Table 6

Mean $\pm$ standard deviations for significant FA clusters obtained from the TBSS analyses for HP vs. attempter vs. non-attempter. All clusters showed a reduced FA in patient (attempter, non-attempter) groups compared to the HP group ($p < 0.05$ after FWE correction unless otherwise indicated).

Groups	Cluster	HP (N=46)	Suicide Attempters (N=13)	Non-Attempters (N=39)	% Change
HP > NA	1	0.62 $\pm$ 0.02	0.60 $\pm$ 0.02	0.59 $\pm$ 0.02	-5.08%
	2	0.48 $\pm$ 0.02	0.46 $\pm$ 0.03	0.45 $\pm$ 0.02	-6.67%
	3	0.54 $\pm$ 0.02	0.52 $\pm$ 0.03	0.51 $\pm$ 0.02	-5.88%
	4	0.47 $\pm$ 0.02	0.45 $\pm$ 0.02	0.44 $\pm$ 0.02	-6.82%
	5	0.52 $\pm$ 0.02	0.50 $\pm$ 0.03	0.49 $\pm$ 0.03	-6.12%
	6	0.61 $\pm$ 0.04	0.57 $\pm$ 0.06	0.57 $\pm$ 0.05	-7.02%
NA > A [*]	1	0.41 $\pm$ 0.07	0.35 $\pm$ 0.05	0.41 $\pm$ 0.05	-17.14%

[†]Suicide attempters vs. non-attempters.

Abbreviations: A=attempter, FWE=family-wise error, FA=fractional anisotropy, HP=healthy participant, NA=non-attempter, TBSS=tract-based spatial statistics.

^{*}
 $p < 0.01$, uncorrected.