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Relationship between suicidality and impulsivity in bipolar I disorder: a diffusion tensor imaging study

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Abstract

Background—Impulsivity is characteristic of individuals with bipolar disorder and may be a contributing factor to the high rate of suicide in patients with this disorder. Although white matter abnormalities have been implicated in the pathophysiology of bipolar disorder, their relationship to impulsivity and suicidality in this disorder has not been well-investigated.

Methods—Diffusion tensor imaging scans were acquired in 14 bipolar disorder patients with a prior suicide attempt, 15 bipolar disorder patients with no prior suicide attempt, and 15 healthy volunteers. Bipolar disorder patients received clinical assessments including measures of impulsivity, depression, mania, and anxiety. Images were processed using the Tract-Based Spatial Statistics method in the FSL software package.

Results—Bipolar disorder patients with a prior suicide attempt had lower fractional anisotropy (FA) within the left orbital frontal white matter ($p < 0.05$, corrected) and higher overall impulsivity compared to patients without a previous suicide attempt. Among patients with a prior suicide attempt, FA in the orbital frontal white matter region correlated inversely with motor impulsivity.

Conclusions—Abnormal orbital frontal white matter may play a role in impulsive and suicidal behavior among patients with bipolar disorder.

Keywords

bipolar disorder; brain; diffusion tensor imaging; impulsivity; MRI; suicide

Patients with bipolar disorder have one of the highest lifetime suicide attempt rates among individuals with psychiatric disorders (1) and when left untreated, have a 5–15% risk of

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committing suicide (2). Predicting which patients with bipolar disorder will attempt suicide is often difficult and is based on clinician judgment and patient self-report. Recent magnetic resonance (MR) imaging studies suggest, however, that neurobiological markers may assist in the identification of patients with psychiatric disorders at increased risk of suicide (3–5). In particular, there is evidence that patients with affective disorders who have previously attempted suicide demonstrate an increase in the presence and severity of white matter hyperintensities relative to both healthy controls and to patients who have not attempted suicide. Moreover, these findings have been reported and replicated in children (6) and adults (4, 5, 7) with affective disorders. Evidence that hyperintensities are more prevalent in patients with a suicide history compared to patients without a suicide history suggests that white matter abnormalities may be related to suicidality (8). These abnormalities are nonspecific, however, and the use of other imaging modalities optimized for white matter examination, such as diffusion tensor imaging (DTI), may be helpful to elucidate the relationship between white matter integrity and suicidality.

The orbital frontal cortex (OFC) has strong connections with the amygdala, thalamus, and basal ganglia, as well as the cingulate and temporal cortices, suggesting a central role for this region in coordinating and refining responses to a wide range of stimuli (9). Functional MR imaging (fMRI) studies demonstrate OFC involvement in decision making (10), impulsivity (11), and emotion regulation (12), highlighting the particular relevance of this region for bipolar disorder (13, 14). Indeed, a large body of literature demonstrates structural (15–22) and functional (23–35) OFC abnormalities in patients with bipolar disorder relative to healthy controls. A growing body of evidence suggests that OFC abnormalities are linked to suicidality across different diagnostic categories, including major depressive disorder (36–38), epilepsy (39), and schizophrenia (40). Moreover, a recent comprehensive review of brain imaging studies and suicidal behavior reported that structural and functional abnormalities within the OFC, along with the dorsolateral prefrontal cortex, were most strongly associated with suicidality (41).

Impulsivity has been demonstrated to be a critical feature of bipolar phenomenology (42, 43) that is often observed among patients who complete (44) or attempt (43) suicide, and is present even during euthymia (42, 45). MR imaging studies suggest that orbital frontal white matter abnormalities may play a significant role in impulsive behavior among patients with psychiatric disorders. For example, an association between abnormal medial OFC white matter and impulsivity has been reported in cocaine dependence (46, 47), attention deficit hyperactivity disorder (48), and schizophrenia (49, 50). Recently, Matsuo and colleagues (51) demonstrated a significant negative correlation between the volume of the anterior genu of the corpus callosum and impulsivity in bipolar disorder patients who had a suicide attempt history. Given that axons crossing the genu connect right and left OFCs, this finding supports the hypothesis that abnormal orbital frontal white matter is associated with impulsivity. Particularly noteworthy is that this relationship was not observed among bipolar disorder patients without a suicide attempt history, nor was it observed among healthy controls. This suggests that the relationship between abnormal orbital frontal white matter and impulsivity may be specific to patients with bipolar disorder with a prior suicide attempt history.

In this study we used DTI to investigate white matter integrity among bipolar disorder patients with and without a history of suicide attempts compared to age- and sex-matched healthy volunteers. We hypothesized that patients with a history of suicide attempts would have lower fractional anisotropy (FA) in the orbital frontal white matter and higher impulsivity compared to patients without a history of suicide attempts and healthy volunteers. We further predicted that lower FA in the orbital frontal white matter of patients with a history of suicide attempts would be associated with higher impulsivity.

Methods and materials

Subjects

Twenty-nine patients with bipolar I disorder were recruited from the Zucker Hillside Hospital in Glen Oaks, NY, USA. Diagnoses were assessed using the Structured Clinical Interview for DSM-IV disorders (SCID) (52), as well as medical records when available, and were confirmed through a consensus conference involving psychiatrists and psychologists. In addition, 15 healthy volunteers were recruited from local newspaper advertisements and through word of mouth in the community. Suicide history was assessed in all patients using the Columbia Suicide History Form (53). For the current study, a patient was considered to have made an attempt if he or she reported having ever committed one or more self-injurious acts that were intended to result in death. We classified patients as those who have made one or more suicide attempts (n = 14), and those who have never attempted suicide (n = 15). Additional clinical measures administered to patients included the HamiltonAnxiety (HAM-A) (54) and Hamilton Depression (HAM-D) (55) Rating Scales, the Clinician-administered Rating Scale for Mania (CARS-M) (56), and the Barratt Impulsivity Scale, version 11 (BIS-11) (57). The BIS-11 is a measure of trait-impulsivity composed of three main factors: an *attentional* factor, which measures the ability to tolerate cognitive complexity; a *motor* factor, which measures the tendency to act spontaneously and without thinking ahead; and a *nonplanning* factor, which measures the degree to which one has a sense of the future. Clinical scale scores were not available for one participant, and impulsivity scores were not available for three participants in each of the patient groups.

Of the patients with a suicide attempt history, 6 were being treated with antipsychotic medication, 10 were taking mood stabilizers, 3 were not taking any psychotropic medication, and medication information was missing for one participant (see Table 1). All patients who had not attempted suicide were being treated with either antipsychotics (n = 14) and/or mood stabilizers (n = 14). In the groups of patients with and without a history of suicide attempts, there were three and five patients, respectively, that had a lifetime comorbid diagnosis of substance abuse or dependence. All participants denied substance abuse or dependence in the month preceding the scan. In the group of patients with a history of suicide attempts, comorbid diagnoses included: anorexia nervosa (n = 1), panic disorder with (n = 1) and without (n = 1) a history of agoraphobia, anxiety disorder not otherwise specified (NOS) (n = 2), posttraumatic stress disorder (PTSD) (n = 2), generalized anxiety disorder (n = 1), specific phobia (n = 1), and bulimia nervosa (n = 1). In the group of patients without a history of suicide attempts, comorbid diagnoses included: obsessive-compulsive disorder (n = 1) and agoraphobia without a history of panic disorder (n = 1). Exclusion criteria for healthy volunteers included the presence of any Axis I major mood or psychotic disorder (lifetime) as determined by the non-patient version of the SCID (58). One healthy volunteer met criteria for a past substance use disorder. Exclusion criteria for all study participants included MR imaging contraindications, serious medical conditions that could affect brain functioning, a history of a loss of consciousness for greater than five minutes, and mental retardation as assessed by clinician judgment and/or review of medical records. This study was approved by the North Shore–Long Island Jewish Medical Center Institutional Review Board, and written informed consent was obtained from all study participants.

MR imaging methods

Participants underwent MR imaging at the Long Island Jewish Medical Center on a GE 1.5T whole body MR imaging system that included diffusion-weighted volumes with diffusion gradients applied along 21 non-parallel directions ($b = 1000$ mm/sec^2), and three volumes without diffusion weighting ($b = 0$). Each volume consisted of 45 contiguous (no gap) 2.5

mm thick axial slices acquired parallel to the anterior-posterior (AC-PC) commissural line using a ramp sampled, spin-echo, single shot echo-planar imaging (EPI) method [repetition time (TR) = 12.2 sec, echo time (TE) = minimum, matrix size = 88 × 88, field of view (FOV) = 22 cm]. In addition, high-resolution anatomical reference scans were acquired using a three-dimensional Fast Spoiled Gradient Recalled (SPGR) sequence with IR Prep (TR = 10.1 msec, TE = 4.3 msec, TI = 600 msec, matrix size = 256 × 256, FOV = 22 cm, slice thickness = 1.5 mm, number of slices = 124). An oblique axial fast spin echo scan (TR = 4 sec, TE = 20/100 msec, matrix size = 256 × 256, FOV= 22 cm, slice thickness = 5 mm) was acquired to yield T2-weighted (TE = 100 msec) and proton density (TE = 20 msec) images.

Tract-based Spatial Statistics (TBSS) analysis

Images were processed using the TBSS method (59) in the FSL software package (Oxford Centre for Functional MRI of the Brain, Oxford, UK). Preprocessing steps included eddy-current correction using the FSL Diffusion Toolbox, skull-stripping using the Brain Extraction Tool (60), and the creation of FA images by fitting the tensor model to each voxel. Raw FA images were then aligned into MNI152 space using FNIRT, FSL's nonlinear registration tool. To create a mask comprised of a set of voxels representing the center of each white matter tract from the participants being compared, the aligned FA images were combined to form mean FA 'skeletons'. Individual subject data were projected onto each skeleton mask and fed into voxelwise statistical analysis. We conducted pair-wise contrasts using the randomise tool in FSL. In each contrast, we examined the entire white matter skeleton using independent samples *t*-tests with the following input parameters: number of permutations = 10,000; $p < 0.05$ corrected using the family-wise error rate; smoothing factor = 5; median *t*-value within the cluster of voxels ≥ 3. Age was included as a statistical covariate. Due to the number of comparisons, we report only those differences that survived strict type-I error correction using the family-wise error rate. FA data were exported to SPSS 11.5 for Windows (SPSS, Chicago, IL, USA) to examine their relationship to clinical measures using Spearman Rank order correlations ($p < 0.05$). These clinical measures included scores on the BIS-11, CARS-M, HAM-A, and HAM-D, as well as age at illness onset. Ancillary analyses compared patients who were (n = 20) and were not (n = 8) taking antipsychotic medication.

Voxelwise analysis

We also conducted a completely independent analysis using our previously published voxelwise methods (61–62) to confirm differences in FA that survived correction for multiple comparisons in the TBSS approach. Briefly, three main image registration steps were conducted as follows: non-brain tissue was removed from the SPGR volumes using the Brain Extraction Tool (60) and these cropped SPGR volumes were then nonlinearly registered to the Montreal Neurologic Institute's 'Colin27' brain using the Automatic Registration Toolbox (ART) (63). Each cropped SPGR volume was then linearly registered to the individual's T2/proton density volumes using ART, resulting in a resliced SPGR volume with the same orientation and voxel size as the T2/proton density volumes. This resliced SPGR volume was used as a mask to delete non-brain regions from the T2/proton density volumes. Segmentation into white matter, gray matter, and cerebrospinal fluid was performed by inputting all three image sets (cropped and resliced SPGR volume, cropped T2/proton density volumes) into the FAST segmentation program (64) in FSL. The resulting white matter segmentation volumes were then transformed into standard (Colin27) space using ART, averaged, and thresholded at 70% to yield a conservative white matter mask for the sample. Distortion correction of the DTI volumes was accomplished by nonlinearly registering subjects' b = 0 volume to their cropped T2 volume using ART. FA maps were computed in native space after derivation of the eigenvalues of the diffusion tensor using

previously described methods (65) and then nonlinearly registered to the 'Colin27' brain using ART by combining all three registration steps into a single 3-D displacement field. Both the registered FA maps and the white matter mask were smoothed using a 3-D isotropic Gaussian kernel of FWHM = 3 mm. Voxelwise statistics were performed only on voxels within the white matter mask and were limited to contrasts that yielded significant results in the TBSS analysis. Given the confirmatory nature of this analysis, clusters that survived correction at an alpha level of 0.001 and consisted of at least 10 voxels were considered statistically significant.

Clinical variables

We compared both groups on BIS-11 subscale and total scale scores, as well as on the CARS-M, HAM-D, HAM-A, and age at illness onset using independent groups *t*-tests. We did not control for multiple comparisons given the small sample size; however, we computed the effect size for each comparison to provide an estimate of the difference between groups. To more fully investigate clinical variables associated with impulsivity, we conducted correlational analyses on BIS-11 subscale and total scores, and the CARS-M, HAM-D, HAM-A, and age at illness onset.

Results

The three groups did not differ significantly in distributions of age, sex, or laterality quotient (Table 1). In addition, patient groups did not differ significantly in age at illness onset or distribution of patients with a comorbid substance abuse/dependence diagnosis. Patients with and without a suicide history did not differ significantly from each other in depression, anxiety, or mania scores (Table 1). At the time of the scan, the majority of patients were euthymic based on symptom rating scales. Patients with a suicide attempt history had significantly higher total impulsivity scores compared to those without an attempt [$t(21) = 3.08$, $p = 0.006$; partial eta-squared = 0.311]. Post-hoc analyses indicated significant effects for the Nonplanning domain [$t(21) = 2.19$, $p = 0.04$; partial eta-squared = 0.19] with trends toward significance for the Attention [$t(21) = 1.96$, $p = 0.06$; partial eta-squared = 0.14], and Motor domains [$t(21) = 2.08$, $p = 0.05$; partial eta-squared = 0.17]. Age at illness onset was negatively associated with the Attention impulsivity domain across both patient groups ($r = -0.46$, $p = 0.02$).

The TBSS analysis revealed a 14-voxel cluster of significantly [$t(27) = -2.634$; $p < 0.05$, corrected using the family-wise error rate] lower FA among patients with a history of suicide attempts compared to patients without an attempt along a white matter tract in the left OFC (centroid was at $x = -18$, $y = 50$, $z = 4$; see Fig. 1, panels A and C). Using strict family-wise error correction there were no significant FA differences across the brain between healthy volunteers compared to either patients with a history of suicide attempts or patients without a history of attempts. In post-hoc analyses, we extracted FA values within the cluster that differed between patients with and without a history of suicide attempts to compare with healthy volunteers. Results indicated that patients with a previous history of suicide attempts had significantly [$t(26) = -2.376$, $p < 0.05$] lower FA within this cluster compared to healthy volunteers. There were no significant group differences within this cluster in patients without a history of suicide attempts compared to healthy volunteers. Our independent voxelwise analysis confirmed the main TBSS finding in that an 18-voxel cluster of significantly ($p < 0.001$) lower FA in patients with a history of suicide attempts was identified compared to patients without any attempt (centroid: $x = -17$, $y = 51$, $z = 2$; see Fig. 1, panels B and D). The distance between the centroids obtained from the two independent approaches was 2.5 mm (size of a single voxel in the raw DTI volumes).

We examined the clinical correlates of the abnormal white matter cluster identified among patients with a history of suicide attempts. There was a significant negative correlation between mean FA within the extracted OFC cluster and motor impulsivity within the group of patients who had previously attempted suicide (Spearman's $\rho = -0.69$, $p = 0.02$), but not among patients without a prior suicide attempt. There were no significant correlations between OFC FA and either the anxiety, depression, or mania clinical scales either within or across the two patient groups.

A greater number of patients who had not attempted suicide were taking antipsychotics compared to patients who had attempted suicide ($p < 0.05$) (Table 1). We thus performed the TBSS analysis to compare the entire skeleton between patients who were ($n = 20$) or were not ($n = 8$) taking antipsychotic medications. There were no regions of significantly different FA between the groups; moreover, visual inspection of the uncorrected FA results did not reveal any consistent directional pattern between these groups.

Discussion

In this study we used DTI to investigate the brain white matter in bipolar disorder patients with a history of suicide attempts compared to bipolar disorder patients without any suicide attempts. The main finding of our study is that patients with a history of suicide attempts had lower FA in the left OFC and higher impulsivity compared to patients without a history of suicide attempts. Moreover, among patients with a history of suicide attempts, lower FA in the OFC correlated significantly with motor impulsivity. Our findings converge with a growing body of evidence implicating OFC abnormalities in the pathogenesis of bipolar disorder and suggest that this region may play a critical role in mediating the relationship between impulsivity and suicidal behavior in this disorder.

Several lines of evidence support the notion that white matter is altered in bipolar disorder, and recent DTI investigations have localized the majority of these alterations to pathways that interconnect frontal and temporal regions with subcortical structures and to interhemispheric tracts such as the corpus callosum (8, 66, 67). Such findings in white matter are consistent with prevailing models of the neurobiology of this disorder (e.g., 13, 14) that posit abnormalities in an anterior-limbic network subserving emotion generation and regulation. The OFC is strongly connected with many subcortical structures that are involved in the generation and maintenance of emotion, and it is hypothesized that the OFC may modulate the functioning of these structures (e.g., 10). The white matter of the OFC is largely comprised of reciprocal connections between this region and subcortical structures such as the amygdala, in addition to cortico-cortical connections (9). Given that the white matter represents the anatomical substrate of structural connectivity in the brain, a defect in this tissue in the OFC may be indicative of altered connectivity between this region and the subcortical structures with which it is linked. Supporting this hypothesis, evidence has been reported for abnormal functional (35) and structural (22) connectivity between the OFC and the amygdala in bipolar disorder. It is conceivable that a disruption within corticolimbic circuitry may contribute to attenuated OFC modulation of subcortical activity, resulting in a loss of refinement in systems involved in decision-making, impulsivity, and emotional regulation (e.g., 13, 14, 68). Thus, patients at increased risk of suicide and/or those who have previously attempted suicide may demonstrate this disruption to a greater degree than patients with a lower suicide risk.

Increased impulsivity among the subgroup of patients with a history of suicide attempts is consistent with previous studies linking impulsivity and suicidality in general (69), and in patients with bipolar disorder in particular (70, 71). Impulsivity, like suicidality, is a complicated construct consisting of many factors. The BIS-11 assesses three empirically

derived factors of trait impulsivity: toleration of cognitive complexity/ability to sustain attention (assessed via the Attention subscale); degree of spontaneity and regard for consequences (Motor subscale); and future-orientation (Nonplanning subscale). Patients with a history of suicide attempts scored significantly higher than patients without this history on the total score with comparable effects across the Nonplanning, Motor, and Attention domains. Higher levels of impulsivity have been associated with a more severe course of illness among patients with bipolar disorder, and a significant positive relationship has been reported between number of mood episodes and impulsivity (70). Swann and colleagues (70) also reported a significant relationship between age at illness onset and attentional impulsivity, a finding that we replicate in the present sample. It may be that earlier-onset forms of the disorder are associated with a greater degree of impairment in focusing one's attention on the task at hand.

The significant inverse correlation between the Motor subscale of the BIS-11 and mean FA within the left OFC cluster in patients with a history of suicide attempts suggests that abnormal OFC white matter may be a component of a common mechanism underlying both impulsivity and suicidality in bipolar disorder. Given the wealth of evidence for alterations in the serotonergic system in suicide completers and attempters (see 72 for a review), and the localization of several of these abnormalities to the ventral prefrontal cortex (73), it is possible that altered white matter in the OFC is related to dysfunction within this system. Evidence from positron emission tomography studies indicates that patients with a history of medically severe suicide attempts have lower serotonin synthesis in the OFC relative to healthy controls (74). Reports of decreased serotonin binding (73), as well as the upregulation of serotonin receptors (75) in the ventral prefrontal cortex of suicide victims, could be related to alterations in the serotonergic projections reaching this region from the dorsal raphe. It is conceivable that the region of lower FA identified in the present study is indicative of such altered connectivity. More broadly, abnormalities within the serotonergic system may be related to hypoactivation in the OFC, which may then lead to impulsive and even suicidal behavior (76). Given the evidence that serotonin plays an important role in moderating aggressive and impulsive behavior (see 77 for a review) the present findings may represent a mechanism through which serotonergic dysfunction is related to impulsive and suicidal behaviors.

Our data implicate left hemisphere dysfunction in both impulsivity and suicidality in bipolar disorder. This finding is consistent with a recent fMRI study demonstrating abnormal activity in the left OFC in participants with a history of suicide attempts relative to affective and healthy control groups during the evaluation of risky versus safe choices (38). Behavioral results from the same study indicated that the group with a history of suicide attempts made significantly less advantageous decisions compared to both affective and healthy controls. Previous research has demonstrated that the left OFC is involved in the representation of the value of a reinforcer (78), in the selection of a goal-directed response (79), and in the prediction of an immediate reward (80). Taken together with research demonstrating an association between low levels of serotonin and an increased preference for an immediate over a delayed reward (81), it is possible that an abnormality in left OFC white matter is related to the same mechanism underlying the relationship between serotonergic abnormalities and suicidal behavior. Future studies linking serotonergic abnormalities, OFC structural and functional abnormalities, and suicidal behavior are needed to clarify this potential relationship.

There are several limitations to this preliminary study that should be considered. First, the sample size was small and these findings need to be replicated in other cohorts. The small size of the cluster identified is likely a result of this small sample size and our corrections for multiple comparisons. Indeed, the use of a more liberal alpha enlarged the cluster size in

both analyses and suggested that larger portions of the tract(s) comprising this region are abnormal. In addition, due to the small number of participants who met criteria for past alcohol/substance abuse (n = 4) or dependence (n = 1), we were unable to examine the potential relationship of these variables to white matter abnormalities or impulsivity. The small sample size also precluded an investigation of how factors such as the number and/or lethality of attempts may have impacted the results. Finally, it is not possible to discount the potential for non-attempting participants in the current study to attempt suicide in the future. There is limited evidence to suggest that the mean age of a first suicidal attempt in patients with bipolar disorder is in the late twenties (82) and that such attempts occur within a mean of approximately 8–9 years after illness onset (82, 83). Although the majority (66.7%) of participants in the non-attempting group was older than 29-years of age and had been ill for at least eight years, it remains a possibility that some of these participants may attempt suicide in the future.

Despite these limitations, our results suggest that impulsivity and suicidal behavior may be related to abnormal left OFC white matter. This finding emerged despite a small sample size, conservative type-I error correction, and two completely independent methods of image analysis. Future studies incorporating both functional and diffusion tensor imaging are needed to more fully examine the functional correlates of abnormal white matter integrity in bipolar disorder patients at increased risk of suicidality.

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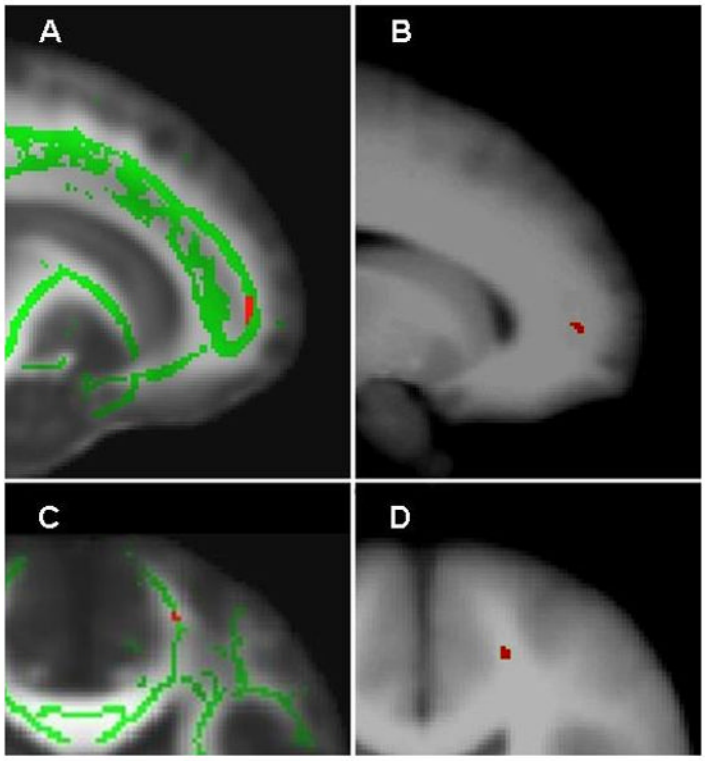

Fig. 1.

Illustration of white matter region showing lower fractional anisotropy in patients with bipolar disorder and a history of suicide attempts compared to patients with bipolar disorder without a history of suicide attempts shown in sagital (A and B) and axial (C and D) slices. Panels A and C show the results from the tract-based spatial statistics analysis. The tract 'skeleton' is shown in green and represents the center of the major white matter tracts. Panels B and D show the results from an independent voxelwise analysis that is not dependent on a tract-invariant skeleton. All images are presented in radiologic convention.

Table 1

Sample characteristics

	Patients with a previous suicide attempt (n = 14)	Patients without a previous suicide attempt (n = 15)	Healthy volunteers (n = 15)	Statistic
Demographic variables				
Age	33.3 (14.1)	36.5 (12.3)	33.7 (12.6)	$F = 0.27$
Sex, male/female	9/5	9/6	8/7	$\chi^2 = 0.37$
Laterality quotient[a]	0.88 (0.14)	0.89 (0.12)	0.89 (0.22)	$F = 0.02$
Education, years	14.43 (2.40)	14.07 (2.70)	15.00 (1.90)	$F = 0.58$
Clinical variables[b]				
HAM-D	6.8 (5.7)	5.4 (2.9)	–	$t = 0.83$
HAM-A	5.6 (5.2)	4.1 (3.8)	–	$t = 0.92$
CARS-M	5.9 (9.5)	7.1 (8.5)	–	$t = -0.38$
BIS-11 (total score)[c]	70.7 (8.4)	60.2 (8.0)	–	$t = 3.10$ $p < 0.01$
Age at illness onset, years	20.8 (9.8)	24.8 (10.0)	–	$t = -1.00$
Patients receiving antipsychotic medication (%)[d]	46.2	93.3	–	$\chi^2 = 7.60$
Patients receiving mood-stabilizing medication (%)[d]	76.9	93.3	–	$\chi^2 = 1.53$
Patients with a history of substance use disorder (%)	21.4	33.3	–	$\chi^2 = 0.51$
No. of suicide attempts	2.0 (1.1)	–	–	–
Lethality of suicide attempts[e]	2.1 (1.4)	–	–	–
Tract-based spatial statistics analysis				
Left OFC cluster fractional anisotropy	504.0 (68.3)	566.0 (59.2)	547.0 (47.3)	$F = 4.29$ $p < 0.05$

Data are presented as mean ± standard deviation (SD) unless otherwise indicated. Fractional anisotropy values are multiplied by a factor of 1000. P-values were not significant, except for the Barratt Impulsivity Scale, version 11 (BIS-11) total score, patients receiving antipsychotic medication, and left orbital frontal cortex (OFC) cluster functional anisotropy (see table for p-values). HAM-D = Hamilton Depression Rating Scale; HAM-A= Hamilton Anxiety Rating Scale; CARS-M = Clinician-administered Rating Scale for Mania.

[a] Laterality quotient was based on a modified, 20-item version of the Edinburgh inventory and was computed by the formula: (Total R − Total L)/(Total R + Total L) where Total R and Total L refer to the total number of right- and left-hand items scored, respectively.

[b] Clinical scale scores were missing for one participant in the patient group without a history of suicide attempts.

[c] BIS total scores were missing for three participants in each of the patient groups.

[d] Medication information was missing for one participant in the group with a history of suicide attempts.

[e] Lethality of suicide attempts was coded using the Columbia Suicide History Form (53).