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Altered White Matter Microstructure in Adolescents with Major Depression: A Preliminary Study

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Abstract

Objective—Major Depressive Disorder (MDD) occurs frequently in adolescents, but the neurobiology of depression in youth is poorly understood. Structural neuroimaging studies in both adult and pediatric populations have implicated fronto-limbic neural networks in the pathophysiology of MDD. Diffusion Tensor Imaging (DTI), which measures white matter (WM) microstructure, is a promising tool for examining neural connections and how they may be abnormal in MDD.

Method—We used two separate approaches to analyze DTI data in adolescents with MDD (n=14) compared with healthy volunteers (n=14).

Results—The first, hypothesis-driven approach was to use probabilistic tractography to delineate tracts arising from the subgenual anterior cingulate cortex (ACC). Adolescents with MDD demonstrated lower fractional anisotropy (FA) in the WM tract connecting subgenual ACC to amygdala in the right hemisphere. The second, exploratory approach was to conduct a voxel-wise comparison of FA. This analysis revealed ten clusters where adolescents with MDD had significantly lower (uncorrected) FA than the healthy group within WM tracts including right and left uncinate and supragenual cingulum.

Conclusions—These preliminary data support the hypothesis that altered WM microstructure in fronto-limbic neural pathways may contribute to the pathophysiology of MDD in adolescents.

Keywords

depression; adolescents; diffusion tensor imaging; white matter; neurodevelopment

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This article is discussed by Dr. Ryan in an editorial on page xxx.

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INTRODUCTION

Major Depressive Disorder (MDD) is a leading cause of disability worldwide,[1] and the incidence of MDD rises dramatically in adolescence.2 Fronto-limbic neural networks mediate emotional processing3 and this system has been implicated in the pathophysiology of MDD in adults4, 5 and in youth.6–16 In particular, the subgenual anterior cingulate cortex (ACC) has been centrally implicated in MDD circuitry in adults17–19 and adolescents.8, 20 Of critical importance, adolescent MDD emerges in the context of ongoing maturation of neural connections.21–29 In large part, these connections depend upon myelinated axons, the primary constituent of white matter (WM). Since myelination[30] and increases in WM volume21, 31 continue into adulthood, a close examination of WM organization in adolescents with MDD promises to advance current understanding of the developmental pathophysiology of depression.

Diffusion tensor imaging (DTI) is an advanced technique for examining WM microstructure, thus providing information that can estimate the integrity of pathways within neural networks. A commonly used metric in DTI studies is fractional anisotropy (FA), which estimates the degree to which tissue organization limits diffusion of water molecules in brain WM.32 Several recent reports have emerged using DTI to examine FA in patients with mood disorders.33 Methodological approaches to detecting FA differences between populations include (1) focusing on a region of interest, and (2) conducting a voxel-wise comparison of FA throughout the brain.

To facilitate investigation of WM integrity within a hypothesized region of interest, a technique that is well suited for delineating the desired WM tract is probabilistic tractography. By modeling diffusion properties, this technique estimates the direction of fiber orientation and reconstructs the WM pathway.[34] Once probabilistic tractography has delineated the connection, the resulting tract can then be treated as a region of interest, and used to extract FA for group comparison.[35, 36] Probabilistic tractography approaches have now been used facilitate investigations of FA in fronto-limbic pathways in adults with bipolar disorder[36, 37] and schizophrenia,[36] as well as in healthy individuals with varying genotypes of the serotonin transporter polymorphism.[35]

To explore FA differences between two populations across the brain, a common approach is to conduct a voxel-wise group comparison. Since we are still in the early stages of understanding the relevant neural circuitry, model-free approaches provide the advantage of the potential to identify pathological regions that were not predicted. Several relevant studies using a voxel-wise comparison approach have reported lower FA in diverse cortical areas in adults with MDD,[38] adults with bipolar disorder,[39] and adolescents with bipolar disorder.[40, 41] Despite early evidence suggesting that abnormal WM development may play a role in the pathophysiology of MDD,[42, 43] no studies to date have reported using either of these DTI methods to examine WM in adolescents with MDD.

The purpose of this study was to measure microstructural integrity of WM in adolescents with MDD versus healthy comparison volunteers using DTI. We used two approaches for data analysis to compare FA between groups. (1) We first used probabilistic tractography to delineate WM tracts extending from the subgenual ACC. These tracts were then used to quantify and compare FA between groups. We have previously reported that adolescents with depression had lower measures of resting-state functional connectivity within a fronto-limbic network extending from the subgenual ACC.44 Based on that previous finding, and on adult models emphasizing the central importance of sugbenual ACC in MDD,17, 18 we predicted that adolescents with depression would demonstrate lower FA in these tracts. (2)

Second, to explore FA group differences across the brain, we conducted a voxel-wise comparison of FA using Tract-Based Spatial Statistics (TBSS), an advanced tool utilizing a non-linear registration followed by projection onto an alignment-invariant tract representation.45 We predicted that this model-free approach would replicate previous studies that have identified lower FA in various cortical WM areas in adults with depression.[38, 46] Specifically, based on the theory that fronto-limbic networks are dysregulated in MDD,[4, 5] we predicted this brain-wide method would identify group differences indicating lower FA in adolescents with MDD within fronto-limbic WM tracts.

METHOD

Participants

Thirty adolescents (16 depressed, 14 healthy) ranging from 15 and 19 years were recruited to participate in this study. Exclusion criteria for all subjects consisted of an Intelligence Quotient (IQ) < 80 as measured by the Wechsler Abbreviated Scale of Intelligence,[47] significant medical or neurological disorders, MRI contraindications (e.g., metal implants, claustrophobia, etc.) and, in females, a positive urine pregnancy test. For the comparison group, healthy adolescents were recruited from community postings, and participants that met criteria for any major current or past DSM-IV diagnosis were excluded. For the depressed group, adolescents with MDD were recruited from the psychiatric inpatient and day hospital programs at the University of Minnesota Medical Center-Fairview Hospital, as well as through community postings. Exclusionary psychiatric disorders for the depressed group included: (i) bipolar disorder, (ii) schizophrenia, (iii) a pervasive developmental disorder, (iv) an eating disorder with active symptoms in the past 12 months, and (v) a substance-related disorder with history of use in the past 60 days. Other comorbidities that routinely occur in adolescents with moderate to severe depression48 were permitted, provided that MDD was the primary diagnosis. Of the 16 adolescents with MDD that were recruited, one was excluded due to an IQ score <80, and one participant was too anxious to complete the scanning session.

The study was approved by the institutional review board of the University of Minnesota. For participants age 18 and over, signed informed consent was obtained; those under age 18 provided assent, and a parent or guardian provided signed consent.

Clinical Assessment

For each participant, DSM-IV Axis I diagnosis was established based on a consensus between independent parent and child interviews conducted by a child and adolescent psychiatrist (KC) and a clinical psychologist (BKD) using the Schedule of Affective Disorders and Schizophrenia for Children – Present and Lifetime Version (K-SADS-PL).49 Additional scales were used to assess severity and types of symptoms including (a) The Beck Depression Inventory-II (BDI-II),50 (b) Global Assessment of Functioning (DSM-IV) and (c) duration of current illness (number of months).

Neuroimaging: scan acquisition procedures

All subjects were scanned using a research-dedicated Siemens Trio 3 Tesla scanner (Erlangen, Germany) located at the Center for Magnetic Resonance Research at the University of Minnesota. Diffusion was measured along 30 non-collinear directions. A dual spin echo, single shot, echo planar imaging sequence was used: TR= 8000ms, TE=83ms, 128×128, FOV=256mm, voxel size=2×2×2mm, 64 slices, b value = 1000, GRAPPA=2 (5 minutes). A gradient echo fieldmap sequence was also acquired to correct the DTI data for geometric distortions caused by magnetic field inhomogeneities: TR=700ms, TE=4.62ms/

7.06ms; flip angle=90°, voxel dimensions identical to the DTI data, magnitude and phase contrasts.

Data Analysis

1. Probabilistic Tractography—Diffusion weighted images were analyzed using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Probtrackx (FSL) was used to delineate tracts directly associated with the subgenual ACC, and these tracts were then used to compare FA within those tracts between groups. Using coordinates from published literature as the centers of mass,[17, 51] and adjusting slightly in order to place the regions of interest (ROIs) in relevant WM, ROIs were created in the MNI152 standard brain for subgenual ACC (right: 10,22,− 16; left: −10, 22, −16), amygdala (right: 32,0, −22; left: −32,0, −), and supragenual ACC (right: 8,16,28; left: −8,16,28). To create ROIs, voxels centered on these coordinates were selected, and the FSL command *dil* was used twice to enlarge the ROI to a cube of voxels with a final volume of $1000mm^3$ (see Supplement 1). In order to conduct the fiber tracking in the native diffusion space, these ROIs were then linearly aligned to the native space FA map using a 12 degree of freedom affine registration. To obtain this registration, the FA map of each subject was first aligned to the MNI152 brain using FLIRT (FSL), and the resulting transformation matrix was inverted and applied to each of the ROIs. For each individual, two tracts were created in each hemisphere, first extending from the subgenual ACC ROI seed to the amygdala ROI targets, and secondly from the subgenual ACC seed to the supragenual ACC ROI targets. Probtrackx was operated in single mask mode (seed mask= each individual's subgenual ACC ROI) with a waypoint mask (target masks, either the individual's amygdala ROI mask or the supragenual ACC mask). We included all other default parameters, including a curvature threshold of ±78.5 degrees (minimum angle between steps). A mask consisting of all voxels with an FA ≤ 0.15 was also generated and identified as a "termination mask" in the probtrackx program. When samples reach this mask, they are terminated to prevent samples from passing through regions of high noise. A connectivity distribution was generated in each hemisphere by sending 5000 samples from each voxel in the seed volume to the target mask. Each connectivity distribution was normalized based on the number of samples that successfully reached the target mask from the seed. We set a 5% threshold to reject low-probability voxels and reduce outlier-induced noise. In the experience of our lab, a 5% threshold is reliable across repeated sessions, and successfully removes noise while retaining enough samples that the tract is viable. The distributions were then converted into binary masks. The resulting thresholded tracts were visually inspected to confirm that the pathways appeared anatomically correct, with no voxels appearing outside of the expected pathway. In some cases, the probabilistic tractography algorithm did not successfully delineate a tract, leading to reductions in sample sizes as indicated below. Values for mean FA for each tract for each individual were extracted and exported to SPSS. Group comparison was conducted using analysis of covariance, including a statistical correction to account for group differences in IQ (see Table 1).

2. Voxel-wise comparison—TBSS[45] was used for inter-subject registration of the DTI data. First, data were inspected for motion artifacts, and distortions due to eddy currents and simple head motion were addressed using an affine registration. Non-brain tissue was removed using the brain extraction tool (BET) from the FSL package. FA was calculated for each voxel after fitting the diffusion tensor model to each voxel using FMRIB's Diffusion Toolbox (FDT) from the FSL package. The FSL tool Phase Region Expanding Labeller for Unwrapping Discrete Estimates (PRELUDE) was used to phase unwrap the phase difference contrast field map image before the voxel values were converted into a map of radians per second. The FA maps were then corrected for magnetic field homogeneity induced geometric distortions caused by the EPI readout by applying the radians per second image

using FMRIB's Utility for Geometrically Unwarping EPIs (FUGUE, http://www.fmrib.ox.ac.uk/fsl/fugue/index.html) from the FSL package. The distortion corrected FA map of each subject was aligned to a template brain using a nonlinear registration. For the template brain, we chose to use an average FA map consisting of 72 typically-developing adolescents that had been constructed using data from a separate study at our institution.[52] The template brain, and thus the FA map of each subject, was in a standard space (MNI152, Montreal Neuroimaging Institute). FA volumes from all 28 subjects in MNI space were then averaged and the derived mean FA image was minimized to generate a template skeleton embodying the center of all tracts representative of the entire group. An FA threshold of 0.20 or higher was set to exclude peripheral tracts that might lead to erroneous interpretations due to anatomic inter-subject variability or partial volume effects. Each subject's aligned FA data were projected onto this template skeleton.

A voxel-wise comparison was completed using Randomise (fmrib.ox.ac.uk/fsl/randomise/index.html) to test for between-group differences in FA. We included a cluster threshold of $T_{[26]} \geq 2.05$ and a statistical correction for IQ. To do this, full-scale IQ scores were de-meaned, and included as a nuisance regressor in the model. Since the IQ variables were de-meaned, DTI data was also de-meaned by including the FSL command *D* within the randomize command. We used stringent tests to correct for type 1 error: family-wise error correction (conducted within the randomize program), AlphaSim Monte Carlo simulation (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim), and false discovery rate (FDR; http://www.fmrib.ox.ac.uk/fsl/randomise/fdr.html). A second, more exploratory approach that evaluates results from uncorrected data on patients with mood disorders38, 39 was also used. For this part of the analysis, we selected relevant clusters by following the methods of Versace and colleagues39 in their study using TBSS to examine WM microstructure in adults with bipolar disorder. Accordingly, we accepted clusters of at least 5 contiguous voxels with a $p<0.001$. We used the cluster program available in FSL (Jenkinson, 2002) to extract all clusters across the brain in the uncorrected group comparison dataset that met these criteria. Although we could not correct for multiple comparisons across the brain, we sought to demonstrate significance using a small-volume correction as conducted by Versace and colleagues.[39] Accordingly, for each cluster selected in the method described above, we created an anatomically defined regional mask within the WM tract that contained 100 times the number of voxels of each cluster. A small volume correction was then completed using FDR. Anatomic localization of each cluster was determined using the FSL atlas tool using the pertinent available anatomic templates (MNI atlas, Talairach atlas, Harvard-Oxford cortical and subcortical structural atlases, and Johns Hopkins University DTI-based WM atlas). Brain imaging results were prepared for display using the tbss_fill script from the FSL package, which displays results superimposed upon the WM skeleton from the group TBSS analysis.

RESULTS

Participants

As described in Table 1, the two groups were comparable on demographic characteristics with the exception of IQ. Although IQ was used in both groups to exclude participants with IQ<80, IQ was not a part of the matching procedure. Both groups had above-average IQ, but the healthy group had a higher average score (114.3 vs. 104.9, $t(26)=2.433$, $p=0.022$). This potential confound was addressed as noted above in the analyses.

This sample of adolescents with depression had moderate to severe illness, with mean duration of illness over 2 years, and mean GAF and BDI-II scores of 45 and 27, respectively. Most (83%) of the MDD group had one or more current comorbid anxiety disorders, including Generalized Anxiety Disorder (n=7), Social Phobia (n=3), Panic

Disorder (n=1) and Post Traumatic Stress Disorder (PTSD) (n=2). A fourth of the sample had comorbid Attention Deficit Hyperactivity Disorder (ADHD), and approximately a third had a past diagnosis of a substance use disorder but were free of any use for at least two months. The majority of the adolescents with depression (n = 11, 79%) were being treated with medication (with duration of treatment ranging from one month to eight years). At the time of the scan, one subject was medication naïve and two subjects had been medicated but were medication-free for one month prior to the scan.

Probabilistic Tractography

Probabilistic tractography was used to delineate tracts originating from the subgenual ACC, projecting dorsally to the supragenual ACC and ventrally to the amygdala in each hemisphere. Within those tracts, we measured WM microstructure indexed by FA. The primary finding was in the tract connecting the right subgenual ACC and the right amygdala, where patients (N=14) demonstrated lower mean FA (depressed FA=0.31, control FA=0.34, F=7.152, p=0.013, Cohen's d= 1.0) compared with the healthy group (N=13). Lower FA was also observed in the left hemisphere tract connecting left subgenual ACC to left amygdala, but this did not reach significance (N=28, F=1.537, p=0.227, Cohen's d= 0.59). No significant group differences were observed in the tracts connecting the subgenual ACC dorsally to the supragenual ACC in either hemisphere (left, N=27: 13 depressed/14 healthy; right, N=14: 5 depressed/9 healthy) See Supplement 2).

Voxel-Wise Comparison

In the voxel-wise comparison, no group differences were found that withstood whole-brain correction for multiple comparisons. In our exploratory analysis of uncorrected data, we identified ten clusters in which FA was significantly lower in the depressed group compared to the healthy adolescent group ($p \leq 0.001$, uncorrected; $p \leq 0.05$, FDR small volume corrected). The locations for these clusters are listed in Table 2. Standard brain atlases available in FSL (http://www.fmrib.ox.ac.uk/fsl/fslview/index.html) were used to identify the most likely WM tracts that contained these clusters. The resulting labels included the left and right uncinate fasciculi, the left and right inferior-fronto-occipital fasciculi, left anterior cingulum, and left superior longitudinal fasciculus (see Figure 1 and Table 2). In this exploratory analysis, no clusters with significantly higher FA in the depressed group were observed.

DISCUSSION

In this report, using two separate DTI analyses we document lower FA in specific WM tracts in adolescents with MDD. These findings provide preliminary evidence supporting the hypotheses that the pathophysiology of MDD in adolescents involves altered organizational microstructure of WM pathways within front-limbic neural networks.

Our first, hypothesis-driven approach was to use probabilistic tractography to delineate the WM tracts extending from the subgenual ACC dorsally to the supragenual ACC, and ventrally to the amygdala. We predicted that these tracts would show evidence of diminished WM integrity,indexed by lower mean FA values. This hypothesis was based on our previously reported finding of lower resting-state functional connectivity arising from the subgenual ACC in this sample of adolescents with depression.44 The focus of our work on the subgenual ACC has been based on research in adults suggesting that the subgenual ACC may represent a "hub" in the fronto-limbic networks that go awry in MDD.19, 53 Deep brain stimulation of this area in adults with MDD has been shown to alter functional activity within fronto-limbic regions,[17] and growing evidence using structural (volumetric)[8] and functional MRI20 has also implicated the subgenual ACC in adolescents with MDD.

DTI tractography has been used to explore the microstructural integrity of WM pathways associated with this region in healthy adults,[53, 54] but the present study is the first to report the use of DTI tractography to investigate subgenual ACC-associated WM pathways in adolescents with MDD.

By comparing FA within the WM pathways yielded by tractography, we found that adolescents with MDD had lower FA in the tract connecting subgenual ACC to amygdala in the right hemisphere. This evidence of diminished organization in WM microstructure in this connection is supportive of current MDD models in which the ACC provides deficient regulatory input to the amygdala.[5, 55] The tract that we have delineated in this study is likely encompassed by the uncinate fasciculus, whose fibers connect the medial temporal cortex (amygdala and hippocampus) with the orbitofrontal cortex, including the subgenual ACC (BA 25).[56] The data presented here converge with a prior tractography report showing lower FA in the left uncinate fasciculus both in adults with bipolar disorder and in adults with schizophrenia compared to healthy volunteers.36 Together, these findings suggest that this connection may be implicated in a broad range of neuropsychiatric disorders.

Our second, exploratory approach was to search for group differences in FA throughout the brain. Based on uncorrected results from our voxel-wise analysis, we provide preliminary evidence of reduced FA in ten WM regions in adolescents with MDD compared to healthy participants. No clusters were identified in the opposite direction, supporting our hypothesis that fronto-limbic WM tracts would have impaired microstructural integrity in fronto-limbic pathways. While these uncorrected findings should be interpreted with caution, they are supportive of currently proposed anatomical models of fronto-limbic networks in MDD.[4, 5] Specifically, we identified several clusters within bilateral tracts labeled as uncinate, thus converging with our tractography data. As discussed above, our detection of disruptions within this connection support the hypothesis that MDD patients have diminished regulation of amygdala responses to stress due to decreased integrity within connections with frontal regions. We also identified one cluster in WM near the left supragenual ACC, which also provides regulation to the amygdala.51 Impaired connectivity in this network is evident in fMRI studies in adults with MDD.[57] This analysis also identified clusters of lower FA in cortical WM tracts that were not predicted (i.e., in the parietal and occipital lobes), raising the possibility that the underlying process may be more wide-spread than hypothesized under current models. This possibility awaits confirmation from future studies.

These preliminary voxel-wise results add to two prior voxel-wise analyses of DTI data in non-elderly patients with MDD which both also showed lower FA in various cortical WM areas. The first of these reports failed to withstand whole-brain FDR correction.[38] With a larger sample, the more recent work detected significant, corrected findings for lower FA in cortico-limbic WM pathways.[46] Thus we expect that our findings, even after whole-brain correction, would likely be confirmed in a larger sample of adolescents with MDD.

Conclusions based on these results must take into account limitations pertaining to the study sample. First, most of the participants with MDD were undergoing treatment with medications. The potential effects of medication on WM integrity are still poorly understood. However, since prior DTI research in adults with MDD has reported lower FA compared to healthy volunteers in a treatment-naïve sample,[38] it is unlikely that the findings here can be ascribed solely to a medication effect. Indeed, it is plausible that the results would have been more robust if treatment-naive adolescent patients had served as participants. For instance, in older adults with depression, DTI studies have documented higher FA in the ACC in patients that achieve remission after treatment of depression.[58, 59] Similarly, previous neuroimaging studies in adults using PET have found depression-related abnormalities of subgenual ACC metabolism[19, 60] that were reversed by successful

treatment with antidepressant medications. Future work using DTI before and after medication will be necessary to confirm findings and to further explore how treatment may impact WM microstructure in adolescents with MDD.

Given high rates of comorbidity in this sample of moderate to severely depressed adolescents, future efforts will need to clarify the specificity of the reported findings. MDD was the primary diagnosis and the focus of care, yet most patients in this sample had one or more secondary comorbid diagnoses. The most frequent comorbid condition was anxiety. Inclusion of anxiety disorders in MDD studies is standard because depression and anxiety are so highly comorbid in adolescents[61] that exclusion of anxiety disorders would result in a highly atypical sample. Similarly, ADHD precedes depression in many adolescents,[62] and inclusion of patients with ADHD is common in adolescent MDD studies.[63] Finally, although subjects denied all use of substances for 60 days prior to the scan, our sample included 5 subjects with a history of a substance use disorder. Substance use disorders commonly co-occur with depression,[64] arguably making our sample more representative. While the inclusion of these subjects is a limitation, it was noted that these subjects did not represent outliers in the analysis. Continued efforts to investigate the specific impact of depressive illness versus each of the comorbid secondary disorders on WM microstructure are warranted.

The application of DTI to study WM microstructure is still an emerging methodology, and the field continues to develop new ways to address limitations. One issue that remains controversial is the ideal acquisition time. We acknowledge that increasing the number of averages in the DTI sequence would have improved the signal to noise ratio. In our experience with pediatric imaging, a short acquisition time is most feasible. Thus, for this preliminary study, we decided to use a single average 30 direction scan to maximize study tolerability by reducing total scanner time (5 minutes). Notably, acquisition times of this length have been used successfully by other groups.39, 46 We found that all of our 28 subjects (depressed and healthy) tolerated the scan well, and in fact we lost no data due to movement artifact, suggesting that for future efforts it will be feasible to acquire DTI scans with two averages (10 minutes), increasing the signal to noise ratio by 40%.

DTI tractography research has also varied in study design. Tractography can serve to generate pathways of interest that can then be used to measure local DTI scalar measures such as FA,[35, 36] as we have done here. Other possibilities include deriving indices of "connection strength, "[65] or calculating the number of reconstructed fibers in a tract.[37] In the experience of our laboratory, quantifying connection strength is less reliable than extracting mean FA from the tracts, perhaps because connection strength indices are influenced by factors such as head size, ROI size, and data quality.

Finally, although DTI is currently our best tool for estimating WM integrity, precise anatomical measurement of WM can not be safely attained in humans. One problem inherent to DTI is the assumption that the FA measured in a given region represents WM from one major fiber tract. In reality, crossing fibers may occur within the region measured, and thus a lower FA measurement would be erroneously interpreted as having “lower connectivity”. Given this, DTI results should be interpreted with caution; advances in this science such as meta-analyses and multi-modal neuroimaging approaches will clarify how group FA differences can shed light on “connectivity”.

In conclusion, using DTI we report altered microstructure within specific WM tracts in adolescents with MDD. These findings are supportive of the hypothesis that the pathophysiology of adolescent MDD involves abnormal fronto-limbic neural networks, and advances this model by providing evidence for decreased integrity in the WM tract

connecting subgenual ACC to amygdala in adolescents with depression. Future research in larger samples of treatment-naive adolescents with MDD is needed to confirm findings and to investigate how treatment interventions may impact WM microstructure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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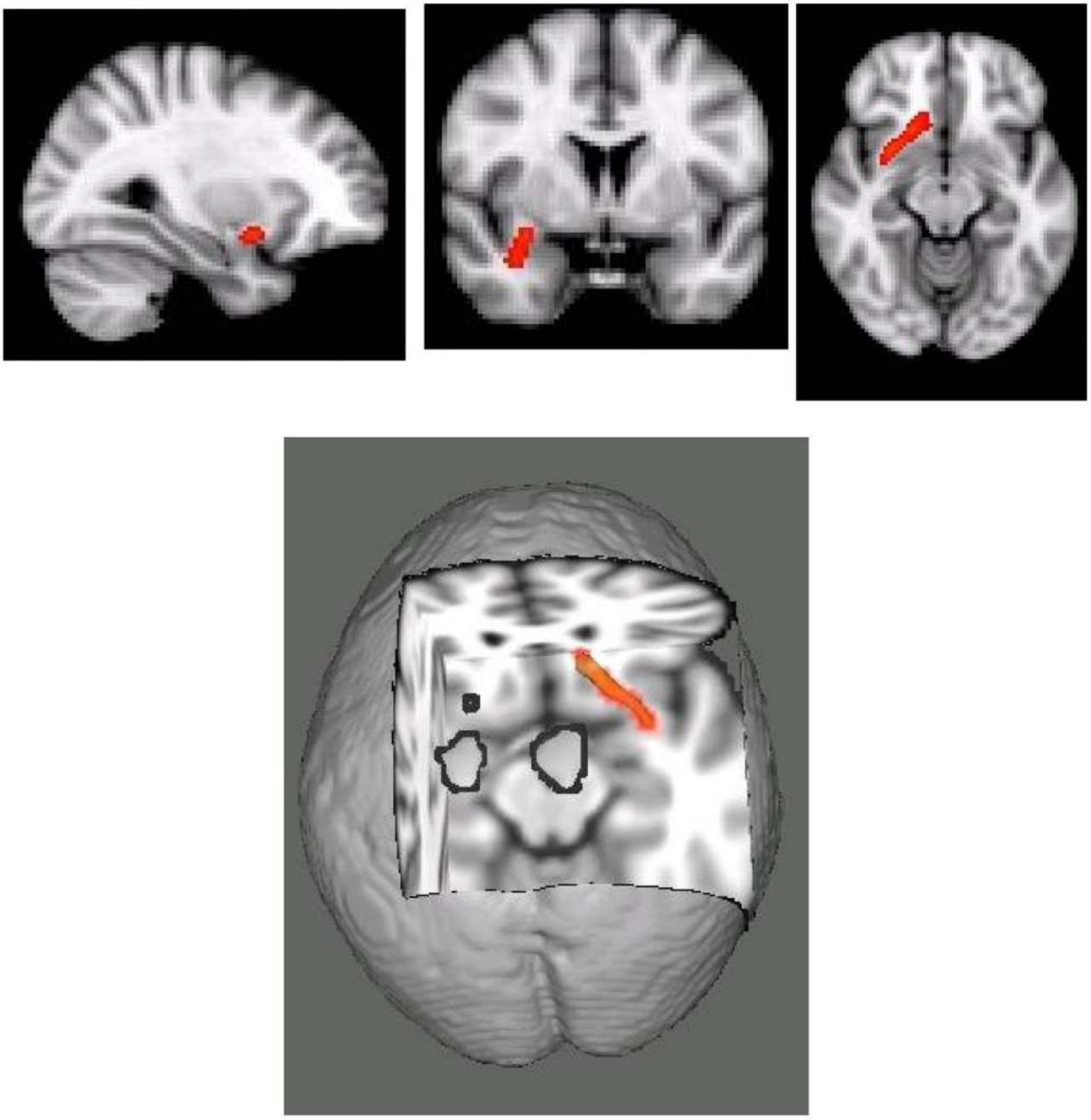

Figure 1.
Fiber tracking results: Red= group average for right subgenual ACC – amygdala tract (N=27). ACC = Anterior Cingulate Cortex;

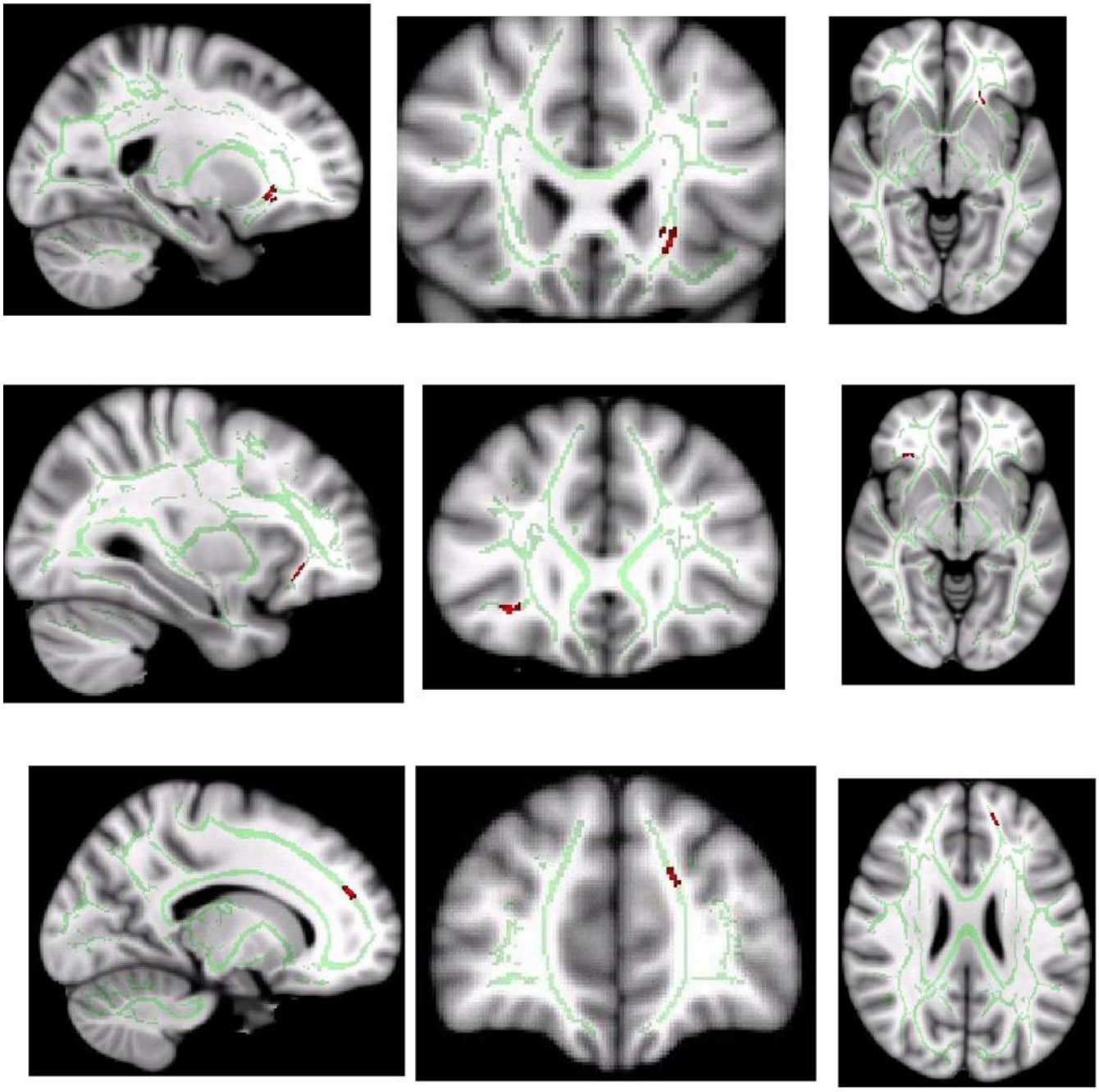

Figure 2.
TBSS results. Select images are shown, corresponding clusters highlighted in Table 2. Green =FA skeleton; Red = clusters of significantly lower (uncorrected) FA in MDD group. Top row: left uncinate. Middle row: right uncinate. Bottom row: anterior cingulum.
FA = Fractional Anisotropy
TBSS = Tract-Based Spatial Statistics
MDD = Major Depressive Disorder

Table 1

Demographic and Clinical Characteristics of Depressed and Healthy Adolescents

Characteristic	**MDD *n*=14**	**Controls *n*=14**
Age (mean years±[a]S.D.)	16.79±1.29	16.81±1.5
Gender (*n* male/ *n* female)	4/10	6/8
IQ (mean ±S.D.)	104.9±10.1	[b]114.3±10.4
Ethnicity: *n*(%)		
Caucasian	10 (71)	9 (64)
African American	2 (14)	2 (14)
Hispanic	2 (14)	0
Asian	0	2 (14)
Other	0	1 (7)
Illness History		
Duration of Illness (mean months±S.D.)	33.9±30.3 [c](1–96)	0
Medication-naïve/ Medication-free/ Medicated, n(%)	1/2/11 (7/14/79%)	14/0/0 (100/0/0%)
Global Assesment of Functioning (mean±S.D.)	43.9±9.7 [c](31–60)	No information
Medication class: *n*(%)		
[d]Selective serotonin reuptake inhibitors	9 (64)	0
[e]Serotonin and Norepinephrine Reuptake Inhibitors	1 (7)	0
[f]Tricyclic Antidepressants	1 (7)	
[g]Mood stabilizers	2 (14)	0
[h]Atypical Antipsychotics	2 (14)	0
[i]Stimulants	2 (14)	0
[j]Selective Norepinephrine Reuptake Inhibitor	1 (7)	0
[k]Benzodiazepines	1(7)	
[l]**BDI-II** (mean±S.D.)	29.0±11.8 [c](15–47)	No information
Current Comorbidity (secondary diagnoses): *n*(%)		
[m]ADHD	3 (21)	0
Substance use disorder (in remission)	5 (36)	0
Any Anxiety Disorder	12 (86)	0

[a]Standard Deviation;

[b]t(26)= 2.433, p=0.022.

[c]Range;

[d]Selective Serotonin Reuptake Inhibitors included fluoxetine (n=3), sertraline (n=1), citalopram (n=4), escitalopram n=1);

[e]Serotnonin and Norepinephrine Reuptake Inhibitors included venlafaxine (n=1);

[f]Tricyclic Antidepressants included Nortryptiline (n=1);

[g] Mood Stabilizers included lamotrigine (n=1) and oxcarbazepine (n=1);

[h] Atypical Antipsychotics included aripiprazole (n=1) and quetiapine (n=1);

[i] Stimulant medications included amphetamine/dextroamphetamine (Adderall) (n=2);

[j] Selective Norepinephrine Reuptake Inhibitors included atomoxetine (n=1);

[k] Benzodiazepines included clonazepam (n=1);

[l] Beck Depression Inventory-II;

[m] Attention Deficit Hyperactivity Disorder.

MDD = Major Depressive Disorder; BDI-II = Beck Depression Inventory-II

Table 2

List of clusters where adolescents with MDD had significantly lower FA (p<0.001, uncorrected) compared to the healthy group. Bold rows correspond with brain images displayed in Figure 1. IFOF=Inferior Fronto-occipital fasciculus, SLF=Superior Longitudinal Fasciculus; MDD = Major Depressive Disorder; MNI = Montreal Neuroimaging Institute; FA = Fractional Anisotropy

No. voxels	MNI coordinates	Hemisphere	White Matter Tract	Corresponding cortical area(s)	Tmax value	Cohen *d*	FA values Mean (S.D.) Healthy/Control
13	−37, 18,35	Left	No label	Middle frontal	4.05	0.93	.28 (.11)/ .20 (.07)
10	28,−70,14	Right	IFOF	Occipital (Cuneous)	3.61	1.48	.68 (.04)/ .60 (.06)
10	**−22,23,−5**	**Left**	**Uncinate**	**Orbitofrontal**	**4.12**	**1.47**	**.46 (.04)/ .40 (.04)**
9	**32,30,−6**	**Right**	**IFOF/Uncinate**	**Orbitofrontal cortex, insula**	**4.11**	**1.89**	**.37 (.07)/ .25 (.05)**
7	−28,−71,1	Left	IFOF	Occipital	3.82	1.68	.65 (.05)/ .58 (.04)
7	26,17,−7	Right	Uncinate	Orbitofrontal cortex, insula	4.07	1.44	.52 (.05)/ .45 (.05)
6	24,−56,31	Right	IFOF	Parietal cortex (Precuneous)	3.60	1.09	.41 (.06)/ .35 (.06)
6	**−15,45,25**	**Left**	**Cingulum**	**Medial frontal**	**3.91**	**1.39**	**.45 (.05)/ .39 (.04)**
5	−47,−39,8	Left	SLF	Temporal	3.63	1.28	.48 (.06)/ .41 (.06)
5	37,−62,−4	Right	IFOF	Occipital	4.02	0.68	.43 (.09)/ .38 (.08)