White Matter Correlates of Adolescent Depression: Structural Evidence for Frontolimbic Disconnectivity

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Abstract

Objective—Despite the significant prevalence of adolescent depression, little is known about the neuroanatomical basis of this disorder. Functional dysregulation in frontolimbic circuitry has been suggested as a key neural correlate of adult and adolescent depression impeding emotional regulation. However, less is known about whether this dysregulation is overlaid on impaired white matter microstructure. Guided by neuroimaging findings, we test the a priori hypotheses that adolescent depression is associated with alterations in white matter microstructure in the 1) uncinate fasciculus (UF) and 2) cingulum bundles.

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Method—Diffusion tensor magnetic resonance imaging (DTI) data were obtained on 52 unmedicated adolescents with major depressive disorder (MDD) and 42 matched controls. We calculated fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD) for bilateral UF and cingulum. We also completed a voxelwise comparison of participants with depression and control participants using tract-based spatial statistics (TBSS).

Results—Adolescents with depression had significantly lower FA and higher RD in bilateral UF; no significant differences were observed in cingulum. TBSS results additionally revealed lower FA values in the white matter associated with the limbic-cortical-striatal-thalamic circuit, corpus callosum, and anterior and superior corona radiata.

Conclusion—Unmedicated adolescent depression is associated with reduced fractional anisotropy in emotion regulatory networks, which may underlie the functional differences in frontolimbic circuitry characterizing depressive disorder. Given the relatively recent onset of depression in our sample, our findings in the context of the current literature provide preliminary evidence that reduced fractional anisotropy in the UF could be a predisposing risk factor for depression.

Keywords

Adolescent major depression; white matter; diffusion tensor imaging; uncinate fasciculus; emotion regulation

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Introduction

Depression during adolescence affects 8-20% of all youth [1-3] and as much as quadruples the odds of developing adult depression. [4] Adolescence appears to be a particularly sensitive period in the development of depression as rates of this disorder increase dramatically. [5] Vulnerability to depression may therefore be related to atypical maturational changes in the brain. [6] Understanding the neuroanatomical basis of adolescent depression may yield important insights into the process by which normally developing neural circuitry may go awry in this disorder. Therefore, identifying the underlying etiology and neurobiology of adolescent depression has important clinical implications that may not only guide efforts to improve treatment, but may also provide insights for the prevention of adult depression and associated significant health and social problems.

Models of depression highlight the role of widely distributed yet interactive networks of cortical-striatal and cortical-limbic pathways involved in the regulation of mood. [7,8] Emotional and cognitive sequelae of depression may result from dysfunction in frontal regions (e.g. medial prefrontal cortex, mPFC) that poorly regulate reactivity of limbic structures (e.g. amygdala), which are involved in affective processing. [7] Indeed, functional magnetic resonance imaging (fMRI) studies of adult major depressive disorder (MDD) have demonstrated increased amygdala activity, [9,10] and reduced top-down modulation of amygdala reactivity by paralimbic regions and PFC in patients with depression. [11,12] While there is mounting evidence using fMRI that depression earlier in life may be similarly characterized, [13-18] much less is known about the underlying white matter microstructure associated with adolescent depression.

Diffusion tensor imaging (DTI) is a noninvasive imaging method that permits inference of brain anatomy based on the diffusion of water within the brain. [19] Fractional anisotropy (FA) measures the degree of diffusion anisotropy and is the most commonly used DTI metric. Reflecting fMRI evidence of dysregulated frontolimbic pathways, the few studies of adult depression that have targeted a priori, anatomically defined white matter tracts have focused primarily on the uncinate fasciculi (UF)[20,21] and cingulum bundles.[20] The UF connects the hippocampus and amygdala with the ventrolateral and orbitomedial regions of the PFC,[7,8,22] while the cingulum bundles extend from the subgenual anterior cingulate cortex and connect distinct brain regions that are involved in a variety of emotional and motivational processes implicated in depression.[7,22,23] There is one prior study of white matter microstructure in adolescents; however, while this study found some evidence for reduced FA in regions overlapping with UF, it was also confounded by the fact that the majority of participants with depression were receiving several different types and classes of pharmacological treatment.[9,10,24]

Based upon the reviewed literature, we hypothesized that adolescent depression is associated with reduced FA in the UF and cingulum bundles. We test our hypotheses using DTI in the largest sample to date of unmedicated adolescents with a primary diagnosis of MDD and healthy, well-matched controls. DTI data can be analyzed using both whole-brain and tract-specific methods; however, we emphasize a priori tract-based hypotheses for which there is a theoretical and empirical justification. We use probabilistic tractography to examine two anatomically defined white matter tracts: the bilateral UF and cingulum bundles. We also use a whole-brain, voxelwise approach to further explore depression-related differences in white matter.

Method

Participants

Ninety-four adolescents (52 with depression, 42 healthy controls) ranging in age from 13 – 17 years participated in this study, which was approved by the institutional review boards of University of California (UC), San Diego, UC San Francisco, Rady Children's Hospital, and the County of San Diego. All participants gave written informed assent, and their parents/legal guardians provided written informed consent. Participants were compensated for their time.

Healthy control adolescents were recruited from the San Diego area by means of posted flyers, e-mail, and the Internet. Participants with MDD were recruited from 35 adolescent psychiatric clinics spread widely throughout the San Diego County area.

Clinical Assessment

All adolescents with potential depression were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS-PL),[25] and diagnoses were determined by a board-certified child and adolescent psychiatrist. All participants with depression met full criteria for a primary diagnosis of MDD and were excluded if they had a comorbid diagnosis of psychosis, bipolar disorder, or substance abuse.

Healthy adolescents were excluded from the study if they had any Axis I psychiatric disorder, which was determined using the computerized Diagnostic Interview Schedule for Children version 4.0 (DISC-IV)[26] and the Diagnostic Predictive Scale (DPS).[27] Control participants were also excluded if they had any family history of mood or psychotic disorders in first- or second-degree relatives.

Severity of depression was assessed through both a clinician ratings scale, the Children's Depression Rating Scale-Revised (CDRS-R),[28] and a self-report scale, the Reynolds Adolescent Depression Scale (RADS-2).[29] CDRS-R scores were used to further characterize study groups; controls with scores higher than 54 and MDD participants with scores lower than 55 were excluded. Psychosocial functioning was assessed using the Children's Global Assessment Scale (CGAS).[30]

Given the high rates of comorbid anxiety in adolescent depression, we also assessed anxiety symptoms[31] with the Multidimensional Anxiety Scale for Children (MASC).[32]

Additional exclusion criteria for all participants included: a performance score of less than 70 on the Wechsler Abbreviated Scale of Intelligence (WASI),[33] inability to fully understand and cooperate with study procedures, contraindications for MRI (e.g., metallic implants, claustrophobia, pregnancy or the possibility thereof), left-handedness, prepubertal status (Tanner stage 1 or 2), substance abuse, history of neurological disorders (e.g., head trauma, seizures), misuse of prescription drugs or more than two alcohol drinks per week, and the use of medications with a CNS effect within 2 weeks prior to scanning. Parental socioeconomic status was measured using the Hollingshead Two Factor Index of Social Position, [34] and participants self-reported their ethnicity (Hispanic, Non-Hispanic).

Demographic and Clinical Scales Analysis

All statistical analyses were conducted in R.[35] Between-group differences were assessed by means of Welch t-tests for age, the performance subscale of the WASI, CDRS-R, MASC, and RADS-2. While all of our participants were fluent English speakers, for some, English was their second language. Therefore, we measured IQ solely on the basis of the performance measure of the WASI. All depression scales were standardized. Group differences in gender and number of rejected directions were assessed using a χ^2 test of equal proportions. We used the Wilcoxon Rank Sum test to determine group differences in the Hollingshead Socioeconomic Index, CGAS, and Tanner Stage.

MR Data Acquisition

All scanning was conducted on a 3T MR750 GE (Milwaukee, WI) scanner at the UCSD Center for Functional Magnetic Resonance Imaging. High-resolution sagittal T1-weighted anatomical images were acquired using a fast spoiled gradient echo sequence: TR/TE=8.1ms/3.17ms, flip angle=12°, 256×256 matrix, 168 sagittal slices 1×1×1mm voxels. Diffusion data were measured along 30 directions using a dual spin echo, single-shot, echo planar imaging sequence: TR/TE=7200ms/86.5ms, flip angle=90°, 96x96 matrix, 50 axial slices, b-value: 1500s/mm^2, 1.875×1.875×2.5mm voxels. We averaged 2 separate excitations (NEX=2) to maximize the signal to noise ratio. Gradient echo field maps were also acquired to permit compensation for magnetic field inhomogeneity: TR/TE1/

TE2=1000ms/4.4ms/5.5ms, flip angle=12°, 128×128 matrix, 50 axial slices, 1.875×1.875×2.5mm voxels.

Data Analysis

MR Data Analysis

All analyses were conducted using FSL 4.1.9.[36]

Anatomical Analysis

T1-weighted images were bias-field corrected,[37] skull stripped, and transformed to MNI152 space using an affine transform[38] followed by non-linear refinement.[39]

Diffusion Data

DTI images were processed using FUGUE software to compensate for B_0 inhomogeneity.[40] Images were skull-stripped and outlier directions were censored from the analysis. Outliers were determined using 3dToutcount software from AFNI.[41] A direction (volume) was rejected if the fraction of outliers in the volume was greater than 2 standard deviations from the mean outlier count across the entire 4D volume (For more details see Supplement 1, available online). Rejected directions were inspected visually, as were volumes near the 2 standard deviation threshold. A linear affine transformation was applied to diffusion-weighted images to correct for the distortions caused by motion and eddy currents.[42] The diffusion vector was rotated to adjust for the registration step. Finally, a tensor model was fit to these images using FMRIB's Diffusion Toolbox (FDT),[36] yielding fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD) maps in native space. RD and AD are additional DTI metrics that may contribute further insight into the character of white matter differences. AD refers to diffusion in the same direction of the fiber tract, and RD refers to diffusion perpendicular to the fiber tract.

Probabilistic Tractography

For our a priori tracts (bilateral UF and cingulum bundles), masks in standard space were extracted from ICBM-DTI-81 atlas[43] and reverse-transformed to native space by serially applying the inverse of the previously calculated nonlinear warpfield from T1 to MNI152 space and the inverse of the rigid-body transformation from DTI space to T1 space for the application of probabilistic tractography. Examples of these tracts in diffusion space for one representative subject can be seen in Figure S1, available online).

Probtrackx, run in single mask mode in DTI space, was used to delineate tracts of interest. Tractography was performed with the following constraints: minimum FA value of 0.15, curvature threshold of 78.5°, step length of 0.5mm, and within only one hemisphere. We chose a curvature threshold of 78.5° based on prior studies,[24,44,45] including the only other study of white matter microstructure in adolescent MDD.[24] A connectivity distribution was generated by seeding 5000 sample fibers from each voxel in the seed mask.

For all resulting tracts, images were thresholded such that those voxels with less than a 5% probability of being connected to the seed masks were eliminated. Eliminating voxels at this

threshold is frequent in the literature[44] and is also consistent with the only other published study of white matter microstructure in adolescent MDD.[24] All connected components were identified (26-connectivity in 3D), and we retained only the largest connected component to exclude physiologically implausible tracts. Across all subjects, the largest disconnected component deleted was no greater than 5 voxels in size. An example of retained and eliminated tracts can be seen in Figure S2 (available online). All resulting tracts were visually inspected for anatomical plausibility. Mean FA, RD, and AD were extracted from voxels within this largest connected component.

Group and Correlational Analyses

Between-group differences in the mean FA extracted for each tract were assessed using linear mixed effects (LME) models implemented in R,[35] where the participant was treated as a random effect. All models were adjusted for covariates that significantly differed between groups. If a significant FA difference was found, we examined whether there were also significant differences in RD and AD using the same modeling strategy.

Voxelwise Analysis

Voxelwise statistical analysis of the FA data was conducted using Tract-Based Spatial Statistics (TBSS).[46] All participants' FA images were aligned into a common space using the FNIRT nonlinear registration tool,[39] which uses a b-spline representation of the registration warp field.[47] Next, the mean FA image was created and thinned to make a mean FA skeleton that represents the centers of all tracts common to all participants. Each participant's aligned FA data was then projected onto this skeleton. The resulting data was subjected to voxelwise permutation-based nonparametric methods[48] (5000 permutations) that corrected for multiple comparisons across space and incorporated threshold-free cluster enhancement (TFCE).[49] Statistical maps were thresholded at p 0.05 (TFCE-corrected for family-wise errors) for the group main effects.

Sensitivity Analyses

We also conducted sensitivity analyses to examine whether head motion, outliers, or participants with MDD and comorbid attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder (PTSD), enuresis, social phobia, oppositional defiant disorder (ODD), or conduct disorder (CD) influenced our FA results. To examine the effect of outliers, we re-ran LME models excluding those observations with FA values greater than two standard deviations from the mean. To examine the effect of comorbidity on our results, we re-ran our LME models and TBSS analyses excluding those participants in the depressed group with the above-listed comorbidities. Finally, to examine the effect of head motion on our results, we included average motion parameters for each subject in our LME models (see Supplement 1, Materials, available online, for details).

Results

Demographic and Clinical Scales

The mean age of our sample was 16.1 years old (SD=1.4, range 13.1-17.9) and 61% were female. Control participants did not differ significantly on age, gender, or socioeconomic

status from those with depression. The MDD group reported marginally greater Tanner stage scores than the healthy controls (*p*=0.05). The controls reported significantly greater performance IQ than the participants with MDD (*p*=0.01). Therefore, in all group comparisons of white matter microstructure, we adjusted for performance IQ and Tanner stage. As expected, the participants with MDD endorsed significantly greater levels of depression and anxiety on all scales (CDRS-R, RADS-2, MASC) and lower levels of psychosocial functioning than the controls (all *p*<0.001; see Table 1). Mean duration of illness was 2.1 (SD=1.9) years. Many of our participants with MDD had additional comorbidities (see Table 1 for more details).

Tract-Specific Results

After adjusting for performance IQ and Tanner stage, adolescents with depression showed significantly reduced mean FA values in bilateral UF (right: $F_{(1,88)}$=7.52, *p*=0.007; left: $F_{(1, 88)}$=13.86, *p*<0.001-Figure 1). Participants with depression also showed reduced FA in bilateral cingulum (cingulate portion), though these results were not significant (right: $F_{(1, 88)}$=3.34, *p*=0.07; left: $F_{(1, 88)}$=3.64, *p*=0.057).

To further understand white matter microstructure within tracts demonstrating FA differences, we also investigated between-group differences in RD and AD (see Figure 1). Adolescents with depression showed significantly greater RD in left UF ($F_{(1,88)}$=6.59, *p*=0.012), though only marginally so in the right UF ($F_{(1, 88)}$=3.93, *p*=0.05). Similar to FA findings, RD in bilateral cingulum was greater, though not statistically significant (right: $F_{(1,88)}$=3.09, *p*=0.07; left: $F_{(1, 88)}$=3.48, *p*=0.06; results not shown in Figure 1). We observed no significant differences in AD in any of the tracts.

TBSS Results

We also conducted a TBSS voxelwise comparison between groups. We found many significant differences between control adolescents and those with depression (TFCE-corrected). In all regions where there was a significant group difference, participants with depression had reduced FA compared with controls. In addition to finding significant differences overlapping with our tract-based hypotheses (bilateral differences in UF shown in Figure 2C), we also found significant differences in the genu and body of the corpus callosum (Figure 2A), the anterior and superior corona radiata (Figure 2D,E,F), the inferior fronto-occipital fasciculi (Figure 2C), and the internal and external capsule (Figure 2B,E). Internal capsule and external capsule findings suggest involvement of the limbic-cortical-striatal-thalamic circuit. For interpretability, we have included visualization of selected cortical regions that have been found to be dysfunctional in depression when displaying our TBSS results. All images are in MNI152 space.

Sensitivity Analyses

Our sensitivity analysis excluding outliers suggests that our findings are robust to the effects of extreme observations. Excluding participants with FA values greater than 2 standard deviations from the mean (3 MDD and 1 control) did not influence either the significance of our findings or the effect size (see Table S1, available online). Additionally, we re-ran our LME models and TBSS analyses excluding those MDD participants with MDD and

comorbid ADHD, PTSD, enuresis, social phobia, ODD, or CD (MDD: n=33; control: n=42). With respect to the tract-based analyses, participants with MDD still had significantly reduced FA values and higher RD compared to controls in bilateral UF with comparable effect sizes. Cingulum FA findings remained nonsignificant (see Table S2). Our TBSS results on this more refined sample were not substantively different from the larger analysis; however, while the same white matter tracts were identified, some of the significant clusters were smaller (see Figure S3, available online). Finally, we also examined the effect of incorporating motion parameters into our adjusted models in the complete sample (MDD: n=52; control: n=42). Including these parameters had no effect on our results (see Table S3, available online).

Discussion

In the current study, we examined differences in white matter microstructure in a large sample of unmedicated adolescents with MDD and matched healthy controls. Our study yielded several novel findings. In our a priori probabilistic tracts, we found significantly reduced mean FA and higher mean RD values in bilateral UF in adolescents with clinical depression compared to healthy controls. Finally, our voxelwise analysis identified several other white matter tracts that may be involved in the pathophysiology of adolescent depression, including limbic-cortical-striatal-thalamic circuits.[7,50]

Our finding that adolescents with depression have reduced fractional anisotropy in bilateral UF provides initial evidence of structural deficits that may underlie the functional differences in frontolimbic circuits observed in adolescent depression. The UF is particularly relevant to the study of depression as it connects inferior frontal regions, such as the anterior cingulate cortex (ACC), mPFC and orbitofrontal cortex (OFC) with medial temporal regions, such as the amygdala and hippocampus.[22] The ACC, OFC, and mPFC all play an important role in regulating amygdala reactivity,[7,51] and many fMRI studies have highlighted these regions in both adolescent[14-16,18,52] and adult depression.[53] In the only other DTI study to date of adolescents with depression, Cullen et al. (2010) used TBSS and found evidence of reduced FA in a small number of voxels overlapping with the left UF. Two recent tract-based studies of white matter microstructure in adults with depression found evidence of reduced FA in the left UF[20] and in an anterior, dorsal subsection of the UF.[21] Interestingly, one small study of geriatric depression found lower FA in left UF only among those whose depression manifested at an early age (mid-to-late adolescence).[54] Given the relatively recent onset of depression in our sample, our findings in the context of the current literature provide preliminary evidence that reduced fractional anisotropy in the UF could be a predisposing risk factor for depression.

Notably, in bilateral UF where FA values were significantly reduced in the group with depression compared to controls, RD values were significantly higher, but no differences in AD were observed. Previous studies in animal models measuring DTI in vivo suggest that the combination of higher RD with lower FA values is a plausible noninvasive biomarker of poor myelination (as opposed to axonal injury).[55] One potential explanation for our findings is that tracts critical to emotion regulation are poorly myelinated in adolescent MDD, which may underlie a reduction in their capacity to moderate thoughts and feelings generated in

limbic regions of the brain. A recent DTI study of adult MDD also found decreased FA and increased RD in right UF in participants with depression.[20] The authors concluded that adult depression might result from a demyelination process. It is notable that we found the same pattern of differences in white matter microstructure in our sample of adolescents with depression and with relatively short disease histories, suggesting that there is a similar underlying neurobiological mechanism linking both adolescent- and adult-onset depression. Future longitudinal studies that 1) employ novel DTI metrics (such as the hindrance modulated orientational anisotropy [HMOA] index)[56] that are more suited to examining myelination and 2) include participants with depression across the life course with varying age of onset and duration of illness may help clarify the exact nature of white matter differences that increase risk for adolescent depression.

Voxelwise analyses revealed several white matter tracts involved in mood regulation in which depressed subjects had significantly lower FA values than controls. Specifically, we found evidence of structural differences of the limbic-cortical-striatal-thalamic circuit in adolescent depression. This particular circuit has been highlighted due to the central role of the medial PFC in organizing emotional signals from the limbic system and in self-referential processing.[7] Depression has been hypothesized to result from reduced transmission of information from the limbic system to the PFC via the striatum and its associated white matter tracts within the internal capsule.[50] Our whole-brain analysis suggests that depressed adolescents have lower FA values in several tracts that facilitate communication within this network, including the internal capsule, external capsule, UF, and inferior fronto-occipital fasciculus.

However, not all differences identified in voxelwise analysis overlapped with white matter tracts specifically related to mood regulation. We also found large differences in both the body and genu of the corpus callosum, with significantly lower FA values in adolescents with depression relative to healthy controls. White matter differences in this area have been reported in several studies of adult MDD,[57-59] and across multiple psychiatric conditions including schizophrenia,[60] bipolar disorder,[61] and ADHD.[62] The corpus callosum is the largest white matter tract in the brain and provides interhemispheric communication and integration of emotional, cognitive, linguistic, and perceptual processing.[63] The genu in particular integrates input from the left and right anterior cingulate, bridging attention and emotion.[64] It also integrates signals from the bilateral insula incorporating internal and external homeostatically relevant information to inform behavior.[65]

Interestingly, corpus callosum differences have been observed in association with early life stress of varying severity (e.g. maltreatment, institutionalization, and stressful life events) in children (posterior corpus callosum),[66] adolescents (posterior corpus callosum),[67] and adults (genu).[68] As early life stress is also a strong predictor of depression as well as other mood, substance, and behavior disorders,[69] perhaps corpus callosum differences either mediate or precipitate effects of early life stress on mental health. As such, white matter differences in corpus callosum may serve as a sensitive, though not specific, indicator of psychiatric risk that could be used to identify candidates for primary prevention. These questions should be further explored in future research that includes measures of early life stress.

Although we did not find significant differences in the cingulum bundles from either our probabilistic tract-based or TBSS analyses, our tract-based findings trended in the anticipated direction, with adolescents with depression exhibiting lower FA than controls. However, in the subsample of participants with MDD without comorbidities, these results were no longer approaching significance. Given its role in connecting multiple regions of the brain that span many functions affected by depression (e.g. attention, memory, and emotion regulation), the cingulum has been the focus of several recent white matter studies of adult depression[20] and depression risk.[23,70] While one study found evidence that the cingulum may be involved in adolescent depression, these differences were identified in a small number of voxels that included participants with depression on a variety of medications, possibly confounding these results.[24] Overall, few studies to date provide compelling evidence that cingulum differences are associated with clinical depression in adolescents.

Our results significantly contribute to the dearth of white matter microstructure studies addressing adolescent depression and have several potentially important clinical implications for the treatment and prevention of adolescent depression as well as other major pediatric psychiatric disorders. Our findings suggest that altered white matter microstructure of the UF may be a reliable biomarker of adolescent depression, and that changes to these structures may correlate with and predict treatment responsiveness. Additionally, our pattern of DTI findings in the UF indicates that white matter structures facilitating emotion regulation may be poorly myelinated in adolescent depression. This has implications for the study of factors that may contribute to poor myelination (e.g. genetics, adverse experience, nutritional exposures) as well as the development of novel preventive interventions and clinical therapies that could promote myelination during adolescent development. Finally, our whole-brain analysis indicates that many white matter tracts in the forebrain, including the corpus callosum, have reduced FA in depression. Such widespread differences suggest that generalized delayed white matter development may be characteristic of adolescent depression. Several studies of age-related change in white matter microstructure suggest that FA values increase during adolescence in the tracts identified in our voxelwise analysis.[71-74] Future longitudinal studies will be essential to better understand the developmental time course of white matter microstructure in adolescents at risk for depression.

Our findings must be interpreted in light of the limitations of our study. We are unable to infer causal relations between underlying white matter microstructure and the development of adolescent depression due to our cross-sectional study design. However, the fact that all our participants with depression were unmedicated with relatively short durations of illness better suggests that our neuroanatomical findings are more likely to be related to depression than in similar studies without these characteristics. Although we recruited a large number of participants with depression that were identified with a rigorous screening protocol, it remains unclear how generalizable our findings are to other populations of adolescents, given the homogeneity of our sample (e.g. all participants reflect the demographics of San Diego County). Furthermore, while we conducted sensitivity analyses excluding participants with MDD and a wide range of comorbidities, we did not exclude participants with anxiety in this sub-analysis. Anxiety is highly comorbid with MDD in clinical populations,[31] and

excluding subjects with anxiety from our analyses would reduce our ability to generalize our findings to typical adolescents with MDD that are seen in clinical practice.

Additionally, we used a non-isotropic voxel size in acquiring our DTI scans. Recent reviews on DTI methodology suggest that an isotropic voxel size may be more ideal for fiber tracking.[75] Nonisotropic voxel size is more likely to lead to an underestimate of FA values in tracts in which there are crossing fibers. Despite this limitation, we believe that this aspect of our DTI protocol would not have biased our results in a particular direction. Finally, we averaged the results of 2consecutive scans (NEX=2) prior to correcting each scan for motion, an approach that reduced our ability to identify artifacts. Future studies should acquire multiple repetitions of the diffusion directions and perform averaging in the data processing pipeline after correction for eddy currents and motion to avoid this problem.

In summary, we present the first evidence of widespread white matter differences in a large study of un-medicated adolescents with depression and matched healthy controls. To our knowledge, this is the largest DTI study to date of adolescent depression. White matter tracts associated with adolescent depression in our study included bilateral UF and white matter structures overlapping with the limbic-cortical-striatal-thalamic circuit. Notably, the pattern of DTI findings in the UF (i.e., reduced FA and increased RD in the depressed group) suggests that the neuroanatomical basis for adolescent depression may partially result from poor myelination of emotion regulatory circuitry. Our study population helps to inform potential risk factors for depression as adolescents with depression are less likely than adults to have experienced prolonged illness duration, which may have independent effects on brain structure.[76] Our findings suggest that lower fractional anisotropy in tracts important to emotion regulation may be a predisposing risk factor for depression in early life. Whether this pattern of findings is due to a delay in white matter tract development in adolescents with depression that may rebound over time, or is a stable characteristic of the disorder, should be assessed in future longitudinal studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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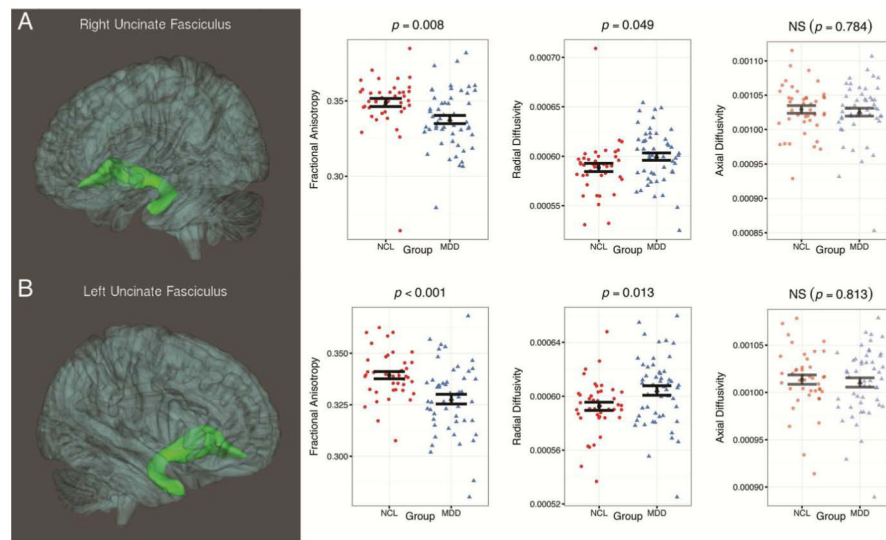
Figure 1.
Three-dimensional images of the probabilistic tractography results for (A) right uncinate fasciculus and (B) left uncinate fasciculus. Note: the images represent the group mean surface of the tracts. Scatterplots indicate distributions of fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD) in the control group (NCL) and the group with major depressive disorder (MDD). The black shapes indicate the corresponding means of FA, RD, and AD for each group, while the black bars indicate standard error of the mean. Only a priori tracts with significant differences in FA values between groups are shown.
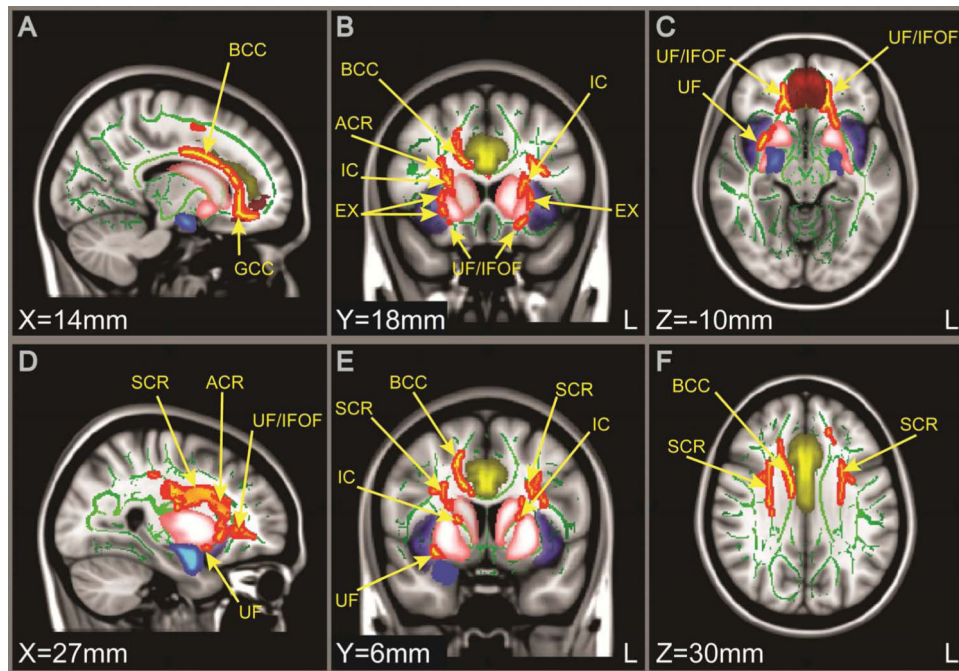
Figure 2.
Tract-based spatial statistics (TBSS) results comparing fractional anisotropy (FA) values in control adolescents and those with depression. Note: FA maps show sagittal, coronal, and axial views (from left to right). Green voxels represent the mean white matter skeleton from the entire sample, and red-yellow voxels represent white matter regions with lower FA in participants with major depressive disorder (MDD) compared with controls ($p<.05$, threshold-free cluster enhancement [TFCE]-corrected). In no regions were FA values significantly higher for participants with depression. Yellow (cingulate), blue (amygdala), purple (insula), red (frontal medial cortex), and pink (striatum) represent grey matter regions adjacent to the white matter tracts identified. ACR = anterior corona radiata; BCC = body of corpus callosum; EX = external capsule; GCC = genu of corpus callosum; IC = internal capsule; IFOF = inferior fronto-occipital fasciculus; SCR = superior corona radiate; UF = uncinate fasciculus.

Table 1

Descriptive Characteristics of the Analytic Sample

Characteristic	NCL[a]	MDD[a]	DF	Statistic[b,c]	P-value
Number of participants (n)	42	52			
Gender (M / F)	16 / 26	21 / 31	NA	X^2=0.05	0.82
# of directions rejected due to motion/outlier	2 ± 0 (1-4)	1.5 ± 0.7 (1-3)	NA	W=1274.00	0.12
Age at time of scan (years)	16 ± 0.2 (13.2-17.9)	16.2 ± 0.2 (13.1-17.9)	86.3	t=−0.66	0.51
Hollingshead socioeconomic score	29 ± 20.8 (11-77)[†]	40 ± 26.7 (11-70)[†]	NA	W=867.00	0.12
Tanner score	4 ± 0.7 (3-5)[†]	4.5 ± 0.7 (3-5) [1][†]	NA	W=803.50	0.05
WASI performance	105.4 ± 1.7 (84-125) [1]	99.2 ± 1.7 (70-124)	88.33	t=2.61	0.01
CGAS	90 ± 6.7 (75-100) [1][†]	65 ± 14.8 (40-85)[†]	NA	W=2065.00	<.0001
CDRS-R	33 ± 0.7 (30-48) [1]	72.5 ± 1.1 (55-85)	80.76	t=−30.27	<.0001
RADS-2 total score	41.7 ± 1.2 (30-56) [2]	65.8 ± 1 (41-80)	78.5	t=−15.00	<.0001
MASC	30.3 ± 2.1 (10-62) [3]	57.3 ± 1.9 (22-87) [2]	80.81	t=−9.61	<.0001
Hispanic ethnicity (yes/no)	23 / 42	28 / 52	NA	X^2=0.0002	0.99
Comorbid Diagnoses in the MDD Group					
GAD		16			
Dysthymic Disorder		9			
ADHD		5			
Social Phobia		2			
Enuresis		2			
Anxiety Disorder NOS		2			
ODD		1			
Conduct Disorder		1			

Note: ADHD = attention-deficit/hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised; CGAS = Children's Global Assessment Scale; DF = degrees of freedom; GAD = generalized anxiety disorder; MASC = Multidimensional Anxiety Scale for Children (Standardized); MDD = major depressive disorder; NA = not applicable; NCL = control; NOS = not otherwise specified; ODD = oppositional defiant disorder; RADS-2 = Reynolds Adolescent Depression Scale-2 (Standardized); WASI = Wechsler Abbreviated Scale of Intelligence

[a]Entries are of the form: mean ± standard error of the mean (SEM; min - max) or median ± median absolute deviation (MAD; min - max) if indicated by †. The optional number in [] indicates the number of missing items of data.

[b]Statistic: W, Wilcox rank sum test; χ2, χ2 test for equality of proportions; *t*, Student's T test.

[c]Statistics for clinical scales refer only to participants surviving motion and outlier correction.