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White Matter Changes in Healthy Adolescents at Familial Risk for Unipolar Depression: A Diffusion Tensor Imaging Study

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Alterations in white matter integrity of several cortical and subcortical circuits have been reported in relation to unipolar major depressive disorder. It is not clear whether these white matter changes precede the onset of illness. In all, 13 adolescent volunteers with no personal or family history of a psychiatric disorder (controls) and 18 adolescent volunteers with no personal history of a psychiatric illness including depression, but who were at high risk for developing unipolar depression by virtue of parental depression (high-risk youth), underwent diffusion tensor imaging studies. An automated tract-based spatial statistics method, a whole-brain voxel-by-voxel analysis, was used to analyze the scans. Population average diffusion parameter values were also calculated for each tract. Adolescents at high risk for unipolar depression had lower fractional anisotropy (FA) values in the left cingulum, splenium of the corpus callosum, superior longitudinal fasciculi, uncinate, and inferior fronto-occipital fasciculi than did controls. Altered white matter integrity in healthy adolescents at familial risk for unipolar depression suggests that it might serve as a vulnerability marker for the illness.
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INTRODUCTION

Unipolar depression is among the leading causes of disability worldwide (The World Bank, 2006). Adolescence is the highest risk period for the development of unipolar depressive disorder, and there is evidence for an increasing secular trend (Hankin *et al*, 1998; Kessler *et al*, 2005). There are also data demonstrating that early depressive episodes recur or persist into adult life along with ongoing psychosocial difficulties, including disruption in interpersonal relationships, early pregnancy, low educational attainment, poor occupational functioning and unemployment, as well as increased risk for suicidal behavior (Rao and Chen, 2009). A better understanding of the etiology and pathophysiology of adolescent depression will have significant personal and public health impact.

Adolescent depression emerges in the context of ongoing maturational changes in the brain (Ernst and Korelitz, 2009; Paus *et al*, 2008). In the gray matter, these changes take the form of increased myelination of different cortical connections with a net reduction in volume, but these changes may or may not be related to synaptic pruning (Benes *et al*, 1994; Giedd *et al*, 1999; Giorgio *et al*, 2010; Gogtay *et al*, 2004; Huttenlocher, 1979). There is a simultaneous increase in white matter density associated with increases in the diameter and myelination of the axons forming the fiber tracts alongside increased neuronal size and proliferation of the glia (Giedd *et al*, 1999; Giorgio *et al*, 2010; Asato *et al*, 2010; Paus, 2010; Schmithorst and Yuan, 2010). Disturbances in these developmental patterns can adversely affect behavioral, emotional, and cognitive control (Ernst and Korelitz, 2009; Paus *et al*, 2008).

In vivo structural and functional imaging studies, as well as postmortem investigations of adults suggest that cortical–subcortical neural circuits have an important role in the pathogenesis of depression, especially frontal–striatal–thalamic and limbic–thalamic–frontal networks (Mayberg, 2003; Price and Drevets, 2010; Rogers *et al*, 1998). Limited structural and functional imaging data in pediatric populations also support these models (Pine, 2002; Rosenberg *et al*, 2006). White matter abnormalities constitute one element of these dysfunctional networks (Fields, 2008; Maller *et al*, 2010; Sexton *et al*, 2009). The white matter connects proximal and distal brain regions and creates large-scale neural networks facilitating complex behaviors (Fields, 2008; Le Bihan, 2003).

Diffusion tensor imaging (DTI) is a noninvasive technique for studying the orientation and integration of white

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matter tracts *in vivo* by measuring the diffusion of water in the neural tissue (Moseley *et al*, 1990; Basser *et al*, 1994). Water diffuses more easily along the axis of a fiber bundle than across it, as structures such as the axon membrane and myelin sheath hinder diffusion across the bundle. This directional dependence in water diffusion can provide quantitative measures of white matter microstructural integrity (Beaulieu, 2009). A commonly used metric in DTI is fractional anisotropy (FA) (Pierpaoli and Basser, 1996). FA reflects aspects of membrane integrity and myelin thickness, and decreased FA is associated with disruption of the white matter (Beaulieu, 2009). Several DTI studies have reported reduced FA in adult patients with depression, particularly in the frontal and temporal regions (Kieseppa *et al*, 2010; Maller *et al*, 2010; Sexton *et al*, 2009; Shimony *et al*, 2009). Microstructural white matter abnormalities were also detected during the first episode of depression in young adult patients (Ma *et al*, 2007) and in depressed adolescents (Cullen *et al*, 2010). However, it is not clear whether white matter changes precede the clinical manifestation of illness. The evidence of premorbid white matter abnormalities would suggest that they are vulnerability markers for depression and potentially can be helpful in identifying individuals at greatest risk for the disorder.

The present investigation was undertaken to examine white matter tract integrity in healthy adolescents who were at high risk for developing unipolar depression by virtue of family history. Genetic factors explain about 50–90% of the variance in FA in large portions of the white matter (Chiang *et al*, 2009a, b; Kochunov *et al*, 2010; Liu *et al*, 2010), and might serve as a vulnerability marker in at-risk individuals. Hence, we hypothesized that adolescents at familial risk for unipolar depression, without clinical manifestation of the disorder, will have reduced FA values in white matter tracts. Tract-based spatial statistics (TBSSs 1.0, FMRIB Center, Oxford, UK), a relatively new software package specifically designed for the analysis of diffusion-weighted data (Smith *et al*, 2006), was used for whole-brain analysis. TBSS was developed to alleviate alignment problems related to standard voxel-wise analysis. It measures and compares individual subject's FA values within the core or skeletons of white matter voxels. Unlike conventional voxel-wise analysis, no spatial smoothing is necessary wherein the amount of smoothing can significantly affect the final results. In addition to TBSS analysis, structural integrity of full white matter tracts was assessed using a digital white matter atlas (Mori *et al*, 2008) to test whether a specific white matter tract detected by TBSS was disrupted entirely. This reduces false-positive results of local voxel-based group comparisons.

MATERIALS AND METHODS

Participants

With approval from the local Institutional Review Board, 13 adolescent controls and 18 youth at high risk for depression were recruited. All participants were between 12 and 20 years of age (controls: mean age = 15.5 years, SD = 3.0; high risk = 15.7 ± 2.3 years), and at the Tanner stage III, IV, or V of pubertal development (controls: 15.4, 23.1, and 61.5%, respectively; high risk: 16.7, 16.7, and 66.6%, respectively) (Marshall and Tanner, 1969, 1970). Adolescents at high risk for depression had no personal history of a psychiatric disorder, including depression, but at least one biological parent had a history of unipolar major depressive disorder. Controls were free from any type of psychopathology in their lifetime. They were not included in the study if any first-degree relative had a history of a major psychiatric disorder. All participants were medically healthy and free from alcohol or illicit drug use, as determined by physical examination, full chemistry panel, thyroid function tests, electrocardiogram, and urine drug screens. Females with suspected pregnancy were excluded from the study on the basis of a urine pregnancy test.

Sociodemographic Information

Information on race/ethnicity was gathered from self-report, and socioeconomic status (SES) was assessed using the Hollingshead Scale (Hollingshead, 1975). Intelligence quotient (IQ) was estimated from vocabulary and block design scores using the Wechsler Intelligence Scale for Children (WISC IV) (Wechsler, 2003) for ages <16 years and WISC III (Wechsler, 1997) was used for ages $\geqslant 16$ years.

Diagnostic Evaluation

Symptoms of psychiatric disorders were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—the Present and Lifetime Version (K-SADS-PL). The K-SADS-PL is a semi-structured interview designed to ascertain the present and lifetime history of psychiatric illness according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders—Version IV) criteria (Kaufman *et al*, 1997). Probes and objective criteria are provided for individual symptoms at both diagnostic and subthreshold levels. Interrater and test–retest reliability were established, as well as convergent and discriminate validity (Kaufman *et al*, 1997). The K-SADS-PL was administered separately to the parent and the adolescent, and both were re-interviewed to resolve any discrepancies. Summary scores were tabulated on the basis of information obtained from both informants. The Hamilton Depression Rating Scale (Hamilton, 1960), a depression severity measure, and Children's Global Assessment Scale (Shaffer *et al*, 1983), a global psychosocial functioning measure, were also completed. The adolescent participants completed the Beck Depression Inventory (BDI) for self-assessment of depression severity (Beck *et al*, 1961).

The Family History-Research Diagnostic Criteria (FH-RDC), a semi-structured interview, was used for evaluation of psychiatric disorders in family members (Andreasen *et al*, 1977). A parent was interviewed regarding lifetime psychiatric disorders in all first-degree relatives of the adolescent subject (including the self, spouse, and all offspring). The FH-RDC is sensitive to obtaining information from knowledgeable relatives (Thompson *et al*, 1982).

DTI Acquisition

A 3-T Philips Achieva Magnetic Resonance System was used. DTI data were acquired using a single-shot echo-planar imaging sequence with the SENSE parallel imaging

scheme (SENSitivity Encoding, reduction factor = 2.3). The imaging matrix was 112×112 with a field of view of $224 \times 224\,mm^2$ (nominal resolution of 2 mm), which was zero filled to 256×256. Axial slices of 2.2 mm thickness were acquired parallel to the anterior–posterior commissure line. A total of 65 slices covered the entire hemisphere and brainstem without a gap. Echo time and repetition time were 97 ms and 7.78 s, respectively, without cardiac gating. Diffusion weighting was encoded along 30 independent orientations and the *b*-value was $1000\,s/mm^2$ (Jones *et al*, 1999). The imaging time for each sequence was 5 min and 15 s. To increase the signal-to-noise ratio, two repetitions were performed, with a total imaging time of 12 min. Automated image registration was performed on raw diffusion-weighted images to correct distortion caused by eddy current (Woods *et al*, 1998). Six elements of the 3×3 diffusion tensor were determined by multivariate least-squares fitting of diffusion-weighted images. The tensor was diagonalized to obtain three eigenvalues (λ_{1-3}) and three eigenvectors (v_{1-3}). Anisotropy was measured by calculating FA (Pierpaoli and Basser, 1996). Tensor fitting and FA calculation were performed using DtiStudio (Jiang *et al*, 2006).

Data Analysis

Voxel-wise comparison. TBSS from the FMRIB software library (FSL, http://www.fmrib.ox.ac.uk/fsl) was used for voxel-wise comparison (Smith *et al*, 2006). This voxel-wise method compared the FA values of each group at the core or skeletons of the white matter to effectively alleviate the partial volume effects. Modifications were made to the standard TBSS processing pipeline to better incorporate information of white matter labeling from a digital white matter atlas developed at the Johns Hopkins University (JHU ICBM-DTI-81; Mori *et al*, 2008). In particular, the single subject template used for nonlinear registration process in TBSS is identical to the template used for establishing the digital white matter atlas JHU ICBM-DTI-81. In this manner, all subjects' FA data were transformed into the JHU ICBM-DTI-81 space, and atlas labeling is overlaid to the mean skeleton in the JHU ICBM-DTI-81 space, such that each skeleton voxel could be categorized into 1 of the 50 major tracts. The details of this method combining TBSS and digital white matter atlas can be found in a previous publication (Fan *et al*, 2010).

A voxel-wise comparison was conducted in the JHU ICBM-DTI-81 space by using Randomise of TBSS. The significant clusters with $p < 0.001$ (uncorrected) in the skeleton voxels of white matter were identified. To avoid false-positive results due to noise, only clusters with continuous voxels > 10 and averaged FA values > 0.25 were retained using homemade IDL (ITT, Boulder, CO) programs. FA values at the voxels of these clusters were measured to calculate the averaged FA value of each subject with the skeletonized FA data (all_FA_skeletonised) provided by TBSS outcome. The white matter tract to which each cluster belongs was identified with labeling of the ICBM-DTI-81 atlas. These averaged FA values represent the FA measurement of each subject at the cluster location. Group average and SD were calculated, and Student's *t*-tests were performed on the basis of FA measurements at the clusters. In addition, after small-volume FDR correction analysis from Versace *et al* (2008) and Cullen *et al* (2010), anatomically defined regional masks containing ~ 1000 skeleton voxels were selected in the relevant white matter tract and the FSL statistical tool was used for multiple comparison correction of the small volume.

Tract-level comparison. Tract-level analysis was based on FA values at the skeleton voxels after TBSS registration, projection, and skeletonization steps. The entire white matter tract was considered to be possibly disrupted if it contained filtered significant clusters revealed by analyses mentioned in the voxel-wise comparison. In most cases, these clusters are small portions of the entire white matter tract. To test whether a tract was disrupted, FA values of all skeleton voxels of a specific tract were averaged. Student's *t*-tests were performed with these averaged FA values for tracts containing significantly disrupted clusters. For this exploratory study, no multiple comparison correction was used for the tract-level statistical comparison. As the template used for nonlinear registration in TBSS is the same as that used to generate the JHU ICBM-DTI-81 atlas, white matter labeling from the JHU ICBM-DTI-81 atlas could cover the entire skeletons of major white matter tracts. The overlaid region of the white matter skeleton and the JHU ICBM-DTI-81 atlas with a specific white matter labeling was used to calculate the averaged FA representing the integrity of the entire tract.

Figure 1 depicts the TBSS integration process. As shown in Figure 1a, several steps of the TBSS functions were used to project the FA value of the white matter to the skeleton or core of the white matter with FA data of all subjects at the atlas space. Figure 1b depicts the ICBM-DTI-81 atlas. By transferring the labeling of the individual white matter tract (eg, the genu of the corpus callosum), we can label the skeleton FA data of all subjects in the ICBM-DTI-81 space, as shown in Figure 1c. Atlas labeling is then overlaid to the mean skeleton in the ICBM-DTI-81 space, such that each skeleton voxel could be categorized into 1 of the 50 major tracts.

RESULTS

Sociodemographic and Clinical Characteristics of the Sample

The demographic and clinical features of the sample are outlined in Table 1. The groups did not differ significantly with respect to age, gender, ethnicity/race, pubertal status, SES, IQ, or psychosocial functioning. The high-risk group reported significantly more depressive symptoms (BDI score), but the mean score was within the normal range.

Relationship between White Matter Changes and Sociodemographic/Clinical Features

None of the white matter tracts were associated with sociodemographic or clinical variables.

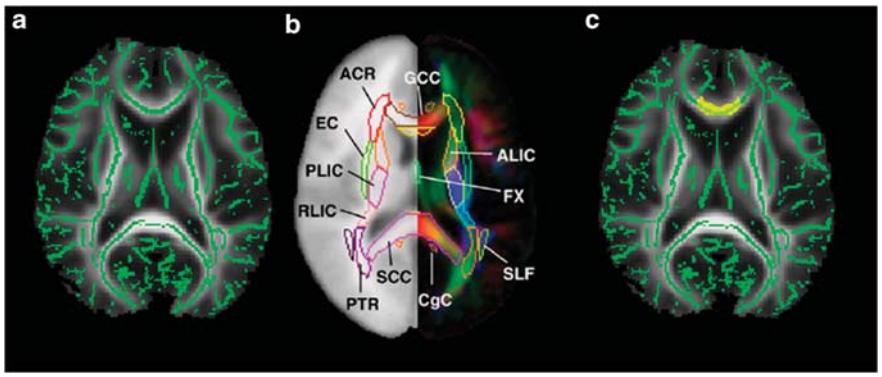

Figure 1 Illustration of tract-based quantification of fractional anisotropy of white matter tracts. Skeleton of the averaged FA, shown in green in panel (a), is overlaid on the gray-scale averaged FA map. Panel (b) shows the correspondent axial slice of JHU digital white matter atlas with left side average diffusion weighted image and right side color-encoded DTI map. As an example, by transforming the labeling of GCC from the atlas (b) to (a), the GCC voxels are in yellow (c) averaged FA value at the skeleton voxels covered by yellow in (c) is used to represent FA of this tract. GCC, genu of the corpus callosum; ACR, anterior corona radiata; EC, external capsule; PLIC, posterior limb of internal capsule; RLIC, retrolenticular limb of internal capsule; PTR, posterior thalamic radiation; SCC, splenium of the corpus callosum; CgC, cingulate cortex; SLF, superior longitudinal fasciculus; FX, fornix; ALIC, anterior limb of internal capsule.

Table 1 Sociodemographic and Clinical Characteristics by Diagnosis

	Control ($n=13$)	High risk ($n=18$)	Statistics	*p*-value
Age (years)	15.5 (3.0)	15.7 (2.3)	0.22	NS
Gender			*0.01*	*NS*
Male	6 (46.2)	8 (44.4)		
Female	7 (53.8)	10 (55.6)		
Ethnicity			*0.30*	*NS*
Caucasian	4 (30.8)	5 (27.8)		
Non-Caucasian	9 (69.2)	13 (72.2)		
Pubertal status			*0.20*	*NS*
Tanner stage III	2 (15.4)	3 (16.7)		
Tanner stage IV	3 (23.1)	3 (16.7)		
Tanner stage V	8 (61.5)	12 (66.6)		
Socioeconomic status[a]	46.1 (9.7)	40.7 (6.3)	1.83	NS
Beck Depression Inventory	1.9 (3.8)	7.1 (5.9)	2.57	0.02
Hamilton Depression Scale	1.7 (1.5)	2.5 (2.7)	0.98	NS
Global Assessment Scale[a]	86.4 (5.0)	81.2 (9.7)	1.64	NS
Intelligence quotient[a]	106.0 (15.3)	101.7 (15.6)	0.59	NS

[a]Higher score is associated with higher socioeconomic status or higher level of functioning.
Data in parentheses reflect SD or percentages.

Voxel-Wise Comparison of White Matter Changes

The high-risk group had significantly lower FA values in several white matter tracts, including the left cingulum bundle, left and right superior longitudinal fasciculus (SLF), left and right combined bundles of uncinate (UNC) and inferior fronto-occipital fasciculus (IFO), and the splenium (posterior-third of the corpus callosum) (see Table 2). It seems that the significant clusters ($p<0.001$, uncorrected; $p<0.05$, after FDR correction of small volume) are not widespread, but quite localized in the white matter (see Figure 2). Including the BDI score as a covariate did not alter the results. Compared with controls, the high-risk group did not show significantly higher FA values in any white matter tracts.

Tract-Level Comparison of White Matter Changes

In these analyses, the high-risk group manifested disruptions only in the left and right SLF (uncorrected $p=0.02$ for left SLF and $p=0.03$ for right SLF) and splenium (uncorrected $p=0.03$), suggesting that a large portion of the skeleton voxels in these two tracts have decreased FA values.

DISCUSSION

To the best of our knowledge, this is the first report of white matter tract changes in healthy adolescents at familial risk for unipolar depression. These findings suggest that adolescents at high risk for developing unipolar depression manifest disruptions in several white matter tracts, including the cingulum, SLF, UNC-IFO, and corpus callosum, before the clinical manifestation of the disorder.

A combined voxel-wise and tract-level analysis was applied in this study. Voxel-wise analysis revealed local white matter structural changes. Although these local changes are significant, they cannot be used to represent the entire white matter tracts, which contain many more skeleton voxels than the small clusters. Therefore, a further comparison at the tract level was conducted. Nevertheless, the tract-level analysis has its limitation, which would inevitably exclude the tracts that lack significant reduction in overall FA values, thereby possibly missing changes in some potential regions. For example, despite the lack of a significant difference in the entire cingulum bundle, the disruption of a small cluster in it should not be neglected for the role of the cingulum in emotional network (Mayberg, 2003; Price and Drevets, 2010).

These results should be interpreted with caution for the following reasons. The participants were recruited from a group of volunteers based on stringent inclusion/exclusion criteria, and the findings might not be generalizable to community samples of adolescents. The sample sizes were modest and the findings should be replicated in larger samples. In this exploratory study, we did not control for multiple comparisons because we wanted to identify potential white matter changes associated with familial risk for unipolar depression. Hence, some reported changes might result from chance findings. Pubertal status was assessed only from physical characteristics (Marshall and Tanner, 1969, 1970), and gonadal steroid levels were not obtained. Gonadal steroids can potentially influence depressive symptoms and brain development (Angold *et al*, 1999; Neufang *et al*, 2009). Although the BDI score (or other clinical variables) did not correlate with FA values in any of the white matter tracts, the higher BDI score in the high-risk group could have contributed to the reduced white matter integrity (Williamson *et al*, 2010). The groups did not differ significantly on sociodemographic factors and these variables did not affect the FA values. Nevertheless, the modest sample sizes might have mitigated their effects on white matter integrity. Despite these limitations, a state-of-the-art voxel-based method with relatively stringent criteria was used to examine white matter tract changes. In addition, the structural integrity of the entire white matter tracts was compared between the high-risk and control groups with the per-tract average of FA values. The tract-level analysis indicated structural changes of entire tracts and helped reduce false-positive outcomes, which could result from noise effects or local FA changes (eg, caused by crossing fibers) in the voxel-wise analysis.

Table 2 Voxel-Based Clusters in Which Adolescents at Familial Risk for Depression had Significantly Lower Fractional Anisotropy ($p<0.001$, uncorrected; $p<0.05$, after FDR correction of small volume) Compared with Controls

	Control ($n=13$)	High risk ($n=18$)	Statistics	*p*-value
Cingulum (left)	0.41 (0.05)	0.34 (0.03)	5.12	0.0001
Superior longitudinal fasciculus				
Left	0.52 (0.03)	0.45 (0.03)	5.57	0.0001
Right	0.49 (0.05)	0.43 (0.04)	3.49	0.0008
UNC-IFO				
Left	0.62 (0.05)	0.55 (0.04)	3.79	0.0003
Right	0.59 (0.05)	0.51 (0.06)	3.65	0.0005
Splenium of corpus callosum	0.72 (0.07)	0.57 (0.09)	4.52	0.0001

Abbreviation: UNC-IFO, combined uncinate and inferior fronto-occipital fasciculus.
Data in parentheses reflect SD.

Previous research has demonstrated evidence of genetic control on the variability in cerebral white matter through FA analysis (Chiang *et al*, 2009a, b; Kochunov *et al*, 2010; Liu *et al*, 2010). Moreover, genetic factors have been shown to mediate the association between white matter integrity and cognitive performance (Chiang *et al*, 2009b). Linkage analysis identified c15q25 to be associated with FA (Kochunov *et al*, 2010), which has also been implicated in early-onset recurrent major depressive disorder (Holmans *et al*, 2004; Shyn and Hamilton, 2010). Reduced FA in major white matter tracts in adolescents at familial risk for depression, coupled with its high heritability, suggests that it might be an endophenotype of genetic susceptibility for depression. Although decreased FA was not associated with depressive symptoms in this study, in a large cohort of nonreferred adolescents at high- and low-familial risk for depression ($n=320$), higher frequency of depressive symptoms was associated with lower FA in several white

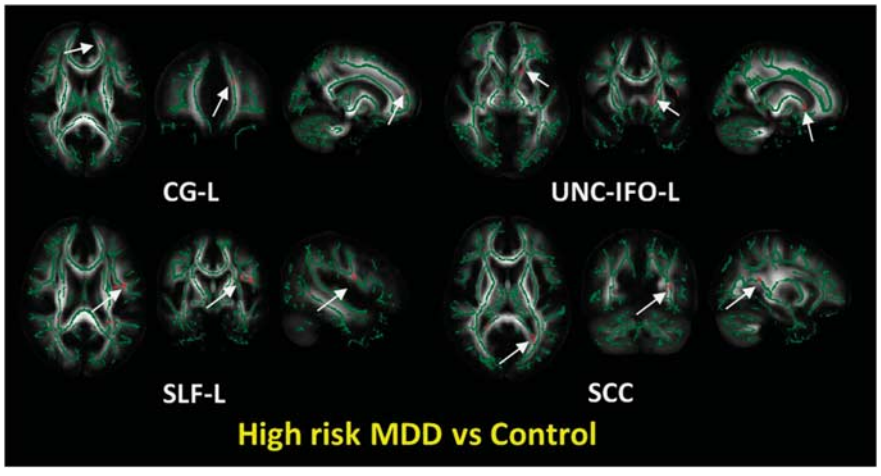

Figure 2 The significant clusters obtained from voxel-wise comparisons between control and high-risk groups. Green color indicates white matter skeletons, and red color shows clusters with significant FA reduction in the high-risk group ($p<0.001$). Underlying gray scale images are the averaged FA maps, depicting different tracts. The left, middle, and right columns of each panel show the images of axial, coronal, and sagittal views, respectively. White arrows indicate clusters of the specified white matter tracts in the left cerebral hemisphere if multiple clusters are shown in the image. FA, fractional anisotropy; CG-L, left cingulate, SLF-L, left superior longitudinal fasciculus; SCC, splenium of the corpus callosum; UNC-IFO-L, left uncinate-inferior fronto-occipital fasciculus.

matter tracts, including the SLF and splenium (Williamson *et al*, 2010). Longitudinal follow-up of these cohorts will determine whether reduced FA in high-risk youth will predict the onset of depression. Simultaneous incorporation of environmental factors will provide information on gene–environment interactions in determining the risk for unipolar depression (Johansen-Berg, 2010).

Consistent with previous reports (Cullen *et al*, 2010; Maller *et al*, 2010; Sexton *et al*, 2009), reduced FA was observed in the cingulate gyrus. The cingulum bundle links the cingulate gyrus to the hippocampus and parahippocampal gurus (Schmahmann *et al*, 2007). The cingulate cortex is crucial for a wide range of emotional and motivational processes, as well as for spatial working memory, and is involved in the pathophysiology of depression (Mayberg, 2003; Price and Drevets, 2010; Schmahmann *et al*, 2007; Shimony *et al*, 2009). In the current study, changes in the cingulum bundle were localized (observed only in voxel-wise analysis).

SLF is a major bidirectional association tract connecting large parts of the frontal cortex with the parietal, temporal, and occipital lobes. It comprises several subtypes and each subtype is involved in specific behavioral and cognitive functions (Schmahmann *et al*, 2007). Lower FA in SLF has been reported in some studies of unipolar depression (Cullen *et al*, 2010; Zou *et al*, 2008). The UNC links the rostral portion of the temporal lobe (eg, amygdala and hippocampus) to the inferior portions of the frontal lobe (orbital and medial prefrontal cortices). The UNC has a prolonged period of development (Lebel *et al*, 2008). The function of UNC is not known, but it is believed to be involved in cognitive and socio-emotional regulation, and alterations in this tract have been associated with various psychiatric disorders, including depression (Cullen *et al*, 2010; Schmahmann *et al*, 2007; Sexton *et al*, 2009). The IFO connects the inferior and lateral margins of the occipital lobe to the inferolateral and dorsolateral regions of the frontal lobe, and it is involved in emotional visual function (Catani *et al*, 2002). Alterations in emotional visual perception and reduced FA in IFO have been observed in depression (Cullen *et al*, 2010; Kieseppa *et al*, 2010; Phillips *et al*, 2003). The observed reduction in FA values in these tracts in adolescents at high familial risk for depression before the clinical manifestation of illness suggests that reduced FA might be a vulnerability marker for unipolar depression.

The corpus callosum is the largest commissural projection in the central nervous system, and it comprises extensive networks subserving not only the motor and sensory systems but also memory, attention, emotion, language, and intelligence (Gazzaniga, 2000; Paul *et al*, 2006; Tamietto *et al*, 2007). The corpus callosum develops throughout childhood and adolescence (Giedd *et al*, 1999; Keshavan *et al*, 2002), and disruptions in this maturational process might be associated with behavioral and emotional disorders. The splenium specifically communicates somatosensory information between the two halves of the temporal lobe and the visual center at the occipital lobe. Altered FA in the corpus callosum has been reported in adult unipolar and bipolar depression (Kieseppa *et al*, 2010; Maller *et al*, 2010; Sexton *et al*, 2009). A recent study of adolescents with bipolar disorder, many of whom were in the euthymic state, also reported reduced FA throughout the corpus callosum (Barnea-Goraly *et al*, 2009). These findings, together with results from the current study and from a larger sample of adolescents at familial risk for depression (Williamson *et al*, 2010), suggest that reduced FA in the corpus callosum might be a trait marker for mood disorders, and possibly the splenium might be more vulnerable.

In summary, white matter tract changes were observed before the manifestation of clinical symptoms of depression in at-risk adolescents. Longitudinal studies with larger samples will determine whether the observed microstructural white matter changes in high-risk youth are associated with increased vulnerability for developing depressive disorder, which could have potential implications for identifying youngsters at highest risk for the disorder.

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DISCLOSURE

The authors declare no conflict of interest.

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