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White Matter Disruptions in Adolescents Exposed to Childhood Maltreatment and Vulnerability to Psychopathology

Hao Huang[1,2], Tejasvi Gundapuneedi[1] and Uma Rao*[,3,4,5,6]

[1]Advanced Imaging Research Center, The University of Texas Southwestern Medical Center, Dallas, TX, USA; [2]Department of Radiology, The University of Texas Southwestern Medical Center, Dallas, TX, USA; [3]Center for Molecular and Behavioral Neuroscience, Meharry Medical College, Nashville, TN, USA; [4]Department of Psychiatry and Behavioral Sciences, Meharry Medical College, Nashville, TN, USA; [5]Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, TN, USA; [6]Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, TN, USA

Childhood maltreatment has been known to produce long-lasting impairments in behavioral, cognitive and social functioning, but their underlying mechanisms are not well-understood. A better understanding of their underlying mechanisms will aid in developing effective preventive interventions. Nineteen adolescent volunteers with no personal history of a psychiatric illness, but who were exposed to maltreatment during childhood, and 13 adolescent volunteers with no personal or family history of a psychiatric disorder (controls) underwent diffusion tensor imaging (DTI) studies. The participants were then followed longitudinally at 6-month intervals for up to 5 years to determine the onset of mood and substance use disorders. The associations among fractional anisotropy (FA) values obtained from the DTI scans at baseline and psychopathology at follow-up were examined. At baseline, adolescents exposed to childhood maltreatment had significantly lower FA values in the left and right superior longitudinal fasciculi, right cingulum bundle projecting to the hippocampus, left inferior fronto-occipital fasciculus, and splenium of the corpus callosum compared with controls. Adolescents who developed major depressive disorder at follow-up had significantly lower FA values in the superior longitudinal fasciculi and the right cingulum-hippocampal projection compared with their counterparts who did not develop the illness. Adolescents who developed substance use disorder during follow-up had significantly lower FA values in the right cingulum-hippocampal projection than their counterparts without the disorder. These preliminary results suggest that white matter disruptions observed in adolescents exposed to childhood maltreatment may be associated with increased vulnerability to psychopathology, specifically depressive and substance use disorders.
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INTRODUCTION

Adolescence is a crucial developmental stage marked by a confluence of physical, biological, psychological, and social challenges (Blakemore *et al*, 2010). There are significant physical maturational changes (eg, the onset of puberty), social-cognitive advances (eg, ability for more abstract-thinking and generalizations across situations and time), interpersonal transitions (eg, changes in social roles in family and peer relationships), and social-contextual changes (eg, school transitions). Although these maturational transitions offer tremendous opportunities for youth, because the developing brain regions underlying emotional, cognitive, and behavioral systems mature at different rates, this developmental period also is marked by heightened vulnerability to psychopathology (Ernst and Korelitz, 2009).

Specifically, adolescents with a history of childhood maltreatment constitute a high-risk group for the development of psychopathology. Stress endured in early life, during a time of neural plasticity, may induce cognitive and other neural changes, which may predispose individuals to a variety of emotional-behavioral disorders, mood and substance use disorders among others (Enoch, 2011; Heim and Binder, 2012). For example, several preclinical and clinical investigations have shown an association between early-life stress and alterations in gray and white matter in pediatric and adult samples (McCrory *et al*, 2010; Teicher *et al*, 2006). However, it is not clear whether these alterations, in fact, directly increase vulnerability to psychopathology. To our knowledge, research on the association between neural changes and psychopathology in individuals exposed to childhood maltreatment has been limited to cross-sectional study designs. In the current pilot study, we examined

*Correspondence: Dr U Rao, Center for Molecular and Behavioral Neuroscience, Meharry Medical College, 1005 Dr DB Todd Jr Boulevard, Nashville, TN 37208, USA. Tel: +1 615 327 6875, Fax: +1 615 327 6144. E-mail: urao@mmc.edu
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whether healthy adolescents who had no prior history of psychopathology but who had been exposed to maltreatment during childhood show alterations in white matter tracts and whether these alterations are associated with an increased likelihood of developing mood and/or substance use disorders during prospective follow-up.

Diffusion tensor imaging (DTI), a type of magnetic resonance imaging (MRI), is capable of delineating *in vivo* microstructural changes of white matter tracts noninvasively by measuring the water diffusion in these tracts (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 on structural integrity of white matter. Fractional anisotropy (FA), a DTI-derived metric, characterizes the shape of the diffusion tensor and is sensitive to white matter disruption. It reflects aspects of membrane integrity and myelin thickness, and decreased FA is usually associated with disruption of white matter (Beaulieu, 2009). DTI also offers the measurement of orientation of the white matter tracts. Individual white matter tracts can be traced through tractography with primary eigenvector of diffusion tensor. DTI has been used to study the white matter architecture and integrity of both normal and disease states, also including neuropsychiatric disorders (Thomason and Thompson, 2011). Using this technique, white matter disruptions have been reported in post-institutionalized children (Eluvathingal *et al*, 2006) or young adults exposed to maltreatment during their life span (Choi *et al*, 2009, 2012). The present investigation not only extends these findings in an adolescent population with no prior history of psychiatric problems, but it also evaluated whether the observed white matter disruptions are associated with increased vulnerability to psychopathology during prospective follow-up.

MATERIALS AND METHODS

Participants

This is part of a larger investigation examining risk factors associated with the development and clinical course of mood and substance use disorders in adolescents. The study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center, and all research procedures were performed after obtaining informed consent from the parent and assent from the adolescent. Nineteen adolescents exposed to childhood maltreatment and 13 controls were recruited. Participants were included in the maltreated group if they experienced physical abuse, sexual abuse, and/or witnessed domestic violence lasting 6 months or longer. Both groups were free from lifetime psychiatric illness at the time of recruitment. None of the participants in the maltreated group had an active involvement with the Child Protective Services, and all were living with their biological parents at the time of enrollment in the study. The controls were excluded if any first-degree relative had a history of major psychiatric disorder, or if they were exposed to maltreatment or other major trauma. 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.

Sociodemographic Information

Information was obtained on age, gender, ethnicity/race, and pubertal status (Marshall and Tanner, 1969, 1970). Socioeconomic status (SES) was assessed with the Hollingshead Four-Factor Scale (Hollingshead, 1975). Scaled scores from the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) for ages <16 years (Wechsler, 2003), or Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) for ages >16 years (Wechsler, 1997), were used to estimate the intelligence quotient (IQ).

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 present and lifetime history of psychiatric illness according to Diagnostic and Statistical Manual of Mental Disorders – Version IV (DSM-IV) criteria (American Psychiatric Association, 1994; Kaufman *et al*, 1997). Probes and objective criteria are provided for individual symptoms at both diagnostic and subthreshold levels. Inter-rater and test–retest reliability have been 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 based on the information obtained from both informants.

The Family History-Research Diagnostic Criteria (FH-RDC), a semi-structured interview, was used for the 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).

Ancillary Psychiatric Measures

The clinician completed the Children's Depression Rating Scale – Revised Version (CDRS-R) to determine the severity of depressive symptoms (Poznanski and Mokros, 1996). The CDRS-R is a 17-item scale, and the items are rated on a 7-point scale for 14 items and on a 5-point scale for three items, yielding a total raw score of 17–113. A score of $\leqslant 28$ is indicative of no/minimal symptoms and a score $\geqslant 40$ is indicative of depression. The clinician also completed the 31-item Hamilton Depression Rating Scale (HDRS), which also includes items for atypical depressive symptoms (Hamilton, 1960). The Children's Global Assessment Scale (CGAS), a global psychosocial functioning measure, was completed by the clinician (Shaffer *et al*, 1983). The CGAS is a numeric scale from 1 to 100, with 10-point anchors, and higher scores are indicative of better psychosocial functioning.

The adolescents completed the Beck Depression Inventory – Version 2 (BDI-II) for self-assessment of depression severity (Beck *et al*, 1961). The BDI-II contains 21 items, each item scored on a scale value of 0 to 3 with the total score ranging from 0 to 63. A score of $\leqslant 13$ is indicative of no/minimal depression and a score of $\geqslant 20$ is indicative of clinical depression. The Drug Use Screening Inventory (DUSI) was used to assess substance-related problems. The DUSI is a self-report instrument designed to assess the severity of alcohol/drug abuse and related psychiatric and psychosocial problems, and it has good psychometric properties (Kirisci *et al*, 1995). It consists of 149 'yes/no' questions in 10 domains, including substance use and its effects on multiple social domains. A rating above 0.3 on the overall-problem density score is considered as a substance-related problem.

Early-Life Adversity

Information on early-life adversity was obtained with a semi-structured interview, the Childhood Adversity Interview (Dienes *et al*, 2006). The adolescent participant and parent were interviewed separately. Information was obtained on seven subtypes of childhood adversity that persisted for 6 months or longer (including separation/loss of caretaker, life-threatening illness/injury in the self or others, physical neglect, emotional abuse/assault, physical abuse/assault, witnessing domestic violence, and sexual abuse/assault), and occurred before age 10 years. The adverse impact (1 = no adversity and 5 = most severe form of adversity) was based on summaries of events, circumstances and their contexts. Information from both informants was combined for the summary ratings. An early-life adversity score was tabulated from the sum of ratings from the seven adversity domains.

DTI Acquisition

A 3T Philips Achieva Magnetic Resonance System was used. DTI data were acquired using a single-shot, echo-planar imaging (EPI) sequence with 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 (AC–PC) line. A total of 65 slices covered the entire hemisphere and brainstem without a gap. The echo time (TE) and repetition time (TR) were 97 ms and 7.78 s, respectively, without cardiac gating. The diffusion weighting was encoded along 30 independent orientations and the *b*-value was 1000 s/mm^2. Imaging time for each sequence was 5 min and 15 s. To increase the signal-to-noise ratio (SNR), two repetitions were performed, with a total imaging time of 12 min. Automated image registration (AIR) 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-square fitting of diffusion weighted images. The tensor was diagonalized to obtain three eigenvalues (λ_{1-3}) and eigenvectors (v_{1-3}). The tensor fitting and FA calculation were done using DtiStudio (Jiang *et al*, 2006).

Follow-Up Evaluation

The participants were followed longitudinally at 6-month intervals for up to 5 years, to obtain information on the onset of mood and substance use disorders. In addition to the K-SADS-PL, the Longitudinal Interval Follow-up Evaluation (LIFE) was used to document the development of these disorders during each follow-up evaluation. The LIFE is a semi-structured instrument used for charting the clinical course of depression and other psychiatric disorders during longitudinal follow-up (Shapiro and Keller, 1979). Development of a mood/substance use disorder episode was defined as a rating of 5 on the Psychiatric Status Rating (PSR) component of the LIFE for a minimum of 4-week duration. Information from the diagnostic assessments was rated by an independent clinician 'blind' to the baseline clinical and DTI data.

DTI Data Analysis

Voxel-wise comparison and cluster analysis. Voxel-based morphometry (VBM) reveals the voxel-wise disruption of white matter after registering FA maps of all subjects to a template space. The tract-based spatial statistics (TBSS; FMRIB Software Library, FMRIB Center, Oxford, UK) (FSL, http://www.fmrib.ox.ac.uk/fsl), a software package specifically designed for the analysis of diffusion-weighted images (Smith *et al*, 2006), was used to compare the FA values of each group at core or skeletons of the white matter to effectively alleviate the partial volume effects. For better alignment with the digital white matter atlas from Johns Hopkins University (JHU ICBM-DTI-81) (Mori *et al*, 2008), EVA single subject FA map (instead of FA map from one of the subjects) was used as a template for nonlinear registration. In this way, all the subjects' FA data were transformed into JHU ICBM-DTI-81 space.

The voxel-wise comparison was conducted in the JHU ICBM-DTI-81 space by using Randomise of TBSS. The significant clusters with $p \leqslant 0.0005$ (uncorrected) in the skeleton voxels of white matter were identified. To avoid false positive results due to noise, only clusters with continuous voxels >15, $p < 0.05$ from voxel-wise TBSS analysis and averaged FA values >0.2 were retained with home-made Interactive Data Language programs (IDL; ITT, Boulder, CO). FA values of these cluster voxels were measured to calculate the averaged FA at the clusters for each subject with the skeletonized FA data (all_FA_skeletonized) provided by TBSS outcome (Cullen *et al*, 2010; Huang *et al*, 2011). The white matter tract to which each cluster belongs was identified with ICBM-DTI-81 atlas. The group average and standard deviation were calculated with FA measurements at the clusters. Correction of false discovery rate (FDR) was conducted when comparing FA values of the disrupted clusters. To correct for multiple comparisons, *p*-values were calculated for skeleton voxels in a small volume consisting of skeleton voxels with the number 100 times the number of cluster voxels and surrounding the clusters (Versace *et al*, 2008; Cullen *et al*, 2010). Generalized linear model from R software package (R2.13.1) was used for *p*-value calculation with or without age and IQ as covariates. Adjusted *p*-values after FDR correction were also calculated with R software.

3D demonstration of the clusters and tracts. With the DTI data from white matter atlas template (EVA), the tractography (FACT; Mori *et al*, 1999) was conducted to trace the tracts that showed significant clusters in the TBSS analysis. DTI data of EVA are from a single subject. EVA DTI data were co-registered with the atlas used for TBSS analysis, hence no DTI data transformation was needed to demonstrate the disrupted clusters from TBSS analysis and traced tracts from EVA DTI data in the same space. Spheres centered at the centers of disrupted clusters of these tracts, and a radius of 10 voxels was generated for each cluster to highlight the locations of the clusters.

Tract-level comparison. In addition to voxel-wise analysis through TBSS, the integrity of individual white matter tracts were assessed by using all skeleton voxels of a specific tract as region of interest (ROI). This approach tested if the structure of a specific white matter tract was altered entirely. Tract-level analysis was based on the 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 cluster analyses mentioned above. In most cases, these clusters are small portions of the entire white matter tract. Since 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 JHU ICBM-DTI-81 atlas could cover the entire skeletons of major white matter tracts. There are two types of digital white matter atlas in JHU ICBM-DTI-81 space. The first type of atlas only covers core (innermost) of white matter tracts which are identified with unique discrete numbers. The second type of atlas is featured with continuous probabilistic labeling from 0 to 100% and each tract is represented by an image volume. For a more complete coverage including both core and peripheral white matter tracts, a threshold of 10% was applied to the second type of atlas to binarize the probabilistic labeling and resultant binary image volume was used as the mask for tract-level analysis. The overlaid region of the white matter skeleton and binarized mask of a specific white matter tract was used to calculate the averaged FA representing the integrity of the entire tract. In order to test whether the entire tract was disrupted, Student's *t*-tests were performed with these averaged FA values for tracts containing disrupted clusters. The details of tract-level comparisons can be found in a previous publication (Huang *et al*, 2012). The analyzed 18 tracts consisted of major white matter tracts in the human brain. They included left and right anterior thalamic radiation (ATR-L/R), left and right corticospinal tract (CST-L/R), left and right cingulum bundle in cingulate gyrus (CGC-L/R), left and right cingulum bundle projecting to hippocampus (CGH-L/R), forceps major (F-major) and forceps minor (F-minor) of corpus callosum, left and right inferior fronto-occipital fasciculus (IFO-L/R), left and right inferior longitudinal fasciculus (ILF-L/R), left and right superior longitudinal fasciculus (SLF-L/R), and uncinate fasciculus (UNC-L/R). Student's *t*-tests were conducted for tract-level FA comparisons. Bonferroni correction was applied for multiple comparisons.

Table 1 Sociodemographic and Clinical Characteristics Stratified by Group

	Controls ($n=13$)	Maltreated ($n=19$)	Statistic	p
Age (years)	16.00 ± 2.74	15.89 ± 2.79	0.11	NS
Gender (male/female)	6/7	5/14	1.35	NS
Ethnicity (Caucasian/non-Caucasian)	9/4	12/7	0.13	NS
Tanner stage (III/IV/V)	3/1/9	4/3/12	0.46	NS
Socioeconomic status[a]	47.69 ± 8.10	43.42 ± 6.84	1.61	NS
Intelligent quotient (IQ)[a]	108.00 ± 13.03	102.89 ± 15.09	0.99	NS
Children's Global Assessment Scale[a]	85.15 ± 7.29	81.00 ± 7.94	1.50	NS
Children's Depression Rating Scale	18.31 ± 1.75	19.37 ± 2.41	1.61	NS
Hamilton Depression Rating Scale	0.31 ± 0.63	0.79 ± 0.92	0.99	NS
Beck Depression Inventory	0.15 ± 0.38	0.58 ± 0.84	1.50	NS
Drug Use Screening Inventory	0.08 ± 0.06	0.13 ± 0.39	1.50	NS
Childhood Adversity	7.62 ± 0.65	14.70 ± 3.98	6.32	0.0001

Data are presented as mean values and standard deviations, or as raw numbers.
[a]Higher score is associated with higher socioeconomic status or higher level of functioning.

Along-the-tract analysis. For the tracts that had a general integrity change, the along-the-tract FA values of control and maltreated groups were measured and compared to reveal the structural profile of these tracts. The specific tracts were segmented into two parts, the superior and inferior, by an axial plane at $z=90$ in MNI coordinate. For each segment, the cross-section of sequential coronal and axial planes and the white matter mask from probabilistic atlas were used as ROI to calculate the mean and standard deviation of FA in the sequential planes, respectively.

RESULTS

Sociodemographic and Clinical Characteristics of the Sample

Demographic and clinical features of the sample are outlined in Table 1. The groups did not differ significantly with respect to sociodemographic or clinical features, with the exception of early-life adversity. As expected, the maltreated group scored higher on the early-life adversity measure compared with controls. Ratings on all the psychopathology scales were in the normal range. Four participants from the maltreated group had a family history of psychiatric disorder.

Voxel-Wise Comparison of White Matter Changes at Baseline

The maltreated group had significantly lower FA values in several white matter tracts including the SLF-L and SLF-R, CGH-R, IFO-L, F-major compared with controls (see Table 2; also Supplementary Figure 1 in the Online Publication). There were four separate clusters in SLF-L, whereas single

Table 2 Clusters of Skeleton Voxels Based on Group Differences in Fractional Anisotropy

	Control ($n=13$)	Maltreated ($n=19$)	#Voxels	No covariate		Age and IQ as covariates	
				t	*p*	*t*	*p*
Superior longitudinal fasciculus (R)	0.49 ± 0.05	0.39 ± 0.09	16	3.88	0.0005	3.57	0.001
Superior longitudinal fasciculus (L)							
Cluster 1	0.32 ± 0.04	0.25 ± 0.04	21	4.88	<0.0001	4.78	<0.0001
Cluster 2	0.40 ± 0.05	0.32 ± 0.07	15	3.64	0.001	3.51	0.002
Cluster 3	0.45 ± 0.05	0.38 ± 0.05	15	4.29	0.0002	4.39	0.0001
Cluster 4	0.50 ± 0.07	0.39 ± 0.08	16	3.83	0.0006	3.82	0.0007
Cingulum-hippocampus projection (R)	0.32 ± 0.05	0.25 ± 0.04	35	4.51	<0.0001	4.45	<0.0001
Inferior fronto-occipital fasciculus (L)	0.51 ± 0.06	0.39 ± 0.07	41	5.14	<0.0001	5.49	<0.0001
Forceps major	0.72 ± 0.06	0.59 ± 0.09	21	4.60	<0.0001	4.57	<0.0001

Data are presented as means and standard deviations.

clusters were found for the rest of the white matter tracts listed above. Compared with controls, the maltreated group did not show significantly higher FA values in any white matter tract. After FDR correction, the *p*-values for all disrupted clusters listed in Table 2 are <0.05 with or without age and IQ as covariates. The maltreated group had a higher proportion of females than controls (albeit not statistically significant). The maltreated sample was reduced to match the control group on gender ratio, and the initial group differences persisted in the reduced sample.

Tract-Level Comparison of White Matter Changes at Baseline

The maltreated group manifested disruptions of only SLF-L ($p\leqslant0.05$) at the tract level, suggesting that large portions of the skeleton voxels in this tract had decreased FA values. After Bonferroni correction, there was no significant FA difference between maltreated and control groups in any of the 18 tested tracts.

FA Profiles of SLF-L in Control and Maltreated Groups at Baseline

The reconstructed SLF-L and four clusters (represented by red spheres) in this tract are shown in the left panel of Figure 1. In the right panel, the FA profiles along superior and inferior segments of the SLF-L in control and maltreated groups are shown. FA values in the maltreated group were lower than controls along the two segments of the tract. The differences were dramatic at the clusters identified from TBSS analysis and also pointed by the arrows in the plots of the FA profile (right panel of Figure 1).

3D Demonstration of the Clusters, Associated Tracts and Individual FA Measurements at Clusters at Baseline

The locations of disrupted clusters in the white matter tracts of CGH-R, IFO-L, SLF-R, and F-major, represented by red spheres, are illustrated in the upper panels of Figure 2. The FA measurements from individual subjects in maltreated and control groups also are displayed in the corresponding lower panels.

Relationship of White Matter Changes with Sociodemographic and Clinical Features

None of the sociodemographic variables (namely age, gender, ethnicity, SES, Tanner stage, and IQ) correlated with white matter tracts. After controlling for these variables, early-life adversity correlated negatively with SLF-R ($r_{24}=-0.50$, $p\leqslant0.01$), SLF-L ($r_{24}=-0.63$, $p\leqslant0.001$), CGH-R ($r_{24}=-0.63$, $p\leqslant0.001$), IFO-L ($r_{24}=-0.60$, $p\leqslant0.001$) and F-major ($r_{24}=-0.56$, $p\leqslant0.005$). After accounting for the sociodemographic factors, SLF-R correlated positively with CGAS ($r_{24}=0.40$; $p\leqslant0.05$), and negatively with CDRS ($r_{24}=-0.39$, $p\leqslant0.05$) and HDRS ($r_{24}=-0.55$, $p\leqslant0.005$), whereas SLF-L showed the same pattern at a trend level [CGAS ($r_{24}=0.36$; $p\leqslant0.10$); HDRS ($r_{24}=-0.34$, $p\leqslant0.10$); and DUSI ($r_{24}=-0.33$, $p\leqslant0.10$)]. Family psychopathology did not significantly affect FA values in the maltreated group.

Follow-Up Information

Recruitment did not occur simultaneously and, therefore, not all subjects were studied longitudinally for the same time period. The groups were comparable on the mean follow-up interval (3.42 ± 0.98 years in controls, and 3.46 ± 0.81 in the maltreated group; $t_{30}=0.13$, NS). At follow-up, six participants (one control, and five maltreated) developed unipolar major depressive disorder and five developed substance use disorder (one control, and four maltreated). Two participants from the maltreated group developed both disorders. Participants with ($n=9$) and without ($n=23$) psychopathology did not differ significantly with respect to follow-up interval (3.31 ± 0.61 and 3.49 ± 0.95 years, respectively, $t_{30}=0.52$, NS).

Association Between Baseline DTI Measures and Follow-Up Psychopathology

Mean FA values in the specified tracts that distinguished control and maltreated groups at baseline are given in

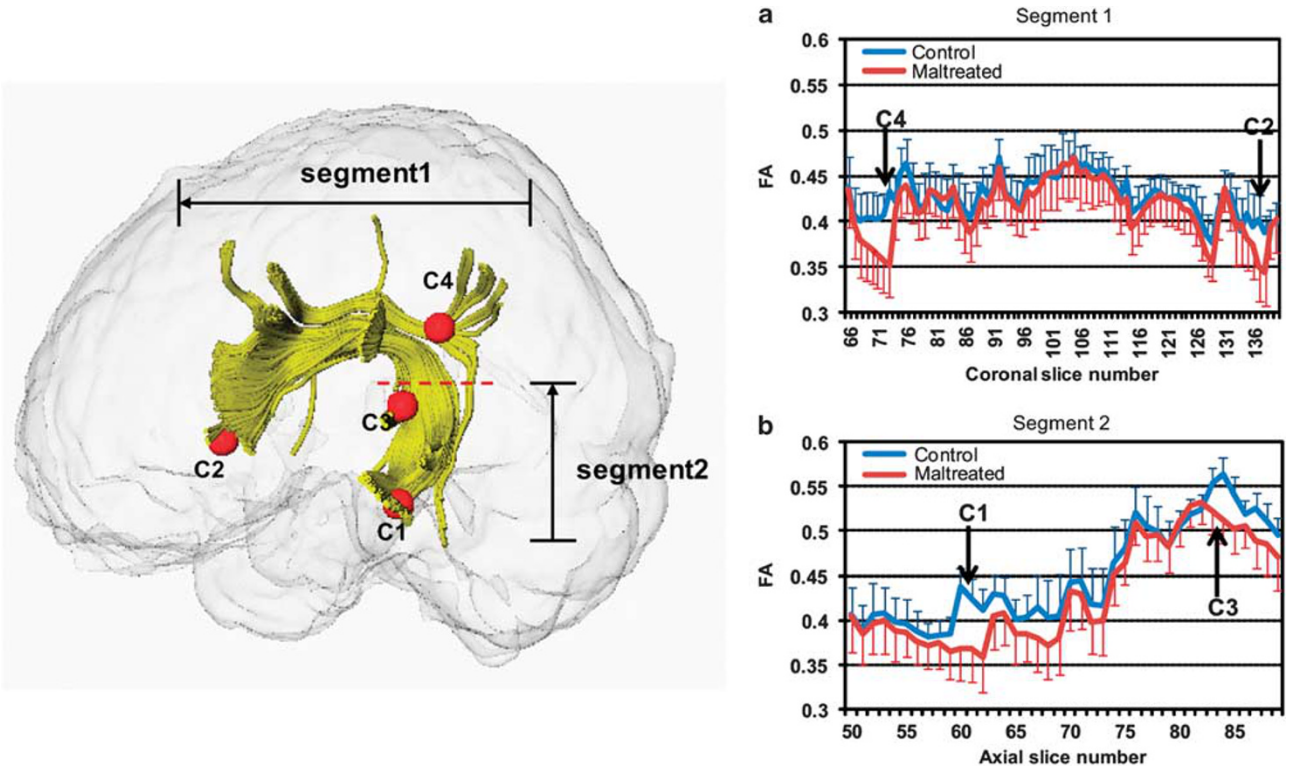

Figure 1 FA profiles of the two segments of left superior longitudinal fasciculus. Dramatic FA differences between maltreated and control group in the FA profile coincide with the locations of disrupted clusters (C1, C2, C3, and C4) (a and b). The three-dimensionally reconstructed fiber bundles of left superior longitudinal fasciculus and four disrupted clusters of this tract are also shown on the left panel.

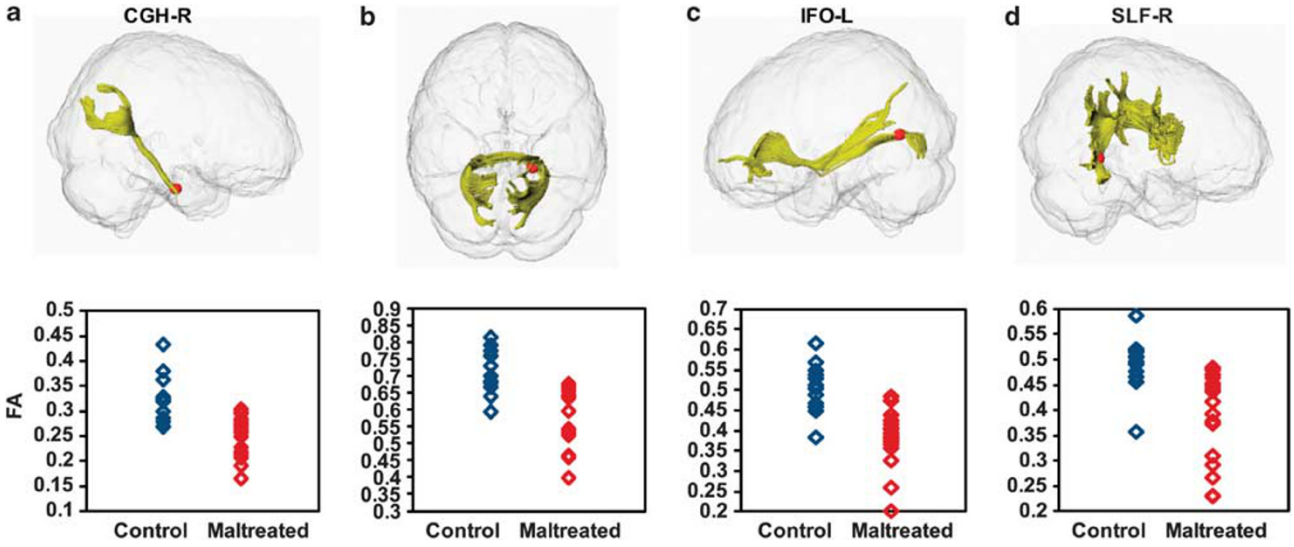

Figure 2 Detailed FA measurements from individual subjects at the disrupted clusters of CGH-R (a), F-major (b), IFO-L (c), and SLF-R (d). The locations of clusters (red spheres) in the three-dimensionally reconstructed correspondent white matter fiber bundles are also illustrated in the upper panels. CGH-R = right cingulum bundle projecting to hippocampus; SLF-L/SLF-R = left or right superior longitudinal fasciculus; F-major = forceps major (splenium) of the corpus callosum; IFO-L = left inferior fronto-occipital fasciculus.

Table 3, now stratified based on psychopathology (having a mood and/or substance use disorder) at follow-up. After controlling for the follow-up period, participants who developed psychopathology had significantly lower FA values in the SLF-R, SLF-L, and CGH-R. The two clusters (1 and 2) from Segment 1 accounted for the association between SLF-L and psychopathology.

The association between baseline DTI measures and mood (or substance use) disorder was examined in the maltreated group. After accounting for the differential follow-up interval among participants, those who developed depression had lower FA values in SLF-R ($F_{2,16} = 17.84$, $p \leqslant 0.001$), SLF-L ($F_{2,16} = 16.19$, $p \leqslant 0.001$), and CGH-R ($F_{2,16} = 11.48$, $p \leqslant 0.005$) compared with their counterparts

Table 3 Mean FA Values of Groups Stratified on the Onset of Psychiatric Disorder at Follow-up

	No disorder ($n=23$)	Disorder ($n=9$)	F^a	p
Superior longitudinal fasciculus (R)	0.46 ± 0.06	0.36 ± 0.11	10.46	0.003
Superior longitudinal fasciculus (L)	0.39 ± 0.05	0.33 ± 0.06	8.92	0.006
Cluster 1	0.29 ± 0.05	0.24 ± 0.04	5.16	0.03
Cluster 2	0.37 ± 0.06	0.31 ± 0.09	4.33	0.05
Cluster 3	0.41 ± 0.06	0.41 ± 0.06	0.01	NS
Cluster 4	0.45 ± 0.09	0.40 ± 0.10	1.94	NS
Cingulum-hippocampus projection (R)	0.30 ± 0.05	0.24 ± 0.04	11.39	0.002
Inferior fronto-occipital fasciculus (L)	0.44 ± 0.10	0.42 ± 0.04	0.57	NS
Forceps major	0.65 ± 0.10	0.62 ± 0.11	0.94	NS

Data are presented as mean values and standard deviations.
[a]*F*-value is the group effect after controlling for the follow-up interval.

who did not develop the disorder. With respect to substance use disorder, only CGH-R discriminated the groups ($F_{2,16}=4.95$, $p\leqslant 0.05$).

DISCUSSION

The study found that adolescents without a prior history of psychopathology, but with exposure to maltreatment during childhood, had reduced FA values in SLF-L, SLF-R, CGH-R, IFO-L, and F-major compared to their counterparts with no prior history of early-life adversity. Moreover, the observed white matter disruptions at baseline, specifically SLF-L, SLF-R, and CGH-R, were associated with increased vulnerability to unipolar depression and/or substance abuse.

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. 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 brain development (Herting *et al*, in press). Also, the voxel-based method cannot focus on specific brain regions. Despite these limitations, a state-of-the-art voxel-based method with relatively stringent criteria was utilized to examine white matter tract changes. In addition, the structural integrity of entire white matter tracts was compared between maltreated and control groups. Tract-level analysis indicated the structural changes of entire tracts and helped reduce the false positive findings, which could result from noise effects or local FA changes (eg, caused by crossing fibers) in VBM analysis.

To our knowledge, there are only four published reports on white matter tract changes in individuals exposed to childhood maltreatment. In the first study, children who were subjected to early socioemotional deprivation in Romanian orphanages exhibited reduced FA values in the left uncinate fasciculus (Eluvathingal *et al*, 2006). In the second investigation, maltreated children with posttraumatic stress disorder had reduced FA values in the medial and posterior parts of the corpus callosum (Jackowski *et al*, 2008). In the third study, young adults who experienced parental verbal abuse during childhood had reduced FA values in the left arcuate fasciculus, CGH-L, and the left fornix (Choi *et al*, 2009). In the fourth report, young adults exposed to domestic violence in childhood had reduced FA values in the left inferior longitudinal fasciculus (Choi *et al*, 2012). The divergent findings across studies may be due to differences in sample characteristics (age, type of childhood adversity, presence of psychiatric problems in the maltreated group, etc.). Additionally, all studies had modest sample sizes. Future investigations should include larger samples in addition to addressing the other methodological issues.

SLF is a large association fiber bundle connecting cortical regions of frontal, parietal, temporal, and occipital lobes. Bilaterally, SLF is involved in executive functioning (Makris *et al*, 2005). Asymmetry, with a dominance of this tract in the left hemisphere, has been observed (Catani *et al*, 2007). The traditional understanding about SLF-L is that it connects Broca and Wernicke areas, and hence is mainly related to language function. However, the terminations of this tract cover lateral frontal, prefrontal, premotor, dorsolateral parietal, fronto-parietal, pareito-occipital, parieto-temporal, temporal, and insular regions. The extensive cortical connections of this tract suggest that SLF-L may be involved in more brain functions besides language (Bernal and Ardila, 2009). Consistent with our finding, a study of young adults exposed to parental verbal abuse found disruption in the left arcuate fasciculus, the fronto-temporal branch of SLF-L (Choi *et al*, 2009). The clinical implications of SLF disruption in the maltreated group are not known. However, the association of SLF disruption with depression suggests the critical role of this tract in both emotional regulation and executive functioning (Cullen *et al*, 2010; Makris *et al*, 2005).

The cingulum bundle is a white matter tract that underlies cingulate cortex, and all connections entering and exiting the cingulate gyrus pass through this bundle. Additionally, it includes projections between prefrontal and parahippocampal cortices (Goldman-Rakic *et al*, 1984) and projections to the median raphe nucleus that terminate in the dorsal hippocampus (Azmitia and Segal, 1978). More advanced emotional and cognitive processes and social behavior (ie, self-regulation) appear to depend on the maturation of prefrontal cortex and limbic system interconnectivity (Disner *et al*, 2011; Heatherton and Wagner, 2011). This network also is involved in the modulation of emotional and cognitive processes during stress (Campeau *et al*, 2011). Reduced FA in CGH-R was associated with increased vulnerability to both depressive and addictive disorders. In contrast to our finding of CGH-R disruption in the maltreated group, another study found reduced FA in the left fusiform gyrus (with projections from cingulum to the posterior tail of the hippocampus) in young adults exposed to parental verbal abuse (Choi *et al*, 2009). These differences might be attributed to population differences as

individual differences exist in hemispheric emotional valence (Schiffer *et al*, 2007).

IFO connects inferior-lateral and dorsolateral frontal cortex with posterior temporal cortex and occipital lobe, and it is involved in emotional visual function. Alterations in emotional visual perception and reduced FA in IFO have been implicated in neuropsychiatric disorders, also including depression (Cullen *et al*, 2010; Huang *et al*, 2011) and substance abuse (Jacobus *et al*, 2009; Lebel *et al*, 2008). The forceps major connects the occipital lobes and crosses the midline via the splenium of the corpus callosum. It is involved in the integration of somatosensory and visual information in the two hemispheres (Gazzaniga, 2000; Tamietto *et al*, 2007).

In conclusion, white matter tract disruptions were observed in adolescents exposed to maltreatment during childhood, and these disruptions were associated with increased vulnerability to unipolar depression and substance use disorder. These preliminary findings may have potential implications for identifying youngsters at highest risk for these disorders and targeted preventive interventions.

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DISCLOSURE

The authors declare no conflict of interest.

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