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Atypical Frontal-Striatal-Thalamic Circuit White Matter Development in Pediatric Obsessive Compulsive Disorder

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Abstract

Objective—Atypical development of frontal-striatal-thalamic circuitry (FSTC) has been hypothesized to underlie the early course of obsessive-compulsive disorder (OCD); however, the development of FSTC white matter tracts remains to be studied in young patients.

Method—To address this gap, we scanned 36 patients with pediatric OCD compared to 27 healthy controls, aged 8 to 19 years, with diffusion tensor imaging (DTI) to measure fractional anisotropy (FA), an index of white matter coherence. Tract-based spatial statistics (TBSS) were used to test differential effects of age on FA, across the whole brain, in those with OCD compared to healthy youth, followed by analyses in a priori regions of interest (anterior corpus callosum, anterior cingulum bundle and anterior limb of the internal capsule [ALIC]) to further characterize developmental differences between groups.

Results—Patients with OCD showed more pronounced age-related increases in FA than controls in regions of interest, as well as several other white matter tracts. In patients, greater FA in anterior cingulum bundle correlated with more severe symptoms after controlling for age.

Conclusions—Our findings support theories of atypical FSTC maturation in pediatric OCD by providing the first evidence for altered trajectories of white matter development in anterior corpus callosum, anterior cingulum bundle, and ALIC in young patients. Steeper age-related increases of FA in these and other select white matter tracts in OCD, compared to healthy controls, may derive from an early delay in white matter development and/or prolonged white matter growth, but confirmation of these possibilities awaits longitudinal work.

Keywords

development; frontal-striatal-thalamic circuit; fractional anisotropy; diffusion tensor imaging; obsessive compulsive disorder

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INTRODUCTION

Neuroimaging research has repeatedly implicated frontal-striatal-thalamic circuitry (FSTC) in the pathophysiology of obsessive-compulsive disorder (OCD) ¹. While this work has predominantly focused on altered volume and function of frontal, striatal, and thalamic gray matter, accumulating evidence in OCD shows alteration of white matter connections between FSTC regions, including the fibers that connect left and right frontal cortices within the anterior corpus callosum ^{2, 3}, the cingulum bundle (CB) ^{2, 4, 5}, and the anterior limb of the internal capsule (ALIC) ^{3, 6}. The source of these white matter abnormalities in OCD remains unknown but may derive from atypical development of FSTC, ⁷ given the onset of illness during childhood and adolescence in up to 80% of patients ⁸.

Atypical development of FSTC-relevant white matter tracts in pediatric OCD is suggested by abnormal age-related changes in resting state functional connectivity of striatum and thalamus with anterior cingulate cortex ⁹, since integrity of white matter tracts may underlie resting state networks ¹⁰. Indeed, abnormally increased fractional anisotropy (FA) in the corpus callosum and cingulum bundle ^{2, 4} have been demonstrated in young patients, further implicating white matter in the pathophysiology of illness from early in its course. In one study, greater FA in various white matter tracts, including the ALIC, associated with greater OCD symptom severity ², suggesting that FA increases may play a pathological role in OCD, near illness onset. However, whether age differentially associates with FA in OCD compared to healthy youth remains unknown.

To characterize the development of white matter during the early course of OCD, we measured FA in a sample of patients with pediatric OCD and healthy youth across a wide age range. Based on prior work, theoretical models, and recent evidence for atypical FSTC development in OCD ^{7, 9}, we hypothesized that patients with OCD, compared to controls, would exhibit differential relations of age with FA in white matter tracts connecting FSTC regions, including anterior corpus callosum, cingulum bundle, and ALIC.

METHOD

Study Participants

DTI data was acquired in 49 patients with pediatric OCD (26 F; 13.0 ± 2.8 years) and 42 healthy controls (24 F; 13.6 ± 3.2 years), ages 8.0 to 19.9 years. All participants were right-handed, excepting one patient and one control who used right and left hands with equal preference. Given the potential for artifacts to confound diffusion tensor imaging (DTI) results ¹¹, every image was checked for quality by 2 independent raters blinded to diagnosis. Quality was assessed by visual inspection of each diffusion weighted image comprising the DTI data set. Participant data sets were excluded if there was white pixel artifact (banding) or movement-related signal degradation. White pixel and/or movement artifact was identified in one or more of the 15 acquired DTI volumes in 13 patients with OCD and 14 healthy participants, and change in head position between DTI and field map acquisition prevented pre-processing in one additional healthy participant. Removal of these participants

left 36 patients with pediatric OCD and 27 healthy controls (Table 1) with high-quality data for analysis.

Patients with pediatric OCD were recruited from the Pediatric Anxiety and Tic Disorders Program within the department of psychiatry at the University of Michigan and from the surrounding community. Control participants were recruited from the community. Participants with serious medical/neurological illness, head trauma, and intellectual disability were excluded. Patients were excluded if they had a lifetime diagnosis of autistic disorder, Asperger syndrome, schizophrenia, other psychotic disorder, bipolar I disorder, substance-related disorder, or anorexia nervosa. Control participants had no history of any Axis-I disorder. After complete description of the study, written informed consent/assent was obtained.

All participants were characterized using the Kiddie-Schedule for Affective Disorders-Present and Lifetime Version (K-SADS PL)¹², administered by a masters-level clinician with expertise in pediatric OCD, and by self-report on the Multidimensional Anxiety Scale for Children (MASC)¹³, the Child Depression Inventory (CDI),¹⁴ and the Child Behavior Checklist (CBCL)¹⁵. The Schedule for Obsessive-Compulsive and Other Behavioral Syndromes (SOCOBS)¹⁶ and Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS)¹⁷ were administered to patients to confirm OCD diagnoses, pinpoint age of onset, and assess current and lifetime symptom severity.

For inclusion, patients were required to have a lifetime diagnosis of OCD. Thirty-three had a current diagnosis, while 3 had a past diagnosis with minimal current symptoms (i.e., in remission, defined as CYBOCs < 6)¹⁸. Patients were included across a wide range of current OCD severity (CYBOCs 1 to 32) to support analyses testing associations between current symptoms and FA. For generalizability, we included patients with secondary diagnoses of separation anxiety disorder (SAD, n = 3), social phobia (n = 2), generalized anxiety disorder (GAD, n = 7), specific phobia (n = 2), panic disorder (n = 2), major depression (n = 6), dysthymia (n = 1), tics (n = 11), impulse control disorder (n = 2), and attention-deficit/hyperactivity disorder (ADHD, n = 2). Nine patients had OCD only, 15 had one comorbidity, and 12 had two comorbidities. Eighteen patients were unmedicated, and 18 were taking medications including fluoxetine (n = 10; augmented by aripiprazole in one, quetiapine in another); sertraline (n = 6); paroxetine (n = 1); and guanfacine (n = 1). Of the 18 unmedicated patients, 6 had previously taken a selective serotonin reuptake inhibitor (SSRI) and 1, a psychostimulant.

DTI acquisition and preprocessing

A b=0 and 15 noncollinear diffusion-weighted images were acquired on a GE 3T Excite 2 scanner with an echo-planar sequence (220 mm FOV, 128x128 matrix, 3.0 mm thick, skip 0.1 mm, TE=70 ms, TR=9000 ms, b=800 s/mm²). Field maps were acquired with the same spatial locations. Movement artifact and eddy current distortion were corrected in FSL using standard algorithms^{19, 20} applied to each of the 15 diffusion-weighted images. Field maps were used to unwarp diffusion weighted images due to echo-planar readout of the DTI sequence²¹.

Corrected images were used to calculate tensor elements to determine FA maps²². FA maps were spatially normalized to Montreal Neurological Institute (MNI) standard space using tract-based spatial statistics (tract-based spatial statistics [TBSS] v1.2) pipeline within FSL²³.

Whole-brain analysis

Whole-brain, voxel-wise statistical analyses of FA maps were implemented using TBSS v1.2²³. These analyses used a permutation-based nonparametric inference t-test within the general linear model framework with 10,000 permutations²⁴. Group and age vectors were entered into the model to test for differences between groups (controlling for age), main effects of age (controlling for group) and group differences in age effects. A separate model, including only patients, was constructed to test the effect of symptom severity on FA, while controlling for age. T-value maps were augmented using threshold-free cluster enhancement and considered significant at $p < .05$, corrected for multiple comparisons throughout the brain²⁵. The anatomical locations of significant effects were characterized with the Johns Hopkins University (JHU) ICBM-DTI-81 white-matter labels atlas²⁶.

Region of interest analysis

Guided by evidence for regional abnormalities of FA in OCD across anterior corpus callosum (CC) subregions²⁷, we generated ROIs for the genu, anterior body, and mid-body of the CC according to Hofer and Frahm²⁸. Additional regions of interest (ROI) were the anterior cingulum bundle (CB) and the anterior limb of the internal capsule (ALIC), derived using the JHU ICBM-DTI-81 White Matter Labels Atlas²⁶. For the anterior CB volume, the JHU ICBM-DTI-81 cingulum bundle was cut at $y = 0$ to produce an anterior portion. FA was extracted from the spatially normalized images, averaged across voxels in each spatial ROI. Given that we had no a priori hypotheses regarding laterality, FA values for left and right anterior CB and ALIC were averaged together. Using SPSS, the effects of group, age, and group $\times$ age interactions, entered simultaneously, were tested as predictors of FA in each ROI. Among patients, partial correlations of FA with OCD symptom severity and age of onset were tested, controlling for age at time of scanning (2-tailed with α level set at 0.05, uncorrected).

RESULTS

Whole-brain analyses

In the whole-brain analysis, there was no effect of group (controlling age); however, effects of age (controlling group) and group $\times$ age interaction were significant. Positive effects of age (controlling group) were noted in a number of white matter tracts (see Table S1, available online). Group $\times$ age interactions were found in hypothesized regions including anterior corpus callosum, from genu ($y = 36$) through mid-body ($y = -12$), an isolated region of left anterior cingulum bundle (centered at $-7, 21, 24$) and bilateral ALIC (Figure 1), but also in several other white matter tracts including the right splenium, right PLIC, right posterior thalamic radiations, bilateral external capsule, anterior and superior corona radiata, and superior longitudinal fasciculus (see Table S2, available online). To interpret group $\times$ age interactions, the linear effects of age were tested within each group (OCD, HC separately) at

$p < .05$, corrected for multiple comparisons throughout the brain. Patients with OCD exhibited positive effects of age on FA in the same white matter tracts involved in the group $\times$ age interactions (Figure S2), but no negative effects of age. There were no positive or negative effects of age in healthy participants.

ROI analyses

In the primary analysis, mean FA values for a priori ROIs (see Table S3, available online) were tested for effects of group, age, and group $\times$ age interactions using linear regression (Table 2). There were no main effects of group, excepting a trend towards lower FA in patients than controls in the CC genu ($p = .06$), and no main effects of age, but, consistent with the whole-brain analysis, group $\times$ age interaction effects were significant in anterior corpus callosum (genu, anterior body and mid-body), anterior cingulum bundle and, at trend level, in ALIC. For each ROI, group $\times$ age interactions were driven by greater age-related increases of FA in patients than controls (Figure 2). Excluding patients with remitted OCD (CYBOCs < 6 ; $n = 3$) did not change results, excepting the loss of trend-level group $\times$ age interactions in ALIC (see Table S4, available online).

To test the potential effects of medication status, comorbidity, and gender on results, terms for these characteristics were included in separate linear regression models. In all cases, group $\times$ age interaction effects remained significant (See Tables S5-S7 and Figures S3-5, available online). No effects of medication status or comorbidity were observed ($p > .22$), excepting trend-level negative effects of comorbidity on FA in the genu of the CC ($p = .08$) and anterior CB ($p = .12$). A main effect of gender was observed on FA in the CC genu ($p = .04$), driven by less FA in boys than girls. To further assess for potential effects of gender, we added the 3-way interaction term (i.e., group $\times$ age $\times$ gender, Table S8) to the model, and again found that group $\times$ age interactions remained significant. The 3-way interaction term reached trend-level significance in anterior cingulum bundle ($p = .06$), driven by greater age-related increases of FA in OCD than healthy participants for girls relative to boys, but did not predict FA for any other ROI ($p > .59$).

Given the differential association of age with FA in patients compared to controls, post hoc t-tests were conducted to test for group differences in FA within childhood (8 – 11 years), early adolescent (12 – 15 years) and late adolescent (16 – 19 years) subgroups (see Table S9, available online). In patients compared to controls, we observed lower FA in CC genu and anterior body for the youngest subgroup ($t[2, 18] = 2.5, p = .02$ and $t[2, 18] = 2.2, p = .04$, respectively), whereas for the oldest subgroup, we found greater FA in CC anterior body and anterior CB ($t[2, 19] = -2.4, p = .03$ and $t[2, 19] = -2.2, p = .04$, respectively).

Finally, we examined group $\times$ age interactions that were *not* predicted a priori (i.e. from whole-brain analysis) to assess whether these effects were driven by the same pattern as in the anterior CC, anterior CB and ALIC ROIs. For this analysis, FA was extracted from representative locations using 3mm spherical ROIs (see Table S2, available online) and plotted against age for each group. Greater positive effects of age on FA in patients with OCD than on healthy participants were observed (see Figure S3, available online).

Correlational analyses in patients

Possible associations between OCD symptom severity and FA were tested in whole-brain and ROI analyses, controlling for age. In whole-brain analyses, no significant effects of OCD symptom severity on FA were observed. By contrast, FA from the anterior CB region of interest positively correlated with OCD severity based on CYBOCs total ($r = .37, p = .03$; Figure 3) and obsessive subscales ($r = .37, p = .03$) and, at a trend level, the compulsive subscale ($r = .29, p = .09$). Trend-level positive correlations of FA in ALIC with CYBOCs total ($r = .31, p = .07$) and compulsive ($r = .32, p = .06$), but not obsessive ($r = .22, p = .20$) subscale, scores were also observed. Exploratory analyses using FA from spherical ROIs (defined by the whole-brain group $\times$ age interaction) suggested association with CYBOCs in right splenium and posterior thalamic radiation (see Table S10, available online). Given the influence of symptom severity on FA in patients and the possible impact of age at illness onset, we tested correlations between age and FA in a priori ROIs, controlling these factors. Positive age-FA correlations remained (see Table S11, available online).

DISCUSSION

This study used DTI to test for differences in white matter development in patients with pediatric OCD compared to healthy controls. Mean FA values for each group did not significantly differ; however, age-related increase of FA in anterior corpus callosum (CC), anterior cingulum bundle (CB), and ALIC was greater in patients than in controls, based on both whole-brain and ROI analyses. Whole-brain analyses also revealed greater age-related increase of FA in other white matter tracts, including the splenium of the corpus callosum, posterior limb of the internal capsule (PLIC), corona radiata, and superior longitudinal fasciculus (SLF). In patients, greater FA in anterior cingulum bundle correlated with greater OCD symptom severity, suggesting a relationship between white matter in this region and illness expression. The findings from this cross-sectional study point towards altered white matter development in pediatric OCD, but must be considered tentative until confirmed by longitudinal work.

The location of atypically developing white matter in anterior CC, anterior CB, and ALIC in pediatric OCD is consistent with prior evidence implicating abnormal function and structure of frontal-striatal-thalamic circuitry (FSTC) ¹. The anterior CC contains white matter fibers connecting right and left prefrontal, premotor and supplementary motor cortex ²⁸ – areas of abnormal function and volume in numerous studies of OCD ¹. The anterior CB, distinguished functionally and anatomically from retrosplenial and parahippocampal CB, contains fibers that connect emotion processing regions such as amygdala to anterior cingulate cortex (ACC), ²⁹ a region in which abnormally increased resting state metabolism and hyperactive response to cognitive demands have been repeatedly observed ¹. The ALIC contains white matter pathways connecting frontal lobe and thalamus. Thus, collectively, anterior CC, anterior CB and ALIC represent the key white matter tracts connecting the FSTC nodes on which neurocircuit models of OCD are based.

Steeper age-related increase of FA in anterior CC, anterior CB, and ALIC may be consistent with delayed development of FSTC white matter in patients with pediatric OCD compared to healthy youth. However, other interpretations are possible. This finding could reflect

abnormal white matter development that may never “catch up” to healthy maturation, or, alternatively, protracted development that, if persistent, could result in increased white matter in individuals with childhood-onset illness as they progress into adulthood. Abnormal increase of FA with age in OCD did not appear to be driven by medication or comorbidity. Moreover, the effect was consistent across genders, though it tended to be more pronounced in girls than boys with OCD in anterior CB. In patients, positive age-FA correlations were observed when controlling age of onset, suggesting that greater age-related increase of FA in OCD compared to healthy youth cannot be explained by illness chronicity.

Group differences in the relationship between age and FA were driven by a robust positive effect of age in patients, but also by the absence of an age effect in healthy controls. This negative finding in our healthy participants represents a departure from prior research showing that white matter volume³⁰ and myelination³¹ continue to increase into early adulthood, but it is consistent with emerging DTI research that shows development of white matter microstructure (e.g., FA) to follow different trajectories³². In fact, regionally specific, nonlinear changes of FA occur with age, characterized by initial increases, subsequent plateau, and even decreases over the lifespan^{33, 34}. In a cross-sectional study of 202 healthy individuals, ages 5 to 30 years of age, FA values peaked at 11 years in the anterior CC and at 15 years in the ALIC and then plateaued, whereas FA in the CB continued to increase through the early twenties. A longitudinal follow-up of the same cohort revealed FA increases predominantly in children (5 to 11 years), whereas the majority of adolescent and adult subjects showed no change or decreasing FA, including in the anterior CC and CB (ALIC not reported)³³. In select white matter tracts, including the SLF, larger proportions of adolescent participants exhibited increasing FA³³, leading the authors to conclude that increases in white matter microstructure plateau by adolescence in some tracts (e.g., CC) but continue into adulthood in other tracts (e.g., SLF).

Based on this literature and the age range of our sample (14.1 ± 2.9 years), it is not entirely surprising that there were no significant effects of age on FA in anterior CC, ALIC, or anterior CB in our analyses of healthy youth. White matter in these regions may have reached a plateau in our healthy, predominantly adolescent-aged participants, while still increasing in patients with OCD. Greater positive effects of age in OCD compared to healthy participants in other white matter tracts, including the SLF, were also observed. These effects were not predicted and should be interpreted with caution but, notably, were significant at the whole-brain level.

If FA in anterior CC, anterior CB, and ALIC continues to increase beyond adolescence in OCD, one might expect abnormally increased FA in these regions adult patients. Greater FA has been reported in adult OCD in the CC^{3, 5}, CB^{5, 6}, ALIC^{3, 6} and other white matter tracts including SLF and anterior corona radiata in some reports. However, an equal number of reports have found decreased FA in these regions in adult patients compared to healthy controls²⁷. Meta-analysis of DTI research in OCD suggests that conflicting results across studies may derive from sample heterogeneity due to demographics, medication status, illness chronicity, and imaging methodology^{27, 35}. Our results suggest that developmental stage is also an important factor for interpreting DTI studies of OCD. Indeed, inverted U-shaped trajectories of FA development have been documented in healthy participants³⁴, but

over a much wider range of ages (8 – 85) than included in our study. DTI research in patients compared to matched controls from childhood into older adulthood will be needed to assess whether shifts in the timing of this quadratic function (e.g. earlier peaks for healthy, later peaks for OCD) may best describe developmental differences in white matter integrity, based on FA, over the life span.

In contrast to prior reports ^{2, 4}, we did not find patients with pediatric OCD to exhibit greater mean FA than healthy controls. Given our finding of altered white matter trajectories in pediatric OCD, averaging FA values across 8- to 19-year-old patients compared to controls could obscure group differences that might be observed if participants were selected from a more tightly bracketed age range. After subdividing our 8- to 19-year-old sample into child, early adolescent, and later adolescent age groups, we found evidence of lower FA in 8- to 11-year-old child patients, but higher FA in 16- to 19-year-old adolescent patients compared to same-aged healthy controls in select JHU-defined ROIs (genu, anterior CC body and anterior CB), suggesting that inclusion of older versus younger subjects may increase the likelihood finding greater FA. On the other hand, Gruner et al ⁴ found abnormally increased FA in the CB of similarly aged participants (9 to 17 years) with OCD, underscoring the possibility that unique sample characteristics, data acquisition, or pre-processing steps may drive discrepancies between studies.

Our results and those of Zarei and colleagues ² show greater FA in FSTC tracts correlates with more severe OCD and suggest that age-related increases in FA pathologically contribute to the disorder. The localization of greater OCD severity with greater FA in the anterior cingulum bundle links to prior task-based research using functional MRI and event-related potentials to demonstrate hyperactivity of the ACC in response to errors in children and adults with OCD ^{36, 37} and related theory that ACC-based hypersensitivity to errors could drive repetitive attempts to correct perceived mistakes in patients ³⁸. Theoretically, increased white matter microstructure might drive *or* result from greater signaling through FSTC that, on the basis of abnormally increased metabolism and resting state connectivity, has been hypothesized to underlie OCD ^{1, 9}.

Greater age-related increase in FA has been previously observed in youth with ASD compared to healthy controls. As with our study, group×age interactions were driven by positive correlations of age with FA in ASD, but not typically developing youth in the CC body ^{39, 40}, as well as SLF ³⁹ and posterior limb internal capsule ⁴⁰. Abnormally reduced FA in CC and SLF was also found in patients, leading the authors to suggest that age-related increases in FA could support the improved life-functioning typically observed as patients with ASD mature. On the other hand, greater increase of FA in anterior CB from pre- to posttrauma correlates with higher posttrauma anxiety ⁴¹, raising the possibility that FA increases, at least in this region, may reflect a pathological reaction to stressful life events. Greater FA in anterior CB in our sample was associated with more severe symptoms in OCD, but whether high FA represents a precipitant or sequela of illness remains unknown.

There are several limitations and caveats of this study. While scatterplots of our data do not suggest age effects were outlier-driven, our analyses were based on linear regression in a relatively small sample, across a wide age range and, as such, may have been susceptible to

selection bias. Although controlling for medication and comorbidity status did not change primary results, half of the patients in our sample were medicated (predominantly SSRI) and over half had comorbid psychopathology, and it is possible that different results could be observed in cleaner samples. Inclusion of patients with low levels of current symptom severity could have contributed to our findings, including failure to find overall group differences in FA; however, when remitted patients were excluded, findings remained essentially unchanged. Moreover, it is unlikely that differences in symptom severity drove group×age interactions in our sample, since positive associations of age and FA in the patient group were significant, even after controlling for CYBOCS scores. Finally, IQ was not formally tested; therefore, we cannot rule out the possibility that between-group differences in the variation of IQ with age could have influenced our findings.

In this DTI study, we demonstrated more pronounced age-related increases of FA within FSTC white matter tracts in patients with pediatric OCD compared to healthy youth between the ages of 8 to 19 years. Our results may reflect delayed and/or protracted white matter development in pediatric OCD, but research including both younger and older participants will be needed to distinguish between these possibilities. Importantly, these developmental findings must be considered tentative until confirmed by longitudinal work. The positive relationship of OCD severity with FA in anterior CB suggests a key role of FA in illness expression; however, establishing whether age-related increases in FSTC white matter microstructure may drive OCD pathology, or result from it, awaits longitudinal study in which change in FA can be correlated to emergence of and/or fluctuation in symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Diffusion Tensor Imaging tract-based spatial statistics (TBSS) p -value maps fully corrected for multiple comparisons of voxel-wise group differences in positive linear effects of age on fractional anisotropy (FA) for obsessive-compulsive disorder (OCD) compared to healthy youth. Note: Results are displayed at significant levels ($p < 0.05$, fully corrected for multiple comparisons) in Montreal Neurological Institute (MNI) standard space. Red-yellow clusters indicate locations in which patients exhibit greater positive relationship of age with mean FA than do controls ($p < 0.05$). The color bar indicates age-related difference between in FA values, which ranges from 0.0 to 1.0. ALIC = anterior limb of the internal capsule; CB = the cingulum bundle; CC = corpus callosum.

Figure 2.

Scatterplots showing greater positive relationship of age with mean fractional anisotropy (FA) in patients (circles, solid line) than controls (triangles, dashed line) in the midbody of the corpus callosum, anterior cingulum bundle, and anterior limb of the internal capsule (ALIC).

Figure 3.

Partial regression plot showing positive correlation of mean fractional anisotropy (FA) in the anterior cingulum bundle with obsessive-compulsive disorder (OCD) symptom severity when controlling for age. Note: Residual values are plotted; actual values ranged from .33 to .48 for FA and from 1 to 32 for total Children's Yale-Brown Obsessive Compulsive Scale scores. Filled circles represent patients taking medication at the time of scanning.

Table 1

Subject Characteristics

	OCD	HC	Statistic	P
Sample Size	36	27		
Age	14.1 (2.9)	14.7 (3.1)	$t = .75$	.46
Gender	20 F	16 F	$\chi^2 = .26$	.61
MASC	49.3 (16.8)	25.3 (12.6)	$t = -6.2$	<.001
CDI	9.9 (6.6)	2.6 (3.1)	$t = -5.3$	<.001
CYBOCs (Present)	16.7 (7.8)	n.a.	n.a.	n.a.
CYBOCs (Lifetime)	27.0 (7.0)	n.a.	n.a.	n.a.
Age of Onset	7.3 years (3.1)	n.a.	n.a.	n.a.

Note: CDI = Children's Depression Inventory; CYBOCS = Children's Yale-Brown Obsessive Compulsive Scale; HC = healthy controls; MASC = Multi-dimensional Anxiety Scale for Children; n.a. = not available; OCD = obsessive-compulsive disorder.

Table 2

Linear Regression Modeling of Group, Age and Group $\times$ Age Interaction Effects on Fractional Anisotropy (FA) in A Priori Regions of Interest (ROI)

ROI	Group	Age	Group $\times$ Age
Anterior Corpus Callosum			
Genu	$\beta = -.017, p = .06$	$\beta = -.002, p = .44$	$\beta = .007, p = .03$
Anterior body	$\beta = -.002, p = .85$	$\beta = -.004, p = .12$	$\beta = .010, p = .006$
Mid-body	$\beta = .004, p = .73$	$\beta = .000, p = .94$	$\beta = .010, p = .03$
Anterior Cingulum Bundle	$\beta = .003, p = .75$	$\beta = .001, p = .59$	$\beta = .006, p = .04$
ALIC	$\beta = .000, p = .94$	$\beta = .002, p = .15$	$\beta = .002, p = .09$

Note: Bolded text indicates p-value $< .05$, italicized text indicates trend-level significance ($p = .05 - .10$).

ALIC = anterior limb of the internal capsule.