Neuropsychopharmacology (2012) 37, 2730–2739

www.neuropsychopharmacology.org

White Matter Abnormalities in Pediatric Obsessive-Compulsive Disorder

Patricia Gruner*[,1,2], An Vo[3], Toshikazu Ikuta[1,2], Katie Mahon[1,2], Bart D Peters[1,2], Anil K Malhotra[1,2,4,5], Aziz M Uluğ[3,5] and Philip R Szeszko[1,2,4,5]

[1]Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Manhasset, NY, USA; [2]Psychiatry Research, Zucker Hillside Hospital, North Shore-LIJ Health System, Glen Oaks, NY, USA; [3]Susan and Leonard Feinstein Center for Neurosciences, Feinstein Institute for Medical Research, Manhasset, NY, USA; [4]Department of Psychiatry, Hofstra North Shore-LIJ School of Medicine, Hempstead, NY, USA; [5]Department of Molecular Medicine, Hofstra North Shore-LIJ School of Medicine, Hempstead, NY, USA

Obsessive-compulsive disorder (OCD) is a prevalent and often severely disabling illness with onset generally in childhood or adolescence. Although white matter deficits have been implicated in the neurobiology of OCD, few studies have been conducted in pediatric patients when the brain is still developing and have examined their functional correlates. In this study, 23 pediatric OCD patients and 23 healthy volunteers, between the ages of 9 and 17 years, matched for sex, age, handedness, and IQ, received a diffusion tensor imaging exam on a 3T GE system and a brief neuropsychological battery tapping executive functions. Patient symptom severity was assessed using the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS). Patients with OCD exhibited significantly greater fractional anisotropy compared to matched controls in the left dorsal cingulum bundle, splenium of the corpus callosum, right corticospinal tract, and left inferior fronto-occipital fasciculus. There were no regions of significantly lower fractional anisotropy in patients compared to controls. Higher fractional anisotropy in the splenium was significantly correlated with greater obsession severity on the CY-BOCS in the subgroup of psychotropic drug-naïve patients. Among patients, there was a significant association between greater fractional anisotropy in the dorsal cingulum bundle and better performance on measures of response inhibition and cognitive control. The overall findings suggest a pattern of greater directional coherence of white matter tracts in OCD very early in the course of illness, which may serve a compensatory mechanism, at least for response inhibition functions typically subserved by the cingulum bundle.
Neuropsychopharmacology (2012) **37,** 2730–2739; doi:10.1038/npp.2012.138; published online 8 August 2012

Keywords: obsessive-compulsive disorder; child; white matter; diffusion tensor imaging; functional correlates; response inhibition

INTRODUCTION

Obsessive-compulsive disorder (OCD) is an anxiety disorder characterized by recurrent and persistent obsessions or compulsions that are recognized as excessive or unreasonable, cause marked distress, are time consuming, and/or interfere with normal functioning (American Psychiatric Association, 1994). The disorder can be severely disabling and usually begins in childhood (Pauls *et al*, 1995), with prevalence rates among children and adolescents reported to be as high as 2–4% (Kiejna *et al*, 2002). Despite the prevalence and severity of the disorder, neuroimaging and neuropsychological research in OCD is limited and few studies have examined the disorder in children and adolescents close to illness onset.

*Correspondence: Dr P Gruner, Psychiatry Research, Zucker Hillside Hospital, 75-59 263rd Street, Glen Oaks, NY 11004, USA, Tel: +1 718 470 8609, Fax: +1 718 343 1659, E-mail: pgruner@nshs.edu
Received 22 November 2011; revised 19 June 2012; accepted 29 June 2012

Neurobiological models of OCD propose aberrations in frontal–striatal–thalamic–cortical loops in the pathogenesis of OCD in adults and children, including abnormalities of the anterior cingulate cortex, orbitofrontal cortex, thalamus, and basal ganglia (Harrison *et al*, 2009; Insel, 1992; Maia *et al*, 2008). Although structural and functional abnormalities of the gray matter nodes comprising these circuits have been repeatedly implicated, findings have been inconsistent regarding the precise locations of neuroanatomical abnormalities as well as the direction of findings. A review of pediatric studies (Huyser *et al*, 2009) concluded that several studies of children and adolescents with OCD indicate abnormalities of the putamen, globus pallidus, and thalamus (eg, Rosenberg *et al*, 1997b; Szeszko *et al*, 2004), whereas studies of adults tend to implicate the caudate nucleus and orbitofrontal cortex (eg, Robinson *et al*, 1995; Szeszko *et al*, 1999). The results of two recent meta-analyses, including adult and pediatric samples, however, both implicated less anterior cingulate gray matter in OCD; one study reported smaller volumes in bilateral anterior cingulate/dorsal medial frontal gyri and greater volumes of

bilateral lenticular nuclei (Radua and Mataix-Cols, 2009) and the other study identified smaller volume in the left anterior cingulate and bilateral orbitofrontal cortex, and greater volumes of the bilateral thalami. (Rotge *et al*, 2009).

There is now increasing evidence that the white matter pathways comprising cortical–striatal–thalamic–cortical loops may also be abnormal in OCD. The majority of diffusion tensor imaging (DTI) studies in OCD to date have investigated white matter tract coherence in adults (see Fontenelle *et al* (2009) for a review), but these studies of adults with OCD have been inconsistent, with some studies reporting lower (Garibotto *et al*, 2010; Nakamae *et al*, 2011; Saito *et al*, 2008; Szeszko *et al*, 2005) or higher (Li *et al*, 2011; Yoo *et al*, 2007) fractional anisotropy (FA) in patients, while other studies reported significant variation depending on the specific white matter bundle or region of interest examined (Cannistraro *et al*, 2007; den Braber *et al*, 2011; Menzies *et al*, 2008).

The inconsistency in adult white matter findings in OCD may be associated with confounding factors, such as cohort effects, drug exposure, illness duration, and treatment history. For example, Yoo and colleagues (2007) found greater white matter integrity (higher FA) in adult OCD patients compared to controls in the corpus callosum, the internal capsule, and the white matter superolateral to the right caudate that was no longer evident following 12 weeks of citalopram treatment. A potential advantage of using child cohorts to examine the neurobiology of OCD is that it limits confounds such as medication history and illness duration. Moreover, the use of child cohorts permits the examination of potential abnormalities early in the course of the illness when the brain is still under considerable development. To date, however, only one study has examined a pediatric OCD sample using DTI. Zarei and colleagues (2011) examined adolescents with OCD compared to age-matched controls and reported higher FA in patients in multiple white matter tracts, including the left inferior longitudinal fasciculus, right inferior front-occipital fasciculus, corpus callosum splenium and genu, the left cingulum bundle, and bilateral corticospinal tract.

Executive functioning deficits, such as response inhibition and set shifting, are often reported in adults with OCD (Abramovitch *et al*, 2011; Bannon *et al*, 2002; Chamberlain *et al*, 2006; Penades *et al*, 2007) and have been linked to aberrations in frontal–subcortical circuitry, especially in the anterior cingulate. Response inhibition, in particular, may deserve particular attention in OCD, as an inability to inhibit recurrent, intrusive thoughts and/or repetitive behaviors appears to be a core illness feature (Bannon *et al*, 2002). It should be acknowledged, however, that not all studies have implicated response inhibition deficits in OCD (Beers *et al*, 1999; Ciesielski *et al*, 2011; Krishna *et al*, 2011). Specifically, Beers and colleagues (1999) found no cognitive impairments in psychotropic medication-naïve children with OCD compared to age-matched controls, and Krishna and colleagues (2011) found no significant difference in performance between psychotropic medication-naïve adults with OCD and matched controls on the majority of neuropsychological tests, including measures of set shifting and response inhibition. Moreover, little research has been directed at discerning the functional correlates of white matter pathology in OCD.

In this study, we examined white matter abnormalities in OCD in a child and adolescent cohort of patients using DTI and the relationship between abnormal white matter integrity and their clinical and neuropsychological correlates. We hypothesized that patients with OCD would have greater fractional anisotropy (FA) in white matter bundles comprising frontal–striatal–thalamic–cortical circuitry, including the cingulum bundle and internal capsule, and that these white matter aberrations would be correlated with symptom severity and executive functioning in patients.

MATERIALS AND METHODS

Participants

In all, 23 pediatric patients with a DSM-IV diagnosis of OCD and 23 healthy controls matched for sex, age, handedness, and IQ participated in this study. All participants were between the ages of 9 and 17 years. Demographic and clinical characteristics for the sample are illustrated in Table 1. Diagnoses were based on the Schedule for Affective Disorders and Schizophrenia for School-Age-Children, Present and Lifetime Version (K-SADS-PL) (Kaufman *et al*, 1997). All pediatric OCD patients underwent a detailed clinical assessment by a licensed psychologist experienced in the assessment of OCD. Four patients had a comorbid major depressive disorder, four had comorbid anxiety disorders (two had social anxiety disorder and two had panic disorder), and five met the criteria for attention deficit hyperactivity disorder. Nine patients were psychotropic drug-naïve at the time of the scan, two were free of treatment with psychotropic drugs for at least 30 days before the scan, and the remainder were being treated with selective serotonin reuptake inhibitors (SSRIs) ($n = 12$). All healthy controls were assessed using the K-SADS-PL and were determined to be free of any current or past psychiatric disorder. Exclusion criteria for all participants included: (1) MRI contraindications; (2) significant medical illness; (3) prior psychosurgery; (4) DSM-IV diagnosis of Tourette syndrome, schizophrenia, schizoaffective disorder, delusional disorder, brief reactive psychosis, bipolar disorder, substance-use disorder, or mood disorder with psychotic features; (5) DSM-IV mental retardation; and (6) pregnancy. All procedures were approved by the North Shore-LIJ Institutional Review Board and written informed consent was obtained from all parents along with written assent from participants.

Clinical/Neuropsychological Assessments

All children with OCD were interviewed using the Children's Yale-Brown Obsessive-Compulsive Scale (Scahill *et al*, 1997). All participants also completed the Multidimensional Anxiety Scale for Children to evaluate general anxiety symptoms and severity. Handedness was assessed using the Edinburgh Handedness Inventory. Intellectual ability was estimated using the Wechsler Abbreviated Scale of Intelligence. All participants were administered a brief neuropsychological battery tapping executive functions, including the Stroop Color Word Test, the Wisconsin Card Sorting Test (WCST-64), the Controlled Oral Word Association Test (COWAT), and the Trail Making Test

Table 1 Sample Characteristics

	Patients with OCD ($n=23$)	Healthy volunteers ($n=23$)	d.f.	Statistic	p-Value
Age	14.3 (2.1)	14.2 (2.2)	44	$t=-0.23$	NS
Sex (M/F)	13/10	12/11	1	$\chi^2=0.09$	NS
Handedness (R, L)	19/4	17/6	1	$\chi^2=0.51$	NS
Full-scale IQ	106.0 (15.1)	106.8 (11.1)	43	$t=0.84$	NS
MASC	42.14 (22.43)	39.73 (16.25)	41	$t=-0.41$	NS
CY-BOCS obsessions	13.09 (2.92)				
CY-BOCS compulsions	13.78 (2.28)				
CY-BOCS total	26.87 (4.48)				
Medication status					
Psychotropic med naïve	9				
Past SSRI(s)	2				
Current SSRI(s)	12				

Abbreviatons: CDRS, Children's Depression Rating Scale; CSF, cerebrospinal fluid; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; MASC, Multidimensional Anxiety Scale for Children; NS, not significant; SSRI, selective serotonin reuptake inhibitor.
Notes: Data are presented as mean ± SD within parentheses, unless otherwise indicated. There were missing data for the following variables: IQ (1 patient); MASC total (2 patients, 1 volunteer).

(TMT). Neuropsychological data were unavailable for one patient; one control subject was missing data from the TMT and one control subject was missing data from the WCST.

We converted all scores to *z*-scores based on the reference group of 23 healthy volunteers. To minimize Type 1 error, we first computed a global executive functioning score for each subject based on the *z*-scores from the full battery of tests. This global executive functioning score was comprised of the interference score from the Stroop Color Word Test, categories completed on the WCST, total fluency score on the COWAT, and time to completion on Trails B of the TMT. To assess specifically response inhibition and cognitive control, we also computed a cluster score comprised of performance on the two measures requiring stimulus–response selection despite competing streams of information, the Stroop Color Word Test, and Trails B of the TMT. All tasks were given equal weight in the equations. We used Pearson's product moment correlations to examine the clinical and neuropsychological correlates of FA measures with α set to 0.05 (two-tailed).

DTI Procedures

All participants received an MR imaging exam on a GE Signa HDx 3.0 T system. Participants were scanned using anatomical sequences for segmentation and sequences for DTI. The DTI sequence included volumes with diffusion gradients applied along 31 non-parallel directions and five volumes without diffusion weighting (TR = 14 000 ms, TE = min, matrix = 128 × 128, FOV = 240 mm). Each volume consisted of 51 contiguous 2.5-mm axial slices acquired parallel to the anterior–posterior commissural line using ramp sampled, spin-echo, single-shot echo-planar imaging. Data acquisition used parallel imaging with an acceleration factor of 2.

DTI Processing

Images were corrected for Eddy current-induced distortions and head motion using the Eddy current correction routine in FSL. Using the brain extraction tool in the FMRIB software library (Smith, 2002), non-brain tissue was removed from the images. Diffusion tensor components for each brain pixel were then calculated and FA maps were determined for all subjects using FSL. We used the DTIFIT tool with the weighting option in FSL to fit a diffusion tensor model to the raw diffusion data at each voxel. The FA maps were then registered to the Montreal Neurological Institute template (MNI-152: $1 \times 1 \times 1\,mm^3$) using a 12-parameter affine transformation (FLIRT) (Jenkinson *et al*, 2002). Images were smoothed using an $8 \times 8 \times 8\,mm^3$ kernel, and compared group-wise (OCD *vs* healthy volunteers) using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Our statistical approach involved using the *p*-value based on the spatial extent of the nearest cluster (Friston, 1997). Thus, in this study we used a voxel-level threshold of $p<0.005$, a cluster size threshold of 250 contiguous voxels, and finally a cluster extent correction of $p<0.05$ to determine significant findings. Following the identification of clusters, we computed mean FA values in each cluster for all subjects, and additionally used these clusters as seed regions in visualizing the white matters tracts that differed between groups as described previously (Uluğ *et al*, 2009; Vo *et al*, 2012). In this approach, all diffusion-weighted images from all subjects in a group are registered to the template, and the gradient vectors are reoriented for tensor calculation. All data in each group of subjects are processed together to calculate the eigenvectors and to visualize the group tracts. Specifically, we used the Track Vis software (www.trackvis.org) to map white matter tracts starting from the significant clusters in patients and healthy volunteers. Fiber tracking parameters were identical for the two groups.

RESULTS

Fractional Anisotropy

Patients with OCD exhibited significantly higher FA compared to matched healthy volunteers in four white matter tracts: the left dorsal cingulum bundle ($p=0.005$; $k_E=638$), the splenium of the corpus callosum ($p=0.007$; $k_E=567$), the right corticospinal tract ($p=0.008$; $k_E=552$), and the left inferior fronto-occipital fasciculus ($p=0.043$; $k_E=286$) (see Figures 1–4 and Table 2). No regions of significantly lower FA in the patients compared to healthy volunteers were identified at this threshold. *Post hoc* analyses revealed no significant differences in FA between medicated and psychotropic drug-naïve OCD subjects in these four regions. For the areas of higher FA, radial diffusivity was significantly lower in patients than controls in all four white matter regions: the left dorsal cingulum bundle ($t=2.98$; $p=0.005$), the splenium ($t=3.88$; $p<0.001$), the right corticospinal tract ($t=3.88$; $p<0.001$), and the left inferior fronto-occipital fasciculus ($t=4.28$; $p<0.001$). Axial diffusivity was significantly higher in

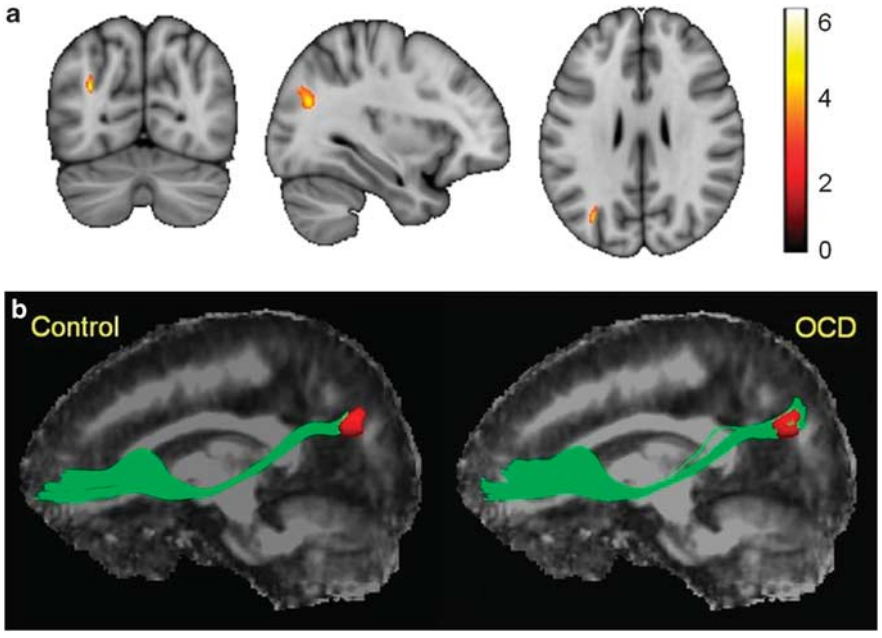

Figure 1 Inferior fronto-occipital fasciculus (IFOS). (a) Voxels showing significant cluster of higher fractional anisotropy (FA) in left posterior IFOS in obsessive-compulsive disorder (OCD) patients compared to controls. (b) Group tractography of the left inferior IFOS with fibers passing through the significant cluster of higher FA.

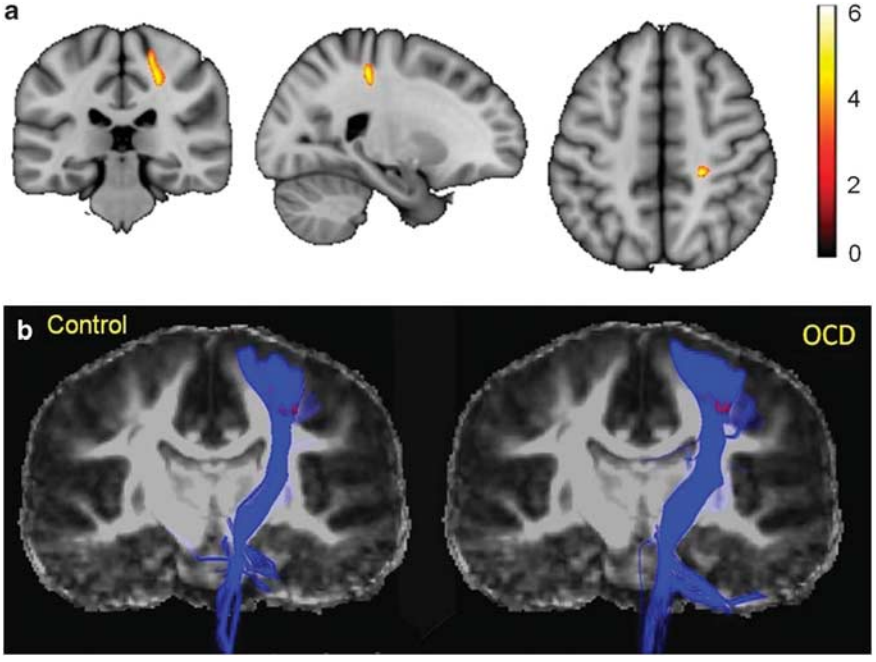

Figure 2 Corticospinal tract. (a) Voxels showing significant cluster of higher fractional anisotropy (FA) in the right corticospinal tract in obsessive-compulsive disorder (OCD) patients compared to controls. (b) Group tractography of the right corticospinal tract with fibers passing through the significant cluster of higher FA.

patients than controls in the left dorsal cingulum bundle ($t = 2.91$; $p = 0.006$) and the left fronto-occipital fasciculus ($t = 2.40$; $p = 0.021$).

Neuropsychological Functioning

There was a trend for patients to perform worse than controls on the global measure of executive functioning ($t\ (41) = 1.97$, $p = 0.055$). No significant difference in performance between the patients and controls was demonstrated on the cluster score for response inhibition/cognitive control ($t\ (42) = 1.22$, $p = 0.23$). *Post hoc* analyses comparing group performance on each of the individual tests of executive functioning revealed that the patients and controls only differed significantly on categories completed of the WCST ($t\ (42) = 1.97$, $p = 0.013$). We examined this

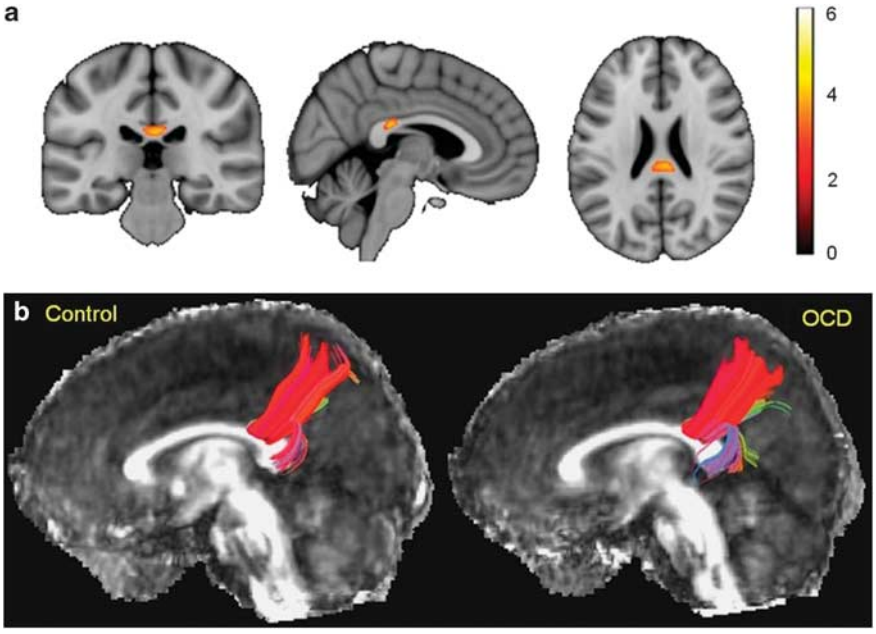

Figure 3 Splenium of corpus callosum. (a) Voxels showing significant cluster of higher fractional anisotropy (FA) in the splenium in obsessive-compulsive disorder (OCD) patients compared to controls. (b) Group tractography of the splenium of the corpus callosum with fibers passing through the significant cluster of higher FA.

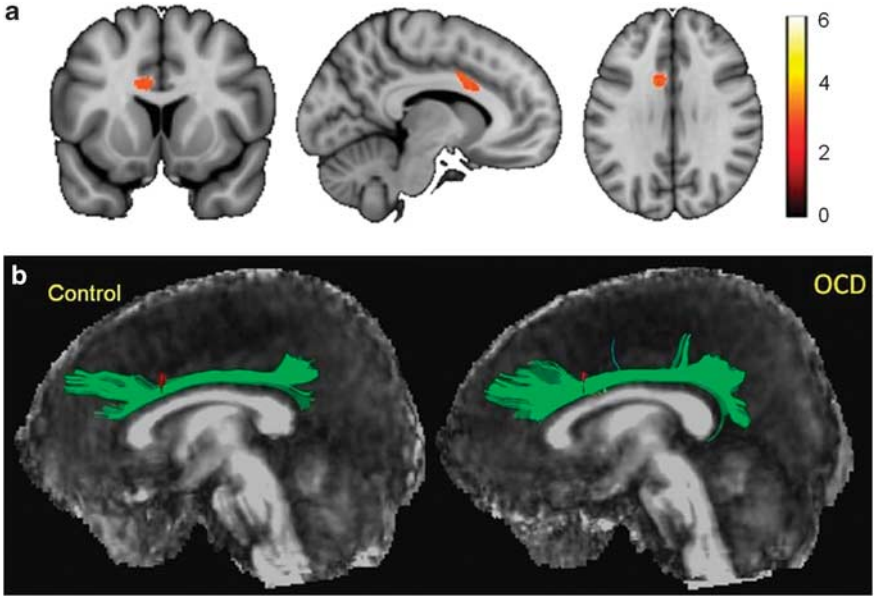

Figure 4 Cingulum bundle. (a) Voxels showing significant cluster of higher fractional anisotropy (FA) in the left dorsal cingulum bundle in obsessive-compulsive disorder (OCD) patients compared to controls. (b) Group tractography of the left cingulum bundle with fibers passing through the significant cluster of higher FA.

effect further by comparing performance of the medicated and psychotropic drug-naïve patients separately. Findings revealed that the patients taking SSRIs completed significantly less categories than controls on the WCST ($t(31) = 2.96$, $p = 0.006$). There was, however, no significant difference on this measure between the psychotropic medication-naïve patients and the controls. There was no significant difference between the medication-naïve patients and the control group on any of the measures.

Correlations with Symptom Severity

There were no significant correlations between symptom severity and the four FA measures in patients. Subgroup analyses, however, revealed that FA in the splenium was significantly and positively correlated with total obsessions on the CYBOCS in the subgroup of psychotropic drug-naïve patients ($r(7) = 0.67$, $p = 0.047$), but not in the subgroup of medicated patients ($r(12) = -0.07$, $p = 0.841$). However, the

Table 2 White Matter Regions of Higher FA in Pediatric OCD Patients Compared to Healthy Controls

	Region	Peak MNI coordinates			Cluster size (voxels)	FA			Group	Tracts
		x	*y*	*z*		Control	OCD	*p*<	Control	OCD
1	Left inferior fronto-occipital fasciculus	−32	−70	24	286	0.286 ± 0.106	0.403 ± 0.086	0.0001	664	1114
2	Right corticospinal tract	22	−32	50	552	0.340 ± 0.087	0.457 ± 0.054	0.0001	4004	8253
3	Splenium of corpus callosum	4	−29	22	567	0.496 ± 0.138	0.638 ± 0.108	0.0005	5557	6993
4	Left cingulum bundle	−14	9	30	638	0.292 ± 0.090	0.391 ± 0.103	0.001	2671	4036

The peak coordinates, cluster size, FA value, *post hoc p*-value, and the number of tracts of each significant cluster are provided. Given the same tractography setting such as FA threshold, seed volume, etc, the number of group tracts represents all the visualizable tracts in the entire group of subjects.

difference between these two correlations was not statistically significant ($z = -1.74$; $p = 0.08$; two-tailed).

Correlations with Neuropsychological Measures

Higher FA in the left dorsal cingulum bundle correlated significantly and positively with the global executive functioning score ($r\ (20) = 0.43$, $p = 0.047$) and the response inhibition/cognitive control cluster score ($r\ (20) = 0.67$, $p = 0.001$) among patients, but not healthy volunteers ($r\ (19) = -0.03$, $p = 0.90$; $r\ (19) = 0.06$, $p = 0.79$). There was a significant difference in the correlations between FA in the left dorsal cingulum bundle and the response inhibition/cognitive control domain score between the patient and healthy control groups ($z = 2.29$; $p = 0.02$; two-tailed). Higher FA in the left dorsal cingulum bundle was correlated significantly with better performance on the Stroop Color Word Test ($r\ (20) = 0.46$, $p = 0.032$) and Trail Making Test—Part B ($r\ (20) = 0.43$, $p = 0.045$) among patients, but not with WCST ($r\ (20) = -0.07$, $p = 0.76$) or COWAT ($r\ (20) = 0.27$, $p = 0.23$) performance. *Post hoc* analyses indicated that higher FA in the left dorsal cingulum bundle and better response inhibition/cognitive control performance was significant in the psychotropic drug-naïve patients ($r\ (7) = 0.76$, $p = 0.018$), but not in the medicated patients ($r\ (9) = 0.39$, $p = 0.23$), although the difference between these correlations was not statistically significant ($z = 1.08$; $p = 0.28$; two-tailed).

DISCUSSION

Our data provide strong evidence for abnormalities in several white matter tracts in pediatric OCD and suggest that they are present early in the course of illness and before extensive pharmacological intervention. Our results are highly consistent with Zarei and colleagues (2011), who also reported higher FA in several white matter tracts in adolescents with OCD, including the four regions identified in this study. While the study by Zarei and colleagues (2011) found more extensive regions of greater FA in adolescents with OCD than the current study, our data provide evidence for higher FA within select white matter regions earlier in the course of illness (our cohort was, on average, 2.3 years younger) and examines the neuropsychological correlates of these abnormalities. Moreover, investigation of axial and radial diffusivity in *post hoc* analyses in our study revealed that axial diffusivity was significantly higher and radial diffusivity significantly lower in patients compared to controls. Taken together, our results may be indicative of axonal- and myelin-related pathology, respectively (eg, Song *et al*, 2002, 2003, 2005) or related to alterations in fiber architecture in patients, and thus may have implications for furthering our understanding regarding white matter deficits in OCD. An important advantage of our study compared to several other DTI studies in OCD includes the use of healthy volunteers individually matched to OCD patients for potentially confounding variables, including age, sex, and intellectual functioning.

Our findings are consistent with the hypothesis that myelination may be occurring prematurely in children and adolescents with OCD (Zarei *et al*, 2011). These data thus support the hypothesis that OCD may be a neurodevelopmental disorder (Huyser *et al*, 2009; Rosenberg and Keshavan, 1998) with potentially differing patterns of pruning and myelination occurring throughout development and raises the intriguing possibility that these abnormalities could serve as biomarkers in the disorder. While there is a critical need for longitudinal studies to confirm these initial findings, several cross-sectional studies support the possibility for a developmentally mediated dysplasia in OCD, although findings have not always been consistent regarding the direction of associations. For example, Rosenberg and colleagues (1997a) found that psychotropic medication-naïve children with OCD lacked age-associated increases in corpus callosum size observed in healthy children. In contrast, Carmona and colleagues (2007) reported a positive relationship between age and left caudate gray matter volume in children with OCD, but not in healthy children.

There is increasing evidence implicating the anterior cingulate in children and adults with OCD, including findings of two recent meta-analyses: one that found less gray matter in the bilateral anterior cingulate (Radua and Mataix-Cols, 2009) and another that found less gray matter in the left anterior cingulate (Rotge *et al*, 2009). Moreover, functional neuroimaging studies have consistently reported greater brain activity in the anterior cingulate in adult patients with OCD during symptom provocation (Adler *et al*, 2000; Breiter *et al*, 1996; Rauch *et al*, 1994), during executive functioning tasks in both pediatric (Huyser *et al*, 2010) and adult samples (van den Heuvel *et al*, 2005), and in

adults while at rest (Swedo *et al*, 1989). In addition, recent studies indicate altered functional connectivity of the anterior cingulate in pediatric OCD patients (eg, Fitzgerald *et al*, 2010). Prior DTI studies in adults have reported lower FA within the cingulate region (Cannistraro *et al*, 2007; Garibotto *et al*, 2010; Szeszko *et al*, 2005), thus highlighting potentially critical sampling differences in child *vs* adult patient populations (or possibly methodological differences) that may be strongly relevant to the interpretation of neurobiological models of OCD. Moreover, inconsistencies may be partially due to differences in medication and treatment histories of patients, given prior findings that reported higher FA in adults with OCD may be reduced through treatment with SSRIs (Yoo *et al*, 2007). Our findings thus extend this prior DTI work in adult OCD by implicating the white matter comprising the left cingulum in pediatric patients and providing a potential mechanism through which aberrant connectivity could relate to gray matter structural alterations.

The finding of higher FA in the corpus callosum among patients converges with empirical findings from structural (Fontenelle *et al*, 2011; Mac Master *et al*, 1999; Park *et al*, 2011; Rosenberg *et al*, 1997a) and diffusion tensor (Bora *et al*, 2011; Fontenelle *et al*, 2011; Nakamae *et al*, 2011; Saito *et al*, 2008) neuroimaging studies implicating abnormalities in this region in OCD. In particular, several studies noted abnormalities specifically in the splenium among patients. For example, Park and colleagues (2011) reported greater area and thickness in the caudal portion of the splenium in adults with OCD compared to healthy volunteers and Rosenberg and colleagues (1997a) reported greater splenium size in psychotropic drug-naïve pediatric patients with OCD that correlated with symptom severity. It is noteworthy that both human and animal studies indicate that the splenium interconnects the corpus callosum with posterior parietal and occipital cortices (de Lacoste *et al*, 1985; Jarbo *et al*, 2011; Pandya *et al*, 1971; Putnam *et al*, 2010), thus implicating abnormalities in posterior brain regions that could play a role in a wide range of OCD phenomenology involving visual processing, including increased attention towards irrelevant details (Koch *et al*, 2012).

Our findings also indicate higher FA in OCD patients in a posterior region of the left inferior fronto-occipital fasciculus. The inferior fronto-occipital fasciculus is one of the major efferent and afferent projections to the frontal lobes. It runs from the lateral portion of the frontal lobe to the posterior parietal and occipital cortex, transversing the external and extreme capsules of the basal ganglia along the way and is the only direct connection between the occipital and frontal lobes (Garibotto *et al*, 2010; Wakana *et al*, 2004). As Garibotto and colleagues (2010) point out the involvement of the parietal and occipital cortex in OCD, although less well established, could play a role in OCD clinical phenomenology, including distressful, intrusive imagery (Garibotto *et al*, 2010) and excessive visual attention to OCD-related themes.

Despite findings of white matter abnormalities in OCD, their functional correlates have not been well-investigated either in pediatric or adults cohorts. We found that higher FA in the left dorsal cingulum bundle in patients was correlated with better performance on two measures of response inhibition/cognitive control, the Stroop Color Word Test, and Trails B of the TMT. Importantly, this portion of the cingulum bundle is believed to play a critical role in cognitive functions, including response selection and cognitively demanding information-processing tasks. Specifically, the corresponding portion of the anterior cingulate is known to be activated by cognitively demanding tasks that involve stimulus–response selection despite competing streams of information (Bush *et al*, 2000), such as the Stroop Color Word Test and Trails B of the TMT. The finding that higher FA in this region was correlated with better performance among patients, in the absence of group differences in neuropsychological functioning on these tasks, is consistent with the hypothesis that these abnormalities may serve a compensatory mechanism, thus allowing patients to perform commensurate with healthy individuals in the face of competing and conflicting information. The finding that greater dorsal left dorsal cingulum bundle FA was associated with greater response inhibition and cognitive control may seem inconsistent with the finding that greater splenium FA was associated with greater OCD symptoms, but it is important to acknowledge that these findings were observed in different tracts that may have differing effects on OCD phenomenology.

The overall findings of this study implicate a pattern of higher FA in OCD in childhood and adolescence. Although we did not identify significant differences in FA between medicated and psychotropic drug-naïve patients, it is conceivable that FA differences are more robust in children and thus less affected by the relatively short treatment histories of children, and/or that higher FA in pediatric OCD is related to premature myelination and is not consistent across the lifespan. Investigation of subgroup analyses regarding medication effects revealed that there was a positive relationship between FA in the splenium and symptom severity in the subgroup of patients who were psychotropic drug-naïve, but not in the subgroup of patients who were being treated with SSRIs. In addition, we found that the effect of greater dorsal left dorsal cingulum bundle FA being associated with greater response inhibition and cognitive control was driven by the psychotropic drug-naïve patient group, and was less robust in medicated patients. It is, however, important to exercise caution in interpreting these results given the reduced statistical power of the small sample sizes and the fact that the correlations in medicated patients and psychotropic drug-naïve patients were not significantly different from each other. The pattern of results in this study suggests the possibility that medication may be subtly altering the course of white matter development in ways that affect the relationship between white matter and its clinical correlates. It is worth noting, however, that Zarei and colleagues reported that symptom severity correlated positively with greater FA in white matter tracts in various regions across their entire sample of adolescents with OCD, only a portion of whom were medication naïve. Longitudinal studies are necessary to determine how developmental aberrations in white matter in OCD may change with age and/or treatment history.

There were several limitations to this study that should be acknowledged. Our sample included both medicated and psychotropic drug-naïve patients and subgroup analyses limit our power to draw firm conclusions regarding the

potential effects of medications. The age range of our sample was broad, including both prepubescent children and adolescents and the effects of hormonal measures on white matter indices could not be investigated. We also note that higher FA could conceivably result from partial voluming in surrounding structures. Moreover, it should also be acknowledged that we did not employ cardiac gating, which could have potentially affected our findings particularly with regard to the corpus callosum, that smoothing could diminish accuracy regarding the localization of findings, and that our FA results could be affected by the use of linear registration algorithms (Smith *et al*, 2006).

In sum, we report a pattern of higher FA within white matter tracts of pediatric OCD patients suggesting that white matter abnormalities play a role in OCD pathogenesis early in the course of the disorder. Moreover, our findings suggest that higher FA in the cingulum bundle may be serving a compensatory mechanism, allowing pediatric patients to inhibit certain pre-potent responses and perform commensurate with healthy individuals in the face of competing and conflicting information.

ACKNOWLEDGEMENTS

This work was funded by the International Obsessive Compulsive Disorder Foundation, National Institute of Mental Health (R01 MH076995), an Advanced Center for Intervention and Services Research (P30 MH090590), and NSLIJ General Clinical Research Center (M01 RR018535). We thank the children and parents who participated in this study.

DISCLOSURE

Dr Gruner, Dr Vo, Dr Ikuta, Dr Mahon, Dr Peters, Dr Malhotra, Dr, Uluğ, and Dr Szeszko declare no conflicts of interest. Dr Gruner, Dr Vo, Dr Ikuta, Ms,. Mahon, Dr Peters, and Dr Uluğ declare that, except for income received from their primary employers, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest. Dr Szeszko has received compensation from Boehringer Ingelheim. Dr Malhotra has received compensation from Eli Lilly, Schering-Plough/Merck, Sunovion Pharmaceuticals, Genomind, and Shire.

REFERENCES

Abramovitch A, Dar R, Schweiger A, Hermesh H (2011). Neuropsychological impairments and their association with obsessive-compulsive symptom severity in obsessive-compulsive disorder. *Arch Clin Neuropsychol* **26**: 364–376.

Adler CM, McDonough-Ryan P, Sax KW, Holland SK, Arndt S, Strakowski SM (2000). fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. *J Psychiatr Res* **34**: 317–324.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington, DC.

Bannon S, Gonsalvez CJ, Croft RJ, Boyce PM (2002). Response inhibition deficits in obsessive-compulsive disorder. *Psychiatry Res* **110**: 165–174.

Beers SR, Rosenberg DR, Dick EL, Williams T, O'Hearn KM, Birmaher B *et al* (1999). Neuropsychological study of frontal lobe function in psychotropic-naive children with obsessive-compulsive disorder. *Am J Psychiatry* **156**: 777–779.

Bora E, Harrison BJ, Fornito A, Cocchi L, Pujol J, Fontenelle LF *et al* (2011). White matter microstructure in patients with obsessive-compulsive disorder. *J Psychiatry Neurosci* **36**: 42–46.

Breiter HC, Rauch SL, Kwong KK, Baker JR, Weisskoff RM, Kennedy DN *et al* (1996). Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Arch Gen Psychiatry* **53**: 595–606.

Bush G, Luu P, Posner MI (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* **4**: 215–222.

Cannistraro PA, Makris N, Howard JD, Wedig MM, Hodge SM, Wilhelm S *et al* (2007). A diffusion tensor imaging study of white matter in obsessive-compulsive disorder. *Depress Anxiety* **24**: 440–446.

Carmona S, Bassas N, Rovira M, Gispert JD, Soliva JC, Prado M *et al* (2007). Pediatric OCD structural brain deficits in conflict monitoring circuits: a voxel-based morphometry study. *Neurosci Lett* **421**: 218–223.

Chamberlain SR, Fineberg NA, Blackwell AD, Robbins TW, Sahakian BJ (2006). Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *Am J Psychiatry* **163**: 1282–1284.

Ciesielski KT, Rowland LM, Harris RJ, Kerwin AA, Reeve A, Knight JE (2011). Increased anterior brain activation to correct responses on high-conflict Stroop task in obsessive-compulsive disorder. *Clin Neurophysiol* **122**: 107–113.

de Lacoste MC, Kirkpatrick JB, Ross ED (1985). Topography of the human corpus callosum. *J Neuropathol Exp Neurol* **44**: 578–591.

den Braber A, van't Ent D, Boomsma DI, Cath DC, Veltman DJ, Thompson PM *et al* (2011). White matter differences in monozygotic twins discordant or concordant for obsessive-compulsive symptoms: a combined diffusion tensor imaging/voxel-based morphometry study. *Biol Psychiatry* **70**: 969–977.

Fitzgerald KD, Stern ER, Angstadt M, Nicholson-Muth KC, Maynor MR, Welsh RC *et al* (2010). Altered function and connectivity of the medial frontal cortex in pediatric obsessive-compulsive disorder. *Biol Psychiatry* **68**: 1039–1047.

Fontenelle LF, Bramati IE, Moll J, Medlowitcz MV, de Oliveira-Souza R, Tovar-Moll F (2011). White matter changes in ocd revealed by diffusion tensor imaging. *CNS Spectr* **16**: (e-pub ahead of print).

Fontenelle LF, Harrison BJ, Yucel M, Pujol J, Fujiwara H, Pantelis C (2009). Is there evidence of brain white-matter abnormalities in obsessive-compulsive disorder? A narrative review. *Top Magn Reson Imag* **20**: 291–298.

Friston KJ (1997). Testing for anatomical specified regional effects. *Hum Brain Mapp* **5**: 133–136.

Garibotto V, Scifo P, Gorini A, Alonso CR, Brambati S, Bellodi L *et al* (2010). Disorganization of anatomical connectivity in obsessive compulsive disorder: a multi-parameter diffusion tensor imaging study in a subpopulation of patients. *Neurobiol Dis* **37**: 468–476.

Harrison BJ, Soriano-Mas C, Pujol J, Ortiz H, Lopez-Sola M, Hernandez-Ribas R *et al* (2009). Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Arch Gen Psychiatry* **66**: 1189–1200.

Huyser C, Veltman DJ, de Haan E, Boer F (2009). Paediatric obsessive-compulsive disorder, a neurodevelopmental disorder? Evidence from neuroimaging. *Neurosci Biobehav Rev* **33**: 818–830.

Huyser C, Veltman DJ, Wolters LH, de Haan E, Boer F (2010). Functional magnetic resonance imaging during planning before and after cognitive–behavioral therapy in pediatric obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* **49**: 1238–1248, 1231–1235.

Insel TR (1992). Toward a neuroanatomy of obsessive-compulsive disorder. *Arch Gen Psychiatry* **49**: 739–744.

Jarbo K, Verstynen T, Schneider W (2011). *In vivo* quantification of global connectivity in the human corpus callosum. *NeuroImage* **59**: 1988–1996.

Jenkinson M, Bannister P, Brady M, Smith S (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage* **17**: 825–841.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P *et al* (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* **36**: 980–988.

Kiejna A, Rymaszewska J, Kantorska-Janiec M, Tokarski W (2002). Epidemiology of obsessive-compulsive disorder. *Psychiatr Pol* **36**: 539–548.

Koch K, Wagner G, Schachtzabel C, Schultz CC, Straube T, Gullmar D *et al* (2012). White matter structure and symptom dimensions in obsessive-compulsive disorder. *J Psychiatr Res* **46**: 264–270.

Krishna R, Udupa S, George CM, Kumar KJ, Viswanath B, Kandavel T *et al* (2011). Neuropsychological performance in OCD: a study in medication-naive patients. *Prog Neuropsychopharmacol Biol Psychiatry* **35**: 1969–1976.

Li F, Huang X, Yang Y, Li B, Wu Q, Zhang T *et al* (2011). Microstructural brain abnormalities in patients with obsessive-compulsive disorder: diffusion-tensor MR imaging study at 3.0 T. *Radiology* **260**: 216–223.

Mac Master FP, Keshavan MS, Dick EL, Rosenberg DR (1999). Corpus callosal signal intensity in treatment-naive pediatric obsessive compulsive disorders. *Prog Neuropsychopharmacol Biol Psychiatry* **23**: 601–612.

Maia TV, Cooney RE, Peterson BS (2008). The neural bases of obsessive-compulsive disorder in children and adults. *Dev Psychopathol* **20**: 1251–1283.

Menzies L, Williams GB, Chamberlain SR, Ooi C, Fineberg N, Suckling J *et al* (2008). White matter abnormalities in patients with obsessive-compulsive disorder and their first-degree relatives. *Am J Psychiatry* **165**: 1308–1315.

Nakamae T, Narumoto J, Sakai Y, Nishida S, Yamada K, Nishimura T *et al* (2011). Diffusion tensor imaging and tract-based spatial statistics in obsessive-compulsive disorder. *J Psychiatr Res* **45**: 687–690.

Pandya DN, Karol EA, Heilbronn D (1971). The topographical distribution of interhemispheric projections in the corpus callosum of the rhesus monkey. *Brain Res* **32**: 31–43.

Park HY, Park JS, Kim SH, Jang JH, Jung WH, Choi JS *et al* (2011). Midsagittal structural differences and sexual dimorphism of the corpus callosum in obsessive-compulsive disorder. *Psychiatry Res* **192**: 147–153.

Pauls DL, Alsobrook II JP, Goodman W, Rasmussen S, Leckman JF (1995). A family study of obsessive-compulsive disorder. *Am J Psychiatry* **152**: 76–84.

Penades R, Catalan R, Rubia K, Andres S, Salamero M, Gasto C (2007). Impaired response inhibition in obsessive compulsive disorder. *Eur Psychiatry* **22**: 404–410.

Putnam MC, Steven MS, Doron KW, Riggall AC, Gazzaniga MS (2010). Cortical projection topography of the human splenium: hemispheric asymmetry and individual differences. *J Cogn Neurosci* **22**: 1662–1669.

Radua J, Mataix-Cols D (2009). Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *Br J Psychiatry* **195**: 393–402.

Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR *et al* (1994). Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Arch Gen Psychiatry* **51**: 62–70.

Robinson D, Wu H, Munne RA, Ashtari M, Alvir JM, Lerner G *et al* (1995). Reduced caudate nucleus volume in obsessive-compulsive disorder. *Arch Gen Psychiatry* **52**: 393–398.

Rosenberg DR, Keshavan MS (1998). A.E. Bennett Research Award. Toward a neurodevelopmental model of obsessive-compulsive disorder. *Biol Psychiatry* **43**: 623–640.

Rosenberg DR, Keshavan MS, Dick EL, Bagwell WW, MacMaster FP, Birmaher B (1997a). Corpus callosal morphology in treatment-naive pediatric obsessive compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* **21**: 1269–1283.

Rosenberg DR, Keshavan MS, O'Hearn KM, Dick EL, Bagwell WW, Seymour AB *et al* (1997b). Fronto-striatal measurement of treatment-naïve pediatric obsessive compulsive disorder. *Arch Gen Psychiatry* **54**: 824–830.

Rotge JY, Guehl D, Dilharreguy B, Tignol J, Bioulac B, Allard M *et al* (2009). Meta-analysis of brain volume changes in obsessive-compulsive disorder. *Biol Psychiatry* **65**: 75–83.

Saito Y, Nobuhara K, Okugawa G, Takase K, Sugimoto T, Horiuchi M *et al* (2008). Corpus callosum in patients with obsessive-compulsive disorder: diffusion-tensor imaging study. *Radiology* **246**: 536–542.

Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK *et al* (1997). Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry* **36**: 844–852.

Smith SM (2002). Fast robust automated brain extraction. *Hum Brain Mapp* **17**: 143–155.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE *et al* (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage* **31**: 1487–1505.

Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *NeuroImage* **20**: 1714–1722.

Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *NeuroImage* **17**: 1429–1436.

Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH *et al* (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage* **26**: 132–140.

Swedo SE, Schapiro MB, Grady CL, Cheslow DL, Leonard HL, Kumar A *et al* (1989). Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Arch Gen Psychiatry* **46**: 518–523.

Szeszko PR, Ardekani BA, Ashtari M, Malhotra AK, Robinson DG, Bilder RM *et al* (2005). White matter abnormalities in obsessive-compulsive disorder: a diffusion tensor imaging study. *Arch Gen Psychiatry* **62**: 782–790.

Szeszko PR, MacMillan S, McMeniman M, Chen S, Baribault K, Lim KO *et al* (2004). Brain structural abnormalities in psychotropic drug-naïve pediatric patients with obsessive-compulsive disorder. *Am J Psychiatry* **161**: 1049–1056.

Szeszko PR, Robinson D, Alvir JM, Bilder RM, Lencz T, Ashtari M *et al* (1999). Orbital frontal reductions in obsessive-compulsive disorder. *Arch Gen Psychiatry* **56**: 913–919.

Uluğ A, Argyelan M, Eidelberg D (2009). Early registration of diffusion tensor images for group tractography (abstract). *Magma* **22**(Suppl 1): 107.

van den Heuvel OA, Veltman DJ, Groenewegen HJ, Cath DC, van Balkom AJ, van Hartskamp J *et al* (2005). Frontal–striatal

dysfunction during planning in obsessive-compulsive disorder. *Arch Gen Psychiatry* **62**: 301–309.

Vo A, Argyelen M, Eidelberg D, Uluğ AM (2012). Early registration of diffusion tensor images for group tractography of dystonia patients. *J Magnet Reson Imag* (in press).

Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S (2004). Fiber tract-based atlas of human white matter anatomy. *Radiology* **230**: 77–87.

Yoo SY, Jang JH, Shin YW, Kim DJ, Park HJ, Moon WJ *et al* (2007). White matter abnormalities in drug-naive patients with obsessive-compulsive disorder: a diffusion tensor study before and after citalopram treatment. *Acta Psychiatr Scand* **116**: 211–219.

Zarei M, Mataix-Cols D, Heyman I, Hough M, Doherty J, Burge L *et al* (2011). Changes in gray matter volume and white matter microstructure in adolescents with obsessive-compulsive disorder. *Biol Psychiatry* **70**: 1083–1090.