

White Matter Abnormalities in Obsessive-compulsive Disorder

A Diffusion Tensor Imaging Study

Philip R. Szeszko, PhD; Babak A. Ardekani, PhD; Manzar Ashtari, PhD; Anil K. Malhotra, MD; Delbert G. Robinson, MD; Robert M. Bilder, PhD; Kelvin O. Lim, MD

Context: Several neurobiological models of obsessive-compulsive disorder (OCD) posit a primary role for dysfunction of the anterior cingulate gyrus. Both functional and structural neuroimaging studies have implicated anterior cingulate gray matter abnormalities in the pathophysiology of OCD, but there has been little investigation of the anterior cingulate white matter in this disorder.

Objective: To test the hypothesis that patients with OCD have abnormal white matter microstructure in the anterior cingulate gyrus compared with healthy volunteers as inferred from diffusion tensor imaging. Additional analyses examined group differences in white matter integrity across the entire brain.

Design, Setting, and Participants: Fifteen patients with a DSM-IV diagnosis of OCD and 15 healthy volunteers matched for age, sex, and handedness underwent diffusion tensor imaging and structural magnetic resonance imaging examinations. Fractional anisotropy (FA), a robust intravoxel measure of water self-diffusion, was compared between groups on a voxel-by-voxel basis in the anterior cingulate white matter after standardization in Talairach space.

Main Outcome Measures: Clinical ratings of symptom severity (ie, Yale-Brown Obsessive-Compulsive Scale) and FA.

Results: Compared with healthy volunteers, patients demonstrated significantly lower FA bilaterally in 3 areas of the anterior cingulate gyrus white matter. Additional analyses conducted across the rest of the brain white matter revealed lower FA bilaterally in the parietal region (supramarginal gyri), right posterior cingulate gyrus, and left occipital lobe (lingual gyrus). No areas of significantly higher FA were observed in patients compared with healthy volunteers. Lower FA in the parietal region correlated significantly with higher Yale-Brown Obsessive-Compulsive Scale scores.

Conclusions: These preliminary findings provide evidence of an abnormality that involves the anterior cingulate white matter in the pathogenesis of OCD and are consistent with neurobiological models that posit a defect in connectivity in the anterior cingulate basal ganglia-thalamocortical circuit. White matter abnormalities in other brain regions may also be implicated in the neurobiology of OCD.

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OBSESSIVE-COMPULSIVE DISORDER (OCD) has a prevalence rate of 2% to 3% and is often chronically disabling, with concomitant impairments in interpersonal and occupational functioning.¹ Studies that investigate the pathophysiology of OCD are therefore of considerable importance, because they may ultimately inform treatment strategies. Several models of OCD neurobiology suggest that the basal ganglia and by extension the striatal-thalamic and thalamocortical circuits play a role in the disorder but differ in which regions are

primarily important.²⁻⁵ In general, the model of frontostriatal-thalamic involvement in OCD has been generally well supported by magnetic resonance imaging (MRI) and functional neuroimaging studies,⁶⁻¹⁰ although some contradictory reports have been reported for the caudate nucleus.¹¹⁻¹³ Important questions remain, however, regarding the potential role of structural and functional abnormalities in other brain regions hypothesized to play a key role in the neurobiology of OCD.

The anterior cingulate gyrus may have particular relevance for the neurobiology of OCD. Functional neuroimaging stud-

Author Affiliations are listed at the end of this article.

ies report hypermetabolism in the cingulate gyrus during symptom provocation^{6,14,15} and while at rest,¹⁶ which decreases after pharmacotherapy with a serotonin reuptake inhibitor.¹⁷ In addition, a defect in anterior cingulate metabolic activity has been linked to abnormal neuropsychological functioning in OCD.^{18,19} Cingulate hyperactivity could play a role in abnormal conflict detection as part of an overactive action-monitoring system in OCD²⁰ and conceivably activate an anterior cingulate basal ganglia–thalamocortical circuit without concomitant sensory input or motivation to perform a behavior, thus causing it to be completed compulsively.²

Consistent with studies that implicate anterior cingulate metabolic hyperactivity in OCD are the results from 2 independent structural neuroimaging studies^{8,21} that report more anterior cingulate gray matter in patients with OCD compared with healthy volunteers. More anterior cingulate gray matter in patients could represent the neuroanatomical substrate for the increased metabolic activity observed in functional neuroimaging studies. In contrast to studies that examined the anterior cingulate gray matter in OCD, there has been little investigation of the anterior cingulate white matter. In our prior study,⁸ we did not observe anterior cingulate white matter volumetric abnormalities at the gross anatomical level in patients with OCD. Because the anterior cingulate white matter forms the physical foundation for connectivity to other cortical²² and subcortical²³ brain regions implicated in the pathophysiology of OCD, however, it has strong relevance to neurobiological models of the disorder. It is therefore plausible that an abnormality that involves the anterior cingulate white matter plays a role in the neurobiology of OCD, albeit at the microstructural level.

Diffusion tensor imaging (DTI) represents an *in vivo* MRI technique that can be used to examine white matter microstructure in humans. This technique permits the quantification of the directionality and coherence of water self-diffusion. Tissues with highly regular fibers have high anisotropy, whereas those with less regular fibers, such as gray matter, have low anisotropy. Measures of water self-diffusion appear to have implications for understanding the anatomical organization of white matter and represent an important tool for *in vivo* mapping of anatomical connectivity in humans.^{24,25} Diffusion tensor imaging has been used to examine white matter microstructure in schizophrenia,^{26–31} but its use in other neuropsychiatric disorders has been limited. Several studies^{32–35} reported white matter volumetric alterations in OCD at the gross anatomical level using MRI volumetry, suggesting that DTI could be useful in further clarifying the potential role of white matter abnormalities in the neurobiology of the disorder.

In this study we investigated potential white matter abnormalities in patients with OCD compared with healthy volunteers as inferred from DTI. We hypothesized that patients with OCD would differ in integrity of anterior cingulate white matter microstructure compared with healthy volunteers. Secondary analyses investigated white matter across the entire brain.

Table 1. Sample and Clinical Characteristics

Characteristic	Patients With OCD (n = 15)	Healthy Comparison Subjects (n = 15)
Age, mean ± SD, y	38.5 ± 10.9	38.5 ± 11.8
Sex, No. M/F	10/5	10/5
Handedness, No. R/L	9/6	9/6
Race, No. white/African American/Indian	14/1/0	12/1/2
Education, mean ± SD, y	14.8 ± 1.8	15.9 ± 1.8
Age at onset, mean ± SD, y	16.9 ± 7.7	
Total Y-BOCS score, mean ± SD,	25.9 ± 4.4	
Obsessive subscale	12.4 ± 2.8	
Compulsive subscale	13.5 ± 2.0	
HARS score, mean ± SD	12.1 ± 8.9	
HDRS score, mean ± SD	13.9 ± 4.9	

Abbreviations: HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; L, left; OCD, obsessive-compulsive disorder; R, right; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

METHODS

STUDY PARTICIPANTS

Fifteen adult outpatients with a *DSM-IV* diagnosis of OCD and 15 healthy volunteers matched for age, sex, and handedness participated in this study (see **Table 1** for sample characteristics). Patients were recruited through the OCD Clinic at The Zucker Hillside Hospital in Glen Oaks, NY. There is no overlap between this sample and the sample in our previous studies.^{12,36} All patients were interviewed by a licensed clinical psychologist (P.R.S.) and diagnosed using the Structured Clinical Interview for Axis I *DSM-IV* Disorders—Patient Edition.³⁷ Final diagnoses were established using all available clinical material during a consensus conference that involved 2 board-certified adult psychiatrists and a psychologist. All patients had a primary diagnosis of OCD. Four patients had a comorbid major depressive disorder (3 recurrent [1 mild, 2 moderate] and 1 with a single episode, severe, without psychotic features), 1 had panic disorder with agoraphobia, 2 had social phobia, 1 had an eating disorder not otherwise specified, 1 had depressive disorder not otherwise specified, and 9 had OCD as their sole diagnosis. All but 3 patients were receiving medications for their OCD at the time of the MRI examination; these medications included paroxetine hydrochloride, 2 patients; fluvoxamine maleate, 3; fluoxetine hydrochloride, 3; sertraline, 1; olanzapine, 1; quetiapine fumarate, 4; divalproex sodium EC, 1; lamotrigine, 1; clonazepam, 1; clomipramine hydrochloride, 1; and venlafaxine hydrochloride, 1. We classified patients according to the 5 clinical dimensions defined by Mataix-Cols et al.³⁸ Using these criteria, we found that patients' predominant obsessions/compulsions were as follows: symmetry/ordering, 1; hoarding, 1; contamination/cleaning, 5; aggressive/checking, 6; and sexual/religious, 2. Mean age at onset was 16.8 years (SD, 7.4 years).

Exclusion criteria for patients and healthy comparison subjects included (1) cardiac pacemakers or other metallic implants or artifacts; (2) significant medical illness, including neurologic (including Gilles de la Tourette, Huntington disease, Parkinson disease, encephalitis, strokes, aneurysms, tumors, central nervous system infections, degenerative brain diseases, or trauma), pulmonary, cardiac, renal, hepatic, endocrine, or metabolic (including dehydration) disorders; (3) prior psychosurgery; (4) current or past *DSM-IV* substance abuse or dependence; (5) *DSM-IV* dementia, delirium, schizophrenia,

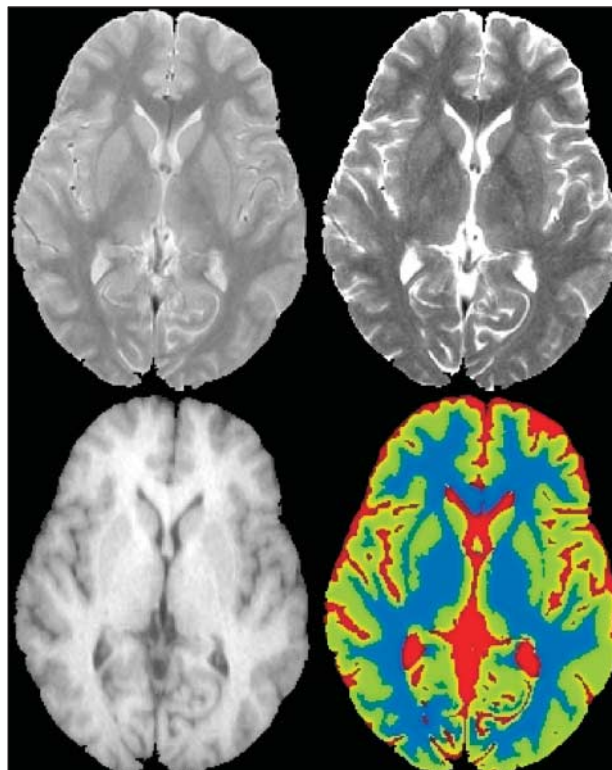


Figure 1. Three-channel brain segmentation.

schizoaffective disorder, delusional disorder, brief reactive psychosis, or psychotic disorder not otherwise specified; (6) *DSM-IV* mental retardation based on clinical interview and psychosocial history; and (7) pregnancy. There was no history of psychiatric illness in healthy comparison subjects as determined from the Structured Clinical Interview for *DSM-IV* TR Axis I Disorders–Non-patient Edition³⁹ or in any first-degree relative. All procedures were approved by the North Shore–Long Island Jewish Health System Institutional Review Board, and written informed consent was obtained from all participants.

CLINICAL ASSESSMENTS

All subjects were administered the Yale-Brown Obsessive Compulsive Scale (Y-BOCS),⁴⁰ the 17-item Hamilton Depression Rating Scale,⁴¹ and the Hamilton Anxiety Rating Scale.⁴²

HANDEDNESS

Classification of handedness was based on a modified version of the Edinburgh Inventory, which consisted of 20 items.⁴³ The total number of right (R)- and left (L)-hand items were scored, and the laterality quotient was computed according to the following formula: $(\text{Total R} - \text{total L}) / (\text{total R} + \text{total L})$. This yielded a total laterality quotient for each subject that ranged from +1.00 (totally dextral) to –1.00 (totally nondextral). Subjects with a laterality quotient greater than 0.70 were classified as dextral and the rest as nondextral.⁴⁴

MRI PROCEDURES

The MRI examinations were conducted at the Long Island Jewish Medical Center on a 1.5-T whole-body superconducting system (General Electric, Milwaukee, Wis). All scans were reviewed by a neuroradiologist and a member of the research team. Any scan with significant artifacts was performed again. We

minimized movement by stabilizing the head with cushions and tape before scanning. A total of 26 DTI volumes were obtained from each subject and included 25 volumes with diffusion gradients applied along 25 nonparallel directions ($b = 1000 \text{ s/mm}^2$; number of excitations = 2) and 1 volume without diffusion weighting ($b = 0$; number of excitations = 2). Each volume consisted of 23 contiguous axial slices (slice thickness = 5 mm) acquired parallel to the anteroposterior commissural line using a ramp sampled, spin-echo, single shot echo-planar imaging method (repetition time [TR] = 10 seconds, echo time [TE] = 86.7 milliseconds, matrix = 128×128 , field of view [FOV] = 22 cm). Using the DTI data, diffusion tensor maps and, subsequently, fractional anisotropy (FA) maps were computed. We did not find any evidence of systematic ghosting on the DTIs as determined from a quantitative in-house quality control program and from visual inspection of images.

To provide a high-resolution anatomical reference, 124 contiguous coronal images (slice thickness = 1.5 mm) were acquired through the whole head using a 3-dimensional fast spoiled gradient (SPGR) sequence with inversion recovery preparation (TR = 10.1 milliseconds, TE = 4.3 milliseconds, inversion time = 600 milliseconds, FOV = 22 cm, matrix = 256×256), producing nominal in-plane resolution of $0.86 \times 0.86 \text{ mm}$. In addition, an oblique axial fast spin echo scan (TR = 4 seconds, TE = 20 milliseconds/100 milliseconds, FOV = 22 cm, matrix = 256×256) was acquired at the same slice positions as the DTIs and provided contiguous 5-mm-thick proton density (PD) and T2-weighted (T2) images. The fast spin echo PD and T2 volumes were used to reduce spatial distortion on the DTIs and for image segmentation.

IMAGE PROCESSING

Image processing was conducted with 3 image registration steps based on previously published methods.^{28,45–47} First, nonbrain regions were automatically removed from the SPGR volumes using the Brain Extraction Tool of the FSL software package.⁴⁸ In some cases, the Brain Extraction Tool results were improved manually using the MEDx software package.⁴⁹ Using the cropped SPGR volumes, the total intracranial volume for each subject was computed. The subject with the median intracranial volume was transformed into Talairach space⁵⁰ using the AFNI software package⁵¹ and used as the target (template) image. The cropped SPGR volumes from the other subjects were matched to the target volume with an in-house nonlinear registration software program.^{45,46} This algorithm is based on previously published methods^{32–54} with additional features for computational efficiency.

Second, for each subject, the cropped SPGR volume was registered to their fast spin echo T2/PD volumes.⁴⁷ This yielded a resliced SPGR volume with the same orientation and voxel size as the T2/PD volumes. The resliced SPGR volume of each subject was used as a mask to delete nonbrain regions from the T2/PD volumes of the same subject. The resulting image sets (ie, cropped T2/PD and cropped and resliced SPGR) were used as 3 channels in the FSL-FAST software package to create a white matter mask for each subject after segmentation of the brain into white matter, gray matter, and cerebrospinal fluid (**Figure 1**). Individuals' white matter masks were also transformed into Talairach space. The transformed white matter masks were averaged and thresholded at 40% to obtain a white matter mask for the group.²⁸

Third, to correct for the spatial distortion of the DTI echo-planar imaging data, the $b = 0$ DTI volume was registered to the cropped T2 volume using an in-house nonlinear registration program.^{45,46} **Figure 2** shows a slice from the original and distortion-corrected $b = 0$ DTI.

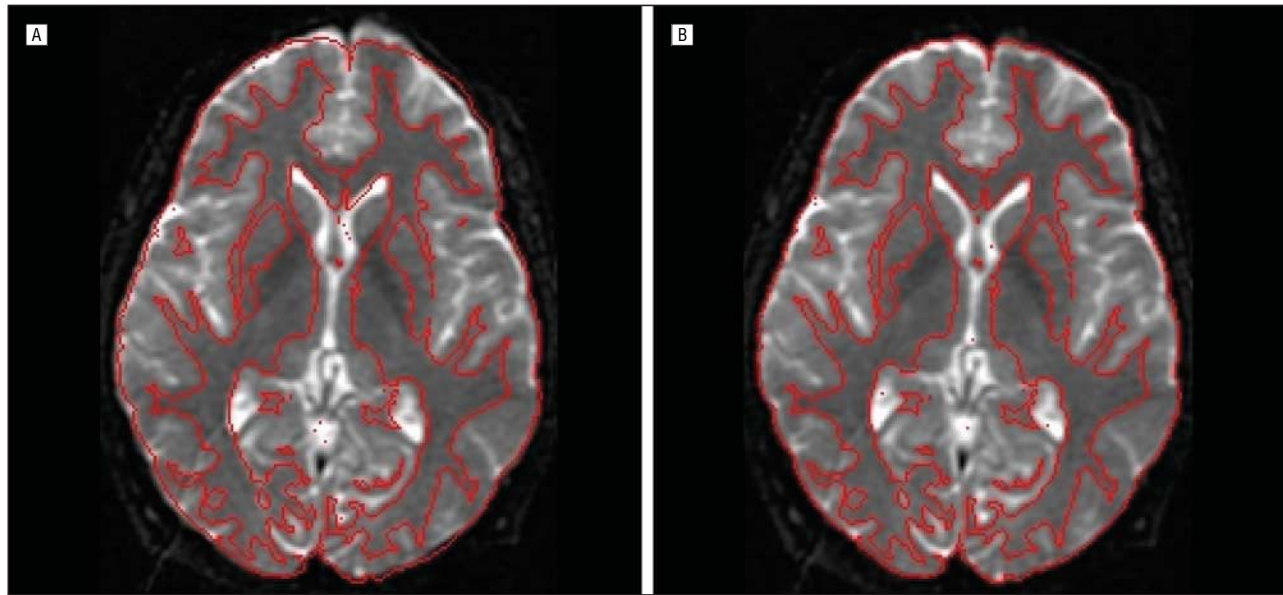


Figure 2. White matter boundaries superimposed on an original $b=0$ diffusion tensor imaging slice (A) and on the distortion-corrected diffusion tensor imaging slice (B).

An FA map was computed from the DTI volumes for each subject following derivation of the eigenvalues of the diffusion tensor matrix for each voxel using methods described by Basser and Pierpaoli⁵⁵ and Basser.⁵⁶ The FA map of each subject was transformed into Talairach space by combining the 3 transformations: (1) intersubject nonlinear deformation of the SPGR volume to the target volume; (2) intrasubject linear rigid-body transformation of the SPGR volume to the T2/PD volume; and (3) nonlinear intrasubject registration of the DTI to the T2 volume for distortion correction. The resulting transformation was then applied to the original FA map by a single interpolation operation. Thus, we obtained 30 FA maps (15 patients and 15 healthy volunteers) of matrix size $161 \times 191 \times 151$ and voxel size $1 \times 1 \times 1 \text{ mm}^3$ in common Talairach space. Both the registered FA and white matter images were smoothed with a 3-dimensional isotropic Gaussian kernel with $\sigma=3 \text{ mm}$.

An operator manually traced the anterior cingulate gyrus region of interest on the target SPGR volume according to methods described previously.^{8,57,58} Briefly, the boundaries of the anterior cingulate gyrus were (anterior, posterior, ventral, dorsal) tip of the cingulate sulcus, connection of the superior and precentral sulci, callosal sulcus, and cingulate sulcus. Voxels within the anterior cingulate were classified as either white or gray matter using the information from the segmented white matter maps of all subjects, which had been transformed into Talairach space.

STATISTICAL ANALYSES

Group differences in demographic variables were examined using independent groups t tests. The χ^2 tests were used to examine differences in joint classifications of discrete variables. Two-sample t tests were performed at each voxel on the FA values within the anterior cingulate white matter between patients and controls. Voxels that had a t statistic greater than 3.05 ($P < .005$; 2-tailed) and were part of a spatially contiguous cluster with a size of 20 voxels or greater in the anterior cingulate white matter were considered to have significantly different FA in patients compared with healthy volunteers. We chose this combination of α level and cluster size to maintain a balance between type I and type II error rates given possible inflation of type I error due to multiple comparisons but also acknowl-

edging that tests at nearby voxels have strong interdependencies.^{59,60} Additional analyses examined group differences in white matter integrity across the entire brain using the same α level and spatial extent threshold. Pearson product-moment correlations were used to examine the relationship between FA and clinical measures.

RESULTS

Patients with OCD and healthy comparison subjects did not differ significantly in distributions of age, sex, handedness, race, or education (Table 1). An illustration of the intersubject registrations of the FA maps for patients and healthy comparison subjects is provided in **Figure 3**. Significantly decreased FA in patients compared with healthy volunteers was observed in 3 noncontiguous areas of the anterior cingulate gyrus white matter. These regions are illustrated in **Figure 4** and **Figure 5**, and Talairach coordinates are provided in **Table 2**. To rule out the effects of depression on these findings, we compared patients who had OCD without a comorbid diagnosis of depression with the group of healthy volunteers and found significantly ($P < .05$) decreased FA among patients compared with healthy volunteers in each of the 3 regions as in the original analysis.

Examination of the rest of the brain white matter revealed several additional areas of decreased FA in patients that included the right posterior cingulate gyrus, bilateral supramarginal gyri within the parietal lobes, and the left lingual gyrus within the occipital lobe. The corresponding Talairach coordinates for these regions are provided in Table 2. No areas of significantly higher FA were observed in any part of the brain white matter in patients compared with healthy volunteers.

We also examined the clinical correlates of lower FA within the patient group. To minimize type I error in these analyses, we computed an average measure of FA for the 3 regions within and 4 regions outside the anterior cin-

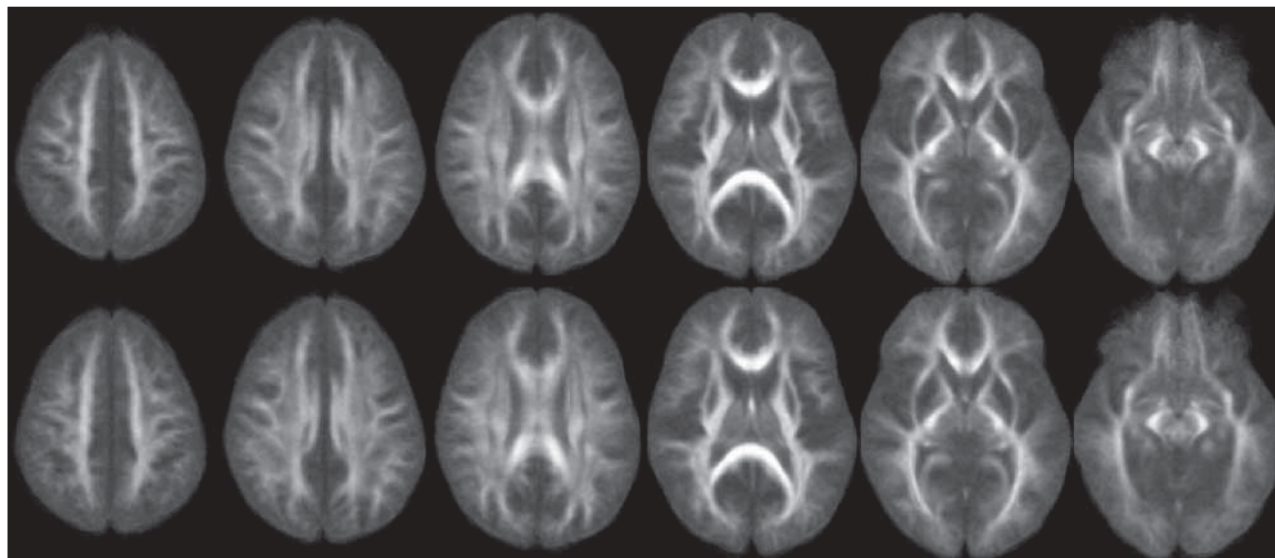


Figure 3. Average fractional anisotropic images for patients (top row) and healthy comparison subjects (bottom row). Images from left to right correspond to 45, 35, 25, 15, and 5 mm above the anteroposterior plane and -5 mm below the anteroposterior plane.

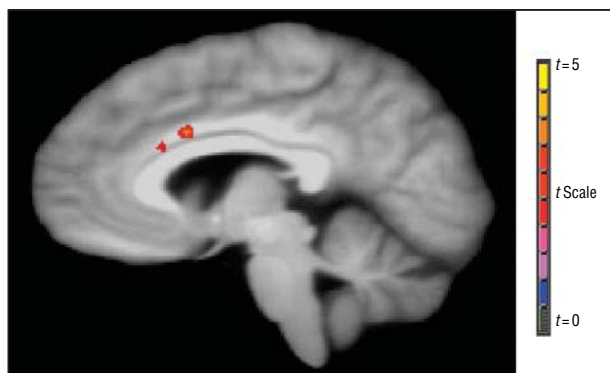


Figure 4. Fractional anisotropic reductions in patients with obsessive-compulsive disorder vs healthy comparison subjects in the left hemisphere anterior cingulate white matter rendered onto a T1-weighted image (threshold $t=3.05$).

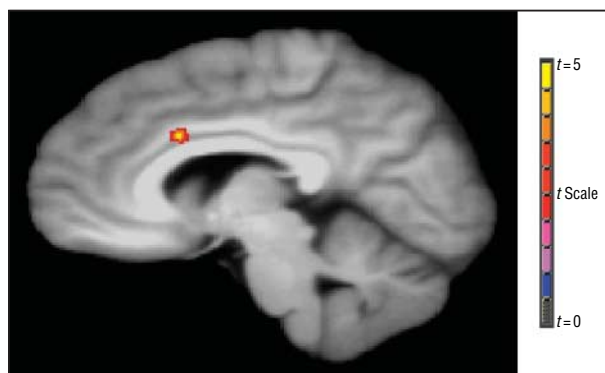


Figure 5. Fractional anisotropic reductions in patients with obsessive-compulsive disorder vs healthy comparison subjects in the right hemisphere anterior cingulate white matter rendered onto a T1-weighted image (threshold $t=3.05$).

gulate that differed significantly between the 2 groups. These analyses revealed that Y-BOCS scores correlated significantly with the average measure of FA across the 4 regions outside the anterior cingulate ($r=-0.59$, $df=15$, $P=.02$) but not with the average measure of FA across the 3 regions within the anterior cingulate ($P>.05$). Investigation of the regions outside the anterior cingulate revealed that greater Y-BOCS scores correlated significantly with lower FA in the parietal lobe white matter bilaterally ($r=-0.58$, $df=15$, $P=.02$). Lower parietal lobe FA correlated significantly with the obsession subtotal ($r=-0.60$, $df=15$, $P=.02$), although comparable but non-significant effects were observed for the compulsion subtotal ($r=-0.44$, $df=15$, $P=.10$). None of the FA measures correlated significantly with either the Hamilton anxiety or depression scores ($P>.05$).

COMMENT

These preliminary findings provide evidence of abnormal white matter microstructure in OCD as inferred from

DTI. Specifically, we found lower FA bilaterally within the anterior cingulate gyrus white matter in patients compared with healthy volunteers. These findings converge with prior studies that implicate functional^{16,14,16,17} and structural^{8,21} abnormalities in the anterior cingulate gray matter in OCD and are consistent with neurobiological models of OCD that posit a defect in the anterior cingulate basal ganglia–thalamocortical circuit.² White matter microstructural alterations, as assessed via DTI, may reflect abnormalities in the myelin sheath and/or directional coherence of fiber tracts.

Few studies have examined the brain white matter in OCD despite its relevance to models of abnormal brain circuitry that posit a defect in connectivity. Several studies reported white matter structural abnormalities in OCD as assessed via MRI volumetry. Rosenberg et al³² found that all of the corpus callosum regions they measured (except for the isthmus) were significantly larger in patients with OCD than in controls. In a subsequent report,³³ these authors presented evidence that developmental abnormalities in genu size among patients with OCD may arise from abnormalities in myelination. They

Table 2. Areas of Decreased Fractional Anisotropy in Patients With Obsessive-compulsive Disease Compared With Healthy Volunteers

Talairach Coordinates*			t Value	df	Cluster Size	P Value	Anatomical Region
x (+Right)	y (+Anterior)	z (Superior)					
-6	12	32	4.15	28	48	<.005	Anterior cingulate
6	14	31	4.70	28	111	<.001	Anterior cingulate
-6	22	27	3.48	28	42	<.005	Anterior cingulate
5	-23	38	3.74	28	28	<.005	Posterior cingulate
37	-52	35	3.42	28	23	<.005	Supramarginal gyrus
-46	-40	35	3.44	28	26	<.005	Supramarginal gyrus
-17	-80	0	3.77	28	63	<.005	Lingual gyrus

*Talairach coordinates represent the centroid of the region.

interpreted their findings of increased genu myelination in patients as altering signal transduction and the function of ventral prefrontal-striatal association circuits. In another study, Jenike et al³⁴ reported that, compared with healthy controls, patients with OCD had significantly less total white matter across the brain. That report extended prior findings of decreased posterior white matter in a separate sample of patients by Breiter and colleagues.³⁵ Findings of white matter abnormalities in OCD may represent evidence of impaired connectivity and contribute to the pathogenesis of the disorder. In a previous study,⁸ no group differences occurred in anterior cingulate white matter volume between psychotropic drug-naïve patients with OCD and healthy comparison subjects. Those findings, in combination with the present results, suggest that DTI may be more sensitive in detecting white matter abnormalities than MRI volumetry. One caveat, however, is that anterior cingulate microstructural alterations were not widespread in the present study, and thus, it is possible that localized abnormalities in anterior cingulate white matter volume may have previously gone undetected in patients with OCD.⁸

Our findings are consistent with prior studies that demonstrated the involvement of the anterior cingulate in several functions relevant to the phenomenology of OCD. For example, the anterior cingulate plays a role in monitoring and resolving conflict during information processing,⁶¹ and such functions may be disrupted in OCD in the context of an overactive action-monitoring system.^{20,62} Moreover, the anterior cingulate has been linked with contextual fear conditioning⁶³ and reward expectancy,⁶⁴ both of which are highly relevant to behavioral theories regarding negative reinforcement in OCD. Also, neuropsychological deficits observed on tasks of response inhibition and self-guided spontaneous behavior may also be relevant to OCD and have been linked with dysfunction of the anterior cingulate prefrontal circuit.⁶⁵

Interestingly, anterior cingulate white matter abnormalities observed in the present study were in close proximity to the site where cingulotomies are performed for the treatment of severe, treatment-refractory OCD.⁶⁶ An abnormality that involves the white matter in the anterior cingulate could contribute to the pathogenesis of OCD through aberrant connectivity with other cortical and sub-

cortical brain regions with which it maintains connections.^{23,67} This possibility has received some support from a neurosurgical study⁶⁶ that identified caudate nucleus volume reductions, which correlated significantly with total cingulate lesion volume, in patients with OCD who received cingulotomies.

An abnormality in white matter microstructure was also identified in the posterior cingulate gyrus. Given the strong neuroanatomical connections between the posterior cingulate and other brain regions implicated in the pathophysiology of OCD, including the anterior cingulate⁶⁸ and orbital frontal region,⁶⁹ a defect in connectivity that involves the posterior cingulate may also play a role in the neurobiology of OCD. Although several models of OCD neurobiology emphasize abnormalities in the anterior cingulate, some modest functional neuroimaging evidence exists of dysfunction of the posterior cingulate in OCD.^{9,70} In that regard, our findings converge with the findings of Rauch et al,⁷¹ who reported that preoperative relative regional cerebral metabolic rates for glucose within the right posterior cingulate cortex correlated significantly with subsequent reduction in symptom severity after anterior cingulotomy. Similarly, a structural neuroimaging study⁷² reported a volumetric reduction in the posterior cingulate when comparing postoperative to preoperative MRI data.

This study also identified several other brain white matter regions in which patients had lower FA compared with healthy subjects, including the white matter of the supramarginal gyri within the parietal lobes, which correlated inversely with OCD symptom severity. These findings thus raise the possibility that parietal lobe white matter microstructure plays a role in mediating obsessions and compulsive behavior, possibly through disruption of cortical-cortical and/or cortical-subcortical connectivity with other brain regions implicated in the pathophysiology of OCD. This possibility would be broadly consistent with functional neuroimaging studies that identify parietal lobe dysfunction in OCD⁷³⁻⁷⁵ and event-related potential and neuropsychological studies, implicating a defect in striatofrontoparietal connectivity.^{76,77} Our findings also converge with magnetoencephalographic studies⁷⁸ that report paroxysmal rhythmic activity in the supramarginal gyri of patients with OCD and a positron emission tomographic study⁷⁹ that demon-

strated that cerebral glucose metabolism in the parietal region correlated with OCD severity. The supramarginal gyrus has been linked with several functions relevant to the phenomenology of OCD, including dynamic aspects of executive functioning,⁸⁰ set shifting,⁸¹ goal setting in planned behavior,⁸² inhibition,⁸³ and short-term action planning.⁸⁴

Decreased FA within the white matter of the lingual gyrus was also observed in patients compared with healthy volunteers. Although the lingual gyrus is known to play a role in mediating visual word processing and analyzing complex features of visual forms,⁸⁵ other data suggest that it may function more broadly. Specifically, several studies⁸⁶⁻⁸⁸ reported extrastriate activity, including in the lingual gyrus, during viewing of pleasant and unpleasant stimuli, supporting a role for this part of the brain in processing emotionally charged visual stimuli. Such activations could not be attributed to increased visual stimulation as a result of eye movements.⁸⁶ Similarly, Critchley et al⁸⁹ identified an association between lingual gyrus neural activity and the generation and representation of somatic arousal using a skin conductance paradigm. These authors interpreted their findings as providing evidence that early visual processing and concomitant modulation through arousal are adaptive for an organism to facilitate processing of relevant sensory information. This interpretation might have relevance for anxiety disorders such as OCD where an abnormality in arousal and sensory processing is considered important to phenomenology.⁹⁰

We did not observe significant group differences in white matter integrity in other brain regions implicated in the pathophysiology of OCD, including the orbital frontal lobe and striatal regions. The lack of such findings may be related to the heterogeneous nature of OCD, sample size issues (if the effects in these regions are of a smaller magnitude compared with the anterior cingulate), and possible differences in the normal directionality of white matter fibers in those regions. Moreover, we could not address whether the findings of lower FA in the different brain regions observed in this study should be considered regionally distinct in OCD. Some evidence exists, however, that the anterior cingulate has strong neuroanatomical connections with the posterior cingulate^{68,91} and posterior parietal cortices,^{92,93} thus raising the possibility that a network that involves these regions may be disrupted in OCD. Recent studies⁹⁴ have demonstrated that mapping the pattern of white matter connectivity in the brain can be accomplished through fiber-tracking algorithms. Such techniques, especially in combination with functional neuroimaging modalities such as positron emission tomography and functional MRI, could be fruitful in elucidating the relationship between white matter abnormalities and functional deficits in OCD.

This study has several limitations that preclude firm conclusions. It could not be determined whether the white matter abnormalities observed in these regions reflected the primary pathophysiology of the disorder or were a consequence of abnormalities in other brain regions. In addition, a possible limitation of voxelwise analysis is the problem of multiple comparisons and the in-

creased risk of a type I error. To limit this possibility, however, we investigated FA only in the brain white matter and restricted the primary analysis to the anterior cingulate, which has been demonstrated to be structurally and functionally abnormal in previous neuroimaging studies. It is therefore noteworthy that we did not observe any areas of increased FA in patients even when we examined the white matter across the entire brain, thus strengthening the specificity of the observed findings. Nevertheless, these findings should be considered preliminary until replicated in larger samples using other DTI sequence parameters. Another potential study limitation is that most patients were receiving psychotropic medications at the time of the MRI examination, and the potential effects (if any) of these medications on FA have yet to be determined.

In summary, our findings provide evidence of white matter abnormalities in the pathogenesis of OCD at the microstructural level. Future studies should examine the pattern of connectivity between the anterior cingulate and other brain regions to better understand the purported role of white matter abnormalities in OCD.

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Author Affiliations: Department of Psychiatry Research, The Zucker Hillside Hospital, North Shore–Long Island Jewish Health System, Glen Oaks, NY (Drs Szeszko, Malhotra, and Robinson); Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY (Drs Szeszko, Malhotra, and Robinson); Nathan S. Kline Institute for Psychiatric Research, Center for Advanced Brain Imaging, Orangeburg, NY (Dr Ardekani); Department of Radiology, North Shore–Long Island Jewish Health System, New Hyde Park, NY (Dr Ashtari); UCLA Neuropsychiatric Institute and Geffen School of Medicine, Los Angeles, Calif (Dr Bilder); and Department of Psychiatry and Center for Magnetic Resonance Research, University of Minnesota, Minneapolis (Dr Lim).

Correspondence: Philip R. Szeszko, PhD, Department of Psychiatry Research, The Zucker Hillside Hospital, 75-59 263rd St, Glen Oaks, NY 11004 (szeszko@lij.edu).

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