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# Alteration of fractional anisotropy and apparent diffusion coefficient in obsessive–compulsive disorder: A diffusion tensor imaging study

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ABSTRACT

Background: Abnormalities of fractional anisotropy (FA) have been reported in previous diffusion tensor imaging (DTI) studies in patients with obsessive–compulsive disorder (OCD). However, there are some inconsistencies in the results and the apparent diffusion coefficient (ADC) has not been investigated. The goal of this study was to investigate white matter abnormalities and water diffusivity, as reflected by FA and ADC, using DTI in patients with OCD.
Methods: Fifteen patients with OCD and 15 healthy volunteers underwent DTI. Voxelwise analysis was used to compare FA in white matter and ADC in gray matter/white matter of the two groups.
Results: Compared with healthy volunteers, the patients had higher FA in the bilateral semioval center extending to the subinsular white matter; and a higher ADC in the left medial frontal cortex. There were no areas with a significantly lower FA or ADC in patients compared with healthy volunteers.
Conclusions: A significantly higher FA was found in regions associated with the emotion of disgust and a trend for a higher ADC was found in a region associated with the regulation of emotions. These findings suggest that neurocircuits involved in disgust processing may play an important role in the pathophysiology of OCD.



## 1. Introduction

Obsessive–compulsive disorder (OCD) is a common psychiatric disorder characterized by the presence of obsessions, compulsions or both. OCD has a lifetime prevalence rate of 2% to 3% in the general population and is marked by significant and often chronically disabling functional impairment. OCD is considered to be among the twenty leading causes of disability in the United States and other countries (Michaud et al., 2006). Abnormal feedback loops within cortical–striatal–thalamic–cortical circuits have been hypothesized to play a key role in the pathophysiology of OCD (Rapoport and Wise, 1988; Baxter et al., 1992). Moreover, a recent genetic family-based association study showed that oligodendrocyte lineage transcription factor 2 (OLIG2), which is an essential regulator in the development of cells that produce white matter (myelin), is associated with OCD (Stewart et al., 2007). However, little attention has been paid to the functional white matter network in patients with OCD.

The diffusion tensor imaging (DTI) technique has made it possible to examine white matter microstructure in humans. DTI detects self-diffusion of a water molecule. Water molecules can diffuse freely in solution without obstacles, but in human tissue (and especially in white matter) water molecules diffuse anisotropically along neural fibers. Indices used to interpret DTI data include fractional anisotropy (FA) and the apparent diffusion coefficient (ADC). FA reflects 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. Therefore, FA abnormalities in white matter may reflect abnormalities in the myelin sheath and/or directional coherence of fiber tracts. The ADC reflects the degree of apparent water diffusivity: tissues without obstacles, such as cerebrospinal fluid (CSF), have high water diffusivity, whereas those with obstacles, such as white matter, have low diffusivity.

Szeszko et al. (2005) found white matter abnormalities characterized by lower FA in the bilateral anterior cingulate gyrus region, bilateral parietal region (supramarginal gyri), right posterior cingulate gyrus, and left occipital lobe (lingual gyrus). Cannistraro et al. (2007) also reported lower FA in the right cingulum bundle, and higher FA in

*Abbreviations:* ADC, apparent diffusion coefficient; DTI, diffusion tensor imaging; ECS, extracellular space; FA, fractional anisotropy; NAA, *N*-acetylaspartate; OCD, obsessive–compulsive disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

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the left cingulum bundle and the left anterior limb of the internal capsule in patients compared with healthy volunteers. Both studies reported FA abnormalities in the anterior cingulate region. Evidence from structural MR (Valente et al., 2005) and functional neuroimaging (Rauch et al., 1994) has also implicated anterior cingulate abnormalities in the pathogenesis of OCD. However, a recent DTI study in drug-naïve OCD patients showed no FA abnormalities in the anterior cingulum (Yoo et al., 2007). Thus, the results of previous studies are inconsistent. Given this background, we performed DTI to investigate FA abnormalities in the whole brain, with particular attention to the anterior cingulum.

We also examined the ADC, which has not been investigated previously in patients with OCD. ADC abnormalities were originally reported in neurological diseases such as multiple sclerosis and temporal lobe seizures (Maldjian and Grossman, 2001; Londono et al., 2003). However, ADC has recently been investigated in psychiatric disorders such as schizophrenia and mood disorder (DeLisi et al., 2006; Regenold et al., 2006; Shin et al., 2006), and DeLisi et al. have suggested that ADC may be more sensitive to brain abnormalities compared to volume assessments. Therefore, the ADC may be of value in understanding the mechanism of OCD.

## 2. Methods

### 2.1. Participants

The subjects were 15 adult patients diagnosed with OCD according to DSM-IV criteria and 15 healthy volunteers matched for age, sex, handedness, and education (Table 1). We defined duration of illness as the time from the beginning of the present episode to the time of MRI acquisition. All except one of the patients had a single episode; one patient had two episodes with a long inter-episode period of full recovery in his clinical history. Patients were recruited at the Kyoto Prefectural University of Medicine Hospital, Kyoto, Japan. All patients were primarily diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID). One patient had a comorbid mild major depressive disorder, 1 had a dysthymic disorder, and 13 had OCD as their sole diagnosis. At the time of the MRI examination, all patients were receiving medication for OCD, including fluvoxamine (10 patients), paroxetine (4 patients), milnacipran (1 patient), trazodone (1 patient), lithium carbonate (1 patient), and clonazepam (2 patients). We classified patients according to the 5 clinical dimensions defined by Mataix-Cols et al. (1999). Using these criteria, the predominant obsessions/compulsions were as follows: symmetry/ordering (2 patients), hoarding (0 patients), contamination/cleaning (6 patients), aggression/checking (6 patients), and sexual/religious (1 patient). All patients were tested using the Japanese version of the Yale-Brown Obsessive Compulsive Scale(Y-BOCS) (Nakajima et al., 1995).

Exclusion criteria for patients and healthy volunteers were cardiac pacemakers or other metallic implants or artifacts; significant disease, including neurologic (Tourette syndrome, Huntington disease, Parkinson disease, encephalitis, stroke, aneurysms, tumors, central nervous system infections, degenerative brain diseases, or trauma), pulmonary, cardiac, renal, hepatic, endocrine, or metabolic (including dehydration) disorders; prior psychosurgery; current or past DSM-IV substance abuse or dependence; DSM-IV dementia, delirium, schizophrenia, schizoaffective disorder, delusional disorder, brief reactive psychosis, or a psychotic disorder not otherwise specified; DSM-IV mental retardation based on a clinical interview and psychosocial history; and pregnancy.

There was no history of psychiatric illness in the healthy volunteers, as determined using the Structured Clinical Interview for DSM-IV Axis I Disorders-Non-patient Edition (SCID-NP) or in any first-degree relatives. Classification of handedness was based on a modified 25-item version of the Edinburgh Inventory. All procedures were approved by the Medical Committee on Human Studies, Kyoto Prefectural University of Medicine (Serial No.: C-144). After a complete description of the study was given to the subjects, written informed consent was obtained from all participants.

**Table 1**
Demographic and clinical characteristics of patients with obsessive–compulsive disorder and healthy volunteers

| | Patients ($N$=15) | | Healthy volunteers ($N$=15) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Age (years) | 29.7 | 6.9 | 29.1 | 6.0 |
| Sex (male/female) | 9/6 | | 9/6 | |
| Handedness (left/right) | 1/14 | | 1/14 | |
| Education (years) | 15.2 | 2.2 | 15.7 | 1.8 |
| Age at onset (years) | 19.6 | 8.0 | | |
| Duration of pharmacotherapy (years) | 4.0 | 4.1 | | |
| Total Y-BOCS score | 29.0 | 5.3 | | |
| Obsessive subscale | 14.8 | 2.5 | | |
| Compulsive subscale | 14.2 | 2.8 | | |

Abbreviation: Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

### 2.2. MR data acquisition

Images were obtained with a whole-body 1.5-Tesla MR system (Gyroscan Intera; Philips Medical Systems, Best, The Netherlands) and a six-channel phased-array head coil. DTI was performed using a single-shot echo-planar technique (TR=6000 ms, TE=88 ms, flip angle=90°). DTI data were obtained with a spin echo Stejskal–Tanner sequence with 15 motion-probing gradient orientations. A $b$ value of 1000 s/mm$^2$ was used with averaging of two times. A set of 128×53 data points was recorded using the parallel imaging technique (Kyriakos et al., 2000). This allows the image to be reconstructed in half as many encoding steps and thus reduces the unique geometric image distortion of echo-planar imaging. Therefore, the true resolution of the images was equivalent to 128×106 pixels. Forty-two sections were obtained with a thickness of 3 mm, without intersection gaps. The field of view was 230 mm. The FA and ADC maps were obtained using DTI-Studio, version 2.4.01 software (Johns Hopkins University, Baltimore, MD, USA). A board-certified neuroradiologist (K.Y.) reviewed all scans and found no gross abnormalities in any of the subjects.

### 2.3. Image processing

Image analysis was performed using SPM2 software developed in the Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, running in MATLAB 6.5 (Mathworks, Sherborn, MA). Spatial normalization is an essential preprocessing step in SPM-based analysis (Gispert et al., 2003; Good et al., 2001). The contrasts of the FA and ADC maps differ from those of the T1-weighted and T2-weighted template images provided with SPM2. Thus, FA and ADC templates specific to this study were created using data from all participants. Each $b$=0 image in native space was standardized onto the T2 template supplied with SPM2, and the normalization parameter was applied to the respective $b$=0, FA and ADC maps. The normalized maps were smoothed with an 8-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel, and each mean image ($b$=0 template, FA template, ADC template) was created. Then, all FA and ADC maps in native space were transformed onto the stereotactic space by registering each image with the customized FA and ADC templates, respectively. The customized $b$=0 template was segmented using SPM2 protocol. Using Eqs. (1) and (2) in the ImCalc function in SPM2 yielded high probability white matter binary mask