

# Diffusion Abnormalities in the Primary Sensorimotor Pathways in Writer's Cramp

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**Objective:** To determine whether there are diffusion abnormalities along the fibers connecting sensorimotor regions, including the primary sensorimotor areas and the striatum, in patients with writer's cramp using voxel-based diffusion analysis and fiber tracking. Recent studies have shown structural changes in these regions in writer's cramp.

**Design:** Patient and control group comparison.

**Setting:** Referral center for movement disorders.

**Participants:** Twenty-six right-handed patients with writer's cramp and 26 right-handed healthy control subjects matched for sex and age.

**Interventions:** Clinical motor evaluations.

**Main Outcome Measures:** Fractional anisotropy changes and results of fiber tracking in writer's cramp.

**Results:** Diffusion-tensor imaging revealed increased fractional anisotropy bilaterally in the white matter of the posterior limb of the internal capsule and adjacent structures in the patients with writer's cramp. Fiber tracking demonstrated that fractional anisotropy changes involve fiber tracts connecting the primary sensorimotor areas with subcortical structures.

**Conclusions:** Diffusion abnormalities are present in fiber tracts connecting the primary sensorimotor areas with subcortical structures in writer's cramp. These abnormalities strengthen the role of the corticosubcortical pathways in the pathophysiologic mechanisms of writer's cramp.

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**W**RITER'S CRAMP IS A task-specific form of primary dystonia.<sup>1</sup> Structural imaging studies have shown the involvement of the sensorimotor circuit in dystonia. Early morphological imaging studies in patients with stroke reported that dystonia was observed after damage in several subcortical areas, including the basal ganglia, the thalamus, and less often the cerebellum,<sup>2-4</sup> suggesting a role for the basal ganglia in dystonia. A common hypothesis to explain the pathophysiologic mechanisms of dystonia is that defects in the basal ganglia and particularly the indirect pathway result in impaired suppression of unwanted excessive muscle activity that is observed in dystonia.<sup>5</sup> Subsequent progress in image analysis methods, such as voxel-based statistical comparisons in gray matter density, allowed the detection of structural changes in primary dystonia. Changes in gray matter density were reported in writer's cramp in the basal ganglia, sensorimotor cortex, thalamus, and cerebellum.<sup>6,7</sup> Similar imaging approaches allowed detection of gray matter changes in other forms of primary dystonia.<sup>8,9</sup> These observations suggest that writer's cramp may be associated with dys-

function not only of the basal ganglia but also of several brain structures interconnected within the sensorimotor network.

More recently, diffusion-tensor magnetic resonance imaging (DTI) has shown its ability to assess white matter integrity. In white matter, water diffusion is directionally dependent, predominating along the direction of axons.<sup>10</sup> This property can be quantified using various objective measures, the most popular being fractional anisotropy (FA). Fractional anisotropy is computable using region-of-interest measurements or tractography, as well as voxelwise measurements, and quantifies diffusion anisotropy within a voxel.<sup>10</sup> From DTI findings, axonal orientation within each voxel can be estimated on the basis of its alignment with the direction of fast diffusion.<sup>10</sup> Then, by relating the predominant diffusion orientation among neighboring voxels, 3-dimensional pathways macroscopically representing axonal bundles can be obtained using the technique called tractography.<sup>11</sup> With the use of DTI, changes in FA were reported in the subcortical white matter of the sensorimotor cortex in *DYT1* carriers.<sup>12,13</sup> Therefore, diffusion abnormalities may involve fibers connecting the sensorimo-

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tor cortex with subcortical structures. In this report, we combined voxelwise cross-subject statistics and tractography to test this hypothesis and to evaluate white matter abnormalities in patients with writer's cramp.

## METHODS

### PARTICIPANTS

The study included 26 patients with writer's cramp (9 men and 17 women; age range, 21-65 years; mean [SD] age, 42.8 [13.2] years) and 26 control subjects matched for sex and age at the group level (11 men and 15 women; age range, 20-65 years; mean [SD] age, 41.5 [15.0] years). All of the patients were examined by a movement disorders specialist (M.V.). The inclusion criteria for patients included the presence of disabling writer's cramp (task-specific dystonia triggered by writing, with no impairment during any other motor task) and the identification of a predominant abnormal posture or abnormal movement responsible for the difficulty in writing.<sup>14</sup> No patient had received botulinum toxin in the past 6 months. Although writer's cramp is said to be a condition with a male predilection, we had a female preponderance in our group of patients, which corresponds to our usual recruitment of patients.<sup>14,15</sup> Controls were neurologically healthy subjects recruited from the departments of neurology and neuroradiology of our institutions through advertisements. None of the patients or controls were taking concomitant medication. The study was approved by the local ethics committee and was in accordance with the Declaration of Helsinki. Informed written consent to participate in the study was obtained from all patients and healthy controls.

### IMAGING PROTOCOL

All subjects underwent DTI at 1.5 T (GE Medical Systems, Milwaukee, Wisconsin) using a quadrature birdcage head coil for signal reception. The DTI axial sections were obtained using the following settings: repetition time, 10 seconds; echo time, 88 milliseconds; flip angle, 90°; matrix, 128 × 128; field of view, 380 × 380 mm<sup>2</sup>; slice thickness, 3 mm, no gap; 4 averages; and acquisition time, 5 minutes 20 seconds. Diffusion weighting was performed along 6 independent directions, with a b value of 900 s/mm<sup>2</sup>. A reference image with no diffusion weighting was also obtained. The imaging volume covered most of the brain except for the lower two-thirds of the cerebellum. Therefore, the cerebellum was not included in the analysis. Raw diffusion-weighted data were corrected for geometric distortions secondary to eddy currents by using a registration technique based on the geometric model of distortions.

### DTI ANALYSIS

#### Voxel-Based Diffusion Data Analysis

We performed statistical parametric mapping (SPM) analysis using the SPM5 package (Wellcome Department of Neurology, Institute of Neurology, London, England). The non-diffusion-weighted (b0) images were normalized to the Montreal Neurological Institute T2-weighted template. The FA maps were then spatially transformed using the same settings and smoothed with gaussian kernels with a full-width at half maximum of 8 mm. To check for possible residual misalignment errors<sup>16</sup> between the 2 groups of subjects, we visually compared the averaged normalized FA images of each group. There was no topological difference between the 2 groups, in particular in the area of the posterior limb of the internal capsule (**Figure 1**). We performed

group comparisons using SPM5 and analysis of covariance. We used age as a confounding variable in all statistical analyses. All tests on FA were performed using an absolute FA threshold of greater than 0.2, such that voxels with FA values of less than 0.2 were not considered for analysis. This threshold restricts the analysis to consider white matter voxels only.<sup>17</sup> For group analysis, we used a height threshold of  $P < .001$  throughout the whole brain. We ultimately considered clusters of FA significant at  $P < .05$  corrected for multiple comparisons. In the following paragraphs, we called these clusters *FA abnormalities*.

### Fiber Tracking and Template Creation

To determine which fiber tracts were affected by the FA abnormalities evident in the voxel-based analysis, we performed fiber tracking using the FA abnormalities, transformed into the native space, as seeding points. The procedure included the following steps. The FA abnormality obtained during the voxel-based group comparison was first saved as a 3-dimensional image. This image was "denormalized" to the native space of each subject by using the deformation toolbox of the SPM5 software. For each subject, we computed the individual inverse transform of the b0 images and then applied this transformation to the FA abnormalities. We performed the fiber tracking using in-house software (Odyssee; Institut National de Recherche en Informatique et en Automatique, Odyssee Project Team). The fiber-tracking algorithm was based on the fiber assignment by means of the continuous tractography method<sup>11</sup> with an FA threshold of 0.2 and a principal eigenvector-turning angle threshold of 30° between 2 connected pixels. The fibers created in the previous section were used for the creation of tract templates using SPM5 as follows: (1) fiber tracts were converted to binary masks (0 for pixels that did not contain fiber and 1 for pixels that contained fiber); (2) the normalization matrix calculated previously was applied to the masks of each subject's tracts; and (3) the normalized binary masks of the 52 subjects were used to generate probabilistic maps, in which each pixel had information about the probability of containing a tract over the group of the subject (SPM5 software,  $P < .01$ , corrected for a false discovery rate).<sup>18</sup>

### Individual Fibers Statistical Analysis

The resultant statistical maps of the population were used to quantify FA values at each z-coordinate in the normalized DTI space. For that, the probabilistic maps of the white matter tracts were superimposed on each normalized FA map to calculate the FA intensities along the tract using the following equation<sup>19</sup>:

$$FA = \sum(\pi \times FA_i) / \sum \pi,$$

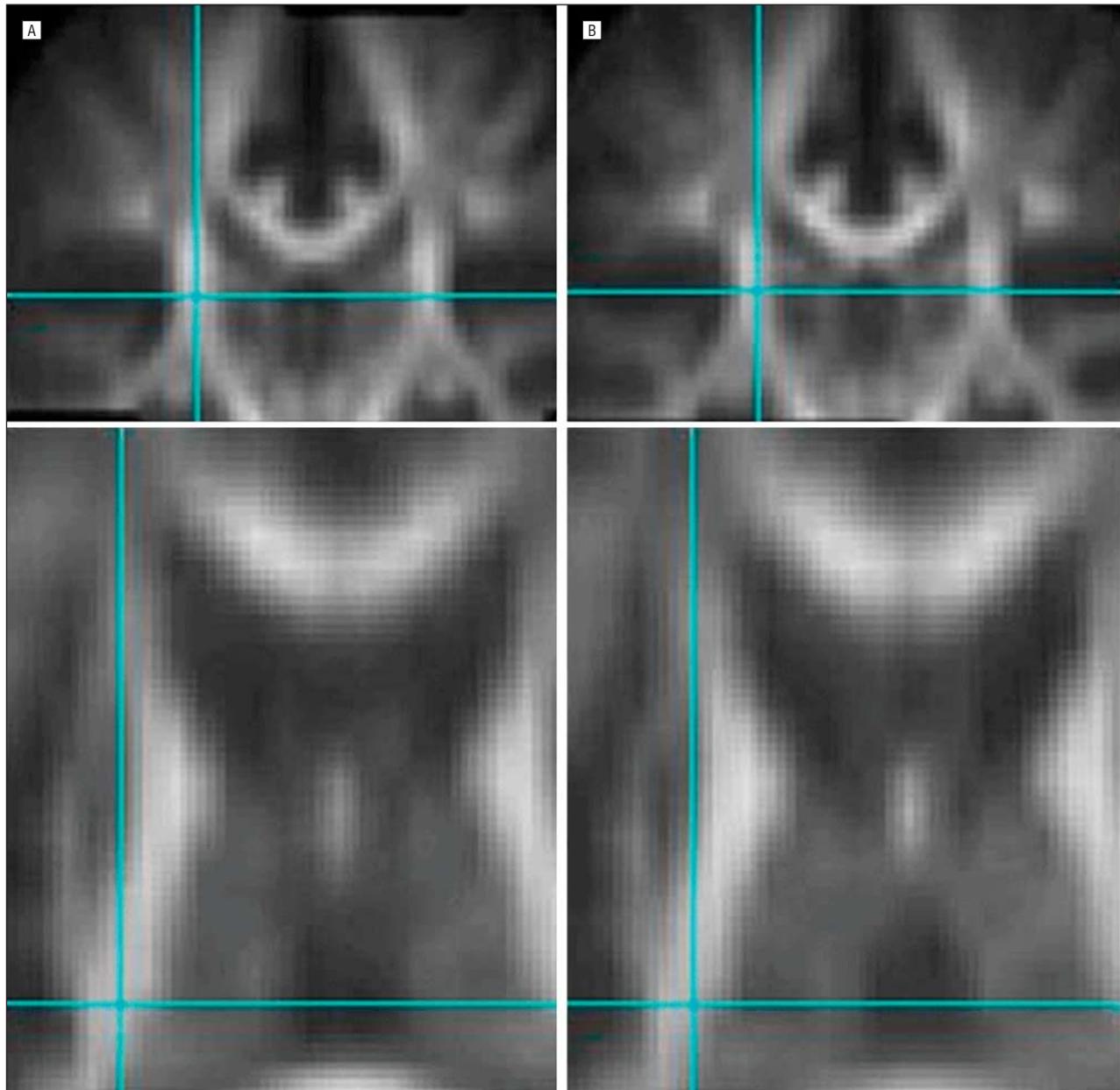
where  $\pi$  is the probability of the *i*th voxel occupied by the reconstructed tract divided by the total number of subjects, and  $FA_i$  is the FA value of the *i*th voxel.

Differences between patients and controls were calculated along the superior-inferior z-axis using an independent-samples *t* test. The level of statistical significance was set at  $P < .05$ .

## RESULTS

### VOXEL-BASED ANALYSIS

There were areas of significant increase in FA (FA abnormalities) in the patients with writer's cramp compared with controls (**Figure 2**). The FA increases in patients were located in the white matter of the posterior limb of the internal capsule, in the adjacent thalamus (ventroposterolateral nuclei) (peak *z* score for the left hemisphere, 4.62 [MNI coordinates, -24, -24, and 12]; peak *z* score for the



**Figure 1.** Coronal and axial normalized and unsmoothed fractional anisotropy sections averaged across the 26 patients with dystonia (A) and the 26 control subjects (B). No topological difference was apparent between the 2 groups in the area of the internal capsule (crossbar) (Montreal Neurological Institute coordinates, -24, -24, and 12).

right hemisphere, 4.72 [MNI coordinates, 27, -27, and 12]), and in the white matter of the left posterior centrum semiovale ( $z$  score, 4.41 [MNI coordinates, -36, -48, and 15]). No area of decreased FA was found in patients.

#### DETERMINATION OF THE AFFECTED FIBER TRACTS

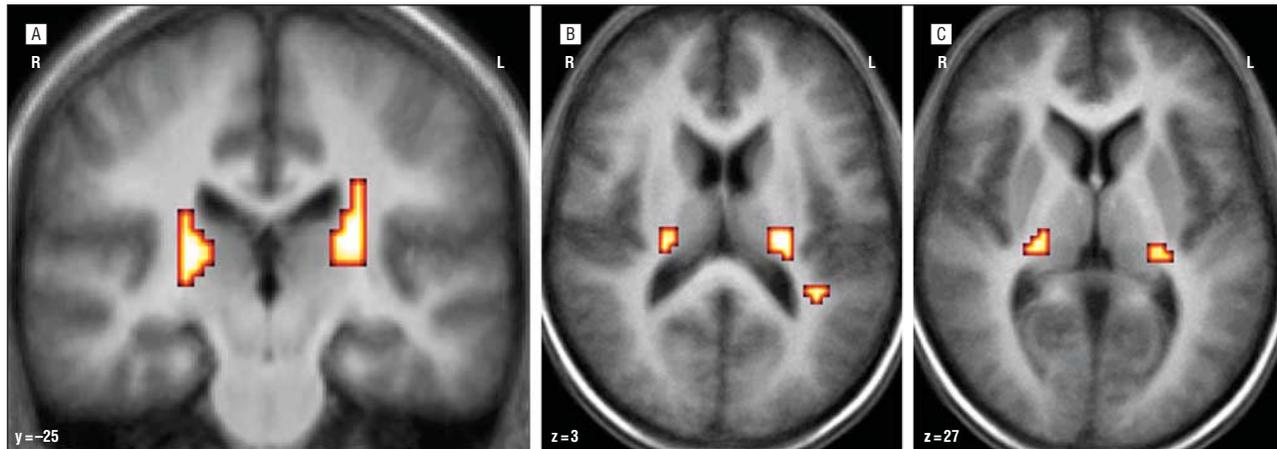
Fiber tracking performed using the FA abnormalities as seeding points showed that tracts passing through the area of FA abnormalities were directed to the primary motor or sensory areas (**Figure 3**) and to the brainstem. These connections were very consistent across subjects, observed for 51 of 52 hemispheres in the controls and in all of the patients. In 1 control, the

tract reconstruction stopped in the area of the centrum semiovale.

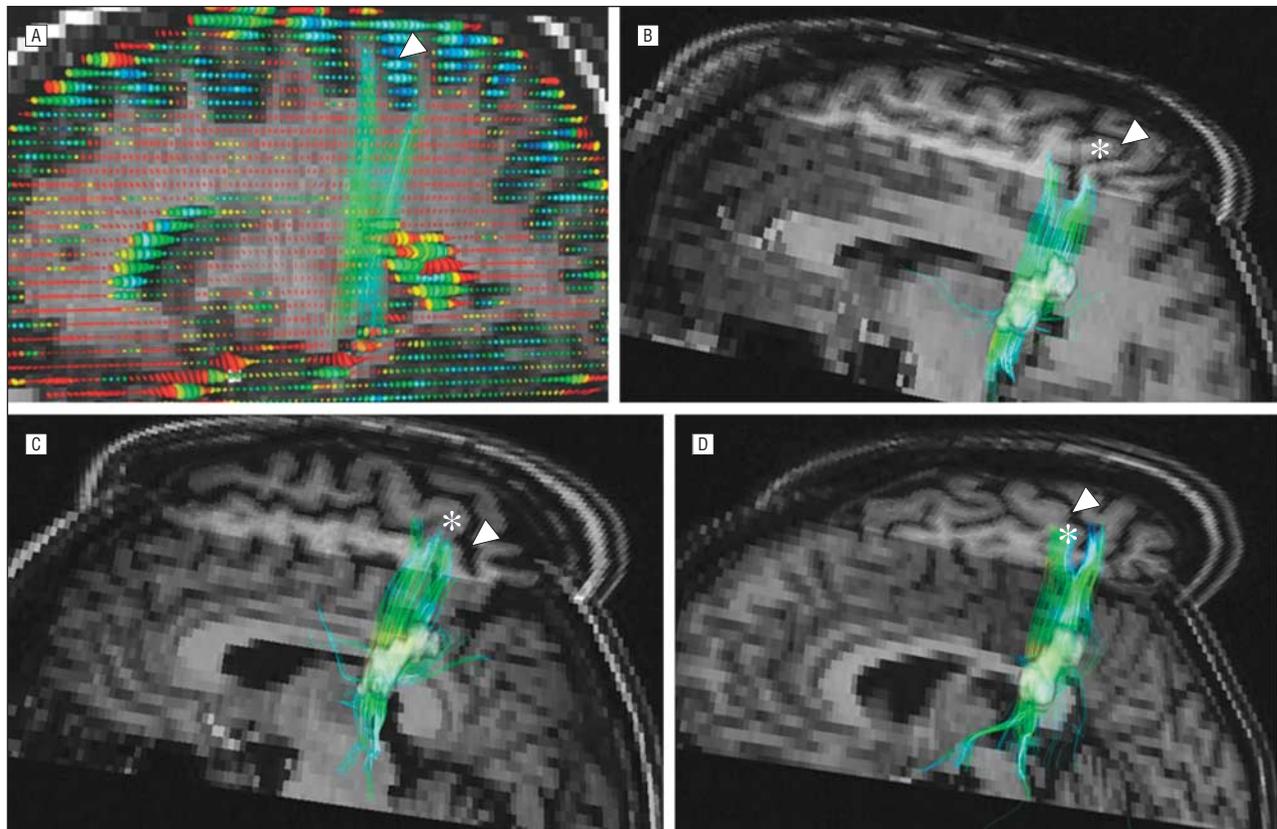
Probability values were lower at the rostral end of the template in the vicinity of the primary sensorimotor cortex. In this area, there was a high interindividual variability in the trajectory of the tracts.

#### STATISTICAL ANALYSIS AND INDIVIDUAL FIBER TRACKING

The spatially normalized FA values over the craniocaudal course of the tracts for the 2 groups are shown in **Figure 4**. Fractional anisotropy varied widely along the tracts and had a similar course in the patients and controls. In the right hemisphere, FA was significantly increased from the up-



**Figure 2.** Statistical parametric maps (SPMs; Wellcome Department of Neurology, Institute of Neurology, London, England) showing the area of fractional anisotropy increase in patients with writer's cramp (clusters significant at  $P < .05$ , corrected for multiple comparisons). Statistical parametric maps are superimposed on the group average of the normalized T1-weighted images of all patients (a coronal view passing at the y-coordinate of  $-25$  [A] and 2 axial views passing at the z-coordinates  $3$  [B] and  $27$  [C]). Clusters significant at  $P < .05$  corrected for multiple comparisons were observed in patients in the white matter of the posterior limb of the internal capsule, the adjacent thalamus and striatum bilaterally, and the white matter in the left posterior centrum semiovale. L indicates left, R, right.

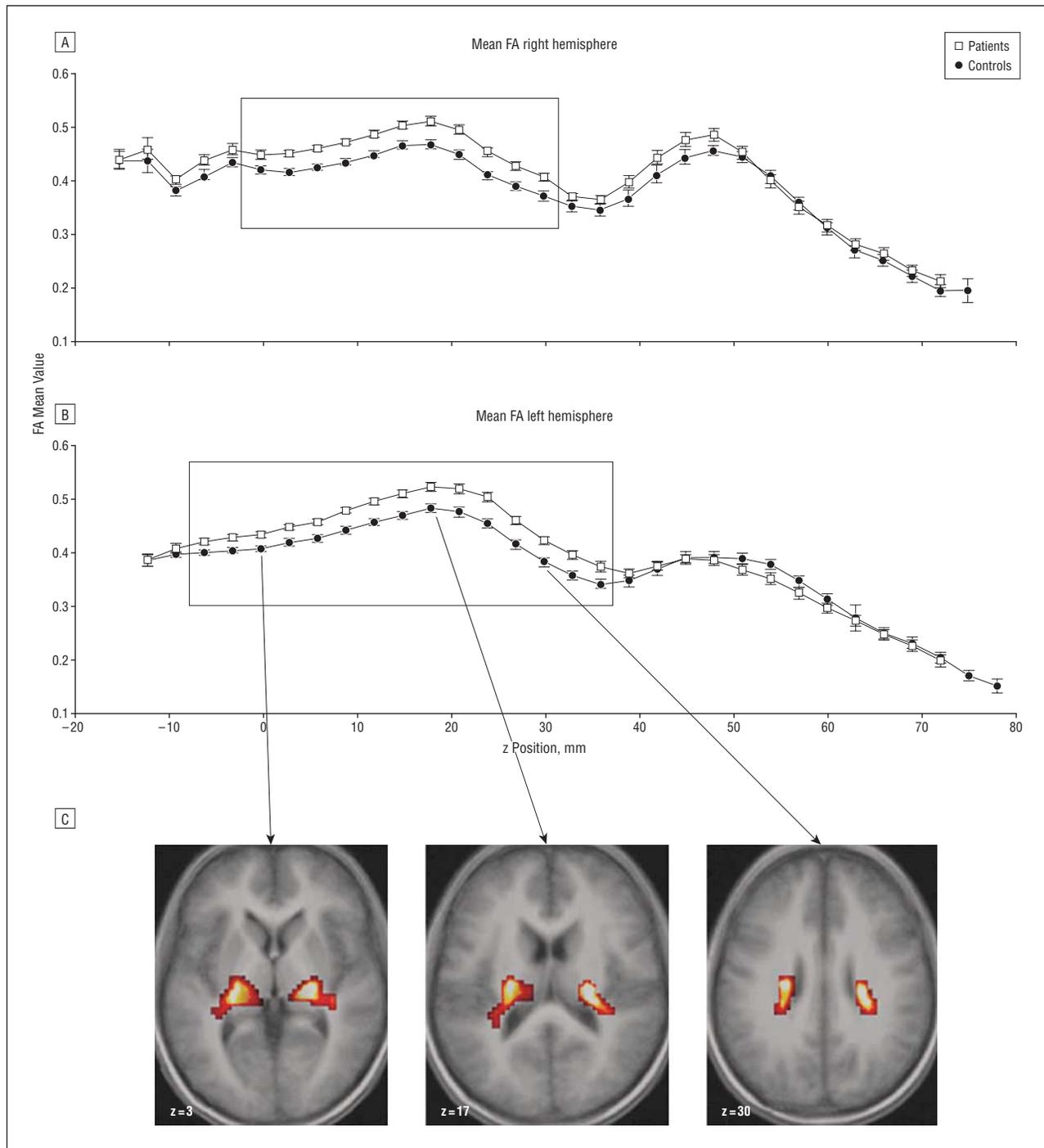


**Figure 3.** Fiber tracts reconstruction using the fractional anisotropy (FA) abnormalities as seeding points. A, Fiber tract and tensor ellipsoids superimposed on the sagittal view of 1 subject. B-D, Fiber tracking performed in 3 representative subjects, using the FA abnormality in the right hemisphere as seeding points, shows the position of the fiber tracts relative to the sensorimotor area. The reconstructed tracts are overlaid on a multiplanar view of the 3-dimensional T1-weighted image. Tracks passing through the area of FA abnormalities were directed to the primary motor or sensory areas near the hand area. Asterisks indicate the hand area of the primary motor cortex; arrowheads indicate the central sulcus.

per part of the pons caudally to the level of the corona radiata cranially (z-coordinates,  $-6$  to  $36$ ). In the left hemisphere, FA was significantly increased from the lower part of the posterior limb of the internal capsule to the level of the corona radiata cranially (z-coordinates,  $0$ - $30$ ). Areas of significant differences between the patients and controls matched the voxel-based results.

#### COMMENT

Our results show FA abnormalities in the fiber tracts connecting the primary sensorimotor areas with subcortical structures in writer's cramp. These abnormalities were detected at the level of the posterior third of the poste-



**Figure 4.** Between-group comparison of fractional anisotropy (FA) measurements (y-axis) along the template tracts at each z-coordinate of the Montreal Neurological Institute template (x-axis) for the right (A) and left (B) hemispheres in patients and control subjects. Each point in parts A and B corresponds to data points at each z-coordinate. Mean (SEM) values of the mean z-coordinates at which FA was significantly increased in patients compared with healthy controls are indicated by the box. Template tracts (C) are overlaid on the mean anatomical images of the patients in the axial plane at z-coordinates 3, 17, and 30.

rior internal capsule. With the use of DTI, several studies have shown that this area includes the corticospinal tract.<sup>20,21</sup> Fiber tracking confirmed the involvement of the corticospinal tract. Fractional anisotropy abnormalities shown by the voxel-based analysis probably also involved thalamocortical and corticostriatal fibers because the area of FA abnormality included parts of these 2 structures adjacent to the internal capsule or was located in their vicinity. These findings suggest that writ-

er's cramp is associated with abnormal anatomical connectivity of the corticosubcortical sensorimotor structures and strengthen findings of the role played by sensorimotor structures and their connections in the pathophysiologic mechanisms of the disease.

Our results are in accordance with previous studies that demonstrated anatomical abnormalities in the corticosubcortical sensorimotor networks in focal dystonia. Structural abnormalities have been reported in the bilateral peri-

landic cortex and thalamus by using voxel-based morphometry in cases of writer's cramp.<sup>6,7</sup> Functional abnormalities have also been described by using physiological and functional imaging methods in regions in which the voxel-based morphometry analysis showed structural abnormalities.<sup>22,23</sup> Abnormal activation patterns during performance of motor tasks<sup>24-26</sup> and abnormal fludeoxyglucose F 18 metabolism<sup>27-29</sup> were reported in the primary sensorimotor areas and the basal ganglia. Disorganized representation of the fingers in the sensorimotor cortex<sup>30,31</sup> or of body parts in the putamen<sup>32</sup> were observed in patients with primary dystonia. Previous studies have also shown impaired corticospinal excitability in focal hand dystonia through the use of transcranial magnetic stimulation in the sensorimotor area.<sup>33</sup>

Diffusion abnormalities have already been reported in patients with dystonia. Increased FA was observed in the bilateral putamen and caudate nucleus.<sup>34,35</sup> In contrast, reduced FA has been reported in the subgyral white matter of the sensorimotor area bilaterally in symptomatic and asymptomatic subjects carrying the *DYT1* and *DYT6* mutations.<sup>12,13</sup>

Manifesting carriers had a more pronounced FA reduction in this area compared with their nonmanifesting counterparts. Reduced FA was also reported in the dorsal pontine brainstem in the vicinity of the superior cerebellar peduncle.<sup>13</sup> In cervical dystonia, reduced FA was reported in the frontal middle gyrus,<sup>36</sup> the corpus callosum,<sup>34,35</sup> and the right thalamus and nearby white matter.<sup>36</sup> In a mix of 4 patients with cervical dystonia and 2 patients with hand dystonia, an abnormal hemispheric asymmetry in diffusion was observed in the region of the internal capsule and disappeared after administration of botulinum toxin.<sup>37</sup> In contrast to previous results, we observed increased FA but no asymmetry in a larger series of patients when we used a fully automated whole-brain method.

Several structural imaging studies also suggested that the cerebellum or its connections may be implicated in the pathophysiologic mechanisms of dystonia.<sup>7,38,39</sup> In the present study, because of technical limitations of the scanner, the cerebellum could not be included in the imaging volume. Therefore, whether there are diffusion abnormalities in the cerebellum in patients with writer's cramp remains to be investigated.

The significance of FA changes in dystonia and the explanation for these differences between studies are not known. Multiple factors result in FA changes in white matter and fiber tracts, including axon density, axonal membrane integrity, axon diameter, myelination, and coherence of fiber orientation.<sup>40</sup> Reduced FA may therefore be secondary to a loss of fibers or correspond to disrupted connections. Increased FA may result from increased fiber coherence or more ordered tissue containing large numbers of similarly aligned neurons. Recently, increased FA was evident in transgenic mice overexpressing the human mutant torsin A.<sup>41</sup> In these mice, FA was increased in the posterior part of the striatum, the cerebellum, and the motor cortex. Torsin A is involved in cytoskeletal dynamics and is immunostained in axons.<sup>42</sup> Therefore, overexpression of torsin A could be associated with changes in water diffusion in axons, although the mechanism is unknown. In gray matter nuclei such as the putamen,<sup>34,35</sup> increased FA may reflect increased cellularity in agreement with voxel-based morphometry stud-

ies that demonstrated gray matter volume increase in the basal ganglia in dystonia.<sup>9,39</sup>

Tractography results and tensor fitting<sup>43</sup> can be improved by increasing the number of diffusion-weighting directions (with isotropic angular density).<sup>44</sup> In this study, sampling diffusion with a higher number of directions probably would have improved tractography. For example, one might expect that more connections would have been obtained with the hand area of the sensorimotor cortex, whereas fibers were directed slightly more medially in the present study.

Significant FA abnormalities were detected at the level of the internal capsule, but not superiorly at the level of the centrum semiovale. The lack of significance in this area may be secondary to fiber crossing. Alternatively, in the centrum semiovale, the corticospinal tract spreads toward its cortical projection areas and demonstrates a higher interindividual variability. This could result in higher FA variability and could decrease the sensitivity of abnormal FA detection. Furthermore, higher sampling density can improve tractography in areas of fiber crossing such as the centrum semiovale, corresponding to an area of reduced FA.

In conclusion, this study suggests that writer's cramp is associated with microstructural changes involving fibers that carry afferents and efferents to the primary sensorimotor cortex. However, it is unknown how these changes relate to the physiopathology of the disease.

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### Correction

**Error in Author Affiliation.** In the Original Contribution titled "Diffusion Abnormalities in the Primary Sensorimotor Pathways in Writer's Cramp" by Delmaire et al, published in the April issue of the *Archives* (2009; 66[4]:502-508), an error occurred in the Author Affiliations paragraph on page 507. In that paragraph, the affiliation for Christophe Lenglet, PhD, was incorrect. The entire paragraph should have appeared as follows:

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