Clinical Correlates of White Matter Tract Degeneration in Progressive Supranuclear Palsy

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Objectives: To use diffusion tensor imaging to assess white matter tract degeneration in progressive supranuclear palsy (PSP) and to investigate correlates between tract integrity and clinical measures.

Methods: Fractional anisotropy and mean diffusivity were measured using region of interest analysis and tract-based spatial statistics.

Results: Compared with controls, abnormal diffusivity was observed predominantly in the superior cerebellar peduncles, body of the corpus callosum, inferior longitudinal fasciculus, and superior longitudinal fasciculus in patients with PSP. Fractional anisotropy values in the superior cerebellar peduncles correlated with disease severity ($r = -0.59$, $P = .006$), inferior longitudinal fasciculus correlated with motor function ($r = -0.51$, $P = .02$), and superior longitudinal fasciculus correlated with severity of saccadic impairments ($r = -0.45$, $P = .047$).

Conclusions: The results of this study demonstrate that PSP is associated with degeneration of the brainstem, association, and commissural fibers and that this degeneration likely plays an important role in clinical dysfunction.

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Progressive supranuclear palsy (PSP) is a neurodegenerative disorder characterized by a symmetrical akinetic-rigid syndrome with vertical supranuclear gaze palsy and falls within the first year of onset of the disease.1,2 It is characterized by deposition of tau,3 with pathologic changes and degeneration affecting the white matter, particularly brainstem tracts,3,4 with less involvement of the cortex. Imaging studies have similarly found more severe involvement of white matter than cortical gray matter in PSP.5-7 White matter tract degeneration is therefore likely to be a contributor to many symptoms observed in patients with PSP.

The integrity of specific white matter tracts can be assessed using diffusion tensor imaging (DTI), which measures water diffusion in the brain and can measure directional information and visualize specific white matter tracts. A few DTI-based studies have been performed in PSP and have demonstrated abnormalities in the superior cerebellar peduncles,8-10 cingulate gyrus,9 and corpus callosum,10,12 although these studies failed to identify correlations between these tracts and clinical features in PSP,8,12 likely because of the small numbers of subjects. In addition, these studies did not investigate correlations between clinical measures and degeneration of association fibers in PSP.

The aim of the present study was to investigate white matter tract abnormalities in a large, well-characterized cohort of patients with PSP and to assess correlations between white matter tract integrity and performance on several different
standardized and validated clinical scales. We used carefully placed regions of interest (ROIs) to measure directional water diffusion (fractional anisotropy [FA]) and mean diffusivity (MD) on specific tracts, including superior cerebellar peduncle, corticospinal, and corticobulbar tracts. In addition, because PSP has been associated with neocortical volume loss, we assessed corpus callosum and multiple association fibers. To provide independent validation of the ROI-based findings, we assessed voxel-level abnormalities in white matter tracts, using the automated and unbiased technique of tract-based spatial statistics (TBSS).

### METHODS

#### PARTICIPANTS

Twenty patients who met clinical research criteria for probable PSP were included in this study. All those with PSP who were evaluated in the Department of Neurology, Mayo Clinic, between August 1, 2009, and April 30, 2010, were consecutively enrolled (n=26) into a prospective longitudinal PSP study by a neurodegenerative specialist and PSP expert (K.A.J.). All participants underwent 3.0T DTI scanning, with 42 directions and detailed clinical evaluation. Only patients with neocortical volume loss, using affine transformations to minimize distortions due to eddy currents.

All PSP patients underwent clinical and neurologic examination and completed standardized and validated testing with the following batteries: Mini-Mental State Examination (MMSE), Frontal Behavioral Inventory (FBI), Frontal Assessment Battery, PSP Rating Scale (PSPRS), and Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale (parts I, II, and III) (MDS-UPDRS). Eye saccades were also graded using a 5-point Parkinson’s Disease Rating Scale (parts I, II, and III). Participants were excluded if they met only possible criteria for PSP did not consent to undergo 3.0T magnetic resonance imaging (MRI), if MRI was contraindicated, or if MRI revealed a lesion that would affect final analysis (eg, large stroke, tumor, or hemorrhage).

All PSP patients underwent clinical and neurologic examination and completed standardized and validated testing with the following batteries: Mini-Mental State Examination (MMSE), Frontal Behavioral Inventory (FBI), Frontal Assessment Battery, PSP Rating Scale (PSPRS), and Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale (parts I, II, and III) (MDS-UPDRS). Eye saccades were also graded using a 5-point scale completed using clinical impression (PSP Saccadic Impairment Scale, see Box for details).

Twenty healthy individuals who were age- and sex-matched to the PSP cohort were prospectively recruited and served as controls. All controls performed within normal limits on standardized neurologic and neuropsychological testing and had the same DTI acquisition sequence as the PSP cohort.

#### IMAGE ACQUISITION

A standardized protocol was performed on a 3.0T scanner (GE Medical Systems, Milwaukee, Wisconsin). The DTI acquisition consisted of a single-shot echo-planar pulse sequence in the axial plane, with a repetition time of 10 200 ms, an in-plane matrix of 128x128, a field of view of 35 cm, a phase field of view of 0.66, 42 diffusion encoding steps and 4 nondiffusion-weighted T2 images, and a section thickness of 2.7 mm (2.7-m isotropic resolution). Parallel imaging with a sensitivity encoding factor of 2 was used. Each of the 42 diffusion-weighted images was registered to the nondiffusion-weighted (ie, b0) volumes, using affine transformations to minimize distortions due to eddy currents.

#### ROI ANALYSIS

Maps of FA, color-coded FA, and MD were computed from these 42 diffusion-weighted images (DiffStudio). Regions of interest were placed on specific tracts on the color-coded FA maps (Analyze software; Biomedical Imaging Resource, Mayo Clinic, Rochester, Minnesota) by one rater (J.L.W.) blinded to study-related diagnosis. Regions of interest were placed using anatomic landmarks on axial images, with coronal and sagittal images viewed simultaneously to guide placement. To assess brainstem white matter tracts, ROIs were placed on corticospinal tracts and middle cerebellar peduncles at the level of thepons and in the superior cerebellar peduncles at the level of the decussation (Figure 1). Projection fibers were assessed with ROIs in the anterior limb, genu, and posterior limb of the internal capsule (Figure 1). Two ROIs were placed in the posterior limb: one in the lateral rostral third to sample the corticofugal fibers/superior thalamic radiation and the other positioned laterally in the caudal third to sample the corticospinal fibers.
tracts. Association fibers were assessed with ROIs placed in the inferior longitudinal fasciculus, uncinate fasciculus, superior longitudinal fasciculus, and anterior and posterior cingulum bundle. The superior longitudinal fasciculus was sampled at 3 positions: anterior descending tracts branching into the inferior frontal lobes, posterior descending tracts branching into the posterior temporal lobes, and superior horizontal fibers usually positioned adjacent to the most superior slice that contains the lateral ventricles. Regions of interest were also placed on the corpus callosum, including genu, splenium, and uppermost portion of the body. The location of many of these ROIs has been previously illustrated.21 The selection of these ROIs was performed independently from, and prior to the completion of, the TBSS analysis and was based on findings from previous studies.8-12 Excellent interrater reproducibility for these ROI measurements has been demonstrated.21

All ROIs were measured separately for left and right hemispheres except the corpus callosum. Once the ROIs had been placed using color-coded FA maps, they were overlaid on FA and MD maps to calculate mean FA and MD for each ROI. Because of the potential problem of partial volume effects, the maximum FA from each ROI was also assessed.

TRACT-BASED SPATIAL STATISTICS

Images were brain extracted (with use of the BET22 utility from the FSL package).23 and FA and MD maps were generated (FSL Diffusion Toolbox).24 Voxel-wise statistical analysis of FA and MD data was performed (TBSS25; http://www.fmrib.ox.ac.uk/fsl). The FA images for all participants were first aligned into a common space using a nonlinear registration tool (ITK).26 The subject who was the most representative from the entire cohort of PSP and controls was selected automatically as the target, and FA images of all other subjects were nonlinearly aligned to it. Following this step, all images were affinely transformed into Montreal Neurological Institute space. All images were averaged, and this mean image was thinned to create a mean FA skeleton, which represents the centers of all tracts common to the subjects. A threshold of the FA skeleton was set at more than 0.25 to include the major white matter pathways but exclude peripheral tracts that may have significant intersubject variability and/or partial volume effects with gray matter and cerebrospinal fluid. Each subject’s assigned FA data were then projected onto this skeleton, and the resulting data were fed into voxelwise cross-subject statistics. The transformations applied to the FA images were also applied to the MD images, and tract-based statistics were calculated for MD. Two-sample 2-sided t tests were performed using both FA and MD images to compare PSP and control groups. Results were assessed after correction for multiple comparisons, using familywise error correction, at P < .05.

STATISTICAL ANALYSES

Statistical analyses were performed (JMP Software, version 6.0.0; SAS Institute, Inc, Cary, North Carolina) with the α value set at .05. A χ2 test was used to compare categorical data across groups of interest. Two-sample t tests assuming unequal variances were used to compare continuous data between groups. For any ROIs that showed significant findings or trends in the PSP group when compared with the control group, we performed a pairwise correlation analysis between both FA and MD values and scores on the MMSE, PSPRS, FBI, Frontal Assessment Battery, PSP Saccadic Impairment Scale, and MDS-UPDRS tests. Linear regression analysis was used to adjust for disease severity. Receiver operating characteristic curve analysis was used to assess diagnostic specificity and sensitivity.

## Table 1. Demographics and Clinical Characteristics of the PSP and Control Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n=20)</th>
<th>PSP (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, No. (%)</td>
<td>11 (55)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Educational level, y</td>
<td>14.9 (2.9)</td>
<td>14.5 (2.5)</td>
</tr>
<tr>
<td>Age at examination, y</td>
<td>69.4 (7.3)</td>
<td>68.3 (7.2)</td>
</tr>
<tr>
<td>Age at PSP onset, y</td>
<td>NA</td>
<td>64.7 (6.9)</td>
</tr>
<tr>
<td>Time from PSP onset to examination, y</td>
<td>NA</td>
<td>3.6 (1.8)</td>
</tr>
<tr>
<td>Scalea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBI (/72)</td>
<td>NA</td>
<td>11.2 (11.4)</td>
</tr>
<tr>
<td>FAB (/18)</td>
<td>NA</td>
<td>13.7 (2.1)</td>
</tr>
<tr>
<td>PSPRS (/100)</td>
<td>NA</td>
<td>35.5 (15.7)</td>
</tr>
<tr>
<td>PSIS (/5)</td>
<td>NA</td>
<td>3.1 (0.7)</td>
</tr>
<tr>
<td>MMSE (/30)</td>
<td>NA</td>
<td>27.3 (3.7)</td>
</tr>
<tr>
<td>MDS-UPDRS I (/52)</td>
<td>NA</td>
<td>10.0 (4.6)</td>
</tr>
<tr>
<td>MDS-UPDRS II (/52)</td>
<td>NA</td>
<td>19.0 (10.8)</td>
</tr>
<tr>
<td>MDS-UPDRS III (/132)</td>
<td>NA</td>
<td>38.5 (16.2)</td>
</tr>
</tbody>
</table>

Abbreviations: FAB, Frontal Assessment Battery; FBI, Frontal Behavioral Inventory; MDS-UPDRS, Movement Disorder Society-sponsored Unified Parkinson’s Disease Rating Scale; MMSE, Mini-Mental State Examination; NA, not applicable; PSIS, PSP Saccadic Impairment Scale; PSP, progressive supranuclear palsy; PSPRS, PSP Rating Scale.

2Highest possible score on the scales represented as (/score).

PARTICIPANT DEMOGRAPHICS

Group demographics and clinical test scores are presented in Table 1. There were no significant differences between the PSP and control groups in sex ratio, age at MRI, or educational level.

GROUP COMPARISONS

The ROI-based results of FA and MD for the PSP and control groups are provided in Table 2 and Figure 2. No significant differences were observed between the left and right volumes; therefore, the mean was used for further analysis. The PSP group showed decreased FA and increased MD in the superior cerebellar peduncle, superior portion of the superior longitudinal fasciculus, and body of the corpus callosum, with decreased FA also observed in the anterior superior longitudinal fasciculus and inferior longitudinal fasciculus, and increased MD in the genu of the internal capsule. The same trends for differences across groups were identified when the maximum FA values were assessed. The superior cerebellar peduncle showed the most dramatic differences between the PSP and control groups and provided excellent discrimination between groups (area under the receiver operating characteristic curve, 0.96 for FA and 0.92 for MD). For specificity of 95%, FA had a sensitivity of 85% (cut point 0.75) and MD had a sensitivity of 80% (cut point 631 × 10⁻⁴ mm²/s) in differentiating PSP from controls. The supplemental eFigure (http://www.archneurol.com) shows the superior cerebellar peduncle ROI overlaid on FA images for a selection of PSP and control subjects.
Similar findings were observed with the TBSS analysis (Figure 3), with the PSP group once again showing reduced FA in superior cerebellar peduncles, body of the corpus callosum, anterior and superior aspects of the superior longitudinal fasciculus, and inferior longitudinal fasciculus. Some additional regions of reduced FA were also observed in pontine crossing fibers, cerebral peduncles, fornix, optic tract, and thalamus. No regions of increased MD were observed in the PSP group compared with the controls after correction for multiple comparisons. In addition, no regions were identified that showed decreased FA or increased MD in the control group compared with the PSP group, with or without correction for multiple comparisons.

Table 2. Region of Interest–Based FA and MD Results for the PSP and Control Groups

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Control (n=20)</th>
<th>PSP (n=20)</th>
<th>P Value</th>
<th>Control (n=20)</th>
<th>PSP (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST</td>
<td>0.62 (0.08)</td>
<td>0.59 (0.05)</td>
<td>.12</td>
<td>681 (65)</td>
<td>717 (81)</td>
<td>.13</td>
</tr>
<tr>
<td>MCP</td>
<td>0.79 (0.10)</td>
<td>0.79 (0.09)</td>
<td>.86</td>
<td>623 (47)</td>
<td>630 (64)</td>
<td>.71</td>
</tr>
<tr>
<td>SCP</td>
<td>0.85 (0.05)</td>
<td>0.67 (0.10)</td>
<td>&lt;.001</td>
<td>577 (40)</td>
<td>690 (62)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AIC</td>
<td>0.57 (0.08)</td>
<td>0.54 (0.07)</td>
<td>.22</td>
<td>755 (82)</td>
<td>750 (86)</td>
<td>.86</td>
</tr>
<tr>
<td>GIC</td>
<td>0.62 (0.07)</td>
<td>0.60 (0.07)</td>
<td>.45</td>
<td>723 (58)</td>
<td>785 (70)</td>
<td>.005</td>
</tr>
<tr>
<td>PIC rostral</td>
<td>0.66 (0.05)</td>
<td>0.64 (0.06)</td>
<td>.45</td>
<td>695 (64)</td>
<td>734 (72)</td>
<td>.08</td>
</tr>
<tr>
<td>PIC caudal</td>
<td>0.67 (0.04)</td>
<td>0.66 (0.06)</td>
<td>.09</td>
<td>725 (67)</td>
<td>732 (53)</td>
<td>.71</td>
</tr>
<tr>
<td>UNC</td>
<td>0.48 (0.08)</td>
<td>0.49 (0.06)</td>
<td>.51</td>
<td>710 (85)</td>
<td>743 (44)</td>
<td>.13</td>
</tr>
<tr>
<td>ILF</td>
<td>0.52 (0.04)</td>
<td>0.47 (0.05)</td>
<td>.002</td>
<td>778 (57)</td>
<td>803 (83)</td>
<td>.27</td>
</tr>
<tr>
<td>SLF anterior</td>
<td>0.43 (0.05)</td>
<td>0.39 (0.04)</td>
<td>.01</td>
<td>772 (74)</td>
<td>780 (81)</td>
<td>.75</td>
</tr>
<tr>
<td>SLF posterior</td>
<td>0.54 (0.06)</td>
<td>0.51 (0.08)</td>
<td>.32</td>
<td>737 (46)</td>
<td>753 (47)</td>
<td>.28</td>
</tr>
<tr>
<td>SLF superior</td>
<td>0.62 (0.06)</td>
<td>0.58 (0.06)</td>
<td>.04</td>
<td>690 (36)</td>
<td>719 (49)</td>
<td>.04</td>
</tr>
<tr>
<td>AC</td>
<td>0.45 (0.04)</td>
<td>0.46 (0.06)</td>
<td>.54</td>
<td>822 (73)</td>
<td>810 (67)</td>
<td>.60</td>
</tr>
<tr>
<td>PC</td>
<td>0.57 (0.06)</td>
<td>0.55 (0.06)</td>
<td>.25</td>
<td>671 (49)</td>
<td>693 (47)</td>
<td>.15</td>
</tr>
<tr>
<td>GCC</td>
<td>0.79 (0.05)</td>
<td>0.77 (0.05)</td>
<td>.17</td>
<td>817 (40)</td>
<td>829 (65)</td>
<td>.49</td>
</tr>
<tr>
<td>SCC</td>
<td>0.87 (0.05)</td>
<td>0.86 (0.04)</td>
<td>.63</td>
<td>701 (86)</td>
<td>729 (62)</td>
<td>.25</td>
</tr>
<tr>
<td>BCC</td>
<td>0.72 (0.07)</td>
<td>0.63 (0.09)</td>
<td>.002</td>
<td>783 (87)</td>
<td>896 (107)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: AC, anterior cingulum; AIC, anterior limb of the internal capsule; BCC, body of corpus callosum; CST, corticospinal tracts at the level of the pons; FA, fractional anisotropy; GCC, genu of corpus callosum; GIC, genu of the internal capsule; ILF, inferior longitudinal fasciculus; MCP, middle cerebellar peduncle; MD, mean diffusivity; PC, posterior cingulum; PIC, posterior limb of the internal capsule; PSP, progressive supranuclear palsy; SCC, splenium of corpus callosum; SCP, superior cerebellar peduncle; SLF, superior longitudinal fasciculus; UNC, uncinate fasciculus.

Figure 2. The distribution of fractional anisotropy (FA) (A) and mean diffusivity (MD) (B) values for participants with progressive supranuclear palsy (PSP). To aid in comparison, FA and MD values were centered at the region of interest (ROI)–specific control group mean (defined as zero on the horizontal axis) and thus can be interpreted as differences between PSP and controls for each white matter tract ROI. The boxes indicate the 25th, 50th (median), and 75th percentiles of the distributions while the horizontal lines extending from the boxes stop at the most extreme data points within 1.5 interquartile ranges, and solid circles indicate outliers. AC indicates anterior cingulum; BCC, body of corpus callosum; CST, corticospinal tracts at the level of the pons; GCC, genu of corpus callosum; GIC, genu of the internal capsule; ILF, inferior longitudinal fasciculus; MCP, middle cerebellar peduncle; PC, posterior cingulum; PIC, posterior limb of the internal capsule; PSP, progressive supranuclear palsy; SCC, splenium of corpus callosum; SCP, superior cerebellar peduncle; SLF, superior longitudinal fasciculus; UNC, uncinate fasciculus.
CLINICAL CORRELATIONS

Significant correlations were observed between the FA values in the superior cerebellar peduncles and performance on the FBI (r = −0.48, P = .03), PSPRS (r = −0.59, P = .006), MMSE (r = 0.48, P = .03), MDS-UPDRS I (r = −0.49, P = .03), MDS-UPDRS II (r = −0.54, P = .01), and MDS-UPDRS III (r = −0.47, P = .04) tests (Figure 4). However, the relationships between the superior cerebellar peduncles and the FBI, MMSE, MDS-UPDRS I, MDS-UPDRS II, and MDS-UPDRS III tests were not significant when the analyses were adjusted for PSPRS, ie, disease severity. Significant correlations were observed between both FA and MD values in the inferior longitudinal fasciculus and performance on the MDS-UPDRS II (FA, r = −0.51, P = .02; MD, r = 0.55, P = .01) and MDS-UPDRS III (FA, r = −0.47, P = .04; MD, r = 0.45, P = .05) tests (Figure 4). A significant correlation was also observed between the anterior portion of the superior longitudinal fasciculus and the PSP Saccadic Impairment Scale (r = −0.45, P = .047). This correlation was improved when the outlier in Figure 4 was removed (r = −0.60, P = .007) and remained significant after adjusting for disease severity (P = .03). Time from onset of PSP to scan did not correlate with any of the DTI ROI measurements.

COMMENT

This study demonstrates white matter tract degeneration in the superior cerebellar peduncles, corpus callosum, and association fibers in PSP and shows that this degeneration is associated with clinical dysfunction in PSP.

The superior cerebellar peduncles were the tracts that showed the most significant decreases in FA and increases in MD in the PSP group compared with the control group, which provided excellent discrimination between groups. This finding confirms those of previous DTI studies8-10,27 and concurs with the fact that demyelination and microgliosis have been observed in these structures at pathology examination.2,28,29 Volume loss of the superior cerebellar peduncles has also been observed in PSP.4,30,31 This finding contrasts with the relative preservation of the middle cerebellar peduncle. In this study we found significant correlations between FA values in the superior cerebellar peduncles and performance on tests of disease severity, including the PSPRS, FBI, MMSE, and MDS-UPDRS. Each of these tests measures different aspects of motor, cognitive, and behavioral ability, and the results of all were highly correlated with PSPRS, suggesting that performance on each test is associated with disease severity. Our results therefore suggest that FA measures in the superior cerebellar peduncle could be an excellent marker of disease severity in PSP. These results also demonstrate disruption of the dentatorubrothalamic tract, which runs through the superior cerebellar peduncles to the contralateral ventrolateral nucleus of the thalamus.32 In fact, TBSS analysis demonstrated reduced FA in the thalamus, which likely reflects degeneration of this system. The thalamus is predominantly a gray matter structure and so was not sampled.
in the ROI-based analysis; however, it contains a system of myelinated fibers (internal medullary lamina) that separate thalamic subdivisions that were likely detected by TBSS. Previous studies have been able to demonstrate increased MD only in the gray matter of the thalamus in PSP.

Significantly reduced FA and increased MD were also observed in the body of the corpus callosum in the PSP group, but no significant changes were observed in the splenium or genu. These findings may reflect degeneration of the commissural fibers connecting adjacent regions of gray matter loss in the posterior frontal and premotor cortex that are commonly observed in PSP.

Previous studies have similarly identified changes in diffusivity and volume loss in anterior-middle portions of the corpus callosum. However, measurements of FA and MD in the body of the corpus callosum in this study did not correlate with any clinical measures, suggesting that it is not directly associated with the symptoms of PSP.

Diffusivity changes were also observed in association fibers, namely, the inferior longitudinal fasciculus and superior longitudinal fasciculus. Correlations were identified between both FA and MD values in inferior longitudinal fasciculus and scores on the MDS-UPDRS parts II and III, which assess motor function. Interestingly, recent DTI studies investigating healthy aging found similar associations between abnormalities in the inferior longitudinal fasciculus and motor function and visual-motor coordination. The inferior longitudinal fasciculus connects visual cortices to the inferior, middle, and superior temporal lobes and has been suggested to subserve a “direct short-latency pathway” of visual processing. Visual-motor coordination is indeed likely to play a role in performance on a number of the items assessed using the MDS-UPDRS, such as toe and finger tapping and hand movements. Performance on the MDS-UPDRS parts II and III, however, also correlated with diffusivity in the superior cerebellar peduncles, suggesting that motor function may involve a complex network of systems in PSP.

Reductions in FA were observed in both the anterior descending tracts and the horizontal superior tracts of the superior longitudinal fasciculus. These tracts project to the posterior frontal lobes, regions that become atrophic in PSP. Anterior superior longitudinal fasciculus FA correlated with performance on the PSP Saccadic Impairment Scale, which grades severity of eye movement abnormalities that occur in PSP. This is a novel finding but plausible because, although several structures in the brainstem determine the direction, amplitude, and velocity of saccades, functional MRI and positron emis-

![Figure 4. Scatterplots with least-squares lines showing significant correlations between fractional anisotropy (FA) values and clinical measures in the participants with progressive supranuclear palsy (PSP). An outlier in the anterior superior longitudinal fasciculus (SLF) vs PSP Saccadic Impairment Scale (PSIS) correlation is highlighted by an arrow. Once this outlier was removed the correlation improved ($r = -0.60, P = 0.007$). ILF indicates inferior longitudinal fasciculus; MDS-UPDRS, Movement Disorder Society–sponsored Unified Parkinson’s Disease Rating Scale; PSPRS, PSP Rating Scale; and SCP, superior cerebellar peduncle.](https://archneur.jamanetwork.com/article.aspx?articleid=398366)
diffusion tomography studies demonstrate that voluntary saccades are under cortical control and the frontal and supplemental eye fields are known to play a role in saccadic eye movements. Our results suggest a possible cortical element to saccadic abnormalities in PSP, perhaps involving the frontal eye fields and premotor cortices, mediated by the superior longitudinal fasciculus.

It is clear from the TBSS analysis that reductions in FA were more severe than increases in MD in our PSP cohort, suggesting that directional diffusivity, and hence degeneration of the white matter tracts, is predominantly affected in PSP. A number of pathologic mechanisms could be contributing to breakdown of diffusion along white matter tracts: (1) tau deposition observed within axons and the outer mesaxon of myelinated fibers, (2) phagocytosis of myelin by macrophages (activated microglia) that are found in white matter tracts in PSP, and (3) Wallerian degeneration. The degree of demyelination in the superior cerebellar peduncle has been shown to correlate with tau burden, not microglial burden, in PSP, suggesting that tau may be responsible for the degeneration of white matter tracts, although further pathological studies will be needed to understand these biologic mechanisms.

Strengths of this study include the fact that all patients were prospectively assessed with a standardized battery of clinical assessments and the number of patients was large, especially for a rare disorder like PSP. In addition, we used 2 independent DTI analysis techniques. One could argue that results from small ROIs placed on specific tracts may not be representative of the entire tract, although the similarity across the ROI-based and TBSS analyses supports the validity of the data. Furthermore, TBSS analysis showed significant findings after correction for multiple comparisons, increasing confidence in the results. One limitation of using DTI to assess white matter tract dysfunction in PSP is that the resolution of the scans limits the ability to identify and measure very small tracts that may also be playing important roles in the disease, such as the subthalamic fasciculus connecting subthalamic nuclei to basal ganglia. Our analysis of maximum FA demonstrated that the ROI results were unlikely to be confounded by partial volume averaging, although this could be a problem in the TBSS analysis for thin tracts such as the fornix.

This study provides a detailed characterization of the patterns of white matter tract degeneration in patients with PSP and demonstrates correlations between these patterns and symptoms. Abnormal diffusivity was observed within brainstem tracts, such as the superior cerebellar peduncles, as well as in the body of the corpus callosum and some association fibers. Degeneration of the superior cerebellar peduncles seems to be an excellent marker of disease severity in PSP. In addition, degeneration of the inferior longitudinal fasciculus appears to be associated with motor function, and the superior longitudinal fasciculus appears to be associated with ocular motor abnormalities.

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Author Contributions: Study concept and design: Whitwell and Josephs. Acquisition of data: Whitwell, Kantarci, Edmonson, Jack, and Josephs. Analysis and interpretation of data: Whitwell, Master, Avula, Kantarci, Eggers, Jack, and Josephs. Drafting of the manuscript: Whitwell and Josephs. Critical revision of the manuscript for important intellectual content: Whitwell, Master, Avula, Kantarci, Eggers, Edmonson, Jack, and Josephs. Obtained funding: Josephs. Administrative, technical, and material support: Master, Avula, Kantarci, and Edmonson. Study supervision: Jack and Josephs.

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