ORIGINAL ARTICLE

Diffusion tensor tract-specific analysis of the uncinate fasciculus in patients with progressive supranuclear palsy

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KEYWORDS
Diffusion tensor imaging; DTI; MRI; Progressive supranuclear palsy; PSP; Uncinate fasciculus; Dementia

Summary
Objectives: The uncinate fasciculus (UF), a major white-matter tract connecting the frontal and temporal lobes, is related to cognitive/behavioral function. Recently, the UF has been suggested to constitute an indirect pathway of the “semantic ventral pathway” in association with the inferior longitudinal fasciculus (ILF). This retrospective study aimed to evaluate damage to the UF and ILF in patients with progressive supranuclear palsy (PSP) using diffusion tensor tract-specific analysis.

Material and methods: Diffusion tensor imaging (DTI) of 16 PSP patients with Richardson’s syndrome (PSP-RS) and 21 age-matched volunteers were obtained. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values for the bilateral UF and ILF were calculated by tract-specific analysis. Student’s \( t \) test was used to evaluate the differences between the patients and controls. Also, voxel-based morphometry (VBM) was performed using 3D T1-weighted images to explore the regional atrophy of gray matter in the patients.

Results: In patients with PSP-RS, FA of the left UF was significantly decreased compared with the controls, while significant increases in ADC were found in the UF and ILF bilaterally. VBM analysis showed significant clusters of reduced gray matter in the frontal cortex (predominantly in the lateral orbitofrontal cortex, pars opercularis and mesial frontal cortex) and subcortical nuclei (midbrain, caudate and thalamic).

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Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder characterized by supranuclear vertical gaze palsy, postural instability and falls, akinesia, axial rigidity, speech disturbances and cognitive impairment [1–3]. PSP is one of the most common parkinsonian disorders, after Parkinson’s disease and dementia with Lewy bodies (DLB) [4]. Although its diagnostic criteria are based mainly on motor impairment [5], cognitive decline and behavioral abnormalities are always present, and dementia is frequently observed [6,7]. PSP has been recently classified into two major clinical entities [8]. The most common form was originally described by Richardson and, hence, is called “Richardson’s syndrome” (PSP-RS), while its other form is known as “PSP-parkinsonism” (PSP-P). Features of PSP-RS include falls, cognitive dysfunction, supranuclear gaze palsy and postural instability in the early stages of the disease. On the other hand, in PSP-P, parkinsonism dominates the early clinical picture, and an initial moderate response to L-dopa may be present. Falls, gaze palsy and dementia may or may not occur and, when they do, are usually late manifestations of the disease in PSP-P.

Diffusion tensor imaging (DTI) is a non-invasive technique that enables visualization in three dimensions (3D), and quantification of the organization and integrity of white-matter fiber tracts in the human brain in vivo [9–12]. Diffusion tensor-derived parameters such as fractional anisotropy (FA) and the apparent diffusion coefficient (ADC) are thought to reflect microarchitectural brain-tissue integrity. FA is a measure of the directionality of water diffusion, whereas the ADC reflects average diffusivity independent of tissue directionality [13]. FA and ADC measurements have been used as markers of microstructural alterations that may even be undetectable on conventional T1- or T2-weighted images [14,15]. In addition, DTI provides useful information on the anatomy of specific fiber tracts [16]. Previous DTI studies in PSP have used region-of-interest (ROI) analysis of DTI metrics [17–19], voxel-based analysis [20] and tract-based spatial statistics (TBSS) [21]. Tract-specific analysis is another promising method that enables both visualization of fiber pathways and quantitative analysis of the specific tract in its entirety. Reportedly, it is also more reproducible and tends to show diffusion abnormalities more clearly compared with ROI analysis [22,23].

The uncinate fasciculus (UF) is a major white-matter tract connecting the anterior temporal lobe with the medial and lateral orbitofrontal cortex [24,25]. Although the function of the UF is still not completely understood [26], the UF is considered part of the limbic system, being a critical structure involved in emotion and memory [27], with a possible role in the formation and retrieval of episodic memory [28–33], and it may also belong to a ventral language pathway [33,34]. Decreased FA in the UF has been reported in patients with Alzheimer’s disease, amnestic mild cognitive impairment, semantic dementia, frontotemporal lobe dementia and amyotrophic lateral sclerosis [35–39].

The inferior longitudinal fasciculus (ILF) is a white-matter tract that connects the temporal and occipital lobes [40]. It has been suggested to play a role in visual object recognition [41] and in linking object representations to their lexical labels [42,43]. Decreased FA in the ILF has been reported in frontotemporal lobe dementia, Alzheimer’s disease, dementia with diffuse Lewy body disease, Huntington’s disease and PSP [17,44–47]. Moreover, it has recently been suggested that the UF and ILF subserves an indirect pathway of the “semicircular ventral pathway” [48,49].

Although often classified clinically as an atypical parkinsonian disorder, PSP is a tauopathy that is closely related to corticobasal degeneration (CBD) and is, therefore, also linked to tau-positive frontotemporal dementia disorders [50,51]. The aim of the present study was to examine the UF and ILF, which are both considered to be related to dementia, using tract-specific DTI analysis, and also regional cortical atrophy, using voxel-based morphometry (VBM) analysis in patients with PSP-RS.

Materials and methods

Subjects

Twenty-two patients diagnosed with probable PSP, according to National Institute of Neurological Disorders and Society for Progressive Supranuclear Palsy (NINDS-SPSP) diagnostic criteria [5], were included in this retrospective study. Excluded were six patients with significant cerebrovascular disease (cortical infarction, multiple lacunar infarction and either periventricular hyperintensity or deep white-matter hyperintensity greater than Fazekas grade 1) [52] on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images. All diffusion-weighted images were visually inspected for apparent artifacts due to patient motion or metallic dental prostheses. Overall, 16 patients with PSP (six women and ten men; mean age: 71.4 ± 6.0 years, age range: 58–80 years) were enrolled in the study. All of these patients were classified as PSP-RS, with falls, cognitive dysfunction, supranuclear gaze palsy, abnormalities of saccadic eye movements and postural instability as the predominant clinical features in the first 2 years of the disease [8]. None of them met the criteria for PSP-P (having at least three of the following in the first 2 years: predominant bradykinesia or tremor; positive response to L-dopa; asymmetrical onset; and limb dystonia) [8]. Also enrolled were 21 age-matched controls (nine women and 12 men; mean age: 70.9 ± 8.0 years, age range: 57–84 years), none of whom had any neurological and/or psychiatric conditions or cognitive complaints, or were taking any antipsychotic medications. Written informed consent was obtained from all of these healthy volunteers. The institutional review
board did not require informed consent for this retrospective review.

**MRI acquisition**

All magnetic resonance imaging (MRI) examinations were performed using a 1.5-T MRI system (Symphony or Vision; Siemens, Erlangen, Germany) with a standard head coil. DTI data were acquired using a transverse slice orientation and the following parameters: single-shot echo-planar imaging; motion probe gradients (MPG) in 64 directions (b values = 0 and 1000 s/mm²); matrix = 96 × 96; TR 11,200 ms; TE 106 ms; flip angle 90°; voxel size 2.5 × 2.5 × 2.5 mm³; NEX 1; and acquisition time 12 min. Axial T2-weighted images (TR 3800 ms, TE 95 ms, FOV 230 × 230 mm², matrix 512 × 281, 5-mm thickness, NEX 1 and acquisition time 3 min) and coronal FLAIR images (TR 9000 ms, TE 100 ms, FOV 230 × 230 mm², matrix 256 × 192, 5-mm thickness, NEX 1 and acquisition time 4 min) were also obtained. Volumetric T1-weighted images were acquired using magnetization-prepared rapid acquisition of gradient-echo sequences (144 sagittal sections, TR 1600 ms, TE 2.64 ms, flip angle 15°, voxel size 1.23 × 1.23 × 1.23 mm³, NEX 1 and acquisition time 5.5 min).

**DTI data post-processing**

Diffusion tensor data were transferred to an off-line workstation, and DTIStudio version 2.4 software (H. Jiang, S. Mori, Department of Radiology, Johns Hopkins University, Baltimore, MD, USA) was used for tensor calculations and tractography [53,54]. Directional color-coded FA maps were also produced. Fiber tractography was performed on the basis of fiber assignments derived by means of the continuous tracking method [54,55]. Termination criteria for fiber tracking included an FA < 0.18 and a turning angle of two consecutive vectors > 70°.

Tractography of the bilateral UF and ILF was performed using the two-ROI method [56,57]. For UF tractography, seed and target ROIs were determined according to the methods of Sato et al. [39] and Yasmin et al. [35]. Seed ROIs were set manually in the frontal part of the UF in the coronal plane through the genu of the corpus callosum. A sagittal reconstructed section of the color-coded FA map was used to determine coronal sections at the level of the genu of the corpus callosum. Target ROIs were set over the white matter in the coronal plane at the most anterior part of the temporal stem (Fig. 1). For the ILF, the method of Wakana et al. [58] was used. Using a parasagittal slice, a coronal section at the posterior edge of the cingulum was selected. The seed ROI was placed to include the entire posterior lobe. For the target ROI, the most posterior coronal slice in which the temporal lobe was not connected to the frontal lobe was selected. The target ROI included the entire temporal lobe (Fig. 2). Using the color-coded FA maps, a neuroradiologist, who was blinded to the patients’ information, placed these ROIs precisely and objectively. The anatomy of the UF and ILF generated by tractography (Fig. 3) closely resembled previously published data [26,55]. The FA and ADC of the entire generated UF and ILF fiber tracts were calculated by DTIStudio software, and analyzed using Student’s t test and PASW Statistics 18 software. P values < 0.05 were considered to indicate statistical significance.

**Voxel-based morphometry**

Voxel-based morphometry (VBM) analysis was performed, using the SPM5 (statistical parametric mapping) software package (http://www.fil.ion.ucl.ac.uk/spm) and running on MATLAB (MathWorks, Natick, MA, USA). Images were processed using an optimized VBM script according to Good et al. [59]. The MRI scans were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), using the standard unified segmentation model in SPM5. The segmented images were then normalized to a standard brain template. Finally, the spatially normalized images were modulated to ensure that the overall amount of each tissue class was not altered by the spatial normalization procedure and also smoothed, using an 8-mm full-width-at-half-maximum (FWHM) Gaussian kernel. The final voxel resolution was 2.0 × 2.0 × 2.0 mm³.

The smoothed GM images were analyzed using a multiple-regression design. Age, gender and total brain volume were entered into the design matrix as nuisance covariates. T-statistic maps were created for each voxel in the standard atlas space to reflect differences in GM. The significance threshold was P < 0.001 (uncorrected) for a seed level, and P < 0.05 (uncorrected) for a cluster level.

**Results**

In patients with PSP-RS, FA of the left UF was significantly decreased compared with the controls, while significant increases in ADC were found in the UF and ILF bilaterally (Table 1). Cortical GM atrophy in PSP-RS was predominantly in the frontal cortex, particularly within the inferior frontal gyrus and mesial frontal cortex bilaterally. Atrophy within the inferior frontal gyrus was maximum in the orbitofrontal cortex surrounding the horizontal ramus of the lateral fissure and in the posteroinferior portion of the pars opercularis (Fig. 4). Multiple areas of regional cortical atrophy were also seen in the rostrodorsal midbrain, caudate nucleus, mediodorsal thalamus, insula, hippocampal gyrus and cerebellum (Table 2).

**Discussion**

The present study is the first to demonstrate diffusion abnormalities in the UF and ILF in patients with PSP-RS, using tract-specific DTI analysis. In addition, VBM analysis showed frontal cortical atrophy in these patients, predominantly within the lateral orbitofrontal cortex, pars opercularis and mesial frontal cortex. The loss of tissue integrity in the UF appeared to be related to atrophy in the orbitofrontal cortex, as the UF is an association fiber connecting the orbitofrontal cortex with the anterior temporal lobe.

Pathologically, neurofibrillary tangles, tau-positive astrocytes, and occasional ballooned argyrophilic neuronal degeneration involving the brain stem, basal ganglia and frontal lobe are the hallmarks of the disease process in PSP [51,60]. Anterior frontal lobe dysfunction is the most
disabling cognitive deficit in PSP, and is partly due to marked deafferentation in the prefrontal areas, resulting from degeneration of striatothalamocortical pathways [61]. Our present VBM results appear to agree with these pathological features. Moreover, the patterns of regional atrophy within the frontal lobe were well correlated with the clinical deficits seen in PSP. In particular, atrophy of the lateral orbitofrontal cortex has been reported to correlate with behavioral and cognitive changes in PSP [62,63]. Atrophy in the medial frontal cortex and insula was in accordance with the pattern of neuropsychological dysfunction frequently found in patients with PSP, such as frontal apathy [64,65]. Degeneration of the frontal operculum may be responsible for the language disturbances described in PSP patients [66]. Our present results were also consistent with those of previous VBM or volumetry studies [20,62–64,67–69].

Table 1 Fractional anisotropy and apparent diffusion coefficient values in the uncinate fasciculus and inferior longitudinal fasciculus.

<table>
<thead>
<tr>
<th></th>
<th>PSP-RS (n = 16)</th>
<th>Controls (n = 21)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>FAright UF</td>
<td>0.435 ± 0.021</td>
<td>0.446 ± 0.018</td>
<td>0.098</td>
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<tr>
<td>ADCright UF [10⁻³ mm²/s]</td>
<td>0.810 ± 0.044</td>
<td>0.775 ± 0.032</td>
<td>0.009*</td>
</tr>
<tr>
<td>FAleft UF</td>
<td>0.430 ± 0.027</td>
<td>0.449 ± 0.018</td>
<td>0.017*</td>
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<tr>
<td>ADCleft UF [10⁻³ mm²/s]</td>
<td>0.797 ± 0.052</td>
<td>0.761 ± 0.037</td>
<td>0.019*</td>
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<tr>
<td>FAright ILF</td>
<td>0.471 ± 0.037</td>
<td>0.489 ± 0.030</td>
<td>0.11</td>
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<tr>
<td>ADCright ILF [10⁻³ mm²/s]</td>
<td>0.810 ± 0.061</td>
<td>0.773 ± 0.041</td>
<td>0.035*</td>
</tr>
<tr>
<td>FAleft ILF</td>
<td>0.467 ± 0.035</td>
<td>0.472 ± 0.027</td>
<td>0.65</td>
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<tr>
<td>ADCleft ILF [10⁻³ mm²/s]</td>
<td>0.816 ± 0.063</td>
<td>0.780 ± 0.031</td>
<td>0.029*</td>
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PSP-RS: progressive supranuclear palsy with Richardson’s syndrome; FA: fractional anisotropy; ADC: apparent diffusion coefficient; UF: uncinate fasciculus; ILF: inferior longitudinal fasciculus.

*P < 0.05.
Figure 2  ROI placement for tractography of the inferior longitudinal fasciculus (ILF). A. The seed ROI is set, using the coronal plane of a color-coded FA map, at the posterior edge of the cingulum. B. The target ROI is set, using the most posterior coronal slice in which the temporal lobe is not connected to the frontal lobe. C, D. The corresponding b = 0 images represent the spatial orientations.

<table>
<thead>
<tr>
<th>MNI coordinates (mm)</th>
<th>Z-score</th>
<th>P (uncorrected)</th>
<th>Region</th>
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<tr>
<td>x</td>
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<tr>
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<td>-36</td>
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<td>10</td>
<td>16</td>
<td>6</td>
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<td>-44</td>
<td>3.78</td>
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</table>
The UF is believed to be critical for episodic memory and its disruption has been found to cause severe memory impairment [27,28,32]. As already mentioned, atrophy of the lateral orbitofrontal cortex has been reported to correlate with cognitive/behavioral deficits in PSP [62,63], and the UF is an association fiber connecting the orbitofrontal cortex to the anterior temporal lobe. Furthermore, significant correlations between DTI metrics in the UF and cognitive/behavioral measures have been reported in patients with frontotemporal dementia [70]. PSP is a tauopathy that is closely related to other tau-positive frontotemporal dementia disorders, including frontotemporal lobe dementia and CBD [18,50,51]. Thus, there is a rationale for suspecting that decreased FA in the UF is correlated with cognitive/behavioral deficits in PSP.

The present results of tract-specific analysis of the ILF were also consistent with a previous report of ROI analysis describing abnormal diffusivity in the ILF in PSP patients [17]. Recently, it has been suggested that the "semantic ventral pathway" could be made up of two parallel pathways within the temporal lobe:

- a direct pathway, the inferior fronto-occipital fasciculus, that connects the posterior temporal areas and the orbitofrontal region;

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**Figure 3** Three-dimensional views of the generated tractography of the UF and ILF. A. Right lateral view of the right UF. B. Right lateral view of the right ILF.

**Figure 4** Statistical parametric mapping shows significant gray-matter (GM) volume loss in patients with progressive supranuclear palsy (PSP) compared with matching controls, as rendered on the GM images from a single control subject. The threshold for display is $P<0.001$ (uncorrected), and the Z-scores are indicated by color temperature according to the scale. MNI coordinates (mm) by section. A. $x=-39$. B. $x=6$. C. $x=-4.6$. D. $y=-13$. E. $y=-4$. F. $y=11$. G. $y=50$. H. $z=-18$. I. $z=-1.6$. J. $z=55$. 
an indirect pathway that is subserved by the UF and ILF [42,43].

Decreased FA in the fronto-occipital fasciculus has been reported in PSP [18]. Our present results suggest that patients with PSP could have impairment to the indirect pathway of the “semantic ventral pathway” as well as of the direct pathway.

Other previous reports of ROI analysis have shown decreased FA in the corpus callosum, superior longitudinal fasciculus and superior cerebellar peduncle in patients with PSP [17,19]. Padovani et al. [20] used voxel-based analysis of DTI data to explore diffusion abnormalities throughout the brain, and showed decreased FA in the superior longitudinal fasciculus, anterior part of the corpus callosum, arcuate fasciculus, posterior thalamic radiations and internal capsule. However, they found no significant changes in either the UF or ILF. In fact, applying voxel-based analysis to DTI data has been criticized in terms of accuracy of spatial normalization, size of the smoothing kernel and use of a general linear model for statistical analysis assuming a normal signal distribution [71]. Knake et al. [21] applied TBSS to investigate DTI abnormalities in PSP and also found no significant changes in the UF and ILF. Although TBSS overcomes the problems of voxel-based analysis as regards alignment and spatial smoothing [72], it might be insensitive to the degeneration or loss of integrity in the WM periphery, as the maximum FA value of the specific tract is extracted and exclusively analyzed [73].

The tract-specific analysis used in our present study is less operator-dependent and tends to show diffusion abnormalities more clearly in comparison to ROI analysis [22,23]. It also enables confirmation of the anatomical location by visualizing the fiber pathways, and avoids contamination from adjacent structures.

Nevertheless, the present study has a few limitations. First, this was a retrospective study, and comparisons between DTI results and measures of cognitive/behavioral functions were lacking. Second, the number of patients was small, as is to be expected with a relatively rare disease, so it is still necessary to demonstrate any clinicoradiological correlations in a prospective study design involving a larger number of patients. Third, it could not be confirmed whether the UF and ILF are similarly impaired in the different types of PSP. A recent VBA study has reported different topographical distributions of GM and WM atrophy in PSP-RS compared with PSP-P [69]. Also, diffusion abnormalities may differ between these two entities, and may possibly account for the differences in clinical features. Finally, confirmation of the clinical diagnoses by post-mortem examination was not available. However, given the excellent specificity of the probable NINDS-SPSP clinical criteria [74], this should have little effect on our present findings. Further investigation of WM impairment in PSP-RS in comparison to other subtypes of PSP or other dementia disorders could also be informative, as the extent of WM impairment, for example, may differ among PSP subtypes.

In conclusion, the present study results indicate that the UF and ILF are both affected in patients with PSP-RS. Damage to the UF is thought to be related to atrophy in the orbitofrontal cortex, and may possibly correlate with the cognitive/behavioral impairment seen in PSP-RS. Our findings have also suggested that PSP-RS patients might have some impairment of the “semantic ventral pathway”, which is subserved by the UF and ILF.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


