Voxel based morphometry reveals a distinct pattern of frontal atrophy in progressive supranuclear palsy

C Brenneis, K Seppi, M Schocke, T Benke, G K Wenning, W Poewe

**Background:** Frontal lobe atrophy is a well known neuropathological feature of progressive supranuclear palsy (PSP), accompanied by characteristic neuropsychological deficits.

**Objective:** To determine subregional frontal lobe atrophy patterns in patients with PSP using voxel based morphometry (VBM).

**Methods:** VBM is an observer unbiased volumetry which allows the investigation of the entire brain. An optimised protocol for normalisation, segmentation, and correction for volume changes in preprocessing was used. Grey matter, white matter, and cerebrospinal fluid (CSF) partitions in 12 patients with probable PSP were compared with 12 healthy controls matched for age and sex.

**Results:** In PSP patients, the following cortical areas were decreased in volume ($p_{corr} < 0.05$): the prefrontal cortex, predominantly the medial frontal gyri and a cluster in the left lateral middle frontal gyrus; the insular region including the frontal opercula; both supplementary motor areas; and the left medio-temporal area (V5). White matter comparisons revealed a volume reduction in both frontotemporal regions and the mesencephalon. Analysis of the CSF compartment showed no significant regional changes between the groups.

**Conclusions:** Frontal atrophy in PSP predominantly involves mesio-frontal targets of striatal projections. This atrophy pattern probably accounts for cardinal PSP associated behavioural deficits.

Progressive supranuclear palsy (PSP) is one of the most frequent parkinsonian syndromes; its hallmarks are supranuclear gaze palsy, postural instability, and cognitive deficits. Although consensus criteria for clinical diagnosis of PSP have been developed, patients with PSP may be misdiagnosed as having idiopathic Parkinson’s disease, multiple system atrophy, corticobasal degeneration, dementia with Lewy bodies, or Alzheimer’s disease because of overlapping clinical features such as akinetic-rigid syndrome, dementia, and apraxia. Impaired neuropsychological function is present in up to 60–70% of PSP patients, with cognitive slowing deficits in executive functions, and attention being the most prominent findings. Neuropathologically, PSP is characterised by the presence of abundant neurofibrillary tangles, tau positive astrocytes, and occasional balloononed argyrophilic neuronal degeneration involving the basal ganglia, brain stem, and frontal lobe. Various functional imaging studies suggest that certain frontal lobe subregions are preferentially involved in PSP, including posterior or superior areas. In the present study we used voxel based morphometry (VBM) to map the atrophy patterns within the frontal lobe of clinically diagnosed PSP patients. VBM is a magnetic resonance (MR) based volumetric tool, observer and region of interest (ROI) independent, allowing the determination in vivo of volumetric changes in grey matter, white matter, and cerebrospinal fluid (CSF).

**METHODS**

**Patients and controls**

Twelve patients with probable PSP diagnosed according to the NINDS-SPSP criteria and 12 controls matched for age and sex with normal T1 weighted MR images were included in the study. All patients were examined by an experienced movement disorder specialist (GKW). Motor impairment as well as levodopa response were rated during the OFF state as defined by the CAPSIT protocol, using the motor examination section of the unified Parkinson’s disease rating scale (UPDRS-III) (KS).

**Magnetic resonance protocol**

A single MRI scan of all subjects was done on a 1.5 Tesla MR scanner (Magnetom Vision, Siemens). The imaging protocol comprised a sagittal T1 weighted FLASH three dimensional sequence with a repetition time (TR) of 9.7 ms, an echo time (TE) of 4 ms, a slice thickness of 1.5 mm, a matrix of $256 \times 256$, and a field of view of 230 mm.

**Data analysis**

SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK) implemented in Matlab 5.3 (Mathworks Inc, Sherborn, Massachusetts, USA) was used for prestatistical image processing and statistical analysis.

**Template creation**

To avoid potential bias from the scanner and normalisation process, a customised template was created including all T1 weighted images of the participating subjects. Each image was first spatially normalised into standardised MNI (Montreal Neurological Institute) space using a 12 parameter affine transformation and a non-linear normalisation by $7 \times 8 \times 7$ basis functions. Following normalisation, a mean image was created which was smoothed with an 8 mm FWHM isotropic Gaussian kernel.

**Abbreviations:** MNI, Montreal Neurological Institute; NINDS-SPSP, National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy; PSP, progressive supranuclear palsy; ROI, region of interest; SPECT, single photon emission computed tomography; UPDRS, unified Parkinson’s disease rating scale; VBM, voxel based morphometry
Normalisation and segmentation
The images of the subjects were warped to match the customised template applying a 12 parameter affine transformation and non-linear spatial normalisation using discrete cosine \((7\times8\times7)\) basis functions. Following reslicing onto a small voxel size of \(1\times1\times1\) mm to minimise partial volume effects,\(^{26}\) the images were segmented into grey matter, white matter, and CSF. A correction of intensity non-uniformity was incorporated to compensate for variations in tissue density values caused by the head position relative to the coil in the scanner. Therefore, the “lot of correction” algorithm as provided by SPM99 was applied to the images. To remove missegmented areas (for example, the dural venous sinus) from statistical analysis, the grey matter partitions were multiplied by a binary mask which was created with a function of SPM99 called brain extraction.

Modulation and smoothing
A modulation of the segmented partitions was undertaken to compensate for volume changes in non-linear spatial normalisation by multiplying the voxel densities with the Jacobian determinants.\(^{19,20}\) This processing allows an analysis of the absolute amount of volume, whereas the unmodulated data would test for differences in concentration.

Finally, the modulated grey matter, white matter, and CSF partitions were convolved with a Gaussian kernel filter of \(10\times10\times10\) mm FWHM in order to render the data more normally distributed and to compensate for inexact spatial normalisation.\(^{21}\)

Statistical analysis
The normalised, segmented, modulated, and smoothed data were statistically tested using the general linear model based on the Gaussian field theory. Global differences in voxel intensities were used as confounding covariate (ANCOVA); grand mean scaling was set at 100. The significance level was set at \(p<0.05\), corrected for multiple comparison across the entire brain volume. Brain stem atrophy is a well known phenomenon in PSP.\(^{22,23}\) Therefore areas in the brain stem were corrected for small volumes with a radius of 20 mm at the peak maxima. Finally, the MNI coordinates of significant clusters were converted to Talairach coordinates.

RESULTS
Demographic and clinical features
Table 1 summarises the clinical findings. There was no significant difference in age between patients and controls (mean (SD): PSP, 67.5 (6.6) years; controls, 60 (5.8) years). The mean value of UPDRS motor subscore was 38.9 (10.9). Disease duration in the patients was 2.7 (0.9) years.

Voxel based morphometry
In PSP patients, significant \((p_{\text{uncorr}}<0.05)\) volume loss was observed in several cortical areas. The atrophy pattern predominantly involved the medial frontal gyri of both hemispheres and the insular regions including the frontal opercula (fig 1). Additional clusters of atrophy were found in both supplementary motor areas, the left middle frontal gyrus on the lateral surface, and the left temporo-occipital region corresponding to area MT/V5.

A more liberal significance level of \(p_{\text{uncorr}}<0.001\) detected grey matter of both primary sensorimotor cortices. Table 2 summarises Talairach’s coordinates and \(z\) values of significant volumetric changes in PSP compared with controls.

DISCUSSION
To our knowledge this is the first volumetric study determining subregional frontal atrophy patterns in PSP patients using VBM. The fully automated whole brain technique avoids many of the constraints of ROI analysis but it incorporates a series of preprocessing steps that may cause systematic bias. It is therefore important to be cautious about ascribing volume differences to a disease effect. Furthermore it is also important to recognise the effect of variability on the ability of VBM to detect volume differences. In order to meet these potential limitations we have applied an optimised protocol to the images, which involved the creation of a customised template, eliminating missegmented grey matter areas, and modulating the segmented data by the

| Table 1 Demographic and clinical data in patients with progressive supranuclear palsy (PSP) and controls |
|-------------------------------------------------|---------------|-----------|-----------|------------------|
| Group (n)                                      | Age (years)   | UPDRS-III | DD (years) | L-Dopa response: |
| No or poor/moderate/good                      | PSP (12)      | 67.5 (6.6)| 38.9 (10.9) | 2.7 (0.9)        | 11/1/0           |
| Controls (12)                                 | 60 (5.8)      |           |            |                  |                  |

Values are mean (SD) or n.

DD, disease duration; UPDRS-III, unified Parkinson’s disease rating scale – motor examination.
Jacobian determinants to compensate for the volume changes in spatial normalisation.

Frontal lobe atrophy is widely regarded a key neuropathological feature of PSP. Several studies have shown that the posterior frontal cortex is affected in most if not all patients with PSP. However, no systematic necropsy studies have been carried out investigating subregional cortical atrophy patterns. To date, a single three dimensional MRI volumetric study reported significant frontal lobe atrophy in PSP patients with a predilection for the posterior frontal cortex.

Previous functional imaging studies have also shown abnormalities in several subregions of the frontal lobe in PSP patients. Glucose metabolism was reduced, particularly in the superior half of the frontal lobes and in the motor/premotor regions; a similar pattern of reduced regional cerebral perfusion in frontal lobe was reported in a SPECT study. Furthermore, studies using proton magnetic resonance spectroscopy indicated neuronal loss or degeneration in PSP patients involving predominantly mesio-frontal areas.

In contrast to a previous ROI based morphometric study, the basal ganglia—including the putamen and caudate nucleus as well as the globus pallidus—were not significantly reduced in volume in our study. However, mesencephalic volume loss was significant, consistent with previous ROI based findings and probably reflecting the severe midbrain tau pathology that is present in most PSP patients. The failure to detect basal ganglia volume loss probably reflects methodological limitations, including a rather conservative significance level.

Overall, VBM identified a distinct frontal atrophy pattern in PSP patients involving predominantly mesio-frontal areas.

### Table 2 Grey matter and white matter atrophy in progressive supranuclear palsy compared with normal controls

<table>
<thead>
<tr>
<th>Location</th>
<th>BA</th>
<th>Peak coordinates (mm)</th>
<th>Peak z score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grey matter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesial frontal gyrus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>10</td>
<td>−3 50 −5</td>
<td>5.5</td>
</tr>
<tr>
<td>Right</td>
<td>10</td>
<td>5 51 −7</td>
<td>5.4</td>
</tr>
<tr>
<td>Left</td>
<td>10</td>
<td>−3 38 31</td>
<td>4.7</td>
</tr>
<tr>
<td>Right</td>
<td>10</td>
<td>4 28 35</td>
<td>4.7</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>9</td>
<td>−50 36 11</td>
<td>4.0</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>6</td>
<td>−6 −28 66</td>
<td>4.9</td>
</tr>
<tr>
<td>Right</td>
<td>6</td>
<td>8 −25 53</td>
<td>5.0</td>
</tr>
<tr>
<td>Insular cortex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td>−35 10 5</td>
<td>4.9</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td>44 1 0</td>
<td>5.9</td>
</tr>
<tr>
<td>Frontal operculum</td>
<td></td>
<td>−38 21 5</td>
<td>4.6</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td>38 22 5</td>
<td>4.6</td>
</tr>
<tr>
<td>Temporo-occipital region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td>−65 −50 11</td>
<td>4.0</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>White matter</strong></td>
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</tr>
<tr>
<td>Frontotemporal</td>
<td></td>
<td></td>
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<tr>
<td>Left</td>
<td></td>
<td>−41 11 12</td>
<td>5.7</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td>37 13 13</td>
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<tr>
<td>Mesencephalon</td>
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<td></td>
<td></td>
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<tr>
<td>Left cerebral peduncle</td>
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<td>−8 −12 −15</td>
<td>3.9</td>
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<tr>
<td>Right cerebral peduncle</td>
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<td>8 −11 −15</td>
<td>4.4</td>
</tr>
<tr>
<td>Central</td>
<td></td>
<td>2 −18 −8</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Anatomical location, Brodmann area (BA), Talairach’s coordinates (x, y, z), and z values of clusters with reduced volume (p<0.05 corrected for multiple comparison).
We propose that meso-frontal atrophy accounts for cardinal features of the PSP associated behavioural disorder, including deficits of cognitive and motor initiation.

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