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 (pcorr <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.

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 256x256, 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 7x8x7 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 (7×8×7) basis functions. Following reslicing onto a small voxel size of 1×1×1 mm to minimise partial volume effects,24 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.18 19 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 10×10×10 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 (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.

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 (puncorr<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.

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.

Table 1: Demographic and clinical data in patients with progressive supranuclear palsy (PSP) and controls

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Age (years)</th>
<th>UPDRS-III</th>
<th>DD (years)</th>
<th>L-Dopa response</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSP (12)</td>
<td>67.5 (6.6)</td>
<td>38.9 (10.9)</td>
<td>2.7 (0.9)</td>
<td>11/1/0</td>
</tr>
<tr>
<td>Controls (12)</td>
<td>60 (5.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 within the precentral region of PSP patients. The atrophy in the temporo-occipital area could partly reflect atrophy of area MT/V5. This area participates in pathways mediating smooth pursuit and saccades, and requires further study. The atrophy in the temporo-occipital area was significant, consistent with previous ROI studies and probably reflecting the severe mid-brain tau pathology that is present in most PSP patients.

Our study shows preferential volume loss of mesio-frontal areas in PSP patients compared with age and sex matched controls. It is well established that striato-cortical projections are organised in several fronto-subcortical loops. Mesio-frontal targets of striatal projections were found to be engaged in the regulation of motor initiation, response selection, motivation, and other goal directed behaviours. In addition to their motor impairment, most PSP patients show “frontal” behavioural symptoms such as apathy, combined with an impairment of executive functions, action initiation and set shifting, and memory. Thus preferential involvement of mesio-frontal areas in the pathology of PSP as seen in this study is in accordance with the pattern of neuropsychological dysfunction consistently found in PSP patients. A correlation of frontal neuropsychological deficits with frontal hypometabolism and total frontal atrophy has been documented.

VBM of the grey matter partition also showed a remarkable atrophy in the left temporo-occipital area and both insular regions. Atrophy of the insular cortex is seen in Alzheimer’s disease, dementia with Lewy-bodies, and frontotemporal dementia, but its precise clinical correlate remains unclear and requires further study. The atrophy in the temporo-occipital area could partly reflect atrophy of area MT/V5. This area participates in pathways mediating smooth pursuit and saccades, oculomotor functions that are severely affected in PSP. Other components of the pursuit and saccade pathways include frontal eye fields, supplementary eye fields, thalamus, cerebellum, and brain stem. Although these areas have all been incriminated in the oculomotor disorder of PSP, our present study failed to detect significant volume loss except for left sided area MT/V5. The unilaterality of this finding as well as the lack of volume loss in other central oculomotor pathway components may again reflect conservative significance levels as well as the small sample size. Further studies are needed to establish the role of MT5/V5 in the pathogenesis of oculomotor disorders associated with PSP.

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 mid-brain tau pathology that is present in most PSP patients.

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>Medial 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>Right</td>
<td></td>
<td></td>
<td></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></td>
<td></td>
</tr>
<tr>
<td>Left</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>19/39</td>
<td>-65 -50 11</td>
<td></td>
</tr>
<tr>
<td><strong>White matter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontotemporal</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<td>5.2</td>
</tr>
<tr>
<td>Mesencephalon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left cerebral peduncle</td>
<td></td>
<td>-8 -12 -15</td>
<td>3.9</td>
</tr>
<tr>
<td>Right cerebral peduncle</td>
<td></td>
<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 mesio-frontal atrophy accounts for cardinal features of the PSP associated behavioural disorder, including deficits of cognitive and motor initiation.

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**REFERENCES**

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