Frontal atrophy correlates with behavioural changes in progressive supranuclear palsy


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Summary
Regional brain volumes were measured in 21 patients with progressive supranuclear palsy (PSP), 17 patients with Parkinson’s disease and 23 controls using 3D MRI-based volumetry. Cortical, subcortical and ventricular volume measures were correlated with global indices of motor disability and cognitive disturbance. All MRI measures, including hippocampal volume, were preserved in Parkinson’s disease. Patients with PSP could be distinguished from both Parkinson’s disease and controls by whole brain volume loss, ventricular dilatation and disproportionate atrophy of the frontal cortex. Caudate nucleus volume loss additionally differentiated PSP from controls, but was modest in severity and proportionate to whole brain volume loss. The present study identifies disease-specific differences in the topography of brain atrophy between PSP and Parkinson’s disease, and has potential implications for the in vivo radiological differentiation of these two disorders. In PSP, the variance in frontal grey matter volume related to measures of behavioural disturbance, confirming the use of behavioural tests for ante-mortem case differentiation and suggesting that intrinsic cortical deficits contribute to these clinical disturbances.

Keywords: frontal cortex; Parkinson’s disease; progressive supranuclear palsy; volumetric MRI

Abbreviations: ADL = activities of daily living; CDR = Clinical Dementia Rating; FBI = Frontal Behavioural Inventory; H&Y = Hoehn and Yahr; ICV = intracranial volume; IQ = intelligence quotient; MMSE = Mini-Mental State Examination; PSP = progressive supranuclear palsy; UPDRS = Unified Parkinson’s Disease Rating Scale; WMC = white matter change

Introduction
Progressive supranuclear palsy (PSP) is one of the most frequently encountered extrapyramidal disorders after Parkinson’s disease (Litvan, 1999; Nath et al., 2001). In addition to their movement disorder, patients with PSP have a variety of behavioural disturbances, often in association with impairment of executive function (Litvan et al., 1996b). Disruption of cortical–subcortical brain circuits (Masterman and Cummings, 1997) is postulated to be responsible for these clinical features (Litvan et al., 1996b). To date, only one in vivo MRI volumetric study has been published on PSP, with measures limited to subcortical brain structures (Schulz et al., 1999). Our post-mortem work found an association between cognition and frontal, but not subcortical, atrophy in PSP (Cordato et al., 2000). In contrast, in vivo and post-mortem studies suggest a relationship exists between hippocampal volume and the severity of cognitive disturbances in Parkinson’s disease (Riekkinen et al., 1998; Cordato et al., 2000). There have been no similar correlative clinical volumetric studies performed in vivo for PSP. The present study further examines the relationship between behavioural disturbances, broad indices of cognitive decline and measures of cortical (frontal lobe), subcortical (caudate nucleus), medial temporal (hippocampus) and global brain (whole brain, ventricular system) volumes in PSP and Parkinson’s disease. The structures chosen are those previously implicated from studies of cognitive and behavioural disturbances in these disorders (Litvan et al., 1996b; Masterman and Cummings, 1997; Riekkinen et al., 1998; Cordato et al.,...
2000). These volumetric measures were additionally tested for their ability to independently predict diagnostic phenotype.

**Methods**

**Case selection**

Thirty-eight community-dwelling age- and sex-matched patients with PSP or Parkinson’s disease were recruited from the Movement Disorders Clinic of a large University of Sydney teaching hospital (Westmead Hospital) and by neurologists from the Sydney Movement Disorder Society. PSP and Parkinson’s disease cohorts were selected to approximate the mid stage of their respective disease courses, as indicated by average disease durations (Hughes et al., 1992; Santacruz et al., 1998). PSP and Parkinson’s disease cases at similar stages of their respective disease courses typically differ in the duration of their illness as well as on scoring using standardized disease severity indices including the Hoehn and Yahr scale (H&Y; Hoehn and Yahr, 1967) and the Unified Parkinson’s Disease Rating Scale (UPDRS; Fahn et al., 1987). Accordingly, the mid-stage PSP and Parkinson’s disease cohorts examined for the present study were not inappropriately matched for duration of illness, H&Y or UPDRS scores.

Twenty-one patients satisfied diagnostic criteria established by the National Institute of Neurological Disorders and Stroke (NINDS) and Society for Progressive Supranuclear Palsy Inc. for PSP (18 probable and three possible; Litvan et al., 1996a). Subsequent pathological confirmation of PSP was available in two subjects. All PSP cases had progressive symmetric parkinsonism (axial greater than limb) with postural instability and electro-oculographically confirmed vertical supranuclear palsy (Vidailhet et al., 1994; Litvan et al., 1996a). Unsuccessful levodopa challenges (as reported by patients, carers and treating neurologists) were administered to 17 of the 21 PSP cases at some stage of their disease course (nine out of 17 cases tried on 150–500 mg daily; eight out of 17 cases tried on ≥500 mg daily). Levodopa was not tried in the remaining four PSP cases on the basis of clinical diagnosis alone. Nevertheless, 13 out of 21 PSP cases were regularly medicated with levodopa at the time of study (mean dose 420 ± 165 mg daily). For comparison, 17 patients satisfying clinical criteria for Parkinson’s disease (16 probable, one possible), as defined by the United Kingdom Parkinson’s Disease Brain Bank (Hughes et al., 1992) and by Gelb et al. (1999), were selected. All Parkinson’s disease cases had a levodopa-responsive and treated (mean levodopa dose 676 ± 357 mg daily) akinetic-rigid syndrome (limb greater than axial) in the absence of supranuclear ophalmoplegia (confirmed by electro-oculography; Vidailhet et al., 1994; Litvan et al., 1996a). Cases with identifiable causes of parkinsonism (including previous encephalitis and neuroleptic medication exposure) as well as patients exhibiting atypical clinical features such as alien limb syndrome, autonomic failure or cerebellar signs were excluded.

For comparison, 23 age- and sex-matched normal controls without neurological, psychiatric or neuroradiological abnormalities were recruited from spouses, care-givers and friends of the patients in addition to hospital and community volunteers. Entry criteria for controls included functional independence on the Barthel’s Activities of Daily Living (ADL) Scale (score = 100; Mahoney and Barthel, 1965) as well as scores of zero on the Clinical Dementia Rating (CDR) Scale (Hughes et al., 1982), ≥27 on the Mini-Mental State Examination (MMSE; Folstein et al., 1975) and <10 on the Geriatric Depression Scale (Yesavage et al., 1982). Written informed consent was obtained from each subject according to the Helsinki Declaration and the project was approved by the Human Research Ethics Committee of the Western Sydney Area Health Service.

Mandatory exclusion criteria for disease and control cases included history of ischaemic heart disease, cardiac/coronary artery surgery, major head injury, drug/alcohol abuse, major psychiatric or focal neurological disorders, and structural lesions including substantial white matter change on proton density and T2-weighted MRI brain images (see Imaging for details of MRI sequences). An experienced neuroradiologist (M.S.) reviewed all MRI films. White matter change was assessed using a previously reported 60-point scale (Cleary et al., 1994). Investigators were blinded to patient identity and clinical diagnosis for these analyses. The exclusion criterion for white matter change was a consensus score >20 (raters N.J.C. and S.J.W.). Of the 61 cases included for study, the majority (n = 59) had white matter change scores <10, with only two controls registering scores between 10 and 20. No case fulfilled current clinical criteria for Alzheimer’s disease (McKhann et al., 1984), vascular dementia (Roman et al., 1993) or dementia with Lewy bodies (McKeith et al., 1996). Demographic data for the study groups are shown in Table 1.

**Evaluation of clinical features**

All disease and control cases underwent the same standardized specialist neurological assessment administered by one clinician (N.J.C.) with history (verified by collateral source) and physical examinations performed within 2 weeks of MRI acquisition. In addition to the standard measures utilized for the above criteria, disease severity was quantified using the H&Y scale as well as the mentation, ADL and motor examination components of the UPDRS. These scales have been validated as measures of disease severity in both Parkinson’s disease (Richards et al., 1994; Louis et al., 1996) and PSP (Cubo et al., 2000). Behavioural disturbances were estimated using the frontal behavioural inventory (FBI; Kertesz et al., 1997) while the pre-morbid IQ was assessed using the National Adult Reading Test (Nelson and O’Connell, 1978). For Parkinson’s disease cases with motor fluctuations (n = 12), H&Y and UPDRS scores are reported in
the OFF state (i.e. when levodopa effect wore off). MMSE and pre-morbid IQ scores were acquired in the ON phase (i.e. when levodopa was having a beneficial clinical effect).

Average test scores for each group are given in Table 1.

### Imaging

Sixty-one patients and controls underwent MRI scanning at Westmead Hospital, Sydney on a Siemens Magnetom Vision 1.5 tesla scanner (Siemens AG, Erlangen, Germany). Three-dimensional magnetization-prepared rapid gradient-echo (MPRAGE) sequences \[9.7/4/1/12 \text{[TR (repetition time)/TE (echo time)/NEX (number of excitations)/FA (flip angle)]}, \] 246 × 1.02 mm thick contiguous coronal slices were acquired for volumetric analysis. Proton density and T2-weighted MRI brain images \[4224/20–120/1/180 \text{[TR/TE/NEX/FA]}, \] 24 × 5 mm thick contiguous transverse slices were acquired for detection of structural abnormalities. No information indicating case identity or clinical diagnosis appeared on the scans. MRI image files were transferred from digital optical disc to a SGI O2 workstation (Silicon Graphics Inc., Mountain View, Calif., USA) and randomly coded to ensure patient confidentiality in addition to blinded rating of all data.

#### Delineation of regions of interest and volume estimation

One rater (N.J.C.) performed all MRI volume measurements from the MPRAGE dataset using ANALYZE 7.5 software (Mayo Clinic, Rochester, Minn., USA). The volumetric analyses were performed ~6 months following completion of all clinical assessments and MRI scan acquisitions at a separate site in Melbourne, Australia (CNRAU/MHRI). Investigator N.J.C. was blinded to patient identity and clinical diagnosis for all analyses.

### Intracranial volume (ICV)

ICV was measured by manually tracing the outer margin of the dura mater on 1.02 mm thick sagittally orientated images with a previously described one in 10 random and systematic sampling strategy (Eritaia et al., 2000).

### Whole brain volume

This was estimated using a validated 3D morphometric procedure (Velakoulis et al., 1999). Intensity thresholding maximally separated brain from neighbouring extracerebral structures to produce minimum and maximum pixel values. These values were applied to all slices in a series of erosions and dilatations resulting in a segmented whole brain binary image that included the brainstem and cerebellum, but not the ventricles, cisterns or sulcal cerebrospinal fluid. The binary image was multiplied algebraically with the original grey scale data file to produce a ‘stripped’ whole brain grey scale image. The ‘stripped’ coronal images were subsequently reconstructed three-dimensionally and the volume estimated by volume rendering. This image file was also used for the ensuing hemisphere and frontal lobe volume estimation procedures (see below).

### Left and right hemisphere volumes

Right hemisphere segmentation was achieved by manually editing away the entire left hemisphere from the whole brain

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Table 1: Demographic details and major disease severity indices

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PSP</th>
<th>PD</th>
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<tbody>
<tr>
<td>Gender (M: F)</td>
<td>14 : 9</td>
<td>14 : 7</td>
<td>13 : 4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.5 ± 7.2</td>
<td>70.3 ± 6.4</td>
<td>67.7 ± 6.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.0 ± 9.7</td>
<td>169.1 ± 8.6</td>
<td>170.1 ± 9.4</td>
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<tr>
<td>Handedness (R : L)</td>
<td>23 : 0</td>
<td>18 : 3</td>
<td>15 : 2</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>N/A</td>
<td>47.7 ± 34.0</td>
<td>94.3 ± 35.5</td>
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UPDRS
- Total score* | 0.6 ± 1.7 | 45.1 ± 20.2 | 32.3 ± 12.5 |
- Mentation subscore* | 0.3 ± 0.5 | 2.6 ± 1.9 | 1.8 ± 1.0 |
- ADL subscore* | 0.1 ± 0.3 | 19.3 ± 10.1 | 11.6 ± 6.2 |
- Motor subscore* | 0.3 ± 0.5 | 23.1 ± 10.1 | 18.9 ± 7.4 |
- H&Y stage*    | 0 ± 0    | 3.8 ± 1.1 | 2.6 ± 0.7 |
- FBI          | 0.2 ± 0.8 | 21.3 ± 12.0 | 4.9 ± 4.5 |
- MMSE†        | 29.4 ± 0.9 | 25.4 ± 3.2 | 28.6 ± 1.2 |
- Education level (years) | 11.7 ± 2.8 | 9.8 ± 2.6 | 11.3 ± 3.3 |

Values are mean ± standard deviation. FBI = frontal behavioural inventory (maximum 72); H&Y = Hoehn and Yahr (maximum 5); MMSE = Mini-Mental State Examination (maximum 30); N/A = not applicable; PD = Parkinson’s disease; UPDRS = Unified Parkinson’s Disease Rating Scale (total maximum 140, mentation maximum 16, ADL maximum 52, motor maximum 72). *For patients responsive to levodopa, scores given in the OFF state. †For patients responsive to levodopa, scores acquired in the ON state. ‡PSP different from PD (t-test, \( P < 0.05 \)). §PSP different from controls and PD (ANOVA, Bonferroni; \( P < 0.05 \)). ¶PSP different from controls (ANOVA, Bonferroni; \( P < 0.05 \))
image file. The right hemisphere was then subtracted algebraically from the original image leaving an edited left hemisphere. Hemisphere volumes were estimated using similar techniques to those described above.

**Ventricle volumes**
The volumes of the aqueduct, lateral, third and fourth ventricles were estimated as a whole. Non-ventricular structures of intermediate or low intensity were manually assigned pixel values well above those of the ventricular system on each contiguous 1.02 mm thick coronal slice. Intensity thresholding subsequently separated ventricles from brain and other edited tissue. The resulting binary image was reconstructed three-dimensionally and the volume estimated using volume rendering as previously described for whole brain volume determinations.

**Volume of frontal lobe grey matter**
Frontal lobe dissection was performed using previously validated anatomical criteria (Aylward et al., 1998). First, the surfaces of left and right postcentral and superior temporal gyri were identified and manually ‘painted’ on 3D reconstructions of the whole brain image file. Non-frontal lobe structures were then edited away manually and the remaining AC–PC (anterior commissure–posterior commissure) orientated frontal cortex arbitrarily sub-divided into frontal pole (all cortex anterior to genu of corpus callosum) and posterior frontal cortex (frontal cortex posterior to frontal pole; see Fig. 1). Stereological point counting was used to estimate the frontal grey matter volume (Aylward et al., 1998), as this method proved the most reliable and efficient for grey–white differentiation. A randomly positioned and orientated grid of points (x and y spacing = 5 mm, mean points per coronal slice = 625) was overlayed on the edited frontal lobe images. The number of points falling on frontal grey matter was counted manually for each contiguous 1.02 mm thick coronal slice and then summed for volume estimation according to Cavalieri’s principle (Cavalieri, 1653).

**Caudate nucleus volume**
The lateral ventricle was used to define the anterior, posterior, medial and superior boundaries of the caudate nucleus. The inferior border was defined by the stria terminalis and nucleus accumbens (demarcated by a line connecting the inferior margin of the lateral ventricle with the inferior border of the internal capsule), while the white matter of the internal capsule defined the lateral caudate boundary. Left and right caudate perimeters were traced manually on each contiguous 1.02-mm thick coronal slice and the volumes for each slice (area delineated multiplied by slice thickness) were summed to calculate the total caudate volumes for each hemisphere. Fig. 1 illustrates delineation of the left caudate nucleus on coronal brain slices.

**Hippocampus volume**
Left and right hippocampal perimeters were traced manually on each contiguous 1.02 mm thick coronal slice using previously defined anatomical criteria (Velakoulis et al., 1999). Hippocampal volumes for each slice (area delineated multiplied by slice thickness) were summed to calculate total hippocampal volumes for each hemisphere.

**Reliability of volume measures**
 Interrater reliability between two independent raters (N.J.C. and S.J.W.) was estimated on the basis of 10 randomly selected volume determinations for individual regions of interest. Measures were acquired with raters blinded to patient identity and clinical diagnosis. Intraclass correlations for inter-rater reliability ranged from 0.86 for hippocampal volumes (3% mean error) to 0.996 for ICV (<1% mean error). An intraclass correlation coefficient for intra-rater reliability of regional volume estimates was determined by re-measuring at least 10 randomly selected images for each structure (rater N.J.C.). For all regions, this coefficient was above 0.96 (hippocampus, 3% mean error), with values exceeding 0.99 for intracranial, ventricular and whole brain volume measures (<1% mean error).

All volumetric measures were normally distributed, except for the ventricular volume. To correct for positive skew, ventricular volumes were transformed logarithmically.

**Analyses**

**Clinical variables**
Groups were compared using χ² tests for categorical variables (sex and handedness) and one-way analyses of variance for continuous variables (age, height, education level, pre-morbid IQ and MMSE). Differences in disease duration and severity (UPDRS, H&Y and FBI) between Parkinson’s disease and PSP were evaluated using unpaired t-tests. Clinical data are expressed as means ± standard deviations.

**Volumetric variables**
For group analyses, region of interest volumes were divided by the ICV to normalize for inter-individual variations in cranial size. Groups were assessed using analyses of covariance (univariate analysis for ventricular volume; repeated measures analyses for non-ventricular volumes using left and right values as well as anteroposterior divisions for the frontal lobe). Systematic laterality of volume measures was not identified in any diagnostic group. Covariance controlled for possible confounding effects of age, height, pre-morbid IQ/education level and whole brain volume. Although diagnostic groups were matched for gender, the effect of this variable on each volume measure was evaluated separately using two-way analyses of variance with both sex
and diagnosis as factors. All volume measures were larger in males than females; however, this difference only reached significance for intracranial [11.4% larger in males, $F(1,55) = 11.2, P = 0.001$] and ventricular [21.7% larger in males, $F(1,55) = 10.4, P = 0.04$] volumes. Gender differences in intracranial and ventricular volumes disappeared when analyses were co-varied for peak adult height and there were no interactions between sex and clinical diagnosis for any volume measure. Hence, gender was not factored into subsequent analyses. Post hoc group comparisons of the volumetric data were based on estimated marginal means with Bonferroni adjustments for multiple comparisons. These tests were repeated on the Parkinson’s disease and PSP cases covarying for disease duration and severity. Data are

Fig. 1 Three-dimensional MRI reconstructions demonstrating segmented frontal cortex (A and B), and tracings on coronal MRI images for the volumetric measurement of the caudate nucleus (C, D and E). (A) Volume rendered, three-dimensional reconstructions of partially edited frontal cortex. Left image is from a superior perspective; right view is from a latero-superior perspective. (B) Fully dissected frontal cortex is subdivided into posterior frontal cortex (left), and frontal pole (right). (C–E) Representative coronal MR images demonstrating manual edge tracings of the left caudate nucleus.
expressed as estimated marginal means ± 95% confidence intervals.

**Clinicoradiological correlations**
Since ICV was included as an independent variable for these analyses, volumetric measures uncorrected for cranial volume were used (left and right combined). Analyses were performed separately for Parkinson’s disease and PSP groups. The clinical variables selected reflected observed clinical differences between Parkinson’s disease and PSP (see Results). For Parkinson’s disease, independent variables were age, disease duration, UPDRS–motor, UPDRS–ADL, ICV and whole brain volume. For PSP, independent variables included age, disease duration, UPDRS–total, FBI, MMSE, ICV and whole brain volume. Stepwise linear regression analyses were used to examine the relative contribution of these independent variables to changes in uncorrected MRI volumes for major brain regions (whole brain, ventricular, frontal, caudate and hippocampal volumes) when analyses were repeated using whole brain volume. When whole brain volume was examined as a dependent variable, it was excluded as an independent variable. Statistical associations were obtained with $P_{in} = 0.05$ and $P_{out} = 0.1$. For all other analyses, statistical significance is reported at the $P < 0.05$ level.

**Predictive statistics**
Left and right volumetric measures were combined for these analyses. A discriminant analysis was performed in which ICV-corrected regional volume measures (whole brain, ventricular, frontal, caudate and hippocampal volumes) were entered as independent variables in order to determine the structural measure(s) contributing most to the discrimination of the three diagnostic groups.

**Results**

**Clinical variables**
Twenty-three controls, 17 Parkinson’s disease and 21 PSP cases ranging in age from 58 to 84 years were examined. Due to selection criteria, diagnostic groups were matched for mean age, sex, handedness, mean peak adult height (range 150–183 cm) and mid-disease stage, but differed in their diagnostic indicators, disease severity indices (UPDRS scores $t = 2.4, P = 0.02$; H&Y scores $t = 4.4, P < 0.001$) and durations (mean disease duration $t = -4.1, P < 0.001$) (see Table 1).

Except for H&Y scores in Parkinson’s disease, disease severity indices correlated or trended towards a correlation with disease duration for both parkinsonian disorders (Parkinson’s disease $\beta = 0.30, P = 0.25$, Parkinson’s disease $\beta = 0.47, P = 0.07$; PSP $\beta = 0.40, P = 0.08$, PSP $\beta = 0.47, P = 0.03$). Nine PSP cases had questionable or mild memory impairment (CDR scores of 0.5 or 1) while ‘healthy’ CDR scores of zero were registered for all remaining PSP, Parkinson’s disease and control cases. These findings are reflected in significantly worse MMSE performance of the PSP group compared with controls and Parkinson’s disease cases ($F(2,58) = 22.9, P < 0.001$; see Table 1). Similarly, behavioural disturbance scores (FBI) were greater in PSP than Parkinson’s disease ($t = 5.6, P < 0.001$; see Table 1), with evidence for specific frontotemporal dementia (FBI score $\geq 27$; Kertesz et al., 1997) again limited to PSP ($n = 8$). Pre-morbid IQ was lower in PSP and Parkinson’s disease cases compared with controls ($F(2,44) = 5.1, P = 0.01$). However, IQ estimates were available for fewer than half of the 21 PSP cases largely due to dysarthria interfering with National Adult Reading Test interpretation. Education level correlated with pre-morbid IQ (Pearson correlation 0.4, $P = 0.004$) and was used as a surrogate for IQ estimates in subsequent analyses.

**Volumetric variables**
Patients with PSP could be distinguished from both Parkinson’s disease patients and controls by atrophy of the whole brain [8% volume reduction, $F(2,57) = 18.8, P < 0.001$], ventricular dilatation [77% volume increase, $F(2,57) = 19.2, P < 0.001$] and frontal grey matter atrophy [19% volume reduction, $F(2,58) = 54.7, P < 0.001$; see Figs 2 and 3]. These results remained unchanged when analyses were covaried for disease duration and severity. Further analysis revealed that advancing age was associated with the first two variables [greater whole brain atrophy $F(1,56) = 27.1, P < 0.001$ and ventricular dilatation $F(1,56) = 21.8, P < 0.001$]. Differences in frontal and ventricular volumes in PSP were maintained when analyses were repeated using whole brain volume corrected data instead of ICV normalized values [13% reduction, $F(2,58) = 30.8, P < 0.001$ and 63% increase, $F(2,57) = 24.2, P < 0.001$]. There was also a significant interaction between diagnostic group and antero-posterior distribution of frontal atrophy [$F(2,58) = 2.3, P < 0.001$, with proportionately greater volume reduction in the posterior frontal cortex (21% reduction) versus the frontal pole (15% reduction) of PSP cases. Caudate nucleus volume only differed between PSP and controls [15% reduction; $F(2,57) = 5.7, P < 0.004$]. Caudate atrophy was not, however, apparent when analyses were repeated using whole brain volume corrected data. Hippocampal volume (normalized for either ICV or whole brain volume) was not significantly different between any of the diagnostic groups. There were no significant differences between Parkinson’s disease patients and controls on any of the volume measures.

**Clinicoradiological correlations**
To understand the contributions of several clinical and radiological variables to the volumetric measures, separate stepwise linear regression analyses were performed for PSP and Parkinson’s disease cases. For PSP, 73% of the variance in frontal grey matter volume was explained by variation in whole brain volume [$F(2,18) = 28.5, \beta = 0.82, P < 0.001$] and
total FBI ($\beta = -0.25, P = 0.04$) but not MMSE scores. For Parkinson’s disease, 76% of the frontal grey matter variance was explained by variance in whole brain volume [$F(2,14) = 26.9, \beta = 0.85, P < 0.001$] and UPDRS–ADL ($\beta = -0.41, P = 0.005$) but not UPDRS–motor scores. As expected, ICV accounted for almost 80% of the variance in whole brain volume measurements for both PSP [adjusted $r^2 = 0.79, F(1,19) = 76.2, \beta = 0.90, P < 0.001$] and Parkinson’s disease [adjusted $r^2 = 0.77, F(1,15) = 53.0, \beta = 0.88, P < 0.001$], supporting its use for data normalization. However, age only contributed to the variance for ventricular [adjusted $r^2 = 0.24, F(1,15) = 6.1, \beta = 0.54, P = 0.03$] and caudate [adjusted $r^2 = 0.30, F(1,15) = 7.7, \beta = -0.58, P = 0.01$] volumes in Parkinson’s disease but not for PSP. Disease duration did not contribute significantly to the variance of any volume measure.

**Predictive statistics**

A discriminant function analysis was performed to determine whether the volume measures could be useful predictors of diagnostic group. This resulted in two significant canonical discriminant functions. The second discriminant function added significantly to the discrimination provided by the first.

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**Fig. 2** Graphs of MRI volumetric brain measures for PSP, Parkinson’s disease (PD) and controls. For each brain region, individual volumes as well as estimated marginal means with 95% confidence intervals are graphed separately for PD, PSP and controls. *$P < 0.001$ compared with controls and PD. **$P = 0.01$ compared with controls. Volumes are normalized for total ICV (%). (A) Mild to moderate whole brain volume loss was found in cases with PSP compared with PD and controls [$F(2,57) = 18.8, Eta = 0.4, P < 0.001$]. (B) Marked, disproportionate frontal grey matter atrophy was found in PSP compared with PD and controls [$F(2,58) = 54.7, Eta = 0.7, P < 0.001$]. (C) Prominent ventricular dilatation was present in PSP cases compared with PD and controls [$F(2,57) = 19.2, Eta = 0.4, P < 0.001$]. (D) Modest caudate atrophy in PSP compared with controls. Atrophy was proportionate to whole brain volume loss [$F(2,58) = 4.8, Eta = 0.1, P = 0.01$]. (E) Hippocampal volume was preserved in PD and PSP.
Discussion

This is the first study to quantify and compare clinical features and in vivo volumes of cortical, subcortical and medial temporal lobe brain structures in PSP and Parkinson’s disease. The most compelling changes related to the frontal lobe of PSP patients. Patients with PSP exhibited features of a dementia of frontal lobe type using the 24-item FBI, sensitive for the detection of behavioural disturbances. This was associated with substantial frontal grey matter atrophy. The severity of frontal behavioural changes correlated with the degree of frontal atrophy. Behavioural disturbances in PSP have previously been attributed to disconnection of the frontal cortex by prominent subcortical pathology (Litvan et al., 1996b). We have previously shown that frontal atrophy not only correlates with cognitive impairment, but also with frontal histopathology in pathologically confirmed cases with end-stage PSP (Cordato et al., 2000). Intrinsic structural changes within the frontal cortex thus appear to contribute to frontal behavioural deficits demonstrated in PSP. The absence of a correlation between MMSE scores and volumetric measures in this disorder is not surprising, as the MMSE is an insensitive measure of frontal lobe dysfunction (Folstein et al., 1975).

The posterior frontal grey matter was proportionately more atrophic than the frontal pole in PSP. MRI spectroscopy (Tedeschi et al., 1997; Abe et al., 2000), PET (Goffinet et al., 1989) and pathological (Hof et al., 1992; Daniel et al., 1995; Hanihara et al., 1995; Vervy et al., 1996; Bergeron et al., 1997) studies in PSP have also demonstrated a predilection for cortical abnormalities in the posterior frontal cortex. Cortical structures responsible for volitional motor activity form the bulk of the posterior frontal cortex (Roland and Zilles, 1996). Frontal atrophy in the present study did not, however, relate to the severity of motor scores in PSP. Although our findings cannot exclude a significant contribution from frontal pathology, they do suggest that parkinsonian motor severity is related more to the extensive subcortical pathology in this disease. Subcortical degeneration has also been primarily implicated in the gaze palsy of PSP (Halliday et al., 2000). It is interesting to note, however, that the frontal eye field, a structure considered important for the normal execution of smooth pursuit and saccadic eye movements (Leigh and Zee, 1999), is also located within the posterior frontal cortex (Luna et al., 1998). We could not explore correlations between frontal cortical structures and the presence of eye signs, as all PSP cases in the present study were required to exhibit gaze palsy.

Ventricular dilatation and atrophy of the caudate nucleus were additionally found in the PSP patients. In many cases, the ventricular dilatation was substantial and apparent to the naked eye. Our findings quantitatively confirm impressions of ventricular dilatation previously reported in qualitative CT (Ambrosetto, 1987) and MRI studies (Schonfeld et al., 1987; Aiba et al., 1997; Schrag et al., 2000) of PSP. Caudate atrophy was modest (~15% atrophy compared with controls)

**Fig. 3** Volume rendered, three-dimensional MRI reconstructions of the whole brain and ventricular system in PSP (A), Parkinson’s disease (B) and a normal control (C). Images all acquired at the same scale and reduced five fold for illustration. Whole brain image, lateral view (left images for A, B and C)—cortical atrophy (particularly frontal) is apparent in PSP (A) compared with Parkinson’s disease (B) and control (C). Lateral view of the ventricular system (middle images for A, B and C)—dilatation of the lateral and third ventricles is apparent in PSP (A) compared with Parkinson’s disease (B) and control (C). Superior view of the ventricular system (right images for A, B and C)—marked dilatation of the lateral ventricles is apparent in PSP (A) compared with Parkinson’s disease (B) and controls (C).
and proportionate to overall whole brain volume loss in PSP. We were unable to replicate the substantial atrophy of the caudate nucleus (~50%) identified by Schulz et al. (1999) in their MRI study of six PSP cases. The magnitude of caudate atrophy reported in the present study is consistent with our post-mortem findings in end-stage PSP cases (Cordato et al., 2000), and corresponds with other macroscopic pathological (Mann et al., 1993), qualitative MRI (Soliveri et al., 1999) and histopathological studies (Probst et al., 1993) of the caudate in PSP.

The present study confirms that all selected MRI volumes, including hippocampal measures were preserved in Parkinson’s disease (Cordato et al., 2000). This contrasts with another methodologically similar MRI study that reported 26% hippocampal atrophy in 12 non-demented Parkinson’s disease patients (Laakso et al., 1996). This value approaches the magnitude of hippocampal atrophy observed in Alzheimer’s disease (Laakso et al., 1996). Our work in pathologically confirmed Parkinson’s disease cases (mean H&Y score 3.9; range 2–5) suggests that mild, non-significant hippocampal atrophy (~10%) occurs later in this disorder, and that the volume of this structure varies both with the severity of parkinsonism and especially with the presence of dementia (Cordato et al., 2000). Riekkinen et al. (1998) similarly identified a relationship in Parkinson’s disease between severity of motor and memory impairment and hippocampal volume in vivo. Hippocampal volume preservation in the present study is therefore not unexpected, as the mean group H&Y score for Parkinson’s disease was 2.6 (range 2–4) and cases with prominent cognitive disturbances were excluded to avoid group contamination with dementia with Lewy bodies. As predicted by our post-mortem work (Cordato et al., 2000), hippocampal volume was also normal in PSP.

Of all the regional brain measures, frontal grey matter volume was most useful in predicting diagnostic phenotype. Indeed, the discriminant function reflecting frontal atrophy was largely responsible for the excellent diagnostic sensitivity and specificity for PSP. The PSP and Parkinson’s disease cohorts in the present analyses were selected to approximate the mid-stage of their disease. It is, however, the in vivo differentiation of early-stage cases that poses the major problem for clinicians. Interestingly, we did not identify a

![Fig. 4 Graph summarizing the results of the discriminant analysis (PSP versus Parkinson’s disease versus controls). Independent variables entered into the analysis were whole brain, ventricular, frontal, caudate and hippocampal volumes. Function 1 mainly reflects the contribution of frontal volume (loading = 0.93) to diagnosis, with a smaller loading from caudate volume (loading = 0.27). Function 2 is a measure of whole brain volume (loading = ±0.51) and, inversely, ventricular volume (loading = 0.60). This can be interpreted as a measure of general atrophy. The hippocampus did not contribute to the discrimination of diagnostic groups. The graph shows the distribution of cases in the discriminant function space, along with the centroids (mean location) for each diagnostic group. The PSP cases are well separated from the other two groups, mainly along function 1, reflecting frontal volumes. There is some overlap between the Parkinson’s disease and control groups, which differ mainly on function 2, reflecting atrophy.](image-url)
relationship between disease duration and any volume measure, even though there was sufficient variability in these measures for the patients selected. This suggests that the frontal atrophy identified in PSP cases could be an early and consistent event, and therefore may be useful in discriminating this disorder from Parkinson’s disease and controls at earlier stages of the disease process.

A comparison of the present study with our previous post-mortem study (Cordato et al., 2000) may identify any progression of brain atrophy during the later stages of the disease process (approximately mid-stage disease for MRI examined cohort versus end-stage disease for post-mortem study). Since ICV for data normalization is not available for post-mortem studies, the remaining discussion compares mean proportional volume changes from control values between the cross-sectional cohorts. For Parkinson’s disease, comparisons of MRI and post-mortem hippocampal volume changes have already been alluded to, while volumes of other commonly measured structures were similar to control values in both studies. Proportionate atrophy of the frontal lobes and caudate nuclei for PSP were essentially identical between our in vivo and post-mortem studies. In contrast, whole brain atrophy was considerably greater for post-mortem PSP cases (~19% volume loss) compared with PSP cases in the present study (~10% volume loss). Importantly, this is consistent with patterns of volume change identified for the two PSP patients included in the present MRI study and followed longitudinally to post-mortem (Cordato et al., 2000). These findings suggest that the volume losses identified in other brain structures (e.g. the parietal cortex) at post-mortem in PSP occur, or at least accelerate, during the later stages of the disease course. The data presented suggest that atrophy of the frontal lobes could be an early feature of PSP, which may help to distinguish it from idiopathic Parkinson’s disease. Longitudinal studies of patients seen at an earlier stage of illness with subsequent post-mortem verification are needed to examine this hypothesis in more detail.

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References
Cavaliere B. Geometria indivisibilibus continuorum nova quadam ratione promota: Ex typographia de Ducijis; 1653.


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