PAPER

Diffusion tensor imaging and voxel based morphometry study in early progressive supranuclear palsy

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Background: A comprehensive characterisation of grey and white matter changes in progressive supranuclear palsy (PSP), the second most common extrapyramidal syndrome after Parkinson disease, is still not available.
Objective: To evaluate grey and white matter changes in mild PSP patients by voxel based morphometry (VBM) and diffusion tensor imaging (DTI), respectively.
Methods: 14 mild PSP patients and 14 healthy controls entered the study and underwent a clinical and neuropsychological evaluation according with a standardised assessment. Each subject had a structural magnetic resonance imaging (MRI) study. Processing analysis of MRI data was carried out according to optimised VBM and fractional anisotropy was determined.
Results: Compared with the controls, in PSP patients VBM analysis showed a significant clusters of reduced grey matter in premotor cortex, frontal operculum, anterior insula, hippocampus, and parahippocampal gyrus, bilaterally. With regard to subcortical brain regions, the pulvinar, dorsomedial and anterior nuclei of the thalamus, and superior and inferior culliculum were affected bilaterally. A bilateral decrease in fractional anisotropy in superior longitudinal fasciculus, anterior part of corpus callosum, arcuate fascicolus, posterior thalamic radiations, and internal capsule, probably involving the cortico-bulbar tracts, was present in PSP patients.
Conclusions: These data provide evidence for both grey and white matter degeneration in PSP from the early disease stage. These structural changes suggest that atrophy of cortical and subcortical structures and neurodegeneration of specific fibre tracts contribute to neurological deficits in PSP.

Progressive supranuclear palsy (PSP) is the second most common neurodegenerative extrapyramidal disorder after Parkinson disease.[1 2] Neurofibrillary tangles, tau positive astrocytes, and occasional ballooned argyrophilic neuronal degeneration involving brain stem, basal ganglia, and frontal lobe represent the neuropathological hallmarks of PSP.[3 4] It is an atypical parkinsonian syndrome characterised by progressive vertical gaze palsy, postural instability with falls, akinesia, axial rigidity, dysphagia, and dementia.[5 6]

Over the past few years, various neuroimaging techniques have been proposed to study PSP for diagnostic purposes.[7–13] The majority of these studies, however, have relied upon visual observations or linear measurement of regions of interest (ROIs), chosen on the basis of knowledge of brain areas pathologically affected in necropsy studies.

Despite many efforts to draw a clear cut picture of the disease, a comprehensive characterisation of grey and white matter changes in PSP patients is still not available, especially at an early stage of the disease.

To study this disease further, we have employed voxel based morphometry (VBM) and diffusion tensor imaging (DTI), two unbiased neuroimaging techniques which have recently been introduced for structural evaluation of the brain in neurological disorders.

VBM, usually undertaken on T1 weighted magnetic resonance images, is a whole brain technique that allows the detection of regionally specific differences in brain tissue composition on a voxel by voxel basis, overcoming methodological limitations of previous anatomical studies.[14] Various data suggest a use for VBM in evaluating neurodegenerative diseases,[13] and there are recent reports that the technique is useful in describing the brain changes of PSP[15] and in differentiating PSP from Parkinson disease.[16]

Nevertheless, even though VBM is undoubtedly reliable in evaluating grey matter abnormalities, there appears to be a lack of sensitivity for white matter voxel based morphometry. This is mainly because of the poor correlation between white matter T1 signal intensities and white matter integrity, leaving the former within apparently normal limits even where there is severe damage.[17 18]

In contrast to this approach based on T1 weighted imaging, diffusion tensor imaging (DTI) provides more subtle information about white matter tissue composition,[19] and allows the demonstration of fibre tracts in vivo.[20–25]

In particular, within cerebral white matter, the coherent orientation of axons constrains water molecules to move preferentially along the main direction of neural fibres, a property called anisotropy. Thus anisotropy can be considered a measurable index of organisation of axons, and allows the precise identification of fibre tracts: the lower the fractional

Abbreviations: BADL, basic activities of daily living; CDR, clinical dementia rating scale; CSF, cerebrospinal fluid; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; DTI, diffusion tensor imaging; FA, fractional anisotropy; FBI, frontal behavioural inventory; FDR, false discovery rate; FWHM, full width at half maximum; GM, grey matter; IADL, instrumental activities of daily living; MMSE, mini-mental state examination; MNI, Montreal Neurological Institute; NPI, neuropsychiatric inventory; PSP, progressive supranuclear palsy; UPDRS, unified Parkinson disease rating scale; VBM, voxel based morphometry; WM, white matter

anisotropy the greater the decrease in fibre coherence of the connecting tract.[17 26 27] It soon appeared that this feature could be exploited to map out the orientation in space of the white matter tracts in the brain, assuming that the direction of the fastest diffusion would indicate the overall orientation of fibres.[19–21]

These observations highlight the importance of considering different neuroimaging techniques for studying grey or white matter abnormalities in neurodegenerative disorders, and prompted the present work, which aimed to characterise the brain changes in the early phase of PSP by the combined used of VBM and DTI.

METHODS

Subjects

Fourteen PSP patients (seven male, seven female; mean (SD) age, 73.0 (5.6) years) recruited from Centre for Neurodegenerative Diseases, University of Brescia, entered the study.

A somatic and neurological evaluation was undertaken in all subjects, along with a routine laboratory examination and brain structural magnetic resonance imaging (MRI).

Motor impairment was evaluated by the motor section of Unified Parkinson Disease Rating Scale (UPDRS-III).[28] Assessment of global cognitive function was carried out according to a standardised battery, including the clinical dementia rating scale (CDR), and the mini-mental state examination (MMSE). The neuropsychological assessment was accomplished by the following tests: Raven coloured progressive matrices, the controlled oral word association test, category fluency, the clock drawing test, Rey complex figure copy and recall, the story recall test, digit span, trail making tests A and B, the token test, and the De Renzi imitation test. Instrumental activities of daily living (IADL) and basic activities of daily living (BADL) were also assessed. Behavioural and psychiatric disturbances were evaluated by the neuropsychiatric inventory (NPI), and the frontal behavioural inventory (FBI).

The National Institute of Neurological Disorders and Stroke (NINDS) Society for PSP (SPSP) criteria were used for patients' inclusion, as follows: gradually progressive disorder; onset at age 40 or older; vertical (upward and downward gaze) supranuclear palsy and prominent postural instability with falls in the first year of the disease onset; and no evidence of other diseases that could explain the above features.[1] A lack of or the poor response to levodopa was considered an adjunctive inclusion criterion. The present series of patients had mild cognitive (MMSE $\geqslant$19) and motor (UPDRS-III $<$30) impairment. All patients fulfilled criteria for probable PSP, and all the subjects included had been followed for at least two years after entering the study. The diagnosis of PSP was confirmed in all cases at the follow up evaluation.

Table 1 Grey matter, white matter, and cerebrospinal fluid total volumes and as fractions of the total intracranial volume in patients with progressive supranuclear palsy and in control subjects

Volume	PSP	Controls	p Value
Grey matter (l)	0.63 (0.06)	0.65 (0.04)	NS
White matter (l)	0.43 (0.05)	0.45 (0.05)	NS
CSF (l)	0.65 (0.11)	0.59 (0.08)	NS
Grey matter/TIV	0.37 (0.05)	0.38 (0.03)	NS
White matter/TIV	0.25 (0.02)	0.27 (0.02)	0.02
CSF/TIV	0.38 (0.04)	0.35 (0.04)	NS.

Values are mean (SD).
CSF, cerebrospinal fluid; PSP, progressive supranuclear palsy; TIV, total intracranial volume.

Stringent exclusion criteria were as follows:

- cerebrovascular disorders, previous stroke, a history of traumatic brain injury, hydrocephalus, or intracranial mass, documented by MRI or another neurological disease;
- other causes of extrapyramidal syndromes according to current clinical criteria;
- significant medical problems;
- major depressive disorder, bipolar disorder, schizophrenia, substance abuse disorder, or mental retardation according to DSM-IV criteria.

Fourteen healthy subjects (seven male, seven female, mean (SD) age, 65.6 (4.1) years) were recruited from among patients' spouses or relatives and were included as normal controls. They were interviewed, assessed for neurological or cognitive dysfunction, evaluated for diseases that were exclusion criteria for the patient group, and underwent the MRI structural brain imaging study.

All participants were right handed, and were made fully aware of the aims of the research. Signed informed consent was obtained from all subjects. The work was conducted in accordance with local clinical research regulations and conformed to the Helsinki Declaration.

Statistics

Demographic and clinical data were compared between PSP and controls using Student's t test or the χ^2 test. All values are expressed as mean (SD). The significant level was set at $p<0.05$. Analysis was conducted using statistical software (SPSS Inc, Chicago, Illinois, USA).

Data acquisition

Magnetic resonance imaging (MRI) was undertaken on a 1.5 T Siemens (Simphony) scanner.

For VBM analysis, three dimensional MPRAGE T1 weighted images were acquired using the following parameters: echo time (TE) = 3930 ms, repetition time (TR) = 2010 ms, flip angle = 15°, and field of view (FOV) = 250 mm. This yielded 176 contiguous 1 mm thick slices.

DTI was carried out using echo-planar (EPI) acquisition at 1.5 T with a standard head coil for signal reception. Axial DTI slices were obtained using the following parameters: matrix = 128×128, TE = 122 ms, TR = 6600 ms, flip angle = 15°, and FOV = 220 mm, no gap (5 mm thickness), voxel size = 1.7×1.7×5 mm. Three averages was used, with signal averaging in the scanner buffer. Diffusion weighting was undertaken along six independent directions, with a b value of 1000 s/mm^2. A reference T2 weighted image with no diffusion weighting was also obtained.

Image analysis

Analyses were run on Matlab 6.5 (MathWorks, Natick, Massachusetts, USA) and SPM2 (Wellcome Department of Cognitive Neurology, London, UK: http://www.fil.ion.ucl.ac.uk/spm).[29]

Voxel based morphometry

Customised a priori and template image creation and preprocessing analyses were carried out using an optimised VBM protocol.[30]

Customised a priori and template image creation

Ad hoc a priori and template images were created. Each participant's T1 scan was segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Spatial normalisation parameters were estimated by matching GM

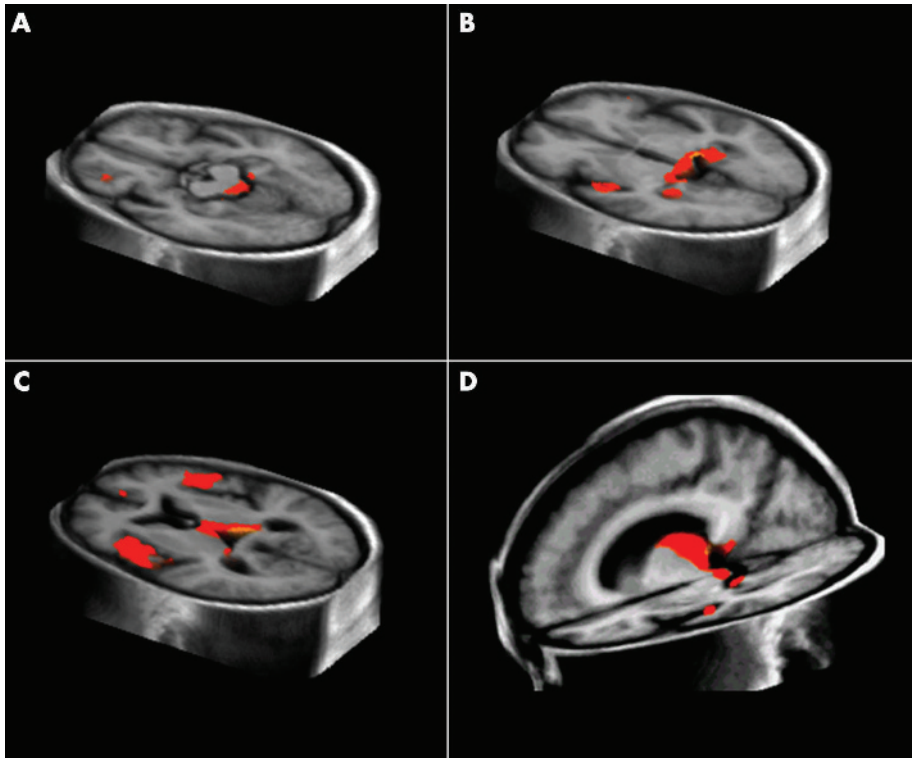

Figure 1 Maps of significant voxels representing regions of reduction in grey matter in patients with progressive supranuclear palsy, superimposed on the mean of their anatomical magnetic resonance images. The specific involvement of collicula (panel A, $z=-12$), hippocampal structures (panel B, $z=-4$), precentral-premotor cortex, orbitofrontal cortex, and thalamus (panel C, $z=8$), and thalamic regions (pulvinar, dorso-medial and anterior nuclei) (panel D, $x=8$ and $z=-9$). The threshold was set at $T=4.17$. See table 2 for coordinates.

tissue with the standard GM template provided by SPM2. The normalisation parameters were applied to the original T1 image. The spatially normalised version of the original anatomical image was segmented in GM, WM, and CSF tissues. Customised a priori and template images were obtained by averaging all subjects' spatially normalised GM, WM, CSF, and T1 images. The mean images were then smoothed with an 8 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

Preprocessing analysis

High resolution anatomical images (in native space) were segmented into GM, WM, and CSF. The SPM segmentation process undertook a cluster analysis with a modified mixture model and a priori information about the likelihood of each voxel being one of a number of different tissue types. A series of automated morphological operations removed unconnected brain voxels from the segmented images.

GM and WM segmented images were thus normalised to customised GM and WM templates and normalisation parameters were reapplied to the initial structural images.

Normalisation was carried out using 16 non-linear iterations and 7×8×7 basis functions. The spatial normalised images were resampled by trilinear interpolation to $1\times1\times1$ mm^3 voxel size.

Optimally normalised MPRG images were then segmented into GM, WM, and CSF segments. In order to restore tissue volumes modified during normalisation processing, Jacobian modulation was applied to normalise GM and WM segments. Modulated GM and WM images were smoothed with a 10 mm FWHM kernel.

To avoid potential bias from the normalisation process, anatomical, grey, and white templates—refereed to a stereotactic space (Montreal Neurological Institute (MNI))—were created, including all T1 weighted images of both PSP and control subjects.

The normalised, segmented, and smoothed data were statistically tested employing a general linear model based on Gaussian field theory, using analysis of covariance (ANCOVA) with the total amount of GM treated as nuisance covariate, in order to detect local areas of relative accelerated loss of GM volume. T statistic maps were created for each voxel in the standard atlas space to reflect differences in GM. Voxel level interferences were used with false discovery rate (FDR) in statistical parametrical mapping at a p value of 0.005, and clusters containing 50 contiguous voxels were reported.[31]

GM, WM, and CSF volumes (litres) and total intracranial volume were calculated both for PSP patients and controls, in order to investigate the effect of the decrease on the global volumes of different tissues.

Diffusion tensor imaging

The fractional anisotropy (FA), an index of directional selectivity of water diffusion, was determined for every voxel according to standard methods,[32] using BrainVisa 1.6 software.

A customized template was obtained taking the average of all participants' T2 ($b=0$) images, previously normalised to the EPI template within MNI standard stereotactic space. Both T2 images and FA maps were normalised by means of a customised template. The T2 normalised images were then segmented. A binary mask of WM was created, starting with the WM image obtained from the segmentation process, in order to include only the voxels belonging to the WM regions in the statistical analysis. The masked FA maps were smoothed with a 10 mm FWHM kernel.

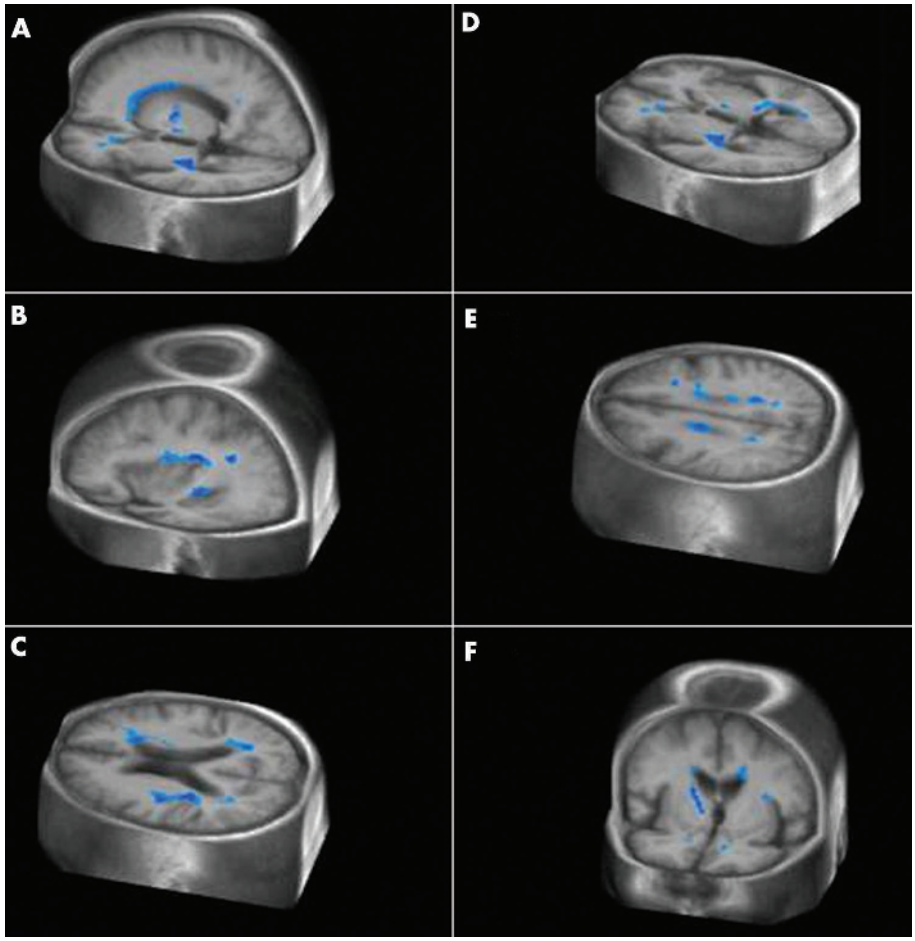

Figure 2 Reduction in fractional anisotropy in patients with progressive supranuclear palsy compared with controls. (A) $x=18$, $z=0$: anterior part of corpus callosum. (B) $x=-34$, $z=-11$: left arcuate fascicolus. (C) $z=18$: left arcuate fascicolus and posterior thalamic radiations. (D) $z=0$: posterior thalamic radiations. (E) $z=34$: superior longitudinal fasciculus. (F) $y=-4$, $z=-5$: internal capsule, probably involving cortico-bulbar tract ($p<0.005$, FDR corrected).

Table 2 Location of the peaks of regional reduction of grey matter volume in patients with progressive supranuclear palsy compared with controls

Brain area	Peak coordinates (mm)			Peak *z* score
	x	*y*	*z*	
Precentral gyrus – premotor cortex (L)	−51	8	12	5.9
Superior frontal gyrus (R-L)	25	60	6	3.9
	−26	63	−8	4.1
Inferior frontal gyrus (L)	−41	52	−10	4.5
	−50	20	10	4.6
Frontal operculum/insula (R-L)	41	19	7	4.8
	46	18	8	5.1
	−46	7	3	5.4
	−41	5	6	4.2
Hippocampal gyrus (R-L)	26	−35	−3	4.8
	−29	−39	−2	5.1
Hippocampal gyrus (R-L)	13	−34	2	7.1
	−14	−37	2	4.7
Thalamus (pulvinar) (R-L)	12	−32	2	7.1
	−5	−28	4	3.7
Thalamus (dorsomedial nucleus) (R-L)	5	−18	10	5.3
	−5	−24	8	3.7
Thalamus (anterior nuclei) (R-L)	11	−15	17	4.8
	8	−12	16	4.8
	−7	−14	16	4.4
Collicula (R-L)	2	−30	−6	4.1
	−5	−31	−7	4.8

$p<0.005$ (false discovery rate corrected), minimum cluster size = 50 voxels, voxel size 1×1×1 mm; *x*, *y*, and *z* values localise the areas of grey matter reduction according to the Montreal Neurological Institute stereotactic coordinates.
L, left; R, right.

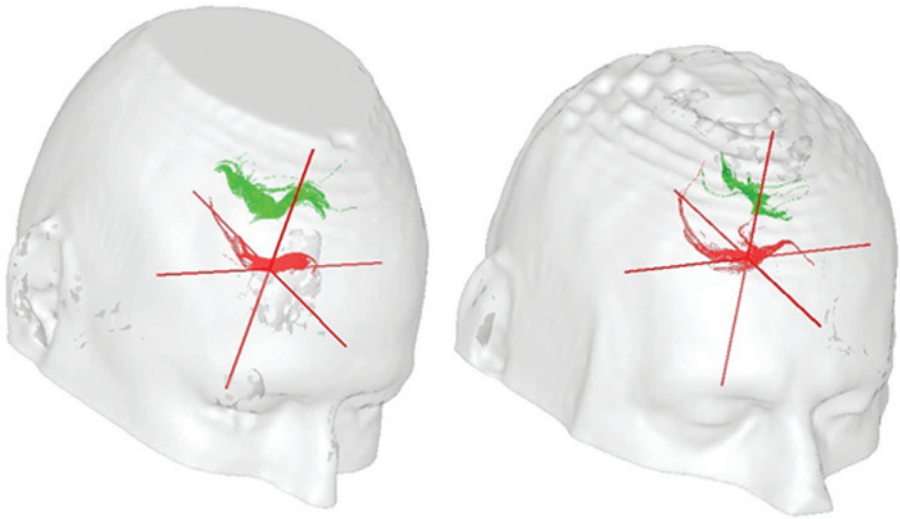

Figure 3 Tracks reconstructed from the anterior part of the corpus callosum (in red) and superior longitudinal fasciculus (in green) are shown. The control subject is on the left, the subject with progressive supranuclear palsy on the right.

The smoothed WM segments were statistically tested employing a general linear model based on Gaussian field theory, using ANCOVA with the total amount of WM treated as nuisance covariate. We used a voxelwise significance threshold of $p<0.005$ (FDR corrected p value).

Anatomical localisation of tracks in a single subject

A single subject analysis was carried out to describe the anatomical localisation of tracks, and for this purpose a healthy control (age 72 years) and a PSP patient (age 70 years; UPDRS, 28; MMSE, 21; IADL, 1/5 lost) were chosen.

The anatomy of white matter bundles in the corpus callosum and the superior longitudinal fasciculus was localised as an example. Fibre tracking was obtained using the FACT algorithm implemented in BrainVisa software.

ROIs in the anterior part of corpus callosum and in the superior longitudinal fasciculus were drawn on the high resolution three dimensional T1 volume previously registered on the T2 images, and fibre bundles passing through the ROIs were then tracked.

RESULTS

Subjects

In PSP patients, mean UPDRS-III was 22.1 (8.9) and mean MMSE was 25.8 (2.7). Mean IADL (lost) was 1.6 (2.3), and BADL (lost), 0.78 (1.4). Behavioural disturbances were present in some of PSP patients, and the most common disorder was apathy, which was present in 50% of cases (7/14). The mean NPI score was 7.2 (10.4).

Symptom onset ranged from two to five years (mean, 3.1 (1.0)).

Voxel based morphometry analysis

As shown in table 1, no difference in global GM, WM, or CSF volumes was found between PSP patients and healthy controls. When absolute volume was expressed as a fraction of total intracranial volume, PSP patients had a significant decreased in the WM fraction compared with the controls.

The results of GM analyses are summarised in table 2 and fig 1. Significant clusters of reduced GM in PSP patients compared with controls were found at symmetrical locations in the precentral-premotor cortex, dorsolateral frontal cortex, frontal operculum and insula, hippocampus, and parahippocampal gyrus ($p<0.005$, FDR corrected). With regard to subcortical brain regions, the following areas were found to be affected bilaterally: pulvinar, dorsomedial and anterior nuclei of the thalamus, and superior and inferior culliculum (fig 2, table 2). The results were explored at $p<0.1$ as well. At this threshold, involvement of the right medial frontal cortex was also found.

The WM comparison did not show any significant difference between PSP patients and controls ($p<0.005$, FDR corrected).

The opposite comparison (patients>controls) both for GM and WM did not show voxels above threshold ($p<0.005$, FDR corrected).

Diffusion tensor imaging analysis

Compared with controls, a decrease in fractional anisotropy was found bilaterally in PSP patients at the followings regions: anterior corpus callosum (fig 2, panel A); left arcuate fascicolus (fig 2, panels B and C); posterior thalamic radiations (fig 2, panels C and D); superior longitudinal fasciculus (fig 2, panel E); and internal capsule, probably involving the corticobulbar tract (fig 2, panel F) ($p<0.005$, FDR corrected).

Fibre tracking analysis in a single subject

In fig 3, tracks reconstructed from the anterior part of the corpus callosum (in red) and superior longitudinal fasciculus (in green) are shown in the control subject (on the left) and the PSP patient (on the right).

DISCUSSION

In this study, a combination of two different techniques of structural brain imaging, VBM and DTI, was adopted in an attempt to shed light on the relation between grey matter and white matter abnormalities in early stages of PSP.

We found that PSP is characterised by bilateral grey matter reductions in the frontal regions, as well as in deep and subcortical grey structures such as the hippocampal gyrus, the thalamus, and the superior and inferior colliculi. Moreover, DTI analysis showed extensive involvement of fibre connecting tracts including the corpus callosum and fibres within the internal capsule (fig 2). These findings, obtained early in the disease course, suggest that PSP is characterised by both grey matter and white matter changes, affecting the main association bundles—that is, the superior

longitudinal fasciculus and the arcuate fasciculus, the commissural connections (the rostrum of the corpus callosum), and the posterior thalamic radiations.

When severe degeneration of grey matter occurs, a consequent wallerian degeneration of fibres should follow. Indeed, the corticobulbar tracts in the internal capsule, receiving fibres from the collicula, were reduced, as were the posterior thalamic radiations originating from the pulvinar.

Thus we have shown in this study that there is degeneration of anatomically and functionally connected grey matter structures, along with their association fibres. This is especially true for the hippocampus and thalamic nuclei, which are connected limbic structures within the memory system, and for the precentral-premotor cortex, pulvinar, and collicula, which may be responsible of the well known vertical gaze palsy in PSP. The degeneration of frontal operculum, together with loss of fibres in the left arcuate fasciculus, may indeed be responsible for the language disturbances described in PSP patients.[33] Further, the atrophy in the frontal medial cortex and insula, along with altered anisotropy of the rostrum of the corpus callosum, may account for the apathy which had been described in PSP patients.[34] Our data also show a marked and significant reduction in white matter, encompassing the grey matter changes detected by VBM. It is possible that in degenerative disease such as PSP a general and diffuse functional impairment (and neuronal loss) of cell populations in the cerebral hemispheres, not detectable by VBM measurements, leads to clear cut changes in the principal fibre connecting tracts, such as those in the corpus callosum and superior longitudinal fasciculus. In this series of patients, we found a significant reduction in white matter as a fraction of total intracranial volume between the PSP patients and normal volunteers, but a lack of significant difference in the other variables considered (table 1). Indeed, we could not show a clear cut link between the white matter as a fraction of total intracranial volume reduction, which refers to the global white matter volume, and the fractional anisotropy reduction, which is related to regional fibre loss.

The demonstration by DTI of white matter changes in PSP thus suggests that white matter pathology is an early marker of the disease, beyond the involvement of grey matter structures. These DTI findings could reflect a broad tau dysfunction involving the microtubules in axons. In fact, a recent necropsy study claimed that tau deposition in tauopathies is found not only in grey matter but in white matter as well.[35]

The data we report here are broadly consistent with those described in a recent VBM study,[14] and further support the claim that structural methods can help in differentiating this disorder from other neurodegenerative diseases with extrapyramidal symptoms.[16 36]

We acknowledge that our study has some limitations. Neuropathological confirmation will be needed, and a larger sample of subjects would be confirmatory. Neuropathological investigations have shown selective brain involvement in PSP, and our present data suggest that specific structural changes may be found in vivo from early in the course of the disease.[37]

This approach provides a completely new way of gaining direct in vivo information on brain tissue loss, and may guide future research investigating the relation between the brain areas involved and the clinical features in different phases of the disease.

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NEUROLOGICAL PICTURE

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Eight-and-a-half syndrome

A 52 year old man with hypertension and diabetes mellitus presented with sudden onset of binocular diplopia on looking to the left side, right facial weakness, and epiphora in the right eye. Ocular motor examination revealed combination of right gaze paresis and right internuclear ophthalmoplegia suggestive of horizontal one-and-a-half syndrome (fig 1A–C). Vertical ocular movements from the primary position were normal (fig 1D, E). In addition, he also had right lower motor neurone facial weakness (fig 1F, G). Cranial MRI showed right paramedian tegmental pontine lesion (fig 2A, B). The lesion was hyperintense on diffusion weighted MRI image (b = 1000 s/mm^2) and hypointense on apparent diffusion coefficient map, compatible with features of acute infarct. Magnetic resonance angiography of intracranial vasculature was normal. The neurological problem was ascribed to lower pontine tegmental infarct due to occlusion of right paramedian pontine perforators. Electrophysiological studies (direct facial nerve stimulation and blink reflex) performed in the second week of illness, revealed incomplete right facial lesion. During evaluation in the third week, adduction lag in the right eye had slightly improved.

Our patient presented with the unique combination of right sided horizontal one-and-a-half syndrome and lower motor neurone seventh cranial nerve palsy. Such a combination of signs (seven plus one-and-a-half) is known as eight-and-a-half syndrome.[1] Involvement of right abducens nucleus, right medial longitudinal fasciculus, and right.

Facial nucleus/fascicles in the lower pontine tegmentum contributed to the observed clinical signs. Thus recognition of this syndrome allows precise localisation of the lesion to lower pontine tegmentum ipsilaterally.

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Consent was obtained for publication of figure 1

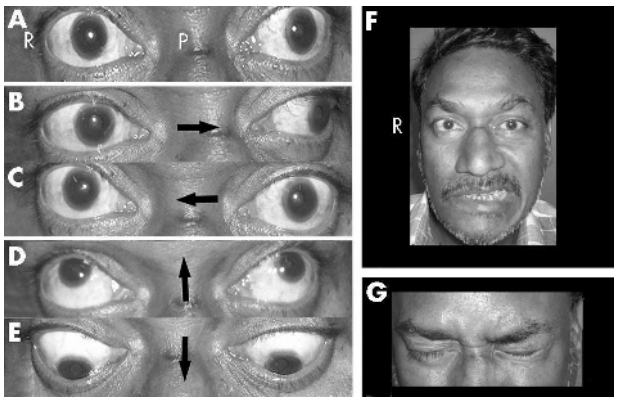

Figure 1 (A–C) Combination of right gaze paresis along with adduction lag in right eye and unimpaired abduction in the left eye (with nystagmus) suggestive of right horizontal one-and-half syndrome. Note the normal vertical eye movements from the primary position of gaze (D, E). (P- Primary position of gaze, arrows point towards the direction of gaze shifts). (F) Right facial weakness evident on clinical examination. (G) Note the right orbicularis oculi weakness on closure of both eyelids. Consent has been obtained for publication of this figure.

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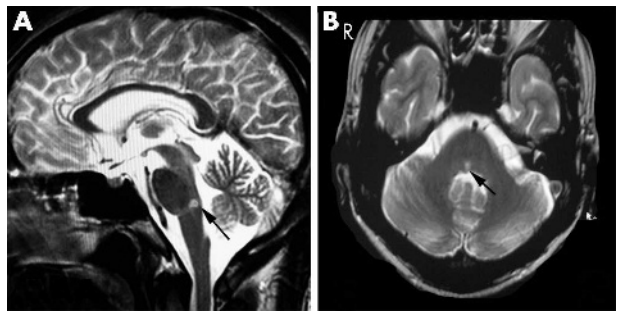

Figure 2 (A) Right paramedian tegmental pontine infarct seen on the T2 weighted saggital magnetic resonance imaging (arrow). (B) The same lesion in transaxial T2 weighted sequence (arrow).