RESEARCH PAPER

Tracking brain damage in progressive supranuclear palsy: a longitudinal MRI study

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ABSTRACT

Objectives In this prospective, longitudinal, multiparametric MRI study, we investigated clinical as well as brain grey matter and white matter (WM) regional changes in patients with progressive supranuclear palsy-Richardson's syndrome (PSP-RS).

Methods Twenty-one patients with PSP-RS were evaluated at baseline relative to 36 healthy controls and after a mean follow-up of 1.4 years with clinical rating scales, neuropsychological tests and MRI scans.

Results Relative to controls, patients with PSP-RS showed at baseline a typical pattern of brain damage, including midbrain atrophy, frontal cortical thinning and widespread WM involvement of the main infratentorial and supratentorial tracts that exceeded cortical damage. Longitudinal study showed that PSP-RS exhibited no further changes in cortical thinning, which remained relatively focal, while midbrain atrophy and WM damage significantly progressed. Corpus callosum and frontal WM tract changes correlated with the progression of both disease severity and behavioural dysfunction.

Conclusions This study demonstrated the feasibility of carrying out longitudinal diffusion tensor MRI in patients with PSP-RS and its sensitivity to identifying the progression of pathology. Longitudinal midbrain volume loss and WM changes are associated with PSP disease course.

INTRODUCTION

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disease associated with 4R tauopathy.[1] The most common clinical presentation of PSP is Richardson's syndrome (PSP-RS), in which patients have insidious early onset of a symmetric akinetic-rigid syndrome with vertical supranuclear gaze palsy, early backward falls and frontal dysfunction.[1 2] There are currently no effective therapies to treat 4R tauopathies. However, new pharmacological agents targeting tau accumulation are being developed. Powerful biomarkers that can accurately measure disease progression and assess the effectiveness of therapeutic interventions are therefore urgent.

Remarkable midbrain and cortical atrophy, usually involving the premotor and prefrontal regions, are typically observed in PSP-RS.[3] More recently, extensive cortical thinning was found in the frontal, temporal, parietal and occipital cortex, cingulum, and insula in patients with PSP-RS compared with controls.[4–6] Several prospective MRI studies followed the progression of brain atrophy in patients with PSP-RS. Rates of atrophy of whole brain, midbrain and basal ganglia are increased in PSP-RS compared with controls.[7–10] Regional grey matter (GM) volume loss in PSP-RS over the course of 6 months or longer has been identified in frontoparietal and temporal cortical regions.[7–9] Decline in frontal lobe[8 9] and midbrain[7–9] volumes correlated with clinical worsening.

White matter (WM) damage has been demonstrated to be a striking feature of frontotemporal lobar degeneration (FTLD) pathology, particularly of tau pathology, which is uniquely associated with specific WM diseases such as astrocytic and oligodendroglial inclusions.[11 12] There is also growing evidence that propagation of tau aggregates from affected to unaffected brain areas may occur along defined anatomical connections within neuronal networks through intercellular transfer.[13] Diffusion tensor (DT) MRI is a valuable non-invasive imaging technique for the assessment of the WM structure of the brain. In patients with PSP-RS, DT MRI abnormalities have been observed predominantly in the superior cerebellar peduncles (SCPs), cerebellum, corpus callosum and frontal WM.[4 5 14–16] In PSP-RS, WM diffusivity alterations have been found to have a more widespread distribution in the brain than GM atrophy.[17] There is also evidence that WM abnormalities correlated with clinical disability and cognitive impairment in these patients.[4 5 14 16 18]

Assessing progression of WM degeneration in PSP-RS may provide surrogate markers of disease progression. Extensive WM volume loss after 1 year in frontal and parietal lobes, brainstem, and cerebellum was observed in patients with PSP-RS using structural MRI.[7] To our knowledge, only one longitudinal DT MRI study reported microstructural WM changes over 6 months in SCPs and left inferior frontal WM in patients with PSP-RS.[19] SCP DT MRI changes were associated with ocular motor decline.[19] The question of whether there is a tight coupling of GM and WM damage over time and with disease progression remains unknown.

In this prospective, longitudinal, multiparametric MRI study, we investigated clinical as well as brain GM and WM regional changes in patients with PSP-RS over 1.4-year follow-up using cortical thickness measures, midbrain volumetry and DT MRI. We also explored the neuroanatomical correlates of clinical, cognitive and behavioural decline associated with the disease.

METHODS

Participants

Twenty-one native Serbian-speaking patients meeting the criteria for probable PSP-RS[2] were consecutively recruited at the Clinic of Neurology, Faculty of Medicine, University of Belgrade, Serbia. Thirty-six age-matched healthy controls were also enrolled. To be included, subjects had to have no (other) neurological, psychiatric and major medical conditions, or history of substance abuse; and no other causes of brain damage, including lacunae, and extensive cerebrovascular disorders on routine MRI. Healthy controls were included if the neurological assessment was normal, Mini-Mental State Examination (MMSE) score was ≥28 and no subjective cognitive complaints were reported. Ten patients with PSP-RS and all healthy controls were part of a previously published cross-sectional study.[15]

Patients with PSP-RS were evaluated at baseline and after a mean follow-up of 1.4 years with clinical rating scales, neuropsychological tests and MRI scans. Experienced neurologists, blinded to MRI results, performed clinical evaluations. Disease severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr stage score, and the PSP Rating Scale (PSPRS).[15] Healthy controls performed clinical, neuropsychological and MRI assessments at study entry only.

All participants (or their caregivers) provided written informed consent prior to study inclusion.

MRI study

Baseline and follow-up brain MRI scans were acquired on the same 1.5 Tesla Avanto scanner. The following MRI sequences were obtained: dual-echo, three-dimensional (3D) sagittal T1-weighted and DT MRI. The online supplementary appendix reports details on MR sequence parameters.

MRI analysis was performed at the Neuroimaging Research Unit, Scientific Institute San Raffaele, Milan, Italy, by a single experienced observer, blinded to subject identity. Details on MRI analysis are provided in the online supplementary appendix. Cortical reconstruction and estimation of cortical thickness were performed on the 3D T1-weighted images using the FreeSurfer V.5.3 image analysis suite (http://surfer.nmr.mgh.harvard.edu/). To evaluate longitudinal cortical changes in patients with PSP-RS, T1-weighted images were automatically processed with the longitudinal stream in FreeSurfer.[20] DT MRI analysis was performed using the FSL (V.5.0.9) tool (http://www.fmrib.ox.ac.uk/fsl/fdt/index.html) and the JIM software package (V.6.0, http://www.xinapse.com). Tract-based spatial statistics V.1.2 (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html) was used to perform both cross-sectional and longitudinal multisubject DT MRI analysis. Midbrain volume was obtained from T1-weighted images using FSL.

A region-of-interest (ROI) analysis on middle cerebellar peduncles (MCPs) and SCPs was also performed. The Johns Hopkins University WM tractography atlas (http://fsl.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html) was used to identify the corresponding ROIs. ROIs were then overlaid onto the mean fractional anisotropy (FA) image of each subject and masked with the WM skeleton. For each subject, mean DT MRI values were derived for each ROI.

Statistical analysis

Demographic, clinical, cognitive midbrain volume, and MCP and SCP DT MRI data

Analyses were run using SAS Release V.9.1. Measures were reported as means and SD or frequencies and percentages for continuous and categorical variables, respectively. Hoehn and Yahr scale scores are shown as median±IQR. Normal distribution assumption was checked by means of Q-Q plot and Shapiro-Wilk test. Group comparisons were performed using Mann-Whitney U test or Pearson's X^2 test for continuous and categorical variables, respectively. Differences in midbrain volumes between patients with PSP-RS and healthy controls at baseline were examined using Mann-Whitney U test. Serial data from patients with PSP-RS (including clinical, cognitive, midbrain volume, MCP and SCP DT MRI values) were analysed using longitudinal linear models accounting for unequally spaced follow-up intervals assuming a spatial power covariance matrix ($P<0.05$, false discovery rate (FDR) corrected for multiple comparisons). We performed a correlation analysis between midbrain volume changes and motor, cognitive and behavioural changes (as reported in table 1), using non-parametric Spearman's rank correlations ($P<0.05$, FDR corrected for multiple comparisons).

Cortical thickness measures

First, a cross-sectional vertex-by-vertex analysis was performed to assess differences of cortical thickness between controls and patients with PSP-RS at baseline, using a general linear model in FreeSurfer. Second, longitudinal changes of cortical thickness measures between baseline and follow-up in patients with PSP-RS were assessed using a paired analysis in FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki/PairedAnalysis), adjusting for time interval between baseline and follow-up scans. Maps showing between-group differences were obtained by thresholding the t-statistic at $P<0.05$, FDR-corrected for multiple comparisons.

WM damage

Baseline between-group comparisons were performed to assess voxel-wise differences in mean (MD), axial (axD) and radial diffusivities (radD), and FA maps using a permutation-based inference tool for non-parametric statistical thresholding ('randomise', part of FSL).[21] Voxel-wise WM change maps for each subject were obtained by subtracting baseline from follow-up DT MRI map (projected onto common skeleton). Then, permutation tests were applied to WM change maps to assess DT MRI alterations over time in PSP-RS group, adjusting for time interval between scans. Correlations between DT MRI and motor, cognitive and behavioural changes (as reported in table 1) were tested using general linear models, adjusting for time interval. For all analyses, the number of permutations was set at 5000,[21] and the resulting statistical maps were thresholded at $P<0.05$, corrected for multiple comparisons at the cluster level using the threshold-free cluster enhancement (TFCE) option.[22]

RESULTS

Demographic, clinical and cognitive data: baseline and longitudinal changes

At study entry, patients with PSP-RS were in a moderate stage of disease as detected by UPDRS, Hoehn and Yahr and PSPRS scales (table 1). They also showed mild to moderate multidomain cognitive deficits and behavioural alterations compared with controls (table 1). Over 1.4-year follow-up, patients with PSP-RS showed significant motor worsening as revealed by the increased scores on UPDRS, UPDRS-III, Hoehn and Yahr and PSPRS (table 1). Over follow-up, they also showed a cognitive decline and more severe apathy (table 1).

Table 1 Demographics, clinical, cognitive and midbrain volume findings in PSP-RS and healthy controls at baseline and follow-up

Demographics	Healthy controls	Patients with PSP-RS	P (patients vs healthy controls)
N	36	21	–
Age at study entry, years	64.8±7.0	62.9±6.5	0.30
Sex (men/women)	21/15	16/5	0.25
Education, years	13.7±3.2	12.0±2.8	0.07
Age at onset, years	–	60.0±6.4	–
Disease duration, years	–	2.9±1.2	–
Time interval between MRI scans, years	–	1.4±0.7 (1.0–3.3)	–

Clinical data		Baseline	Follow-up	P (baseline vs follow-up)
UPDRS total	–	67.6±21.4	91.6±18.9	<0.001
UPDRS-III	–	39.1±12.9	51.3±8.9	<0.001
Hoehn and Yahr	–	3 (2–5)	4 (3–5)	<0.001
PSPRS	–	41.1±13.9	57.4±13.4	<0.001
Cognitive data				
MMSE	28.9±1	25.6±3.4*	22.0±4.6	0.01
ACE-R global	91.6±5.9	75.9±10.6*	67.2±12.5	0.03
ACE-R attention	17.3±0.9	15.3±1.9*	14.3±2.5	0.21
ACE-R fluency	11.0±1.8	6.1±2.7*	5.1±2.2	0.28
ACE-R language	23.9±4.8	23.5±1.6	22.3±2.9	0.14
ACE-R memory	24.0±2.6	18.7±4.8*	16.2±3.7	0.12
ACE-R visuospatial	14.5.±1.8	11.1±2.0*	9.1±4.1	0.12
RAVLT immediate recall	42.3±3.8	30.9±7.6*	22.5±10.6	0.01
RAVLT delayed recall	6.7±0.8	3.8±1.5*	–	–
FAB	16.6±1.4	10.4±4.0*	8.1±3.9	0.12
Mood and behaviour				
HARS	5.3±3.8	7.8±6.2*	8.3±5.3	0.46
HAMD	6.3±4.4	12.1±7.1*	14.5±6.7	0.08
AES	4.3±2.5	20.6±8.7*	26.6±7.6	0.003
NPI	–	14.1±11.8	24.9±15.9	0.004
Normalised midbrain volume, mL	7.96±0.73	6.71±1.12*	6.43±1.32	0.001

Values are mean±SD. Hoehn and Yahr scale scores are shown as median±IQR.
*P<0.05 versus healthy controls at study entry.
ACE-R, Addenbrooke's Cognitive Examination–Revised; AES, Apathy Evaluation Scale; FAB, Frontal Assessment Battery; HAMD, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PSPRS, PSP Rating Scale; PSP-RS, progressive supranuclear palsy Richardson's syndrome; RAVLT, Rey Auditory Verbal Learning Test; UPDRS, Unified Parkinson's Disease Rating Scale.

Cortical thickness: baseline and longitudinal changes

At baseline patients with PSP-RS showed medial and dorsolateral frontal thinning compared with controls at threshold of P<0.05 FDR-corrected (figure 1A; online supplementary E-table 1). Small areas of thinning were detected in temporoparietal and occipital cortical regions, bilaterally (P<0.05 FDR-corrected; figure 1A; online supplementary E-table 1). Over 1.4-year follow-up, patients with PSP-RS did not show cortical thickness changes at threshold of P<0.05 FDR-corrected. Only when using a less stringent threshold (P<0.01, uncorrected) for illustrative purpose small areas of thinning occurred in the frontotemporoparietal regions bilaterally (figure 1B; online supplementary E-table 2).

WM damage: baseline and longitudinal changes

At baseline, patients with PSP-RS presented a distributed WM damage (decreased FA and increased MD, axD and radD) involving the SCPs, cerebellar WM, midbrain and pons, corpus callosum, and the majority of WM associative tracts relative to healthy controls (P<0.05 TFCE-corrected; figure 2A). Over 1.4-year follow-up, PSP-RS showed a widespread pattern of increased MD and radD and decreased FA values with an anterior-to-posterior gradient, involving the corpus callosum, long-association frontoparietotemporal WM tracts and anterior thalamic radiations bilaterally at threshold of P<0.05 TFCE-corrected (figure 2B). A small region of increased axD was also observed in the left anterior thalamic radiations (P<0.05 TFCE-corrected; figure 2B). Infratentorial WM did not show significant longitudinal voxel-wise DT MRI changes at threshold of P<0.05 TFCE-corrected (figure 2B). ROI analysis revealed a significantly increased MD of the right SCP over time in patients with PSP-RS (P=0.04 FDR-corrected; online supplementary E-table 3), while no change was observed in the MCP (online supplementary E-table 3).

Midbrain volume: baseline and longitudinal changes

Patients with PSP-RS showed midbrain atrophy relative to controls at baseline (P=0.001 FDR-corrected; table 1). Over follow-up, patients with PSP-RS showed a significant midbrain volume loss (P=0.001 FDR-corrected; table 1).

Clinicoanatomical correlations

In patients with PSP-RS, midbrain volume loss over time correlated with increases of UPDRS total (r=−0.65; P=0.001 FDR-corrected) and UPDRS-III (r=−0.60; P=0.004 FDR-corrected)

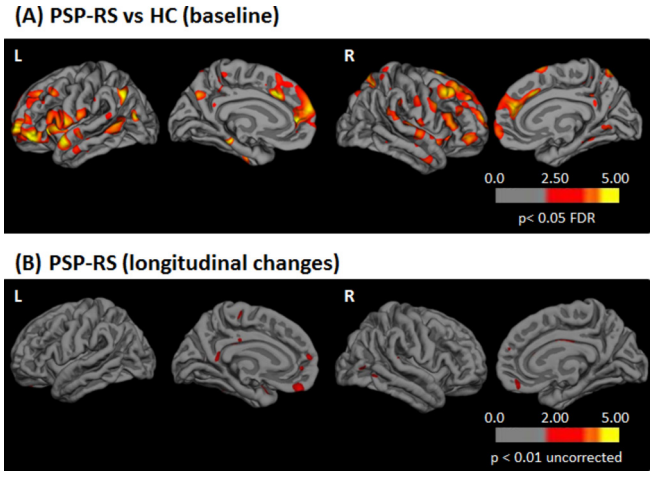

Figure 1 Cortical thickness analysis in patients with progressive supranuclear palsy-Richardson's syndrome (PSP-RS) at baseline and over follow-up. (A) Distribution of cortical thinning on the pial surface in patients with PSP-RS relative to healthy controls (HC) at baseline. Results are false discovery rates (FDR) corrected for multiple comparisons (P<0.05). (B) Cortical thickness changes over follow-up in patients with PSP-RS. Results are shown at P<0.01, uncorrected for multiple comparisons. Colour bar represents t-values. L, left; R, right.

scores, and decreased MMSE (r=0.47; P=0.03 FDR-corrected). No correlations were found between midbrain volume loss and changes in other clinical scales, including the PSPRS. In patients with PSP-RS, PSPRS changes over follow-up were correlated with MD increase in the genu and body of corpus callosum, anterior thalamic radiations, and frontotemporal and frontoparietal WM fibres at threshold of P<0.05 TFCE-corrected (figure 3A). Behavioural changes over follow-up, as detected by the Neuropsychiatric Inventory (NPI), were associated with longitudinal FA decrease and MD increase in the genu of corpus callosum and right WM tracts including anterior thalamic radiations, and frontoparietal WM at threshold of P<0.05 TFCE-corrected (figure 3B). In patients with PSP-RS, NPI changes correlated also with longitudinal MD increase in the body and splenium of corpus callosum, and the left frontoparietal WM at threshold of P<0.05 TFCE-corrected (figure 3B). DT MRI changes did not correlate with other clinical modifications.

DISCUSSION

In this study, we described the longitudinal clinical, cognitive and brain GM and WM changes in patients with PSP-RS. At baseline, patients with PSP-RS showed a typical pattern of brain damage, including midbrain atrophy, prominent frontal cortical thinning (extended minimally to temporoparietal regions) and widespread WM involvement of the main infratentorial and supratentorial tracts that exceeded cortical damage.[3] Longitudinal study showed that PSP-RS exhibited no further changes in cortical thinning, while midbrain atrophy and WM damage significantly progressed with a substantial impact on clinical decline. Interestingly, WM changes in PSP-RS involved mainly supratentorial frontal WM tracts, while cerebellar WM damage did not progress much.

Patients with PSP-RS showed significant midbrain volume loss over 1.4-year follow-up that was also related to disease severity and cognitive worsening, in accordance with previous findings.[7–9]

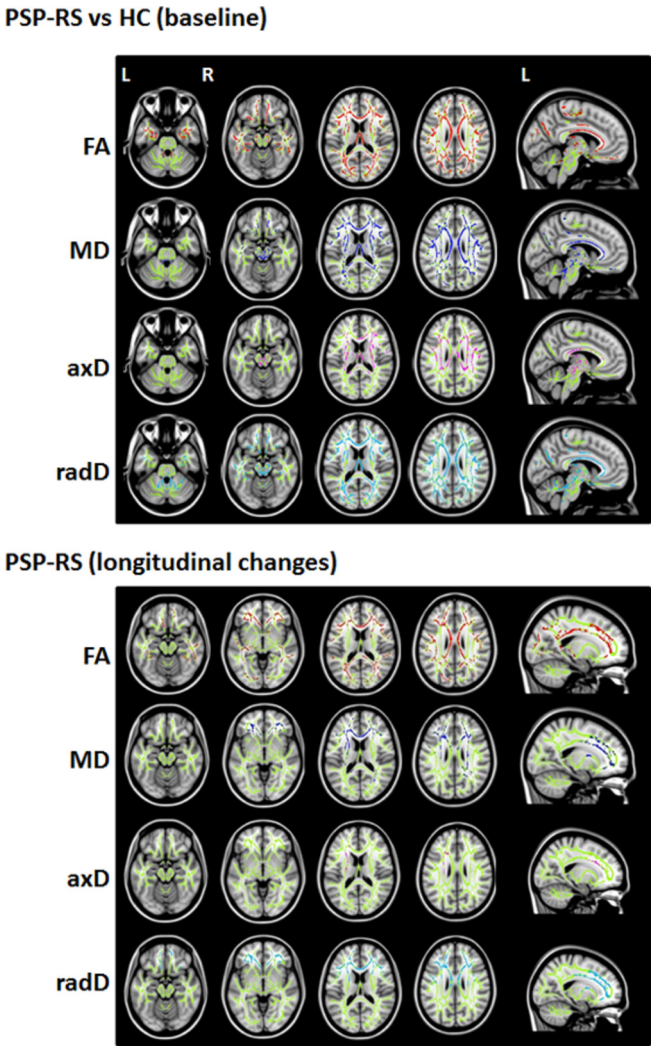

Figure 2 White matter diffusion tensor MRI findings in patients with progressive supranuclear palsy-Richardson's syndrome (PSP-RS) at baseline and over follow-up. (A) Decreased fractional anisotropy (FA, red) and increased mean (MD, blue), axial (axD, pink) and radial diffusivities (radD, cyan) in patients with PSP-RS relative to healthy controls (HC) at baseline. (B) Decreased FA (red) and increased MD (blue), axD (pink) and radD (cyan) in patients with PSP-RS over follow-up. Results are overlaid on the axial and sagittal sections of the Montreal Neurological Institute standard brain in neurological convention (right is right), and displayed at P<0.05 corrected for multiple comparisons at the cluster level using the threshold-free cluster enhancement option. The white matter skeleton is green. L, left; R, right.

We found that progressive WM degeneration is a remarkable feature of PSP-RS, although most WM was already involved at study entry. Diffusivity changes were prominent in supratentorial brain WM tracts, compared with cerebellum where we observed only an increased MD of the right SCP. These findings are partially in contrast with a previous longitudinal DT MRI study reporting over a 6-month follow-up major DT MRI changes in the SCPs and only small regions of damage in the inferior frontal WM.[19] SCP degeneration has been demonstrated in many cross-sectional DT MRI studies of PSP-RS.[5 18 23 24] SCP tract is particularly vulnerable to tau accumulation and its degeneration is a hallmark of PSP pathology.[25] It is plausible that SCP involvement at baseline was already too severe to show additional marked DT MRI changes over time. The shorter follow-up

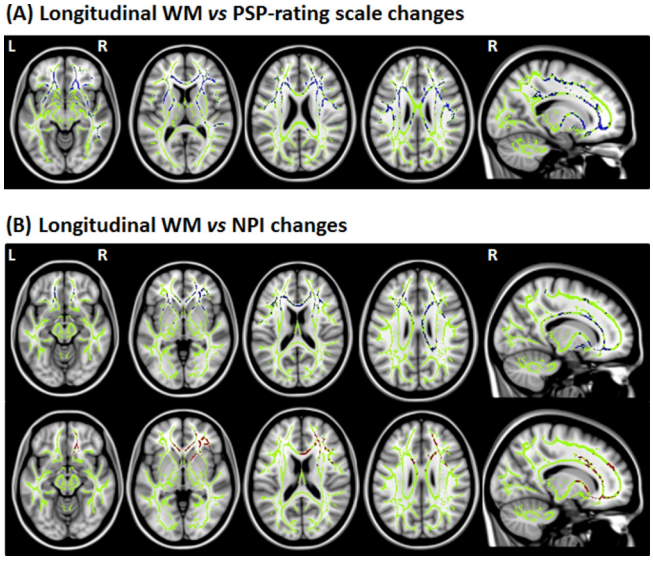

Figure 3 Correlations between clinical worsening and MRI changes over follow-up in patients with progressive supranuclear palsy-Richardson's syndrome (PSP-RS). (A) Significant correlations between PSP Rating Scale (PSPRS) and white matter (WM) mean diffusivity (MD, blue) changes in patients with PSP-RS. (B) Significant correlations between Neuropsychiatric Inventory (NPI) and WM mean diffusivity (MD, blue) and fractional anisotropy (red) changes in patients with PSP-RS. Results are overlaid on the axial and sagittal sections of Montreal Neurological Institute standard brain in neurological convention (right is right), and displayed at P<0.05 corrected for multiple comparisons using the threshold-free cluster enhancement option. The white matter skeleton is green. L, left; R, right.

duration of the previous study[19] (6 months vs 1.4 years) and the fact that our patients with PSP-RS were slightly clinically more advanced, as suggested by UPDRS-III and PSPRS scores, might explain differences among studies. The relatively small patients' sample size in both studies might also have contributed to the inconsistencies in DT MRI results.

Conversely, no significant progression of cortical thinning was detected in patients with PSP-RS, with the damage remaining relatively focal. Some previous regional volumetric studies of PSP-RS showed high rate of atrophy in frontal cortical regions,[7–9] in relation with clinical decline.[8 9] Differences in MRI methodology and statistical testing might explain discrepancies among studies. The previous studies used voxel-based morphometry[7] or measured ROI volumes using automated approaches.[8 9] It is noteworthy that GM volume changes can result from alterations in two cortical components, cortical thickness and cortical surface area. These two measures seem to reflect different structural characteristics of the human cortex and are likely to be driven by distinct cellular factors (ie, the number of cortical columns for cortical surface area and the number of cells within a column for cortical thickness).[26] Considering that GM volume has been more strictly associated with cortical surface area rather than with thickness,[27] results from the present and previous volumetric studies are difficult to be compared. Although more studies are needed to elucidate the relation between the two techniques, it is important to note that cortical thickness measures have been suggested to be more specific than those obtained by volume-based studies in neurodegenerative disorders.[28] Moreover, cortical thickness provides a direct index of cortical morphology that is less susceptible to variations in individual positioning, as the extraction of the cortex follows the GM surface regardless of positional variance, especially in the intrasubject comparison between baseline and follow-up scans.[29]

Corpus callosum changes correlated with the progression of both disease severity and behavioural dysfunction, in keeping with previous cross-sectional results.[5 16 18] This finding is not surprising since the corpus callosum conveys commissural fibres across the hemispheres contributing to motor and high-order cognitive functions, and to interhemispheric integration and transfer of information. We also showed that longitudinal DT MRI changes of frontal WM tracts contribute to clinical and behavioural worsening. These findings expand the cross-sectional evidence of the remarkable clinical impact of frontal circuit disconnection in PSP-RS.[4 5 14 16 18] Abnormalities of association tracts linking the prefrontal areas with parietal cortex, ventral and orbital frontal regions to the anterior temporal lobe, and frontotemporal with occipital areas have been previously related with behavioural abnormalities in neurodegenerative diseases[18 30] including patients with PSP-RS.[31] Overall, our findings of NPI correlations with broad WM degeneration reinforce the hypothesis that neuropsychiatric abnormalities in neurodegenerative disorders are the result of 'disconnection syndrome', rather than the consequence of damage to a particular brain region.[32]

This study is not without limitations. First, diagnosis was not pathologically confirmed. However, the usual clinical features of PSP-RS, which have been confirmed over time in our patients, permit accurate antemortem diagnosis in most cases.[33] Second, patients with PSP-RS were not included at disease onset, in keeping with the well-known diagnostic challenges in the early phase of the disease[2] and the characteristics of PSP samples enrolled in previous longitudinal studies.[7–9 19] Third, healthy controls did not perform longitudinal MRI study; thus, we cannot exclude the possibility that WM changes were partially age-related. However, a previous longitudinal DT MRI study showed that the magnitude of (small) FA changes observed in healthy elderly controls over 1 year was about twofold to threefold less compared with the changes found in patients with behavioural-variant frontotemporal dementia and primary progressive aphasia.[34] Fourth, the follow-up period was relatively long; thus, the higher sensitivity of DT MRI measures relative to regional GM changes over a shorter interval has to be confirmed. In addition, as range of time interval between scans was heterogeneous among patients, it was used to adjust longitudinal analyses. Lastly, our study included only typical PSP-RS cases. Future studies should examine longitudinal MRI changes in atypical variants of PSP.

This study is among the first to demonstrate the feasibility of carrying out longitudinal DT MRI in patients with PSP-RS and its ability to identifying the progression of pathology. Our results demonstrated that both midbrain volume loss and longitudinal WM changes correlated with clinical changes in patients with PSP-RS. Future studies on larger PSP-RS populations in the early stage of the disease are needed to confirm our findings and eventually validate DT MRI as a reliable tool to monitor response to FTLD-tau modifying treatments, as they will become available.

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Contributors FA: study concept/design, analysis/interpretation of data, drafting the manuscript for content. FC, PV, AM and MC: analysis/interpretation of data, revising the manuscript for content. MJ-L and INP: acquisition of data, analysis/interpretation of data, revising the manuscript for content. VSK: study concept/design, interpretation of data, revising the manuscript for content, obtaining funding. MF: study concept/design, interpretation of data, revising the manuscript for content, study supervision and coordination, obtaining funding.

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Competing interests FA is Section Editor of *NeuroImage: Clinical*; has received speaker honoraria from EXCEMED–Excellence in Medical Education and Biogen Idec; and receives research support from the Italian Ministry of Health, AriSLA (Fondazione Italiana di Ricerca per la SLA), and the European Research Council. FC, MJ-L, INP and AM report no disclosures. INP has received speaker honoraria from Boehringer Ingelheim, GSK, EI Pharma, Roche and Actavis. PV has received speaker honoraria from EXCEMED–Excellence in Medical Education. MC has received compensation for consulting and/or serving on advisory boards from Teva Pharmaceuticals and Biogen Idec. VSK has received research grants from the Ministry of Education and Science, Republic of Serbia and the Serbian Academy of Science and Arts; and speaker honoraria from Novartis. MF is Editor-in-Chief of the *Journal of Neurology* ; serves on a scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, EXCEMED, Merck Serono and Teva Pharmaceutical Industries; and has received research support from Biogen Idec, Merck Serono, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer's and Drug Discovery Foundation, and the Jacques and Gloria Gossweiler Foundation (Switzerland).

Ethics approval Local ethical standards committee on human experimentation (Faculty of Medicine, University of Belgrade) approved the study protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

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