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Imaging counterpart of postural instability and vertical ocular dysfunction in patients with PSP: A multimodal MRI study

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ABSTRACT

Introduction: We investigated the imaging counterpart of two functional domains (ocular motor dysfunction and postural instability) in progressive supranuclear palsy (PSP) patients classified according to the new clinical diagnostic criteria.

Methods: Forty-eight patients with probable PSP-Richardson's syndrome (PSP-RS), 30 with probable PSP-parkinsonism (PSP-P), 37 with Parkinson's disease (PD), and 38 controls were enrolled. For each functional domain, PSP patients were stratified by two certainty levels: vertical supranuclear gaze palsy (O1) and slowness of vertical saccades (O2) for ocular motor dysfunction; early unprovoked falls and tendency to fall on the pull-test for postural instability. Voxel-based morphometry (VBM), whole-brain fractional anisotropy (FA) and MR planimetric measurements were analysed and compared across patient groups.

Results: O1 was present in 64%, and O2 in 36% of all PSP patients. All PSP-RS patients showed early unprovoked falls. TBSS whole-brain analysis revealed that superior cerebellar peduncles (SCPs) were the only structures with significantly lower FA values in PSP-RS compared with PSP-P patients. PSP/O1 patients had lower FA values in midbrain than PSP/O2 patients. By contrast, VBM revealed no differences in grey matter volume between PSP patient groups. MR Planimetric measurements confirmed atrophy of midbrain and SCPs, in line with DTI findings.

Conclusions: Our study demonstrates that SCPs were significantly more damaged in patients with PSP-RS in comparison with PSP-P patients, thus suggesting the role of SCPs in developing postural instability. Midbrain damage was less severe in O2 than in O1 patients, suggesting that the degree of vertical ocular dysfunction reflects the severity of midbrain atrophy.

1. Introduction

Recently, the Movement Disorder Society–endorsed PSP Study Group published new diagnostic criteria for the clinical diagnosis of progressive supranuclear palsy-Richardson's syndrome (PSP-RS) and PSP variants, such as PSP-parkinsonism (PSP-P) [1]. This new set of criteria focused on four core functional domains: ocular motor dysfunction, postural instability, akinesia, and cognitive impairment. For each domain, different levels of certainty in performing a diagnosis of PSP were described, depending on the severity of the corresponding clinical symptom. These new criteria for probable PSP-RS were based on the presence of vertical ocular dysfunction associated with postural instability within three years after disease onset, while probable PSP-P was diagnosed in patients with vertical ocular dysfunction associated with levodopa responsive or levodopa resistant parkinsonism, in the absence of early falls [1].

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At the present time contradictory results have been reported using MRI as the neuroanatomical basis of postural instability and ocular dysfunction in patients with PSP [2–7].

In the current study we used voxel-based morphometry (VBM), diffusion tensor imaging (DTI) and brain MR planimetric measurements to investigate the imaging counterpart of two functional domains (ocular motor dysfunction and postural instability) stratified by two certainty levels in probable PSP-RS and PSP-P patients, diagnosed according to the new clinical criteria.

2. Materials and methods

2.1. Study participants

Forty-eight patients with probable PSP-RS, 30 patients with probable PSP-P, 37 patients with idiopathic PD, and 38 age-matched control subjects were consecutively recruited from the Movement Disorders Unit of the Institute of Neurology at Magna Graecia University of Catanzaro, Italy, between 2009 and 2017. Clinical diagnosis for PSP patients was established according to the diagnostic criteria for PSP [8,9] by a trained physician with more than 10 years of experience in movement disorders. All PSP patients were reclassified according to the recent diagnostic criteria for PSP [1]. A subset of patients included in the current study has been previously reported [10]. Clinical diagnoses for PD patients were established according to international diagnostic criteria [11].

For each patient, a complete medical history with neurological examination and clinical assessment was performed. This record included: Unified Parkinson's Disease Rating Scale - Motor Examination (UPDRS-ME) in off-state (off medications overnight) [12]; Hoehn and Yahr (H-Y) rating scale [13]; Mini Mental State Examination (MMSE). Levodopa response was assessed both in the off-state (off medications overnight) and 2 h after drug administration as a clinical improvement of 30% or greater on the UPDRS-ME score. PSP patients were stratified by two levels of certainty for ocular dysfunction: O1 (highest level, vertical supranuclear gaze palsy, VSGP), and O2 (mid level, slowness of vertical saccades). PSP-RS patients were also stratified by two levels of diagnostic certainty for postural instability: P1 (highest level, unprovoked falls within three years of disease onset) and P2 (mid level; tendency to fall on the pull-test within three years of disease onset) [1]. For a diagnosis of probable PSP-RS (PSP-RS/O1 and PSP-RS/O2), O1 or O2 must be associated with P1 or P2, while for a diagnosis of probable PSP-P (PSP-P/O1 and PSP-P/O2) O1 or O2 must be associated with a parkinsonism levodopa resistant (A2) or levodopa responsive (A3) without early postural instability [1]. Reduced velocity (and amplitude) of voluntary upward and downward saccades was considered as the criterion for slowness of vertical saccades. A clear limitation of the range of voluntary gaze in the vertical plane more than in the horizontal plane, affecting both up- and downgaze, more than expected for age, was considered as the highest level of certainty for vertical ocular motor dysfunction [1].

Exclusion criteria for patients were: history of neuroleptic use within the past six months, evidence of clinical features of alternative diagnoses, evidence of normal striatal uptake in dopamine transporter ^{123}I-FP-CIT-SPECT, evidence of MRI scan abnormalities such as vascular lesions in the basal ganglia and radiological signs suggestive of normal pressure hydrocephalus (NPH) [14]. None of the control subjects had a history of neurological, psychiatric or other major medical illnesses. Twenty-seven out of 30 PSP-P patients underwent a telephone interview every year to assess the occurrence of unprovoked falls. All study participants gave written informed consent, which was approved by the Local Institutional Ethical Committee, according to the Helsinki Declaration.

2.2. MR imaging protocol

All patients and control subjects underwent a brain MRI with a 3T MR750 GE MRI scanner and an 8-channel head coil, according to a recently described procedure [15].

2.3. Whole-brain MRI analysis

MRI processing was performed using FSL [16]. Voxel-wise differences in grey matter (GM) volume between groups were investigated using FSLVBM. Diffusion-weighted images were preprocessed (eddy-current and head-motion correction), averaged and concatenated into twenty-eight (1 mean b0 + 27 b1000) volumes. A diffusion tensor model was fitted at each voxel, generating fractional anisotropy (FA) maps. We used TBSS, part of FSL, for post-processing and group analysis of multi-subject FA data [17]. For more details on structural MRI and DTI analysis see Supplementary Material.

2.4. MR planimetric measurements

Automatic measurements of midbrain area and SCPs width were performed according to a previously described procedure [18].

2.5. Statistical analyses

Differences in the distribution of sex and dopaminergic responsiveness were assessed using Fisher's exact test. All demographic, clinical and MR planimetric variables were tested for normality using Shapiro-Wilk's test. Subsequently, variables with normal distribution were compared across groups using ANOVA followed by pairwise t-tests. Non-normally distributed variables, instead, were compared across groups using Kruskal-Wallis test, followed by pairwise Wilcoxon rank-sum test. P-values were corrected according to Holm. All tests were two-tailed, with a significance level of $p = 0.05$. To test for localized GM and FA differences across groups, voxel-wise statistics were performed for each point on the common white matter skeleton using FSL's *randomize* [19]. This tool implements a permutation-based inference on cluster-size ($t > 1$, $P < 0.05$), accounting for “family-wise errors” to control for multiple comparisons

In order to assess the imaging correlates of postural instability and ocular motor dysfunction, we used whole brain analyses (VBM and TBSS) to compare respectively PSP-RS with PSP-P patients and PSP/O1 with PSP/O2 patients. Then, we compared PSP-P and PSP/O2 patients with PD and control subjects to evaluate the structures mainly involved in PSP patients with milder phenotypes. Automatic MR planimetric measures were also performed on the structures where VBM or TBSS showed significant differences between PSP patient groups. Spearman correlations were performed between planimetric and diffusion variables. FA values were averaged over manually selected significant clusters.

3. Results

3.1. Demographic and clinical findings

Demographic, clinical and neuroimaging data of all subjects are summarized in Table 1 and Supplementary Table 1. Patients with PSP-RS showed greater motor and cognitive impairment, and worse levodopa responsiveness than patients with PD, whereas patients with PSP-P showed intermediate values for these clinical variables between PSP-RS and PD patients (Table 1). PSP patients with VSGP (PSP/O1) showed greater motor and cognitive impairment, and worse levodopa responsiveness than those with slowness of vertical saccades (PSP/O2) (Supplementary Table 1). PD patients showed higher cognitive impairment than control subjects, a result that can be due to the presence in PD group of patients with a long disease duration, a condition known

Table 1
Demographic, clinical and imaging data of patients with PSP-Richardson syndrome, PSP-parkinsonism, Parkinson's disease and controls.

Data	PSP-RS (n = 48)	PSP-P (n = 30)	PD (n = 37)	Controls (n = 38)	p value
Sex (M/F)	26/22	23/7	26/11	15/23	0.007[a]
Age at examination, ys[b]	70.9 ± 5.4 (56–84)	73.6 ± 5.1 (61–84)	72.0 ± 5.2 (60–83)	72.6 ± 4.6 (65–80)	0.141[c]
Age at disease onset, ys[b]	66.9 ± 5.6 (51–80)	65.5 ± 5.2 (54–73)	64.2 ± 5.1 (54–77)	\	0.081[d]
Disease duration, ys[b]	4 ± 1.7 (1–8)	8.2 ± 3.1 (4–14)	7.8 ± 3.6 (3–17)	\	< 0.001[c]
MMSE score[e]	20.6 (11–28)	23 (11–26)	24 (14–28)	27 (25–30)	< 0.001[c]
UPDRS-ME score[e]	41 (21–56)	38 (24–48)	29 (18–52)	\	< 0.001[c]
H-Y score[e]	4 (2.5–5)	3 (2–4)	2 (2–4)	\	< 0.001[c]
Levodopa responsiveness[f]	0 (0)	14 (46.6)	37 (100)	\	< 0.001[a]
Brain MRI measurements[b]					
Midbrain area, mm^2	73.9 ± 16.2 (45.0–122.0)	90.2 ± 19.8 (54.0–143.0)	134.5 ± 18.0 (105.0–173.0)	137.5 ± 16.4 (110.0–192.0)	< 0.001[c]
SCPs width, mm	2.67 ± 0.42 (1.58–3.56)	3.23 ± 0.43 (2.26–4.20)	3.91 ± 0.40 (3.20–4.80)	3.77 ± 0.45 (3.00–5.23)	< 0.001[d]

Abbreviations: PSP-RS = progressive supranuclear palsy-Richardson's syndrome; PSP-P = progressive supranuclear palsy-parkinsonism; PD = Parkinson's disease; MMSE = Mini-Mental State Examination; UPDRS-ME = Unified Parkinson's Disease Rating Scale-Motor Examination; H-Y = Hoehn-Yahr. PSP-RS group included 34 patients classified as P1-O1 (PSP-RS/O1) and 14 as P1-O2 (PSP-RS/O2); PSP-P group included 16 patients classified as O1 (PSP-P/O1) and 14 as O2 (PSP-P/O2) (see text). Comparisons among all groups were performed with the following tests.

[a] Fisher's exact test, p-values corrected according to Bonferroni.
[b] Data are expressed as mean ± standard deviation (range).
[c] Kruskal-Wallis test followed by pairwise Wilcoxon rank sum test with Holm correction.
[d] ANOVA followed by pairwise *t*-test with Holm correction.
[e] Data are expressed as median values (range).
[f] Number (percentage) of patients who showed a clinical improvement of at least 30% in comparison with that detected in the off state.

to be associated with cognitive decline [11]. O1 was present in 64.1% and O2 in 35.9% of all PSP patients. Specifically, 70.8% of probable PSP-RS patients were O1 and the remaining 29.2% were O2; probable PSP-P patients were 53.3% O1 and 46.7% O2. All probable PSP-RS patients experienced repeated unprovoked falls within three years after onset of the PSP-related features (P1). According to the new clinical diagnostic criteria [1], none of the probable PSP-P patients developed postural instability within three years of disease onset. We followed up 27 PSP-P patients by telephone interview every year for eight years to assess the occurrence of unprovoked falls. Most of these PSP-P patients (77.8%) developed postural instability after three years from disease onset and within eight years of the follow-up. Fifteen out of 16 (93.7%) PSP-P patients with VSGP (PSP-P/O1) developed postural instability within a 8-year follow up, while only 6 out of 11 (54.5%) PSP-P patients with ocular slowness (PSP-P/O2) developed this feature within the same period of time (Supplementary Fig. 1).

3.2. MRI analysis

3.2.1. VBM

VBM analysis showed no differences in PSP-RS vs PSP-P patients and in PSP/O1 vs PSP/O2 patients. When milder phenotypes (PSP-P and PSP/O2) were compared with PD patients, VBM analysis showed significant GM volume reduction in widespread regions including bilateral prefrontal regions, sensorimotor cortex, caudate nuclei, thalami, midbrain and cerebellar cortex. No differences were found between PD and control subjects.

3.2.2. DTI

When PSP-RS patients were compared with PSP-P patients, the only brain structures which showed significant differences between groups were SCPs. TBSS whole-brain analysis showed lower FA values in SCPs of patients with PSP-RS than in those with PSP-P (Fig. 1). TBSS analysis also showed lower FA values in SCPs and midbrain in PSP-P patients in comparison with PD patients (Fig. 1). When PSP/O1 were compared with PSP/O2 patients, midbrain was the only structure to significantly differ between the two patient groups. TBSS revealed significantly lower midbrain FA values in O1 patients than in O2 patients (Fig. 2). PSP/O2 patients had reduced FA values in SCPs and midbrain in comparison with PD (Fig. 2). As shown in Fig. 1, no differences were found between PD and controls. When milder phenotypes (PSP-P and PSP/O2) were compared with PD patients TBSS showed, in addition to SCPs and midbrain damage, widespread white matter abnormalities mainly in corpus callosum, thalamic radiations and corticospinal tracts (Supplementary Fig. 2).

3.2.3. MR planimetric measurements

The only structures where whole brain analyses showed significant differences between PSP phenotypes were midbrain and SCPs. We thus performed automated MR planimetric measurements of midbrain area and SCPs width and compared them between groups.

As shown in Fig. 3A and 3B, PSP-RS had smaller midbrain area and SCPs width than PSP-P. In addition, both these structures were more atrophic in patients with PSP-P than in PD patients and controls. MR Planimetry revealed reduced midbrain area and SCPs width in PSP/O1 compared to PSP/O2 patients (Supplementary Figs. 3A and 3B). In addition, PSP/O2 patients showed more severe atrophy in both the midbrain and SCPs in comparison to PD patients and controls (Supplementary Figs. 3A and 3B). No differences were found in midbrain area and SCPs width between PD and controls. Differences among groups are reported in Supplementary Table 2. A significant correlation between DTI and planimetric measures was found in both midbrain and SCPs analyses (Supplementary Figs. 4A and 4B).

4. Discussion

This is the first multimodal MRI study focusing on neuroimaging counterparts of two functional domains involved in PSP (postural instability and vertical ocular motor dysfunction), each stratified by two certainty levels (P1 or P2 and O1 or O2).

Postural instability is a very common feature in PSP. A recent retrospective study in pathologically diagnosed patients with PSP demonstrated that falls occurred in 78.6% of cases, representing the most common clinical sign in these patients [20]. The new criteria for clinical diagnosis of PSP [1] expanded the time window for the onset of falls from one year (as required in Litvan's criteria [8]) to three years after the onset of PSP-related features, with an improvement in sensitivity from 37.4% to 51%, respectively [20]. However, the neuroimaging counterpart of postural instability in PSP is still uncertain. A few imaging studies have found a relationship in PSP patients between postural instability and DTI abnormalities in brain regions corresponding to the dentatorubrothalamic tract (DRTT), a brainstem structure including

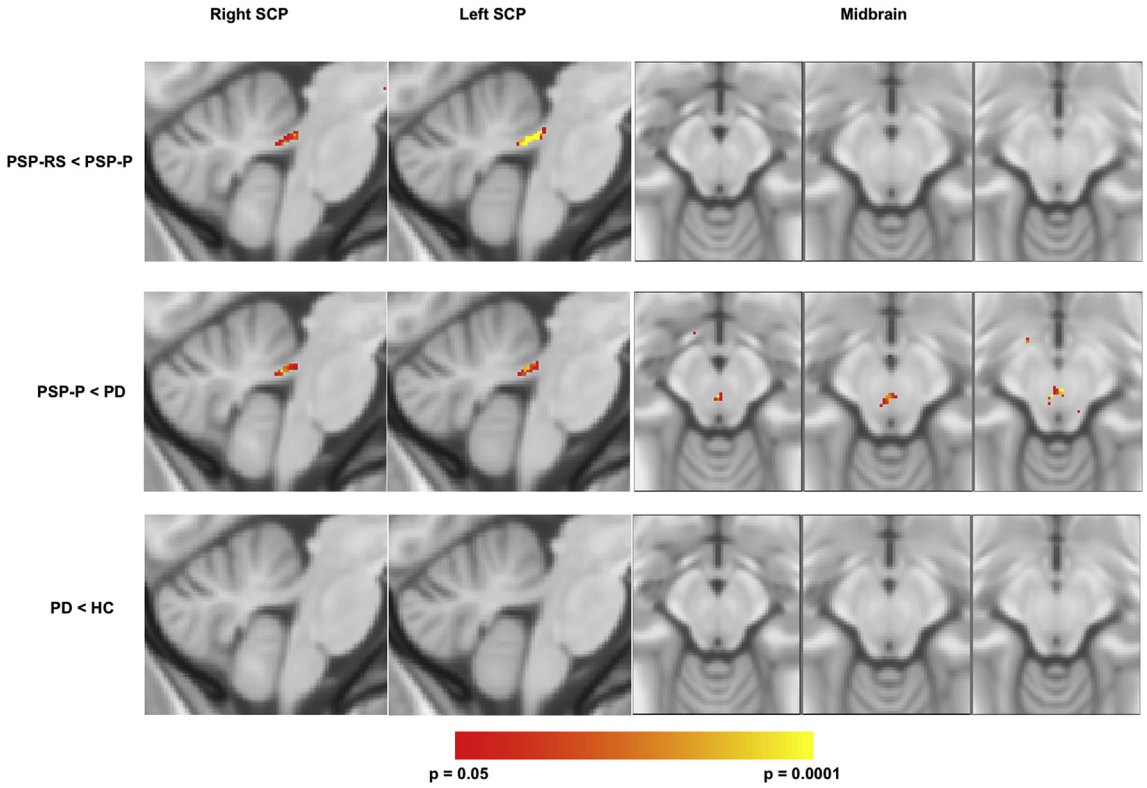

Fig. 1. TBSS results in infratentorial regions for the following FA comparisons: PSP-RS vs PSP-P, PSP-P vs PD and PD vs HC. Abbreviations: TBSS = Tract-Based Spatial Statistics; FA = Fractional Anisotropy; PD = Parkinson's Disease; HC = Healthy Controls; PSP-RS = Progressive Supranuclear Palsy - Richardson Syndrome; PSP-P = Progressive Supranuclear Palsy - Parkinsonism.

SCPs [2,3]. Other authors have reported that postural instability could be related to corpus callosum microstructural damage [4] or thalamic dysfunction [5]. In our study, whole brain DTI analyses showed that SCPs were the only structure to be significantly damaged in patients with early postural instability (PSP-RS) in comparison with PSP-P. MR planimetry showed larger SCPs atrophy in PSP-RS than PSP-P, confirming DTI findings. This evidence suggests that SCPs atrophy may be a specific correlate of early postural instability which characterizes PSP-RS, thus playing a pivotal role in the clinical presentation of these two PSP phenotypes.

Previous whole brain DTI studies comparing PSP-RS with PSP-P found a trend of higher severity in white matter damage in PSP-RS in

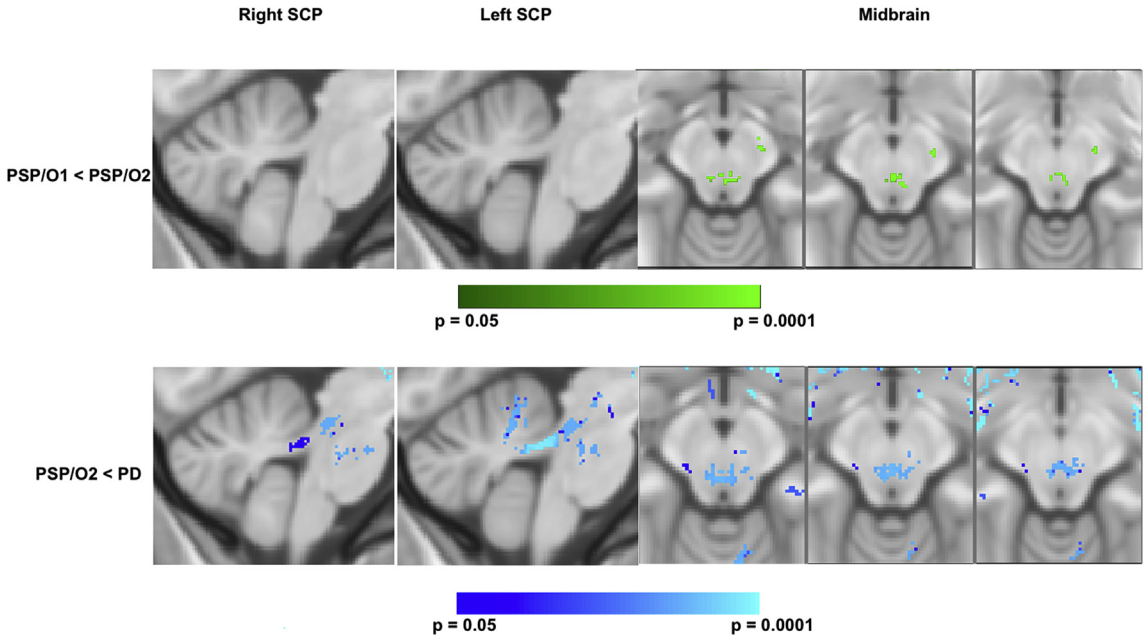

Fig. 2. TBSS results in infratentorial regions for the following FA comparisons: in green-light green, PSP with vertical supranuclear gaze palsy vs PSP with ocular slowness; in blue-light blue, PSP with ocular slowness vs PD. Abbreviations: TBSS = Tract-Based Spatial Statistics; PD = Parkinson's Disease; PSP = Progressive Supranuclear Palsy.

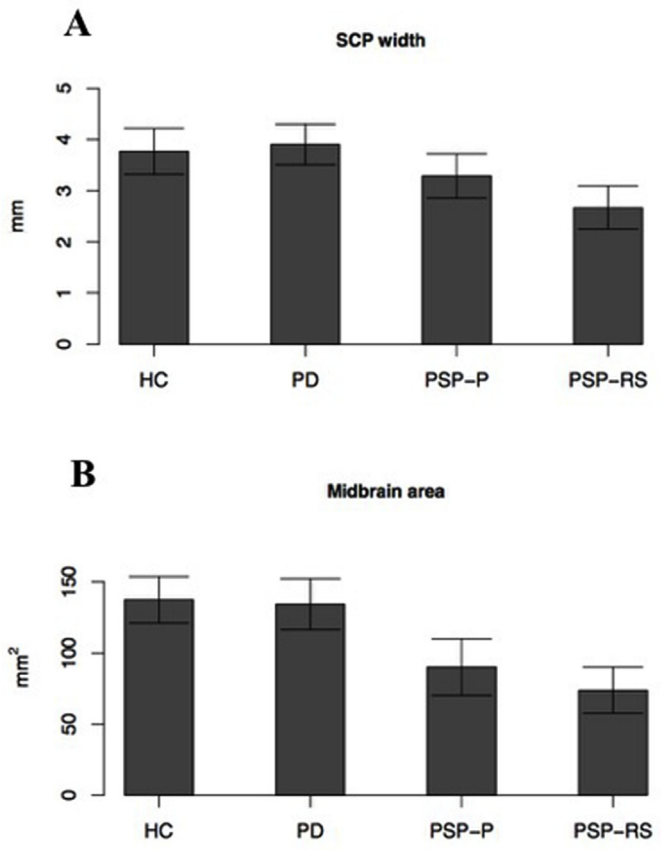

Fig. 3. A) SCPs width values expressed as mean ± standard deviation, in PSP-RS, PSP-P, PD and Controls. Abbreviations: SCPs = superior cerebellar peduncles; PSP-RS = Richardson's syndrome; PSP-P = Progressive Supranuclear Palsy-Parkinsonism; PD: Parkinson's Disease; HC = Controls. PD vs Controls: $p = 0.159$; PSP-RS vs controls: $p < 0.001$; PSP-P vs controls: $p < 0.001$; PSP-RS vs PD: $p < 0.001$; PSP-P vs PD: $p < 0.001$; PSP-RS vs PSP-P: $p < 0.001$. B) Values of midbrain area expressed as mean ± standard deviation, in PSP-RS, PSP-P, PD and Controls. Abbreviations: PSP-RS = Richardson's syndrome; PSP-P = Progressive Supranuclear Palsy-Parkinsonism; PD: Parkinson's Disease; HC = Controls. PD vs Controls: $p = 0.373$; PSP-RS vs controls: $p < 0.001$; PSP-P vs controls: $p < 0.001$; PSP-RS vs PD: $p < 0.001$; PSP-P vs PD: $p < 0.001$; PSP-RS vs PSP-P: $p = 0.001$.

respect to PSP-P at uncorrected level, without finding any significant difference between these two PSP phenotypes [21]. Our results confirm the higher white matter involvement in PSP-RS, and are in line with more recent studies focused on the DRTT, which found higher atrophy and microstructural damage in SCPs in PSP-RS compared to PSP-P [2,22].

Pathological and imaging studies showed SCP atrophy in PSP-RS [23–25]. By contrast, SCPs involvement in PSP-P is uncertain. Pathological studies [26] have found tau-burden in the dentate nucleus in PSP-P, however to our knowledge no pathological data exist regarding SCPs atrophy in this phenotype. Contradictory evidences have also been reported in imaging studies on the involvement of SCPs in PSP-P. Some authors have reported volume reduction and microstructural damage of SCPs in PSP-P [2,27], while others have found no atrophy or microstructural damage of SCPs in this disease [21,28]. Using a multimodal approach based on whole brain DTI and MR planimetry, our study provides imaging evidence that SCPs are also involved in PSP-P. Indeed, we found decreased FA values and reduced width of SCPs in PSP-P patients in comparison with PD. The discrepancy between our study and previous reports not detecting SCPs atrophy in PSP-P may be due to different procedures used to measure SCPs width (automatic vs manual) or to different sample sizes or to different criteria used for classifying PSP-P patients.

The involvement of SCPs in patients with PSP-P, however, was less marked than in patients with PSP-RS, suggesting the hypothesis that the degree of SCPs atrophy may be related to the timing of the appearance of postural instability. In the current study we demonstrated that PSP-RS patients who fell within three years after the disease onset, showed a marked SCPs atrophy while most PSP-P patients (79.3%), who showed lower involvement of SCPs, developed postural instability later on. Of note, 15 out of 16 patients (93.7%) with PSP-P/O1 developed postural instability after three years from the disease onset and within an 8-year follow up, while only 6 out of 11 (54.5%) PSP-P/O2 patients developed this feature within the same period of time, thus suggesting that the timing of appearance of postural instability may be related to the severity of the PSP-P phenotype. In line with a pathological study [29] showing that in patients with PSP-P unprovoked falls can occur very late during the disease course, it is reasonable to hypothesize that O2 patients who do not experienced falls within 8-years of follow up, may develop postural instability later.

Taken together, our data suggest a close relationship between the timing of appearance of postural instability and the degree of SCPs atrophy, thus confirming the role of this brain structure in developing postural instability. Our findings are consistent with the new clinical diagnostic criteria for PSP, in which the early occurrence of falls was the main criterion to differentiate PSP-RS from PSP-P [1].

Vertical ocular motor dysfunction is a specific clinical sign of PSP and pathological studies have highlighted the atrophy of the midbrain tegmentum as being responsible for VSGP in this disease [30]. The neuroanatomical basis of ocular movements has been well studied and it is known that the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and the interstitial nucleus of Cajal (INC), both located in the midbrain tegmentum, are mainly involved in vertical saccades, in the speed and amplitude of movement, respectively. On the other hand, the paramediane pontine reticular formation (PPRS), located in the pontine tegmentum, is mainly involved in horizontal saccades. In the current study we compared PSP patients with different degrees of ocular dysfunction (PSP/O1 vs PSP/O2). TBSS whole-brain analyses showed that the midbrain was the only structure significantly damaged in the O1 patient group (PSP-RS/O1 and PSP-P/O1) compared to the O2 patient group (PSP-RS/O2 and PSP-P/O2). MR planimetry revealed higher midbrain atrophy in PSP/O1 than PSP/O2 patients, confirming the DTI findings. These results are in line with a previous study in PSP patients showing a direct correlation between ocular dysfunction and midbrain volume [6], and confirm that vertical ocular motor dysfunction is linked to microstructural damage and midbrain atrophy. Our study thus provides the imaging counterpart of ocular motor dysfunction clinically stratified by two levels of certainty (O1 and O2), demonstrating that the higher clinical severity of vertical ocular dysfunction (O1) was associated with higher atrophy and microstructural damage in the midbrain. Of note, the O2 patient group (PSP-RS/O2 and PSP-P/O2), showed lower midbrain FA values and midbrain area compared to PD patients. This result is consistent with the new criteria for diagnosing PSP-P because it provides the imaging evidence of midbrain involvement in vertical ocular slowness, thus supporting the inclusion of patients with milder PSP-P phenotype in the new classification.

The main strength of our study is the use of multimodal MRI to reveal imaging correlates of the core functional domains of PSP as defined by the new criteria for the clinical diagnosis of PSP.

Whole brain DTI analysis and MR planimetry provide complementary information on the integrity of brainstem structures assessing microstructural damage or atrophy, respectively. In our study, we found a significant correlation between planimetric and DTI measures in both the midbrain and SCPs, thus supporting the reliability of our findings in detecting imaging correlates of the main signs of PSP. However, whole-brain diffusion analysis and MR planimetry show methodological differences leading to a different feasibility in detecting

brain damage. Indeed, TBSS results are statistical and cannot be directly applied at the individual level, while MR planimetry is a widely used technique that enables brainstem structures to be measured at the individual level. Measuring SCPs width or midbrain area using MR planimetry in PSP patients without postural instability or VSGP may help predict the late appearance of these features in these patients. These findings cannot be obtained using TBSS alone, and future studies on this issue are warranted.

The main limitation of our study is that none of our patients had a histopathological diagnostic confirmation. However, the clinical evaluations were carried out by one author with more than 10 years of experience in movement disorders. Another limitation is the lacking of electrophysiological measurements of ocular movements velocity; thus cannot be excluded that in same patients with PSP clinical evaluation of vertical ocular dysfunction may be in error. However, PSP patients were examined by a physician expert in movement disorders thus making misclassification unlikely. Finally, a further limitation to our study is that patients (PSP and PD) and controls were not sex matched. However, we believe that this difference did not influence our results because the most important findings were obtained in PSP and PD patients who showed male predominance with a similar M/F ratio. In addition, MRI results did not differ between PD patients and controls.

In conclusion, our study provides neuroimaging evidences of the higher severity of SCPs damage in PSP-RS than PSP-P, which reflects the earlier appearance of postural instability in PSP-RS patients. In addition, our study also provides evidence of larger midbrain damage in PSP/O1 than in PSP/O2, demonstrating that a higher clinical severity of ocular dysfunction underlies a more severe midbrain atrophy.

Declaration of interest

None.

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Author's contribution

Andrea Quattrone: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content and final approval of the version to be submitted.

Maria Eugenia Caligiuri: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be submitted.

Maurizio Morelli: acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be submitted.

Salvatore Nigro: acquisition of data, analysis and interpretation of data and final approval of the version to be submitted.

Basilio Vescio: analysis and interpretation of data and final approval of the version to be submitted.

Gennarina Arabia: acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be submitted.

Giuseppe Nicoletti: acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be submitted.

Rita Nisticò: acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be submitted.

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Gaetano Barbagallo: acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be submitted.

Maria Grazia Vaccaro: acquisition of data and final approval of the version to be submitted.

Umberto Sabatini: acquisition of data, analysis and interpretation of data and final approval of the version to be submitted.

Virginia Vescio: acquisition of data, analysis and interpretation of data and final approval of the version to be submitted.

Carlo Stanà: acquisition of data, analysis and interpretation of data and final approval of the version to be submitted.

Federico Rocca: acquisition of data and final approval of the version to be submitted.

Manuela Caracciolo: acquisition of data and final approval of the version.

Aldo Quattrone: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.02.022.

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