RESEARCH PAPER

Midbrain MRI assessments in progressive supranuclear palsy subtypes

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Received 5 June 2019
Revised 22 July 2019
Accepted 19 August 2019

To cite: Picillo M, Tepedino MF, Abate F, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2019-321354

ABSTRACT

Objectives To explore the role of the available midbrain-based MRI morphometric assessments in (1) differentiating among progressive supranuclear palsy (PSP) subtypes (PSP Richardson's syndrome (PSP-RS), PSP with predominant parkinsonism (PSP-P) and the other variant syndromes of PSP (vPSP)), and (2) supporting the diagnosis of PSP subtypes compared with Parkinson's disease (PD) and healthy controls (HC).

Methods Seventy-eight patients with PSP (38 PSP-RS, 21 PSP-P and 19 vPSP), 35 PD and 38 HC were included in the present analysis. Available midbrain-based MRI morphometric assessments were calculated for all participants.

Results Current MRI midbrain-based assessments do not display an adequate sensitivity and specificity profile in differentiating PSP subtypes. On the other hand, we confirmed MR Parkinsonism Index (MRPI) and pons area to midbrain area ratio (P/M) have adequate diagnostic value to support PSP-RS clinical diagnosis compared with both PD and HC, but low sensitivity and specificity profile in differentiating PSP-P from PD as well as from HC. The same measures show acceptable sensitivity and specificity profile in supporting clinical diagnosis of vPSP versus HC but not versus PD. Similar findings were detected for the newer MRPI and P/M versions.

Conclusions Further studies are warranted to identify neuroimaging biomarkers supporting the clinical phenotypic categorisation of patients with PSP. MRPI and P/M have diagnostic value in supporting the clinical diagnosis of PSP-RS.

Classification of evidence This study provides class III evidence that available MRI midbrain-based assessments do not have diagnostic value in differentiating the Movement Disorder Society PSP subtypes.

INTRODUCTION

The Movement Disorder Society (MDS) has recently revised the clinical diagnostic criteria for progressive supranuclear palsy (PSP) providing guidance for recognising the different clinical variants of the disease.[1] A major challenge faced in such process was to determine whether to support the inclusion of neuroimaging biomarkers in the diagnosis of PSP Richardson's syndrome (PSP-RS) as well as in the other variant syndromes of PSP (vPSP), and what role they should play in the diagnostic process.[2]

A number of midbrain-based MRI morphometric measures have shown good sensitivity and specificity for differentiating PSP-RS from other parkinsonian disorders, such as the mid-sagittal midbrain area, the pons area to midbrain area ratio (P/M) and the MR Parkinsonism Index (MRPI).[2] The latter appears to have diagnostic value supporting the clinical diagnosis of PSP-RS compared with multiple system atrophy parkinsonian variant as well as Parkinson's disease (PD).[3–5]

Abnormal MRPI and P/M are also deemed to be supportive of early clinical diagnosis showing evidence for abnormalities before patients meet the criteria for PSP-RS in both retrospective and prospective studies.[6 7] As for other PSP subtypes, little evidence suggests MRPI may have diagnostic value for differentiating PSP with predominant parkinsonism (PSP-P) from PD,[8 9] while scant data are available for vPSP where midbrain involvement is considered less severe.[2]

More recently, upgraded versions of MRPI and P/M including the third ventricle and lateral ventricles width have been implemented (ie, MRPI 2.0 and P/M 2.0).[9 10]

The aim of the present study is to explore the role of available midbrain-based MRI morphometric assessments in (1) differentiating among MDS PSP subtypes (PSP-RS, PSP-P and vPSP) and (2) supporting the diagnosis of MDS PSP subtypes compared with PD and healthy controls (HC).

METHODS

Patients and clinical evaluation

Seventy-eight patients with PSP, 35 PD and 38 HC were included in the present analysis. MDS PSP criteria were retrospectively applied to all consecutive outpatients with PSP enrolled from the Movement Disorders Centers of the University of Salerno and the University of Pisa between November 2015 and December 2018 (online supplemental material).[1]

The application of the MDS PSP proposed diagnostic flow chart was carried by at least two movement disorders specialists (MP, RE, RC and DF) who independently reviewed all the data collected for each subject (including a videotaped motor assessment) and applied the criteria proposed by the task force, as described in detail elsewhere.[11 12] For each reviewed subject subsequent evaluation

was applied only if mandatory inclusion/exclusion criteria (B1, B2, B3) were satisfied. Then, each subject was categorised according to core clinical features (ocular motor dysfunction (O1, O2, O3), postural instability (P1, P2, P3), akinesia (A1, A2, A3), cognitive dysfunction (C1, C2, C3)) and supportive clinical clues (levodopa resistance (CC1), hypokinetic spastic dysarthria (CC2), dysphagia (CC3)) to reach a degree of diagnostic certainty (probable or possible PSP, or suggestive of PSP) and establish the predominance type (PSP-RS, PSP-P, PSP with predominant corticobasal syndrome (PSP-CBS), PSP with progressive gait freezing (PSP-PGF) and PSP with predominant frontal presentation (PSP-F)).[1 13] Information on photophobia (CC4) and postsynaptic striatal dopaminergic degeneration (IF2) was not available for any subject. Severity of the disease was evaluated with the Progressive Supranuclear Palsy Rating Scale (PSP-rs).[14]

Exclusion criteria for enrolment of patients with PD were diagnosis of dementia in accordance with the MDS criteria and H&Y in on state >3. Exclusion criteria for enrolment of HC were the presence of any neurological or psychiatric conditions.

MRI protocol

Seventy-eight per cent (61 of 78) of patients with PSP, as well as all PD and HC, underwent 3T brain MRI with the same scanner (Skyra, Siemens, Erlangen, Germany); the remaining patients had MRI with different scanners (1.5T and 3T).

The MRI protocol included a three-dimensional T1-weighted sequence; sagittal partitions and multiplanar reconstructions were obtained in the conventional transverse and coronal planes.

Morphometric measurements

Midbrain-based measures were retrospectively calculated and included mid-sagittal pons and midbrain areas, middle cerebellar peduncles to superior cerebellar peduncles ratio (MCP/SCP), P/M and MRPI, as well as P/M 2.0 and MRPI 2.0 (figure 1).[2 9] All measures were manually computed according to published methods by the same neuroradiologist (RM) with more than 15 years of experience in neurodegenerative diseases and blinded to diagnosis and phenotypic attribution.[2 9] A subgroup of 14 subjects also underwent automatised calculation of the MRPI (http://mrpi.unicz.it) in order to check agreement between manual and computerised MRPI calculations. Additionally, the same neuroradiologist repeated the measures after 3 months on 12 subjects to assess the intrarater reliability. A second neuroradiologist (ST) with 2 years of experience in neurodegenerative diseases performed the same measures on a subgroup of 10 patients with PSP to calculate the inter-rater reliability.

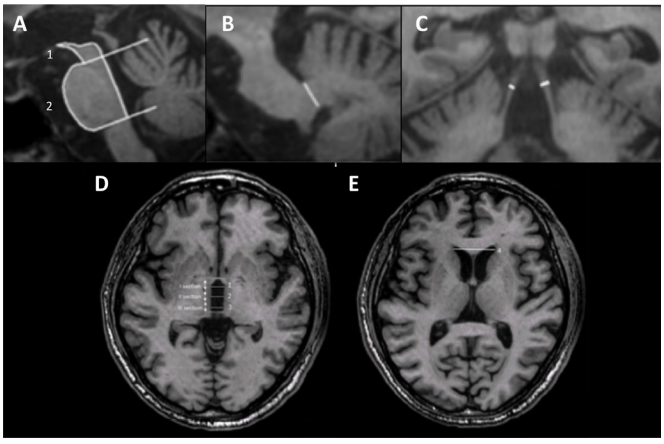

Figure 1 Midbrain MRI assessments included mid-sagittal midbrain (A1) and pons area (A2), middle cerebellar peduncles (B) to superior cerebellar peduncles (C) ratio (MCP/SCP), the pons area (A2) to midbrain area (A1) ratio (P/M), the MR Parkinsonism Index (MRPI) = (P/M) × (MCP/SCP), the P/M 2.0 = (P/M) × (third ventricle width (D)/frontal horns width (E)), and the MRPI 2.0=MRPI × (third ventricle width (D)/frontal horns width (E)). Images (A), (B) and (C) are modified from ref[2]; images (D) and (E) are modified from ref[9].

Statistical analysis

Only patients with complete data were included in the present analysis. After checking for normality distribution with the Kolmogorov-Smirnov test, differences in variables between groups were computed with χ^2 or Kruskal-Wallis, followed by pairwise Wilcoxon rank-sum test. Post-hoc comparisons were run with Bonferroni test.

Receiver operating characteristic curve (ROC) analysis was performed for each MRI morphometric assessment to compute the area under a receiver operating characteristic curve (AUC) (95% CI). For those assessments with AUC ≥0.6, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and diagnostic accuracy in comparison with clinical diagnosis were assessed at the best threshold for classification. Intraclass correlation coefficients were calculated to assess intrarater and inter-rater reliability, as well as to compare manual with computerised assessment of MRPI. Significance level was set at ≤0.05. Data analysis was conducted with SPSS (V.23.0).

Classification of evidence

This diagnostic accuracy study provides class III evidence that available MRI midbrain-based assessments do not have diagnostic value in differentiating MDS PSP subtypes.

RESULTS

Demographic, clinical and imaging data for PSP and PD as well as HC are shown in table 1.

The three groups presented similar age, age at onset, disease duration and gender distribution. All the midbrain-based MRI measures presented significant differences between PSP and PD as well as HC ($p<0.001$).

Demographic, clinical and imaging data for MDS PSP subtypes are shown in table 2.

Our cohort included 38 PSP-RS, 21 PSP-P and 19 vPSP (9 PSP-CBS, 6 PSP-PGF, 4 PSP-F). All patients qualified for a diagnosis of probability but those—by definition—with PSP-CBS.[1] The groups presented similar age, age at onset, disease duration and gender distribution. PSP-RS presented a more severe form of disease compared with PSP-P as assessed with the PSP-rs ($p<0.001$). As for the MRI measures, mid-sagittal midbrain area was significantly smaller in PSP-RS compared with PSP-P ($p<0.001$) and PSP-PGF ($p=0.004$), while P/M was significantly higher in PSP-RS compared with PSP-P ($p<0.001$), PSP-CBS ($p=0.030$) and PSP-PGF ($p=0.030$).

As PSP-CBS, PSP-PGF and PSP-F included a limited number of patients, subsequent analyses were performed considering PSP-RS versus PSP-P versus vPSP.

Midbrain-based morphometric assessments differentiating among MDS PSP subtypes

Figures 2A and 3 show measures differentiating PSP-RS from PSP-P and vPSP with AUC greater than 0.6. The corresponding

Table 1 Clinical and MRI morphometric assessments for PSP, PD and HC

	PSP (78)	PD (35)	HC (38)	P value
Age	70 (52–84)	68 (55–78)	66 (51–81)	0.119
Gender (male/female), n (%)	44/34 (56.4/43.6)	26/9 (74.2/25.8)	21/17 (55.2/44.8)	0.153
Age at onset	66 (51–81)	62 (42–73)	NA	0.101
Disease duration	4 (1–11)	4 (1–13)	NA	0.826
MCP/SCP	2.76 (2.05–4.918)	2.46 (0.87–1.81)	2.37 (1.86–2.98)	**<0.001***†
Mid-sagittal midbrain area (mm^2)	0.79 (0.50–1.48)	1.24 (0.87–1.81)	1.38 (0.95–1.95)	**<0.001***†
Mid-sagittal pons area (mm^2)	4.82 (3.51–6.64)	5.43 (4.36–7.16)	5.35 (4.33–6.96)	**<0.001***†
P/M	5.96 (3.35–8.96)	4.26 (2.95–6.28)	3.78 (2.71–5.27)	**<0.001***†
MRPI	16.46 (7.63–36.63)	10.61 (6.71–16.15)	9.11 (5.8–15.71)	**<0.001***†
P/M 2.0	1.58 (0.62–2.91)	0.94 (0.35–2.04)	0.63 (0.0–1.36)	**<0.001***†
MRPI 2.0	4.39 (1.54–11.89)	2.25 (0.8–4.3)	1.54 (0.0–4.06)	**<0.001***†

Values are shown in median (range), unless otherwise specified. Significant differences in bold.
*PSP vs PD <0.001.
†PSP vs HC <0.001.
HC, healthy controls; MCP/SCP, middle cerebellar peduncles to superior cerebellar peduncles ratio; MRPI, MR Parkinsonism Index; MRPI 2.0, MR Parkinsonism Index version 2.0; NA, not applicable; PD, Parkinson's disease; P/M, pons area to midbrain area ratio; P/M 2.0, pons area to midbrain area ratio version 2.0; PSP, progressive supranuclear palsy.

sensitivity, specificity, PPV, NPV and diagnostic accuracy are shown in table 3.

Midrain-based morphometric assessments in MDS PSP subtypes versus PD and HC

Figures 2B and 4 show measures differentiating MDS PSP subtypes from PD and HC with AUC greater than 0.6. The corresponding sensitivity, specificity, PPV, NPV and diagnostic accuracy are shown in table 4.

Reliability

Intraclass correlation showed excellent intrarater (intraclass correlation coefficient: 0.934, 95% CI 706 to 985, p<0.001) and inter-rater reliability for the manual computation of the MRPI, as well as excellent agreement between manual and computerised MRPI calculation (intraclass correlation coefficient: 0.970, 95% CI 907 to 990, p<0.001). Inter-rater reliability between two different neuroradiologists was also acceptable (intraclass correlation coefficient: 0.850, 95% CI 707 to 890, p<0.001).

DISCUSSION

Here, we showed a primary attempt to apply midbrain-based MRI measures to PSP, also taking into account MDS PSP subtypes (PSP-RS vs PSP-P vs vPSP). While brainstem measures proved able to differentiate PSP-RS from PD and HC, none of them showed an adequate sensitivity and specificity profile in differentiating MDS PSP subtypes (figure 2A, B, table 3). Furthermore, the inclusion of the supratentorial ventricle width into the recent MRPI 2.0 and the P/M 2.0 did not significantly improve overall diagnostic accuracy and balance between sensitivity and specificity of such measures.[9] The MDS PSP phenotypes were recently conceived based on an extensive review of the literature as well as the revision of the largest autopsy-confirmed case series reported so far.[1] However, no data are available on

Table 2 Demographic, clinical and imaging data for MDS PSP subtypes

			vPSP			
	PSP-RS (38)	PSP-P (21)	PSP-CBS (9)	PSP-PGF (6)	PSP-F (4)	P value
Age	71 (52–79)	70 (60–82)	70 (56–77)	70.5 (68–73)	79 (64–849	0.478
Gender, male/female, n (%)	23/15 (60.5/39.5)	11/10 (52.4/47.6)	5/4 (55.6/44.4)	3/3 (50/50)	2/2 (50/50)	NA
Age at onset	66.5 (51–75)	65 (56–80)	66 (52–74)	66.5 (61–71)	73.5 (62–81)	0.490
Disease duration	4 (1–11)	5 (1–8)	4 (2–8)	4.5 (2–7)	3 (2–8)	0.931
PSP-rs	54.5 (28–82)	37 (10–53)	46 (29–50)	28.5 (13–44)	47 (29–49)	**0.003***
MCP/SCP	2.85 (2.05–4.1)	2.67 (2.1–4.91)	2.72 (2.07–3.74)	2.56 (2.05–3.53)	3.33 (2.24–3.72)	0.524
Mid-sagittal midbrain area (mm^2)	0.71 (0.51–1.16)	0.97 (0.63–1.37)	0.86 (0.5–1.48)	0.97 (0.72–1.28)	0.79 (0.72–0.89)	**<0.001†**
Mid-sagittal pons area (mm^2)	4.77 (3.51–5.85)	4.83 (4.08–6.64)	4.3 (3.92–6.10)	5.12 (4.86–5.25)	4.9 (4.18–5.35)	0.129
P/M	6.33 (4.31–6.96)	4.89 (3.35–7.4)	5.54 (3.67–8.52)	5.25 (4.07–7.19)	6.46 (4.69–6.77)	**0.002‡**
MRPI	17.84 (10.35–36.63)	13.75 (7.63–23)	14.02 (9.65–31.49)	14.93 (9.61–17.15)	18.6 (14.6–25.04)	0.069
P/M 2.0	1.75 (0.87–2.91)	1.18 (0.62–2.48)	1.47 (0.79–2.31)	1.16 (0.91–1.99)	1.60 (1.1–2.03)	0.157
MRPI 2.0	4.95 (1.92–11.89)	2.95 (1.54–8.19)	3.77 (2.1–8.64)	4.1 (2.19–5.26)	4.63 (3.43–7.59)	0.121

Data are shown in median (range), unless otherwise specified. Significant differences in bold.
*PSP-RS vs PSP-P <0.001.
†PSP-RS vs PSP-P <0.001; PSP-RS vs PSP-PGF=0.004;
‡PSP-RS vs PSP-P <0.001; PSP-RS vs PSP-CBS=0.030; PSP-RS vs PSP-PGF=0.030;
MCP/SCP, middle cerebellar peduncles to superior cerebellar peduncles ratio; MDS, Movement Disorder Society; MRPI, MR Parkinsonism Index; MRPI 2.0, MR Parkinsonism Index version 2.0; NA, not applicable; P/M, pons area to midbrain area ratio; P/M 2.0, pons area to midbrain area ratio version 2.0; PSP, progressive supranuclear palsy; PSP-CBS, progressive supranuclear palsy with corticobasal syndrome; PSP-F, progressive supranuclear palsy with frontal predominance; PSP-P, progressive supranuclear palsy with parkinsonism; PSP-PGF, progressive supranuclear palsy with progressive gait freezing; PSP-rs, Progressive Supranuclear Palsy Rating Scale; PSP-RS, progressive supranuclear palsy with Richardson's syndrome; vPSP, other variant syndromes of progressive supranuclear palsy.

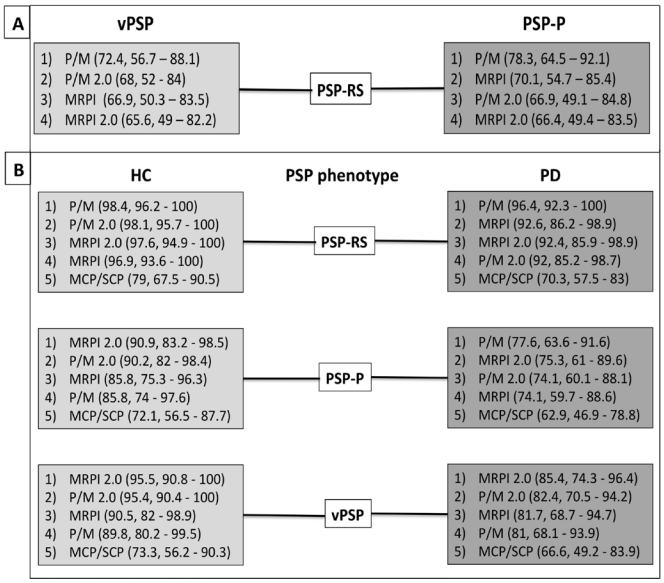

Figure 2 (A) Morphometric assessments differentiating PSP-RS from PSP-P and vPSP with AUC >0.6 (AUC, 95% CI). (B) Morphometric assessments differentiating PSP phenotypes from PD and HC with AUC >0.6 (AUC, 95% CI). AUC, area under a receiver operating characteristic curve; HC, healthy controls; MCP/SCP, middle cerebellar peduncles to superior cerebellar peduncles ratio; MRPI, MR Parkinsonism Index; MRPI 2.0, MRPI, MR Parkinsonism Index version 2.0; PD, Parkinson's disease; P/M, pons area to midbrain area ratio; P/M 2.0, pons area to midbrain area ratio version 2.0; PSP, progressive supranuclear palsy; PSP-P, progressive supranuclear palsy with predominant parkinsonism; PSP-RS, progressive supranuclear palsy with Richardson's syndrome; vPSP, other variant syndromes of progressive supranuclear palsy.

neuroimaging biomarkers of the PSP phenotypes as diagnosed according to the MDS criteria in prospectively enrolled cohorts. We previously demonstrated the feasibility of application of the MDS PSP criteria in real-life clinical settings with the only main issue being the phenotype attribution.[11] As such, inter-rater reliability for clinical phenotypic categorisation was suboptimal (kappa=0.581) with a need for referral to a third evaluator required in 13.6% of cases.[11] In such a scenario, there is a dearth of neuroimaging biomarkers supporting specific phenotypic attribution.

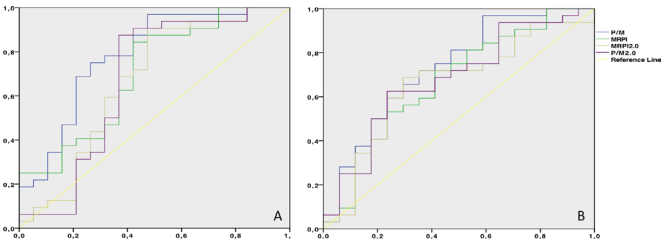

Figure 3 (A) PSP-RS versus PSP-P and (B) PSP-RS versus vPSP. Results from ROC analysis for P/M, MRPI, P/M 2.0 and MRPI 2.0. y axis: sensitivity; x axis: specificity. For details see the text and table 3. MRPI, MR Parkinsonism Index; MRPI 2.0, MR Parkinsonism Index version 2.0; P/M, pons area to midbrain area ratio; P/M 2.0, pons area to midbrain area ratio version 2.0; PSP-P, progressive supranuclear palsy with predominant parkinsonism; PSP-RS, progressive supranuclear palsy with Richardson's syndrome; ROC, receiver operating characteristic curve; vPSP, other variant syndromes of progressive supranuclear palsy.

Table 3 Morphometric assessments differentiating MDS PSP subtypes with AUC >0.6

	AUC >0.6			
PSP-RS vs PSP-P	**MRPI (16.08)**	**MRPI 2.0 (4.36)**	**P/M (5.87)**	**P/M 2.0 (1.27)**
Sensitivity	62.9	72.2	72.2	89.5
Specificity	60	76.2	76.2	57.1
PPV	73.3	83.9	83.9	79.1
NPV	48	61.5	61.5	75
Diagnostic accuracy	61.8	73.6	73.6	77.9
PSP-RS vs vPSP	**MRPI**	**MRPI 2.0**	**P/M (6.13)**	**P/M 2.0 (1.63)**
Sensitivity	NS	NS	63.9	68.4
Specificity	NS	NS	73.7	68.4
PPV	NS	NS	82.1	81.3
NPV	NS	NS	51.9	52
Diagnostic accuracy	NS	NS	67.1	68.4

The best threshold for classification for each morphometric assessment is reported in brackets.
As for PSP-P vs vPSP, ROC analysis demonstrated that none of the brain morphometric assessments had AUC greater than 0.6.
AUC, area under a receiver operating characteristic curve; MDS, Movement Disorder Society; MRPI, MR Parkinsonism Index; MRPI 2.0, MR Parkinsonism Index version 2.0; NPV, negative predictive value; NS, not significant; P/M, pons area to midbrain area ratio; P/M 2.0, pons area to midbrain area ratio version 2.0; PPV, positive predictive value; PSP, progressive supranuclear palsy; PSP-P, progressive supranuclear palsy with parkinsonism; PSP-RS, progressive supranuclear palsy with Richardson's syndrome; ROC, receiver operating characteristic curve; vPSP, other variant syndromes of progressive supranuclear palsy.

In the present study, we confirmed previous findings that among different brainstem measurements, MRPI and P/M have adequate diagnostic value to support PSP-RS clinical diagnosis compared with PD and HC (see ref[2] for a comprehensive list of studies). The addition of the third and lateral ventricles width into the midbrain-based indexes slightly increased MRPI 2.0

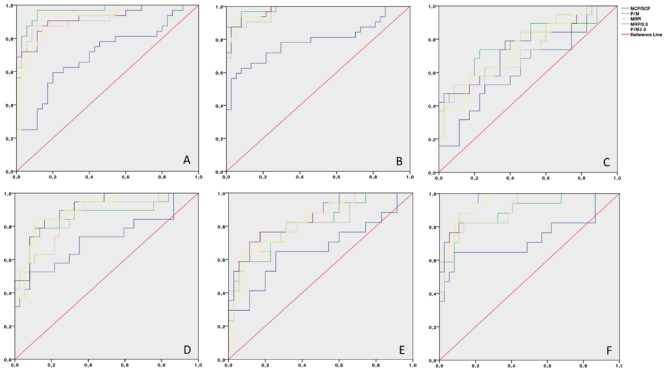

Figure 4 (A) PSP-RS versus PD, (B) PSP-RS versus HC, (C) PSP-P versus PD, (D) PSP-P versus HC, (E) vPSP versus PD, and (F) vPSP versus HC. Results from ROC analysis for P/M, MRPI, P/M 2.0 and MRPI 2.0. y axis: sensitivity; x axis: specificity. For details see the text, figure 3 and table 4. HC, healthy controls; MCP/SCP, middle cerebellar peduncles to superior cerebellar peduncles ratio; MRPI, MR Parkinsonism Index; MRPI 2.0, MR Parkinsonism Index version 2; PD, Parkinson's disease; P/M, pons area to midbrain area ratio; P/M 2.0, pons area to midbrain area ratio version 2; PSP-P, progressive supranuclear palsy with predominant parkinsonism; PSP-RS, progressive supranuclear palsy with Richardson's syndrome; ROC, receiver operating characteristic curve; vPSP, other variant syndromes of progressive supranuclear palsy.

Table 4 Morphometric assessments differentiating PSP and its variants from PD and HC with AUC >0.6

PSP-RS vs PD	MRPI (13.89)	MRPI 2.0 (3.18)	P/M (4.97)	P/M 2.0 (1.17)	MCP/SCP (2.63)
Sensitivity	86.8	89.5	94.4	94.7	67.7
Specificity	91.4	85.7	88.6	85.7	74.3
PPV	91.7	87.2	89.5	87.8	71.9
NPV	86.5	88.2	93.9	93.8	68.4
Diagnostic accuracy	89	87.6	91.5	93.1	67.7
PSP-RS vs HC	**MRPI (11.58)**	**MRPI 2.0 (2.59)**	**P/M (4.77)**	**P/M 2.0 (1.16)**	**MCP/SCP (2.5)**
Sensitivity	91.4	94.7	97.2	94.7	80
Specificity	89.2	92.1	91.2	94.7	78.8
PPV	88.9	93.2	92.1	94.7	71.8
NPV	91.7	94.6	97.1	94.7	78.8
Diagnostic accuracy	90.2	93.4	94.5	97.3	75
PSP-P vs PD	**MRPI (11.7)**	**MRPI 2.0 (2.58)**	**P/M (4.72)**	**P/M 2.0 (1.08)**	**MCP/SCP**
Sensitivity	65	76.2	71.4	66.7	NS
Specificity	74.3	65.7	77.1	68.6	NS
PPV	59.1	57.1	65.2	56	NS
NPV	78.8	82.1	81.8	77.4	NS
Diagnostic accuracy	70.9	69.6	75	67.8	NS
PSP-P vs HC	**MRPI (10.27)**	**MRPI 2.0 (2.2)**	**P/M (4.59)**	**P/M 2.0 (0.97)**	**MCP/SCP (2.44)**
Sensitivity	80	85.7	81	85.7	75
Specificity	75.6	84.2	86.5	89.5	64.9
PPV	64	75	77.3	81.8	53.6
NPV	87.5	91.4	88.9	91.9	82.8
Diagnostic accuracy	77.1	84.7	84.4	88.1	68.4
vPSP vs PD	**MRPI (11.34)**	**MRPI 2.0 (2.47)**	**P/M (4.65)**	**P/M 2.0 (1.05)**	**MCP/SCP (2.63)**
Sensitivity	84.2	84.2	84.2	84.2	63.2
Specificity	68.6	62.9	68.6	62.9	74.3
PPV	59.3	55.2	59.3	55.2	57.1
NPV	88.9	88	88.9	88	78.8
Diagnostic accuracy	74	70.3	74	70.3	70.3
vPSP vs HC	**MRPI (11.32)**	**MRPI 2.0 (2.3)**	**P/M (4.67)**	**P/M 2.0 (0.99)**	**MCP/SCP (2.46)**
Sensitivity	84.2	89.5	84.2	89.5	68.4
Specificity	86.5	89.5	91.9	89.5	64.9
PPV	76.2	81	84.2	81	50
NPV	91.4	94.4	91.9	94.4	80
Diagnostic accuracy	85.7	89.4	89.2	89.4	66

The best threshold for classification for each morphometric assessment is reported in brackets.
AUC, area under a receiver operating characteristic curve; HC, healthy controls; MCP/SCP, middle cerebellar peduncles to superior cerebellar peduncles ratio; MRPI 2.0, MR Parkinsonism Index version 2.0; MRPI, MR Parkinsonism Index; NPV, negative predictive value; NS, not significant; PD, Parkinson's disease; P/M, pons area to midbrain area ratio; P/M 2.0, pons area to midbrain area ratio version 2.0; PPV, positive predictive value; PSP, progressive supranuclear palsy; PSP-P, progressive supranuclear palsy with parkinsonism; PSP-RS, progressive supranuclear palsy with Richardson's syndrome; vPSP, other variant syndromes of progressive supranuclear palsy.

diagnostic value for differentiating PSP-RS from PD and HC, while the diagnostic value of P/M 2.0 did not change significantly (table 4). On the other hand, both MRPI and P/M confirmed their suboptimal sensitivity and specificity profile in differentiating PSP-P from PD as well as from HC, suggesting a limited utility of such biomarkers in supporting the clinical diagnosis of PSP-P in cross-sectional evaluations.[15 16] Contradicting previous findings,[17] our data would suggest that P/M has higher diagnostic accuracy than MRPI in differentiating between PSP-P and PD. As a matter of fact, in our cohort the addition of the supratentorial ventricle width into MRPI 2.0 and P/M 2.0 did not significantly increase diagnostic accuracy of such biomarkers in supporting clinical diagnosis of PSP-P versus PD or versus HC.[9]

Regarding vPSP, our data showed an acceptable sensitivity and specificity profile of MRPI, MRPI 2.0, P/M and P/M 2.0 in supporting clinical diagnosis versus HC, while versus PD the diagnostic value was suboptimal. Taken together our findings support the notion that midbrain atrophy is typically less severe in vPSP than in PSP-RS.[18 19]

Herein we showed the first independent application of MRPI 2.0 and P/M 2.0 in PSP diagnosed according to the MDS criteria after their recent proposal.[9] Excluding MRPI differentiating PSP-RS and PD and MRPI 2.0 differentiating PSP-RS from HC, our optimal cut-off values according to ROC analysis are different from the original description (see online supplemental material for diagnostic accuracy according to cut-off values noted in ref 9). This finding is not surprising, given the data-driven approach of ROC analysis.

From a practical point of view, the analysis of the different indexes suggests some considerations. First, MRPI, MRPI 2.0, P/M and P/M 2.0 all appear to be valuable imaging biomarkers of disease in the differential diagnosis between all PSP phenotypes versus HC. Indeed, the multiparameter evaluation of MRPI and MRPI 2.0 might be especially useful in a research context for evaluating the whole complexity of PSP-related neurodegeneration, while considering, for example, the response to novel treatments. Second, the above-mentioned indexes seem to take into account particular aspects distinguishing PSP from the disease that are mostly considered in the differential diagnosis, that is, PD. Therefore, the introduction of these indexes might be of interest as they can help in the routine differential diagnosis work-up of extrapyramidal motor disorders. However, P/M showed comparable or even superior diagnostic accuracy compared with MRPI in discriminating PSP-RS and PSP-P from PD and HC. As P/M manual computation is much easier to perform and be understood by neuroradiologists and general radiologists not specifically working with extrapyramidal movement disorders (it requires only the mid-sagittal image and two easy-to-perform measurements of the pons and midbrain areas without further specific reconstructed planes or repetitive and less reproducible measurements on the superior and middle cerebellar peduncles), P/M seems to represent a powerful routine diagnostic tool when dealing with patients with PSP clinical features.

Our study has limitations. First, we recognise the lack of pathological confirmation of both diagnosis and phenotypic categorisation, still the gold standard for PSP diagnosis. Although our data are based only on clinical judgement, both the MDS diagnostic flow chart and phenotypic attribution have been applied independently by two experts in movement disorders. In addition, patients with PSP were compared with an age-matched and sex-matched group of HC, and vascular lesions as well as signs suggesting the presence of normal pressure hydrocephalus were carefully excluded in all individuals. As a second drawback, we acknowledge our cohort includes only a cross-sectional evaluation and lacks longitudinal follow-up. However, 72% of our patients already reached a degree of diagnostic certainty of probable PSP, and among those with possible PSP 41% harboured a PSP-CBS phenotype which—by definition—reaches a degree of possibility. Also, the excellent intrarater and inter-rater reliability for the manual computation of the MRPI and a sound agreement between manual and computerised MRPI calculation further strengthen our data. Then, we recognise the number of PD and HC enrolled is half the number of total patients with PSP. However, since our first aim was to characterise midbrain radiological assessments in MDS PSP subtypes, PD and HC only served as control groups. We also acknowledge the number of patients qualifying for vPSP is small. Indeed, further studies are

needed to better characterise radiological biomarkers in vPSP. Finally, we missed to assess midbrain diameter and the cerebral interpeduncular angle. Fair diagnostic accuracy was recently reported for such assessments in differentiating between PSP and non-PSP (including both PD and multiple system atrophy).[20 21]

In conclusion, our study demonstrates that current MRI brainstem assessments do not display an adequate sensitivity and specificity profile in differentiating MDS PSP subtypes. Further studies are warranted to identify neuroimaging biomarkers supporting the clinical phenotypic categorisation of patients with PSP. On the other hand, we confirmed MRPI and P/M have adequate diagnostic value to support PSP-RS clinical diagnosis compared with PD and HC. Our results confirm the suboptimal sensitivity and specificity profile of both the MRPI and P/M in differentiating PSP-P from PD in cross-sectional evaluations as well as from HC, and show for the first time an acceptable sensitivity and specificity profile of MRPI, MRPI 2.0, P/M and P/M 2.0 in supporting the clinical diagnosis of vPSP versus HC but not versus PD.

Acknowledgements We are grateful to the patients who participated in the study and to Susan Ainscough for performing English editing of the text.

Contributors MP: designed and conceptualised the study; major role in the acquisition of data; analysed the data; drafted the manuscript for intellectual content; approval of the version being published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MFT, FA, RE, SP, ST, GV, DF, PC, MC, RC, FE, MTP, PB: major role in the acquisition, analysis and interpretation of data; revised the manuscript for intellectual content; approval of the version being published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. RM: designed and conceptualised the study; major role in the acquisition of data; interpretation of the data; revised the manuscript for intellectual content; approval of the version being published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the EC Napoli3sud (number 101, 19 October 2017), and each subject was included after signing the informed consent form.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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