Radiology

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Planimetric and Linear MRI Markers for Progressive Supranuclear Palsy Classification: A Large Multicohort International Study

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Background: Differentiating progressive supranuclear palsy (PSP) from Parkinson disease and other parkinsonisms is challenging. MRI measures have been investigated, but most studies included small samples, limiting result reliability.

Purpose: To compare the performance of planimetric and linear MRI measurements in differentiating PSP from other parkinsonisms and identify an optimized linear marker.

Materials and Methods: Participants with PSP and non-PSP parkinsonisms and controls were included in this secondary analysis of multiple international prospective studies (enrollment: 2006–2024). The previously established midbrain line, midbrain area, pons to midbrain area ratio, and MR parkinsonism index were compared with a new simple linear marker based on two midbrain measures performed on midsagittal T1-weighted sections (dual-line midbrain PSP index [DMPI]). Logistic regression including DMPI, age, and sex was used to differentiate participants with PSP (PSP–Richardson syndrome, PSP variants) from those with non-PSP parkinsonisms and controls in two large independent cohorts and in a small cohort of participants with pathologically proven diagnoses.

Results: A total of 2111 participants (mean age, 67.8 years ± 8.4 [SD]; 54% male) were included (Italian: 136 PSP, 238 non-PSP, 85 controls; international: 520 PSP, 564 non-PSP, 525 controls). All markers were compared in a subcohort (PSP [*n* = 161]; non-PSP parkinsonisms [*n* = 203]) representative of the overall cohort. All measures showed area under the receiver operating characteristic curve (AUC) values over 0.90 for differentiating PSP from non-PSP parkinsonisms, with the DMPI and midbrain area performing best (AUCs, 0.97 [95% CI: 0.95, 0.98] and 0.95 [95% CI: 0.93, 0.97], respectively) and the DMPI showing the smallest percentage of uncertain cases (gray zone, 29 of 364 participants [7.97%]). In the entire Italian and international cohorts, the DMPI distinguished participants with PSP from those with non-PSP, with AUCs of 0.97 (95% CI: 0.97, 0.98) and 0.96 (95% CI: 0.95, 0.97), respectively. Excellent DMPI performance was also observed in participants with early-stage disease (AUC, 0.97 [95% CI: 0.95, 0.99]) and those with pathologically confirmed diagnoses (*n* = 43) (AUC, 0.94 [95% CI: 0.86, 1.00]).

Conclusion: The DMPI and midbrain area performed well for differentiating PSP from other neurodegenerative parkinsonisms.

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Supplemental material is available for this article.

Differentiating progressive supranuclear palsy (PSP) from Parkinson disease (PD), multiple system atrophy (MSA), and corticobasal syndrome (CBS) is challenging, especially in the early disease stages (1–2). Several structural MRI biomarkers have been proposed to support PSP differential diagnosis (3). Planimetric measures have been investigated in recent studies (4–8), and automated approaches based on volumetry or diffusion tensor imaging have been used, often leveraging machine learning technology (9–12). Among these measures, planimetric and linear measures were focused on the parts of structures where atrophy was most striking; therefore, they typically showed higher classification accuracy than volumetric measures, especially for the midbrain area (13–15). Conversely, entire structures are evaluated in automated volumetry, which provides very stable measures across individuals, making volumetry suitable for measuring disease progression (14). Planimetric markers such as the MR parkinsonism index (MRPI) and MRPI 2.0 have demonstrated good performance in relatively large cohorts (4–8) but are based on complex measurement procedures requiring extensive expertise and/or automation, limiting their routine application for patient diagnosis in hospital settings.

Imaging software that provides automated measures could assist in diagnosis, but there is no universally accepted reference standard algorithm for supporting PSP diagnosis, with issues related to differences across tools, possible failures in noisy images or segmentation errors, expensive costs of licenses and services, and limited availability in hospital settings. Conversely, simple linear MRI measures can be readily performed on T1-weighted images even by nonexperienced technicians, making these measures suitable for clinical practice application. The main limitation of these measures is that the key brain structures affected in PSP are small, especially when atrophic, and the manual measurements may be prone to errors, making standardized procedures and large sample sizes necessary for obtaining robust results. Linear midbrain measurements for differentiating PSP from other parkinsonisms have been investigated in several studies (16–23),

Abbreviations

AD = Alzheimer disease, AUC = area under the receiver operating characteristic curve, CBS = corticobasal syndrome, DMPI = dual-line midbrain PSP index, LR = logistic regression, MRPI = MR parkinsonism index, MSA = multiple system atrophy, PD = Parkinson disease, PSP = progressive supranuclear palsy, PSP-RS = PSP–Richardson syndrome, vPSP = PSP variants

Summary

Comparison of several MRI markers revealed that a simple, generalizable midbrain linear measure and midbrain area accurately support routine differential diagnosis between progressive supranuclear palsy (PSP) and non-PSP parkinsonisms.

Key Results

- In this secondary analysis of multiple prospective studies, the performance of planimetric and linear MRI markers for differentiating progressive supranuclear palsy (PSP) from other parkinsonisms was compared.
- A simple marker for PSP classification in clinical settings was identified, obtained by averaging the measurements of two key midbrain parts on midsagittal MRI scans, termed dual-line midbrain PSP index (DMPI).
- A logistic regression model including DMPI, age, and sex performed well in PSP differentiation (area under the receiver operating characteristic curve, >0.95) and was validated in two large independent cohorts.

but heterogeneous measurements were used, with clear anatomic landmarks often lacking, and these studies were often performed in small groups without validation in independent cohorts, hampering result reliability and generalizability. Moreover, in most studies, participants with PSP–Richardson syndrome (PSP-RS) were compared with participants with PD and control participants (4), with very little evidence in participants with PSP variants (vPSP) (8,13,24,25). Therefore, the aims of this study were to compare the performance of previously established planimetric and linear MRI measurements in differentiating PSP from other neurodegenerative parkinsonisms and identify an optimized linear MRI marker that overcomes the limitations of the previously described linear measures.

Materials and Methods

Ethics approval was obtained from the local ethics committee at each site, and all participants provided written informed consent as per local regulations for the use of their medical records for research purposes. All study procedures were conducted in accordance with the Declaration of Helsinki and Health Insurance Portability and Accountability Act.

Study Participants

This is a secondary analysis of multiple international prospective studies. Participants with available brain MRI data from different multisite cohorts were included. The training cohort included Italian participants recruited at a single institution (University of Catanzaro, Italy). A large international external test cohort included participants from the placebo arms of international PSP clinical trials (ClinicalTrials.gov identifiers NCT03068468, NCT01110720, NCT01049399), the Four Repeat Tau Neuroimaging Initiative (4RTNI), the Parkinson's Progression Markers Initiative (PPMI), two multisite prospective observational studies (DescribePSP [Germany] and PROSPECT [United Kingdom]), and a Greek center (University of Athens, Greece). International control participants were selected from the PPMI, Alzheimer's Disease Neuroimaging Initiative (ADNI), Open Access Series of Imaging Studies 3 (OASIS-3) databases, and University of Athens. Finally, a small independent external test cohort included participants with postmortem pathologic diagnosis from the 4RTNI, PPMI, and University of Turku, Finland. PSP classification was based on clinical criteria, and no MRI measure was used to perform the diagnosis. Inclusion criteria were clinical diagnosis of PSP, MSA, CBS, or PD; available three-dimensional T1-weighted MRI scans; and age 40 years or older. Exclusion criteria were poor MRI quality not allowing accurate measurements, missing demographic information, and diagnostic concerns, as shown in Figure 1. Detailed information on each cohort

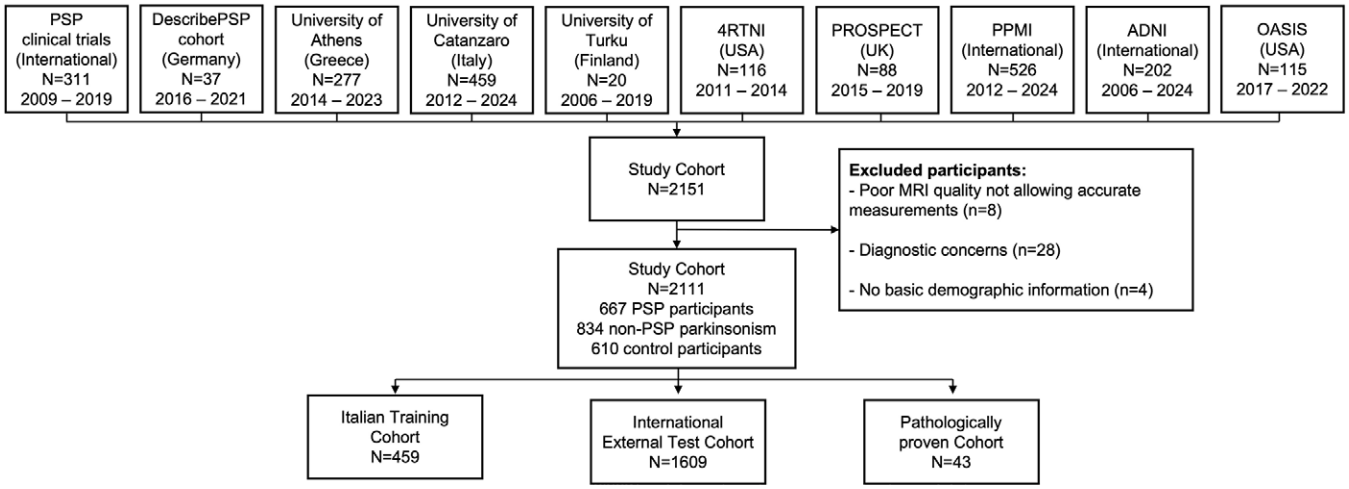

Figure 1: Flow diagram shows participant selection from the different cohorts and inclusion and exclusion procedures. The 28 participants excluded because of diagnostic concerns consisted of participants excluded because of conflicting information in the datasets (n = 12), participants fulfilling criteria for "suggestive of progressive supranuclear palsy (PSP)" but not "possible" or "probable" PSP diagnosis (n = 5), participants classified as having clinically uncertain parkinsonism (n = 9), and participants with other neuropathologic diagnoses (n = 2). Detailed information on all inclusion and exclusion procedures of participants from international datasets is provided in Appendix S1. Details on participant subgroups from each cohort are provided in Table S1. ADNI = Alzheimer's Disease Neuroimaging Initiative, 4RTNI = Four Repeat Tau Neuroimaging Initiative, OASIS = Open Access Series of Imaging Studies, PPMI = Parkinson's Progression Markers Initiative.

is provided in Appendix S1 and Table S1. Available clinical scores were extracted, including Movement Disorder Society–Unified PD Rating Scale part III, or MDS-UPDRS-III, scores (26); Unified MSA Rating Scale, or UMSARS, scores (27) for participants with MSA; and Progressive Supranuclear Palsy Rating Scale, or PSPRS, scores (28) for participants with PSP and CBS.

MRI Scan Acquisition and Linear Measurements

All participants in the training cohort underwent a brain MRI examination with either a 3-T Discovery MR750 scanner (GE HealthCare; *n* = 407) or a hybrid 3-T PET/MRI scanner (Biograph mMR, Siemens Healthcare; *n* = 52), including three-dimensional T1-weighted images (Appendix S1). Participants from the international cohorts underwent brain MRI on 1.5- or 3-T scanners, and available MRI protocol details are provided in Appendix S1. Established midbrain line, midbrain area, pons to midbrain area ratio, and MRPI were obtained as previously described (6,7,15) (Appendix S1). For the newly developed linear marker, two linear midbrain measurements were performed on midsagittal T1-weighted images (Fig 2). A tract termed "line A" was traced to connect the anterior notch of the pontomesencephalic junction and the posterior commissure. A second tract termed "line B" was traced tangent to both the upper anterior border of the pons and the posterior commissure. The midbrain width along these two lines without including the quadrigeminal plate was measured and averaged, (A + B)/2, to calculate the dual-line midbrain PSP index (DMPI). These measurements were manually performed by a neuroradiology technician (I.C., with >3 years of experience) blinded to clinical diagnoses. For a subset of 150 images (50 participants with PSP, 50 participants with PD, and 50 control participants), measurements were performed twice for intrarater agreement analysis. For interrater agreement analysis, measurements were also performed by a second neuroradiology technician (A.S., with <3 years of experience). The time needed by each technician to perform the measurements and obtain the DMPI was recorded for 40 images on two different Digital Imaging and Communications in Medicine, or DICOM, viewers and compared with that for the well-known midbrain area measurements.

Statistical Analysis

Clinical information comparisons were performed with the Fisher test, analysis of variance, Kruskal-Wallis test, *t* test, or Wilcoxon rank sum test, as appropriate. Imaging data (A, B, and DMPI values) were compared across groups with use of analysis of covariance (covariates: age and sex). The percentage difference from control participants and the coefficient of variation for imaging measures was calculated as described in Appendix S1. Associations between imaging and clinical data were investigated using multivariable linear regression models. *P* values were Bonferroni corrected, and the threshold for statistically significant difference was .05. DMPI classification performance was determined with

Table 1: Demographic and Clinical Characteristics of the Overall Cohort

Characteristic	Control Group (*n* = 610)	PD Group (*n* = 643)	MSA Group (*n* = 93)	CBS Group (*n* = 74)	CBS-AD Group (*n* = 24)	PSP-RS Group (*n* = 563)	vPSP Group (*n* = 104)	*P* Value
Sex								<.001*
M	296	399	49	35	11	300	58	
F	314	244	44	39	13	263	46	
Age at examination (y)†	69.6 ± 9.5 (49.0–95.4)	65.9 ± 8.0 (38.0–88.0)	63.4 ± 8.3 (44.5–80.2)	66.0 ± 7.3 (48.3–82.0)	65.6 ± 8.5 (53.0–80.0)	69.0 ± 7.0 (43.0–86.0)	70.0 ± 6.7 (53.0–82.9)	<.001‡
Disease onset (y)	...	62.6 ± 8.2	59.9 ± 8.9	62.1 ± 7.4	63.1 ± 8.8	67.0 ± 7.0	65.7 ± 6.6	<.001‡
Disease duration (y)	...	3.3 ± 3.2	3.6 ± 3.8	3.9 ± 2.6	2.5 ± 1.5	2.6 ± 2.3	4.3 ± 3.1	<.001‡
MDS-UPDRS-III score	...	24.2 ± 11.5	29.4 ± 17.3	33.1 ± 14.8	29.6 ± 18.1	37.9 ± 15.5	39.9 ± 16.9	<.001‡
PSPRS score	...	...	...	25.0 ± 11.9	20.6 ± 12.9	37.3 ± 12.0	32.8 ± 15.3	.002§
UMSARS score	...	...	35.8 ± 17.0	...	...	...	...	...
H-Y score	...	1.7 ± 0.6	3.2 ± 1.1	...	...	3.3 ± 0.8	2.8 ± 0.8	<.001‡

Note.—Unless otherwise specified, data are means ± SDs. The multiple system atrophy (MSA) group included 47 participants with MSA–cerebellar type, 37 participants with MSA–parkinsonian type, and nine participants with indeterminate MSA type. Age at onset and disease duration were available for 342 participants with progressive supranuclear palsy (PSP)–Richardson syndrome (PSP-RS), 101 participants with PSP variants (vPSP), 634 participants with Parkinson disease (PD), 82 participants with MSA, 63 participants with corticobasal syndrome (CBS), and 22 participants with CBS–Alzheimer disease (CBS-AD). Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) scores (motor examination) were available for 147 participants with PSP-RS, 76 participants with vPSP, 604 participants with PD, 59 participants with MSA, 32 participants with CBS, and 23 participants with CBS-AD. Progressive Supranuclear Palsy Rating Scale (PSPRS) scores were available for 447 participants with PSP-RS, 69 participants with vPSP, 55 participants with CBS, and 16 participants with CBS-AD. Unified Multiple System Atrophy Rating Scale (UMSARS) scores were available for 44 participants with MSA. Hoehn and Yahr scale (H-Y) scores were available for 81 participants with PSP-RS, 42 participants with vPSP, 573 participants with PD, and 19 participants with MSA.

* Fisher exact test (female = 0, male = 1) with Bonferroni correction; significant at $P < .001$ in control participants versus participants with PD.

† Data in parentheses are ranges.

‡ Analysis of variance test followed by pairwise *t* tests or the Kruskal-Wallis test followed by post hoc comparisons; *P* values were Bonferroni adjusted for the number of tests (21 tests for age; 15 for onset, duration, and MDS-UPDRS-III score; six for PSPRS and H-Y scores).

§ Wilcoxon rank sum test.

receiver operating characteristic curve analysis and compared with that of other brainstem measures with use of the DeLong test. Optimal cutoffs were identified with the Youden method; moreover, a two-cutoff approach was used, defined as the range between the cutoff corresponding to 95% sensitivity and that corresponding to 95% specificity (termed the "gray zone"), and the percentage of participants with measures falling within the gray zone was determined (lower values indicate better performance).

Logistic Regression Analysis

Subsequently, the best marker for distinguishing participants with PSP from participants with non-PSP parkinsonisms and control participants emerging from the comparison was investigated in the entire study cohort. To this aim, a multivariable logistic regression (LR) classifier was used, including the marker value as predictor and confounding factors (age and sex). The model was trained using default parameters, and model performance was evaluated using the area under the receiver operating characteristic curve (AUC); accuracy, sensitivity, specificity, and positive and negative predictive values were also calculated using a fixed discriminating probability threshold of 50%, which remained the same across cohorts; 95% CIs were calculated as described in Appendix S1. Stratified fivefold cross-validation (repeated five times) was performed to investigate the performance in the training set (Italian cohort, n = 459; 136 participants with PSP, 238 participants with non-PSP parkinsonisms, and 85 control participants), and model performance was validated in the independent external test set (international cohort, n = 1609; 520 participants with PSP, 564 participants with non-PSP parkinsonisms, and 525 control participants). Further analyses were conducted by training the LR model on the entire study cohort and by investigating classification performance in participants with early-stage disease and in participants for whom diagnosis was confirmed postmortem.

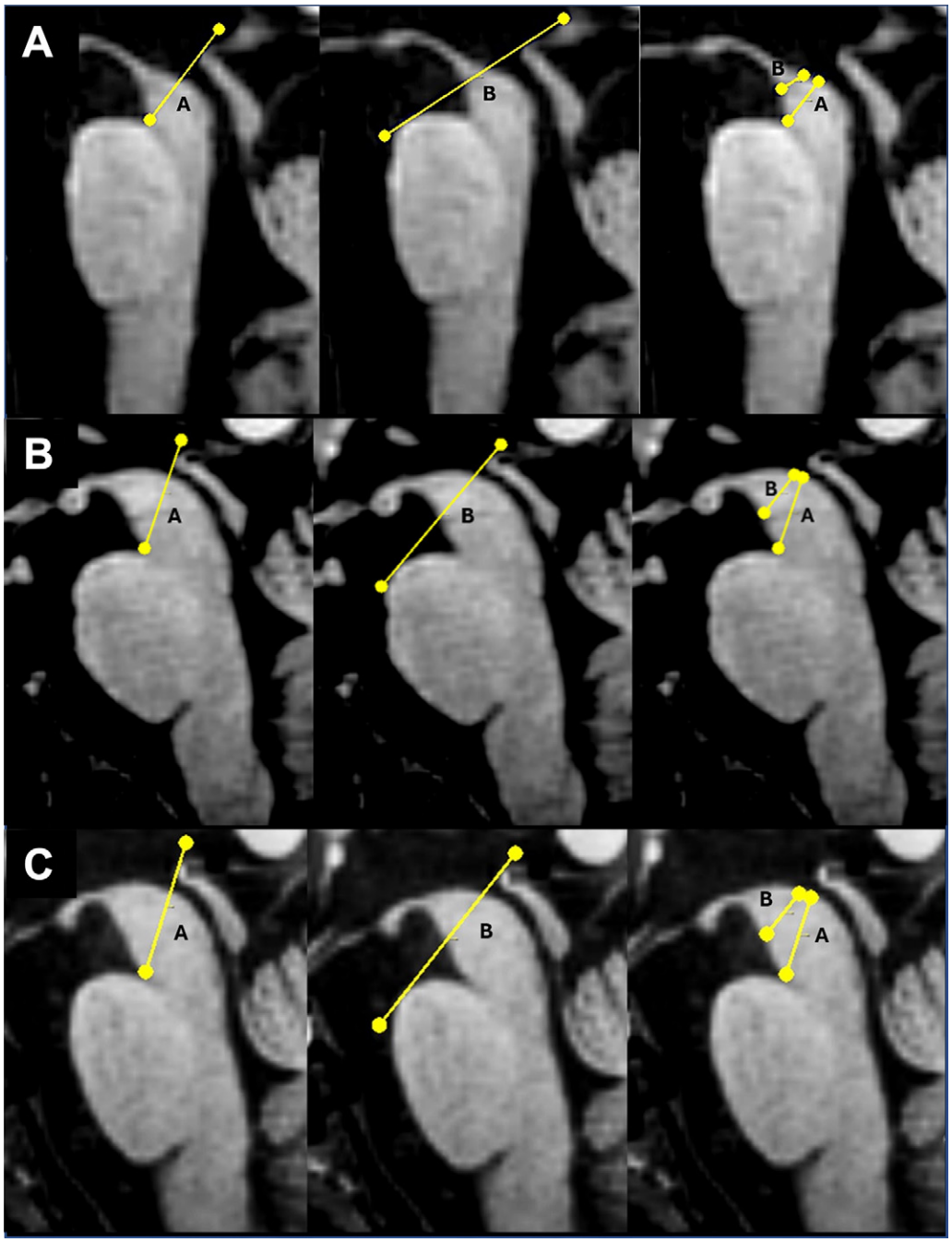

Figure 2: Linear brainstem measurements were manually performed on the midsagittal section of three-dimensional T1-weighted volumetric MRI examinations. Images in a **(A)** 74-year-old male participant with progressive supranuclear palsy (PSP)–Richardson syndrome (upper row), **(B)** 62-year-old female participant with Parkinson disease (PD) (middle row), and **(C)** 63-year-old healthy male participant (bottom row). In the leftmost panels, a line termed "A" was traced from the anterior notch of the ponto-mesencephalic junction to the posterior commissure; the distance between the ponto-mesencephalic junction and the midbrain border was measured. In the middle panels, a second line termed "B" was traced tangent to both the superior border of the pons and the posterior commissure, and the midbrain width along this line was measured. For clarity, the two midbrain measurements (A and B) investigated in this study are shown in the rightmost panels. These two measures were averaged, (A + B)/2, to calculate the dual-line midbrain PSP index (DMPI). The DMPI value was 5.15 in the participant with PSP **(A)**, 10.15 in the participant with PD **(B)**, and 11.10 in the control participant **(C)**.

Linear Measurement Reliability

Intra- and interrater agreement for the DMPI measurement was assessed using two-way random effects intraclass correlation coefficients for absolute agreement based on single measurements. Reliability and performance metrics were evaluated as follows: 0.90 or higher, excellent; 0.75–0.89, good; 0.60–0.74, moderate; and less than 0.60, poor. Detailed explanations of all study procedures and analyses are provided in Appendix S1. Statistical analyses were performed by two authors (M.G.B and B.V.) using R statistical software (version 4.0.4) and Python 3.9 scikit-learn library (version 1.0.1).

Results

Participant Characteristics

The study cohort after exclusion procedures (poor quality MRI, n = 8; diagnostic concerns, n = 28; missing demographic information, n = 4) included 2111 participants (mean age, 67.8 years ± 8.4 [SD]; 1148 [54.4%] male): 667 with PSP (563 with PSP-RS and 104 with vPSP), 834 with non-PSP parkinsonisms (643 with PD, 93 with MSA, and 98 with CBS), and 610 control participants (Fig 1). Study cohort details and a flowchart describing inclusion and exclusion procedures are provided in Table S1 and Figure 1. The participants with PSP and control group were older than the other groups (controls vs MSA, P < .001; controls vs PD, P < .001; PSP-RS vs MSA, P < .001; PSP-RS vs PD, P < .001; PSP-RS vs CBS, P = .047; vPSP vs CBS, P = .005; vPSP vs MSA, P < .001; vPSP vs PD, P < .001). The percentage of male participants was higher in the PD group than the control group. The PSP-RS and PD groups had a shorter disease duration than the CBS and vPSP groups (PD vs CBS, P = .02; PD vs vPSP, P < .001; CBS vs PSP-RS, P < .001; vPSP vs PSP-RS, P < .001). Motor symptom severity was higher in participants with PSP-RS and vPSP than other groups (MDS-UPDRS-III score: PSP-RS vs MSA, P = .006; PSP-RS vs PD, P < .001; vPSP vs MSA, P = .005; vPSP vs PD, P < .001; CBS vs PD, P = .003; Hoehn and Yahr scale score: PSP-RS vs PD, P < .001; PSP-RS vs vPSP, P = .02; vPSP vs PD, P < .001; MSA vs PD, P < .001; PSPRS score: PSP-RS vs CBS, P < .001; PSP-RS vs CBS-AD [Alzheimer disease], P < .001; PSP-RS vs vPSP, P = .01; vPSP vs CBS, P = .02; vPSP vs CBS-AD, P = .04) (Table 1).

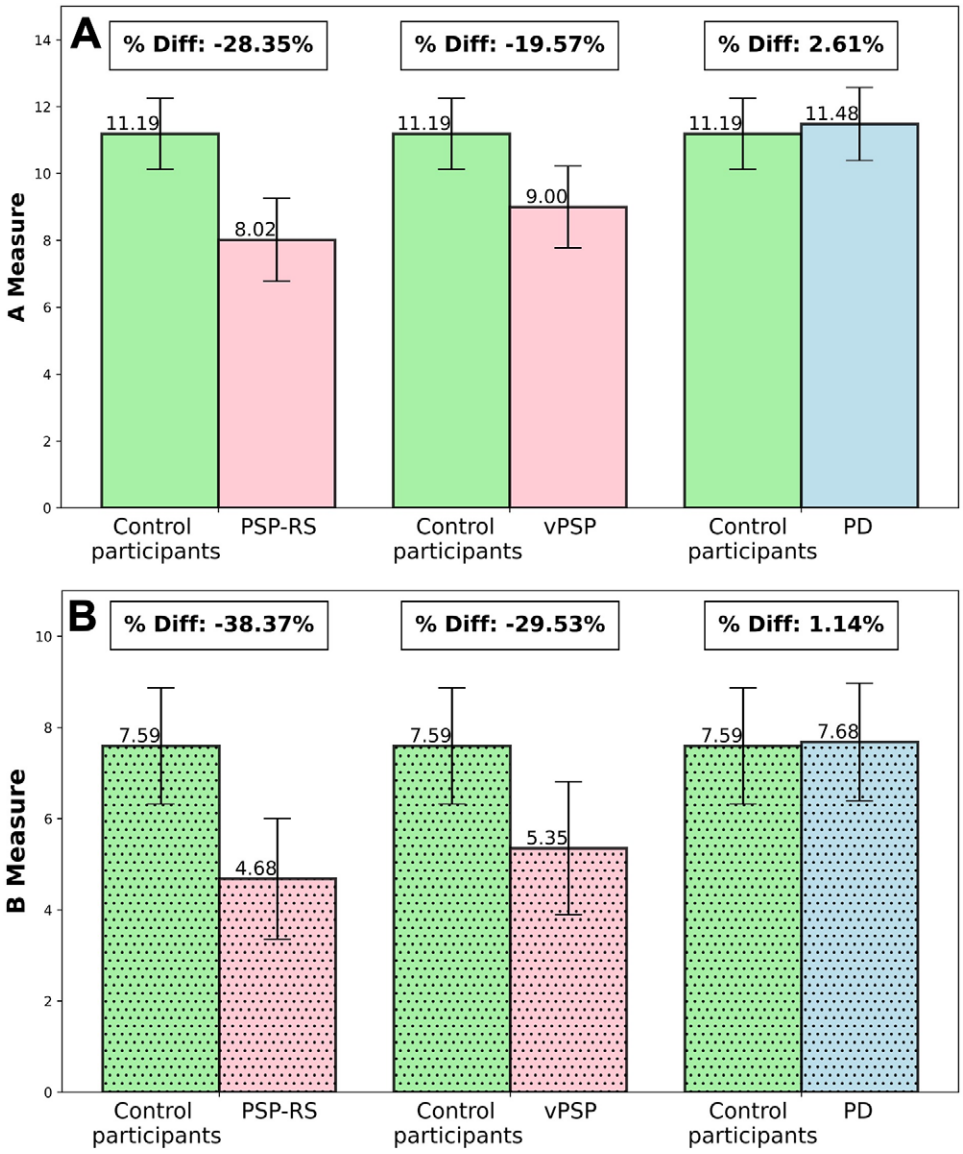

Figure 3: **(A, B)** Bar graphs show the percentage changes in A (upper panel) and B measures (lower panel) in the progressive supranuclear palsy (PSP)–Richardson syndrome (PSP-RS), PSP variants (vPSP), and Parkinson disease (PD) groups with respect to the control group. The mean (printed value) and SD (whiskers) of the percentage change (% Diff) are shown. In analysis of covariance with age and sex as covariates, the percentage change was larger for the B measure than for the A measure in both the PSP-RS and vPSP groups (P < .001). Moreover, the percentage change was larger in the PSP-RS group than the vPSP group (P < .001) for both the A measure and the B measure.

DMPI

The DMPI was obtained by averaging two linear midbrain measurements (Fig 2): line A, assessing midbrain body atrophy, and line B, assessing the atrophy of the anterior midbrain part extending into the mesencephalic beak. The procedure is simple, and a representative video guide is available as Movie 1. Compared with control participants, line A showed larger percentage midbrain atrophy than line B in most participants (558 of 656 [85.1%]) (Fig 3); however, B values showed higher variability in participants with PSP (coefficient of variation: 0.16 for A and 0.29 for B), suggesting that averaging A and B measurements may be an appropriate approach for obtaining reliable data. Moreover, by

Table 2: ROC Classification Performances of Planimetric and Linear MRI Measures in Distinguishing Participants with PSP from Participants with Non-PSP Parkinsonian Syndromes

A: Simple Measures			
Performance Metric	DMPI	Midbrain Line	Midbrain Area
Optimal cutoff	8.02 (7.92, 8.32)	14.65 (14.55, 15.23)	101 (89, 107)
Cutoff for 95% sensitivity and 95% specificity	8.37–7.97	15.45–14.15	109–92
AUC	0.97 (0.95, 0.98)	0.94 (0.91, 0.96)	0.95 (0.93, 0.97)
Accuracy (%)	93.68 (90.93, 95.88) [341/364]	87.09 (82.69, 89.84) [317/364]	88.69 (85.02, 91.74) [290/327]
Sensitivity (%)	92.55 (88.20, 96.27) [149/161]	83.85 (76.40, 93.79) [135/161]	88.19 (77.78, 96.53) [127/144]
Specificity (%)	94.58 (90.15, 97.54) [192/203]	89.65 (76.35, 94.58) [182/203]	89.07 (78.69, 97.28) [163/183]
Percentage of participants in gray zone	7.97 [29/364]	25.55 [93/364]	20.18 [66/327]
B: Combined Indexes			
Performance Metric	M/P Area Ratio	MRPI	MRPI 2.0
Optimal cutoff	0.195 (0.186, 0.204)	14.64 (13.93, 15.13)	2.86 (2.50, 2.97)
Cutoff for 95% sensitivity and 95% specificity	0.215–0.180	12.02–16.98	2.07–3.51
AUC	0.94 (0.91, 0.96)	0.93 (0.90, 0.96)	0.92 (0.89, 0.95)
Accuracy (%)	87.77 (83.79, 90.83) [287/327]	87.89 (84.16, 91.30) [283/322]	88.47 (84.42, 91.59) [284/321]
Sensitivity (%)	85.42 (77.08, 93.06) [123/144]	85.92 (79.58, 92.25) [122/142]	85.92 (78.87, 92.96) [122/142]
Specificity (%)	89.62 (81.97, 95.63) [164/183]	89.44 (83.89, 93.89) [161/180]	90.50 (82.12, 94.97) [162/179]
Percentages of participants in gray zone	24.16 [79/327]	27.95 [90/322]	31.46 [101/321]

Note.—Data in parentheses are 95% CIs, with numbers of participants in brackets. The performances and 95% CIs of all markers shown in the table were calculated using receiver operating characteristic (ROC) curve analysis with the pROC package in R software (R Foundation) with bootstrapping (n = 2000 iterations). Optimal cutoffs with 95% CIs were identified as the values with the highest sum of sensitivity and specificity (Youden method) using the pROC package in R. The performances were calculated in a subcohort of 161 participants with PSP and 203 participants with non-PSP parkinsonisms, representative of the overall cohort and described in detail in Table S3. The dual-line midbrain progressive supranuclear palsy index (DMPI) and midbrain line were measured manually by the same rater and were available in the entire subcohort of 364 participants. Planimetric measures were performed with a previously described, validated, in-house software, as described in Appendix S1; this software showed some failures because of motion artifacts or low contrast to noise ratio not allowing completion of the segmentation procedures, and the measures were available in 327 of 364 participants (89.8%) for the midbrain area and midbrain to pons (M/P) area ratio, 322 of 364 (88.5%) for MR parkinsonism index (MRPI), and 321 of 364 (88.2%) for MRPI 2.0. Beyond ROC curve analysis of performance, a two-cutoff approach was used, and the percentage of participants with measures in a possible "gray zone" was compared for each marker. This gray zone was defined as the range between the cutoff corresponding to 95% sensitivity and that corresponding to 95% specificity. A smaller percentage of participants in the gray zone indicated fewer uncertain results and thus a more powerful marker. The cutoff values corresponding to 95% sensitivity and 95% specificity for all markers are shown in the table. The DeLong test was used to compare the performance of the DMPI with that of each of the other markers, and the results were as follows: DMPI versus midbrain line, P = .004; DMPI versus midbrain area, P = .12; DMPI versus M/P area ratio, P = .01; DMPI versus MRPI, P = .01; and DMPI versus MRPI 2.0, P = .006. AUC = area under the ROC curve.

averaging the two measures, the DMPI classification accuracy was less affected by possible measurement errors (Appendix S2, Table S2).

DMPI Manual Measurement Reliability

The DMPI showed intra- and interrater agreement greater than 0.90 (intraclass correlation coefficient: interrater, 0.998; intrarater, 0.999), indicating excellent reliability.

Comparison with Established Planimetric and Linear Markers for PSP

Several planimetric and linear midbrain-based markers were compared, including previously described measures (midbrain line, midbrain area, MRPI, MRPI 2.0) and the DMPI, in distinguishing PSP from non-PSP parkinsonisms. To this aim, a cohort of participants from the PSP (n = 161) and non-PSP (n = 203) groups (Table S3) was generated, including approximately 25% of participants from each group, maintaining balance between the internal and international cohorts, to have a subcohort (n = 364) representative of the entire study cohort. All investigated brainstem-based markers showed excellent classification performances, with AUCs over 0.90 (Table 2). Among them, the DMPI had the highest AUC (0.97 [95% CI: 0.95, 0.98]) and was the only marker showing sensitivity, specificity, and accuracy exceeding 90%. The DeLong test confirmed that the DMPI outperformed most alternative measures (P < .05), with the only exception being the midbrain area (P = .12), which was the second top-performing measure. The percentage of participants with measures falling in the gray zone (uncertain cases) was also investigated. The percentage of participants in the gray zone was smallest for the DMPI (7.97%) compared with other markers (>20%), meaning fewer uncertain results, thus resulting in a more powerful marker (Table 2). Finally, the most promising measures (DMPI and midbrain area) were compared in terms of the average time required for calculation. The measurements were performed by two raters with different

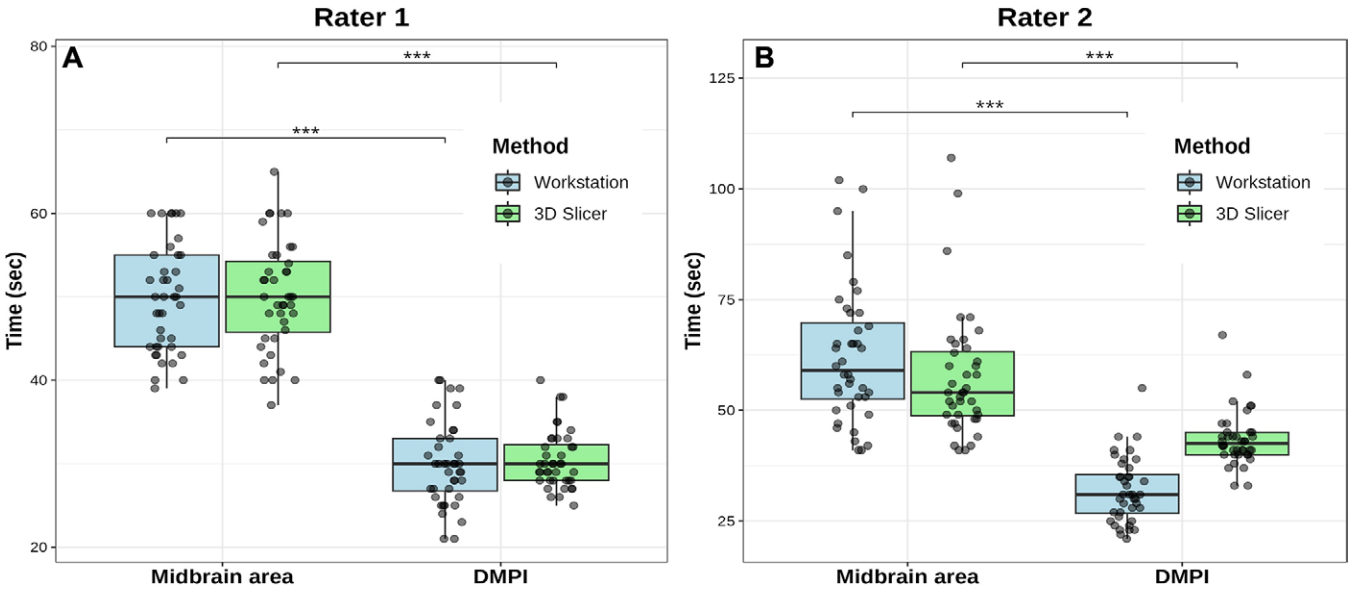

Figure 4: **(A, B)** Box plots shows the time required to measure the dual-line midbrain progressive supranuclear palsy (PSP) index (DMPI) and the midbrain area on 40 MRI examinations (20 in participants with PSP and 20 in participants with Parkinson disease). The measurements were performed by two neuroradiology technicians with different levels of expertise (rater 1: higher expertise, panel **A**; rater 2: lower expertise, panel **B**). The box borders illustrate the IQR, with the median shown as a horizontal line; the whiskers extend to the minimum and maximum values. Differences in time to perform the DMPI or midbrain area measurements were evaluated using the *t* test or Wilcoxon rank sum test, as appropriate. Paired tests were used to investigate differences between raters. The DMPI was faster to measure than the midbrain area in all considered scenarios. Results of the comparisons are as follows: DMPI time, rater 1 versus rater 2 on the workstation: paired Wilcoxon test $P = .16$; DMPI time, rater 1 versus rater 2 on the 3D Slicer (35) Digital Imaging and Communications in Medicine (DICOM) viewer: paired Wilcoxon test $P < .001$; midbrain area time, rater 1 versus rater 2 on the workstation: paired Wilcoxon test, $P < .001$; midbrain area time, rater 1 versus rater 2 on the 3D Slicer DICOM viewer: paired Wilcoxon test $P = .003$. *** = $P < .001$.

levels of expertise, on two different DICOM viewers, and in all cases, the DMPI was faster to calculate than the midbrain area (Fig 4).

DMPI Classification Performances in the Entire Study Cohort

Subsequently, the marker showing the best performance (DMPI) was investigated in the entire study cohort, divided into training and external test cohorts. The PSP group showed smaller DMPI values than the non-PSP and control groups ($P < .001$). In the subgroup analyses, both the PSP-RS and vPSP subgroups showed smaller measures than all non-PSP subgroups, with no evidence of differences among the PD, MSA, and control groups ($P > .05$) (Figs 5, S1). These results were confirmed in a small cohort of participants with pathologically proven diagnoses (Fig S2). Moreover, the DMPI was significantly associated with PSP clinical severity ($\beta = -0.29$, $P < .001$), correcting for age and sex (Fig S3). The DMPI values were lower in the PSP-RS group than the vPSP group ($P < .001$), confirming the more severe midbrain involvement in the PSP-RS subtype (24,29). Among participants with vPSP, DMPI values were lower in those with cortical variants than in those with subcortical variants, especially in participants with PSP with predominant frontal presentation (Fig S4). Participants with CBS had values between those of the PSP group and other groups, but low DMPI values were less commonly observed in participants with CBS-AD (likely underlying AD pathologic features) than in other participants with CBS, confirming higher midbrain atrophy in individuals with CBS with suspected four-repeat tau pathologic characteristics (30). The performance of DMPI was first investigated using standard receiver operating characteristic curve analysis (Table S4). However, midbrain measurements were associated with demographic variables (Table S5); therefore, LR was used, including DMPI, age, and sex. DMPI performance in distinguishing participants with PSP (PSP-RS and vPSP) from participants with non-PSP parkinsonisms (PD, MSA, CBS, CBS-AD) and from control participants in two independent cohorts was investigated. The Italian cohort was used as the training set, and the international cohort was used as the external test set, where the model yielded excellent performance (AUC ≥0.95) in distinguishing participants with PSP from participants with non-PSP parkinsonisms and from control participants (Table 3).

After external testing, to provide more solid grounds for training the LR model, DMPI performance in the entire study cohort was investigated, and AUC values of 0.95 (95% CI: 0.93, 0.97) and 0.96 (95% CI: 0.95, 0.97) were observed in cross-validation in differentiating participants with PSP from participants with non-PSP and control participants, respectively. The sigmoid functions and performances of the LR classifiers are provided in Figures S5 and S6. With use of the LR model based on DMPI, age, and sex, each participant was assigned a probability score of having PSP rather than non-PSP neurodegenerative parkinsonisms. In the entire study cohort, most participants with PSP (518 of 656 [79.0%]) fell into the highest probability quartile, and most participants with non-PSP parkinsonisms (638 of 802 [79.6%]) fell in the lowest probability quartile, meaning that participants with potentially uncertain probability scores close to 50% represented an uncommon scenario (Fig 6). Demographic variables had a relevant impact on individual probability scores, potentially leading to changes in predictions (between PSP and non-PSP parkinsonisms) in 202 of 1458 participants (13.8%) (Table S6).

Notably, LR models also showed excellent performance in distinguishing PSP from non-PSP parkinsonisms in a large subcohort of participants in the early disease stages (within 1, 2, or 3

years from disease onset), yielding AUC values of 0.96–0.97 (Table S7), and in the independent cohort of participants with pathologically proven diagnoses (AUC, 0.94 [95% CI: 0.86, 1.00]) (Fig 5). The LR model performance was finally evaluated in pairwise comparisons across the various participant groups, and AUC values of 0.89 or higher were observed in distinguishing participants with PSP-RS and vPSP from participants with PD, participants with MSA, and control participants (Table S8).

Discussion

We compared the performance of several planimetric and linear MRI measures in distinguishing progressive supranuclear palsy (PSP) from other neurodegenerative parkinsonisms. Among them, a new marker, the dual-line midbrain PSP index, demonstrated excellent accuracy, a low rate of uncertain cases, and a rapid measurement procedure in a large international cohort, showing potential as a practical diagnostic aid in routine practice.

The main PSP radiologic feature is midbrain atrophy, considered a supportive feature in PSP diagnostic criteria (25). Simple linear midbrain measurements help in the differential diagnosis, but these measures typically span only few millimeters, and precise anatomic reference points are often lacking, introducing potential sources of variability. Previous studies focused on linear midbrain measures yielded conflicting results (15–23,31–34) because of small cohorts and heterogeneous measurement methods. For example, the anteroposterior midbrain diameter originally included the quadrigeminal plate (16), while this plate was excluded in other studies, and the diameter was measured on sagittal (19–22,31) or axial (16,20,32–34) images with different orientation with respect to the quadrigeminal plate, using horizontal (17), oblique (19–21,31,32), or vertical lines (22).

In our study, we optimized the midbrain measurement procedures to improve their reliability by introducing a new marker termed DMPI, and we compared this marker with previously described measures. The DMPI values were lower in participants with PSP than in those with non-PSP parkinsonism ($P < .001$), and its lines were easily traceable and reproducible, connecting easily identifiable anatomic landmarks, thereby leading to excellent intra- and interrater agreement.

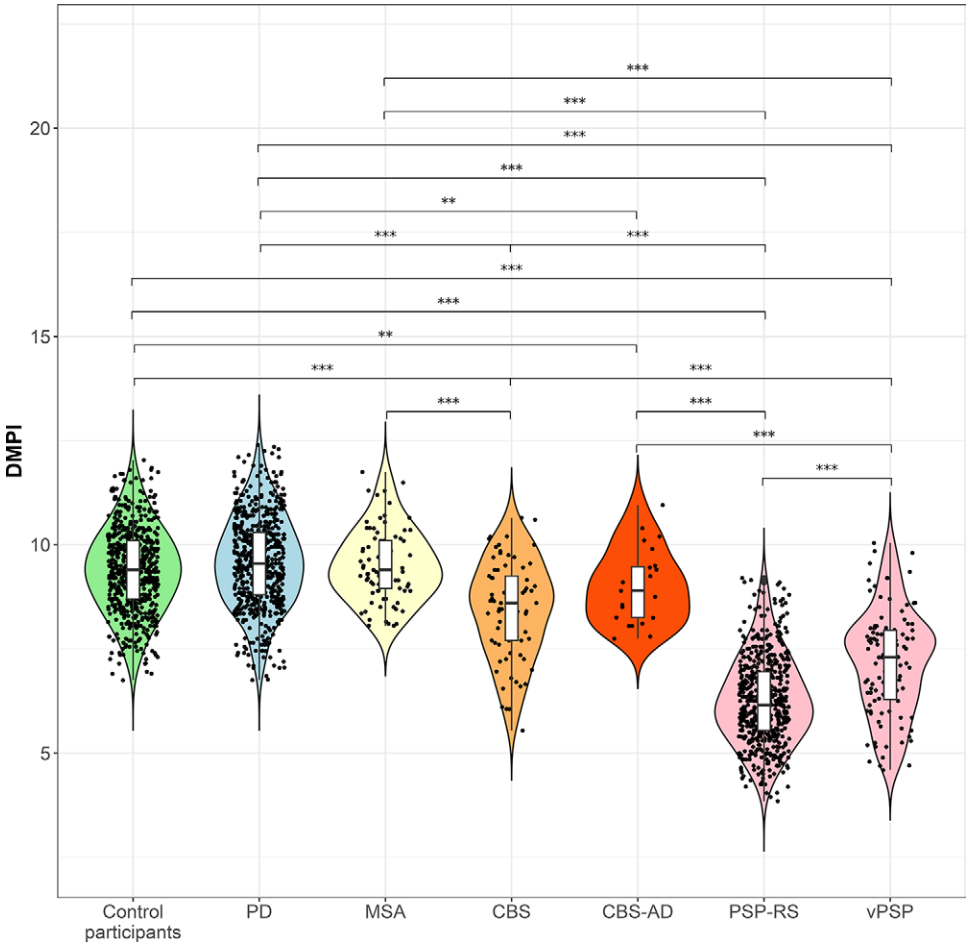

Figure 5: Violin plots of dual-line midbrain progressive supranuclear palsy (PSP) index (DMPI) values across different groups (control participants, participants with Parkinson disease [PD], multiple system atrophy [MSA], corticobasal syndrome [CBS], CBS–Alzheimer disease [CBS-AD], PSP–Richardson syndrome [PSP-RS], and PSP variants [vPSP]) in the entire study cohort (Italian and international cohort, $n = 2068$). Each violin represents the estimated density of the values for each group, highlighting the median (central line in the box plot) and the variability of the data. The overlaid box plots illustrate the IQR and whiskers, while black dots show individual data, without outliers. Analysis of covariance was performed with age and sex as covariates, followed by post hoc comparisons adjusted using Bonferroni correction (for 21 tests), which showed significant *P* values in the following comparisons: PSP-RS group versus control, PD, MSA, CBS, CBS-AD, and vPSP groups, $P < .001$; vPSP group versus control, PD, MSA, CBS, and CBS-AD groups, $P < .001$; CBS group versus control, PD, and MSA groups, $P < .001$; CBS-AD group versus control group, $P = .009$; and CBS-AD group versus PD group, $P = .007$. There was no evidence of differences among the PD, MSA, and control groups. ** = $P < .01$, *** = $P < .001$.

Our study may represent a milestone in the field of linear MRI measurements, since it involved the largest, to our knowledge, international multisite cohort of participants with PSP and non-PSP parkinsonisms investigated to date, ensuring the generalizability of the results. Notably, while most previous studies were focused on PSP-RS and PD (34), our cohort included participants from the full PSP spectrum and the most common degenerative non-PSP parkinsonian syndromes. DMPI performance for PSP classification was tested in an Italian training cohort ($n = 459$; AUC, 0.97 [95% CI: 0.97, 0.98]) and validated in a large independent international external test cohort ($n = 1609$; AUC, 0.96 [95% CI: 0.95, 0.97]). Notably, excellent classification performances (AUC >0.95) were also observed in participants with early-stage disease, when differential diagnosis is more challenging.

We directly compared the performance of several planimetric and linear midbrain-based markers, including previously described measures (midbrain line, midbrain area, midbrain to pons

Table 3: Classification Performances of the Logistic Regression Model Based on the DMPI, Age, and Sex in Distinguishing Participants with PSP from Participants with Non-PSP Parkinsonisms and Control Participants

	PSP vs Non-PSP		PSP vs Control Participants	
Performance Metric	Training (cv)	External Testing	Training (cv)	External Testing
Probability threshold	0.50	0.50	0.50	0.50
AUC	0.97 (0.97, 0.98)	0.96 (0.95, 0.97)	0.98 (0.98, 0.99)	0.95 (0.93, 0.96)
Accuracy (%)	93.32 (88.26, 97.33) [349/374]	90.41 (88.02, 91.86) [980/1084]	95.48 (88.86, 100) [211/221]	86.70 (84.49, 88.70) [906/1045]
Sensitivity (%)	88.24 (77.78, 99.64) [120/136]	85.58 (82.26, 88.48) [445/520]	96.32 (88.89, 100) [131/136]	91.73 (89.02, 93.95) [477/520]
Specificity (%)	96.22 (89.58, 100) [229/238]	94.86 (92.69, 96.85) [535/564]	94.12 (82.35, 100) [80/85]	81.71 (78.14, 84.93) [429/525]
PPV (%)	93.02 (82.76, 100) [120/129]	93.88 (92.72, 96.86) [445/474]	96.32 (90.00, 100) [131/136]	83.25 (79.93, 86.21) [477/573]
NPV (%)	93.47 (88.48, 99.80) [229/245]	87.70 (82.19, 88.44) [535/610]	94.12 (84.21, 100) [80/85]	90.89 (87.92, 93.33) [429/472]

Note.—Data in parentheses are 95% CIs, with numbers of participants in brackets. Model training was performed in the Italian cohort, while external testing was performed in the international cohort. The Italian cohort included 136 participants with progressive supranuclear palsy (PSP), 238 with non-PSP parkinsonisms, and 85 control participants (n = 459); the international cohort included 520 participants with PSP, 564 with non-PSP parkinsonisms, and 525 control participants (n = 1609). Classification performances were calculated with a logistic regression model including as predictors the dual-line midbrain PSP index (DMPI) value, age, and sex. Performance in the training set was evaluated using a stratified fivefold cross-validation (cv), repeated five times; mean values of performances in the validation folds are shown. The model was then applied to the independent testing set. Accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated by using a discriminating probability threshold of 50% (probability ≥50% suggestive of having PSP and probability <50% suggestive of having a non-PSP parkinsonism or being a control participant). AUC = area under the receiver operating characteristic curve.

area ratio, MRPI, MRPI 2.0) and the newly developed DMPI, in distinguishing PSP from non-PSP parkinsonisms. While all investigated markers showed good classification potential, the DMPI demonstrated the best performance, followed by the midbrain area. Both measures were valuable, but using the DMPI resulted in a smaller percentage of participants with uncertain results, and the DMPI was faster to determine on different DICOM viewers, possibly reflecting an easier measurement procedure. On these bases, the findings of our study support the use of DMPI and midbrain area in routine MRI assessment of patients with parkinsonisms. Since the measurements of these markers can be easily performed by technicians, they enable a standardized midbrain atrophy evaluation, and they accurately help in patient classification. We also suggest the use of an individual probability score of having PSP rather than other neurodegenerative parkinsonisms, which can be calculated with the DMPI value, age, and sex and may be included in the neuroradiologist's report. Moreover, this probability score, rapidly obtainable by nonexperienced raters, could enable accurate and cost-effective selection of patients for clinical trials. We provide an easy-to-use probability score calculator based on the LR model at *https://neuroimagingunicz.github.io/mri_calc/*. This calculator is freely available for immediate use.

Our study has several strengths. First, we used a dual midbrain measurement method, comprehensively evaluating different midbrain portions that atrophy to different extents, and we calculated the average of these measures (DMPI), which compensated for small errors potentially affecting linear measures used separately. Second, we validated the DMPI classification performance in a large international multisite cohort, demonstrating the generalizability of the results. Third, we used LR analysis including age and sex, assigning to each participant an objective and quantitative

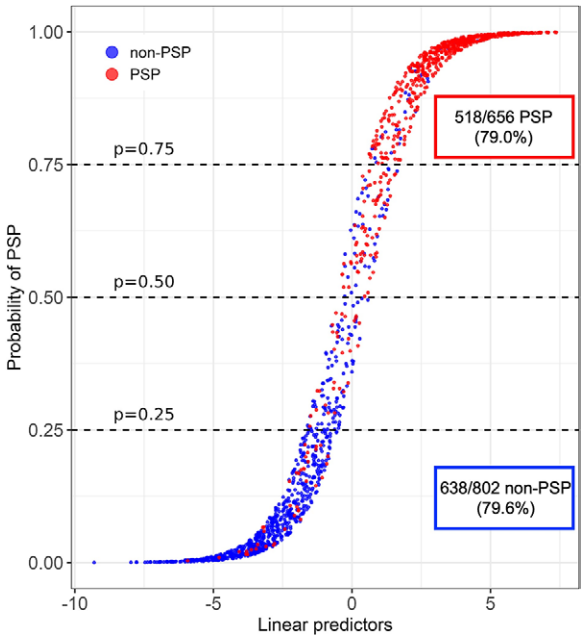

Figure 6: Individual probability scores of having progressive supranuclear palsy (PSP) rather than a non-PSP parkinsonism predicted by the logistic regression model based on the dual-line midbrain PSP index (DMPI) value, age, and sex in the entire study cohort of 656 participants with PSP and 802 participants with non-PSP parkinsonisms (Italian and international cohorts). Most participants with PSP (79.0%) were in the highest probability quartile, whereas most participants with non-PSP parkinsonism syndromes (79.6%) were in the lowest probability quartile. In detail, participants with PSP were distributed as follows: 6.1% in the first quartile, 4.6% in the second quartile, 10.3% in the third quartile, and 79.0% in the fourth quartile. Participants with non-PSP parkinsonisms showed an inverse distribution as follows: 79.6% in the first quartile, 11.7% in the second quartile, 5.0% in the third quartile, and 3.7% in the fourth quartile.

individual probability score of having PSP, which addresses the role of aging and sex, often overlooked in previous studies on planimetric or linear markers.

Our study also has limitations. The first is the lack of postmortem examination to confirm the clinical diagnosis, a limitation intrinsic to most marker studies in the neurodegenerative field. However, we did include a small cohort of participants with pathologically proven diagnoses and found classification performances similar to those observed in the entire cohort. Second, this was a cross-sectional study with no longitudinal data; future research is needed to evaluate the potential of this marker for assessing disease progression. Midbrain atrophy progresses over time (14), and we hypothesize that DMPI values will reduce over time; however, tailored studies are needed to investigate the longitudinal change. Moreover, prospective longitudinal studies may further establish the predictive role of this marker, investigating whether cases considered false-positive will develop PSP features over time.

In conclusion, we provide evidence that midbrain-based MRI measurements, especially the dual-line midbrain progressive supranuclear palsy (PSP) index and midbrain area, can be used to accurately differentiate PSP from other neurodegenerative parkinsonisms. These markers may be incorporated into future PSP diagnostic criteria and used in the neuroimaging assessments of patients undergoing brain MRI for parkinsonisms.

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