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Accuracy of MR markers for differentiating Progressive Supranuclear Palsy from Parkinson's disease

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ABSTRACT

Background: Advanced brain MR techniques are useful tools for differentiating Progressive Supranuclear Palsy from Parkinson's disease, although time-consuming and unlikely to be used all together in routine clinical work. We aimed to compare the diagnostic accuracy of quantitative morphometric, volumetric and DTI metrics for differentiating Progressive Supranuclear Palsy-Richardson's Syndrome from Parkinson's disease.

Methods: 23 Progressive Supranuclear Palsy-Richardson's Syndrome and 42 Parkinson's disease patients underwent a standardized 1.5T brain MR protocol comprising high-resolution T1W1 and DTI sequences. Brainstem and cerebellar peduncles morphometry, automated volumetric analysis of brain deep gray matter and DTI metric analyses of specific brain structures were carried out. We determined diagnostic accuracy, sensitivity and specificity of MR-markers with respect to the clinical diagnosis by using univariate receiver operating characteristics curve analyses. Age-adjusted multivariate receiver operating characteristics analyses were then conducted including only MR-markers with a sensitivity and specificity exceeding 80%.

Results: Morphometric markers (midbrain area, pons to midbrain area ratio and MR Parkinsonism Index), DTI parameters (infratentorial structures) and volumetric analysis (thalamus, putamen and pallidus nuclei) presented moderate to high diagnostic accuracy in discriminating Progressive Supranuclear Palsy-Richardson's Syndrome from Parkinson's disease, with midbrain area showing the highest diagnostic accuracy (99%) (mean ± standard deviation: 75.87 ± 16.95 mm^2 *vs* 132.45 ± 20.94 mm^2, respectively; $p < 0.001$).

Conclusion: Although several quantitative brain MR markers provided high diagnostic accuracy in differentiating Progressive Supranuclear Palsy-Richardson's Syndrome from Parkinson's disease, the morphometric assessment of midbrain area is the best single diagnostic marker and should be routinely included in the neuroradiological work-up of parkinsonian patients.

1. Introduction

The *in vivo* differential diagnosis between Progressive Supranuclear Palsy-Richardson's Syndrome (PSP-RS) and idiopathic Parkinson's Disease (PD) may be difficult (Williams and Lees, 2009; Mahlknecht et al., 2010). Specific alterations at conventional brain MR, such as midbrain and superior cerebellar peduncles (SCP) atrophy, may contribute to the diagnosis of PSP (Mahlknecht et al., 2010; Stamelou et al., 2011), despite their lack of accuracy (Schrag et al., 2000; Mahlknecht et al., 2010; Massey et al., 2012). The retrospective analysis of conventional brain MR in 22 pathologically confirmed PSP showed that the

Abbreviations: AUC, area under the curve; FA, Fractional Anisotropy; MCP, middle cerebellar peduncle; MD, Mean Diffusivity; MRPI, MR Parkinsonism Index; P/M, pons to midbrain ratio; PD, idiopathic Parkinson's disease; PSP-RS, Progressive Supranuclear Palsy-Richardson's Syndrome; ROC, receiver operating characteristics; SCP, superior cerebellar peduncle.

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hummingbird sign and dilatation of 4th ventricle correctly classified patients with 100% specificity but a sensitivity lower than 70% (Massey et al., 2012).

Considering the lack of sensitivity of conventional brain MR, advanced neuroimaging techniques have been used to increase diagnostic accuracy quantifying *in vivo* macro- and micro-structural abnormalities of specific brain regions typically involved in PSP neuropathology.

Volumetric and morphometric analysis of basal ganglia, brainstem and cerebellum, along with diffusion imaging techniques, showed moderate to high diagnostic accuracies in differentiating atypical parkinsonisms from PD, and in particular PSP (Schulz et al., 1999; Cordato et al., 2002; Seppi et al., 2003; Oba et al., 2005; Paviour et al., 2005; Paviour et al., 2006; Nicoletti et al., 2008; Quattrone et al., 2008; Rizzo et al., 2008; Mahlknecht et al., 2010; Wang et al., 2010; Longoni et al., 2011; Morelli et al., 2011; Stamelou et al., 2011; Tsukamoto et al., 2012; Nicoletti et al., 2013; Prodoehl et al., 2013).

Although different quantitative MR techniques may clearly provide a substantial contribution to the differential diagnosis of degenerative parkinsonisms, these techniques are demanding in terms of acquisition time and post-acquisition analysis and unlikely to be used all together in the study of a single patient in the clinical routine. In this study, for the first time, we have compared the diagnostic accuracy of multiple quantitative brain MR markers in the same population of patients PSP-RS or PD, in order to identify one or more MR markers that best differentiate these two parkinsonisms.

2. Methods

2.1. Subjects

This retrospective study included 23 consecutive patients with PSP-RS and 42 consecutive patients with PD who underwent brain MR between 2010 and 2014 as part of their diagnostic workup.

Diagnosis was performed by neurologists with experience in movement disorders (SZ, GC-B, MG, PDM, PC) according to current diagnostic criteria (Litvan et al., 1996; Gelb et al., 1999; Williams and Lees, 2009). All patients with a diagnosis of PSP-RS or PD were included. Demographic and clinical features of PSP-RS and PD patients are summarized in Table 1. Clinical data were obtained from patients and from clinical records collected on the day of the MR scan, at which time 19 patients fulfilled criteria for possible PD and 23 for probable PD, 1 patient was diagnosed as possible PSP-RS and 22 as probable PSP-RS. Because some subjects underwent MR scan years before the re-examination of the data, in all possible PD patients, diagnosis evolved to probable PD. All subjects gave consent to personal data processing for research purposes and the protocol was approved by the local Ethical Committee.

2.2. MRI protocol acquisition

Brain MR studies were performed using a 1.5 Tesla GE Medical Systems Signa HDx 15 system equipped with a quadrature birdcage head coil. Structural imaging included coronal FLAIR T2WI (repetition time, TR = 8000 ms, inversion time, TI = 2000 ms, echo time, TE = 93.5 ms, 3 mm slice thickness with no inter-slice gap), FSE axial T2WI (TR = 7000 ms, TE = 100 ms, 3 mm slice thickness), and 3D volumetric T1WI fast spoiled gradient-echo (FSPGR) images (TR = 12.5 ms, TE = 5.1 ms, TI = 600 ms, 25.6 cm^2 FOV; 1 mm isotropic voxels). We also acquired axial DTI images of contiguous 3 mm slices using a single-shot SE-EPI sequence with TE = 85.4 ms; TR = 10 s; FOV = 32 × 32 cm, in-plane resolution = 128 × 128, 25 diffusion-weighted directions and 7 unweighted scans, b-value = 900 s/mm^2. The total acquisition time was about 27 min.

MR images obtained from each subject were visualized by an expert neuroradiologist (RL) in order to exclude secondary causes of parkinsonism or other abnormalities. All quantitative measurements, such as morphometric, histogram and ROI analyses, were performed by experts in neuroimaging (RL, CaT, SZ) blinded to patients' diagnoses.

2.3. Morphometric analysis

Morphometric measurements were performed on 3D T1-weighted volumetric images according to previously reported methods (Oba et al., 2005). Mean sagittal middle cerebellar peduncle (MCP) diameter, mean coronal SCP diameter, pons and midbrain areas, MCP/SCP ratio, pons to midbrain (P/M) ratio, and MR Parkinsonism Index (MRPI) were calculated (Fig. 1) (Quattrone et al., 2008).

2.4. DTI analysis

Mean Diffusivity (MD) and Fractional Anisotropy (FA) values were calculated in the following ROIs, that were manually selected on T2WI (b = 0) EPI images: medulla, dentate nucleus, pons, MCP, cerebellar white matter, SCP, midbrain (decussation of SCPs), posterior limb of internal capsule, thalamus, globus pallidus, putamen, head of caudate, parieto-occipital and pre-frontal white matter, genu and splenium corpus callosum (Fig. 1). In order to achieve a more global evaluation of median brain DTI parameter values, we created MD and FA histograms of the following structures: brainstem, cerebellar hemispheres, vermis, posterior fossa, brain hemispheres (Fig. 1).

For all symmetrical structures, with the exception of brain hemispheres, MD, FA and histograms values were calculated as means or medians of the values obtained on the right and left sides.

Table 1
Demographic and clinical features of PSP-RS and PD patients at the time of brain MR scan.

		PSP-RS	PD	p-value
N		23	42	
Age at evaluation (years) [mean (SD)]		72.8 (7.1)	64.7 (10.5)	p = 0.001§
Sex [male/female]		12/11	29/13	p = 0.18°
Disease duration (years) [mean (SD) – (range)]		4.2 (2.69) – (10 months–10 years)	4.0 (3.3) – (6 months–15 years)	p = 0.32§
Hoehn-Yahr's modified scale Stage (percentage frequency)	1	0%	13%	p < 0.001^
	1.5	0%	0%	
	2	0%	26%	
	2.5	0%	26%	
	3	47%	33%	
	4	53%	2%	
	5	0%	0%	

Legend: PSP-RS: Progressive Supranuclear Palsy-Richardson's Syndrome; PD: Idiopathic Parkinson's disease; SD: standard deviation.
§ Independent-sample *t*-test.
° χ^2 test.
^ Mann-Whitney test.

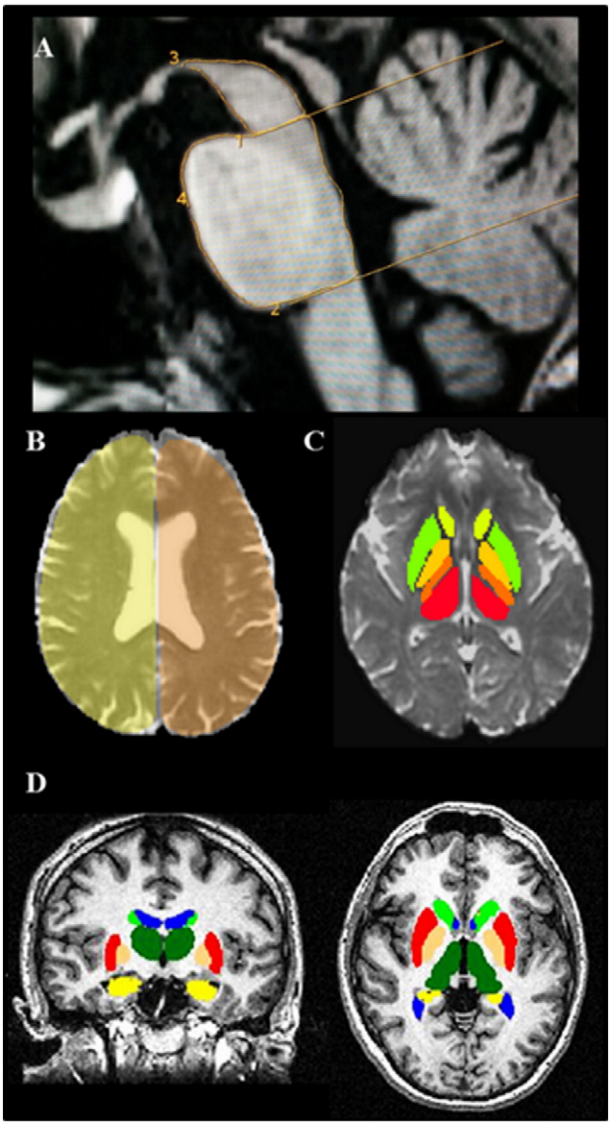

Fig. 1. Examples of quantitative brain MR markers. A. manual morphometric measurement of midbrain and pons area on sagittal 3D T1WI in a patient with Progressive Supranuclear Palsy-Richardson's Syndrome (PSP-RS); B. DTI histograms analysis for right (yellow mask on axial T2WI) and left (orange mask on axial T2WI) brain hemispheres in a PSP-RS patient; C. DTI ROIs analysis: bilateral manual selection of thalamus (red), posterior limb of the internal capsule (orange), globus pallidus (dark yellow), putamen (green) and caudate nucleus head (light yellow) in a patient with idiopathic Parkinson's Disease (PD); D. automatic bilateral segmentation of subcortical gray matter (caudate nucleus, thalamus, putamen, globus pallidus, hippocampus) performed by FIRST software on coronal and axial 3D T1WI in a patient with PD.

2.5. Volumetric analysis

Automatic segmentation of the volumetric images was performed by using FMRIB's Integrated Registration and Segmentation Tool (FIRST) to delineate brainstem, nucleus accumbens, caudate, hippocampus, globus pallidus, putamen and thalamus and lateral ventricles. All evaluated volumes were corrected by a volumetric scaling factor obtained by SIENAX, as previously reported (Fig. 1) (Smith et al., 2002).

2.6. Statistical analysis

The normality of the distribution of study variables was examined by using Shapiro-Wilk test. The gender distribution was compared between groups using Pearson's χ^2 -test. Continuous variables were compared between PSP-RS and PD groups using the independent-sample *t*-test or Mann-Whitney *U*-test, as appropriate. Bonferroni correction for multiple comparisons of measures belonging to the same domain was applied to the probability level. Receiver operating characteristics (ROC) curve analysis was used to analyze the diagnostic accuracy in terms of sensitivity, specificity and area under the curve (AUC, with 95% asymptotic normal confidence interval) of quantitative MR parameters.

The optimal cut-off value balancing sensitivity and specificity was identified as the one corresponding to the maximum value of Youden's index, calculated as [sensitivity + specificity − 1]. The clinical diagnosis based on current criteria for PSP-RS and PD was used as the gold standard (Litvan et al., 1996; Gelb et al., 1999; Williams and Lees, 2009).

AUC values were interpreted according to Swets (1988) as follows: $0.5 < AUC < 0.7$ poor accuracy; $0.7 < AU < 0.9$ moderate accuracy; $0.9 < AUC < 1.0$ high accuracy, $AUC = 1$ perfect test. The difference between AUCs was analyzed using the *Z*-test and DeLong et al.'s method for the calculation of the standard error of the AUC (DeLong et al., 1988).

We also examined whether diagnostic accuracy was improved by using MR variables in combination and adjusting for patients' age using logistic regression analysis with a forward stepwise procedure. MR variables with AUC ≥ 0.80 in univariate analyses were included one at a time in decreasing order of discrimination between PD from PSP-RS. The forward stepwise procedure stopped when additional variables did not contribute further significant information at the $p \leq 0.05$ significance level. ROC curves were calculated for combinations of variables in the same domain and across domains using the Stata command roccomp. Analyses were performed using IBM® SPSS® v.21 and Stata® v.13.1.

3. Results

Patients' characteristics are summarized in Table 1. PSP-RS patients showed a higher mean age at evaluation than PD, while disease duration and gender did not differ significantly between groups. Moreover, the median disease stage of patients with PSP-RS, as assessed by Hoehn and Yahr's modified scale, was higher compared to the PD group (median = 3.5 *vs* 2.5, respectively). No patients were excluded from analysis due to suboptimal brain MR quality. No patients showed brain lesions suggestive of secondary causes of parkinsonism.

Tables 2 and 3 report the comparison of the quantitative MR parameters between PSP-RS and PD patients and the diagnostic accuracy of each parameter, including the cut-off values that provide an optimal balance of sensitivity and specificity. The AUC curves of the markers that best discriminated PSP-RS from PD within each domain are depicted in Fig. 2.

3.1. Morphometric analysis

We found significant differences between PSP-RS and PD patient groups in all measured morphometric parameters. There was a reduction of both mean MCP and SCP diameters as well as of mean pons and midbrain areas in PSP-RS patients compared to PD group (Table 2). MCP/SCP and P/M ratios and MRPI were significantly higher in PSP-RS compared to PD patients (Table 2). Midbrain area, P/M ratio and MRPI showed the highest accuracy (≥95%), with sensitivity exceeding 87% and specificity exceeding 90% in differentiating PSP-RS from PD patents (Table 3), midbrain area showing the highest diagnostic accuracy (99%).

3.2. Volumetric analysis

Volumetric analysis showed a significantly reduced volume of brainstem, nucleus accumbens, globus pallidus, putamen and thalamus in the PSP-RS group compared to PD and a significantly increased lateral ventricular volume (Table 2). Thalamic, putaminal and pallidal volumes

Table 2
Comparisons of quantitative MR parameters between PSP-RS and PD groups. Significant comparisons are marked in boldface.

	PSP-RS mean (±SD)	**PD** mean (±SD)	**p-value** (unpaired *t*-test or Mann-Whitney *U*-test)
Morphometric analysis (Bonferroni-corrected significance level = 0.05/7 = 0.0071)			
Sagittal MCP diameter (mm)	**8.38 (±0.98)**	**9.39 (±0.91)**	**<0.001**
Coronal SCP diameter (mm)	**3.29 (±0.89)**	**4.63 (±1.21)**	**0.001**^
Sagittal MCP diameter/coronal SCP diameter ratio	**2.71 (±0.74)**	**2.12 (±0.41)**	**0.003**^
Pons area (mm^2)	**470.70 (±41.55)**	**540.19 (±65.27)**	**<0.001**^
Midbrain area (mm^2)	**75.87 (±16.95)**	**132.45 (±20.94)**	**<0.001**
Pons/midbrain areas	**6.47 (±1.37)**	**4.14 (±0.61)**	**<0.001**^
MRPI	**17.89 (±7.28)**	**8.73 (±1.97)**	**<0.001**^
DTI MD ($x10^{-3}mm^2/s$)			
ROI analysis (Bonferroni-corrected significance level = 0.05/17 = 0.0029)			
Medulla	0.84 (±0.11)	0.87 (±0.11)	0.453
Nucleus dentatus	0.70 (±0.11)	0.69 (±0.06)	0.313^
Pons	0.86 (±0.08)	0.87 (±0.08)	0.686
MCP	0.73 (±0.12)	0.74 (±0.06)	0.712^
Cerebellar WM	0.68 (±0.04)	0.67 (±0.05)	0.154
SCP	**1.00 (±0.17)**	**0.81 (±0.08)**	**<0.001**^
Midbrain (SCP decussation)	0.91 (±0.13)	0.85 (±0.12)	0.060^
Posterior limb of internal capsule	0.72 (±0.06)	0.71 (±0.03)	0.007^
Thalamus	**0.86 (±0.06)**	**0.79 (±0.04)**	**<0.001**^
Putamen	**0.82 (±0.10)**	**0.75 (±0.03)**	**<0.001**^
Globus pallidus	**0.86 (±0.09)**	**0.77 (±0.07)**	**0.001**^
Caudate (head)	0.83 (±0.13)	0.78 (±0.05)	0.047^
Parieto-occipital WM	**0.96 (±0.18)**	**0.84 (±0.06)**	**<0.001**^
Pre-frontal WM	**0.95 (±0.16)**	**0.81 (±0.06)**	**<0.001**^
Genu corpus callosum	0.95 (±0.10)	0.94 (±0.08)	0.745
Splenium corpus callosum	0.82 (±0.09)	0.81 (±0.08)	0.645
Mean corpus callosum	0.89 (±0.04)	0.88 (±0.05)	0.217^
Histogram analysis (50th percentile) (Bonferroni-corrected significance level = 0.05/6 = 0.0083)			
Right brain hemisphere	**1.00 (±0.09)**	**0.90 (±0.06)**	**<0.001**^
Left brain hemisphere	**0.99 (±0.08)**	**0.91 (±0.06)**	**<0.001**^
Posterior fossa	**0.97 (±0.12)**	**0.85 (±0.05)**	**<0.001**^
Brainstem	**0.99 (±0.11)**	**0.89 (±0.06)**	**0.001**^
Vermis	1.19 (±0.24)	1.04 (±0.13)	0.011^
Cerebellar hemispheres	**0.89 (±0.09)**	**0.80 (±0.04)**	**<0.001**^
DTI FA			
ROI analysis (Bonferroni-corrected significance level = 0.05/12 = 0.0041)			
Medulla	0.37 (±0.12)	0.37 (±0.08)	0.755
Pons	0.36 (±0.07)	0.37 (±0.06)	0.335
MCP	0.61 (±0.09)	0.61 (±0.08)	0.756
Cerebellar WM	0.41 (±0.12)	0.46 (±0.09)	0.057
SCP	**0.54 (±0.10)**	**0.67 (±0.10)**	**<0.001**
Midbrain (SCPs decussation)	**0.39 (±0.07)**	**0.48 (±0.10)**	**<0.001**
Posterior limb of internal capsule	0.68 (±0.06)	0.66 (±0.04)	0.684^
Parieto-occipital WM	**0.32 (±0.05)**	**0.39 (±0.06)**	**<0.001**
Pre-frontal WM	**0.27 (±0.06)**	**0.32 (±0.05)**	**<0.001**
Genu corpus callosum	0.67 (±0.08)	0.67 (±0.08)	0.786^
Splenium corpus callosum	0.76 (±0.07)	0.75 (±0.06)	0.880^
Mean corpus callosum	0.72 (±0.04)	0.71 (±0.05)	0.785
Histogram analysis (50th percentile) (Bonferroni-corrected significance level = 0.05/6 = 0.0083)			
Right brain hemisphere	**0.19 (±0.01)**	**0.21 (±0.01)**	**<0.001**^
Left brain hemisphere	**0.19 (±0.01)**	**0.21 (±0.02)**	**<0.001**^
Posterior fossa	**0.24 (±0.03)**	**0.26 (±0.02)**	**<0.001**
Brainstem	**0.35 (±0.03)**	**0.38 (±0.03)**	**<0.001**
Vermis	0.17 (±0.02)	0.19 (±0.03)	0.002^
Cerebellar hemispheres	0.24 (±0.04)	0.26 (±0.02)	0.002^
Volumetric analysis (mm^3) (Bonferroni-corrected significance level = 0.05/8 = 0.0063)			
Brainstem	**31,638 (±3698)**	**35,907 (±3392)**	**<0.001**
Nucleus accumbens	**611 (±181)**	**752 (±151)**	**0.001**
Caudate	4435 (±909)	4743 (±659)	0.021^
Hippocampus	5039 (±748)	5439 (±718)	0.038
Lateral ventricles	**23,703 (±8704)**	**17,104 (±8966)**	**0.004**^
Globus pallidus	**1865 (±451)**	**2352 (±347)**	**<0.001**
Putamen	**5597 (±807)**	**6468 (±538)**	**<0.001**
Thalamus	**8899 (±726)**	**10,014 (±1028)**	**<0.001**

Legend: PSP-RS: Progressive Supranuclear Palsy-Richardson's Syndrome; PD: Idiopathic Parkinson's disease; MCP: middle cerebellar peduncle; SCP: superior cerebellar peduncle; MRPI: MR parkinsonism index; MD: Mean Diffusivity; FA: Fractional Anisotropy.
^ Mann-Whitney test.

showed the highest diagnostic accuracy among volumetric variables (83%, 83% and 81%, respectively) with sensitivity and specificity equal or higher than 73% and 60%, respectively (Table 3). Moreover, a reduction in brainstem and an increase in lateral ventricular volumes showed moderate accuracy with high sensitivity but low specificity (Table 3).

Table 3
Diagnostic accuracy of quantitative MR parameters, arranged in decreasing order of AUC within each domain. Parameters with an AUC > = 80% are marked in boldface.

MR parameters	AUC (%)	Cut-off value*	Sensitivity (%)	Specificity (%)
Morphometric analysis				
Midbrain area (mm^2)	**99**	**≤102.50**	**96**	**98**
Pons/Midbrain areas	**97**	**≥4.79**	**96**	**90**
MRPI	**95**	**≥10.67**	**87**	**93**
Coronal SCP diameter (mm)	**84**	**≤3.75**	**81**	**74**
Pons area (mm^2)	**82**	**≤496.50**	**87**	**74**
Sagittal MCP diameter (mm)	78	≤8.65	70	83
Sagittal MCP diameter/coronal SCP diameter ratio	73	≥2.81	43	98
DTI MD ($x10^{-3}mm^2/s$)				
ROI analysis				
SCP	**88**	**≥0.94**	**70**	**98**
Pre-frontal WM	**86**	**≥0.82**	**90**	**69**
Thalamus	**84**	**≥0.83**	**70**	**86**
Putamen	**82**	**≥0.77**	**80**	**71**
Parieto-occipital WM	79	≥0.86	85	64
Globus pallidus	77	≥0.80	85	67
Histogram analysis (50th percentile)				
Posterior fossa	**90**	**≥0.90**	**80**	**83**
Cerebellar hemispheres	**86**	**≥0.83**	**85**	**74**
Right brain hemisphere	**85**	**≥0.91**	**90**	**74**
Left brain hemisphere	**84**	**≥0.93**	**80**	**74**
Brainstem	**80**	**≥0.90**	**85**	**67**
DTI FA				
ROI analysis				
SCP	**82**	**≤0.61**	**75**	**80**
Parieto-occipital WM	**82**	**≤0.31**	**98**	**55**
Midbrain (SCP decussation)	79	≤0.45	68	90
Pre-frontal WM	74	≤0.28	83	65
Histogram analysis (50th percentile)				
Right brain hemisphere	**88**	**≤0.20**	**75**	**90**
Left brain hemisphere	**87**	**≤0.21**	**65**	**95**
Posterior fossa	**80**	**≤0.25**	**83**	**75**
Brainstem	76	≤0.35	83	65
Vermis	74	≤0.18	68	80
Volumetric analysis				
Thalamus	**83**	**≤9575.34**	**73**	**90**
Putamen	**83**	**≤5912.80**	**93**	**70**
Globus pallidus	**81**	**≤1969.38**	**93**	**60**
Brainstem	79	≤32,262.07	90	60
Lateral ventricles	72	≥12,544.41	100	48
Nucleus accumbens	71	≤661.47	78	70

Legend: AUC: area under the curve; MRPI: MR parkinsonism index; MCP: mean cerebellar peduncle; SCP: superior cerebellar peduncle; MD: Mean Diffusivity; FA: Fractional Anisotropy.
* Cut-off value corresponded to the maximum Youden's index value.

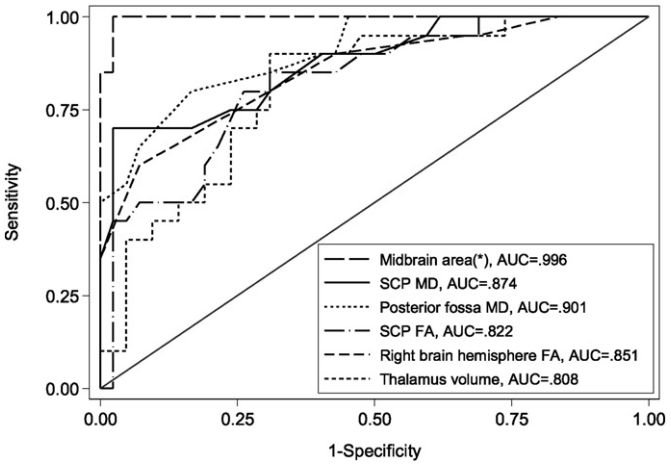

Fig. 2. Area under the curve (AUC) of the best markers within each analysis domain (morphometry, volumetry, DTI ROI, DTI histogram). Legend: SCP: superior cerebellar peduncle; MD: Mean Diffusivity; FA: Fractional Anisotropy. * indicates the best marker with AUC that significantly ($p < 0.05$) outperformed all the other variables in discriminating capacity.

3.3. DTI analysis

ROIs analysis showed significantly increased MD mean values in PSP-RS compared to PD for SCP, pre-frontal WM, thalamus, putamen, parieto-occipital WM and globus pallidus. FA mean values were reduced in the SCP, midbrain (decussation of SCPs), parieto-occipital and pre-frontal WM (Table 2).

At histograms analysis, PSP-RS patients showed, compared to PD, increased median MD and reduced median FA values in right and left brain hemispheres, posterior fossa, brainstem, increased median MD in the cerebellar hemispheres (Table 2) and reduced median FA in cerebellar vermis.

ROC analysis showed a diagnostic accuracy higher than 80% for MD and FA values of SCP, MD of pre-frontal WM, thalamus and putamen, FA values of parieto-occipital WM; median MD and FA values of brain hemispheres and posterior fossa and median MD values of brainstem and cerebellar hemispheres (Table 3). Moreover, these parameters showed moderate to high specificity and sensitivity, with the exception of a specificity lower than 70% for mean pre-frontal white matter mean MD, median brainstem MD, parieto-occipital WM mean FA and a sensitivity lower than 70% for median left brain hemisphere median FA (Table 3).

3.4. Diagnostic accuracy using quantitative MR parameters within specific domains

The ROC analysis of midbrain area, adjusted for age, yielded an AUC of 0.992 (95% CI = 0.978–1.000). No other morphometric variables provided an additional significant contribution. Similarly, in each domain, one marker was sufficient to achieve the maximum discrimination. In particular, after adjustment for age, the best markers were SCP in the DTI-MD ROI domain (AUC = 0.948, 95% CI = 0.896–0.999), posterior fossa in the DTI-MD histogram analysis domain (AUC = 0.900, 95% CI = 0.823–0.978), SCP in the DTI-FA ROI domain (AUC = 0.898, 95% CI = 0.821–0.975), right brain hemisphere in the DTI-FA histogram analysis domain (AUC = 0.879, 95% CI = 0.787–0.971) and thalamus in the volumetric analysis domain (AUC = 0.838, 95% CI = 0.741–0.935).

3.5. Diagnostic accuracy using combinations of variables across domains

We carried out a further analysis to determine whether an incremental accuracy could be achieved by using the best discriminators of each domain, added one at a time in a logistic regression model. As expected, the model with midbrain area reached an almost perfect discrimination and could not be further improved with the addition of variables from other domains. However, when midbrain area was not included, the model with DTI-MD histograms analysis of the posterior fossa alone provided the best discrimination (AUC = 0.901, 95% CI = 0.824–0.979).

The AUCs obtained using the best discriminating parameters for each domain were compared using the *Z*-test. Results (Table 4) indicate that the midbrain area significantly outperformed all the other variables, and that none of the others differed from each other in discriminating capacity.

4. Discussion

To our knowledge, this is the first study to compare the sensitivity, specificity and diagnostic accuracy of several multimodal MR markers (morphometric, volumetric and DTI-derived) in the same population of PSP-RS and PD patients, in order to identify the best diagnostic marker/s to be included in the neuroradiological work-up of parkinsonian patients. The main differences between PSP-RS and PD groups were represented by macro- and micro-structural and changes in the basal ganglia (putamen, pallidus and thalamic nuclei) and in infratentorial structures such as brainstem, cerebellum and cerebellar peduncles, reflecting the distribution of neuropathology in PSP (Dickson et al., 2010).

Our ROC analysis demonstrates that morphometric and DTI parameters have the best diagnostic accuracy in discriminating between PSP-RS and PD. Notably, morphometric analysis showed superior diagnostic accuracy compared to volumetric or DTI metrics in univariate analyses. Midbrain area, P/M ratio and MRPI diagnostic accuracies were higher than 95%, midbrain area being the single MR marker providing the highest accuracy (99%) in differentiating PSP-RS from PD patients, followed by P/M ratio (97%) and MRPI (95%). Moreover, multivariate logistic regression analyses combining measures from different domains showed that midbrain area reached the highest AUC (0.992) in discriminating PSP-RS from PD, and that the addition of other morphometric, DTI and volumetric quantitative MR markers did not increase diagnostic accuracy.

Although our PSP-RS patients presented a longer disease duration, our results are consistent with those of Quattrone et al., who in 2008 proposed a new morphometric index (MRPI) for the differential diagnosis between PSP and other PS, derived from linear MCP and SCP and pons and midbrain area measures (Quattrone et al., 2008). They found a high sensitivity, specificity and positive predictive value of MRPI values ≥ 13.55 (100% for all the three diagnostic properties), of MCP/SCP ratio ≥ 2.69 (78.8%, 88.9% and 68.4%, respectively) and of P/M ratio ≥ 4.88 (90.9%, 93.5%, and 81.1%, respectively (Quattrone et al., 2008). The same group applied morphometric analysis to a cohort of patients with PSP, and probable and possible PD, showing that the M/P ratio was characterized by a moderate accuracy in distinguishing PSP from probable or possible PD (86.8% and 88.2% respectively) while MRPI showed higher accuracy (99.5% and 99.4% respectively) (Morelli et al., 2011). Also Longoni et al. found high diagnostic accuracy, sensitivity and specificity of a P/M ratio ≥ 6.01 (94%, 90% and 96%, respectively) and an MRPI ≥ 13.57 (97%, 100% and 92%, respectively) in discriminating PSP-RS from PD (Longoni et al., 2011). Gama and colleague also found that midbrain area and SCP diameter smaller than 105 mm^2 and 3 mm, respectively, predicted PSP with 95% sensitivity and 80% specificity (Gama et al., 2010). Hussl et al. found a lower diagnostic accuracy, compared to others (Quattrone et al., 2008; Morelli et al., 2011), of both M/P ratio and MRPI in differentiating PSP from PD patients (accuracy = 87.6% *vs* 77.3%, respectively) (Hussl et al., 2010).

DTI metrics have been widely used in the differential diagnosis of degenerative parkinsonian syndromes (Mahlknecht et al., 2010). In the present study increased MD and reduced FA values in SCP showed the highest diagnostic accuracy (88% and 82%, respectively), with moderate-high sensitivity and specificity (70% and 98% for MD; 75% and 80% for FA, respectively), compared with other ROIs considered in our DTI analysis (Table 3). Our findings are in line with previous studies showing that ADC values in the SCP had a moderate-high sensitivity and specificity in discriminating PSP-RS from PD: 90% and 85%, respectively in one study (Rizzo et al., 2008), and 100% and 93.3% in another (Nicoletti et al., 2008). Moreover, we found a moderate to high diagnostic accuracy and moderate to high sensitivity and specificity of increased MD values in thalamus (84%, 70%, 86%, respectively) and pre-frontal white matter (86%, 90%, 69%, respectively).

In our study, automatic volumetric segmentation of brainstem and the basal ganglia showed a lower diagnostic accuracy compared to morphometric and DTI analysis. Schulz et al. found a significantly reduced striatal and brainstem volumes in PSP and MSA compared to PD, allowing 5 out of 6 PSP patients to be discriminated from healthy controls and PD groups (Schulz et al., 1999). Cordato et al. found a significant reduction of whole brain and frontal lobe volume and an increased lateral ventricular volume in PSP compared to PD and healthy controls, but only frontal lobe volume contributed to the differential diagnosis (Cordato et al., 2002).

Possible reasons for the discordance of the results among different studies may be related to methodological issues, including the moderate accuracy of clinical criteria used as the gold standard (Respondek et al.,

Table 4
p-Values of *Z*-test comparisons between the AUCs of the best discriminating RM parameters in each domain.

DOMAIN	TEST		A	B	C	D	E
Morphometric analysis	A	Midbrain area					
DTI-MD ROIs analysis	B	SCP	0.011				
DTI-MD Histograms analysis	C	Posterior fossa (50th percentile)	0.011	0.761			
DTI-FA ROIs analysis	D	SCP	0.001	0.158	0.298		
DTI-FA Histograms analysis	E	Right brain hemisphere (50th percentile)	<0.001	0.213	0.110	0.679	
Volumetric analysis	F	Thalamus	0.001	0.391	0.251	0.924	0.730

Legend: AUC: Area under the Curve; MD: Mean Diffusivity; ROIs: Regions of Interest; SCP: superior cerebellar peduncle; FA: Fractional Anisotropy.

2013; Adler et al., 2014), and the different acquisition and post-processing MR protocols.

Also in our study, the lack of neuropathological confirmation of the diagnosis could lead to a misclassification of patients, in particular some patients classified as PD could be PSP-parkinsonism variant. Moreover, the relatively longer disease of PSP-RS patients of our sample could also explain the highest accuracy of midbrain area compared to previous studies (Oba et al., 2005; Quattrone et al., 2008).

The main limitation of the study is the relatively advanced clinical stage participants included. Other limitations are its retrospective character, and, although no significant differences in disease duration between groups were found, the different speed of disease progression and median severity stage should be taken into account in the interpretation of the results.

The main strengths of this study are represented by the use of a standardized brain MR protocol to the same patient population, allowing the comparison of the diagnostic accuracy of different MR markers, and the inclusion of feasible and time-saving MR techniques that may be easily applied in a clinical setting.

5. Conclusions

Our study demonstrated, in the same patient population with a clear clinical diagnosis, that several quantitative brain MR markers, provide a high diagnostic accuracy in the *in vivo* differential diagnosis between advanced PSP-RS and PD.

In particular, the evaluation of midbrain area is the most accurate single diagnostic marker in the differential diagnosis between PSP-RS and PD (99%), and the *Z*-test demonstrated that none of the others differed from each other in discriminating capacity.

The measurement of midbrain area can easily be performed on conventional sagittal MR images whose inclusion in neuroradiological MR protocols evaluating patients with suspected degenerative parkinsonism, makes the routine acquisition of DTI images unnecessary.

Further prospective and multi-center studies on large cohorts of patients with clinically unclassifiable parkinsonism and earlier disease stages are warranted to confirm our findings and better define accuracy and cut-offs for clinical use.

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