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Track density imaging: A reliable method to assess white matter changes in Progressive Supranuclear Palsy with predominant parkinsonism

Salvatore Nigro[a], Gaetano Barbagallo[b], Maria Giovanna Bianco[c], Maurizio Morelli[b], Gennarina Arabia[b], Andrea Quattrone[b], Sara Gasparini[b,e], Giuseppe Lucio Cascini[d], Aldo Quattrone[f,g,*]

[a] Department of Experimental and Clinical Medicine, Magna Graecia University, Catanzaro, Italy
[b] Department of Medical and Surgical Sciences, Institute of Neurology, Magna Graecia University, Catanzaro, Italy
[c] Department of Health Sciences, Magna Graecia University, Catanzaro, Italy
[d] Institute of Radiology, Nuclear Medicine Unit, Magna Graecia University, Catanzaro, Italy
[e] Regional Epilepsy Center, "Great Metropolitan Hospital", Via Melacrino, Reggio Calabria, Italy
[f] Institute of Bioimaging and Molecular Physiology, National Research Council, Catanzaro, Italy
[g] Neuroscience Center, Magna Graecia University, Catanzaro, Italy

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ABSTRACT

Introduction: Track density imaging (TDI) has been proven to be a useful approach able to investigate white matter (WM) anatomical integrity in several neurodegenerative conditions, such as Parkinson's disease (PD) and classical phenotype of Progressive Supranuclear Palsy (PSP) also known as Richardson's syndrome (RS). To the best of our knowledge, no studies have assessed WM changes in PSP-predominant parkinsonism (PSP–P) patients by using a TDI approach, and no studies have explored the potential role of these changes in discriminating patients with PSP-P from those with PSP-RS and PD.

Methods: We used TDI to characterize WM changes in 31 PSP-P compared to 36 PSP-RS, 36 PD and 37 healthy controls (HC). Then, a support vector machine (SVM) approach was used to evaluate the performance of TDI in discriminating between patient groups.

Results: Relative to HC and PD patients, decreased track density in PSP-P patients was found in several WM regions such as the midbrain, superior cerebellar peduncles, cerebellum and corticospinal tract. By contrast, higher values of track density were observed in PSP-P patients compared to PSP-RS. SVM approach using TDI differentiated patients with PSP-P from PD and PSP-RS with an area under the curve of 0.90 and 0.76, respectively.

Conclusions: Our findings suggest that TDI may represent a useful approach for characterizing WM changes in PSP-P patients representing a potential new MRI biomarker in distinguishing this PSP phenotype from PD.

1. Introduction

Progressive supranuclear palsy with predominant parkinsonism (PSP–P) represents the second most common subtype, comprising a third of autopsy-confirmed PSP cases [1]. In the early stage of the disease, PSP-P phenotype shows a clinical picture similar to that observed in patients with Parkinson's Disease (PD) characterized by asymmetric onset, tremor, early bradykinesia, non-axial dystonia and a moderate response to levodopa medications. In addition, PSP-P patients show a later age at onset, a longer disease duration and a more favourable disease course compared with the most common PSP-Richardson's syndrome (PSP-RS) [1,2].

Clinical differentiation of PSP-P from PD, due to significant overlap of clinical symptoms between these two diseases, may be challenging especially in the early stages of the disease [3]. Moreover, clinical features suggestive of PSP, such as vertical supranuclear gaze palsy or postural instability with backward falls, occur later or never in PSP-P patients making their clinical differentiation from PD even more difficult [1–3]. However, the correct diagnosis of PSP-P is important for earlier suitable patient prognosis, and selection of the most appropriate management and treatments.

Over the past two decades, several neuroimaging biomarkers have been proposed to help the differentiation of PSP from other parkinsonian syndromes [4–6]. In particular, white matter (WM) degeneration

* Corresponding author. Neuroscience Centre, Magna Graecia University, Catanzaro, Italy.
E-mail address: quattrone@unicz.it (A. Quattrone).

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evaluated using diffusion tensor imaging (DTI) has been demonstrated to be a striking feature of PSP-RS [7–10]. At present, however, few studies have assessed DTI measures in PSP-P showing similar although slightly less severe patterns of WM abnormalities compared with PSP-RS [10–13].

In recent years, track-weighted (TW) imaging has been proven to be a useful approach able to investigate WM anatomical integrity both in healthy controls and in several pathological conditions [14–16]. In this approach, DTI and fiber-tracking algorithm are used to reconstruct whole brain WM pathways and then to extract more detailed information about WM tract properties, such as the number of streamlines in each voxel (i.e., track density imaging, TDI) or their average length [14,15]. To date, only one study has focused on TDI changes in patients with classic phenotype of PSP (PSP-RS), showing a significantly decrease in fiber density in several supra- and infra-tentorial tracts compared with PD and healthy controls [16]. Moreover, WM alterations in the superior cerebellar peduncle (SCP) were able to distinguishing PSP-RS patients from those with PD with an area under the curve (AUC) of 0.98 [16].

To the best of our knowledge, no studies have assessed WM alterations in PSP-P patients by using a TDI approach, and no studies have explored the potential role of these changes in discriminating patients with PSP-P from those with PD. Then, the primary objective of our study was to characterize WM changes in patients with PSP-P relative to controls using TDI. Subsequently, we sought to investigate the differences in spatial distribution and severity of WM damage in PSP-P compared to PSP-RS and PD patients, and to evaluate the possible usefulness of a classification approach based on fiber density values for differentiating these extrapyramidal conditions.

We tested 3 hypotheses: (i) track density maps capture WM changes in PSP-P patients relative to healthy controls, (ii) PSP-P patients show track density decreases in WM tracts compared to PD patients but a less severe pattern of WM alterations compared to PSP-RS, and (iii) track density maps can discriminate patients with PSP-P from those with PD and PSP-RS with high sensitivity and specificity.

2. Methods

2.1. Patients

Sixty-seven patients with PSP (31 PSP-P and 36 PSP-RS), 36 patients with idiopathic PD and 37 sex and age-matched healthy controls were consecutively recruited at the Movement Disorders Unit of the Institute of Neurology, Magna Graecia University of Catanzaro, Italy. A subset of patients included in the current study has been previously reported [16].

All participants met the following inclusion criteria: (1) male or female aged between 50 and 85 years; (2) absence of vascular brain lesions, brain tumor and/or WM hyperintensity on MRI scan and (3) no presence of significant movement artifacts on MRI that would impair registration and then TDI analysis.

Clinical diagnoses for all patients were established according to internationally diagnostic criteria and expert guidelines [17,18] by one trained physician (M.M.) with more than 10 years of experience in movement disorders. Patient disability was scored using the Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS-ME) [19], and disease severity using the Hoehn and Yahr rating scale [20]. We also used the Mini-mental state (MMSE) to assess cognitive performance in all patients [21]. Levodopa response was assessed both in the off-state (off medications overnight) and 2 h after drug administration as a clinical improvement of 30% or greater on the UPDRS-ME score. In each participant, a clear limitation of the range of voluntary gaze in the vertical more than in the horizontal plane, affecting both up- and downgaze, were considered as criterion for vertical supranuclear gaze palsy (O1 level). Reduced velocity (and amplitude) of voluntary upward and downward saccades was considered as the criterion for slowness of vertical saccades (O2 level). According to new PSP diagnostic criteria, the O1 and O2 levels must be associated with postural instability (P1, repeated unprovoked falls within 3 years; or P2, tendency to fall on the pull test within 3 years) for a diagnosis of PSP-RS, while these ocular signs must be associated with A2 (parkinsonism levodopa resistant) or A3 (parkinsonism levodopa responsive) for a diagnosis of PSP-P.

All study participants gave written informed consent, and the study was approved by the Local Institutional Ethical Committee, according to the Helsinki Declaration.

2.2. MRI acquisition

MRI scans were obtained on a 3 T Unit and using an 8-channels head coil (Discovery MR-750, General Electric, Milwaukee, WI). See Supplementary Material for more details.

2.3. Image processing: TDI construction

TDI construction was performed as described in previous studies [14–16]. Briefly, diffusion weighted images were corrected for eddy current distortions using FMRIB's Diffusion Toolbox (FDT, part of FMRIB Software Library FSL, http://www.fmrib.ox.ac.uk/fsl). Then, MRtrix (http://www. mrtrix.org) was used to estimate fiber orientation distributions using the constrained spherical deconvolution (CSD) method and fiber tracking was performed employing the following tracking parameters: number of tracks = 10, 000, 000, FOD magnitude cutoff for terminating tracks = 0.1, minimum track length = 10 mm, maximum track length = 200 mm, minimum radius of curvature = 1 mm, tracking algorithm step size = 0.2 mm. To improve the quantitative nature of whole-brain streamlines reconstructions Spherical-deconvolution Informed Filtering of Tractograms was also used [22]. Next, fiber tracts were spatial normalized and track density images were generated, with $1 \times 1 \times 1\ mm^3$ isotropic voxels. Of note, fiber tracts were spatial normalized using Advanced Normalization Tools (ANTS, http://www.picsl. upenn.edu/ANTS/). For each subject the average pathlength map (APM) was calculated dividing the total pathlength map (TMP) by track density image. The APMs were then rigidly aligned to the MNI152 1 mm T1 template and used to build a template through 4 iterations, beginning with an initial affine transformation followed by greedy symmetric diffeomorphic normalization (SyN). For each subject, the transformations (rigid, affine, warp) were individually inverted and applied in inverse order to a unit warp field generated in the final template space. Then, the tracks were normalized into template space with MRtrix, by warping each point along the fibers. This process ensured that the length of the streamlines was normalized together with the spatial location [14,15].

2.4. Statistical analysis

The difference in sex distribution among groups was evaluated using Chi-square test.

The Shapiro-Wilk test was first used to check for normality of continuous data. Subsequently, variables with normal distribution were compared across groups using ANOVA followed by pairwise t-tests. Non-normally distributed variables, instead, were compared across groups using Kruskal-Wallis test, followed by pairwise Wilcoxon rank-sum test.

TDI statistical analyses were performed using Randomize (FSL's tool, 5.000 iterations) [23]. A two-sample *t*-test was used to assess the differences in track density images between groups. Group comparisons were first conducted at a whole-brain level. Then, we restricted our investigation to the SCP, a brain region strongly involved in PSP [4,7,10]. Only clusters with $p < 0.05$ after correcting for family-wise error (FWE) rate were considered statistically significant. Additional analyses were also conducted to assess associations between track

Table 1
Demographic and clinical data of patients with PSP-P, PSP-RS, PD and healthy controls.

	HC	PD	PSP-P	PSP-RS
Participants	37	36	31	36
Sex (men/women)[a]	21/16	23/13	24/7	22/14
Age at examination (years)[b]	70.5 ± 7.1	70.3 ± 6.9	72.1 ± 6.2	70.7 ± 5.9
Disease duration (years)[c]	–	8.0 ± 5.6	7.1 ± 3.5	3.3 ± 1.3
Age at onset (year)[d]	–	62.3 ± 7.8	64.8 ± 5.4	67.4 ± 5.9
Hoehn-Yahr score[e]	–	2.3 ± 0.6	2.9 ± 0.7	3.3 ± 0.7
UPDRS-ME score[f]	–	27.3 ± 9.9	35.4 ± 6.2	37.6 ± 9.3
MMSE score[g]	27.9 ± 1.3	23.5 ± 5.0	21.6 ± 3.9	20.6 ± 4.6
Levodopa responsiveness[h]	–	36 (100)	15 (48.3)	1 (2.7)

All data are expressed as mean ± standard deviation.
Abbreviations: UPDRS-ME = Unified Idiopathic Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; PD = Parkinson's disease patients; PSP-P = Progressive Supranuclear Palsy with predominant parkinsonism; HC = healthy controls; ns = not significant.
[a] P = 0.33 Chi-square test.
[b] P = 0.60 (HC vs PD vs PSP-P vs PSP-RS) ANOVA (Analysis Of Variance).
[c] P < 0.001 (PD vs PSP-P vs PSP-RS) Kruskal–Wallis test; P = ns (PD vs PSP-P), P < 0.001 (PD vs PSP-RS; PSP-P vs PSP-RS) Mann-Whitney *U* test with Bonferroni correction.
[d] P = 0.005 (PD vs PSP-P vs PSP-RS) ANOVA (Analysis Of Variance); P = ns (PD vs PSP-P; PSP-P vs PSP-RS); P = 0.007 (PD vs PSP-RS) *t*-test with Bonferroni correction.
[e] P < 0.001, Kruskal–Wallis test; P = 0.004 (PD vs PSP-P), P < 0.001 (PD vs PSP-RS), P = ns (PSP–P vs PSP-RS) Mann-Whitney *U* test with Bonferroni correction.
[f] P < 0.001, Kruskal–Wallis test, P < 0.001 (PD vs PSP-P; PD vs PSP-RS), P = ns (PSP–P vs PSP-RS) Mann-Whitney *U* test with Bonferroni correction.
[g] P < 0.001 (HC vs PD vs PSP-P vs PSP-RS), Kruskal–Wallis test; P < 0.001 (HC vs PD; HC vs PSP-P; HC vs PSP-RS), P = ns (PD vs PSP-P; PD vs PSP-RS; PSP-P vs PSP-RS) Mann-Whitney *U* test with Bonferroni correction.
[h] Number (percentage) of patients who showed a clinical improvement of at least 30% in comparison with that detected in the off state.

density images and measures of disease severity, duration and cognitive functions in PSP and PD patients.

A binary support vector machine (SVM) approach was used to classify (i) patients with PSP-P versus those with PD, (ii) patients with PSP-P versus those with PSP-RS and (iii) patients with PSP-RS versus those with PD. In particular, Pattern Recognition for Neuroimaging Toolbox (PRoNTo) was used for pattern recognition using TDI as input images [24]. Classification analyses were first performed considering the voxels of significant difference in track density between patient groups at whole-brain level. Subsequently, classification analyses were performed using the significant voxels that belong to the SCP (see Supplementary Material).

3. Results

3.1. Demographic and clinical data

Demographic and clinical characteristics of all subjects are summarized in Table 1. PSP patients, PD patients and healthy subjects had similar age and gender distributions. Patients with PSP-RS showed greater disease severity than those with PD and PSP-P based on H–Y and UPDRS.

3.2. Voxel-wise analysis of TDI

Relative to HC and PD patients, PSP-P patients showed a significant decrease in the number of streamlines relative in the brainstem, anterior thalamic radiation, superior longitudinal fasciculus, superior corona radiata, SCP and corticospinal tract (Fig. 1). Similar findings were observed between patients with PSP-RS and those with PD (Supplementary Material, Fig. S1). No significant difference was found between patients with PSP-P patients and those with PSP-RS at a whole brain level. However, at $p < 0.05$ uncorrected, PSP-RS showed regions of decreased tract density in the SCP, superior longitudinal fasciculus and cingulate gyrus bilaterally compared to PSP-P patients (Supplementary Material, Fig. S2).

Restricting the analysis at superior cerebellar peduncles voxels, statistically significant decreases in the number of streamlines were found in PSP-P patients, relative to PD patients and HC. By contrast, patients with PSP-P showed statistically significant higher values of track density in the SCP when compared to PSP-RS patients (Fig. 2). No statistically significant differences in TDI were observed between PD patients and healthy controls.

3.3. Correlation with behavioral data

No significant correlation was found between track density values and clinical variables in PSP and PD patients.

3.4. Classification of PSP-P, PSP-RS and PD patients

SVM analysis differentiated PSP-P patients from PD patients with area under the ROC curve (AUC) of 0.90, 25 out of 31 PSP-P patients and 29 out of 36 PD patients were correctly classified (Fig. 3). We observed no improvement of the classification performance in distinguish PSP-P and PD patients when we restricted the analysis to the SCP voxels (Table 2).

Because we did not find significant differences between the two PSP phenotypes at whole-brain level, SVM analysis to distinguish PSP-P from PSP-RS was conducted only considering the voxels of significant difference found restricting the comparison between the two groups to the SCP. In this way, we observed an AUC of 0.76 in differentiating patients with PSP-P from those with PSP-RS (Table 2, Fig. 3).

Concerning the differentiation of PSP-RS from PD, 33 out of 36 PSP-RS patients and 32 of out 36 PD patients were correctly classified at a whole-brain level (AUC = 0.94). The AUC reached a value of 0.96 restricting the analysis to the voxels of SCP (Table 2**)**.

4. Discussion

This is the first study to assess in vivo the regional distribution of WM abnormalities in PSP-P patients using TDI. PSP-P patients were characterized by a widespread pattern of fiber density decrease in the superior corona radiata, superior longitudinal fascicle, corticospinal tract, brainstem and SCP. Fiber density values also allowed to distinguishing patients with PSP-P from those with PD and PSP-RS with a moderate accuracy.

In the last decade, several MRI methods have been used to characterize WM properties changes in PSP [7–12,16,25,26]. Although WM degeneration evaluated using DTI has been demonstrated to be a striking feature of PSP and several DTI metrics have been proposed as potential markers to differentiate this degenerative parkinsonian syndrome [4], tensor model suffers from severe limitations, like the inability to resolve complex fiber configurations within a voxel at the commonly used spatial resolutions [27]. Then, in the last years a number of improvements were performed to get more reliable estimates, using more complex data acquisition and reconstruction strategies [27–29].

TDI has been proven to be a useful approach able to explore WM integrity in several pathological conditions [14–16]. Track density values may be calculated on a grid which can be much finer than the acquisition resolution providing a higher anatomical resolution and a novel anatomical contrast that cannot be obtained with conventional MRI [28]. Moreover, the use of the CSD provides reliable fiber orientation estimations, even in voxels comprised of multiple fiber

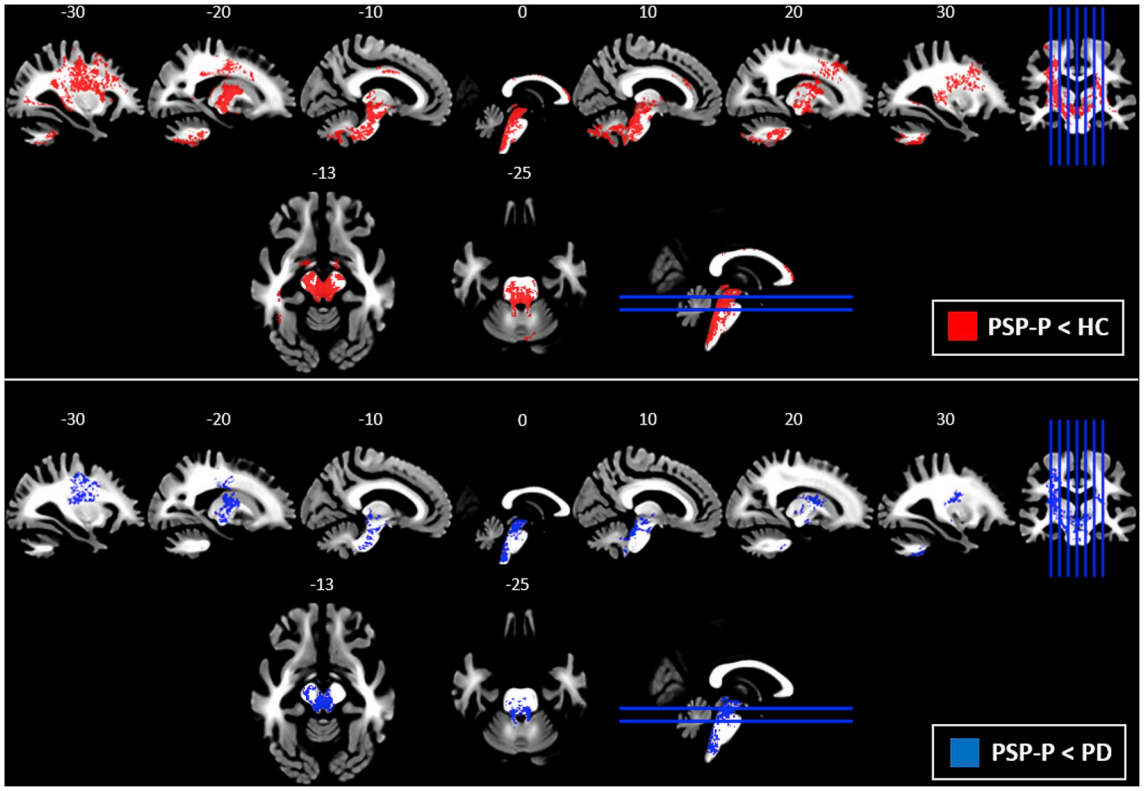

Fig. 1. Overview of the decreases in track density. Upper panel: statistical map of decreased track density in PSP-P patients relative to HC; bottom panel: statistical map of decreased track density in PSP-P patients relative to PD patients. Clusters shown are significant at pFWE < 0.05, estimated with threshold-free cluster enhancement.
Abbreviations: PD = Parkinson's disease patients; PSP-P = Progressive Supranuclear Palsy with predominant parkinsonism; HC = healthy controls; FWE = threshold-free cluster enhancement.

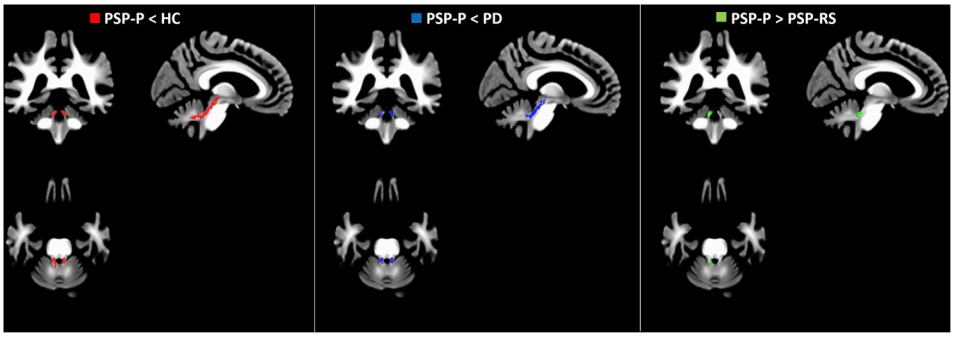

Fig. 2. Overview of track density changes in the superior cerebellar peduncles. Left panel: statistical map of decreased track density in PSP-P patients relative to HC; central panel: statistical map of decreased track density in patients with PSP-P relative to those with PD; right panel: statistical map of increased track density in patients with PSP-P relative to those with PSP-RS. Clusters shown are significant at pFWE < 0.05, estimated with threshold-free cluster enhancement.; Abbreviations: PD = Parkinson's disease patients; PSP-P = Progressive Supranuclear Palsy with predominant parkinsonism; PSP-RS = Progressive Supranuclear Palsy - Richardon's Syndrome; HC = healthy controls; FWE = threshold-free cluster enhancement.

populations, generating more robust tracts reconstruction [30]. In our recent study, we demonstrated that TDI was a useful approach to investigate WM changes in PSP-RS classical phenotype [16]. Relative to PD patients, PSP-RS patients were characterized by a decreased density involving the corpus callosum, arcuate fascicle, superior longitudinal fascicle, brainstem, thalami radiation, cerebellar WM and CST bilaterally. Moreover, TDI abnormalities in the SCP allowed to differentiate patients with PSP-RS from those with PD with a very high accuracy (AUC = 0.98) [16].

In the present study, PSP-P patients showed WM density changes in several supra- and infra-tentorial brain regions compared both to PD and to healthy controls. Similar findings were observed in PSP-RS patients compared with PD patients, even if these WM changes were more widespread relative to PSP-P patients. These findings were in line with previous cross-sectional and longitudinal DTI studies showing similar patterns of reduced FA and increased MD in PSP-P and PSP-RS patients [11,12,26]. Moreover, our results further confirmed the involvement of dentatorubrothalamic tract occurring in patients with PSP [10]. Indeed, the spatial distribution of WM abnormalities seen in SCP was consistent with the results of a recent study reporting DTI alterations in parts of the DRTT such as the SCP and the dentate nucleus of the PSP group [10].

Concerning SVM classification, we observed that TDI was a powerful approach to support the clinical diagnosis of PSP-P. In particular, track density values were able to distinguishing PSP-P patients from PD with an AUC of 0.90 (sensitivity and specificity of 81%), demonstrating to achieve similar or higher classification performance than previous studies using solely diffusion tensor imaging parameters such as FA and

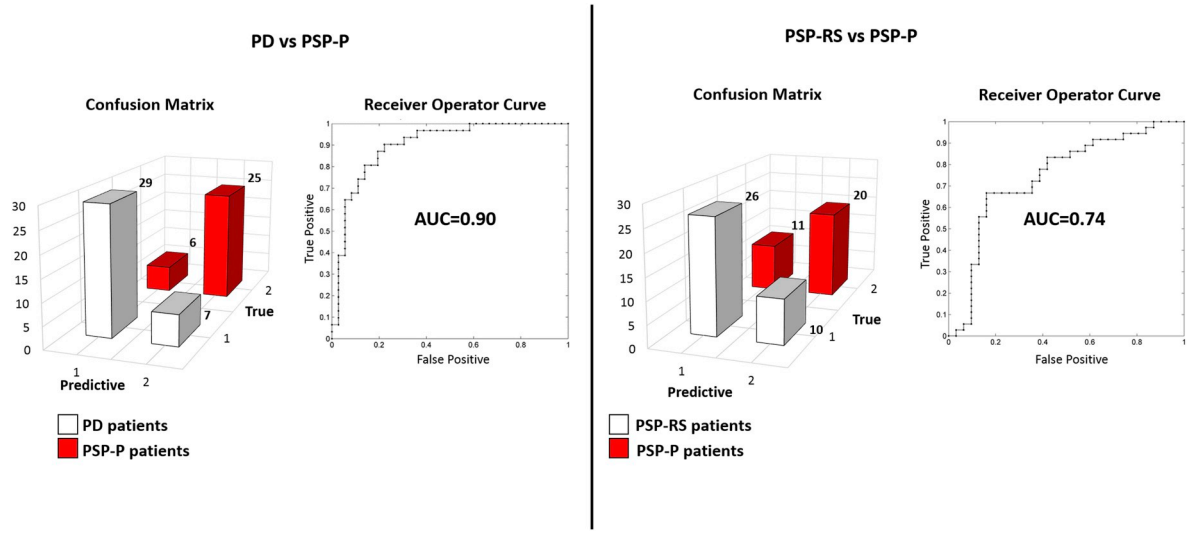

Fig. 3. Supported vector machine (SVM) classification. Left panel: performance of SVM approach in distinguishing patients with PSP-P from those with PD; Right panel: performance of SVM approach in distinguishing patients with PSP-P from those with PSP-RS; Abbreviations: AUC = area under the curve; PD = Parkinson's disease patients; PSP-P = Progressive Supranuclear Palsy with predominant parkinsonism; PSP-RS = Progressive Supranuclear Palsy - Richardon's Syndrome.

Table 2
Differentiation between patients with PSP-P, PSP-RS and PD using TDI. In the upper side: classification analysis was performed considering the voxels of significant difference in track density between patient groups at whole-brain level; in the lower side: classification analysis was performed using the significant voxels that belong to the superior cerebellar peduncle.

Classification Analysis considering TDI alterations at whole-brain level					
	AUC	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
PD vs PSP-P	0.90	81	81	78	83
PSP-P vs PSP-RS	–	–	–	–	–
PD vs PSP-RS	0.94	81	89	88	82
Classification Analysis considering TDI alterations in the SCP					
	AUC	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
PD vs PSP-P	0.86	78	68	72	74
PSP-P vs PSP-RS	0.74	72	65	69	65
PD vs PSP-RS	0.96	92	89	89	91

Abbreviations: AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value; PD = Parkinson's disease patients; PSP-P = Progressive Supranuclear Palsy with predominant parkinsonism; SCP = Superior cerebellar peduncle.

MD [10,13]. We did not find any improvement in classification performance between PSP-P and PD when we restricted the SVM analysis to SCP voxels. By contrast, a higher AUC was observed in the differentiation of PSP-RS from PD when the classification analysis was conducted on SCP voxels. This finding, together with the higher values of track density observed in PSP-P when compared to PSP-RS, suggested that track density decrease in this region was a prominent feature of PSP-RS and it could explain the balance and posture deficits that characterize PSP-RS, but not PSP-P, already at the early stages of disease [12]. Indeed, the SCP contains ascending pathways to the brainstem reticular and vestibular nuclei, which play a major role in the neural control of both body and head posture. This result was also in line with our recent study showing the key role of SCP in developing postural instability in PSP [12]. Of note, we did not find any significant correlation between streamline density and individual performance in motor and cognitive tests. As suggested in a previous study, this may be due to compensatory mechanisms by exogeneous factors, such as anti-Parkinsonian medications at the time of clinical testing, endogeneous processes (i.e., neural network compensatory mechanisms), or a combination of both [15].

The current study has some limitations which have to be pointed out. None of our patients had a histopathological diagnostic confirmation even if clinical evaluation was performed according to the most recent diagnostic criteria for PSP, and was carried out by one of the authors with more than 10 years of experience in movement disorder. Moreover, all patients were scanned under medication. In this way, we could reduce movement artefact, which causes severe and significant inaccuracies to DTI analysis. However, the influence of medications on DTI results is poorly understood and requires further investigation. Iron deposits may also affect changes in diffusivity properties and then caution is needed when using DTI for diagnosis of various neurological diseases involving abnormal iron deposition. Finally, longitudinal studies are required to assess whether these abnormalities in white matter fiber density are predictive of the clinico-pathological evolution in PSP-P.

Despite these limitations, our study has a number of strengths. First, DTI and fiber-tracking algorithm were used to reconstruct whole brain WM pathways allowing to extract more detailed information about WM tract properties in comparison to previous studies using sole use of diffusion properties. Second, we used a relatively large sample of PSP-P patients (31 PSP-P patients) in comparison to previous studies exploring the ability of diffusion properties in characterize and differentiate PSP-P patients [9,12]. Third, recent DTI studies used a region of interest based approach in distinguishing PSP-P patients from PD focusing their attention to infra-tentorial structures without considering the contribution of WM supra-tentorial areas in classification analysis [10,13]. In the present study, we found WM changes in both supra- and infra-tentorial areas in patients with PSP-P compared to those with PD suggesting that the investigation of WM integrity at a whole-brain level could improve the characterization of PSP-P patients.

5. Conclusions

We found that PSP-P patients were characterized by reduced track density in several supra- and infra-tentorial WM regions such as the midbrain, cerebellar peduncles, cerebellum and corticospinal tract, relative to PD patients and controls. Moreover, track density values allowed a moderate accuracy in the differentiation of patients with PSP-P from those with PD.

All together, these findings show that track density imaging may provide new useful MRI markers to characterize WM alterations in PSP-

P and to distinguish these patients from PD patients and controls. Moreover, this technique might offer a promising metric to support the diagnostic work-up of PSP phenotypes.

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Author's contribution

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

Gaetano Barbagallo: acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be submitted.

Maria Giovanna Bianco: acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be submitted.

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

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

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

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

Giuseppe Lucio Cascini: acquisition of data, analysis and interpretation of data and final approval of the version to be submitted.

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

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.10.020.

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