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Neuropsychiatric and cognitive profile of early Richardson's syndrome, Progressive Supranuclear Palsy-parkinsonism and Parkinson's disease

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ABSTRACT

Introduction: The two main variants of Progressive Supranuclear Palsy (PSP), Richardson's syndrome (PSP-RS) and PSP-parkinsonism (PSP-P), share motor and non-motor features with Parkinson's disease (PD) particularly in the early stages. This makes the precocious diagnosis more challenging. We aimed at defining qualitative and quantitative differences of neuropsychiatric and neuropsychological profiles between PSP-P, PSP-RS and PD patients recruited within 24 months after the onset of symptoms, in order to clarify if the identification of peculiar cognitive and psychiatric symptoms is of help for early PSP diagnosis.

Methods: PD (n = 155), PSP-P (n = 11) and PSP-RS (n = 14) patients were identified. All patients were submitted to clinical, neurological, neuropsychiatric diagnostic evaluation and to a comprehensive neuropsychiatric and neuropsychological battery. Predictors of PSP-P and PSP-RS diagnosis were identified by multivariate logistic regressions including neuropsychiatric and neuropsychological features that differed significantly among groups.

Results: The three groups differed significantly at the Apathy Rating Scale score and at several neuropsychological domains. The multivariate logistic regressions indicated that the diagnosis of PSP-RS was predicted by phonological verbal fluency deficit whereas the presence of apathy significantly predicted the PSP-P diagnosis.

Conclusion: Peculiar neuropsychiatric and neuropsychological symptoms are identifiable very precociously in PSP-P, PSP-RS and PD patients. Early phonological verbal fluency deficit identifies patients with PSP-RS whereas apathy supports the diagnosis of PSP-P.

1. Introduction

Progressive Supranuclear Palsy (PSP) is the second most common degenerative parkinsonism after idiopathic Parkinson's disease (PD) [1]. Despite of profound neuropathologic differences, PSP and PD share similar features, including bradykinesia, loss of dexterity and gait disturbances that may complicate the differential diagnosis particularly early along disease course. Further increasing the diagnostic challenge, recent clinic pathological data distinguished several clinical phenotypes of PSP including the PSP-parkinsonism (PSP-P), characterized by asymmetric onset of symptoms, tremor, early bradykinesia, non-axial dystonia and a response to levodopa, that more closely overlaps with PD than the classic description of 'Richardson's syndrome' (PSP-RS) [2].

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PSP patients in the advanced stages consistently suffer from more severe affective and cognitive symptoms, including apathy, depression, executive and visual-spatial deficits, than patients with PD [3,4]. The question arises as to whether differences of the pattern and severity of neuropsychiatric and neuropsychological symptoms among PD, PSP-P and PSP-RS are precociously detectable, along the time span of potential motor symptom overlap.

The results of previous studies are rather contradictory [5–7]. Aarsland et al. described increased apathy and disinhibition in PSP patients in comparison with PD patients [5]. Lee et al. [6] reported more robust impairment of verbal memory and processing, planning and set-shifting in a small cohort of PSP with respect to PD patients, all recruited within the first five years of the illness. Conversely, Borroni et al. [7] found similar neuropsychiatric and neuropsychological features in patients suffering from several degenerative parkinsonisms (PD, PSP, corticobasal degeneration, dementia with Lewy bodies). Data concerning a shorter frame time after the onset of motor symptoms are, however, missing. Further, a detailed investigation using a complete neuropsychiatric and cognitive battery in early PSP-P and PSP-RS patients is still lacking.

The aim of this study was to investigate comprehensive neuropsychiatric and cognitive profiles in PSP-P and PSP-RS patients examined within 24 months from motor symptom onset, and to compare possible dysfunctions with those found in PD. We hypothesized that discrete neuropsychiatric and neuropsychological profiles may be identified in early phases of PSP-RS, PSP-P and PD.

2. Methods

2.1. Participants

The study was carried out on 180 consecutive patients. Inclusion criteria were: a) age between 40 and 80 years; b) diagnosis of degenerative parkinsonism (i.e., PD, PSP-RS and PSP-P), with onset of symptoms dating less than 24 months at enrollment. Patients were recruited during scheduled visits at the Outpatient Services for Movement Disorders of our Institutions in the period between May 2006 and January 2014.

Exclusion criteria were: a) co-morbidity with major, not stabilized, medical illnesses; b) known or suspected history of alcoholism, drug dependence or abuse, other neurological disorders, head trauma and mental disorders (apart from mood and anxiety disorders) according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition - Text Revision (DSM-IV-TR) [8]; c) presence of vascular brain lesion or neoplasm at CT or MRI brain scan; d) noncompliance with testing procedure.

All patients were regularly followed-up in our outpatient clinics. Clinical diagnosis of either PD (n = 155) or PSP (n = 25) were confirmed over a minimum of three years follow-up from symptom onset, according to the criteria by Gelb et al. [9] and Litvan et al. [1]. Specifically, according to diagnostic proposal of PSP phenotypes by Williams et al. [2,10], that is currently the reference classification to distinguish between PSP-P and PSP-RS, 14 patients were classified as PSP-RS since falls, supranuclear gaze palsy, postural instability and levodopa resistance were the predominant clinical features within the first 24 months from symptoms onset; eleven patients were classified as PSP-P as they showed in the first 24 months of the disease abnormality of saccadic eye movements, positive response to levodopa, asymmetric onset and postural instability. After a minimum of three years follow-up, the phenotype of PSP-P patients more closely overlapped the PSP-RS patients with severe postural instability (11/11), falls (7/11), supranuclear gaze palsy (11/11) and abnormal saccades (11/11) (Table 1).

Dopamine replacement therapy dosages were calculated as daily levodopa equivalents. The following conversion table was applied: 100 mg levodopa = 1 mg pramipexole = 5 mg ropinirole = 5 mg rotigotine. Within each group, the number (and %) of subjects receiving antidepressant, benzodiazepines and/or antipsychotic therapy was calculated.

The protocol was approved by the Ethical Committee of the Santa Lucia Foundation IRCCS, and each subject signed the informed consent before enrollment.

2.2. Sociodemografic and clinical assessment

The demographic and neurological features of patients were collected at enrollment by neurologists with expertise on parkinsonisms. The severity of motor symptoms was measured by the Unified Parkinson's Disease Rating Scale - part III scale (UPDRS-III).

Within 2 weeks from enrollment, all subjects underwent a structured psychiatric interview (SCID-P) for the identification of psychiatric disorders according to the DSM-IV-TR criteria. Apathy was diagnosed according to the adaptation by Starkstein [12] of the Marin criteria [13]. All psychiatric diagnoses were made by a senior psychiatrist.

Severity of anxiety symptoms was quantified by the Hamilton Anxiety Rating Scale (HARS). Severity of depressive symptoms was investigated by the Beck Depression Inventory (BDI) (total score, psychic and somatic sub-scores). Apathy severity was quantified by means of the Apathy Rating Scale (ARS). The Parkinson's Psychosis Rating Scale (PPRS) was used to assess the severity of psychotic symptoms.

All patients were submitted to a detailed neuropsychological evaluation including: *i.* the MMSE, a global index of cognitive impairment with scores ranging from 30 (no impairment) to 0 (maximum impairment); *ii.* tests taken from the Mental Deterioration Battery, a comprehensive neuropsychological battery that includes verbal and non-verbal tasks such as the Rey's 15-word test – Immediate Recall (RIR) and Delayed Recall (RDR) to evaluate short- and long-term episodic verbal memory, with total scores given by the total number of words recalled at each test, and the Phonological (PVF) and Semantic (SVF) Verbal Fluency test to assess language abilities, in which the total score is the total number of words produced during each test; *iii.* the Copy of the Rey-Osterrieth picture test (CRO) and Delayed Recall of the Rey-Osterrieth picture test (DRO) for evaluating complex constructional praxis and long-term visual memory, with score ranging from 0 (maximal impairment) to 36 (no impairment) at both tests; *iv.* the Stroop Word-Color Test (SWCT) to assess frontal abilities of simple attention, attention shifting and control, that consists of 3 parts: in the “word reading” task participants were asked to read as quickly as possible Italian words for colors (i.e., red, blue and green) that were printed in black ink on a white sheet; in the “color naming” task participants were shown a series of blue, red and green dots and were asked to name the colors as quickly as possible; finally, in the “interference time” task, Italian words indicating colors were printed in different colored ink (e.g., the word “red” was printed in blue ink) and participants were asked to name the color of the printed word (in the example, “blue” was the correct answer) as quickly as possible. If the case of an error, subjects were stopped and requested to go back to the previous word. All tests have been described in details elsewhere [11].

Neuropsychiatric symptom severity and neuropsychological performances were assessed by 3 trained neuropsychologists. Acceptable inter-rater reliability was defined as $k > 0.80$.

2.3. Ancillary assessment of emotion recognition and executive functions

We also assessed the recognition of facial emotion expressions

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and executive functions to investigate some cognitive and behavioral features possibly linked to apathy. The Penn Emotion Recognition Test (PERT) was used to assess facial emotion recognition ability. This is a standardized and validated test [14] of 96 color photographs of facial expressions of five emotions (happiness, sadness, anger, fear, disgust) and neutral faces. The participants viewed the pictures of the facial expressions on the computer screen. Then, they had to label the basic emotions by choosing one out of the six possibilities (i.e., anger, sadness, disgust, fear, happiness, neutral).

Wisconsin Card Sorting Test – short form (WCST-SF) [11], was used to explore executive functions. WCST-SF requires matching 48 cards to four key cards by color, shape, and number and choosing the six correct categories from feedback given by the examiner. The WCST-SF was scored for total number of achieved categories and failures to maintain set, that is, the total number of perseverative and non-perseverative errors. Data on PERT and WCST-SF were available only for a subset of the study sample. In particular, 138 PD, 9 PSP-P and 9 PSP-RS patients underwent the PERT examination and 154 PD, 11 PSP-P and 11 PSP-RS patients the WCST-SF. These data were analyzed only in relationship with apathy.

2.4. Statistical analysis

Differences in demographic, clinical, neuropsychiatric and neuropsychological features among groups were assessed by the chi-squared test for categorical variables and by a series of Kruskal-Wallis H tests for continuous variables followed by Mann-Whitney *U* test post-hoc comparisons when appropriate. The neuropsychiatric and neuropsychological independent variables that differed significantly after Bonferroni's correction for multiple comparisons ($n = 13$; i.e., BDI psychic, BDI somatic, HARS, ARS, RIR, RDR, CRO, DRO, PVF, SVF, SWCT word reading, SWCT color naming, SWCT interference time; $p < 0.05/13 = p < 0.0038$) among groups were then included in a multivariate logistic regression analysis to identify predictors of PSP subtype diagnosis (considered as dependent variable). The reference category was diagnosis of PD.

Further, as an ancillary analysis, we ran a multivariate logistic regression analysis, considering PSP-P, PSP-RS and PD diagnosis as dependent variables and including as independent variables both neuropsychiatric categorical variables (i.e., diagnosis of depression and apathy) that were significantly different among groups and the predictor(s) selected by the former regression model. Again the reference category was diagnosis of PD.

Finally, in an explorative analysis, differences among groups in scores of PERT and WCST-SF were assessed by a series of Kruskal-Wallis H tests followed by Mann-Whitney *U* test post-hoc comparisons when appropriate. The Spearman's rank-order correlation coefficient was computed in each group (i.e., PD, PSP-P, PSP-RS) to assess the relationship between ARS score and WCST-SF scores. Given the exploratory nature of these last analyses, correction for multiple comparisons was not applied and the level of statistical significance was accepted as p less than 0.05.

3. Results

3.1. Demographic and clinical features of the study cohort

The three groups did not differ significantly in any demographic and clinical features (Table 1), apart from UPDRS-III score that was higher in PSP-RS patients in comparison with PD patients (Table 1).

3.2. Neuropsychiatric rating scales

Table 2 shows the results of neuropsychiatric rating scales represented by continuous values. The three groups differed significantly only in the ARS score. PD patients scored better than other two groups. Differences among groups at BDI scores did not survive after correction for multiple comparisons.

3.3. Neuropsychiatric diagnoses

As to neuropsychiatric diagnoses, frequencies of apathy and depressive disorder were significantly different among groups. Indeed, diagnoses of apathy and depression were more frequent in both PSP subtypes with respect to PD patients (Table 2).

3.4. Neuropsychological rating scales

Table 3 shows the results of the neuropsychological rating scales. A global cognitive screening using the MMSE showed significant difference among groups. PSP-RS patients suffered from decreased global cognitive level when compared to PD patients. The comprehensive neuropsychological battery indicated significantly worse performances of PSP-P and PSP-RS patients at several neuropsychological domains as compared to PD patients. In particular, PSP-RS patients scored worse than PD patients at RIR, CRO, PVF, SVF and all SWCT. Further, PSP-RS patients scored worse than PSP-P patients at CRO (approached significance), PVF and SWCT word reading and color naming. Differences emerged between PSP-P and PD patients at PVF, SVF and SWCT color naming and interference time.

3.5. Predictors of PSP diagnosis

Based on the results of Kruskal-Wallis H tests, we included in the logistic regression analysis as potential predictors of PSP subtypes the ARS, RIR, CRO, PVF, SVF and SWCT scores. MMSE score was not included, being an index of global cognitive functioning. In this logistic regression model, PVF score (OR = 0.844, 95% CI = 0.742–0.960; p = 0.0096) significantly predicted PSP-RS diagnosis. ARS score only approached significance in predicting PSP-P diagnosis (OR = 1.09, 95%CI = 0.995–1.21; p = 0.06). In a second multivariate logistic regression model, we included as independent predictors of PSP subtypes the neuropsychiatric diagnoses of apathy and depression and PVF score, being the only cognitive predictor identified by the first logistic regression model. In accordance with the results of the previous multivariate logistic regression model, PVF score (OR = 0.769, 95%CI = 0.680–0.870; p < 0.0001) significantly predicted PSP-RS diagnosis. The diagnosis of apathy (OR = 9.360, 95%CI = 1.654–52.956; p = 0.0114) significantly predicted the PSP-P diagnosis.

3.6. Ancillary analysis: emotion recognition and executive functions

PSP-RS patients scored worse than PD at all WCST-SF sub-scores. Further, PSP-RS displayed worse score than PSP-P at WCST-SF non-perseverative errors and achieved categories. No differences emerged between PD and PSP-P patients (Table 4).

Table 4 shows results of facial emotion recognition of PD, PSP-P and PSP-RS. The three diagnostic groups differed significantly in the recognition of facial emotions expressing sadness and in the recognition of neutral faces. PSP-RS patients failed in recognizing sadness compared to both PD and PSP-P patients. PD patients recognized better than PSP-P neutral faces, with results of PSP-RS

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Table 1
Demographic and clinical features of patients with PD, PSP-P and PSP-RS.

	PD (n = 155)	PSP-P (n = 11)	PSP-RS (n = 14)	H	df	Kruskal-Wallis P	Post Hoc analysis (Mann-Whitney)		
							P PD vs. PSP-P	P PD vs. PSP-RS	P PSP-P vs. PSP-RS
Age (years)	67.2 ± 7.47 (91.197)	65.4 ± 6.6 (69.273)	68.9 ± 7.5 (99.464)	2.268	2	0.322	na	na	na
Disease duration (months)	15.3 ± 8.4 (88.971)	15.3 ± 9.4 (89.682)	18.75 ± 5.2 (108.071)	1.728	2	0.421	na	na	na
Education (years)	10.5 ± 4.5 (90.926)	11.9 ± 5.2 (107.136)	8.8 ± 3.9 (72.714)	2.763	2	0.251	na	na	na
UPDRS-III score	15.9 ± 9.3 (82.224)	21.2 ± 11.3 (107.944)	25.0 ± 6.5 (134.000)	10.184	2	0.006	0.127	0.004	0.229
Levodopa (mg/day)	95.2 ± 148.1 (90.045)	172.7 ± 214.9 (106.136)	62.5 ± 122.8 (83.250)	1.273	2	0.529	na	na	na
Dopamine Agonist Equivalents (mg/day)	85.1 ± 130 (92.803)	140.9 ± 253.8 (94.227)	7.1 ± 26.7 (62.071)	4.527	2	0.104	na	na	na
Levodopa Equivalents (mg/day)	180.3 ± 188.5 (92.010)	313.6 ± 406.3 (106.136)	69.6 ± 143.5 (61.500)	5.457	2	0.065	na	na	na
	PD	**PSP-P**	**PSP-RS**	**χ2**	**df**	**P**			
Sex (male, %)	84 (54,2%)	7 (63%)	6 (42,8%)	1.112	2	0.573	na	na	na
Under Antidepressant drugs n (%)	15 (9.7%)	2 (18.2%)	4 (28.6%)	4.930	2	0.085	na	na	na
Under Benzodiazepine n (%)	21 (13.5%)	1 (9.1%)	1 (7.1%)	0.616	2	0.735	na	na	na
Under Antipsychotic drugs n (%)	2 (1.3%)	0 (0%)	1 (7.1%)	2.882	2	0.237	na	na	na

Clinical features of PSP patients

	PSP-RS T0 (n = 14)	PSP-RS T1 (n = 14)	PSP-P T0 (n = 11)	PSP-P T1 (n = 11)
Falls	12 (85.7%)	14 (100%)	0 (0%)	7 (63%)
Postural Instability	14 (100%)	14 (100%)	3 (30%)	11 (100%)
Supranuclear gaze palsy	14 (100%)	14 (100%)	2 (18%)	11 (100%)
Abnormal saccades	14 (100%)	14 (100%)	7 (63%)	11 (100%)
Asymmetric symptoms	2 (14%)	1 (7%)	9 (85%)	6 (54%)
Response to Levodopa	2 (14%)	0 (0%)	6 (54%)	2 (18%)
Speech disturbance	8 (57%)	11 (78%)	3 (30%)	6 (54%)

Data represent mean ± SD (Mean Rank); na = not applicable.
T0 = within 24 months from motor symptoms onset; T1 = ≥ three years follow-up from symptom onset.

Table 2
Neuropsychiatric evaluation and frequency of neuropsychiatric diagnoses of patients with PD, PSP-P and PSP-RS.

	PD (n = 155)	PSP-P (n = 11)	PSP-RS (n = 14)	H	df	Kruskal-Wallis P	Post Hoc analysis (Mann-Whitney)		
							P PD vs. PSP-P	P PD vs. PSP-RS	P PSP-P vs. PSP-RS
BDI total	8.4 ± 6.4 (86.210)	10.5 ± 5.2 (114.045)	13.6 ± 9 (119.500)	7.634	2	0.022	0.08	0.02	0.584
BDI psychic	4.9 ± 4.5 (85.723)	6.7 ± 3.6 (116.409)	8.4 ± 5.7 (123.036)	9.481	2	0.009	0.054	0.011	0.529
BDI somatic	3.4 ± 2.6 (88.010)	3.8 ± 2.1 (100.182)	5.1 ± 4 (110.464)	2.789	2	0.248	na	na	na
HARS	8.4 ± 4.9 (89.516)	8.4 ± 2.9 (96.682)	9.0 ± 5 (96.536)	0.398	2	0.820	na	na	na
ARS	8.0 ± 6.3 (83.606)	14.0 ± 9.5 (118.500)	19.4 ± 9.6 (144.821)	21.105	2	<0.0001*	0.032	<0.0001	0.218
PPRS	6.8 ± 1.2 (87.577)	7.0 ± 0.9 (105.227)	7.4 ± 1.4 (106.00)	2.528	2	0.282	na	na	na
	PD	**PSP-P**	**PSP-RS**	**χ2**	**df**	**P**			
Depression (Y) (% Y)	51 (32.9%)	7 (63.6%)	9 (64.3%)	8.91	2	0.012	na	na	na
Anxiety (Y) (% Y)	16 (10.3%)	0 (0%)	1 (7.1%)	1.374	2	0.503	na	na	na
Apathy (Y) (% Y)	4 (2.6%)	3 (27.3%)	3 (21.4%)	19.225	2	<0.0001	na	na	na

Data represent mean ± SD (Mean Rank).
BDI = Beck Depression Inventory; HARS = Hamilton Anxiety Rating Scale; ARS = Apathy Rating Scale; PPRS = Parkinson's Psychosis Rating Scale.
*Significant after Bonferroni's correction for multiple comparisons (n = 13); $p < 0.05/13 = p < 0.0038$; na = not applicable.

vs. PD approaching statistical significance.

Additionally, we performed a Spearman's rank-order correlation splitted by group (i.e., PD, PSP-P, PSP-RS patients) to assess the relationship between ARS score and WCST-SF sub-scores. In PSP-RS group, we found significant correlations between ARS score and WCST-SF non-perseverative errors (Rho = 0.775, p = 0.014), between ARS score and WCST-SF perseverative errors (Rho = 0.791, p = 0.12) and between ARS score and WCST-SF achieved categories (Rho = −0.773, p = 0.014). No significant correlations were found in PSP-P group. In PD group, the only significant correlation observed was between ARS score and WCST-SF non-perseverative errors (Rho = 0.165, p = 0.04).

4. Discussion

Our results confirm the hypothesis that PSP-P, PSP-RS and PD patients are well characterized by peculiar patterns of neuropsychiatric and cognitive symptoms detectable from the very early stages of the disease. It is of fundamental importance to highlight that the differential diagnosis among these disorders is frequently

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Table 3
Neuropsychological evaluation of patients with PD, PSP-P and PSP-RS.

	PD (n = 155)	PSP-P (n = 11)	PSP-RS (n = 14)	H	df	Kruskal-Wallis P	Post Hoc analysis (Mann-Whitney)		
							P PD vs. PSP-P	P PD vs. PSP-RS	P PSP-P vs. PSP-RS
MMSE	28.1 ± 1.9 (95.481)	27.3 ± 2.4 (74.682)	24.9 ± 4 (47.786)	11.838	2	0.003*	0.193	0.001	0.147
RIR	35.9 ± 10.5 (95.626)	30.1 ± 8.7 (66.955)	26.2 ± 9.9 (52.250)	11.290	2	0.003*	0.077	0.003	0.477
RDR	6.9 ± 3.4 (93.297)	6.1 ± 2.0 (82.955)	5.0 ± 3.0 (65.464)	3.909	2	0.142	na	na	na
CRO	28.1 ± 5.9 (97.106)	25.4 ± 5.4 (68.636)	18.6 ± 8.5 (34.536)	20.579	2	<0.0001*	0.073	<0.0001	0.052
DRO	14.03 ± 5.7 (94.287)	12.2 ± 6.3 (76.273)	10.4 ± 6.9 (59.750)	6.515	2	0.038	na	na	na
PVF	29.3 ± 11.1 (98.939)	21.6 ± 14.6 (63.909)	9.0 ± 6.6 (17.964)	34.061	2	<0.0001*	0.029	<0.0001	0.019
SVF	18.4 ± 5.6 (97.861)	14.9 ± 6.3 (65.409)	10.1 ± 4.4 (28.714)	25.329	2	<0.0001*	0.044	<0.0001	0.070
SWCT word reading	17.2 ± 6.6 (83.297)	18.8 ± 5.1 (105.182)	35.2 ± 18.2 (158.714)	27.830	2	<0.0001*	0.157	<0.0001	0.002
SWCT color naming	23.7 ± 7.6 (82.748)	28.3 ± 7.8 (115.227)	46.7 ± 24.9 (156.893)	28.638	2	<0.0001*	0.039	<0.0001	0.011
SWCT interference time	48.6 ± 20.7 (83.045)	74.4 ± 44.4 (120.818)	93.8 ± 41.3 (149.214)	24.673	2	<0.0001*	0.020	<0.0001	0.163

Data represent mean ± SD (Mean Rank); na = not applicable.
MMSE = Mini Mental State Examination; RIR = Rey's 15-words test - Immediate Recall; RDR = Rey's 15-words - Delayed Recall; CRO = Copy of the Rey-Osterrieth picture; DRO = Delayed Recall of the Rey-Osterrieth picture; PVF = Phonologic Verbal Fluency; SVF = Semantic Verbal Fluency; SWCT = Stroop Word-Color Test.
*Significant after Bonferroni's correction for multiple comparisons (n = 13); $p < 0.05/13 = p < 0.0038$.

Table 4
Ancillary data on executive functions and facial emotion recognition of patients with PD, PSP-P and PSP-RS.

	PD (n = 154)	PSP-P (n = 11)	PSP-RS (n = 11)	H	df	Kruskal-Wallis P	Post Hoc analysis (Mann-Whitney)		
							P PD vs. PSP-P	P PD vs. PSP-RS	P PSP-P vs. PSP-RS
WCST-SF perseverative errors	3.19 ± 4.27 (85.851)	3.64 ± 5.22 (86.545)	7.46 ± 7.26 (127.545)	6.893	2	0.032	0.966	0.009	0.07
WCST-SF non-perseverative errors	3.14 ± 2.77 (86.146)	2.72 ± 2.24 (81.409)	6.55 ± 4.85 (128.545)	7.337	2	0.025	0.781	0.008	0.020
WCST-SF categories	5.36 ± 1.21 (90.692)	5.55 ± 1.04 (99.045)	3.64 ± 2.34 (47.273)	7.958	2	0.019	0.594	0.006	0.024
	PD (n=138)	**PSP-P (n=9)**	**PSP-RS (n=9)**	**H**	**df**	**Kruskal-Wallis P**	**Post Hoc analysis (Mann-Whitney)**		
							P PD vs. PSP-P	**P PD vs. PSP-RS**	**P PSP-P vs. PSP-RS**
Anger	8.09 ± 2.33 (79.054)	7.89 ± 1.69 (74.611)	8.0 ± 2.35 (73.889)	0.181	2	0.913	na	na	na
Sadness	9.42 ± 3.55 (81.529)	9.89 ± 3.06 (84.278)	4.78 ± 2.39 (26.278)	12.793	2	0.002	0.878	0.0004	0.004
Disgust	6.61 ± 2.98 (78.942)	6.22 ± 2.64 (75.500)	6.33 ± 3.28 (74.722)	0.116	2	0.944	na	na	na
Fear	8.32 ± 3.01 (79.996)	7.89 ± 1.76 (71.833)	7.11 ± 3.10 (62.222)	1.516	2	0.469	na	na	na
Happiness	15.15 ± 1.32 (80.725)	15.11 ± 0.93 (72.111)	13.00 ± 3.91 (50.778)	3.903	2	0.142	na	na	na
Neutral	10.82 ± 3.89 (82.199)	7.78 ± 3.67 (47.722)	8.22 ± 4.02 (52.556)	8.071	2	0.018	0.027	0.06	0.791

WCST-SF = Wisconsin Card Sorting Test-short form.

complicated at the onset by the overlap of motor symptoms of Parkinsonism. Few data are available on this topic in patients with PSP-P and PSP-RS. Here, we applied to our cohort a comprehensive neuropsychological and neuropsychiatric battery and a formal psychiatric diagnosis, as opposed to previous studies [7,15,16]. In this context, our results clearly indicate that, within 24 months from the onset of symptoms, there is a continuum of severity from the milder PD, throughout PSP-P, to PSP-RS. In particular, a poor performance in phonologic verbal fluency may be supportive of a diagnosis of PSP-RS, whereas the presence of apathy may predict PSP-P subtype.

Our findings enhance the previous observation by Lee et al. [6] of more robust impairment of verbal memory and processing, planning and set-shifting in PSP as compared to PD patients, by showing that significant neuropsychological differences between the two disorders may be identified already in the first 24 months after symptom's onset. Conversely, our findings appear in contrast with those by Borroni et al. [7], who reported similar patterns of neuropsychiatric and cognitive alterations among patients recruited in the early stages of different degenerative parkinsonisms (i.e., PD, PSP, corticobasal degeneration, dementia with Lewy bodies). Several factors, including the study design, inclusion/exclusion criteria, and the methodologies applied, may contribute at justifying these discrepancies. The study by Borroni et al. [7] was designed to identify possible differential patterns of neuropsychiatric and/or cognitive symptoms in patients affected by degenerative parkinsonisms matched for level of global cognition (MMSE score), whereas we enrolled consecutive patients to get a more naturalistic picture of the neuropsychiatric/cognitive features in PSP-RS, PSP-P and PD, with the aim of identifying quantitative and qualitative differences precociously during disease course. Depression, apathy, executive and visual-spatial impairments were, indeed, identified as core neuropsychiatric and neuropsychological features of early PSP and PD in both studies, however our investigation demonstrates the higher prevalence and severity of these symptoms in very early PSP-RS and PSP-P as compared to PD subjects.

Our data add insights into the clinical variability among patients with the two main subtypes of PSP. This is line with *post-mortem* pathological studies indicating that differences in regional burden of tau pathology account for the clinical heterogeneity observed in patients with PSP-RS and PSP-P [17,18]. Indeed, patients with PSP-P

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had less severe tau pathology than those with PSP-RS, milder symptom presentations and relatively better prognosis. Therefore, as stated by Williams and Lees [10], PSP-P and PSP-RS represent two separate points on a spectrum of clinical features related to PSP tau pathology. We demonstrate that this assumption is reflected by neuropsychiatric and cognitive characteristics as well, PSP-P exhibiting milder clinical phenotype than PSP-RS. Following the notion that apathy represents one of the most important clinical features of patients with PSP [5], PSP-RS and PSP-P did not differ as to severity of continuous score of apathy but a higher frequency of formal apathy diagnosis was observed in PSP-P patients. Accordingly, the clinical definition of apathy, conceptualized by Marin [13] and further adapted by Starkstein [12], recognizes behavioral, cognitive and emotional symptoms reflecting disruption of distinct aspects of goal directed behavior (GDB) and includes both a lack of inward emotional experience and a reduced expression of emotions. GDB impairment is sustained by the inability to flexible shifting between behaviors and to maintaining purposeful behaviors despite internal or external distractors. Consequently, since the cognitive control has been demonstrated as one substrate of apathy itself, reduced cognitive flexibility may be one contributor to higher levels of apathy [19]. Nevertheless, apathy could not been conceptualized merely as a lack of flexibility but rather as a complex process in which both emotional and executive impairments contribute. Hence, our data demonstrate that PSP-RS patients are more compromised in both components. Further, our ancillary data indicated that in PSP-RS apathy is correlated with impaired executive functions. Interestingly, PSP-RS and PSP-P patients did not show differences in WCST-SF perseverative errors, a component that better describes the cognitive flexibility and is more closely related to the ability to respond to changing goals. The underlying mechanisms responsible for apathy may be seen as dysfunctions occurring at the level of structures sustaining elaboration, execution and control of GDB, such as prefrontal cortex (PFC) and basal ganglia [20]. Actually, neuropathological [21] and *in vivo* imaging studies [22,23] in PSP patients, assessed globally as a single disorder, demonstrated dorsal striatum, thalamus and midbrain atrophy, cortical atrophy of prefrontal areas and connectivity disruption within networks linking brainstem, basal ganglia and cortex. Based on cognitive and neuropsychiatric evaluations, our results suggest that the clinical hallmarks of such anatomical substrates may be detectable from the very early stages of the disease. However, correlation with imaging data goes beyond the purpose of our investigation.

Within this frame of a functional “prefrontal-like” syndrome, interestingly the predictor of PSP-RS diagnosis was PVF impairment, measured by a test of linguistic abilities that represents also a task of self-activation of cognitive strategies. Indeed, the dorsolateral PFC (Brodmann Area 46) is involved in executive functions as well as in phonological processing during word generation [24,25]. The correct functioning of verbal fluency is associated with activation of a diffuse cortical network [26,27]. Schofield and collaborators [27] demonstrated, by neuroimaging techniques in confirmed pathological cases of PSP, that cortical atrophy and frontal lobe tau pathology are more severe in PSP-RS than in PSP-P patients. Rittman and colleagues recently demonstrated that verbal fluency distinguishes between PSP and PD with high sensitivity and high specificity [28]. Our results extend previous reports [28–30] showing that verbal fluency tests discriminate well between PSP-RS and PD patients already in the first 24 months of the disease.

In our cohort, PSP-RS patients displayed higher prevalence and severity of depression as compared to PD cases. Nevertheless, it is of interest that neither severity of depressive symptoms nor clinical diagnoses of depression were definitive predictors of PSP-RS diagnosis. This advocates for a distinct nature of apathy and depression in PSP (as well as in other disorders), rather than the former being a symptom of the latter and stresses the impairment of affective and emotional tone since the very early stages in PSP patients. Indeed, our ancillary results on emotion processing indicate that the impairment of facial emotion recognition of sadness characterizes PSP-RS patients. Nevertheless, PSP-P patients showed a worse performance of PD on the recognition of neutral faces due to the attribution of emotional saliency to unrecognized neutral expressions. These results further clarify our previous observation of compromised emotion processing in PSP and PD patients [14]. In fact, on the light of these new results, the difference in emotion recognition we have previously described between PD and PSP patients seems to be driven by PSP-RS group. In our previous study, we found that PSP patients displayed significantly lower recognition of happy emotional faces. This result did not emerge here. Given the shorter disease duration we considered in the present study, we can speculate that the impairment in the happiness recognition emerge later in the disease course. In reality, in the present study PSP-RS patients have more difficulty in recognizing happy faces than PD and PSP-P patients and considering happy faces are recognized very well by non PSP-RS patients, this may have a clinical relevance. Thus, further studies should clarify this issue. Taken together these precocious deficits in facial emotion recognition could determinate the early difficulties on social and relational abilities.

We also acknowledge the limitations of our study. Our PSP patients were enrolled within Movement Disorders Outpatient Services, suggesting the presence of predominant “motor” phenotype of the disease, and therefore possibly underestimating the global prevalence and severity of cognitive and behavioral impairment in the early PSP population. However, this was indeed our main purpose, that is to establish if peculiar neuropsychiatric and neuropsychological profiles may precociously help in the differential diagnosis among patient with atypical Parkinsonism, when very often motor profiles are overlapping. Further, here we did not administer behavioral scales to both patients and caregivers. Thus the caregiver point of view is lacking in the present study. The relative small sample size of PSP-P and PSP-RS patients advocates for further studies on larger series to confirm our findings. Finally, we do not have autoptic confirmation of our diagnosis.

In conclusion, our study demonstrates a different severity of neuropsychiatric and cognitive symptoms in PSP-P and PSP-RS with respect to PD, recruited within 24 months after onset of clinical symptoms. Specifically, we found that verbal fluency impairment and apathy diagnosis are more supportive of diagnosis of PSP-RS and PSP-P respectively, rather than PD. These findings indicate that comprehensive cognitive and psychiatric evaluations might be useful and cost-effective contributors to the diagnostic work-up of patients with progressive Parkinsonism in the very early stages.

Conflicts of interest

None.

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Individual contribution and authorship

1) the conception and design the study, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be submitted.

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