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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Characteristics and progression of cognitive deficits in progressive supranuclear palsy vs. multiple system atrophy and Parkinson's disease

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Abstract
Cognitive impairment is frequent in progressive supranuclear palsy (PSP) and less common in multiple system atrophy (MSA), but characteristics and progression compared with Parkinson's disease (PD) need to be properly defined. We evaluated 35 PSP with Richardson's syndrome (PSP-RS), 30 MSA as well as 65 age-, sex-, and education-matched PD with an extensive clinical and neuropsychological assessment, allowing Level II cognitive diagnosis. Eighteen PSP, 12 MSA and 30 PD had a second evaluation between 12 and 18 months (mean 15 months) after the first assessment. PSP performance at Montreal Cognitive Assessment (MoCA), verbal fluencies (phonemic and semantic tasks), Stroop test (Error and Time), Digit Span Sequencing (DSS), incomplete letters of Visual Object and Space Perception (VOSP) and Benton's Judgment of Line Orientation (JLO) performance were significantly poorer at baseline compared to PD and MSA. Executive, language and visuospatial abilities declined longitudinally in PSP, but not in PD and MSA. After 1.5 year, 16% of PSP converted to dementia. Our study provides evidence that cognitive progression is more severe and rapid in PSP-RS than PD and MSA. Further, we observed that MoCA, verbal fluency (particularly semantic), DSS and Benton's JLO are valuable tests to detect cognitive progression in PSP-RS and may be proposed as possible biomarker to assess efficacy of disease modification strategies.

Keywords Progressive supranuclear palsy · Parkinson's disease · Longitudinal study · Verbal fluency · Visuospatial functions · Executive functions

Introduction

Progressive supranuclear palsy (PSP) is a rapidly progressive neurodegenerative diseases characterized by abnormal cerebral tau-protein aggregations (Williams and Lees 2009). The most common clinical presentation of PSP is Richardson's syndrome (PSP-RS), in which patients have early and prominent gait and postural instability, frequent falls and abnormal vertical eye movements (supranuclear gaze palsy) (Ali et al. 2019; Litvan et al. 1996; Höglinger et al. 2017). In addition to motor deficits, PSP patients present pronounced cognitive and neuropsychiatric changes (Gerstenecker 2017). There is general consensus that fronto-executive deficits dominate the neuropsychological profile of PSP (Gerstenecker et al. 2013). In this regard, verbal fluency dysfunctions, particularly phonemic, have been reported as distinct cognitive deficits vs. Parkinson's disease (PD) and multiple system atrophy (MSA) (Fiorenzato et al. 2016; Rittman et al. 2013). Recently, we reported that the phonemic fluency subitem included in the Montreal Cognitive Assessment (MoCA) is sensitive in detecting cognitive deficits in PSP, while the Mini-Mental State Examination (MMSE) is less helpful (Fiorenzato et al. 2016). Further, previous studies reported deficits in visuospatial processing, memory and language in PSP (Bak et al. 2006; Burrell et al. 2014). However, the exact nature of cognitive dysfunctions in this pathology and its clinical relevance still need to be explored.

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Indeed, it is worth to investigate whether PD clinical criteria for mild cognitive impairment (MCI) and dementia (Dubois et al. 2007; Litvan et al. 2012) can be applied to PSP-RS. Using these criteria, an exploratory study found dementia in about the 10% of MSA patients (Auzou et al. 2015).

Moreover, tests that can best detect cognitive progression are still not defined (Soliveri et al. 2000). This is important given the ongoing attempts of disease modification by monoclonal antibodies and the need to define not only motor but also cognitive biomarkers of progression. In addition, definition of impaired cognitive domains can be important in differential diagnoses among different PSP variants and versus PD and MSA.

Only few longitudinal studies evaluated cognitive progression in PSP (Rittman et al. 2013; Soliveri et al. 2000). However, they were based on unclassified PSP cases and used mostly screening tools or brief neuropsychological assessments, without exploring the full spectrum of cognitive functions (attention/working memory, executive, memory, visuospatial and language domains).

Based on these considerations, we have now expanded our previous work (Fiorenzato et al. 2016), and used a comprehensive battery to identify tests that best characterize PSP and could be predictive of cognitive evolution. We also applied PD-cognitive criteria to evaluate the severity of cognitive deficits in PSP.

Materials and methods

Patients

This study included 35 PSP and 30 MSA patients referred consecutively, and 65 PD matched for age, education and sex. All patients were evaluated at baseline with neuropsychological, neuropsychiatric and motor assessment. Among these patients, 18 PSP, 12 MSA and 30 matched PD underwent a second evaluation after a mean of 15-month follow-up (range 12–18 months). Patients were recruited at the Parkinson's Disease and Movement Disorders Unit, Neurology Clinic, University of Padua, Italy; and at the San Camillo Hospital in Venice, Italy, between June 2012 and August 2017. Our PSP patients were all PSP-RS by 1996 criteria (Litvan et al. 1996) and also met the newer diagnostic criteria for probable PSP-RS (Höglinger et al. 2017). Probable MSA was diagnosed according to the established criteria (Gilman et al. 2008) and PD according to UK Parkinson's Disease Society Brain Bank diagnostic criteria (Gelb et al. 1999). This present study was approved by the Venice Research Ethics Committee of Venice, Italy. Written informed consent was obtained from all study subjects after full explanation of the procedure involved, according to the 1964 Declaration of Helsinki and its later amendments.

Clinical and neuropsychological assessment

Patients' motor symptom severity and their impact on daily functioning were assessed with Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts III and II, respectively. Levodopa (LEDD) and dopamine agonist equivalent daily (DAED) doses were calculated (Tomlinson et al. 2010), as well as the presence of ongoing anticholinergic treatments.

Our neuropsychological battery was developed to include at least two tests for each cognitive domain (i.e., attention/working memory, executive, memory, language and visuospatial/visuoperceptive functions), to diagnose dementia and MCI according to Level II PD criteria (Dubois et al. 2007; Litvan et al. 2012), namely attention/working memory domain were tested with the Trail Making Test (TMT B-A) (Giovagnoli et al. 1996) and Digit Span Sequencing (DSS) of Wechsler Adult Intelligence Scale-Fourth Edition (Wechsler 2008). Executive functions were evaluated with the Stroop Color/Word test (Caffarra et al. 2002) and phonemic fluency (Novelli et al. 1986a). Memory was assessed with word-paired-associated task (WPAT) and prose memory tests (Novelli et al. 1986b). Language was tested with the semantic fluency task and Novelli's Naming Test (Novelli et al. 1986a). Visuospatial and visuoperceptive functions were assessed by the Benton's Judgment of Line Orientation (JLO) test (Gullett et al. 2013), and Visual Object and Space Perception (VOSP) battery incomplete letters subtask (Warrington and James 1991). MMSE and MoCA were used to assess general cognitive functions. We assessed the presence of depression, anxiety, apathy and quality of life using the Beck Depression Scale (BDI-*II*), State–Trait Anxiety Inventory (STAI Y-1, Y-2), Starkstein's Apathy Scale and 8-item version of Parkinson's disease quality of life (PDQ-8), respectively (Yamanishi et al. 2013). In this study, we have applied these criteria to PSP and MSA patients, as currently there are no available cognitive guidelines for atypical parkinsonisms. Further, subjective cognitive complaints and their impact on daily functioning were assessed during the clinical interview using the Parkinson's Disease Cognitive Functional Rating Scale (PD-CFRS) (Kulisevsky et al. 2013), while functional autonomy was evaluated with activities of daily living (ADL) and instrumental ADL (IADL) scales. Patients underwent clinical and neuropsychological assessment in the morning after the intake of medications.

MMSE and MoCA total scores were adjusted for age and education, and z scores were calculated for all the cognitive tests according to the published Italian normative data. Further, we reverse z scores of those tests assessing reaction time (Trail Making Test and Stroop Color/

Word test) to have consistent z scores, namely a positive z score indicates a performance above the average, while a negative z score below the normative population average. We classified patients as MCI if the z score for a given test was at least 1.5 standard deviation (SD) below appropriate norms in two tests (e.g., within a single cognitive domain or at least one test in two or more cognitive domains) (Litvan et al. 2012). Presence of dementia was assessed based on cognitive examination, functional autonomy and neuropsychiatric assessment (Dubois et al. 2007). Subjects without cognitive deficits were defined as cognitively normal (NC).

Statistical analyses

Three-level one-way analysis of variance (ANOVA) was used to compare sociodemographic and clinical data between PSP, MSA and PD groups at baseline. Between-group differences in neuropsychological measures were investigated using a three-level one-way analysis of covariance including disease duration, as this variable presented intergroup differences. Pearson's Chi-squared test was run to compare categorical variables (sex and MSA subtypes). Distribution normality was checked with Kolmogorov–Smirnov tests and homogeneity of variance with Levene's test. Further, to verify if the whole sample ($n = 130$) and the followed-up subsample ($n = 60$), differed in sociodemographic and clinical variables, a one-way ANOVAs was used.

Due to the small sample size that remained at follow-up, a non-parametric method was adopted to run longitudinal analyses. Within-group comparisons (follow-up vs. baseline) were analyzed with Wilcoxon signed-rank test. One-year rate change was calculated for the performance at each cognitive test, whose score changed significantly. Spearman's rank correlations between cognitive tests and relevant clinical variables, such as motor symptoms (as assessed by MDS-UPDRS-III) or dopaminergic medications, were sought when useful to clarify the results. Finally, frequencies across cognitive states (NC, MCI and dementia) were calculated.

All statistics were performed using SPSS version 24 (IBM SPSS, Chicago, IL) and statistical significance threshold was set at $p \leq 0.05$. Post hoc analyses, followed by Bonferroni correction for multiple comparisons, were applied when appropriate.

Results

Demographic, clinical and cognitive characteristics at baseline

As shown in Table 1, PSP were older than MSA patients ($p = 0.009$), while PD patients were in the same range for age, sex and education with the other groups. PSP and MSA had shorter disease duration than PD patients ($p = 0.002$ and $p = 0.003$, respectively) and more severe motor symptoms ($p < 0.0001$). Of note, motor deficits in PSP and MSA had higher impact on daily functioning compared to PD ($p < 0.0001$). PSP patients were on lower LEDD and DAED doses than PD ($p = 0.007$ and $p = 0.004$, respectively). In addition, PSP and MSA patients were characterized by reduced functional autonomy (as assessed by ADL) ($p < 0.001$), which was linked also to cognitive dysfunctions (using the PD-CFRS) only in PSP patients ($p < 0.001$).

PSP had the worst performance on global cognitive scales (MMSE and MoCA) (see Table 1). Further, PSP showed more severe executive (Stroop test Time and Errors, DSS, phonemic and semantic fluencies) and visuospatial deficits (VOSP and Benton's JLO) than the other groups. Of note, PSP impairment was clinically meaningful in MMSE, MoCA, Stroop test, and Benton's JLO, as average scores were below cut-off or 1.5SD.

From a behavioral standpoint, PSP patients showed more severe apathy than PD ($p < 0.001$). Moreover, PSP and MSA were more depressed ($p < 0.004$) and reported reduced quality of life ($p < 0.001$) compared to PD.

The whole sample ($n = 130$) and the subsample ($n = 60$) that was followed prospectively had similar demographic and clinical variables (Online Resource 1).

Clinical and cognitive follow-up

Clinical, neuropsychological and functional autonomy progression data at follow-up are reported in Table 2.

Mean follow-up interval was 15.25 months (12–18 min–max values). Motor severity and its impact on functional autonomy decreased significantly in PSP and MSA groups. This is in line also with ADL and IADL scores that decreased significantly in each group. Moreover, in PD and PSP groups, cognitive dysfunctions affected also functional autonomy (PD-CFRS), although only seen as a trend for the latter ($p = 0.022$ and $p = 0.052$, respectively).

At mean 15-month follow-up, PSP was the only group, whose performance worsened in MoCA, semantic fluency, DSS and Benton's JLO ($p = 0.029$; $p = 0.033$; $p = 0.023$ and $p = 0.035$, respectively). MoCA total score in PSP decreased 1.60 points in a year. MSA and PD did not show any significant poorer performance in any cognitive tests compared to the baseline, except for MMSE, whose score was significantly lower in PD ($p = 0.042$). In addition, no significant correlation was found between poor performance in MoCA, DSS, Benton's JLO and semantic fluency with motor severity (MDS-UPDRS-III) or LEDD and DAED in PSP group.

Table 1 Between-group comparisons at baseline evaluation of clinical, behavioral and neuropsychological measures of PSP, MSA and PD groups

	PSP ($n=35$)	MSA ($n=30$)	PD ($n=65$)	p value
Clinical measures				
Age, years	69.54 (7.33)	63.70 (6.68)	66.49 (8.45)	**0.012**[b]
Education, years	9.35 (9.63)	9.87 (4.21)	10.25 (4.38)	0.777
Sex (m/f)	18/17	12/18	42/23	0.069
C/P subtypes	na	8/22	na	
Disease duration, years	4.88 (2.92)	4.67 (2.40)	7.28 (3.83)	**< 0.0001**[ac]
MDS-UPDRS II	20.13 (9.57)	21.11 (10.12)	11.66 (7.47)	**< 0.0001**[ac]
MDS-UPDRS-III	38.71 (17.43)	45.07 (21.55)	22.64 (13.80)	**< 0.0001**[ac]
LEDD	499.58 (354.30)	600.70 (393.31)	793.67 (476.61)	**0.006**[a]
DAED	48.23 (72.53)	84.41 (106.49)	123.67 (113.38)	**0.004**[a]
Anticholinesterase (%)	0	0	3	
ADL	4.58 (1.60)	4.37 (1.97)	5.71 (0.52)	**< 0.001**[ac]
IADL	4.64 (2.28)	4.63 (2.30)	5.51 (1.68)	**0.003**[ac]
PD-CFRS	5.09 (4.23)	2.75 (1.74)	2.60 (2.88)	**< 0.001**[ab]
Neuropsychological assessment				
MMSE (cut-off: 26)	24.37 (3.45)[d]	26.17 (2.69)	26.22 (2.50)	**0.026**[a]
MoCA (cut-off: 26)	19.85 (3.94)[d]	23.31 (2.90)[d]	23.12 (4.11)[d]	**0.001**[ab]
WPAT	− 0.51 (1.11)	− 0.5 (0.99)	− 0.42 (1.13)	0.703
TMT B-A	− 0.98 (2.04)	− 0.66 (1.55)	− 0.34 (1.66)	0.156
Stroop (Time)	− 2.55 (2.69)[d]	− 0.5 (1.05)	− 0.65 (1.39)	**< 0.001**[ab]
Stroop (Errors)	− 2.86 (3.64)[d]	− 0.6 (1.74)	− 0.58 (2.6)	**0.005**[ab]
Phonemic fluency	− 0.88 (0.95)	− 0.02 (1.18)	0.22 (1.00)	**< 0.001**[ab]
Semantic fluency	− 0.81 (1.23)	0.32 (1.31)	0.27 (0.99)	**< 0.001**[ab]
DSS (WAIS-IV)	− 0.4 (1.39)	− 0.19 (1.19)	0.31 (1.02)	**0.023**[a]
Prose memory test—recall	− 1.02 (0.94)	− 0.7 (1.22)	− 0.82 (1.1)	0.552
VOSP—incomplete letters	− 1.25 (1.76)	− 0.1 (0.77)	− 0.94 (2.18)	**0.038**[b]
Benton's JLO	− 1.85 (1.89)[d]	− 0.84 (1.48)	− 0.89 (1.34)	0.053
Naming Task Novelli	− 0.22 (1.13)	− 0.52 (3.94)	− 0.21 (1.39)	0.576
Behavioral measures				
PDQ-8	10.96 (6.76)	14.71 (6.84)	8.45 (5.03)	**< 0.001**[ac]
Apathy scale (cut-off: 14)	18.86 (7.32)[d]	14.68 (5.40)[d]	13.10 (5.68)	**< 0.001**[a]
STAI-Y1 (cut-off: 40)	39.30 (7.91)	38.12 (9.63)	38.81 (11.73)	0.861
STAI-Y2 (cut-off: 40)	44.89 (11.14)[d]	42.69 (8.47)[d]	41.78 (11.42)[d]	0.491
BDI-II (cut-off: 14)	15.63 (9.72)[d]	14.52 (8.69)[d]	10.26 (7.01)	**0.004**[ac]

Values are means (SD) and significant differences are in bold type

PSP progressive supranuclear palsy, *MSA* multiple system atrophy, *PD* Parkinson's disease, *C* cerebellar subtypes, *P* parkinsonian subtypes, *na* not applicable, *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale, *LEDD* levodopa equivalent daily dose, *DAED* dopamine agonist equivalent dose, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *WPAT* word-paired-associated task, *TMT* Trail Making Test, *DSS* Digit Span Sequencing, *WAIS-IV* Wechsler Adult Intelligence Scale-fourth edition, *VOSP* Visual Object and Space Perception, *JLO* Judgment of Line Orientation, *ADL* activities of daily living, *IADL* instrumental ADL, *PD-CFRS* Parkinson Disease Cognitive Functional Rating Scale, *PDQ-8* Parkinson's Disease Questionnaire-8, *STAI* State–Trait Anxiety Inventory (form Y1–Y2), *BDI-II* Beck Depression Inventory-II

Post hoc comparison adjusted by the Bonferroni correction for multiple tests: $p \leq 0.05$. Neuropsychological tests are reported as z scores

[a]PSP vs. PD

[b]PSP vs. MSA

[c]PD vs. MSA

[d]Clinically altered performance

Table 2 The significantly most sensitive neuropsychological, clinical and behavioral measures to cognitive decline at 15-month follow-up for each group

	PSP ($n=18$)			*One-year change rate*	MSA ($n=12$)			*One-year change rate*	PD ($n=30$)			*One-year change rate*
	Baseline	Follow-up	*p* value		Baseline	Follow-up	*p* value		Baseline	Follow-up	*p* value	
Clinical measures												
MDS-UPDRS-II	19.33 (8.52)	24.82 (12.06)	**0.039**		19.00 (10.00)	26.77 (13.34)	**0.012**		13.43 (7.76)	12.52 (8.78)	0.641	
MDS-UPDRS-III	38.53 (16.24)	46.18 (16.91)	**0.050**		40.64 (20.34)	48.89 (23.11)	0.067		25.30 (12.90)	25.90 (10.81)	0.114	
ADL	4.47 (1.74)	3.00 (2.00)	**0.002**		5.00 (1.41)	4.00 (2.14)	**0.043**		5.67 (0.61)	5.33 (0.88)	**0.004**	
IADL	4.76 (2.11)	3.17 (2.07)	**0.002**		5.75 (1.96)	3.91 (2.39)	**0.011**		5.00 (1.74)	4.53 (1.43)	**0.038**	
PD-CFRS	4.54 (4.91)	9.41 (7.95)	0.052		2.38 (1.77)	2.80 (2.90)	0.799		2.96 (3.55)	4.48 (4.31)	**0.022**	
Neuropsychological assessment												
MMSE (*cut-off: 26*)	24.12 (4.18)[a]	23.71 (5.15)[a]	0.753	*− 0.53 (2.86)*	27.25 (1.89)	26.10 (2.08)	0.072	*− 0.87 (1.38)*	26.41 (2.20)	25.46 (1.99)[a]	**0.042**	*− 0.61 (1.48)*
MoCA (*cut-off: 26*)	21.00 (3.14)[a]	18.78 (5.57)[a]	**0.029**	*− 1.60 (2.8)*	23.33 (2.64)[a]	23.55 (2.98)[a]	0.609	*− 1.33 (5.23)*	23.33 (3.73)[a]	22.57 (3.81)[a]	0.125	*− 0.67 (2.57)*
Semantic Fluency	− 0.68 (1.35)	− 0.81 (1.41)	**0.033**	*− 0.21 (0.57)*	0.59 (1.10)	0.23 (1.31)	0.083	*− 0.39 (0.68)*	0.11 (0.76)	0.16 (1.14)	0.603	*0.03 (0.67)*
DSS (WAIS-IV)	0.45 (0.92)	− 0.32 (1.00)	**0.023**	*− 0.61 (0.77)*	0.22 (1.33)	− 0.16 (0.81)	0.213	*− 0.28 (0.67)*	− 0.05 (1.25)	− 0.11 (1.11)	0.552	*− 0.14 (0.77)*
Benton's JLO	− 1.30 (1.57)	− 2.06 (1.52)[a]	**0.035**	*− 0.56 (1.8)*	− 1.00 (1.60)	− 1.32 (1.01)	0.670	*− 0.23 (1.27)*	− 0.75 (1.22)	− 1.23 (1.61)	0.187	*− 0.55 (1.21)*

Values are means (SD) and significant differences are in bold type. Neuropsychological tests are reported as *z* scores

MSA multiple system atrophy, *ns* not significant, *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale, *ADL* activities of daily living, *IADL* instrumental ADL, *PD-CFRS* Parkinson's Disease Cognitive Functional Rating Scale, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *DSS* Digit Span Sequencing, *WAIS-IV* Wechsler Adult Intelligence Scale-fourth edition, *JLO* Judgment of Line Orientation, *ADL* activities of daily living, *IADL* instrumental ADL, *PD-CFRS* Parkinson Disease Cognitive Functional Rating Scale

[a]Clinically altered performance

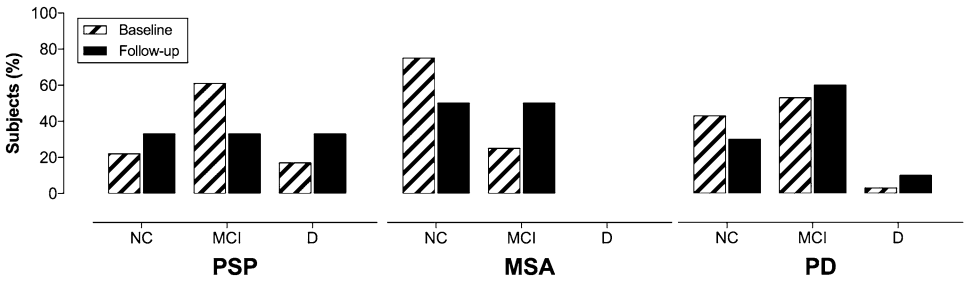

Fig. 1 Percentage of subjects followed longitudinally (18 PSP, 12 MSA and 30 PD) across cognitive states. *NC* normal cognition, *MCI* mild cognitive impairment, *D* dementia, *PSP* progressive supranuclear palsy, *MSA* multiple system atrophy, *PD* Parkinson's disease

Cognitive state change

MSA and PSP patients, despite similar disease duration, showed different distribution of cognitive states at baseline (Fig. 1). In PSP, 22% (4/18) was classified as cognitively normal, 61% (11/18) MCI and 17% (3/18) as dementia. At follow-up (approximately at 6-year disease duration in both disorders), two PSP patients (11%) with MCI converted to cognitive normal state, and 17% (3/18) to dementia as opposed to 25% (3/12) of MSA patients, who had converted to MCI, but none to dementia. Specifically, the two early diagnosed PSP patients who reverted back from MCI to normal cognition presented improved performance at one test belonging to the attentive or executive domain (i.e., Stroop test or TMT B-A). No significant correlation was found between Stroop test or TMT B-A performance and motor severity (UPDRS-III) or dopaminergic medications (LEDD, DAED) in PSP patients.

In PD, although the disease duration was longer compared to PSP and MSA, at baseline, 40% (12/30) was classified as PD-NC, 57% (17/30) as PD-MCI (mainly with multidomain deficits) and 3% (1/30) as having dementia. At follow-up, 10% (3/30) of PD-NC converted to MCI and 7% (2/30) of PD-MCI to dementia.

Discussion

To our knowledge, this is the first study to investigate longitudinal cognitive changes using an extensive neuropsychological battery in PSP-RS classified according the new criteria vs. MSA and PD patients. Our main finding is that PSP-RS patients have similar but more severe deficits in executive and visuospatial functions (as assessed by verbal fluencies, Stroop test, DSS, VOSP and Benton's JLO) than PD, whilst MSA did not show any significant cognitive alterations or changes during the observation period. Most importantly, we found that some of these tests (semantic fluency, DSS and Benton's JLO tests) are particularly suited to monitor cognitive alterations over time in PSP, as their scores significantly changed within the 15-month observation time.

Assessment at baseline showed that PSP have consistently worse performance than PD and MSA patients in MoCA, verbal fluencies (both in phonemic and semantic tasks), Stroop test (Time and Errors), DSS, VOSP and Benton's JLO. These cognitive tests were the most sensitive in showing differences between these parkinsonian syndromes. In addition, some tests (MoCA, semantic fluency, DSS and Benton's JLO) showed also good sensitivity in monitoring PSP cognitive progression.

These results are aligned with previous studies showing fronto-executive deficits, as the core features of PSP cognitive profile (Gerstenecker et al. 2013; Gerstenecker 2017). We extended this evidence by demonstrating that visuospatial dysfunctions can also be observed in PSP patients with cognitive decline (Bak et al. 2006). Our findings showed that visuospatial/perceptive abilities are differently affected in atypical parkinsonian syndromes with MSA showing preserved functions at each time point (T0 and T1) vs. worsening visuospatial performance in PSP-RS.

VOSP incomplete letters subtask is an 'object decision' tasks, which requires visual recognition and recall of degraded letters abilities. It has been related to ventral visual stream ('what'), involving the inferior temporal lobe (Bak et al. 2006; Goodale and Milner 1992) and has been already observed in PSP patients (Bak et al. 2006; Rittman et al. 2013). Indeed, atrophy of temporal areas is one of the most frequent pathological findings of PSP, suggesting greater decline in visuospatial tasks is presumably due to the pathological involvement of this region (Massey et al. 2012).

However, PSP-RS patients presented clinically relevant deficits at first evaluation as well as at follow-up, in the Benton's JLO, a 'spatial location' task, mainly related to the parietal alterations of the dorsal stream of visuospatial processing ('where'). This observation adds to the view that parietal abnormality can also play a part in cognitive alterations in the visuospatial domain (Massey et al. 2012). These findings corroborate previous evidence of Soliveri et al. (2000), which showed PSP poorer performance at Benton's JLO than MSA and PD, although they did not explore the within changes overtime. Of note, we are aware that Benton's JLO test requires vertical shift of attention, which is more difficult for PSP patients because of the vertical gaze palsy, slow horizontal saccades and visual fixation difficulties. Indeed,

we cannot exclude that their performance may have been degraded by these symptoms.

These findings highlight the importance of a visuospatial functions comprehensive assessment, involving both the dorsal and ventral visual processing streams, as both pathways can be impaired in PSP patients.

We also found that cognitive flexibility, inhibition, verbal recall and working memory abilities were impaired in PSP compared to MSA and PD patients. These results corroborate previous findings suggesting that different aspects of executive functions (such as complex problem solving, planning, shifting, behavioral sets maintaining, verbal fluency, and working memory) are altered in PSP (Gerstenecker et al. 2013; Lee et al. 2012).

Specifically, our study shows that at baseline PSP-RS patients were significantly slower and presented poorer inhibition abilities, recalled fewer words and had difficulties in reorganizing number of digits (as assessed by Stroop test, verbal fluencies and DSS task, respectively). Evidence from functional imaging suggests the involvement of mainly frontal areas and striatal regions in Stroop test, DSS and verbal fluencies task performance (Heyder et al. 2004; Shedlack et al. 2009) and are in line with the neuropathological changes in PSP, which tend to be most pronounced in subcortical regions (i.e., subthalamic nucleus, substantia nigra, superior colliculi and internal pallidum) and frontal lobes (Hauw et al. 1994). Overall, these results underline the importance of frontal–striatal-based tests and particularly of verbal fluency assessment as screening instruments for PSP patients vs. PD and MSA.

Verbal fluency is a quick and easy-to-administer test and most importantly for our purpose, it requires minimal motor function making it only marginally affected by motor deficits and dysarthria (Rittman et al. 2013). Cross-sectionally, our results of PSP-RS show deficits in the semantic but even more in the phonemic fluency task, whose performance at both time points (about 19 words in 3 min) confirms this last subtest as a distinctive and psychometrically reliable disease-specific feature, suggesting the use of seven words per minute cut-off (Fiorenzato et al. 2016; Rittman et al. 2013).

Moreover, we observed that semantic fluency performance, showed also high sensitivity in detecting cognitive worsening at follow-up despite preserved naming abilities. This is also in line with evidence of higher level language deficits (namely dynamic aphasia) in PSP which goes behind dysarthric speech. Overall, it seems that PSP-RS patients show impairment in tasks which requires active initiation (letter and category completion) despite preserved abilities in naming, comprehension and repetition (Madden et al. 2019; Robinson et al. 2015).

Although previous functional MRI studies demonstrated a key role of both frontal and temporal areas in the execution of semantic verbal fluency tasks, evidence suggests this task has a stronger association with language rather than the executive domain (Whiteside et al. 2016).

Semantic recall alterations have been reported to be sensitive in differentiating performance across cognitive states and in predicting cognitive decline and dementia also in PD patients (Biundo et al. 2014; Kehagia et al. 2010; Williams-Gray et al. 2007). Within the context of more rapid progression of cognitive abilities in PSP (Soliveri et al. 2000), this task may detect changes in this pathology earlier than in PD. However, additional longitudinal studies are warranted to clarify whether semantic fluency alterations may be a biomarker of cognitive decline in PSP-RS.

Our results indicate that MMSE and MoCA scores are both significantly altered in each cohort, but PSP-RS patients showed the lowest scores as well as greater MoCA progression than PD.

Finally, we observed a difference in cognitive states distribution between PSP, PD and MSA. Specifically, PSP and MSA had similar disease duration, but the percentage of patients with dementia was higher in PSP compared to MSA (33% vs. no patients with dementia). PSP and MSA patients with MCI at baseline had all multidomain deficits, but only patients with PSP-MCI converted to dementia.

Although disease duration was longer in PD than in PSP, and at baseline both groups showed similar proportion of MCI, the percentage of patients who converted to dementia was lower in PD (7% in PD vs. 16% in PSP). Overall, these findings suggest a different pattern of cognitive progression, wherein PSP has the most severe and rapid cognitive decline.

Of note, we did not find MSA patients with dementia—while in a previous study, we had reported a prevalence of dementia between 8 and 11% (Auzou et al. 2015). According to published criteria (Dubois et al. 2007), dementia can be diagnosed if cognitive deficits are severe enough to impact daily functioning. However, in atypical parkinsonisms, this is challenging as functional autonomy is usually impaired due to motor dysfunctions and isolating the cognitive component of impaired functional tasks can be difficult. For this reason, we used for the first time in these populations, the PD-CFRS scale to minimize the influence of motor component in assessing the functional autonomy due to cognitive impairments (Kulisevsky et al. 2013). In this regard, differences in dementia prevalence may be due to different cognitive tools adopted.

Overall, the different characteristics and severity of cognitive alterations in PSP, MSA and PD may also be related to the discrete neuroanatomical process of these pathologies with the involvement of different brain regions.

MSA is characterized by degeneration involving primarily subcortical structures, and cortical pathology is not considered a predominant feature (Papp and Lantos 1994). A recent neuropathological study did not identify neuroanatomical regions associated with cognitive

impairment in MSA (Koga et al. 2016). This is aligned with our previously published volumetric study findings, showing in MSA only an association between frontal focal atrophy and cognitive deficits, and suggesting a marginal contribution of cortical pathology to deficits in cognition (Fiorenzato et al. 2017). By contrast, PSP tau pathology extends from the frontal cortex to the dentate nucleus of the cerebellum, and numerous studies report an association between cortical tau burden and cognitive/behavioral severity (Cordato et al. 2002).

Finally, our findings confirm that apathy and depression are more severe and common in PSP than PD (Gerstenecker 2017). Particularly, apathy seems to be a distinctive feature of PSP-RS, and this can be possibly associated with the distribution of pathology involving frontal regions (Cordato et al. 2002). MSA patients showed depression and reduced quality of life, which were worse than in the other groups; indeed, as previously reported, neuropsychiatric symptoms in MSA strongly correlate with autonomic and motor dysfunctions (Lee et al. 2013).

Our study has important caveats. First, we lack pathological confirmation of clinical diagnoses. However, we applied the most recent clinical consensus criteria (Gilman et al. 2008; Höglinger et al. 2017) and patients were followed up prospectively. Second, we focused only on PSP-RS phenotype and our findings may not apply to other PSP clinical variants. Third, PD patients' disease duration did not match PSP and MSA, but given the different disease course, a match for severity and progression would have been impossible. Therefore, we chose to consider primarily PD patients with similar sex, age and education.

To conclude, we have shown that semantic fluency, DSS and Benton's tests are sensitive tasks to monitor cognitive progression in PSP and may be considered as possible biomarkers of cognitive decline in PSP-RS. This is relevant in light of the ongoing disease clinical trials targeting disease modification.

We have also shown that a detailed cognitive assessment is useful in conjunction with other clinical evaluations—disease progression, response to medication, motor and clinical features—to differentiate PSP from the other parkinsonisms and to support clinical diagnosis.

Taken together, our findings show that cognition in PSP-RS patients is more impaired than MSA. Compared to PD, PSP-RS involves similar cognitive domains but with greater severity and faster decline which can be detected by specific cognitive tests. Additional studies are needed to define the patterns of cognitive and clinical deterioration in other PSP subtypes.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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Informed consent Written informed consent was obtained from all participants.

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