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ORIGINAL COMMUNICATION

Cognitive and behavioral profile of progressive supranuclear palsy and its phenotypes

Andrea Horta-Barba[1,2,3,4,6] · Javier Pagonabarraga[1,2,3,4] · Saül Martínez-Horta[1,2,3,4] · Laura Busteed[1] · Berta Pascual-Sedano[1,2,3,4,6] · Ignacio Illán-Gala[3,4,5] · Juan Marin-Lahoz[1,2,3] · Ignacio Aracil-Bolaños[1,2,3,4] · Jesús Pérez-Pérez[1,2,3,4] · Frederic Sampedro[1,3,4] · Helena Bejr-Kasem[1,2,3,4,6] · Jaime Kulisevsky[1,2,3,4,6]

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Abstract

Background Although several progressive supranuclear palsy (PSP) phenotypes have recently been described, studies identifying cognitive and neuropsychiatric differences between them are lacking.

Methods An extensive battery of cognitive and behavioural assessments was administered to 63 PSP patients, 25 PD patients with similar sociodemographic characteristics, and 25 healthy controls. We analysed differences in phenomenology, frequency and severity of cognitive and neuropsychiatric symptoms between PSP, PD and HC, and between PSP subtypes.

Results Regarding phenotypes, 64.6% met criteria for Richardson's syndrome (PSP-RS), 10.7% PSP with predominant Parkinsonism (PSP-P), 10.7% with PSP progressive gait freezing (PSP-PGF), and 10.7% PSP with predominant speech/language disorder (PSP-SL). Impairment was more severe in the PSP group than in the PD and HC groups regarding motor scores, cognitive testing and neuropsychiatric scales. Cognitive testing did not clearly differentiate between PSP phenotypes, but PSP-RS and PSP-SL appeared to have more cognitive impairment than PSP-PGF and PSP-P, mainly due to an increased impairment in frontal executive domains. Regarding neuropsychiatric disturbances, no specific behavior was more common in any of the PSP subtypes.

Conclusion Motor deficits delineate the phenotypes included in currently accepted MDS-PSP criteria. Cognition and behavioural disturbances are common in PSP and allow us to distinguish this disorder from other neurological diseases, but they do not differentiate between PSP phenotypes.

Keywords Progressive supranuclear palsy · Motor features · Cognition · Behavior · PSP phenotypes

✉ Javier Pagonabarraga
jpagonabarraga@santpau.cat

✉ Jaime Kulisevsky
jkulisevsky@santpau.cat

1 Movement Disorders Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Mas Casanovas, 90-08041 Barcelona, Spain

2 Universitat Autònoma de Barcelona (U.A.B.), Barcelona, Spain

3 Institut d'Investigacions Biomèdiques- Sant Pau (IIB-Sant Pau), Barcelona, Spain

4 Centro de Investigación en Red-Enfermedades Neurodegenerativas (CIBERNED), Barcelona, Spain

5 Memory Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

6 Faculty of Health Sciences, Universitat Oberta de Catalunya (UOC), Barcelona, Spain

Introduction

Progressive supranuclear palsy (PSP) is a rare, adult-onset and rapidly progressive neurodegenerative disease, linked to tau-protein abnormalities, predominantly involving isoforms with four microtubule-binding repeats [1–3]. As the disease progresses, patients experience a triad of motor, cognitive and behavioural disturbances [4].

PSP is characterized by clinical heterogeneity and around 70% of patients receive an incorrect initial diagnosis due to an extensive clinical overlap with other neurological diseases [5]. The most common misdiagnoses of PSP are Parkinson's disease (PD), corticobasal degeneration (CBD), multiple system atrophy (MSA), Alzheimer's disease and frontotemporal dementia [6, 7]. Moreover, a variety of clinical phenotypes of PSP have been identified, differing in their initial clinical presentation, clinical course and disease

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duration [8]. The most common PSP phenotype is Richardson's syndrome (PSP-RS). Other PSP phenotypes are predominant Parkinsonism (PSP-P), progressive gait freezing (PGF), predominant frontal presentation (PSP-F), corticobasal syndrome (PSP-CBS) and predominant speech/language disorder (PSP-SL) [9].

Cognitive impairment and dementia in PSP have classically been considered a prototype of "subcortical dementia" characterized by deficits in tests of executive function and attention, and cognitive slowing [10, 11]. More recently, alterations in memory, visuospatial abilities, language and social cognition have been described, suggesting that cortical and subcortical damage and related cognitive disturbances are also part of the cognitive phenotype of PSP [12, 13]. Cognitive impairment is integral to PSP and approximately 70% of patients will develop dementia along the course of the disease [12, 14–17]. Accordingly, the new criteria of the Movement Disorders Society for clinical diagnosis of PSP (MDS-PSP) include cognitive dysfunction as a core feature of the disease [18].

Neurobehavioral disturbances also arise from the early stages of the disease. They appear in strong association with cognitive deterioration and have a dramatic impact on quality of life and daily functioning [19, 20]. Apathy, social isolation, impulsivity and environmental dependency symptoms gradually increase in severity and are perceived by close relatives and caregivers as major debilitating complications in PSP [19, 20].

To date, most studies on cognitive impairment and behavioral disturbances in PSP have focused on comparing PSP with other parkinsonian disorders (PD, CBD, MSA) and healthy controls (HC). However, few studies have examined the differences between PSP phenotypes. Picillo et al. aimed to characterize cognitive and behavioral disturbances in the various PSP phenotypes using the MoCA and a comprehensive neuropsychological battery but they failed to find consistent differences between phenotypes [22]. In the present study, we aimed to further endorse whether using the FAB and a different neuropsychological battery in a less advanced PSP sample would reveal differences across phenotypes.

The goal of this work was to characterize the cognitive and neuropsychiatric profiles of early PSP patients. We further explored whether the application of extensive neuropsychological and behavioral batteries is able to accurately classify the different PSP phenotypes.

Methods

Participants

Between January 2016 and February 2020, 113 subjects were prospectively recruited from a sample of outpatients regularly attending the Movement Disorders Clinic at Hospital de la Santa Creu i Sant Pau, Barcelona. Sixty-three participants fulfilled the new MDS-PSP clinical criteria and had less than 5 years of disease duration [18]. Using the MDS-PSP diagnostic criteria, we recorded the PSP phenotype that best described the most predominant clinical syndrome [23]. Twenty-five patients meeting criteria for PD and 25 HC patients who were comparable in terms of age, gender, educational level and disease duration were included in the study.

Each patient was interviewed regarding disease onset, years of education and current medication. We used the Progressive Supranuclear Palsy Rating Scale (PSPRS), designed as a quantitative measure of disease severity and disability, as a global assessment of daily activities and behavioural symptoms, ocular motor deficits, and motor impairment causing bulbar symptoms, limb motor deficits, and gait and midline deficits [24].

Exclusion criteria were brain abnormalities in imaging studies, a history of major psychiatric disorders, inability to perform cognitive assessments, cerebrovascular disease, and any brain surgery, including deep brain stimulation surgery.

All participants gave written informed consent to participate in the study. All procedures were performed in accordance with the standards of the local ethics committee (CEIC) at Hospital de la Santa Creu i Sant Pau Barcelona, and in compliance with the 1964 Declaration of Helsinki and its later amendments.

Neuropsychological assessment and group classification

We used the Frontal Assessment Battery (FAB), [25] a brief and recommended cognitive assessment scale with known sensitivity to the frontal cognitive deficits occurring in PSP and PD. In addition, a comprehensive neuropsychological battery exploring five cognitive domains (attention, language, memory, visuospatial skills, and executive functions) and social cognition was also administered to all patients and HC. Attention and working memory were assessed using the forward and backward digit span task and part A of the Trail Making Test. Executive functions were evaluated with phonetic and semantic verbal fluency and the Trail Making Test part B, immediate and delayed verbal memory with the Free and Cued Selective Reminding Test (FCSRT), visual immediate and delayed memory with the Rey-Osterrieth complex figure test, confrontation naming with the Boston Naming test (BNT-60), visuospatial and visuoperceptual abilities with the Visual Object and Space Perception Battery number location and position discrimination subtests, and social cognition with the Benton Facial recognition test. Raw scores were transformed to age and education-corrected

standardized scores using the normative data available for all these tests.

Behaviour was comprehensively explored using the Neuropsychiatry Inventory (NPI), the Frontal Behaviour Inventory (FBI) and the caregiver-administered NPI (CGA-NPI). To more specifically focus on symptoms of apathy and depression, we also administered the informant-based version of the Lille Apathy Rating Scale (LARS-i), the Starkstein Apathy Scale (SAS) and the Geriatric Depression Scale (GDS).

The NPI is a semi-structured instrument which examines ten sub-domains of behavioural functioning, rating them according to frequency and severity. The FBI is a 24-item inventory designed to assess behaviour and personality changes via caregiver report. The LARS-i scale was developed to rate apathy via a caregiver-based structured interview and includes 33 items, divided into 9 domains. The SAS is a 14-item screening test for measuring the presence and severity of apathetic symptoms. The GDS is a 30-item self-report assessment used to identify depression in the elderly. Each neuropsychiatric symptom was considered clinically relevant when the score was over previously validated cut-off scores. Lack of awareness about neurobehavioral symptoms was calculated subtracting CGA-NPI total score from NPI patient total score.

Statistical analysis

Sociodemographic and clinical variables are expressed as means ± standard deviations for continuous variables and as percentages for categorical variables. Differences between groups and between PSP subtypes were analysed with independent two-tailed *t* tests and analyses of variance (ANOVA) for continuous variables, Mann–Whitney test for ordinal data and χ^2 test for categorical variables. ANCOVA analyses including age as a co-variate were performed in the comparisons between PSP subtypes. Significance level was set at $p < 0.05$. Data analysis was performed using the SPSS v21.0 statistical software package.

Results

Sample

Regarding the 63 PSP patients, mean age was 73.4 ± 8 years and disease duration was of 3.5 ± 1.5 years. For the 25 PD patients, mean age was 69.5 ± 8 years and disease duration was of 3.8 ± 1.5 years. Mean age of healthy controls was 65.6 ± 7 years. PSP patients were significantly older than HC ($p < 0.01$), but there were no differences in educational level ($p = 0.13$) or gender ($p = 0.52$) (Table 1).

Regarding PSP subtypes, 64.6% met criteria for PSP-RS ($n = 42$), 10.7% PSP-P ($n = 7$), 10.7% PSP-PGF ($n = 7$), and 10.7% met criteria for PSP-SL ($n = 7$). No major significant differences in age, education or disease duration were found between PSP subtypes. The only difference between phenotypes was age. PSP-PGF patients were significantly older than PSP-P and PSP-SL patients ($p = 0.03$) (Table 2).

Disease severity and motor dysfunction between PSP phenotypes

The PSPRS total score was significantly higher in the PSP group than in PD patients and HC groups (36.9 ± 14 vs. 13.2 ± 4 vs. 1.1 ± 1; $F = 56.3$, $p < 0.001$).

In the comparison between PSP subtypes, ANOVA analysis showed a significant difference in the PSPRS total score ($F = 6.8$, $p = 0.001$). More specifically, the total PSPRS was higher in the PSP-RS group than in the PSP-P (0.07), PSP-PGF (0.04) and PSP-SL (0.004) groups (Table 2). Post hoc analysis of the different PSPRS subscores did not reveal differences in PSPRS history or mentation scores, but showed significant differences in bulbar, ocular motor, limb motor, and gait and midline items. These differences were mainly driven by more severe impairment in the PSP-RS group in ocular motor and limb motor dysfunction. Gait and midline impairment did not differ between PSP-RS, PSP-P and PSP-PGF subtypes, but was significantly higher in PSP-RS than in PSP-SL (Table 2).

Table 1 Clinic and sociodemographic characteristics of all sample

	PSP ($n = 63$)	PD ($n = 25$)	Control ($n = 25$)	*P**	Two sample comparison (Tukey's *p*)
Age	73.4 ± 7.9	69.5 ± 8.1	65.6 ± 7.2	**0.001**	0.128[a]/**0.001**[b]/0.266[c]
Gender (f/m)	37/28	5/15	13/7	$X^2 = 0.020$	$X^2 = 0.013$[a]/0.521[b]/0.011[c]
Education	10.7 ± 3.8	12.1 ± 3.2	12.5 ± 3.9	0.092	0.304[a] /0.130[b]/0.923[c]
Disease duration	3.5 ± 1.5	3.8 ± 1.5	–	0.536	–
PSPRS	36.9 ± 14.1	13.2 ± 3.8	1.1 ± 0.8	**< 0.001**	< 0.001[a]/ < 0.001[b]/0.031[c]

PSPRS Progressive Supranuclear Palsy Rating Scale

[a]PSP vs. PD;[b]PSP vs. Controls; [c]PD vs. Controls

**P* values were determined with ANOVA between PSP phenotypes

Table 2 Clinical and sociodemographic characteristics of PSP phenotypes

	PSP-RS ($n=42$)	PSP-P ($n=7$)	PSP-PGF ($n=7$)	PSP-SL ($n=7$)	P*	Two sample comparison (Tukey's p)
Age, *y*	73.7 ± 7.6	69.3 ± 5.6	81.0 ± 6.4	69.4 ± 8.2	**0.017**	0.53[a]/0.09[b]/0.49[c]/**0.03**[d]/1.00[e]/**0.03**[f]
Gender (f/m)	26/17	3/4	3/4	4/3	$X^2=0.72$	$X^2=0.38$[a]/0.38[b]/0.86[c]/1.00[d]/0.59[e]/0.59[f]
Education, *y*	10.4 ± 3.6	11.7 ± 3.9	9.4 ± 3.2	12.6 ± 5.4	0.39	0.88[a]/0.91[b]/0.52[c]/0.72[d]/0.97[e]/0.42[f]
Disease duration, *y*	3.5 ± 1.8	4.5 ± 1.7	3.5 ± 1.2	2.9 ± 1.5	0.37	0.51[a]/1.00[b]/0.80[c]/0.75[d]/0.31[e]/0.87[f]
PSPRS						
Total score	42.1 ± 11.7	29.4 ± 11.2	28.5 ± 12.4	23.8 ± 17.1	**0.001**	*0.07*[a]/**0.04**[b]/**0.004**[c]/0.99[d]/0.83[e]/0.89[f]
History	8.7 ± 3.3	6.1 ± 2.9	6.1 ± 3.7	5.1 ± 3.7	**0.02**	0.26[a]/0.26[b]/*0.06*[c]/1.00[d]/0.94[e]/0.94 [f]
Mentation	6.8 ± 3.7	3.1 ± 2.6	4.3 ± 2.4	4.6 ± 3.9	**0.03**	*0.06*[a]/0.29[b]/0.39[c]/0.92[d]/0.87[e]/0.99[f]
Bulbar	3.1 ± 1.5	3.0 ± 1.3	1.6 ± 0.9	1.7 ± 1.8	**0.02**	0.99[a]/*0.07*[b]/0.11[c]/0.27[d]/0.36[e]/0.99[f]
Ocular motor	6.9 ± 3.6	2.9 ± 1.9	2.6 ± 4.2	3.7 ± 4.1	**0.003**	**0.04**[a]/**0.02**[b]/0.14[c]/0.99[d]/0.97[e]/0.93[f]
Limb motor	5.8 ± 1.8	4.6 ± 1.1	4.3 ± 1.6	3.4 ± 1.6	**0.003**	0.29[a]/0.13[b]/**0.006**[c]/0.98[d]/0.59[e]/0.78[f]
Gait and midline	10.8 ± 3.9	9.7 ± 5.1	9.7 ± 3.0	5.3 ± 4.8	**0.01**	0.91[a]/0.91[b]/**0.01**[c]/1.00[d]/0.19[e]/0.19[f]

PSPRS Progressive Supranuclear Palsy Rating Scale

[a]PSP-RS vs. PSP-P; [b]PSP-RS vs. PSP-PGF; [c]PSP-RS vs. PSP-SL, [d]PSP-P vs. PSP-PGF; [e]PSP-P vs. PSP-SL; [f]PSP-PGF vs. PSP-SL

*P values were determined with ANOVA between PSP phenotypes

Cognitive and behavioral evaluation between PSP, PD and controls

PSP patients showed significantly higher impairment than PD and HC groups in the Frontal Assessment Battery ($p<0.001$) and in all the cognitive domains explored ($p\leq0.01$). Patients with FAB total score < 14, which is accepted as a cut-off score indicating impact on daily function [26], was seen in a significantly higher percentage of PSP patients (79.3%) than in PD patients (5%) and HC (0%) ($p<0.001$).

Similarly, all neuropsychiatric disturbances explored (FBI, NPI, LARS-i, SAS, GDS) were significantly more severe in the PSP group than in PD and HC.

The neuropsychiatric disturbances that most clearly differentiated the PSP group were the presence and severity of depression, apathy, irritability/lability, and eating disturbances. Apathy was present in more than 65% of the PSP sample. Lack of awareness was significantly more present in PSP than in PD ($p=0.001$). Supplementary Tables 1, 2.

Cognitive and behavioral evaluation between PSP phenotypes

Regarding the cognitive evaluation between PSP phenotypes, few tasks differed significantly between groups. Scores on phonetic and semantic verbal fluency ($p=0.02$), and in FCSRT total free recall ($p=0.004$) and delayed free recall ($p=0.002$) were more impaired in the PSP-RS and PSP-PGF subtypes, respectively. These differences remained significant when age was included as a co-variate in the comparisons. Global cognitive function was slightly more impaired in PSP-RS than in PSP-P ($p=0.07$), but no differences were observed between the other subtypes (Table 3). No significant differences were found between phenotypes in the other cognitive tasks.

Interestingly, the PSP-SL patients in our series did not have impaired phonemic verbal fluency or naming, however they all had impaired semantic verbal fluency. All PSP-SL patients in this study had predominant apraxia of speech with mild associated symptoms of agrammatic PNFA. All PSP-SL patients included met MDS-PSP criteria with predominant apraxia of speech with associated axial rigidity, bilateral rigid-akinetic syndrome and slow vertical saccades with no overt supranuclear gaze palsy.

Although we assessed neuropsychiatric disturbances comprehensively with several tests adapted to PSP patients and caregivers (NPI-P, NPI-C, FBI, LAR-I, SAS, GDS), we did not find any significant differences between PSP subtypes in our sample. Analyzing the percentage of patients impaired in each test as based on validated cut-off scores, we did not find any specific behavioral or neuropsychiatric complication that was more frequent in any specific PSP predominant phenotype (Table 4).

Discussion

In this study, we provide a systematic and comparative analysis of motor, cognitive and behavioural performance in PSP phenotypes defined by currently accepted MDS-PSP diagnostic criteria [18, 23].

In the present sample, we found few differences between PSP phenotypes in terms of cognition and behavioural disturbances, and the differentiation between clinical predominance PSP types in this series was based mostly on the

Table 3 Cognitive performance between PSP phenotypes

	PSP-RS ($n=42$)	PSP-P ($n=7$)	PSP-PGF ($n=7$)	PSP-SL ($n=7$)	P*	Two sample comparison (Tukey's p) X^2(%)
FAB	9.9 ± 3	13.7 ± 3	10.1 ± 10	12.7 ± 3	**0.04**	**0.07**[a]/0.99[b]/0.21[c]/0.25[d]/0.95[e]/0.48[f]
< 14, %	86.5%	50%	85.7%	57.1		0.09
Digit span forward	4.6 ± 1	5.2 ± 1	4.6 ± 1	4.7 ± 1	0.707	0.66[a]/1.00[b]/0.99[c]/0.76[d]/0.88[e]/0.99[f]
≤ 1.5 SD, %	11.1%	0%	14.3%	28.6%		0.459
Digit span backwards	2.7 ± 1	3.5 ± 2	3.3 ± 1	3.1 ± 1	0.386	0.48[a]/0.68[b]/0.84[c]/0.98[d]/0.95[e]/0.99[f]
≤ 1.5 SD, %	25.0%	33.3%	0%	14.3%		0.407
TMTA	151.1 ± 72	82.0 ± 28	159.8 ± 116	112.3 ± 62	0.198	0.25[a]/0.99[b]/0.62[c]/0.32[d]/0.90[e]/0.66[f]
≤ 1.5 SD, %	79.2%	20%	50%	71.4%		0.060
TMTB	284.1 ± 226	276.7 ± 217	170.7 ± 59	210.2 ± 67	0.725	1.00[a]/0.73[b]/0.90[c]/0.86[d]/0.96[e]/0.90[f]
≤ 1.5 SD, %	70.0%	40%	33.3%	80%		0.231
Phonetic verbal fluency	5.3 ± 3	10.0 ± 5	7.3 ± 2	6.2 ± 3	**0.02**	**0.01**[a]/0.53[b]/0.91[c]/0.47[d]/0.20[e]/0.95[f]
≤ 1.5 SD, %	73.5%	0%	28.6%	57.1%		**0.003**
Semantic verbal fluency	8.9 ± 3	13.3 ± 2	9.0 ± 3	9.1 ± 3	**0.02**	**0.008**[a]/1.00[b]/0.99[c]/0.06[d]/0.07[e]/1.00[f]
≤ 1.5 SD, %	76.5%	33.3%	71.4%	100%		**0.051**
ROCF copy time	276.6 ± 125	246.4 ± 106	223.4 ± 212	180.0 ± 93	0.462	0.96[a]/0.84[b]/0.44[c]/0.99[d]/0.85[e]/0.95[f]
≤ 1.5 SD, %	15.4%	20%	20%	0%		0.777
ROCF copy score	22.3 ± 9	30.4 ± 6	26.0 ± 12	32.2 ± 5	0.089	0.29[a]/0.81[b]/0.14[c]/0.85[d]/0.99[e]/0.68[f]
≤ 1.5 SD, %	40%	20%	33.3%	0%		0.081
ROCF delayed recall	8.9 ± 7	12.8 ± 7	10.7 ± 6	13.0 ± 6	0.567	0.71[a]/0.95[b]/0.68[c]/0.96[d]/1.00[e]/0.95[f]
≤ 1.5 SD, %	41.7%	0%	0%	20%		0.329
FCSRT trial 1 free recall	4.3 ± 2	6.4 ± 2	2.8 ± 2	5.2 ± 5	0.116	0.33[a]/0.56[b]/0.79[c]/0.10[d]/0.87[e]/0.31[f]
≤ 1.5 SD, %	12.9%	0%	16.7%	42.9%		0.183
FCSRT total free recall	13.6 ± 6	22.6 ± 6	8.7 ± 7	16.0 ± 7	**0.004**	**0.020**[a]/0.28[b]/0.79[c]/**0.003**[d]/0.27[e]/ 0.15[f]
≤ 1.5 SD, %	41.9%	0%	50%	28.6%		0.270
FCSRT total recall	34.1 ± 9	42.6 ± 6	28.8 ± 12	36.6 ± 14	0.149	0.29[a]/0.64[b]/0.92[c]/0.11[d]/0.73[e]/0.51[f]
≤ 1.5 SD, %	16.1%	0%	50%	28.6%		0.161
FCSRT delayed free recall	5.0 ± 2	9.6 ± 3	3.5 ± 3	6.9 ± 3	**0.002**	**0.006**[a]/0.64[b]/0.37[c]/**0.004**[d]/0.34[e]/0.15[f]
≤ 1.5 SD, %	32.3%	0%	33.3%	0%		0.161
FCSRT delayed total recall	12.4 ± 3	14.8 ± 1	10.3 ± 5	12.6 ± 5	0.178	0.41[a]/0.50[b]/0.99[c]/0.12[d]/0.65[e]/0.60[f]
≤ 1.5 SD, %	9.7%	0%	33.3%	28.6%		0.229
Boston	46.2 ± 6	51.0 ± 9	45.4 ± 11	50.1 ± 8	0.334	0.48[a]/0.99[b]/0.59[c]/0.60[d]/0.99[e]/0.69[f]
≤ 1.5 SD, %	9.7%	16.7%	0%	0%		0.628
VOSP number location	6.1 ± 2	7.6 ± 2	5.1 ± 3	6.7 ± 3	0.320	0.50[a]/0.80[b]/0.93[c]/ 0.28[d]/0.90[e]/0.65[f]
≤ 1.5 SD, %	43.3%	16.7%	71.4%	42.9%		0.265
VOSP position discrimation	17.2 ± 4	19.2 ± 1	18.2 ± 2	18.1 ± 3	0.562	0.55[a]/0.91[b]/0.90[c]/0.95[d]/0.94[e]/1.00[f]
≤ 1.5 SD, %	29.6%	16.7%	0%	28.6%		0.453
Benton Facial Recognition	36.9 ± 10	42.4 ± 5	44.0 ± 4	42.0 ± 11	0.298	0.662[a]/0.39[b]/0.62[c]/0.99[d]/1.00[e]/0.98[f]

FAB, Frontal Assessment Battery; *TMT* Trail Making Test; *ROCF* Rey Osterrieth Complex Figure Test; *FCSRT* Free and Cued Selective Reminding Test; *VOSP* Visual Object and Spatial Perception

[a]PSP-RS vs. PSP-P; [b]PSP-RS vs. PSP-PGF; [c]PSP-RS vs. PSP-SL, [d]PSP-P vs. PSP-PGF; [e]PSP-P vs. PSP-SL; [f]PSP-PGF vs. PSP-SL

*P values were determined with analysis of covariance (ANCOVA) between PSP subtypes with age as covariates

Presence of cognitive impairment was determined according to percentile ≤ 1.5 SD for all cognitive tasks with normative data

ocular motor, limb motor, and gait and midline impairment explored by the PSPRS. Patients with PSP-RS differed from PSP-P and PSP-PGF on the ocular motor score, and patients with PSP-SL showed lower scores on limb motor and gait and midline scores, indicating that this subtype manifests with milder parkinsonian signs during the first years of the disease.

Concerning cognitive evaluation, and as supported by MDS-PSP criteria, cognitive impairment appeared in a high proportion of PSP patients in the first 5 years of the disorder. Executive dysfunction, memory, visuospatial processes, language, and social cognition were more affected in PSP than in PD and HC, with the most affected domains being executive function, visuospatial function, and attention. Memory difficulties were observed in PSP patients. However, in early-middle PSP stages, these difficulties could be attributed to poorer executive control influencing memory encoding [12, 27–29]. Previous studies examining all these domains with

Table 4 Behavioral profile between PSP phenotypes

	PSP-RS ($n=42$)	PSP-P ($n=7$)	PSP-PGF ($n=7$)	PSP-SL (n=7)	P*	Two sample comparison (Tukey's p) X^2(%)
NPI-P total score	11.9 ± 7	10.6 ± 15	11.8 ± 8	10.9 ± 10	0.974	0.98[a]/1.00[b]/0.98[c]/0.99[d]/1.00[e]/0.99[f]
Delusions	0.2 ± 1	0.5 ± 1	0.2 ± 0	0.0 ± 0	0.748	0.82[a]/0.99[b]/0.95[c]/0.88[d]/0.70[e]/0.99[f]
≥ 2, %	5.4%	14.3%	0%	0%		0.601
Hallucinations	0.4 ± 1	0.3 ± 1	2.2 ± 4	0.8 ± 2	0.081	0.99[a]/0.06[b]/0.88[c]/0.15[d]/0.90[e]/0.44[f]
≥ 2, %	13.5%	14.3%	33.3%	14.3%		0.669
Agitation/Agression	0.1 ± 0	0.3 ± 1	0.2 ± 0	0.0 ± 0	0.543	0.66[a]/0.98[b]/0.90[c]/0.94[d]/0.50[e]/0.86[f]
≥ 2, %	0%	14.3%	0%	0%		0.060
Depression	2.0 ± 2	1.6 ± 2	1.7 ± 2	2.0 ± 2	0.970	0.97[a]/0.99[b]/1.00[c]/1.00[d]/0.98[e]/0.99[f]
≥ 2, %	35.1%	28.6%	33.3%	57.1%		0.677
Anxiety	0.2 ± 0	0.9 ± 1	0.7 ± 2	0.0 ± 0	0.097	0.16[a]/0.48[b]/0.96[c]/0.97[d]/0.20[e]/0.45[f]
≥ 2, %	5.3%	14.3%	16.7%	0%		0.539
Euphoria	0.03 ± 0	0.0 ± 0	0.0 ± 0	0.0 ± 0	0.915	0.96[a]/0.96[b]/0.96[c]/1.00[d]/1.00[e]/1.00[f]
≥ 2, %	0%	0%	0%	0%		–
Apathy	5.0 ± 4	2.5 ± 3	2.5 ± 2	3.9 ± 5	0.245	0.37[a]/0.45[b]/0.88[c]/1.00[d]/0.90[e]/0.92[f]
≥ 2, %	75.7%	57.1%	66.7%	57.1%		0.636
Deshinibition	0.2 ± 1	0.7 ± 1	0.7 ± 2	0.0 ± 0	0.332	0.57[a]/0.69[b]/0.90[c]/1.00[d]/0.44[e]/0.53[f]
≥ 2, %	10.8%	14.3%	16.7%	0%		0.760
Irritability/Lability	1.7 ± 2	1.6 ± 2	0.6 ± 1	2.4 ± 2	0.472	0.99[a]/0.60[b]/0.85[c]/0.83[d]/0.88[e]/0.40[f]
≥ 2, %	40%	42.9%	28.6%	71.4%		0.384
Motor disturbances	0.0 ± 0	0.0 ± 0	0.0 ± 0	0.0 ± 0	–	
≥ 2, %	0%	0%	0%	0%		
Nightime Behaviors	1.9 ± 3	1.7 ± 3	1.5 ± 2	0.9 ± 1	0.799	0.99[a]/0.98[b]/0.75[c]/0.99[d]/0.92[e]/0.96[f]
≥ 2, %	37.8%	28.6%	33.3%	14.3%		0.670
Apetite/Eating	0.4 ± 1	0.6 ± 1	1.7 ± 2	0.9 ± 1	0.279	0.99[a]/0.22[b]/0.89[c]/0.52[d]/0.98[e]/0.74[f]
≥ 2, %	10.8%	14.3%	50%	14.3%		0.112
NPI-C total score	16.3 ± 9	10.3 ± 8	12.6 ± 7	13.1 ± 8	0.312	0.33[a]/0.71[b]/0.83[c]/0.95[d]/0.93[e]/0.99[f]
Delusions	0.2 ± 1	0.3 ± 1	0.1 ± 0	0.0 ± 0	0.875	0.99[a]/0.98[b]/0.87[c]/0.98[d] /0.89[e]/0.98[f]
≥ 2, %	9.1%	14.3%	0%	0%		0.653
Hallucinations	0.7 ± 2	0.2 ± 0	0.0 ± 0	0.0 ± 0	0.427	0.76[a]/0.61[b]/0.66[c]/0.99[d]/0.99[e]/1.00[f]
≥ 2, %	12.1%	0%	0%	0%		0.454
Agitation/Agression	0.2 ± 1	0.3 ± 1	0.0 ± 0	0.3 ± 0.5	0.823	0.99[a]/0.84[b]/0.99[c]/0.87[d]/0.99[e]/0.83[f]
≥ 2, %	6.1%	14.3%	0%	0%		0.623
Depression	2.3 ± 3	1.9 ± 3	1.8 ± 1	1.7 ± 1	0.887	0.96[a]/0.96[b]/0.92[c]/1.00[d]/0.99[e]/0.99[f]
≥ 2, %	51.5%	28.6%	57.1%	50%		0.696
Anxiety	0.5 ± 1	0.7 ± 1	0.3 ± 0	0.0 ± 0	0.675	0.98[a]/0.95[b]/0.73[c]/0.90[d]/0.70[e]/0.97[f]
≥ 2, %	12.1%	14.3%	0%	0%		0.609
Euphoria	0.0 ± 0	0.1 ± 0	0.0 ± 0	0.0 ± 0	0.083	0.05[a]/1.00[b]/1.00[c]/0.19[d]/0.22[e]/1.00[f]
≥ 2, %	0%	0%	0%	0%		
Apathy	5.5 ± 4	3.1 ± 3	3.9 ± 3	5.7 ± 4	0.465	0.52[a]/0.77[b]/1.00[c]/0.98[d]/0.68[e]/0.85[f]
≥ 2, %	75.8%	57.1%	71.4%	83.3%		0.714
Deshinibition	0.6 ± 1	0.1 ± 0	0.4 ± 1	0.5 ± 1	0.814	0.78[a]/0.97[b]/0.99[c]/0.97[d]/0.95[e]/1.00[f]
≥ 2, %	15.2%	0%	14.3%	16.7%		0.743
Irritability/Lability	2.4 ± 3	1.7 ± 2	1.6 ± 2	3.0 ± 1	0.628	0.88[a]/0.81[b]/0.94[c]/0.99[d]/0.75[e]/0.69[f]
≥ 2, %	45.5%	42.9%	42.9%	66.7%		0.787
Motor disturbances	0.2 ± 1	0.0 ± 0	0.0 ± 0	0.0 ± 0	0.855	0.93[a]/0.93[b]/0.94[c]/1.00[d]/1.00[e]/1.00[f]
≥ 2, %	0%	0%	0%	0%		0.892
Nightime Behaviors	2.0 ± 3	0.1 ± 0	1.3 ± 2	0.3 ± 0	0.259	0.35[a]/0.91[b]/0.50[c]/0.85[d]/0.99[e]/0.91[f]
≥ 2, %	36.4%	0%	28.6%	0%		0.095
Apetite/Eating	1.5 ± 2	1.7 ± 3	3.1 ± 4	1.7 ± 3	0.504	0.99[a]/0.42[b]/0.99[c]/0.72[d]/1.00[e]/0.72[f]
≥ 2, %	39.4%	28.6%	57.1%	33.3%		0.716

Table 4 (continued)

	PSP-RS ($n=42$)	PSP-P ($n=7$)	PSP-PGF ($n=7$)	PSP-SL (n = 7)	P*	Two sample comparison (Tukey's p) X^2(%)
Anosognosia NPI	−3.6 ± 7	−0.3 ± 9	−1.5 ± 10	−2.8 ± 6	0.618	0.58[a]/0.91[b]/0.99[c]/0.97[d]/0.87[e]/0.99[f]
FBI	23.3 ± 12	12.3 ± 7	17.4 ± 8	21.0 ± 13	0.138	0.08[a]/0.58[b]/0.96[c]/0.82[d]/0.46[e]/0.93[f]
FBI-negative	16.9 ± 8	8.9 ± 5	14.7 ± 7	16.0 ± 10	0.147	0.09[a]/0.91[b]/0.99[c]/0.54[d]/0.36[e]/0.99[f]
FBI-positive	6.4 ± 5	3.4 ± 3	2.7 ± 1	5.0 ± 4	0.510	0.39[a]/0.21[b]/0.87[c]/0.99[d]/0.91[e]/0.78[f]
LARS-i	0.6 ± 16	−16.4 ± 11	−2.86 ± 12	−6.4 ± 19	0.068	0.04[a]/0.94[b]/0.69[c]/0.37[d]/0.63[e]/0.97[f]
≥-16, %	71.1%	28.6%	57.1%	42.9%		0.126
SAS	19.6 ± 9	11.6 ± 4	18.0 ± 12	17.1 ± 8	0.189	0.13[a]/0.97[b]/0.90[c]/0.53[d]/0.64[e]/0.99[f]
≥14, %	70.3%	42.9%	71.4%	71.4%		0.541
GDS	8.4 ± 4	5.7 ± 4	7.9 ± 5	6.4 ± 5	0.332	0.37[a]/0.98[b]/0.63[c]/0.75[d]/0.98[e]/0.90
≥10, %	47.1%	28.6%	28.6%	28.6%		0.604

[a]PSP-RS vs. PSP-P; [b]PSP-RS vs. PSP-PGF; [c]PSP-RS vs. PSP-SL, [d]PSP-P vs. PSP-PGF; [e]PSP-P vs. PSP-SL; [f]PSP-PGF vs. PSP-SL

*P values were determined with analysis of covariance (ANCOVA) between PSP subtypes with age as covariates

Presence of behavior symptomatology was considered clinically relevant with the optimal cut-off determined for each scale

NPI Neuropsychiatric Inventory; *NPI-P* Neuropsychiatric Inventory from participant; *NPI-C* Neuropsychiatric Inventory from caregiver; Anosognosia NPI, *NPI-P* (−) NPI-C; *FBI* Frontal behavior Inventory; *LARS-i* Informant based Lille apathy rating scale; *SAS* Starkstein Apathy Scale; *GDS* Geriatric Depression Scale

the Repeatable Battery for the Assessment of Neuropsychological Status in a large sample of patients, showed PSP to produce clinically meaningful deficits in attention, executive function, language, and visuospatial/constructional abilities. Compared to patients with Alzheimer's disease, PSP patients showed even more severe dysfunction in attention and visuospatial abilities [30, 31]. And when compared with Parkinson's disease and multiple system atrophy, PSP showed the worst performance on global cognitive function, executive function, and visuospatial deficits [32].

In the present series, executive function was the most commonly affected domain, impacting approximately on three quarters of the sample. In line with other studies, we found that both phonological and semantic verbal fluencies are simple and rapid tests that can detect clinically relevant changes from the first years of the disease. However, in our sample, phonemic verbal fluency does not seem to be helpful in the early identification of PSP-P cases. Regarding the comparison between PSP phenotypes, executive dysfunction assessed by the FAB and differences in phonetic and semantic verbal fluencies showed the greater impairment in PSP-RS compared to PSP-P. Greater memory problems assessed by FCSRT free recall were also observed between PSP-RS and PSP-PGF and PSP-P, but we did not find any other differences between phenotypes when looking at specific domains. Thus, despite the extensive battery used, cognitive examination in this series is not accurate enough to distinguish between phenotypes or to characterize different cognitive profiles for each phenotype. This can be explained by the generalized cognitive dysfunction observed in all the PSP subtypes. Other studies aiming to explore the utility of the new MDS-PSP criteria have shown that although present criteria are very useful in differentiating PSP from other disorders, they may not be sufficiently specific to differentiate between the most common phenotypes (e.g.,: PSP-RS from PSP-P) [33]. Similarly, it has been previously shown that almost all PSP patients will develop some degree of psychopathology during the course of the disease, and that the most common symptoms are apathy, depression and irritability [19, 22, 34–36]. No previous studies have clearly delineated the neuropsychiatric profile of the different PSP subtype. In this series we have observed apathy as the most common behavioral symptom in all subtypes, and a high frequency of depression, irritability and eating disturbances in all PSP subtypes. The most frequent abnormal eating behavior observed in our patients had the distinctive features previously labelled as 'greed for food' [37]. PSP patients with eating disturbances were characterized by eating too fast, putting too much food into the mouth, and having irresistible impulses to grab food placed in front of them. In concordance with these results, the FBI showed higher scores in negative events such as indifference, inflexibility, inattention, lack of spontaneity, and personal negligence, and in positive events such as stereotypes, impulsivity, irritability and hyperorality. Discrepancies between patient and caregiver questionnaires were found in all PSP phenotypes, suggesting anosognosia is also a distinctive characteristic of PSP [38, 39].

The generalized cognitive and behavioural dysfunction observed in our patients between PSP phenotypes is in accordance with PET studies analysing the functionality of brain regions in PSP. Although neuropathological studies have observed significant differences in the degree of atrophy between the different PSP phenotypes [40], the

metabolic alterations captured by fluorodeoxyglucose PET have not observed differences in the pattern or severity of metabolism between PSP phenotypes. Only patients with PSP-PGF show more preserved cortical glucose metabolism, but following the same pattern of cortical and subcortical dysfunction [41].

The main limitation of the present study is the absence of a definite pathological diagnosis of PSP. Nevertheless, we based the diagnosis on validated clinico-pathological criteria. Our main contribution is confirmation that the cognitive and behavioural profiles in PSP phenotypes are highly homogeneous. Overall, our findings show that motor deficits delineate the phenotypes included in the currently accepted MDS-PSP criteria, while cognition and behavioural disturbances are very similar. The lack of differences in the phenomenology, frequency and severity of cognitive and neuropsychiatric symptoms between PSP phenotypes indicates that these disturbances are core symptoms associated with PSP pathology, helping us to distinguish PSP from other neurological diseases, but not distinguishing between PSP phenotypes.

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Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflicts of interest Nothing to report.

Ethical standard The study has been approved by the ethical committee of Sant Pau Hospital (Barcelona, Spain). Written informed consent was obtained from all participants and the study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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