

The pattern of verbal, visuospatial and procedural learning in Richardson variant of progressive supranuclear palsy in comparison to Parkinson's disease

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Summary

Aim. Progressive supranuclear palsy (PSP) is regarded either within spectrum of atypical parkinsonian syndromes or frontotemporal lobar degeneration. We compared the verbal, visuospatial and procedural learning profiles in patients with PSP and Parkinson's disease (PD). Furthermore, the relationship between executive factors (initiation and inhibition) and learning outcomes was analyzed.

Methods. Thirty-three patients with the clinical diagnosis of PSP-Richardson's syndrome (PSP-RS), 39 patients with PD and 29 age – and education – matched controls were administered Mini-Mental State Examination (MMSE), phonemic and semantic fluency tasks, Auditory Verbal Learning Test (AVLT), Visual Learning and Memory Test for Neuropsychological Assessment by Lamberti and Weidlich (Diagnosticum für Cerebralschädigung, DCS), Tower of Toronto (ToT) and two motor sequencing tasks. Patients with PSP-RS and PD were matched in terms of MMSE scores and mood.

Results. Performance on DCS was lower in PSP-RS than in PD. AVLT delayed recall was better in PSP-RS than PD. Motor sequencing task did not differentiate between patients. Scores on AVLT correlated positively with phonemic fluency scores in both PSP-RS and PD. ToT rule violation scores were negatively associated with DCS performance in PSP-RS and PD as well as with AVLT performance in PD.

Conclusions. Global memory performance is relatively similar in PSP-RS and PD. Executive factors (initiation and inhibition) are closely related to memory performance in PSP-RS

and PD. Visuospatial learning impairment in PSP-RS is possibly linked to impulsivity and failure to inhibit automatic responses.

Key words: executive functions, memory, progressive supranuclear palsy

Introduction

Since 1974 progressive supranuclear palsy (PSP) was regarded as a prototypic form of subcortical dementia [1–3]. Currently, several syndromes are differentiated within the cluster of PSP: originally described Richardson’s syndrome (PSP-RS), PSP-parkinsonism (PSP-P), pure akinesia with gait freezing (PSP-PAGF), variant with progressive apraxia of speech evolving into progressive non-fluent aphasia (PSP-PNFA) and mixed corticobasal syndrome with PSP clinical features and/or pathology (PSP-CBS) [4, 5]. These variants can be differentiated thanks to specific patterns of motor, cognitive, language and behavior impairment. Clinical heterogeneity of PSP patients is further supported by neuropathological evidence [6].

Gaze palsy (predominantly vertical and downwards), early postural instability and falls, axial rigidity, bilateral and symmetric bradykinesia are the most characteristic motor features of PSP-RS, along with the unresponsiveness of these symptoms to levodopa treatment [1]. Neuropsychological profile of PSP-RS is dominated by executive dysfunction [7], manifesting as impaired initiation, set-shifting and inhibition. Most prominent behavioral manifestations comprise apathy, depression and sleep disturbances as well as agitation, irritability, disinhibition and eating problems [8]. As the overlap of PSP and behavioral variant of frontotemporal dementia (bvFTD) is being increasingly recognized on the basis of neuropsychological [9], neuropsychiatric [8, 10] and also neuroradiological data [9], PSP-RS may be regarded within broad frontotemporal lobar degeneration spectrum [11].

As PSP was originally seen only as atypical Parkinsonian syndrome, this paper addresses the differences between PSP-RS and Parkinson’s disease (PD) in terms of memory function. Both PSP and PD are characterized by slowed acquisition of new material with impaired delayed spontaneous, but not cued, recall [12, 13]. Executive (verbal fluency tasks, sorting tasks, Frontal Assessment Battery) and visual attention tests (Trail Making Test A) have been demonstrated to best differentiate between PSP and PD [12].

In both PSP and PD, declarative (verbal and visuospatial) as well as procedural learning is affected [13, 14]. However, literature lacks a comprehensive comparison of memory profiles in PSP-RS and PD addressing verbal, visuospatial and procedural learning (with predominant cognitive and motor component). This paper aims to analyze if memory and learning profiles are divergent in these diseases. Additionally, the relationship between initiation and inhibition, as aspects of executive function,

to learning outcomes in PSP-RS and PD is also addressed. Differential relationship between executive factors and memory in PSP-RS and PD could potentially further support overlap between PSP and bvFTD.

Material

Thirty-three patients with the clinical diagnosis of PSP-RS according to Litvan et al. criteria [1] (23 with probable and 10 with possible PSP-RS), 39 patients with Parkinson's disease, in line with the United Kingdom Parkinson's Disease Brain Bank criteria [15] and 29 age-, sex – and education-matched healthy controls participated in the study (scoring ≥ 27 on Mini-Mental State Examination – MMSE) (see: Table 1). The patients underwent neurological, neuropsychological and neuroradiological assessments to exclude other pathologies (magnetic resonance imaging (MRI) or computed tomography, if MRI was contraindicated). PSP-RS and PD patients were matched in terms of global (non-disease specific) cognitive performance as measured by MMSE and mood (Beck Depression Inventory – BDI) (see: Table 1). Both patient groups had lower mood than controls. PSP-RS group was comprised of both outpatients and inpatients. All PD patients were tested as outpatients and tests were administered in the “on” phase. All the patients consented to the study participation and the study protocol was approved by local bioethics committee.

Methods

Neurological examination was conducted by a movement disorders specialist (JS), while neuropsychological assessment in patient groups was performed by a neuropsychologist (EJS or DW). Several patients were recruited into the study before Golbe PSP rating scale [16] and criteria for Parkinson's disease dementia by Emre et al. [17] were established, therefore they were not applied. Mini-Mental State Examination (MMSE) was used as a global screening cognitive measure and two verbal fluency tasks were used as screening for executive problems: phonemic (“K” words/60 sec.) and semantic fluency (animals/60 sec.) tasks [18–20]. Mood was assessed with Beck Depression Inventory (BDI) [18]. Verbal learning was tested with 15-word Auditory Verbal Learning Test (AVLT), including 5 immediate recall trials, immediate recognition trial and delayed recall. Visuospatial learning was assessed with modified Visual Learning and Memory Test for Neuropsychological Assessment by Lamberti and Weidlich (Diagnosticum für Cerebralschädigung – DCS) [18]. In order to be able to directly compare DCS results with AVLT, apart from 6 immediate recall trials, recognition task and delayed recall were also measured. Moreover, rotation of stimuli was not counted as error as we wanted to address stimuli retention (internal configuration) and not the retention of its spatial localization, both being clearly dissociable on the

neuronal level [19, 21]. For both tasks percentage of material recalled after delay was computed in the same way to facilitate inter-task comparisons (mean from two immediate recall trials with the highest results was divided by the result of delayed recall and multiplied by 100%).

Procedural learning was assessed by means of two tasks. Firstly, Tower of Toronto (ToT) was used to measure cognitive procedural learning [22]. In this tower task, described in detail by Saint-Cyr et al. [22] the participant attempts to solve a 7-move problem (practice trial using 3 blocks) and then 15-move problem (test trial using 4 blocks: black, red, yellow and white). There are two rules: (1) Only one disc may be moved at a time; (2) A darker disc can never be put on a top of a lighter one. The testing comprises 5 practice trials and then two sets of 5 test trials, with 90-minute interval in between test trials. Lower number of moves represents better performance. Apart from ToT procedural learning index (difference between average number of moves in the first and second test series), ToT planning index and ToT rule violation index (proportion of rule violations to correct moves) were also computed. In line with original instructions task was discontinued if the participant could not successfully perform practice trials. Moreover, test trials were discontinued at patient request due to fatigue and frustration with test failure.

Secondly, motor procedural learning was assessed by means of two three-step Luria motor sequencing tasks. In these tasks there were 3 steps: (1) demonstration of a target sequence by the examiner 5 times; (2) performance of a target sequence with the examiner, unscored, 5 times; (3) scored performance of a target sequence 5 times. One point was awarded for each correctly performed sequence. Motor sequencing score ranged from 0 to 5 for each sequence and 0–10 for a global score.

The neuropsychological testing was usually conducted during 2–3 sessions lasting 60–120 minutes, depending on the patient's fatigue. In patient groups ToT and DCS were administered on separate occasions as they were the most challenging tasks.

Statistical analysis

Statistical analysis was performed with the use of STATISTICA 12. Normality of distribution was tested with Shapiro-Wilk test. Normally distributed data were analyzed with one-way ANOVA, while non-normally distributed variables were analyzed with the use of H Kruskal-Wallis test, non-parametric equivalent of one-way ANOVA, with post-hoc comparisons with Dunn's test. The differences in distribution of qualitative data were tested with chi-square test. Correlation analysis was performed with Spearman's rank correlation coefficient. Statistical significance level was set at < 0.05 for all the analyses.

Table 1. Demographic and basic clinical data

	PSP-RS n = 33 mean \pm SD / median (range)	PD n = 39 mean \pm SD / median (range)	controls n = 29 mean \pm SD / median (range)	p value
Demographics				
age	67 \pm 9	68 \pm 8	71 \pm 11	0.757; s.i. †
education (years)	13 \pm 3	12 \pm 4	11 \pm 4	0.219; s.i. †
male:female	21:20	25:14	15:14	0.351; s.i. ‡
Clinical characteristics				
duration of disease	3 (1 \div 5)	10 (2 \div 20)	–	NA
MMSE	25 (19 \div 30)*	27 (12 \div 30) *	29 (27 \div 30)	< 0.001 §
BDI	16 (1 \div 48)*	17.5 (1 \div 44) *	8 (3 \div 32)	< 0.001 §
phonemic fluency – K	6 (2–21) *	8 (3 \div 21)*	13 (4 \div 25)	< 0.001 §
semantic fluency – animals/60 sec.	11 (4–27) *	16 (4 \div 36)	18 (9 \div 32)	0.001 §

Note: NA– not assessed; BDI – Beck Depression Inventory; MMSE – Mini-Mental State Examination; s.i. – statistically insignificant; † – the differences were analyzed with one-way ANOVA test; ‡ – the differences were analyzed with chi-square test; § – the differences were analyzed with H Kruskal-Wallis test with post-hoc comparisons; * significant difference from controls ($p < 0.05$)

Results

Verbal learning

Both PSP-RS and PD patients recalled fewer words than controls in most learning trials. However, only PD patients had more impaired delayed recall and presented with more intrusions throughout the test than controls, which was not observed to such extent in PSP-RS (see: Table 2).

Table 2. Verbal and visuospatial memory and learning results in patients with Richardson variant of progressive supranuclear palsy (PSP-RS), Parkinson's disease (PD) and controls

	PSP-RS n = 33 median (range)	PD n = 39 median (range)	controls n = 29 median (range)	p value
Verbal learning				
AVLT-I	5 (0 \div 8)	5 (1 \div 8)	5 (2 \div 10)	0.089; s.i.
AVLT-II	7 (1 \div 11)	6 (2 \div 11)	7 (4 \div 13)	0.048
AVLT-III	7 (1 \div 13)	7 (3 \div 13)	8 (5 \div 14)	0.006 ^{a,b}

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AVLT-IV	7(3 ÷ 13)	8 (1 ÷ 13)	11 (5 ÷ 15)	0.001 ^{a,b}
AVLT-V	9 (3 ÷ 14)	9(3 ÷ 14)	11 (7 ÷ 14)	< 0.001 ^{a,b}
AVLT I-V	34 (9 ÷ 58)	35 (13 ÷ 56)	43 (29 ÷ 62)	0.001 ^{a,b}
AVLT – recognition	10 (0 ÷ 15)	10 (-3 ÷ 15)	14 (8 ÷ 15)	< 0.001 ^{a,b}
AVLT – delayed recall	8 (0 ÷ 11)	7(0 ÷ 14)	10 (6 ÷ 14)	< 0.001 ^{a,b}
AVLT – % after delay	85.71 (0 ÷ 143)	80 (0 ÷ 127)	95 (76 ÷ 113)	0.013 ^b
AVLT – sum of intrusions	1 (0 ÷ 11)	6 (0 ÷ 33)	1 (0 ÷ 13)	< 0.001 ^{b,c}
Visuospatial learning				
DCS-I	1 (0 ÷ 5)	2 (0 ÷ 6)	3 (0 ÷ 7)	0.008 ^a
DCS-II	2 (0 ÷ 5)	3 (0 ÷ 8)	4 (2 ÷ 8)	0.001 ^a
DCS-III	3 (0 ÷ 8)	4 (0 ÷ 9)	5 (2 ÷ 8)	0.005 ^a
DCS-IV	3 (0 ÷ 7)	4 (0 ÷ 9)	5 (2 ÷ 9)	0.012 ^a
DCS-V	3 (0 ÷ 8)	5 (0 ÷ 9)	6 (1 ÷ 9)	0.005 ^a
DCS-VI	4 (0 ÷ 8)	5 (0 ÷ 9)	6 (2 ÷ 9)	0.008 ^a
DCS I-VI	16 (0 ÷ 41)	22 (0 ÷ 47)	30 (10 ÷ 50)	0.001 ^{a,b}
DCS – recognition	7 (0 ÷ 9)	7 (-1 ÷ 9)	9 (1 ÷ 9)	0.026
DCS – delayed recall	3.5 (0 ÷ 9)	5 (0 ÷ 9)	6 (1 ÷ 9)	0.011 ^a
DCS – % after delay	80 (0 ÷ 200)	73 (0 ÷ 150)	86 (30 ÷ 120)	0.270; s.i.

Note: the differences among 3 groups were tested with H Kruskal-Wallis test with post-hoc comparisons; ^a significant difference ($p < 0.05$) between PSP-RS and controls; ^b significant difference ($p < 0.05$) between PD and controls; ^c significant difference ($p < 0.05$) between PSP-RS and PD

Visuospatial learning

Visuospatial recall was impaired in PSP-RS relative to controls. Nonetheless, inter-group differences between PSP-RS and controls were not statistically significant in the recognition task and percentage of material recalled following delay. PD patients' performance equaled the one of healthy subjects, apart from summed DCS immediate recall score (summed score from series 1–6), being in PD lower than in controls. (see: Table 2).

Procedural learning

Tower of Toronto turned out to be a very challenging task, especially for PSP-RS patients, only half of whom were able to complete it (see: Table 3). Thus, the similar level of performance in PD and PSP-RS subgroups having completed the test needs to be seen in the context of high percentage of task discontinuation in PSP-RS. However,

qualitative characteristics of performance still do differentiate the groups. ToT-rule violations were significantly more common in PSP-RS. Overall, cognitive procedural learning was more impaired in PSP-RS than PD.

Motor sequencing was impaired in both PSP-RS and PD relative to controls. Although median scores in PSP-RS group are lower than in PD, the differences did not reach statistical significance.

Table 3. Executive function and procedural learning results in patients with Richardson syndrome of progressive supranuclear palsy (PSP-RS), Parkinson's disease (PD) and controls

	PSP-RS n = 33	PD n = 39	controls n = 29	p value
Percentage of participants who were able to complete the whole Tower of Toronto (ToT) task	58%	82%	97%	-
	median (range)	median (range)	median (range)	median (range)
ToT – practice series: mean	11.5 (5 ÷ 25)*	11.6 (7 ÷ 22)*	8.2 (7 ÷ 13)	0.001
ToT – series 1: mean	33.10 (17 ÷ 46)*	31.9 (21 ÷ 50)*	22.4 (16 ÷ 35)	< 0.001
ToT – series 2: mean	31.80(23 ÷ 46)*	30.6 (16 ÷ 49)*	21 (15 ÷ 32)	< 0.001
ToT – procedural learning index	1 (-12 ÷ 16)	0.90 (-19 ÷ 16)	1.3 (-5 ÷ 9)	0.737; s.i.
ToT – planning index	5 (0 ÷ 14)*	7(0 ÷ 14)*	11 (5 ÷ 19)	< 0.001
ToT – number of rule violations	22 (1 ÷ 170)*	11 (1 ÷ 110)	7 (0 ÷ 27)	0.013
Luria 3-step motor sequences (summed, max.10)	3 (0 ÷ 10)*	4.5 (0 ÷ 10)*	10 (6 ÷ 10)	< 0.001
Luria 3-step motor sequence – part 1 (max.5)	2 (0 ÷ 5)*	3.5 (0 ÷ 5)*	5 (4 ÷ 5)	< 0.001
Luria 3-step motor sequence – part 2 (max.5)	0 (0 ÷ 5)*	1.5 (0 ÷ 5)*	5 (1 ÷ 5)	< 0.001

Note: the differences among 3 groups were tested with H Kruskal-Wallis test with post-hoc comparisons; median values (range) are reported in the table; * significant difference from controls ($p < 0.05$)

Executive function and learning

In order to analyze the relationship between executive function and learning outcomes in PSP-RS and PD, phonemic fluency scores (as an indirect measure of initiation) and percentage of rule violations in ToT (as a measure of inhibition) were correlated to the following learning variables: AVLT (summed I-V, delayed recall, percentage after delay, sum of intrusions), DCS (summed I-VI, delayed recall, percentage after delay), Luria 3-step motor sequences (summed score). As only half

of PSP-RS patients completed ToT, learning outcomes from ToT were not included in this analysis.

As predicted, AVLT and DCS raw immediate and delayed recall scores, as well as Luria 3-step sequencing score were positively correlated with the phonemic fluency score, both in PSP-RS and PD (see: Table 4). In contrast, AVLT and DCS recall percentage scores were not associated with the phonemic fluency score. Rule violation index was negatively correlated with all DCS scores in PSP-RS group as well as with immediate and delayed recall scores in PD.

Table 4. Correlation analysis of learning outcomes with initiation and inhibition measures in Richardson variant of progressive supranuclear palsy (PSP-RS) and Parkinson's disease (PD)

	phonemic fluency – initiation		rule violation (percentage) – inhibition	
	PSP-RS	PD	PSP-RS	PD
Verbal learning				
AVLT– summed I–V	0.43*	0.39*	-0.30	-0.48**
AVLT – delayed recall	0.45**	0.40*	-0.02	-0.33
AVLT – recall percentage after delay	0.25	0.23	0.33	-0.11
AVLT – sum of intrusions	0.29	-0.12	-0.09	0.44*
Visuospatial learning				
DCS – summed I–VI	0.54**	0.71**	-0.50*	-0.81**
DCS – delayed recall	0.37*	0.71**	-0.63**	-0.64**
DCS – recall percentage after delay	-0.09	0.35*	-0.47*	-0.17
Motor procedural learning				
Luria 3-step motor sequencing	0.38*	0.51**	-0.12	-0.50**

* $p < 0.05$; ** $p < 0.01$

Discussion

Patients with PSP have earlier and more prominent neuropsychological deficits than individuals with PD [13]. Executive tasks have established discriminatory value in the differential diagnosis of PSP vs. PD [12, 13]. In this paper, we analyzed multi-domain learning performance in patients with PSP-RS and PD with comparable global cognitive status. Most of the previous studies comparing memory performance in PSP and PD analyzed either only logical memory performance [23, 24], only verbal learning [25], verbal learning and logical memory [26] or, if both verbal and visual memory were addressed, visuospatial and procedural learning were not assessed [27,

28]. Thus, this study is to our knowledge the first one to compare verbal, visuospatial and procedural learning in PSP-RS and PD. It shows qualitatively divergent verbal and visuospatial learning profiles in PSP-RS and PD.

Our results show that global verbal learning efficiency is similar in PSP-RS and PD, which is in accordance with previous reports [25, 26]. However, in our study PD patients demonstrated poorer verbal delayed recall (percentage of previously recalled information) than controls and greater tendency to contaminate test items with similar words (higher number of intrusions). This impaired delayed recall suggests more posterior memory profile in PD than PSP-RS, which corresponds to the current notion of posterior-cortical deficits as predictor of earlier conversion to Parkinson's disease with dementia (PD-D) [29]. As Emre et al.'s criteria of PD-D [17] were not applied in our study (significant part of the PD group was assessed before the year of its publication), our PD sample comprised both demented and non-demented PD patients.

To our knowledge, visuospatial learning data in PSP-RS, has not been previously reported. In our study, PSP-RS patients demonstrated greater difficulties in reproducing geometrical patterns with wooden sticks than controls. However, learnt material was well retained over time, which is in accordance with previous reports of delayed reproductions in drawing [27, 28].

Notably, in our study visuospatial and verbal learning performance may have been differentially biased by executive factors. Both verbal and visuospatial learning performance was associated with the initiation factor in PSP-RS and PD. However, in PSP-RS only visuospatial learning ability (and not verbal learning ability) was significantly related to inhibition factor. In PD inhibition factor was positively associated with intrusions in verbal learning. The latter may be explained by the fact that PD patients tended to produce more intrusions than individuals with PSP-RS. Unfortunately, our methodology does not permit to analyze the impact of visuospatial perception and praxis performance on visuospatial learning.

Our results show that cognitive and motor procedural learning are significantly impaired in both PSP-RS and PD. It seems that cognitive procedural learning is more impaired in PSP-RS, as shown by failure-related high rate of task discontinuation in PSP-RS. The most prominent finding is inhibition deficit, observed in PSP-RS patients, who frequently violated task rules. Impulsivity and disinhibition were previously reported in PSP-RS in both cognitive tasks [7, 30] and real-life situations [8, 10]. The presence of impulsivity in PSP-RS is in line with the overlap between PSP and bvFTD. It was recently shown that pattern of cerebral atrophy in PSP overlaps more with bvFTD [9] than with PD [31, 32].

The relationship between executive dysfunction and frontal pathology is well established in PSP. Of note, Giordano et al. [31] have recently demonstrated that executive and visuospatial deficits in PSP were also associated with cerebellar volume.

It is possible that impaired visuospatial learning, observed in a construction task in our study is related not only to executive deficits, but also visuocordination impairment. The latter impairment may be attributed either to the dysfunction of well-recognized cortical-subcortical pathways or cerebellar pathways.

Our study has several limitations. Patient selection was based on the clinical criteria, not pathologically verified and patients with both probable and possible diagnosis of PSP-RS were included. We matched the patients' cognitive status using MMSE and not a more comprehensive test such as Dementia Rating Scale. However, as the specific cognitive testing was quite lengthy, we wanted to make screening relatively short. Also, in learning tasks, delayed recognition was not reported as it was not performed in all participants. Although learning assessment was very comprehensive, memory task performance was not controlled for language, visuospatial and oculomotor performance. Cognitive procedural learning task proved to be too challenging to be completed by all of the participants, so the inter-group comparison results are biased by discontinuation in most severely impaired participants. Also, the use of phonemic fluency score as an indirect measure of initiation may not have been the optimal choice from the methodological point of view. Although, phonemic fluency is regarded as one of the most sensitive executive measures in PSP-RS [33], it has also a strong language component even in individuals without aphasia [34]. Finally, the relationship between pharmacotherapy regimen and memory was not analyzed due to the heterogeneity of medication used in both clinical groups.

Conclusions

Assessment of learning and memory has a secondary role in differentiating between PSP-RS and PD. Executive deficits are much more prominent. Verbal delayed recall is better in PSP-RS than in PD, matched in terms of global cognitive status. Verbal and visuospatial learning outcomes in both PSP-RS and PD are significantly related to executive factors: initiation and inhibition. Visuospatial learning impairment in PSP-RS is possibly linked to impulsivity and failure to inhibit automatic responses. Both in PSP-RS and PD, the executive function, both initiation and inhibition, are related to memory performance.

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