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Executive Dysfunction Is the Primary Cognitive Impairment in Progressive Supranuclear Palsy

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Abstract

Cognitive difficulties appear to be a more prevalent clinical feature in progressive supranuclear palsy (PSP) than previously thought, and significant cognitive impairment is prevalent in a majority of patients PSP patients not considered clinically demented. The neurocognitive performance of 200 patients with PSP across multiple sites was examined with a variety of commonly used neuropsychological tests. Results indicate primary executive dysfunction (e.g., 74% impaired on the Frontal Assessment Battery, 55% impaired on Initiation/Perseveration subscale of the Dementia Rating Scale), with milder difficulties in memory, construction, and naming. These results have important clinical implications for providers following patients with PSP.

Keywords: Progressive supranuclear palsy; Frontal-executive; Parkinsonism; Dementia; Memory

Introduction

Progressive supranuclear palsy (PSP) affects approximately 5.4 in 100,000 adults over the age of 60. These patients present with postural instability and falls, parkinsonism not responding to dopaminergic therapy, and slowing of vertical saccades (Litvan & Hutton, 1998). However, like in other neurodegenerative conditions, PSP patients also present with notable cognitive symptoms (Gerstenecker, Mast, & Litvan, in press). Deficits in verbal fluency (Bak, Crawford, Hearn, Mathuranath, & Hodges, 2005; Grafman, Litvan, Gomez, & Chase, 1990; Kaat et al., 2007; Maher, Smith, & Lees, 1985; Soliveri et al., 2000), naming (Cotelli et al., 2006), attention and executive functioning (Bak et al., 2005; Kaat et al., 2007; Paviour et al., 2005; Robbins et al., 1994), and memory (Litvan et al., 1989) have been reported in patients with PSP.

PSP patients typically perform better on tests evaluating memory than on tests evaluating executive functioning (Aarsland et al., 2003; Bak et al., 2005; Brown et al., 2010). On tasks designed to specifically assess executive functioning, up to 70% to 90% of patients have been observed to be impaired (Brown et al., 2010; Kaat et al., 2007). Furthermore, patients with PSP have been noted to be as impaired as, if not more severely impaired than, patients with Parkinson's disease with dementia, dementia with Lewy bodies, and Alzheimer's disease on a measure commonly used as a screening instrument for executive dysfunction (Dementia Rating Scale Initiation/Perseveration subscale) (Aarsland et al., 2003). Impairment is most severe on tests of verbal fluency with poorer performance on tests of letter fluency than category fluency (Bak et al., 2005; Cotelli et al., 2006). However, category fluency remains significantly impaired in comparison to normative data.

Although most cognitive studies of PSP have been limited by small samples and the use of brief screening measures, Brown and colleagues (2010) analyzed the performance of 311 PSP patients using two cognitive batteries administered in a

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European-based natural history study of Parkinson Plus syndromes (Bensimon et al., 2009). In this study, more than half of the patients displayed global cognitive impairments. When examining individual cognitive domains, executive functioning was most impaired, with nearly three-quarters of the sample exhibiting this dysfunction. Although Brown and colleagues (2010) contributes to a better understanding of cognitive deficits in PSP, other important neuropsychological domains (e.g., memory, naming) were not adequately evaluated. Greater elucidation of the cognitive difficulties in PSP can have clinical and research implications. For example, using a wider battery of cognitive measures, it is possible to determine whether these patients have a primary memory deficit or whether memory deficits are secondary to frontal impairments (Bak et al., 2005; Pillon et al., 1994; van der Hurk & Hodges, 1995), thereby, providing more information about the mechanism of cognitive dysfunction in these patients and suggesting directions for cognitive interventions.

The current study sought to address these issues by examining the cognitive profiles of PSP patients not performing within the dementia range (i.e., scoring above 24 on the Mini-Mental Status Examination [MMSE]; Folstein, Folstein, & McHugh, 1975) using a large prospective, multisite study. Commonly used neuropsychological tests measuring a wide range of abilities including frontal/executive functioning, verbal memory (immediate and delayed recall, cued recall, and recognition memory), naming, and general cognitive functioning were utilized. It was hypothesized that the most impairment would be observed on tests associated with executive functioning (e.g., Frontal Assessment Battery and Dementia Rating Scale Initiation/Perseveration subscale) and that deficits in memory would be largely reflective of frontal/subcortical disturbances (e.g., retrieval deficits).

Methods

Participants

Following approval of institutional review boards at each site, 200 PSP patients were recruited at 13 sites (Baylor University, University of Colorado, Cornell University, Case Western Reserve, Emory University, Kansas University, University of Louisville, University of Alabama Birmingham, University of California at Los Angeles, University of Kansas, Toronto Hospital, Mayo Clinic Jacksonville, and University of Washington). All patients needed to meet the National Institute of Neurological Disorders and Stroke and Society for PSP, Inc. (NINDS-SPSP) (Litvan et al., 1996a) criteria for clinically probable or definite PSP and have an MMSE score of $\geq$24 to be included. By using this MMSE cut-off score, it was thought that it would limit the number of patients who were already considered to be clinically demented. Patients were excluded if they had other central nervous system disorders (e.g., Parkinson's disease, multiple system atrophy, corticobasal degeneration, etc.) or were unable to provide informed consent. Fifteen patients were excluded due to MMSE performance.

After informed consent, patients were evaluated by a clinical team consisting of a movement disorder specialist and trained research assistant to confirm the PSP diagnosis. This evaluation included a neurological history and examination, completion of validated PSP instruments (PSP-Rating Scale; Golbe & Ohman-Strickland, 2007), and the Unified Parkinson Disease Rating Scale (Fahn & Elton, 1987). Videotaping of motor functioning was also collected to monitor consistency among sites. Finally, a baseline neuropsychological evaluation was completed by medical personnel who had received training on the battery from a neuropsychologist. Accuracy of the evaluations was periodically checked at each site by a neuropsychologist, and all scoring and normative score conversions for data used in this study were double-checked by the author of this study.

Measures

The Dementia Rating Scale-2 (DRS-2; Jurica, Leitten, & Mattis, 2001) is a measure of general cognitive functioning that is widely used in geriatric clinical and research assessments. It yields age- and race-corrected scores on six subscales (Attention, Initiation/Perseveration, Construction, Conceptualization, Memory), and an age-, education-, and race-corrected total score (Lucas et al., 1998; Rilling et al., 2005). For all scores, higher values indicate better cognitive functioning. Extensive normative data are available for both Caucasian and African-American elders (Lucas et al., 1998; Rilling et al., 2005).

The Frontal Assessment Battery (FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000) assesses frontal lobe/executive function across six items (similarities, lexical fluency, motor series, conflicting instructions, Go-No-Go, prehension behavior). Each item is scored on a 3-point scale with 18 possible points comprising the FAB total score. Higher scores indicate better cognition. Age- and education-corrected normative data from Appollonio and colleagues (2005) were used.

The California Verbal Learning Test—Second Edition, Short Form (CVLT-II SF; Delis, Kramer, Kaplan, & Ober, 2000) is a measure of verbal learning and memory. Nine words are verbally presented over four learning trials, with a free recall trial after each presentation. After presentation and free recall of an interference list, a free recall trial of the original list is collected. After a 10-min delay, free and cued recall of the original list is queried, as is recognition. Normative data from the test

manual (corrected for age and gender) were used, with higher scores indicating better memory. Although the CVLT-II SF yields many scores, the variables used in this analysis include: total recall (number of words correctly recalled across four learning trials), Trial 1 (number of words correctly recalled on the first learning trial), Trial 4 (number of words correctly recalled on fourth learning trial), Short Delay Free Recall (number of words recalled after a 30-second distracter task), Long Delay Free Recall (number of words correctly recalled after a 10-min delay), Long Delayed Cued Recall (number of words correctly recalled after a 10-min delay with cueing), Recognition Hits (number of words correctly recognized in the recognition trial), Recognition False Positives (number of non-list words indicated in the recognition trial), and Recognition Discriminability Index (a ratio of correct hits and correct rejections during the recognition trial).

The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) is a 60-item measure of confrontational naming. Normative data corrects for age and education (Steinberg, Bieliauskas, Smith, Langellotti, & Ivnik, 2005), with higher scores indicating better naming abilities. Normative data correcting for race are also available (Lucas et al., 2005).

The Progressive Supranuclear Palsy Rating Scale (PSPRS; Golbe & Ohman-Strickland, 2007) assesses the level of impairment in PSP patients. Impairment is assessed across six categories: health history, mentation, bulbar function, eye and lid movement, limb movement, and trunk movement, with each item being rated on a 0–4 Likert scale (0 = no presence of symptom; 4 = severe presence of symptom). A total score is the sum of all items and ranges from 0 to 100. Higher scores are indicative of greater impairment.

The Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987) was originally developed for use in evaluating impairment in Parkinson's disease, but it has also been shown to be a valid and reliable measure when evaluating the PSP patients. The UPDRS comprises 42 items, rated on a 0–4 Likert scale (0 = no presence of symptom; 4 = severe presence of symptom). Three categories are rated: mentation, behavior, and mood; activities of daily living; and motor functioning. A total score is the sum of all items and ranges from 0 to 124. Higher scores are indicative of greater impairment.

The Neuropsychiatric Inventory (NPI; Cummings et al., 1994) is used to assess both the frequency and severity of behavioral abnormalities across 10 domains: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior. Caregivers are asked to rate affected behaviors on a 1–4 scale for frequency (1 occasionally, 2 often, 3 frequently, and 4 very frequently) and a 1–3 scale for severity (1 mild, 2 moderate, 3 severe). Each domain is calculated by multiplying frequency and severity. The NPI total score (range = 0–120) is the product of the 10 domains designed to evaluate for behavioral abnormalities.

Statistical Analyses

For ease of comparison, all cognitive scores were converted into scaled scores (mean of 10.0 ± 3.0) based on their normative data. Four analyses were conducted. First, the prevalence of cognitive impairment was determined on each of the different cognitive measures. For each cognitive measure's total score (and any relevant subscales), the percentage of participants falling into the mildly impaired (i.e., ≤5th percentile) and severely impaired (i.e., ≤1st percentile) ranges was calculated. Secondly, Pearson product–moment correlations were calculated to determine the relationship between cognitive performances on the various measures and clinically relevant variables (e.g., motor and disease factors). Thirdly, to better determine the pattern of memory performance, a series of paired-samples *t*-test were utilized.

(1) Trial 4 versus Short-Delay Free Recall: To look for evidence of interference.
(2) Trial 4 versus Long-Delay Free Recall: To look for evidence of rapid forgetting.
(3) Long-Delayed Free Recall versus Long-Delayed Cued Recall: To look for evidence of benefitting with cueing.
(4) Long-Delayed Free Recall versus Recognition Discriminability Index: To look for evidence of a retrieval deficit.

Finally, a paired samples *t*-test was conducted to determine whether average performance on tests highly associated with executive functioning (FAB and DRS Initiation/Perseveration) was significantly poorer than average performance on tests not as highly associated with executive functioning: DRS Attention, DRS Conceptualization, DRS Construction, DRS Memory, BNT, and CVLT Total Recall.

Results

Demographic, cognitive, and clinical data for the 200 participants are presented in Table 1.

Table 1. Demographics, Parkinsonian severity, and neuropsychiatric functioning

Demographic	Range
Age	53–87
	68 (6.6)
Sex	113 M, 86 F
Education	8–20
	15 (3.5)
Symptom duration (years)	0.6–10
	3.8 (1.6)
UPDRS total	16–102
	51.7 (18.4)
PSP-RS total	13–70
	36.4 (11.2)
NPI	10.82 (9.2)

Note: UPDRS = Unified Parkinson Disease Rating Scale; PSP-RS = Progressive Supranuclear Palsy Rating Scale, NPI = Neuropsychiatric Inventory.

Table 2. Performance on the DRS-2, FAB, and BNT

Measure	Mean score	% Impaired at 5th percentile	% Impaired at 1st percentile
DRS-2 test/subtest			
Total score	124.5 (11.9)		
	4.69 (3.3)	51.0	25.7
Attention	34.77 (2.3)		
	9.9 (2.6)	7.5	3.0
Initiation/perseveration	28.50 (5.9)		
	5.2 (2.9)	55.4	36.1
Construction	4.73 (1.5)		
	7.3 (2.9)	33.2	18.3
Conceptualization	34.21 (3.8)		
	8.4 (2.5)	8.4	2.5
Memory	22.33 (2.7)		
	8.7 (2.9)	17.4	3.5
FAB	12.75 (2.9)		
	0.27 (8.4)	73.9	59.9
BNT	50.60 (9.5)		
	9.5 (4.0)	18.3	10.4

Note. DRS = Dementia Rating Scale, FAB = Frontal Assessment Battery, BNT = Boston Naming Test. In each cell, the top row are raw scores and the bottom row are normatively corrected scale scores (mean and standard deviation in parentheses).

Dementia Rating Scale

Using normatively corrected data, over half of the sample exhibited impairment on the Total score at or below the 5th percentile. Approximately one in four participants had DRS total scores at or below the 1st percentile. Across the six subscales (see Table 2), the Initiation/Perseveration subscale showed the greatest impairment, with 55.4% of patients exhibiting impaired performance at or below the 5th percentile and 36.1% at or below the 1st percentile. No other mean subscale on the DRS-2 fell in the impaired range for the entire sample, although impairments were observed on each subscale for a minority of the participants (e.g., 18.3% fell at or below the 1st percentile on the Construction subscale). Although DRS-2 total did not significantly correlate with disease duration ($r = -.099$, $p = .162$) or UPDRS total ($r = -.131$, $p = .065$), a significant association was observed between DRS-2 total and the PSP-RS ($r = -.301$, $p < .001$). The following DRS-2 subscales were significantly associated with the UPDRS total: Initiation/Perseveration ($r = -.206$, $p = .008$) and Construction ($r = -.285$, $p < .001$). DRS-2 total was significantly associated with UPDRS Motor Functioning ($r = -.225$, $p = .001$). Both DRS-2 Initiation/Perseveration and Construction were significantly associated with UPDRS Motor Functioning ($r = -.255$, $p < .001$ and $r = -.277$, $p < .001$, respectively). Construction was also significantly associated with UPDRS ADL ($r = -.225$, $p = .002$). The following subscales were significantly associated with the PSP-RS: Initiation/Perseveration ($r = -.355$, $p < .001$), Construction ($r = -.368$, $p < .001$), and Conceptualization ($r = -.256$, $p = .001$). DRS-2 Total was significantly associated with PSP-RS Mentation ($r = -.319$, $p < .001$), Ocular ($r = -.293$, $p < .001$), Limb ($r = -.189$, $p = .008$), and Gait

($r = -.213$, $p = .003$). DRS-2 Initiation/Perseveration was significantly associated with PSP-RS Mentation ($r = -.343$, $p < .001$), Ocular ($r = -.327$, $p < .001$), Limb ($r = -.190$, $p = .008$), and Gait ($r = -.227$, $p = .001$). DRS-2 Construction was significantly associated with PSP-RS History ($r = -.301$, $p < .001$), Ocular ($r = -.266$, $p < .001$), Limb ($r = -.274$, $p < .001$), and Gait ($r = -.273$, $p < .001$). DRS-2 Memory was significantly associated with PSP-RS Mentation ($r = -.196$, $p = .006$). No DRS subscale was significantly associated with disease duration.

Frontal Assessment Battery

The mean raw total score on the FAB was 12.75 ± 2.9, which falls below the traditional cutoffs for impairment of 14 and 15 (see Table 2). Using age- and education-corrected normative data, almost 74% of patients were impaired at or below the 5th percentile and almost 60% at or below the 1st percentile. Item score averages are as follows: similarities $= 2.15 \pm 0.8$, lexical fluency $= 1.50 \pm 0.9$, motor series $= 2.05 \pm 0.9$, conflicting instructions $= 2.14 \pm 0.9$, Go-No-Go $= 2.11 \pm 0.9$, and prehension behavior $= 2.8 \pm 0.6$. FAB Total scores were significantly correlated with both the UPDRS and PSP-RS, $r = -.255$, $p < .001$; $r = -.320$, $p < .001$, respectively. FAB total was significantly associated with UPDRS Motor ($r = -.187$, $p = .008$). Significant associations were also observed with PSP-RS Mentation ($r = -.183$, $p < .01$) and Ocular ($r = -.245$, $p = .001$). A significant correlation with disease duration was not observed, $r = -.042$, $p = .558$. More information about the individual items of the FAB (e.g., means and standard deviations, correlations with clinical variables) can be obtained from the corresponding author.

California Verbal Learning Test—Second Edition, Short Form

Compared with age- and gender-corrected normative data, the mean score for Total Recall was at approximately the 23rd percentile (see Table 3), with over 26% of these participants falling at or below the 5th percentile on this score. Using a 1st percentile cutoff, almost 15% of the sample displayed impaired performance. Short and Long Delay Free Recall tended to be within the average range for this large sample of patients with PSP (34th percentile and 39th percentile, respectively), and few (if any) participants' scores fell at or below the 1st percentile. Cueing after a long delay was also average (Long Delay Cued

Table 3. Performance on the CVLT-II SF

Measure	Mean score	% Impaired at 5th percentile	% Impaired at 1st percentile
Trial 1	4.26 (1.5)		
	6.5 (3.9)	26.7	25.2
Trial 2	5.6 (1.5)		
	n/a		
Trial 3	6.27 (1.5)		
	n/a		
Trial 4	6.52 (1.6)		
	7.8 (3.6)	22.7	13.3
Total recall	22.65 (5.3)		
	7.8 (4.2)	24.6	14.4
SDFR	5.93 (1.9)		
	8.86 (3.6)	12.9	1.5
LDFR	5.24 (2.3)		
	9.19 (3.0)	16.0	0.0
LDCR	5.67 (2.1)		
	8.96 (3.4)	21.2	0.0
Recognition			
Hits	8.18 (1.0)		
	8.93 (3.2)	11.4	8.4
False positives	1.81 (2.3)		
	11.5 (3.6)	0.5	0.0
Discriminability	1.5 (0.59)	2.7	1.5
	11.7 (3.4)	37.0	21.2

Note. CVLT-II SF = California Verbal Learning Test-II Short Form. In each cell, the top row are raw scores and the bottom row are normatively corrected scores (mean and standard deviation in parentheses). Scaled scores are not available for Trials 3 and 3. *Z*-scores are reported as raw scores for Recognition Discriminability.

Recall = 36th percentile). Whereas Recognition Hits was average (35th percentile), False Positives were slightly high (69th percentile, with higher scores indicating more false positives) resulting in a lower Discriminability Index (19th percentile).

Since learning and memory has not been well characterized in PSP, a series of paired samples *t*-tests examined various scores on the CVLT-II SF. First, using age- and gender-corrected scores, the participants with PSP performed better on Short Delay Free Recall compared with Trial 4 (−0.38 vs. −0.72, $t[198] = 5.10$, $p < .001$); however, the effect size was small (Cohen's $d = 0.30$). Secondly, performance on Long Delay Free Recall was also better than Trial 4 (−0.27 vs. −0.72, $t[198] = -6.53$, $p < .001$), with a small to medium effect size ($d = 0.42$). Thirdly, cueing did not appreciably improve performance, as Long Delay Free and Cued Recall were comparable (−0.27 vs. −0.34, $t[198] = 1.20$, $p = .23$, $d = 0.07$). Finally, age- and gender-corrected scores were significantly lower for Long Delay Free Recall than for Recognition Discrimination (−0.28 vs. .59, $t[196] = -10.90$, $p < .001$, with a large effect size ($d = .98$).

The following CVLT variables were significantly correlated with the PSP-RS: Trial 1 ($r = -.218$, $p = .002$), Trial 4 ($r = -.169$, $p = .017$), Total Recall ($r = -.186$, $p = .009$), Short Delay Free Recall ($r = -.220$, $p = .002$), Long Delay Free Recall ($r = -.169$, $p = .017$), Recognition False Positives ($r = .179$, $p = .012$), and Recognition Discrimination ($r = -.158$, $p = .027$). Fewer CVLT variables significantly correlated with the UPDRS: Trial 1 ($r = -.197$, $p = .005$), Short Delay Free Recall ($r = -.195$, $p = .011$), and Recognition False Positives ($r = .225$, $p = .002$). The following correlations were significant between CVLT variables and UPDRS and PSP-RS categories: Trial 1 and UPDRS Mentation ($r = -.285$, $p < .001$), PSP-RS History ($r = -.212$, $p = .003$), and Mentation ($r = -.202$, $p = .005$); Short Delay Free Recall and PSP-RS History ($r = -.200$, $p = .005$), Mentation ($r = -.183$, $p = .01$), and Gait ($r = -.208$, $p = .003$); and Recognition False Positives and UPDRS ADL ($r = .194$, $p = .007$), Motor ($r = .237$, $p = .001$), and PSP-RS History ($r = .203$, $p = .004$). No CVLT variable was significantly associated with disease duration.

Boston Naming Test

Based on age-, education-, and race-corrections, 18.3% of patients exhibited impairment at or below the 5th percentile and 10.4% at or below the 1st percentile (see Table 2). Correlations between confrontational naming and the UPDRS, PSP-RS, or disease duration were not significant.

Impairment Across Measures

When using CVLT Total Recall scores and Total scores on the DRS, FAB, and BNT and defining impairment as the 5th percentile or lower, only 15.4% of the entire sample was completely cognitively intact (i.e., no impairments on any test). Conversely, nearly 85% of this sample had impairments on one or more cognitive measures (Table 4). Of these impaired patients, almost two-thirds (63.7%) were impaired on one or two measures at or below the 5th percentile, and 20.9% of the sample were impaired on three or more measures. Although it is difficult to compare across tests, it appears that performance on tests associated with executive functioning was more frequently impaired than performance on tests of memory and naming in our sample. Furthermore, when using Scale Score averages, combined average performance on the FAB and DRS Initiation/Perseveration subtest was significantly poorer than combined average performance on the other measures used in the test battery (DRS Attention, DRS Conceptualization, DRS Construction, DRS Memory, BNT, and CVLT Total Recall), $t(195) = -9.351$, $p > .001$, $d = 1.03$.

Discussion

Although PSP is primarily associated with motor dysfunction (e.g., postural instability, parkinsonism, slow vertical saccades), prior studies have also identified cognitive impairment in these patients. For example, Brown and colleagues (2010) observed that more than half of their PSP patients displayed global cognitive impairments and three-quarters presented

Table 4. Frequency of total number of impaired measures by patient

No. of tests impaired	Number of patients impaired at 5th percentile	Percentage (%) of patients impaired at 5th percentile
0	31	15.4
1	58	28.9
2	70	34.8
3+	42	20.9

with executive dysfunction. In addition to validating the prevalence of cognitive impairment in a large cohort of patients with PSP, the current study sought to examine the relationships between cognition and other clinical indicators of PSP, as well as more closely examine the pattern of memory deficits in this condition.

Consistent with prior studies (Bak et al., 2005; Brown et al., 2010; Kaat et al., 2007; Paviour et al., 2005), at least mild levels of cognitive impairment were observed in most patients with PSP. For example, 51% of the current sample displayed at least mild deficits on a measure of global cognitive functioning (i.e., at or below the 5th percentile on the DRS-2 Total score). These results, which are very similar to those observed in a large European cohort of PSP patients (Brown et al., 2010), would suggest that neurocognitive performance at a level commonly observed in patients with mild dementia is much more typical than previously thought in this disease. Furthermore, although higher than expected, the rates of cognitive impairment observed in this sample are most likely an underestimate due to patients with low MMSE scores being excluded. These findings also have clinical and research implications. Clinically, providers treating these patients should be assessing for significant cognitive decrements, as these cognitive impairments may affect the patients' ability to adhere to treatment protocols. From a research standpoint, notable cognitive impairments may interfere with a patient's ability to provide informed consent (Jefferson et al., 2008).

Interestingly, the rates of impairment on the DRS total score and the FAB were similar to those found in the Brown and colleagues' (2010) study despite no patients being excluded due to low MMSE scores. This may be due to a number of factors. First, the average patient in the current study had five more years of education than the average patient in the study by Brown and colleagues. Given that the MMSE is known to be sensitive to education effects, especially when cutscores are used (Tombaugh & Mcintyre, 1992), it is not surprising that a large number of patients scoring >24 on the MMSE were, nonetheless, identified as globally impaired on the DRS in comparison to age- and education-matched peers. Secondly, the MMSE does not contain a strong executive functioning component (Brodaty, Fay, Gibson, & Burns, 2006). Given that executive dysfunction was the primary deficit observed in this sample of PSP patients, it is not surprising that patients scoring >24 on the MMSE would be identified as impaired by the test battery that was used in this study.

When specific cognitive domains are examined, it appears that PSP patients exhibit a neurocognitive profile dominated by executive dysfunction. Between half and three quarters of patients were at least mildly impaired on two screening measures of executive dysfunction: the Initiation/Perseveration subscale of the DRS-2 (55.4%) and the FAB (73.9%). This finding is also consistent with the suspected neuropathology in PSP, which is thought to involve subcortical/frontal connections (Houghton & Litvan, 2007). Less impairment, however, was observed on another subscale of the DRS-2 that is often thought to tap executive functioning, the Conceptualization subscale (8.4% mildly impaired in the current sample). Although there are similarities between the Conceptualization and Initiation/Perseveration subscales, there are also notable differences that might partially explain some of these discrepancies. For example, the Initiation/Perseveration subscale of the DRS-2 contains items that require more motor output, verbally and manually (e.g., verbal fluency, double alternating movements, reproduction of ramparts), compared with the Conceptualization subscale (e.g., similarities and differences).

Taken together, scores on the FAB and DRS Initiation/Perseveration subtest were significantly lower than scores on the other measures and subtests comprising the test battery. Given that a large effect size was noted, this observation gives compelling evidence that PSP patients experience particular difficulty with tasks containing a strong executive functioning component. Moreover, deficits on these tasks are believed to be indicative of true executive dysfunction and not simply a function of the influence of other factors.

For example, although reductions in cognitive speed can influence performance on the FAB Go/No Go test, the most common error made on this task occurred when patients tapped twice after being asked to tap once or tapped despite being instructed not to do so. If errors on this test were primarily driven by cognitive slowing instead of poor inhibitory control, the most typical error would have been committed due to the patient not tapping before the examiner moved on to the next item in the tapping sequence. Although motor deficits may have contributed to poor performance on tasks such as FAB Conflicting Instructions, FAB Go/No Go, and DRS Initiation/Perseveration, performance on other tasks heavily associated with motor control such as DRS Construction were not as impaired. Also, visual deficits and abnormal eye movements were not believed to have inflated rates of impairment or cause performance deficits on tests of executive dysfunction. In fact, performance was best on tasks most likely to be influenced by visual deficits or eye movement abnormalities (i.e., DRS Conceptualization [Identities and Oddities], DRS Attention [Counting Distraction and Visual Matching], DRS Memory [Visual Memory], and the BNT [confrontational naming]). Finally, given that confrontational naming performance was drastically better than verbal fluency performance, performance on tasks of verbal fluency was not likely a reflection of language deficits.

Although memory functioning has been previously reported in a large cohort of PSP patients (e.g., Brown et al., 2010 found a mean DRS-2 Memory subscale at approximately the 20th percentile), our results present a richer picture of encoding, storage, and retrieval in these individuals. First, compared with age- and gender-matched peers, learning and memory for verbal information tended to fall in the low average to average range for these participants with PSP. Secondly, despite the overall

performance of this sample, a sizeable minority of patients did present with at least mild impairments (i.e., ≤5th percentile). For example, between 16% and 25% of these individuals were mildly impaired on measures of total recall or delayed recall. Thirdly, when various contrast scores were examined, the typical "subcortical" memory profile (Bonelli & Cummings, 2008) was not observed. Whereas subcortical dementias are expected to present with retrieval deficits (Duff, Beglinger, Theriault, Allison, & Paulsen, 2010), these patients demonstrated relatively strong short and long delayed free recall and little additional benefit from cueing. However, a significant dissociation between delayed recall and recognition discrimination indicates that some level of retrieval deficit is present in this sample of PSP patients. Collectively, these results indicate that memory deficits observed in PSP may be more a function of striatofrontal dysfunction as opposed to hippocampal degeneration, consistent with neuropathological (Litvan et al., 1996b) and neuroimaging (Blin et al., 1990) findings.

Overall, these findings are quite consistent with those reported by Pillon and colleagues (1994) with a much smaller sample of PSP patients and using the original version of the CVLT. In the Pillon study, the average number of words recalled increased through the learning trials until it peaked at the final learning trial. For Long Delay Free Recall, the number of words recalled decreased slightly in comparison to the final learning trial. An almost identical pattern was observed in the current study: the number of words recalled peaked at the final learning trial and decreased slightly for the long delay condition. The only appreciable difference between the two studies was noted in performance on Short Delay Free Recall. In the Pillon study, a larger reduction in recall was observed between Short Delay Free Recall and the final learning trial than in the current study.

The typical PSP patient in our sample did not present with notable naming deficits, with the mean score on the BNT falling in the average range. However, like with other cognitive measures, a number of patients did present with impairments on this test (i.e., 18.3% ≤5th percentile, 10.4% ≤1st percentile). Unfortunately, the BNT was our only purer measure of language functioning in this study. Both the FAB and DRS-2 contain verbal fluency items (phonemic and semantic, respectively), but these are not individually normed, so any comparisons should be made with caution.

Although the prevalence of executive dysfunction was outlined in the Brown and colleagues (2010) study, taken together, information in the current study contributes to a richer understanding of the role of executive functioning in the neurocognitive performance of PSP patients. Through inclusion of the CVLT, the contribution of striatofrontal dysfunction versus hippocampal degeneration to memory deficits was better delineated. Also, by including the BNT, it was able to be shown that poor verbal fluency performance was more associated with executive dysfunction than language deficits. Finally, a more detailed discussion of the role of executive dysfunction over-and-above factors that could affect performance on tests of executive functioning (i.e., cognitive slowing and motor deficits) was included.

Based on the results of the current study, it is clear that cognitive impairments can occur in some patients with PSP who, nevertheless, are highly educated and not identified as demented based upon MMSE performance. The current findings also provide some information about how prevalent cognitive disorders might be in this group. In 200 participants, only 15.4% presented completely cognitively intact (i.e., no impairment on any cognitive measure). In other words, more than 4 out of every 5 PSP patients scoring above 24 on the MMSE have at least mild impairments on at least one cognitive measure commonly administered to older adults as part of a neuropsychological battery. However, given that 15 patients were excluded due to low MMSE scores and that conservative estimates of impairment were used despite the sample being highly educated, estimates of impairment prevalence observed in this sample are most likely an underestimate of the prevalence of impairment in the population as a whole. Of these impaired patients, 29% were impaired on only one measure at or below the 5th percentile, 34.7% were impaired on two measures, and 20.9% of the sample were impaired on three or more measures (Table 4). As noted earlier, these findings may have clinical and research implications (e.g., increased need to assess cognition in PSP patients, concern for adherence to treatment protocols, difficulties providing informed consent or understanding complex research protocols).

Not surprisingly, there were a number of associations between some of the cognitive measures and some of the measures of PSP disease severity. The PSP-RS significantly correlated with the DRS-2 Total (and three of its six subscales), FAB total, and multiple variables from the CVLT-II SF. The UPDRS was significantly correlated with fewer cognitive variables. One advantage of the PSP-RS might be that it was specifically designed to assess the signs and symptoms of PSP, whereas the UPDRS was developed to evaluate patients with Parkinson's disease. Regardless of the scale used, the significant correlations all went in the expected directions (e.g., greater PSP impairment associated with worse cognitive performance). It should be noted, however, that the magnitude of these correlations tended to be small, with only 4%–9% of the variance being accounted for. Since so much variance remains unaccounted for, there is a need to examine other variables (e.g., physical, psychiatric, demographic) that may better explain performance on these cognitive measures. It was also interesting that the disease duration did not correlate with any cognitive measures. This may indicate that the disease duration reflects both severity of symptoms and patients' ability to access a specialist for diagnosis.

Despite the considerable findings presented in the current study, there are a number of limitations and future directions to be considered. First, like most other multisite studies of rare disorders, the current sample may not completely represent the

population from which is was drawn. The current participants needed to agree to participate in several hours of testing, they needed to have an MMSE score of ≥24, they needed to be able to provide informed consent, and they could not have other central nervous system disorders. This likely yields a select group of PSP patients, and these results might not generalize to all patients with PSP. Secondly, it has recently been demonstrated by pathological confirmation that PSP can be divided into two phenotypes that are difficult to diagnose during life (Williams et al., 2005). Consequently, to provide a more complete description of the neurocognitive performance of PSP patients, future studies should classify patients according to Williams subtype. Thirdly, although the current battery was an improvement over other studies of cognition in PSP, there are areas that remain in need of additional investigation. For example, measures included in this study were used to screen for general cognitive and domain-specific impairment. Given that executive dysfunction was identified as the dominant impairment, a more elaborate evaluation of executive functioning should be included in future studies so patterns of performance can be used to evaluate for differential impairment in the parallel but independent prefrontal loops. In regards to memory, the CVLT-II SF adequately taps verbal learning and memory, but information about working memory and the encoding, storage, and retrieval of visual information in PSP is needed. Similarly, future studies should further examine language functioning in these patients. Although some patients with PSP have difficulties with verbal fluency and naming, it is unclear whether they also have difficulties with comprehension, repetition, or prosody. Furthermore, the quality of tasks designed to evaluate attention were limited to DRS-2 Attention and not as extensive as some previous studies. Thirdly, the current study examined the relative prevalence of cognitive impairment in PSP; however, it is expected that there are moderators of cognitive functioning in this group. For example, mood can affect attention, learning and memory, and other domains. Future studies might examine the relationship between mood and cognition in these patients. Fourthly, it is helpful to examine the rates of cognitive difficulties in various patient samples, but it may be more informative to examine how these cognitive difficulties affect activities of daily living. In other words, do individuals with mildly impaired FAB scores also have difficulties with managing medications, finances, and driving? Making the associations between cognition and daily functioning will add to the clinical significance of this line of research. Because autopsy confirmation was not available, the possibility of co-morbid disorders such as Alzheimer's disease could not be ruled-out in these patients. Prior research suggests that a large number of PSP patients may have concomitant pathologic changes of Alzheimer's disease (Gearing, Olson, Watts, & Mirra, 1994). This would clearly influence their neuropsychological test performance. Finally, in the current study, clinical diagnostic criteria were used that have been shown to be highly specific but not very sensitive. Future studies may benefit from inclusion of patients using less stringent clinical diagnostic criteria and following patients longitudinally to obtain histopathologic verification. By doing so, a better understanding of the neuropsychological performance of PSP patients may be obtained.

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Conflict of Interest

None declared.

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