ORIGINAL ARTICLE

Neuropsychological Functioning in PLS: A Comparison with ALS

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ABSTRACT: ***Objective:*** In order to characterize the nature and extent of neuropsychological dysfunction in primary lateral sclerosis (PLS), we studied prospectively cognitive, emotional, and behavioral functioning in PLS, and compared performances to functioning in amyotrophic lateral sclerosis (ALS). ***Methods:*** Eighteen patients with PLS and 13 patients with ALS completed a neuropsychological test battery assessing both cognitive skills and emotional/behavioral functioning. ***Results:*** Both PLS and ALS groups scored broadly within normal limits (mean T-scores greater than 40) on all cognitive measures and no significant between-group differences were found with the exception of one variable. However, when examined on a case by case basis, the data revealed considerable heterogeneity amongst patients in both groups. Overall, 39% of PLS patients and 31% of ALS patients were considered cognitively impaired. A higher than expected frequency of abnormal scores was noted for several tests of executive function in both groups, and a majority of PLS patients also exhibited abnormal behavioural symptoms. There was no relationship in PLS or ALS groups between cognitive functioning and disease duration, current site of disease, site of onset, functional status, and respiratory variables. Comparison between the PLS and ALS groups indicated virtually no differences in cognitive test scores and overall emotional/behavioural symptoms. ***Conclusions:*** We observed deficits in cognition and behaviour in a significant proportion of PLS patients which were comparable to those observed in ALS cases. Although deficits were not in the range of frontotemporal dementia, both ALS and PLS cases demonstrated deficits most prominently on tests of executive functioning.

RÉSUMÉ: Fonctionnement neuropsychologique dans la SLP par rapport à la SLA. ***Objectif :*** Nous avons étudié prospectivement le fonctionnement cognitif, émotionnel et comportemental dans la sclérose latérale primaire (SLP) afin de caractériser la nature et l'étendue de la dysfonction neuropsychologique et nous l'avons comparé au fonctionnement dans la sclérose latérale amyotrophique (SLA). ***Méthodes :*** Dix-huit patients atteints de SLP et 13 patients atteints de SLA ont complété une batterie de tests neuropsychologiques évaluant les habiletés cognitives et le fonctionnement émotionnel/comportemental. ***Résultats :*** Les scores dans les deux groupes étaient dans les limites normales (scores T moyen > 40) pour toutes les mesures cognitives et nous n'avons pas observé de différences significatives entre les groupes à l'exception d'une variable. Cependant, à l'examen cas par cas, nous avons constaté une hétérogénéité considérable des données chez les patients des deux groupes. Globalement, 39% des patients atteints de SLP et 31% des patients atteints de SLA avaient un déficit cognitif. Nous avons noté une fréquence plus élevée qu'attendue de scores anormaux pour plusieurs tests de fonction exécutive dans les deux groupes et une majorité de patients atteints de SLP avaient également des symptômes comportementaux anormaux. Il n'y avait pas de relation dans le groupe SLP ou dans le groupe SLA entre le fonctionnement cognitif et la durée de la maladie, la localisation actuelle de la maladie, la localisation de début de la maladie, l'état fonctionnel et les variables respiratoires. La comparaison des deux groupes n'a pas révélé de différences dans les scores aux teste cognitifs et dans les symptômes émotionnels/comportementaux globaux. ***Conclusions :*** Nous avons observé des déficits cognitifs et comportementaux chez une proportion significative de patients atteints de SLP qui étaient comparables à ceux observés chez les patients atteints de SLA. Bien que les déficits n'étaient pas dans l'écart de la démence frontotemporale, tant les patients atteints de SLA que les patients atteints de SLP présentaient des déficits plus évidents aux tests de fonctionnement exécutif.

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Primary lateral sclerosis (PLS) is a rare adult-onset motor neuron disease. The primary clinical symptom is progressive spinobulbar spasticity with a slow and gradual disease course (median of 19 years)[1,2]. Clinical features, related to corticospinal dysfunction, include limb spasticity, spastic bulbar symptoms, pseudobulbar affect, hyper-reflexia, and bilateral Babinski signs. In contrast to amyotrophic lateral sclerosis (ALS), in which both upper motor neuron and lower motor neuron dysfunction is evident, the disease process of PLS is restricted to the upper motor neuron[1].

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Although the contemporary view of ALS is that of a multisystems disorder in which cognitive impairment is a common component, the evidence for cognitive impairment in PLS is less well established. Although there are several reports of normal cognitive functioning in patients with PLS, these studies either lack neuropsychological testing or adequate descriptions of the testing to evaluate its validity[1,3-5]. In contrast, several investigators have reported cognitive impairment or dementia in case studies of patients with PLS[6-9].

To our knowledge, only two systematic group studies of the neuropsychological features of PLS have been undertaken. In a retrospective study of nine patients, mild cognitive deficits (without overt dementia) were observed in executive functioning, psychomotor speed, and memory consistent with subtle frontal deficits[10]. The most sensitive measure was a test of verbal fluency. A more recent longitudinal study found that 16 of 20 PLS patients exhibited moderate deficits in frontal and/or premotor functions compared to controls[11]. In a later publication, these neuropsychological data were further described[12]. Compared to normal controls, all PLS patients were noted to exhibit memory impairment of an executive nature and all but three patients demonstrated "minor" premotor and/or prefrontal impairment. However, no patients met criteria for frontotemporal or other dementia.

Whether PLS and ALS are distinct nosological entities or variants of a spectrum of motor neuron diseases is a long-debated controversy[2,13]. Although PLS has been viewed traditionally as a disease separate from ALS[1,14], its characterization as a distinct entity also has been challenged[2,9,11,13,15]. For example, it has been argued that lower motor neuron symptoms in PLS are not uncommon[11]; many patients with PLS eventually progress to develop lower motor neuron symptoms[13]; and the majority of patients with PLS show neuropathological evidence of spinal motor degeneration similar to ALS[2]. As such, many researchers are proposing that PLS should not be viewed as a discrete nosological entity but rather as a rare, predominantly upper motor neuron variant at one end of the spectrum of MND, with progressive muscular atrophy (predominantly lower motor neuron disease) at the other end[2,9,11].

In order to more crisply define the cognitive and emotional/behavioural deficits of PLS, we undertook a prospective study examining a wide range of cognitive skills, with emphasis on executive processes. In addition, we assessed emotional and behavioral changes, key areas affected in frontotemporal dysfunction. We also directly compared functioning between patients with PLS and ALS. Based on previous literature, we hypothesized that at least mild cognitive impairment would be identified in the PLS patients, and be characterized primarily by executive dysfunction. Furthermore, we predicted that differences between the ALS and PLS groups would be minimal, based on the hypothesis that the two conditions belong to a continuum of disease rather than separate disease processes.

Methods

Participants

Eighteen patients with PLS and 13 patients with ALS were recruited from the Motor Neuron Diseases Clinic at the University of Western Ontario using a convenience sampling technique. Because of the rarity of PLS patients, each patient presenting to the clinic with PLS within a three year time window was offered an opportunity to participate. No patients declined to participate. All PLS patients met the diagnostic Pringle criteria[1] while all ALS patients were diagnosed with definite ALS based on the El Escorial criteria[16]. In addition to neuropsychological testing, all patients underwent pulmonary function testing and completed the ALS Functional Rating Scale – Revised (ALSFRS-R), a rating instrument for monitoring the progression of physical disability in patients with ALS[17]. Informed consent was obtained from all participants. The current study was approved by the research and ethics review board at the University of Western Ontario.

Neuropsychological Evaluation

A neuropsychological test battery, designed to minimize speech production and upper limb motor skills, was administered to all participants. Testing duration was approximately 90 minutes; tests were administered by a trained neuropsychometrist, supervised by the first author. Tests were scored by the psychometrist, and scoring accuracy was confirmed by the first author, who conducted all further analyses. The measures were categorized into five general

Table 1: Neuropsychological tests and variables

Domain	Test	Variables
Executive Skills	WCST	Perseverative Responses
		Total Errors
	COWAT	Total Words
	TWWF	Total Words
	DAT	Total errors
Attention / Concentration	CTT	Mean score 3 Trials
Visual-perception / Visual-construction	MFVPT-R	Number correct
	Block Design (WAIS-III)	Age-scaled score
Memory	RAVLT	Total words Trials 1-5
		Delay recall # of words
		Delayed recognition
	WRMT	Total words correct
		Total faces correct
Emotional/Behavioral Functioning	GDS	Total score
	NPI	Total score
	FBI	Total score

WCST = Wisconsin Card Sorting Test (one deck version); COWAT = Controlled Oral Word Association Test; TWWF = Thurstone Written Word Fluency; DAT = Delayed Alternation Test; CTT = Consonant Trigrams Test; MFVPT-R = Motor-Free Visual Perception Test – Revised; WAIS-III = Wechsler Adult Intelligence Scale – III; RAVLT = Rey Auditory Verbal Learning Test; WRMT = Warrington Recognition Memory Test; GDS = Geriatric Depression Scale; NPI = Neuropsychiatric Inventory; FBI = Frontal Behavioral Inventory

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domains of functioning with particular emphasis on frontal-executive skills (see Table 1). Nine neuropsychological tests were administered with a total of 13 variables analyzed.

Wisconsin Card Sorting Test (WCST, one deck version[18])

This is a widely used nonverbal test of problem-solving, abstract reasoning, and mental flexibility that requires examinees to generate, assess, and modify their responses in response to changing environmental feedback.

Controlled Oral Word Association Test (COWAT[19])

This test requires the spontaneous oral production of words beginning with three designated letters (e.g., C F L or P R W) within a one-minute time frame for each letter.

Thurstone Written Word Fluency (TWWF[20])

This is a written word fluency task involving two components. Part A involves production of words starting with the letter "S" in five minutes. Part B requires production of four-letter words starting with the letter "C" in four minutes. The final score involves the combination of written responses for parts A and B.

Delayed Alternation Test (DAT[21])

A measure of working memory and set-shifting skill in the spatial domain, this test is sensitive to frontal lobe lesions in non-human primates and in humans[21,22]. Although normative data on delayed alternation has not been published, performance of the patients was compared to performance of normal controls.

Consonant Trigrams Test (CTT[23])

This is a demanding auditory-verbal test of working memory, divided attention, and information-processing capacity, sensitive to frontal systems dysfunction.

Motor-Free Visual Perception Test – Revised (MFVPT-R[24])

A measure of visual-perceptual processing, this task requires limited motor responding, and includes assessment of five types of perceptual skill: spatial relationships, visual discrimination, figure-ground, visual closure, and visual memory.

Block Design from the Wechsler Adult Intelligence Scale – III (WAIS-III[25])

This is a well-known task of visual-constructional ability in which the examinee uses red and white blocks to construct replicas of increasingly more complex patterned designs.

Rey Auditory Verbal Learning Test (RAVLT[26])

This is a multiple-trial test of verbal learning and memory which assesses efficiency of learning, immediate and delayed recall, susceptibility to interference, and recognition memory.

Warrington Recognition Memory Test (WRMT[27])

This is an immediate recognition memory test consisting of two separate but parallel subtests, one assessing memory for printed words and the other for photographs of faces.

Many of the tests used in this study required no speech production and only minimal motor requirements (MFVPT-R, DAT, WRMT, Geriatric Depression Scale [GDS]). Other tests requiring motor ability were adapted where necessary to reduce motor requirements. For patients with motor disability, placement of cards in the WCST was done by the examiner instead of the patient, with the patient indicating on which pile they wanted the card to go. In addition, some tasks allowed for either written or oral responses depending on patients' capabilities (e.g., RAVLT, CTT). A detailed language assessment also was administered to all patients, and will be reported separately.

Three self-report questionnaires were used to assess emotional/behavioral factors. The GDS[28], a 30-item depression screening instrument for older adults, was administered to patients. Scores on the GDS were classified as follows: 0-9 – normal; 10-19 – mild; 20-30 – severe. Two other questionnaires were administered to participants' study partners. These were the Neuropsychiatric Inventory (NPI[29]), an instrument assessing the presence and severity of 12 neuropsychiatric disturbances commonly seen in dementia, and the Frontal Behavioral Inventory (FBI[30]), a scale assessing the presence and severity of behaviours commonly seen in dementia associated with frontal lobe dysfunction. Unfortunately, not all of the patients had a study partner and hence, due to the rarity of the disease, we elected to study these individuals in the absence of controls. This was an issue for four of the PLS and three of the ALS patients.

Statistical Methods

All scores were standardized into T-scores (mean of 50, SD of 10) based on published normative data for each test corrected for age (all tests except MFVPT-R) and when available for education (COWAT, TWWF). For the delayed alternation test, one of the authors (M.F.) provided unpublished normative control data (N=15; 6M, 9F; mean age of 61; mean educational level of 14.5 years; mean error score of 5.3, SD of 4.6). A T-score less than 35 (i.e., more than 1.5 SD below the mean) on a specific measure was considered abnormal. A patient's overall performance on the test battery was defined as cognitively impaired if two or more scores were abnormal on at least two different cognitive tests. Within-group correlational analyses were performed using Pearson correlations. Between-group comparisons were performed using 2-tailed t-tests, with significant results considered at $p < 0.05$. The primary analyses involved the descriptive statistics of the two groups, and the between-group analyses investigating differences between the PLS and ALS groups. The secondary analyses were performed after the primary analyses and included the within-group analyses that looked at each patient to determine whether or not they met the study criteria for cognitive impairment – i.e., examining the frequency of cognitive impairment in each sample.

Results

Demographics

Demographic and clinical characteristics of the PLS and ALS participants are detailed in Tables 2 and 3 respectively. The mean age of PLS participants was 58.4 years (SD=8.1); the mean

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Table 2: Demographic and clinical characteristics of PLS participants

Patient	Age	Sex	Education	Disease Duration	ALSFRS-R Score*	Site of Onset	Current Site of Disease	Number of Impaired Scores**
1	65	F	8	26.0	36	L	L+B	2
2	59	F	16	3.5	30	L	L+B	0
3	54	M	12	21.0	34	L	L+B	1
4	67	M	8	7.0	15	L	L+B	4
5	53	M	11	14.0	35	B	L+B	1
6	72	F	15	12.0	41	L	L	1
7	48	M	8	15.5	37	B	L+B	0
8	68	F	17	13.0	39	L	L	0
9	56	M	17	2.0***	31	L	L+B	5
10	69	F	9	7.5	35	L	L+B	0
11	52	F	14	5.5	34	L	L+B	2
12	44	M	16	8.0	45	L	L	2
13	68	F	13	6.0	37	B	L+B	2
14	55	F	12	3.5	41	L	L	0
15	56	M	13	18.0	25	L	L+B	0
16	57	M	15	6.0	30	L	L+B	2
17	49	M	14	3.5	30	L	L	1
18	60	F	12	2.0***	41	L	L	0
X	58.4	9M 9F	12.8	9.7	34	3B 15L	6L 12L+B	1.3

B=bulbar; L=limb; * ALSFRS-R = ALS Functional Rating Scale - Revised; ** Test scores below -1.5 SD; *** Disease duration was only two years at the time of testing; however a diagnosis of PLS has since been confirmed in both participants

educational level was 12.8 years (SD=3.0); and the mean disease duration, as measured from the date of first symptom onset, was 9.7 years (SD=7.0). There were nine men and nine women. The mean age of ALS participants was 51.5 years (SD=8.8); the mean educational level was 15.0 years (SD=2.5); and the mean disease duration was 2.2 years (SD=1.7). There were seven men and six women. The PLS group was significantly older ($t = 2.3$, $p < .05$), less educated ($t = -2.1$, $p < .05$), and had a significantly longer disease duration ($t = 3.8$, $p = .001$) than the ALS patients. There was, however, no significant difference between groups in disease disability as measured by the ALSFRS-R.

Overall Neuropsychological Performance

Both the PLS and ALS groups scored broadly within normal limits (mean T-scores greater than 40) on all cognitive measures (see Table 4). T-tests performed between groups revealed nonsignificant findings ($p > .05$) on all variables except for the Consonant Trigrams test. On this one task, the ALS group performed significantly better than the PLS group ($p = .05$). All PLS participants had speech intelligibility ratings of 85% or greater clear speech, with only two rating at 85%. Mean overall speech intelligibility in the PLS group was greater than 90%. Speech was rated as highly intelligible in all ALS participants. Speech studies were performed on the same day as the neuropsychological studies.

Secondary analyses were also performed in that the data were examined on a case by case basis within each group. This was done to ascertain whether scores were uniformly intact among group members or more heterogeneous in nature. Results indicated considerable heterogeneity within both groups as detailed below.

PLS Group

Seven patients performed within or above normal limits on all measures, four patients performed in the abnormal range on one measure, five patients performed in the abnormal range on two measures, and two patients scored in the abnormal range on four or more measures. In total, 7/18 patients (39%) met our criteria for cognitive impairment.

ALS Group

Four patients performed within or above normal limits on all measures, five patients performed in the abnormal range on one measure, one patient performed in the abnormal range on two measures, and three patients scored in the abnormal range on three or more measures. In total, 4/13 (31%) were considered cognitively impaired.

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Table 3: Demographic and clinical characteristics of ALS participants

Patient	Age	Sex	Education	Disease Duration	ALS-FRS-R Score*	Site of Onset	Current Site of Disease	Number of Impaired Scores**
1	40	F	17	2.0	29	B	L+B	0
2	52	M	12	2.0	20	L	L+B	1
3	47	M	16	1.0	45	L	L	2
4	42	M	14	2.0	44	L	L+B	0
5	53	M	18	1.0	27	B	L+B	1
6	34	M	12	5.0	20	L	L+B	1
7	56	F	16	6.5	23	L	L+B	1
8	60	F	16	1.5	34	L	L+B	1
9	58	F	16	1.0	41	L	L+B	3
10	60	M	10	2.0	41	B	B	4
11	48	F	17	1.0	36	B	L+B	0
12	57	M	13	1.5	32	B	L+B	3
13	63	F	18	1.5	26	L	L+B	0
X	51.5	7M 6F	15	2.2	32	5B 8L	1B 1L 11L+B	1.3

B=bulbar; L=limb; * ALSFRS-R = ALS Functional Rating Scale - Revised; ** Test scores below -1.5 SD

Table 4: Mean T scores for neuropsychological test variables (SD in parentheses) and t-test results for between group comparisons on each variable

Test Variable	PLS Group		ALS Group		t-test p value
COWAT	42.1	(11.7)	45.3	(11.0)	p >.05
TWWF	49.8	(11.6)	48.4	(11.5)	p >.05
DAT	43.3	(12.3)	51.2	(6.6)	p >.05
WCST – PR	52.3	(10.2)	50.0	(15.0)	p >.05
WCST – Tot	50.0	(12.5)	48.0	(14.3)	p >.05
RAVLT – Tot	45.2	(9.5)	50.8	(10.7)	p >.05
RAVLT – Del	48.3	(8.5)	50.8	(9.5)	p >.06
RAVLT- Recog	46.4	(14.1)	45.4	(11.3)	p >.05
CTT	47.2	(11.2)	55.6	(10.2)	p =.05 *
WRMT – Words	56.5	(6.9)	57.7	(10.1)	p >.05
WRMT- Faces	46.5	(11.2)	46.9	(13.1)	p >.05
MFVPT-R	56.7	(7.8)	55.4	(8.3)	p >.05
Block Design	51.6	(5.9)	50.0	(9.3)	p >.05

COWAT = Controlled Oral Word Association Test; TWWF = Thurstone Written Word Fluency; DAT = Delayed Alternation Test; WCST – PR = Wisconsin Card Sorting Test, Perseverative Responses (one deck version); WCST – Tot = Wisconsin Card Sorting Test, Total Errors (one deck version); RAVLT – Tot = Rey Auditory Verbal Learning Test, Total Errors; RAVLT – Del = Rey Auditory Verbal Learning Test, Delayed Recall; RAVLT Recog = Rey Auditory Verbal Learning Test, Recognition memory; CTT = Consonant Trigrams Test; WRMT - Words = Warrington Recognition Memory Test, Words Subtest; WRMT - Faces = Warrington Recognition Memory Test, Faces Subtest; MFVPT-R = Motor-Free Visual Perception Test – Revised; Block Design = Block Design Subtest, WAIS-III

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Neuropsychological Functions Affected

Frequencies of impairment on each test were calculated separately for both groups to characterize the pattern and nature of impairment. The percentage of patients in each group who demonstrated abnormal scores on each of the neuropsychological measures is shown in Table 5. A higher than expected frequency of abnormal scores was noted for several tests across both PLS and ALS groups. Based on the binomial probability distribution, 6.7 percent of healthy individuals would be expected to score below the cut off value of -1.5 SD on a given task. For both groups, the frequency of abnormal scores was significantly different (higher) than the rate predicted by the binomial distribution for the following tests: COWAT (PLS: $\chi^2 = 110.65$; $p < .0001$; ALS: $\chi^2 = 42.50$; $p < .0001$), WRMT-Faces (PLS: $\chi^2 = 20.43$; $p < .0001$; ALS: $\chi^2 = 11.02$; $p < .001$) and RAVLT-Recog (PLS: $\chi^2 = 16.97$; $p < .0001$; ALS: $\chi^2 = 94.46$; $p < .0001$). For the PLS group only, the frequency of abnormal scores was significantly different (higher) for the following additional tests: DAT ($\chi^2 = 6.35$; $p < .02$), TWWF ($\chi^2 = 4.50$; $p < .04$), and CTT ($\chi^2 = 4.50$; $p < .04$). Finally, for the ALS group only, the frequency of abnormal scores was significantly different (higher) than predicted by the binomial distribution for WCST-PR ($\chi^2 = 42.50$; $p < .0001$) and WCST-Tot ($\chi^2 = 11.02$; $p < .001$). As illustrated in Table 5, the groups were similar in demonstrating a zero frequency of impairment on the following measures: RAVLT- Del; WRMT-Words; MFVPT-R; and Block Design. The test with the highest frequency of impairment for the PLS group was the COWAT, with 33% of PLS patients and 23% of ALS patients demonstrating abnormal scores on this measure. Of the patients who were classified as cognitively impaired, 57% of PLS patients and 50% of ALS patients demonstrated abnormal scores on this measure.

Relationship between neuropsychological functioning and disease parameters

Site of Onset

Among PLS patients, 15 cases exhibited limb symptoms at onset, and three showed bulbar symptoms at onset. In the limb-onset group, six patients (40%) were cognitively impaired while in the bulbar-onset group, only one (33%) patient was cognitively impaired. Formal statistical comparison between limb and bulbar groups was precluded by small and uneven groups. Among ALS patients, eight cases exhibited limb symptoms at onset, and five cases showed bulbar symptoms at onset. In the limb-onset group, two patients (25%) were cognitively impaired while in the bulbar-onset group, two patients (40%) were impaired. A t-test between the groups revealed non-significant results.

Current site of disease

Among PLS patients at the time of testing, six patients had limb-only symptoms and 12 had both limb and bulbar symptoms. In the limb only group, only one patient (17%) was cognitively impaired. In the limb and bulbar group, six patients (50%) were cognitively impaired. The difference between the groups was not significant (t-test, $p > .05$). Of the ALS patients, one patient had limb-only symptoms, one patient had bulbar-only symptoms, and 11 patients had both limb and bulbar symptoms. The twopatients with bulbar-only or limb-only symptoms were cognitively impaired. Of the 11 patients with limb and bulbar involvement, two patients were cognitively impaired. Formal statistical comparison could not be completed due to small and uneven groups.

Disease Duration and Severity

No significant correlations were observed for either the PLS or ALS groups between the number of abnormal test scores and either disease duration or severity as measured by the ALSFRS-R score.

Table 5: Percentage of patients with abnormal scores on each neuropsychological variable

Test Variable	PLS Group		ALS Group	
COWAT	33 %	*	23 %	*
WRMT- Faces	18 %	*	15 %	*
RAVLT- Recog	17 %	*	31 %	*
DAT	13 %	*	0 %	
TWWF	12 %	*	8 %	
CTT	12 %	*	8 %	
WCST – PR	11 %		23 %	
WCST – Tot	11 %		15 %	
RAVLT – Tot	11 %		8 %	
RAVLT – Del	0 %		0 %	
WRMT – Words	0 %		0 %	
MFVPT-R	0 %		0 %	
Block Design	0 %		0 %	

COWAT = Controlled Oral Word Association Test; TWWF = Thurstone Written Word Fluency; DAT = Delayed Alternation Test; WCST – PR = Wisconsin Card Sorting Test, Perseverative Responses (one deck version); WCST – Tot = Wisconsin Card Sorting Test, Total Errors (one deck version); RAVLT – Tot = Rey Auditory Verbal Learning Test, Total Errors; RAVLT – Del = Rey Auditory Verbal Learning Test, Delayed Recall; RAVLT Recog = Rey Auditory Verbal Learning Test, Recognition memory; CTT = Consonant Trigrams Test; WRMT - Words = Warrington Recognition Memory Test, Words Subtest; WRMT - Faces = Warrington Recognition Memory Test, Faces Subtest; MFVPT-R = Motor-Free Visual Perception Test – Revised; Block Design = Block Design Subtest, WAIS-III. * Denotes tests in which the frequency of impairment is significantly different (higher) from that expected in healthy individuals as predicted by the binomial probability distribution.

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Respiratory Variables

In order to rule out the effects of respiratory insufficiency on cognitive performances, respiratory variables were examined. The median forced vital capacity (FVC) of PLS participants was 91%, and CO_2 values were all within the normal range. For the ALS group, the median FVC score was 75% and all CO_2 values were also within normal limits.

Emotional / Behavioural Measures

Geriatric Depression Scale

The mean GDS score was within normal limits for both groups (PLS group – 8.3; ALS group – 8.6). Performance was within normal limits for 14 of 17 PLS participants (82%) while only three participants were categorized as severely depressed. Six of 13 ALS patients (46%) were within normal limits while 7 of 13 (54%) were categorized as mildly depressed. None of the ALS patients was categorized as severely depressed.

Neuropsychiatric Inventory (see Table 6)

Fourteen partners of PLS patients completed the NPI. Eight partners (57%) identified symptoms considered outside the normal range, with an overall mean NPI score of 6.2 (range of 0 to 24). The following behavioral categories were endorsed in order of frequency: depression/dysphoria (57%), night-time behavior (36%), agitation (29%), appetite/eating changes (21%), irritability/lability (14%), apathy/indifference (14%), and aberrant motor behavior (7%). Of ten ALS partners who completed the NPI, four partners (40%) identified symptoms outside the normal range, with an overall mean NPI score of 3.0 (range of 0 to 9). The following behavioral categories were endorsed (in order of frequency) in the ALS patients: depression/dysphoria (50%), night-time behavior (40%), irritability/lability (20%), anxiety (20%), agitation (10%), appetite/eating changes (10%), and apathy/indifference (10%). Two of the most frequently endorsed behaviours (depression/dysphoria and night-time behaviour) were the same for both groups. There was no endorsement in either group for delusions, hallucinations, euphoria/elation, and disinhibition. There was no significant difference between groups on the overall NPI score. There was no significant correlation between number of abnormal test scores and NPI scores for either group.

Frontal Behavioral Inventory (see Table 7)

Analysis of the FBI responses indicated a mean score of 9.6 (range of 0 to 26) for the PLS group. The most common symptoms endorsed by partners (N=14) were verbal apraxia (71%), irritability (57%), apathy (43%), logopenia (43%), alien hand (43%), inflexibility (36%), indifference/emotional flatness

Table 6: Symptom frequency for PLS and ALS groups on the Neuropsychiatric Inventory

NPI Symptom	PLS Group	ALS Group
Depression/ Dysphoria	57 %	50 %
Night-time Behaviour	36 %	40 %
Agitation	29 %	10 %
Appetite / Eating Change	21 %	10 %
Irritability / Lability	14 %	20 %
Apathy/ Indifference	14 %	10 %
Aberrant Motor Behavior	7 %	0 %
Anxiety	0 %	20 %
Delusions	0 %	0 %
Hallucinations	0 %	0 %
Euphoria / Elation	0 %	0 %
Disinhibition	0 %	0 %

Table 7: Symptom frequency for PLS and ALS groups on the Frontal Behavioral Inventory

FBI Symptom	PLS Group	ALS Group
Verbal Apraxia	71 %	70 %
Irritability	57 %	40 %
Apathy	43 %	20 %
Logopenia	43 %	40 %
Alien Hand	43 %	30 %
Inflexibility	36 %	10 %
Indifference	29 %	10 %
Restlessness	29 %	50 %
Aggression	29 %	10 %
Hypersexuality	21 %	20 %
Incontinence	21 %	0 %
Disorganization	14 %	20 %
Inattention	14 %	20 %
Concreteness	14 %	20 %
Aspontaneity	14 %	0 %
Loss of Insight	14 %	0 %
Perseveration	14 %	0 %
Poor Judgment	7 %	10 %
Excessive Jocularity	7 %	0 %
Personal Neglect	7 %	0 %
Impulsivity	7 %	0 %
Inappropriateness	0 %	0 %
Hyperorality	0 %	0 %
Utilization Behaviour	0 %	0 %

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(29%), restlessness (29%), aggression (29%), hypersexuality (21%), and incontinence (21%). The mean FBI response score for the ALS group (N=10) was 5.5 (range of 0 to 12). The most commonly endorsed symptoms were verbal apraxia (70%), restlessness (50%), irritability (40%), logopenia (40%), alien hand (30%), apathy (20%), hypersexuality (20%), disorganization (20%), inattention (20%), and concreteness (20%). No PLS or ALS participants scored in the range of frontotemporal dementia as defined by a minimum score of 27[30]. The difference between groups on the overall FBI score was not significant. There were no significant correlations between number of impaired scores and total FBI scores in either the PLS or ALS groups.

Discussion

Our results indicated that on a group level, PLS patients scored broadly within normal limits (mean T-scores greater than 40) on all cognitive measures. However, a secondary analysis which examined the within-group data on a case by case basis revealed considerable heterogeneity among the patients, ranging from average to above-average scores across all measures in some patients to severely impaired scores across numerous cognitive processes in other patients. Although a majority of PLS patients were characterized by their study partners as exhibiting abnormal behavioural symptoms, variability was also evident (though not all study partners were available for the collection of this data). However, for the majority of PLS patients, cognitive, emotional, and behavioural symptoms were subtle and not within the range of frontotemporal dementia. Only 2 of 18 PLS patients showed both cognitive impairment and relatively high scores on the FBI (but not exceeding the cut-off for frontotemporal dementia). As a group, PLS patients did not exhibit significant symptoms of depression.

Although the majority of PLS patients did not demonstrate deficits in cognitive functioning, cognitive impairment, as defined in this study, does not appear to be an unusual or rare symptom of the disease. Using our definition of impairment, more than one third of PLS patients (39%) were classified as cognitively impaired. It is acknowledged that the secondary analysis that was completed to examine the frequency of cognitive impairment in patients was based on an arbitrary definition of cognitive impairment (i.e., at least two scores less than 1.5 SD below the mean) and use of a different definition would likely have yielded different results. However, this definition was judged to be a reasonable criterion for impairment given that several previous studies of ALS patients have utilized similar methodologies, in that the threshold for impairment was met if patients scored below a defined cut off value on two or more tests[31-33]. Furthermore, a recent consensus paper on the diagnosis of cognitive and behavioural syndromes in ALS has suggested that criteria for cognitive impairment be defined as scores at or below the fifth percentile on at least two tests sensitive to executive dysfunction[34]. In the current study, the cut off value of 1.5 SD below the mean was chosen as a compromise between a more lenient value of -1.0 SD (with a higher likelihood of false positive errors) and a more stringent value of -2.0 SD (with a higher likelihood of false negative errors).

A related issue that warrants discussion is the question of whether the observed frequency of cognitive impairment in the ALS and PLS groups is a reflection of normal variability or whether it reflects a pathological process. As it is now well-known that some neurologically healthy individuals demonstrate abnormal scores on neuropsychological testing[35], and the probability of abnormal scores increases as the number of tests increases[36], there is a risk of over-interpreting cognitive impairment in any given sample. Based on the binomial probability distribution, it would be expected that 6.7 percent of healthy individuals would score below the cut off value of -1.5 SD on a given task, and approximately 21.4 percent would be predicted to score below this level on two or more tasks out of 13[36]. For the PLS group, the rate of cognitive impairment (39%) was significantly different (higher) than the predicted rate of the binomial model ($\chi^2 = 19.53$; $p < .0001$). Similarly, for the ALS group, the rate of cognitive impairment (31%) was also significantly different (higher) when compared with the predicted rate of 21.4% from the binomial model ($\chi^2 = 6.028$; $p < .014$). Notwithstanding these results, the use of an appropriate control group would have been helpful for comparison in this study, and is suggested for future studies of this type.

In examining the pattern of abnormality in the test scores, the PLS group demonstrated a higher than expected frequency of impairment based on the binomial distribution on tests measuring oral word generation, memory for faces, verbal source memory, nonverbal working memory, written word generation, and verbal working memory. Interestingly, one of the most frequently impaired measures in this study was oral word fluency, a measure that has been found repeatedly impaired in patients with ALS[37]. This finding is consistent with other research showing that verbal fluency is the most sensitive measure in detecting cognitive impairment in PLS[10].

As with oral word fluency, the other tests found to show a relatively high frequency of impairment in the PLS group are tests similarly purported to measure frontally-based functions, including the Delayed Alternation Test, Thurstone Written Word Fluency, and the Consonants Trigrams Test. Although WRMT-Faces, a task of facial recognition, is not typically described as an executive measure, this is a novel visual-perceptual task which may rely on frontal-executive skills[38]. Another frequently impaired measure in this study, RAVLT-Recog, is designed as a verbal recognition source memory task in which the subject is asked to differentiate his/her recollection of words in terms of three possible sources or origin (List A, List B, or neither list). Given this demand on source memory, this task may also require frontally-mediated ability[39].

There were similarities in performance between the ALS and PLS groups. As with the PLS group, ALS patients as a group scored broadly within normal limits (mean T-scores greater than 40) on all cognitive measures, but also showed considerable variability in performance on a case by case basis. Direct comparison between groups revealed no significant differences on cognitive test variables with the exception of performance on the Consonant Trigrams Test. On this task, both groups performed at least within the average range; however the ALS group performed significantly better than the PLS group. Given that multiple comparisons were done as well as the older age and lesser education of the PLS group, the clinical meaningfulness of this isolated significant finding is questionable. Similar to the lack of cognitive differences, the groups were not significantly

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different in their overall scores on the emotional / behavioural measures including the GDS, NPI, and FBI.

We also observed that the frequency and nature of cognitive dysfunction in PLS and ALS are similar. The percentage of PLS patients classified as cognitively impaired (39 percent) was not significantly different from the percentage of ALS patients classified as cognitively impaired (31%; $\chi^2 = 3.0$; $p > .05$). The two groups also shared a similar pattern of test impairment, with both groups demonstrating a higher than expected frequency of impairment on several frontally-mediated tests including oral word fluency, memory for faces, and verbal source memory. Furthermore, the two groups were completely unimpaired on the same four measures (verbal delayed recall, recognition memory for words, visual-perceptual skill, and visual-constructional ability).

The PLS and ALS groups were also similar with respect to emotional and behavioural symptoms. Although neither group was depressed overall based on a self-report questionnaire, approximately half of available study partners in both groups perceived patients to be depressed or dysphoric. The discrepancy between a lack of depression symptomatology on the GDS and seemingly higher rate endorsed on the NPI appears due to the fact that the GDS is completed by the patients and the NPI is completed by the study partners. Therefore, a possible explanation is that study partners tend to perceive symptoms of depression in the patients who do not themselves perceive depression as an issue.

Furthermore, both groups endorsed relatively high rates of similar behavioural characteristics on the NPI, i.e., depression/dysphoria and night-time behaviour. The groups also shared four behaviours that were not endorsed by any patients: delusions; hallucinations; euphoria/elation; and disinhibition. Similarities between the groups were also seen on the FBI. Verbal apraxia was one of the most frequently reported symptoms for both groups. This symptom was likely endorsed frequently due to changes in speech that are common in both diseases. Five other symptoms were similarly endorsed among the highest in both groups: irritability, apathy, restlessness, logopenia, and alien hand. The relatively high frequency of the latter two symptoms reflects speech and motor impairment inherent in these motor neuron diseases. Three behavioural symptoms were not endorsed by any patients in either group: inappropriateness, hyperorality, and utilization behaviour.

Interestingly, there were no significant correlations between cognitive impairment in either group and various disease parameters including disease duration, site of onset, current site of disease, and overall functional status (ALSFRS-R). However, some analyses were not possible due to low sample sizes. Neither group demonstrated difficulties with respiratory functioning as assessed by forced vital capacity or CO_2 levels.

An important consideration in the neuropsychological assessment of individuals with motor neuron degeneration is selection of tests which minimize the impact of speech and motor dysfunction. Many of the tests used in this study required no speech production and only minimal motor requirements, and other tests requiring motor ability were adapted where necessary to reduce motor requirements. In addition, some tasks allowed for either written or oral responses depending on patients' capabilities. The only task which required significant manual control, Block Design, showed no impairment among any patients. With respect to the timed oral word fluency task (COWAT), there is a reasonable concern that oral-motor dysfunction may affect patients' performances. However, this concern is mitigated by previous research with ALS patients that demonstrates that the vast majority of words (90%) are generated in the first half of the test, suggesting that the limiting factor in this task concerns thought production of the words rather than oral-motor speed in speaking the words[40]. Previous studies also are consistent with this finding, noting a lack of effect of bulbar dysfunction[41] or specifically dysarthria[31] on oral word fluency performance. Finally, we found an equal distribution of impairment on the COWAT in PLS patients who exhibited both limb and bulbar dysfunction (33%) versus those who showed only limb involvement (33%).

Conclusions

Our findings suggest that cognitive and behavioural dysfunctions are not uncommon in PLS. These findings are consistent with the previous limited research indicating impairment in executive skills in patients with PLS[12]. Comparison of patients with PLS and ALS indicates no significant differences in cognitive functioning and overall emotional / behavioural functioning. Our results also suggest a similarity between patients with PLS and ALS in terms of the frequency and nature of cognitive dysfunction. We believe the pattern of findings in both groups reflects a dysexecutive syndrome resulting from dysfunction of frontal lobe circuitry.

With respect to the ongoing debate of whether PLS and ALS are distinct nosological entities or variants of a spectrum of motor neuron diseases, our findings only suggest that the frontotemporal syndromes of PLS and ALS reflect involvement of similar cerebral structures. While our data do not prove that PLS and ALS are part of a continuum, they do add further support to the concept that these conditions lie within a spectrum of disease rather than separate disease processes. However, notwithstanding the blurred distinctions between the two diseases, a continuing diagnostic separation between PLS and ALS may be warranted at this time due to the clinical heterogeneity and markedly different prognoses involved in the two diseases, and to also aid in the expansion of etiological and treatment knowledge with respect to these motor neuron diseases[42-44].

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