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Diverse cognitive impairment after spinal cord injury is associated with orthostatic hypotension symptom burden

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ABSTRACT

This study: 1) compared cognitive functioning between individuals with chronic (>1 year) spinal cord injury (SCI) and non-injured controls and, 2) assessed associations between symptoms of autonomic dysreflexia and orthostatic hypotension with cognitive functioning in SCI participants with a history of unstable blood pressure (BP). Thirty-two individuals with SCI (C4–L2, American Spinal Injury Association Impairment Scale A-D) and thirty age, sex-matched non-injured controls participated in this study. Participants completed a motor-free neuropsychological test battery assessing 1) memory, 2) attention/concentration/psychomotor speed and, 3) executive function.

Nineteen participants with SCI who had injuries ≥T6 and a history of unstable BP also completed the Autonomic Dysfunction Following Spinal Cord Injury (ADFSCI) questionnaire. Cognitive function was significantly lower in people with SCI across measures of memory and executive function compared to non-injured controls. Significant, moderate-to-large associations were observed between cumulative (frequency x severity) orthostatic hypotension and total BP instability symptoms scores, with measures of attention/concentration/psychomotor speed and executive function. These data demonstrate a 10 – 65% reduced performance across specific realms of cognitive functioning in individuals with SCI relative to non-injured controls. Furthermore, cumulative subjective scores for symptoms of unstable BP were associated with diverse cognitive deficits. These findings, in individuals without co-occurring traumatic brain injury, imply cardiovascular dysregulation plays a role in cognitive deficits observed in this population.

1. Introduction

Cognitive dysfunction after spinal cord injury (SCI) is widespread, with 10–60% of this population being afflicted [1]. Declines in cognition after SCI are diverse affecting various domains such as abstract reasoning, memory storage and retrieval, attention, concentration, and problem solving [1–4]. In the general population poor cognitive function is associated with unemployment and lower work performance, reduced health literacy [5], depression [6], and increased mortality [7]. Impaired cognition presents in the sub-acute phase post-SCI, which may impede functional rehabilitation, and worsens over time [8]. Reduced cognitive performance has been demonstrated in chronically-injured SCI individuals compared to age-matched non-injured controls [9]. However, no significant differences were noted in cognitive performance when compared to healthy controls that were ~ 20 years older. Thus, it has been argued that SCI may represent a model of premature aging [10]. The reasons for cognitive impairments in this population are multifactorial [1]. Up to ~60% of individuals with a high-level SCI sustain a concomitant traumatic brain injury (TBI) [11]. Recently, we and others have highlighted that autonomic cardiovascular dysfunctions are contributing factors towards cognitive decline after SCI [1,12,13].

Autonomic dysfunction following upper-thoracic or cervical SCI is widespread, and are often reported to be of a higher importance to those living with this condition than restoring lower extremity motor function [14]. From a cardiovascular perspective, individuals with

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high-level SCI [at or above the 6th thoracic segment (≥T6)] experience extreme BP fluctuations that manifest as periods of transient hypotension (orthostatic hypotension) and hypertension (i.e. autonomic dysreflexia) [15]. Orthostatic hypotension is defined as a decrease in systolic or diastolic BP of more than 20 or 10 mmHg, respectively, within three minutes of becoming upright in posture [16]. Orthostatic hypotension assessed at midlife has been shown to be independently associated with incident dementia and ischemic stroke over a twenty-five year follow-up [17]. Studies in non-disabled, hypotensive individuals have shown decreased ability in sustaining attention and working memory [18–21]. The loss of supraspinal sympathetic nervous system input following high-level SCI leads to systemic hypotension, which is worsened with postural stress and triggered by an impaired hemodynamic balance [22]. SCI individuals who experience hypotensive episodes have previously shown significantly impaired cognitive function in the domains of memory, executive function, and moderate impairment in attention and processing speed [23].

Another form of cardiovascular dysfunction is autonomic dysreflexia, which is experienced by over 90% of individuals with chronic high-level SCI [24,25]. It has been speculated that autonomic dysreflexia contributes to a variety of clinical conditions, including cognitive dysfunction, which is potentially mediated by impairments in cerebrovascular function [26]. During episodes of autonomic dysreflexia, BP can rise as high as 300 mmHg, which can result in stroke, other cerebrovascular trauma, or even death [27]. We have reported as many as 41 autonomic dysreflexia events occur each day (mean = 11/day) in individuals with high-level SCI [28]. Recent evidence in pre-clinical models demonstrates diverse cerebrovascular impairments with chronic exposure to repetitive episodes of transient hypertension following SCI [29]. Chronic hypertension in non-disabled individuals is strongly and consistently associated with cognitive decline [30]. Evidence demonstrates cognitive decline with chronic hypertension essentially encompasses the entire spectrum of cognitive domains including learning and memory, attention, abstract reasoning, executive function, as well as visuospatial, perceptual and psychomotor abilities [31–33]. In addition, a number of recent reviews have documented that hypertension is a causal factor in the development of vascular dementia, as well as mild cognitive impairments [34,35]. To date no study has examined the associations between symptoms of transient episodes of hypotension and hypertension with cognitive functioning in individuals with SCI. Understanding these associations may help identify interventional targets for reducing cognitive impairment in this population.

The aims of this study were to: 1) compare cognitive function between individuals with chronic SCI and age and sex-matched non-injured controls, and 2) test the association between orthostatic hypotension, autonomic dysreflexia and cognitive function in individuals with SCI ≥T6. We hypothesized that those with SCI would have impaired cognitive function across several domains compared to non-injured controls and that symptoms of orthostatic hypotension and autonomic dysreflexia would be associated with a range of cognitive deficits.

2. Methods

Participants included 32 individuals with chronic SCI (>1 year) and 30 aged- and sex-matched non-injured controls. The level and completeness of injury was confirmed using an International Standards for Neurological Classification of SCI (ISNCSCI) examination performed by a trained physician (AVK), which provided an American Spinal Injury Association Impairment Scale (AIS) grade [36]. Participants had no history of cardiovascular disease or TBI, or hearing or language issues that may affect the ability to follow instructions. Demographic information of participants is presented in Table 1. Informed consent was obtained from all participants and the protocol was approved by the University of British Columbia Clinical Research Ethics Board. This study was completed over one visit, which included the ISNCSCI assessment, followed by the completion of a self-reported questionnaire to quantify BP instability and a motor-free neurocognitive assessment battery. Participants with SCI were recruited first. Individuals with SCI responded to recruitment flyers advertised at inpatient (GF Strong Rehabilitation C1enter) and outpatient (Blusson Spinal Cord C1enter) treatment facilities in greater Vancouver. Non-injured controls were recruited from the local community and hospital personnel via posters and social-media platforms.

Table 1
Demographic and injury characteristics for non-injured controls and participants with spinal cord injury.

	Control-AB (n = 30)	SCI (n = 32)	P value
Demographics			
Age (years)	44 ± 11	39 ± 11	0.093
Sex: n (%)			
Male	23 (77%)	25 (78%)	1.000[a]
Female	7 (23%)	7 (22%)	
BDI-II	3.9 ± 5.0	10.8 ± 9.3	**<0.001**
SYS (mmHg)	126 ± 10	107 ± 7	**<0.001**
DIA (mmHg)	77 ± 9	62 ± 5	**<0.001**
Injury characteristics			
Injury Level; n (%)			
Cervical	–	15 (47%)	–
Thoracic	–	16 (50%)	–
Lumbar	–	1 (3%)	–
AIS n (%)			
Motor-complete (A or B)	–	23 (72%)	–
Motor-incomplete (C or D)	–	9 (28%)	–
TSI (years)	–	13 ± 10	–

Values are displayed as mean ± SD for numerical variables and percentages for categorical variables. [a] For frequency data, two-sample tests for equality of proportions without continuity correction were performed.
Abbreviations: AIS, American Spinal Injury Association Impairment Scale; BDI-II, Beck Depression Inventory; DIA, diastolic blood pressure; SYS, systolic blood pressure; TSI, Time Since Injury.

2.1. Assessment of blood pressure instability

For participants with injuries ≥T6, information about symptoms of BP instability were captured through an adapted version of the Autonomic Dysfunction Following SCI (ADFSCI) questionnaire, which was developed for use in both clinical and research settings [28]. The ADFSCI was designed using the Delphi technique by a consortium of experts with experience in treating individuals with SCI. Previous research has demonstrated this questionnaire to have almost perfect test-retest reliability and adequate sensitivity to detect the frequency and severity of autonomic dysreflexia episodes, compared to 24 h ambulatory blood pressure monitoring (ABPM) [28]. The questionnaire asked participants to rate the frequency and severity of specific symptoms related to orthostatic hypotension (six items: dizziness, nausea, fatigue, passing out, lightheadedness, blurred vision) and autonomic dysreflexia (three items: sweating, headaches, goosebumps) experienced on a daily basis. Each item was answered using a 4-point Likert scale with the following anchors: symptom frequency = "*Frequently*", "*Sometimes*", "*Rarely*" and "*Never*", and symptom severity = "*Severely*", "*Moderately*", "*Mildly*" and "*Never*". Symptoms of BP instability were assessed in participants with an SCI ≥T6 (n = =19), with a history of unstable BP fluctuations due to decentralized sympathetic control of splanchnic and lower extremity vasculature [15]. Given the greater prevalence of autonomic dysreflexia and orthostatic hypotension with more severe injuries, only motor-complete injuries (AIS A and B) were included in this component of the study.

For the frequency of each symptom, participants who answered "*Never*" were given a score of 0, "*Rarely*" or "*Sometimes*" were given a score of 1, and "*Frequently*" received a score of 2. The severity of each orthostatic hypotension and autonomic dysreflexia symptom was

Table 2
Neurocognitive function outcomes for non-injured controls and participants with spinal cord injury.

Domain and test	Control-AB (n = 30)	SCI (n = 32)	Mean difference (lower and upper 95% CI)	Cohen's D	P value
Memory					
RAVLT, *total acquisition* (n)*	51.8 ± 9.8	46.9 ± 8.2	**−4.9 (−9.5, −0.4)**	**0.54**	**0.034**
RAVLT, *recall after interference* (n)*	10.4 ± 3.1	8.9 ± 2.9	−1.5 (−3.0, 0.1)	0.50	0.059
RAVLT, *loss after interference* (n)†	2.0 ± 1.8	2.5 ± 1.7	0.5 (−0.4, 1.4)	−0.29	0.242
RAVLT, *long delay free recall* (n)*	10.6 ± 3.2	8.7 ± 2.6	**−1.9 (−3.4, −0.5)**	**0.65**	**0.010**
RAVLT, *recognition* (n)*	13.7 ± 1.7	13.0 ± 1.7	−0.7 (−1.6, 0.1)	0.41	0.097
Attention/Concentration/Psychomotor Speed					
DS, *forward* (n)*	9.1 ± 2.5	8.5 ± 2.2	−0.6 (−1.8, 0.6)	0.25	0.341
DS, *backward* (n)*	5.8 ± 2.1	4.8 ± 2.5	−1.0 (−2.2, 0.2)	0.43	0.096
DS, *score* (n)*	14.9 ± 4.2	13.3 ± 4.2	−1.6 (−3.7, 0.6)	0.38	0.151
TMT, *A* (s)	7.2 ± 2.5	7.3 ± 2.0	0.1 (−1.0, 1.3)	−0.04	0.773
Stroop Test-P2 Time (s)	50.8 ± 11.3	51.9 ± 9.7	1.1 (−4.2, 6.4)	−0.10	0.680
Stroop Test-P3 Time (s)	85.2 ± 18.7	84.5 ± 15.9	−0.7 (−9.5, 8.1)	0.04	0.876
Stroop Test-P3-P2 (s)	34.4 ± 14.4	32.6 ± 11.8	−1.8 (−8.5, 4.9)	0.14	0.593
Executive Function					
TMT, *B* (s)	26.6 ± 14.2	45.7 ± 40.3	**19.1 (3.9, 34.5)**	**−0.63**	**0.016**
TMT, *B-A* (s)	19.4 ± 13.9	38.4 ± 39.6	**19.0 (4.0, 34.1)**	**−0.64**	**0.016**
SDMT (n)*	59.9 ± 11.7	53.3 ± 9.2	**−6.6 (−12.0, −1.3)**	**0.63**	**0.015**
COWAT (n)*	44.7 ± 12.6	40.0 ± 11.7	−4.7 (−10.9, 1.5)	0.39	0.135

Values are shown as Mean ± *S*.D. *P* values and 95% CI's for each metric were reported appropriately depending on the Levene's test for equality of variances. *Higher score indicates better performance. † Loss after interference calculated as trial 5 score minus trial 6 score. *Abbreviations: CI, confidence interval; COWAT, Controlled Oral Word Association Test; DS, Digit Span; RAVLT, Rey Auditory Verbal Learning Test; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test.*

scored similarly, with "*Never*" receiving a score of 0, "*Moderately*" or "*Mildly*" as 1, and "*Severely*" as a score of 2. Total frequency and severity scores were calculated for orthostatic hypotension, autonomic dysreflexia and total (representing absolute BP instability) symptoms by summing the scores across corresponding symptoms to create arbitrary units. The cumulative score (used in Table 3) was calculated by multiplying the numerical values of frequency by severity, for orthostatic hypotension, autonomic dysreflexia and total symptoms, respectively. To minimize the amount of comparisons and to reduce the likelihood of type-II error we felt it pertinent to only present cumulative scores rather than both frequency and severity values.

2.2. Neurocognitive test battery

All neurocognitive assessments were conducted by an experienced research coordinator and required approximately 60 min. Demographic characteristics were gathered and seated BP measured (Dinamap Pro 300V2; General Electric). The following cognitive and behavioral motor-free tests were performed in a fixed order: Rey Auditory Verbal Learning Test (RAVLT), Forward and Backward Digit Span Test (DS), Symbol Digit Modalities Test (SDMT), Verbal Trail Making Test A and B (TMT), Stroop Test, Controlled Oral Word Association Test (COWAT), and Beck Depression Inventory. These tests assessed the following subdomains of: 1) *memory*: Rey Auditory Verbal Learning Test (RAVLT) [37]; 2) *attention/concentration/psychomotor speed*: Forward and Backward DS [37], Trail Making Test (TMT) part A [38], and Stroop Test [39]; 3) *executive function*: Trail Making Test (TMT) part B [38], Symbol Digit Modalities Test (SDMT) [37], and Controlled Oral Word Association Test (COWAT) [37]. This comprehensive neurocognitive test battery has been shown to be reliable in individuals with SCI [40]. All tests were delivered orally to account for motor function disparities between individuals with higher and lower level SCI and non-injured controls. Symptoms of depression were also assessed using the Beck Depression Inventory (BDI-II) [41].

2.3. Statistical analysis

The demographic and injury characteristics of the groups were described as means ± standard deviations or percentages. Following an assessment of normality (Levene's Test for Equality of Variances), differences in demographic variables between groups (control-AB vs. SCI) were assessed using parametric (i.e., independent sample t-tests) or nonparametric comparisons (i.e., Mann-Whitney U test) for continuous numerical variables (age, BDI-II and BP) and a two-sample tests for equality of proportions without continuity correction for categorical variables (sex). The neurocognitive function data were described as means ± standard deviations, along with the mean differences between the groups (with upper and lower confidence intervals). Independent sample t-tests were performed and a standardized difference (Cohen's D) calculated, with the following thresholds: small ($d > 0.20$), medium ($d > 0.50$) and large ($d > 0.80$). Spearman Rank Correlation Coefficients were employed to examine the associations between cumulative (frequency x severity) symptom scores for specific conditions (autonomic dysreflexia and orthostatic hypotension) and total BP instability with neurocognitive test outcomes in a subsample of participants with SCI ≥T6. The following thresholds will be used to quantify the magnitude of associations: small (Rs > 0.1), moderate (Rs >0.3), large (Rs > 0.5), very large (Rs > 0.7). The threshold for statistical significance was set a priori at $p < 0.05$.

3. Results

Participant characteristics are summarized in Table 1, which shows that there were no significant differences between SCI and non-injured controls with respect to age ($p = 0.093$) and sex ($p = 0.999$). On average, individuals with SCI scored significantly higher on the BDI-II ($p < 0.001$) and had lower resting systolic and diastolic BP relative to the non-injured controls (Table 1).

3.1. Differences in neurocognitive test performance between individuals with spinal cord injury and age, sex matched non-injured controls

Compared to the non-injured control group; individuals with SCI had impairments in *memory* and *executive function* domains (Table 2). In the *memory* domain, individuals with SCI recalled ~5 (10%) fewer words in total and recalled ~2 (20%) fewer words after a long delay during the RAVLT compared to the control group. No significant differences were found between SCI and the control group in the domain of *attention/concentration/psychomotor speed*. In the domain of *executive function*, individuals with SCI took approximately twice as long as controls to complete the TMT task. Moreover, non-injured controls scored ~12% higher in the modified SDMT (i.e. de-coded 11% more

Table 3
Associations between neurocognitive function outcomes and cumulative (frequency multiplied by severity) autonomic dysreflexia, orthostatic hypotension and total BP instability symptoms for individuals with spinal cord injury at or above the 6th thoracic level (n = 19).

Domain and Test	Cumulative AD symptoms score		Cumulative OH symptoms score		Cumulative total BP instability symptom score	
	R_S	P	R_S	P	Rs	P
Memory						
RAVLT, *total acquisition* (n)	−0.226	.177	−0.247	.154	−0.196	.210
RAVLT, *recall after interference* (n)	−0.277	.126	−0.096	.348	−0.096	.348
RAVLT, *loss after interference* (n)	0.258	.118	−0.125	.305	−0.077	.378
RAVLT, *long delay free recall* (n)	−0.252	.149	−0.196	.210	−0.232	.170
RAVLT, *recognition* (n)	−0.091	.356	−0.060	.404	.029	.453
Attention/concentration/psychomotor speed						
DS, *forward* (n)	.123	.308	−0.026	.459	−0.052	.416
DS, *backward* (n)	.046	.425	−0.016	.473	−0.015	.475
DS, *score* (n)	.098	.346	.068	.391	.056	.411
TMT, *A* (s)	.375	.057	.314	.095	***.441***	***.029****
Stroop Test P2 (s)	−0.008	.488	***.448***	***.027****	.330	.084
Stroop Test P3 (s)	.187	.222	***.506***	***.014****	***.434***	***.032****
Stroop Test P3-P2 (s)	.176	.236	.244	.157	.330	.084
Executive Function						
TMT, *B* (s)	.188	.221	***.499***	***.015****	***.433***	***.032****
TMT, *B-A* (s)	.213	.191	***.485***	***.018****	***.398***	***.046***
SDMT (n)	.192	.215	.084	.366	.155	.264
COWAT (n)	−0.018	.471	−0.020	.467	−0.055	.411

* $P < 0.05$. Abbreviations: COWAT, Controlled Oral Word Association Test; DS, Digit Span; RAVLT, Rey Auditory Verbal Learning Test; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test.

symbols to numbers) (Table 2).

3.2. Symptoms of blood pressure instability and neurocognitive test performance in individuals with cervical and upper-thoracic spinal cord injury

The associations between neurocognitive test performance and self-reported cumulative burden of autonomic dysreflexia, orthostatic hypotension and total BP instability are presented in Table 3. These associations were performed in individuals with SCI ≥T6, with a history of unstable BP control. No significant associations were observed within the *memory* domain. Cumulative orthostatic hypotension and total BP instability scores displayed moderate, significant positive associations in the *attention/concentration/psychomotor speed* and *executive function* domains. More specifically, individuals with higher cumulative orthostatic hypotension and total symptoms took longer to complete the Stroop Test P2 & P3, TMT B, as well as TMT B-A. A moderate, non-significant (P = 0.057), positive association was seen between autonomic dysreflexia symptoms and the time to count from 1 to 25. No significant associations were observed with cumulative symptoms of autonomic dysreflexia and neurocognitive test performance.

4. Discussion

This study, utilizing a comprehensive and reliable neurocognitive test battery, demonstrates that cognitive function is impaired following SCI. Specifically, test performance in *memory* and *executive functioning* domains were impacted relative to non-injured controls, with this effect being considered of a moderate magnitude. A sub analysis in individuals with SCI ≥T6 and a history of unstable BP control revealed moderate to large associations between cumulative orthostatic hypotension symptom burden and cognitive function. These associations were observed in the cognitive domains of *attention/concentration/psychomotor speed* and *executive function* and were also apparent when all symptoms of BP instability were combined.

Our findings are consistent with previous studies looking at cognition in hypotensive individuals with SCI. For example, Jegede et al. demonstrated significantly reduced memory and moderately reduced attention and processing speed in participants with SCI, who were hypotensive over a 24-h period [23]. We have now extended these findings to show that chronic symptomatic hypotension is linked with cognitive impairment. Cerebral blood flow is regulated by a number of factors including dynamic cerebral autoregulation, cerebrovascular reactivity to changes in arterial blood gas tension, and neurovascular coupling. In high-level SCI unstable cerebral perfusion occurs due to alteration in these regulatory systems [26]. Consequently, cerebrovascular reserve, which reflects the capacity of the cerebrovasculature to maintain adequate blood flow when faced with a decreased perfusion pressure [42], is negatively impacted. In turn, a decline in cerebrovascular reserve will inhibit the capacity for neurovascular coupling to appropriately link neuronal metabolism to cerebral blood flow, and decreased cognitive function may occur as a result [43]. It is conceivable that breakdown of these cerebrovascular regulatory systems after SCI may also underlie the up-to four-fold increased risk of stroke in this population [44]. We have shown previously that when BP was increased in individuals with SCI by using midodrine hydrochloride, an alpha-1 agonist it translated to a 70% improvement in neurovascular coupling [45]. This was reflected by a significant improvement in cognitive function as measured by COWAT.

After combining the symptoms for both orthostatic hypotension and autonomic dysreflexia it was evident that unstable fluctuations in systemic BP are associated with widespread cognitive dysfunction. These conditions can happen multiple times over a 24-h period, in the same individuals with SCI ≥T6 [28], which in extreme cases predispose the cerebrovasculature to an acute hemodynamic insult or in less severe cases, repetitive, cumulative insults may lead to cerebrovascular dysfunction through hyper and hypo-perfusion. Interestingly, recent cross-sectional evidence from our laboratory suggests central arterial stiffness, assessed via carotid-to-femoral pulse wave velocity (cfPWV), was associated with the severity and frequency of objectively measured hypotensive events (using 24-h ABPM) but not autonomic dysreflexia [46]. However, similar to the findings presented herein, the strongest association (r = =0.445, P = =0.02) was observed between cfPWV and combined total autonomic dysreflexia and hypotensive events. These data suggest that BP instability plays a role in arterial stiffening. Such systemic changes are likely to permeate to the cerebrovasculature and it is therefore not surprising that evidence in the able-bodied literature has associated cognitive deficits with increased arterial stiffness [47–49]. It is worth noting that while individuals with SCI below T6 do not experience such widespread BP fluctuations, evidence still suggests a high prevalence of arterial stiffness [50,51], perhaps as a result of physical inactivity [52,53]. Therefore, alterations in vascular morphology may explain the reduced cognitive performance in those participants with injuries below T6 without a history of unstable BP control included in the SCI cohort.

Significant associations were not observed with autonomic dysreflexia symptom burden alone. Autonomic dysreflexia is characterized by transient hypertensive episodes, which have been shown to acutely insult cerebral blood vessels [27,54,55]. Chronic hypertension in able-bodied individuals is strongly associated with cognitive decline, encompassing essentially the entire spectrum of cognitive domains including learning and memory, attention, abstract reasoning, executive function, as well as visuospatial, perceptual and psychomotor abilities [56–58]. Preliminary evidence in rodent models suggests that chronic exposure to repetitive transient hypertension after SCI leads to impaired cerebrovascular functioning of the middle cerebral artery and profibrotic cerebrovascular remodeling [29]. Interestingly, these changes

occurred in the absence of other hallmark cerebrovascular changes (i.e. hypertrophic inward remodeling or reduced cerebral blood flow) associated with chronic steady-state hypertension [59]. It is possible the transient nature of autonomic dysreflexia may present a different mechanistic effect on cerebrovascular remodeling than chronic hypertension. Further research is necessary to elucidate these differences.

4.1. Limitations

This study provides compelling, yet observational, cross-sectional data highlighting associations between symptoms of unstable BP and impaired cognitive function in individuals with SCI ≥T6. Individuals with higher-level SCI who are predisposed to drastic BP fluctuations are likely to be less physically active and experience other secondary comorbidities (i.e. sleep apnea, major depressive disorder, fatigue and impaired glucose tolerance), which may confound the findings of this study [60–63]. Sleep apnea is present in up to 50% of individuals with high-level SCI [64], while depression also affects a large proportion of this population [65]. Although significant differences were noted between groups for symptoms of depression, the group means for the BDI-II are both considered to be within the '*none or minimal depression*' range (0 – 13), indicating non-clinically meaningful differences. We recognize that side effects from pharmacological agents used to manage secondary complications following SCI (i.e. antimuscarinics for the treatment of lower urinary tract dysfunctions and gabapentin to treat neuropathic pain) can also impair cognitive function [66,67]. While not captured in this present study, it has previously been demonstrated that individuals with SCI are prescribed significantly more medications than non-injured counterparts [68] and the potential impact of these drug-drug interactions on cognitive functioning is currently unclear. Future research should consider assessing and controlling for these confounding variables in analyses or study designs to determine the specific factors linked with cognitive decline in this population.

The adapted version of the ADFSCI questionnaire may require refinement. While the reported frequency of autonomic dysreflexia from the ADFSCI questionnaire is closely associated with hypertensive events ascertained from 24-h ABPM, the frequency and severity of orthostatic hypotension symptoms were not significantly associated with objectively measured episodes of hypotension [28]. Therefore, specific symptoms relating to orthostatic hypotension (i.e. nausea, passing out and lightheadedness) may represent other undiagnosed conditions or underlying pathologies that are linked to cognitive impairment besides hypotensive episodes alone. Moreover, not all episodes of autonomic dysreflexia present with immediate critical emergencies. Many episodes can be silent and are therefore undetected by the individual. In light of this, researchers should consider using objective measurement methods to quantify the frequency and severity of unstable BP episodes and determine the interplay with cognitive functioning in individuals with SCI.

5. Conclusions

Diverse cognitive dysfunction is shown in individuals with SCI without a history of TBI relative to age and sex matched non-injured controls. Significant associations are demonstrated between orthostatic hypotension symptom burden and neurocognitive test performance for participants with injuries ≥T6 and a history of unstable BP control, further implicating this condition in the etiology of cognitive impairments in this specific population. However, we caveat that these data are taken from a self-report questionnaire and follow-up work should be conducted with objective monitoring techniques, such as 24-h ABPM to replicate these observations. Future studies are needed to examine whether impaired cerebrovascular function is the mechanism linking aberrant systemic BP changes with cognitive decline in humans following SCI. Rigorous, longitudinal cohort studies are necessary to elucidate the underlying causality of cognitive deficits commonly observed in this population. Animal models should also be employed to develop a deeper mechanistic insight into the impact of unstable BP overtime and subsequent cerebrovascular insults, such as blood-brain barrier breakdown and other brain pathologies (i.e. white matter hyperintensities, lacunar infarcts, gray matter atrophy etc.), and how these link to cognitive impairments in individuals with SCI.

Declaration of Competing Interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.physbeh.2019.112742.

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