Cognitive function after spinal cord injury

A systematic review

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Abstract

Objective

To systematically examine the incidence of cognitive impairment in individuals with spinal cord injury (SCI), as well as identify potential contributing and confounding factors.

Methods

Studies quantitatively reporting cognitive ability after spinal cord injury were searched electronically via Medline, CINAHL, Embase, and PsycINFO. Manual screening for references within articles was also performed. A total of 2,481 studies were screened and a total of 70 were included in this review, 21 reporting cognitive function after SCI compared to an able-bodied control group and 49 with no able-bodied controls. Studies were analyzed for the incidence of impairment and the interactions with concomitant traumatic brain injury, psychological or somatic complaints, decentralized cardiovascular control, sleep apnea, neurologic level of injury, and age.

Results

There is a high volume of evidence reporting substantial cognitive impairment in individuals with SCI. Potential co-contributors include concomitant brain injury, psychological or somatic comorbidities, decentralized cardiovascular control, and sleep apnea. Cognitive functioning was negatively correlated with age. No clear agreement was found for the incidence of cognitive impairment or its association with level of injury.

Conclusion

Current evidence suggests that individuals with SCI should be examined and addressed for cognitive impairment. Future studies aimed at identifying potential secondary causative factors should employ stringent controls for co-occurring brain trauma since it appears to be a major contributor and confounder to impaired cognition.

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Glossary

CBF = cerebral blood flow; **FIM** = Functional Independence Measure; **HCT** = Halstead Category Test; **NUCOG** = Neuropsychiatry Unit Cognitive Assessment Tool; **OSA** = obstructive sleep apnea; **SCI** = spinal cord injury; **TBI** = traumatic brain injury.

Spinal cord injury (SCI) is a physically and psychologically debilitating event, where an individual faces immediate and potentially permanent life changes.^{1–5} Prior to the 1940s, only 10%–20% of individuals survived longer than a few weeks after injury.⁶ Technological advancements have dramatically improved these figures, with up to 90% of individuals now surviving past the first year of injury and nearly 50% surviving for 40 years postinjury.⁷ This has led to the expansion of rehabilitation programs to include gainful employment and community reintegration rather than merely focusing on survival and return of physical function.⁸ Consequently, following acute care, patients undergo exhaustive rehabilitation that involves extensive learning, practicing, and integrating radically new skills.⁹ This daunting task can be severely impeded by impairments in cognitive domains such as memory, learning, and social communication. Therefore, to improve quality of life after SCI, it is important to assess cognitive status and develop focused rehabilitation strategies to mitigate cognitive impairments.

Pioneering work on cognitive health after SCI showed that up to 64% of injured individuals were cognitively impaired.¹⁰ Several subsequent studies have confirmed significant impairments in various cognitive domains as well as the presence of depression and anxiety.^{2,4,11–13} According to a recent report, individuals with SCI have an increased risk of cognitive impairment, approximately 13 times higher than able-bodied individuals.¹⁴ Moreover, cognitive impairment is also a strong predictor of poor social participation post-discharge with 8.4 to 1 odds against employment.¹⁵ In refining the existing care and rehabilitation guidelines, the magnitude of this problem needs to be systematically evaluated. However, some of the early reviews of cognitive impairment after SCI were published in the 1990s,^{2,4} while others were conducted in light of more focused situations, such as a concomitant traumatic brain injury (TBI)^{16,17} or impaired cardiovascular control.^{18,19} None of these reviews is systematic and therefore many relevant studies may have been missed.

Although many studies reported cognitive decline after SCI, the specific findings vary in terms of incidence and the degree of impairment. This is likely due to factors such as the type of test used, neurologic level of lesion, age, educational background, premorbid psychological/learning disabilities, and alcohol and substance abuse. Furthermore, it is also necessary to investigate the effect of other secondary conditions commonly present among individuals with SCI, e.g., TBI, depression, anxiety, pain, fatigue, cardiovascular dysfunction,

and sleep apnea. This review specifically addresses the following questions:

1. What is the current agreement across published studies on the presence of cognitive impairment after SCI?
2. What is the estimated incidence of cognitive impairment after SCI?
3. What are the contributions or confounding effects of a concomitant TBI?
4. Does the presence of psychological comorbidities affect cognitive functioning?
5. Does decentralized cardiovascular control affect cognitive function?
6. Does sleep apnea affect cognitive ability after SCI?
7. Does the neurologic level of lesion correlate with severity of cognitive impairment?
8. Does age affect cognitive function after SCI?

Methods

Search strategy

The search, screening, and selection process was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.²⁰ A keyword literature search was conducted for all scientific publications between 1946 and the present investigating the interaction between SCI and cognitive function in humans via the following databases: Medline, CINAHL, Embase, and PsycINFO. The various keywords for cognitive impairment were searched with SCI keywords using Boolean operators (table e-1; doi.org/10.5061/dryad.rj74424). A manual search was also conducted within the references of relevant articles.

Eligibility criteria

Only studies reporting a quantitative measure of cognitive function after traumatic or nontraumatic SCI were chosen for analysis. Studies were excluded if cognitive function was not reported based on a quantifiable test. Conference abstracts, narrative reviews, and studies published in languages other than English were also excluded. Multiple publications using the same cohort (or a subset of the cohort) were considered for inclusion only when a different outcome measure was reported. In order to produce an unbiased comprehensive review covering most reports of cognitive function after SCI, studies were also included if (1) cognitive function after SCI was reported without comparison against able-bodied controls and (2) cognitive assessment was not the primary goal of the study, but was quantitatively reported. These studies are presented separately in table e-3 (doi.org/10.5061/dryad.

rj74424). Two authors (R.S. and A.V.K.) independently screened all the studies for eligibility criteria. All discrepancies were discussed and resolved by a mutual consensus.

Data were extracted into a table format to depict participants, time since injury, and the types of tests utilized to assess cognitive function. A summary statement of the main outcomes was also generated.

Results

A total of 2,481 articles were retrieved through the electronic search. Individual case studies or case series were excluded with 2 exceptions^{21,22} where the cases were compared to a group of appropriately matched controls. Balanced inclusion of case studies has been suggested to increase the evidence base and strengthen the credibility of systematic reviews.²³ A total of 151 full-text studies were reviewed for eligibility and 70 were included (figure e-1; doi.org/10.5061/dryad.rj74424).

Of the 70 studies selected for this review, 21 (table e-2; doi.org/10.5061/dryad.rj74424) directly compared cognitive function between individuals with SCI and able-bodied controls. In the remaining 49 studies (table e-3; doi.org/10.5061/dryad.rj74424) that did not include an able-bodied control group, the results were reported based on normative data. We first analyzed studies to estimate the incidence of cognitive deficits reported among participants with SCI (table 1). Further analyses included various factors that can potentially contribute to cognitive decline after SCI, such as concomitant TBI (table 2), psychological comorbidities (table 3), decentralized cardiovascular control (table 4), sleep apnea, age (table 5), and neurologic level of lesion (table 6). Some articles were used to address more than one question. Therefore, the studies shown in tables 1 and 6 are the subsets of studies listed in tables e-2 and e-3 (doi.org/10.5061/dryad.rj74424) and are discussed based on the most pertinent outcomes.

Is cognition impaired after SCI?

Considerable heterogeneity was observed across studies in terms of study design, type of cognitive tests utilized, as well as the various domains of cognition assessed such as attention, concentration, executive function, memory, processing speed, and cognitive flexibility. Significant impairment in one or more of these cognitive domains after SCI was reported in the majority of studies (38/70). Of the 21 studies with able-bodied controls, 15 showed impaired cognition and 6 reported no significant alterations in individuals with SCI (table e-2; doi.org/10.5061/dryad.rj74424). Of the 49 studies with no able-bodied controls, 23 showed significant impairments in cognitive functioning while 26 studies reported scores to be within the normative range (table e-3; doi.org/10.5061/dryad.rj74424).

Incidence of cognitive impairment after SCI

To estimate the overall effect of cognitive impairment after SCI, studies were inspected for the proportion of participants

Table 1 Studies reporting the incidence of cognitive impairment after spinal cord injury (SCI)

Authors, year	Incidence
Davidoff et al., 1985 ²⁴	57% (HCT)
Wilmot et al., 1985 ¹⁰	64% (Neuropsychological test battery)
Roth et al., 1989 ²⁵	PA-recall (40%), Rey-recognition (31%), VOCAB (24%), RAVLT (10%), HCT (12%)
Davidoff et al., 1990 ²⁶	FIM (~0%), LM (4%), PA (3%), VOCAB (38%), RAVLT (63%), HCT (12%)
Radanov et al., 1993 ²¹	100% Based on NCT (likely due to small sample size and direct brainstem damage)
Dowler et al., 1995 ²⁷	41% Using SDMT and Stroop test (processing speed)
Dowler et al., 1997 ³⁶	60% (Neuropsychological test battery)
Strubreither et al., 1997 ²⁸	14.50% (Tests for OPS)
Hall et al., 1999 ²⁹	10%–20% (Ceiling effect) at discharge, 3%–11% at year 1, ~0% by year 2 based on FIM scale
Borgaro et al., 2003 ³⁰	Orientation to time (35.3%), orientation to place (5.9%) based on BNIS
Masedo et al., 2005 ³⁷	12% and 24% in communication and social cognition domains respectively on FIM self-report
Holtslag et al., 2007 ³¹	75% Based on HISC (not controlled for other severe trauma)
Tolonen et al., 2007 ³²	67.7% Based on a neuropsychological test battery (all impaired individuals had concomitant TBI)
Bradbury et al., 2008 ³³	Incidence reported only for FIM scale: SCI (0%), SCI + TBI (30%)
Macciocchi et al., 2013 ³⁴	1.33 SD below normative data: HVLTL (34.9%), WAIS-3 DS (6.3%), WAIS-3 LNS (19%), SDMT (53.1%), SCAT (34.9%), CVMT (35.9%)
Purohit et al., 2014 ³⁵	FIM cognitive score <5: comprehension (35%), expression (34%), social interaction (39%), memory (45%), problem solving (50%)
Zonfrillo et al., 2014 ³⁸	FIM cognitive score at or below 5: 52% of individuals with tetraplegia and 33% of those with paraplegia at admission and 19% (both groups) at discharge
Craig et al., 2017 ¹⁴	1 SD below the normative data (28.6%), 2 SD below the normative data (16.6%) based on NUCOG

Abbreviations: BNIS = Barrow Neurological Institute Screen; CVMT = Continuous Visual Memory Test; DS = digit span; FIM = Functional Independence Measure; HCT = Halstead Category Test; HISC = Head Injury Symptom Checklist; HVLTL = Hopkins Verbal Learning Test; LM = logical memory; LNS = letter-number sequencing; NCT = Number Connection Test; NUCOG = Neuropsychiatry Unit Cognitive Assessment Tool; OPS = Organic Psychic Syndrome; PA = Paired Associates; RAVLT = Rey Auditory Verbal Learning Test; SCAT = Category Test-Short Form; SDMT = Symbol Digit Modalities Test; TBI = traumatic brain injury; VOCAB = Vocabulary Subtest (WAIS); WAIS = Wechsler Adult Intelligence Scale.

scoring in the impaired range. A total of 18 studies matched the criteria (table 1).^{10,14,21,24–38}

Eight studies utilized the comprehensive neuropsychological test battery.^{10,25–28,32,34,36} Early reports by Wilmot et al.¹⁰ and

Table 2 Studies reporting the effect of a concomitant traumatic brain injury (TBI)

Author, year	Type of SCI	Outcomes
Davidoff et al., 1985 ²⁴	Both traumatic and nontraumatic	Mean HCT scores were abnormal for both SCI + TBI groups; however, no statistical significance was seen
Wilmot et al., 1985 ¹⁰	Traumatic	43/67 (64%) Of the patients scored as mildly impaired to worse on a neuropsychological test battery
Richards et al., 1988 ⁴⁵	Traumatic	Scores were in the impaired range for HCT at first test; recovery was seen at retest in a pattern similar to TBI
Strubreither et al., 1997 ²⁸	Both traumatic and nontraumatic	47/65 (72.3) Of the patients with a cerebral lesion showed minor to severe degrees of impairment on OPS tests
Tolonen et al., 2007 ³²	Traumatic	On a neuropsychological test battery, 21 individuals showed cognitive impairment; i.e., 67.7% of the total sample and 91.3% of the SCI + TBI subgroup
Bradbury et al., 2008 ³³	Traumatic	Cognitive function was more impaired in SCI + TBI group based on neuropsychological battery; no significant difference was seen using FIM (ceiling effect)
Macciocchi et al., 2004 ⁴⁷	Traumatic	Persons with SCI + TBI showed more impaired cognitive FIM score at admission and discharge from rehabilitation
Macciocchi et al., 2008 ⁴²	Traumatic	TBI severity was associated with lower cognitive FIM scores
Macciocchi et al., 2012 ⁴⁶	Traumatic	Moderate and severe TBI (but not mild TBI) was associated with additional cognitive decline on FIM scale compared to SCI alone
Macciocchi et al., 2013 ³⁴	Traumatic	No additional effect of mild TBI on cognitive decline after SCI on a neuropsychological test battery
Nott et al., 2014 ⁴¹	Traumatic	No additional effect of a concomitant TBI on cognitive decline after SCI using the FIM scale

Abbreviations: FIM = Functional Independence Measure; HCT = Halstead Category Test; OPS = Organic Psychic Syndrome; SCI = spinal cord injury.

Davidoff et al.²⁶ reported the incidence of impairment at 64% and between 3% and 63%, respectively. However, the effect of TBI cannot be ruled out. The incidence of 14.5% reported by Strubreither et al.²⁸ was alarmingly high for participants with a comorbid TBI (72.3%). When excluding the individuals with TBI, Roth et al.²⁵ reported the incidence of cognitive impairment between 10% and 40% across multiple tests. Interestingly, Macciocchi et al.³⁴ showed that 6.3%–53.1% of participants with SCI were impaired across various cognitive domains regardless of a comorbid TBI. In a more chronic setting, Dowler et al.²⁷ reported that 17 years post SCI, the majority of individuals were indistinguishable from controls in memory, attention, executive function, and visuospatial skills, with only processing speed impaired in 41% of the sample. However, a follow-up study by this group used cluster analysis to show that 60% of the participants with SCI were impaired in at least one cognitive domain.³⁶ An incidence of 67.7% was also reported by Tolonen et al.³²; however, all impaired individuals in this report met the diagnostic criteria for TBI.

Five studies reported the incidence of cognitive impairment using individual tests.^{14,21,24,30,31} Based on the Halstead Category Test (HCT), Davidoff et al.²⁴ reported impairment in 57% of participants. In a later study, Borgaro et al.³⁰ used Barrow Neurological Institute Screen to report impaired orientation to time in 35.3% of individuals. A much higher incidence (75%) was reported by Holtslag et al.³¹ using the

Head Injury Symptom Checklist. These participants, however, were major trauma survivors and the effect of other trauma was not controlled for. Similarly, a study analyzing 7 patients with whiplash syndrome (with cervical SCI) reported cognitive impairment in all participants using a number connection test.²¹ However, this study had a much smaller sample size and cognitive impairment was likely a result of direct brainstem damage. Finally, more recent work by Craig et al.¹⁴ showed that 28.6% of participants with SCI scored 1 SD below normal on the Neuropsychiatry Unit Cognitive Assessment Tool (NUCOG).

Five studies reported the incidence of cognitive impairment using the Functional Independence Measure (FIM) instrument.^{29,33,35,37,38} The largest of these (n = 233,778) by Purohit et al.³⁵ showed the incidence of impairment across comprehension (35%), expression (34%), social interaction (39%), memory (45%), and problem-solving (50%) acutely after SCI. Zonfrillo et al.³⁸ reported impaired cognition in 52% of participants with tetraplegia and 33% of those with paraplegia at the time of admission and 19% in both groups at discharge. Interestingly, Hall et al.²⁹ analyzed 3,971 individuals with SCI at the time of discharge and performed follow-up assessments at years 1, 2, and 5 using the FIM scale. This study showed major ceiling effects in 80%–90% of patients at discharge. This range further improved to 89%–97% at year 1 and ~100% by year 2. Similar ceiling effects (i.e., no

Table 3 Studies investigating the effect of psychological/somatic comorbidities

Author, year	Tests for cognitive function	Tests for psychological comorbidities	Correlation	Control for TBI?
Dowler et al., 1995 ²⁷	SDMT, Stroop test, WMS, CVLT, WRMT, WAIS-R, PASAT, COWAT, WCST, HVOT, Line orientation	MMPI	MMPI scores were associated with poorer processing speed	Selectively included the participants with traumatic SCI with a greater possibility of co-occurring TBI
Shnek et al., 1997 ³⁰	Cognitive beliefs questionnaire	CES-D	Cognitive distortions were correlated with depression	Severe head injury cases were excluded
Tun et al., 1997 ⁵¹	Digit span, SWS, LWS, prose recall, CFQ, DAQ, MIA	GDS	No correlation of depression with cognitive test scores	None of the participants had a concomitant TBI
Murray et al., 2007 ⁵²	Self-perceived cognition (RNBI)	Pain subscale of RNBI	Pain was associated with cognitive impairment	Participants had no history of TBI
Jegade et al., 2010 ⁵³	WAIS, CVLT, COWAT, oral trails, Stroop test	BDI-II	No correlation of depression with cognitive function	Incidence of TBI was not different between the groups
Clarke et al., 2012 ⁵⁴	PACCO, RAVLT, Rey-Osterrieth, trail-making, SDMT, COWAT, WAIS	HADS, NEO 5-factor inventory	No correlation with cognitive function	Included participants had no injury to the brain
Craig et al., 2012 ⁵⁶	Iowa fatigue scale	DASS	Cognitive tiredness was linked with depression	9 Of 41 participants (22%) had a mild TBI
Craig et al., 2015 ⁵⁵	NUCOG	Psychiatric interview, HADS	Higher cognitive capacity suggested lower odds of psychological disorder	21.5% Of participants had concomitant TBI
Craig et al., 2017 ⁵⁵	NUCOG	Psych interview, numeric pain scale, HADS	Pain was higher in individuals with cognitive impairment; no effect of fatigue	Same as Craig et al., 2015

Abbreviations: BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; CFQ = Cognitive Failures Questionnaire; COWAT = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; DAQ = Divided Attention Questionnaire; DASS = Depression Anxiety Stress Scales; DSM = Diagnostic and Statistical Manual of Mental Disorders; FSS = Fatigue Severity Scale; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; LWS = Loaded Word Span; HVOT = Hooper Visual Organization Test; MIA = Metamemory In Adulthood; MMPI = Minnesota Multiphasic Personality Inventory; NUCOG = Neuropsychiatry Unit Cognitive Assessment Tool; PASAT = Paced Auditory Serial Addition Test; RAVLT = Rey Auditory Verbal Learning Test; RNBI = Ruff Neurobehavioral Inventory; SCI = spinal cord injury; SDMT = Symbol Digit Modalities Test; SWS = Simple Word Span; TBI = traumatic brain injury; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WCST = Wisconsin Card Sort Test; WMS = Wechsler Memory Scale; WRMT = Warrington Recognition Memory Test; PACCAQ = Post-Hospital Admission Cognitive Complaint Questionnaire.

impairment) were reported by Bradbury et al.³³ in 100% of participants and by Masedo et al.³⁷ in communication (88%) and social cognition (76%). These studies challenged the validity of FIM for cognitive assessment after SCI. The concerns regarding the reliability and use of FIM are discussed later.

The majority of studies report the frequency of cognitive impairment between 10% and 60%; however, there are also multiple reports of no impairment as well as one report of all participants being significantly impaired. Thus, no reliable conclusions can be drawn. The lack of a clear agreement on the incidence of cognitive impairment is possibly attributed to the heterogeneity in the sample population, sample size, study design, time since SCI, types of tests utilized, and the statistical analyses performed.

Effect of a concomitant TBI

Among the most frequent causes of SCI are high kinetic/rapid deceleration accidents such as motor vehicle collisions, falls, sports, and violence.³⁹ Since these accidents are also the most common etiologies for TBI,⁴⁰ 16%–59% of SCI cases report a concomitant TBI.^{41–43} TBI is associated with clinical

manifestations of cognitive impairment including attention deficit, memory loss, and lower executive ability.⁴⁴ With the increasing clinical awareness of its co-occurrence with SCI, TBI is often presumed to be responsible for the cognitive deficits in individuals with SCI.

This section reviews the studies reporting the effect of a concomitant TBI with an SCI. Eleven studies met the criteria (table 2).^{10,24,28,32–34,41,42,45–47} Pioneering work by Davidoff et al.²⁴ showed that acutely after SCI, individuals without a TBI committed fewer errors on HCT compared to those with a concurrent or premorbid TBI. Wilmot et al.¹⁰ also showed that 64% of patients with SCI and a concomitant TBI scored as impaired on multiple neuropsychological tests. Richards et al.⁴⁵ tested individuals at 7 and 38 weeks post SCI and reported cognitive improvement in the same degree and pattern consistent with that reported in TBI cases. Following this, Strubreither et al.²⁸ reported that 20.2% of SCI participants had an associated TBI and 72.3% of SCI + TBI cases showed impairment in performance and personality tests. Similarly, a study by Tolonen et al.³² showed 74% of the SCI sample had a co-occurring TBI and 91% of SCI + TBI cases showed impaired neuropsychological findings. In

Table 4 Studies investigating the effect of decentralized cardiovascular control

Author, year	Cognitive function in relation to cardiovascular control	Control for TBI
Jegade et al., 2010 ⁵³	Memory function was impaired in the hypotensive group compared to the normotensive group	The incidence of TBI was not different between the groups (44% vs 45%)
Wecht et al., 2012 ⁶⁷	Compared to controls, Stroop color test scores were significantly lower in the paraplegic group and not different in the tetraplegic group; cognitive function was associated with systemic hypotension in tetraplegic cases and inappropriate cerebrovascular reactivity in paraplegic cases	One individual had a confirmed history of TBI and 4 individuals had no history of TBI; history of TBI was unknown for remaining participants; the authors acknowledged that the effect of TBI cannot be ruled out
Phillips et al., 2014 ⁶⁹	Individuals with SCI scored lower on verbal fluency task; cognitive functioning was improved with improvements in blood pressure and neurovascular coupling	Individuals with severe TBI were excluded; one participant had minor brain injury due to fall from wheelchair and the follow-up imaging was negative
Wecht et al., 2016 ⁶⁸	Test performance was poorer in SCI; antihypotensive treatment showed no improvements in cognitive performance	Information not provided
Varas-Diaz et al., 2017 ⁷⁰	Poorer cognitive performance did not correlate with autonomic measures such as heart rate variability or root mean square of successive differences of RR intervals	Information not provided

Abbreviations: SCI = spinal cord injury; TBI = traumatic brain injury.

a subsequent report by Bradbury et al.,³³ participants with SCI performed better than those with SCI + TBI on a neuropsychological test battery, but the 2 groups were indistinguishable on the FIM scale due to the aforementioned ceiling effect.

A series of 4 publications by Macciocchi et al.^{34,42,46,47} also reported the effect of co-occurring TBI on cognition after SCI. The first study reported significantly impaired cognition (FIM) in those with SCI + TBI at both admission and discharge compared to those with SCI alone.⁴⁷ The second study showed that cognitive function (FIM) after SCI was inversely proportional to increase in TBI severity.⁴² The third study further examined a subset of this sample using a battery of neuropsychological tests in addition to FIM.⁴⁶ Testing

revealed TBI to have an exacerbating effect on post-SCI cognitive sequelae, with severe TBI in cases of paraplegia and moderate/severe TBI in cases of tetraplegia. Interestingly, the fourth study revealed no significant effect of mild TBI on cognitive impairment after SCI.³⁴

Finally, Nott et al.⁴¹ reported that participants with SCI or SCI + TBI showed no cognitive impairment and received near maximum scores on a cognitive FIM scale, with higher scores than injury severity-matched individuals in the TBI alone group.

Despite some discrepancies, it is evident that a concomitant TBI exacerbates cognitive impairment after SCI. The severity-dependent effect of TBI is also supported. The choice of

Table 5 Studies investigating the correlation with age

Author, year	Participants (age)	Correlation
Tun et al., 1997 ⁵¹	23 Younger adults (25–55 years; mean 39.9) and 23 elderly adults (61–73 years; mean 67.1) with SCI	Younger adults performed significantly better on all tests
New et al., 2007 ⁸²	70 SCI (47% over 60 years, 11% under 40 years)	Negative correlation between age and FIM cognition scores
Jegade et al., 2010 ⁵³	20 SCI (11 hypotensive; mean age 39 years, 9 normotensive; mean age 46 years)	No correlation of age was observed
Schembri et al., 2016 ⁷⁹	104 SCI (mean age 45.6 years)	Younger participants had reduced associations between sleep apnea and cognitive impairment
Craig et al., 2017 ¹⁴	150 SCI (mean age 46.2 years)	Weak negative correlation with NUCOG total ($r = -0.14$, $p < 0.05$), memory ($r = -0.26$, $p < 0.05$), and executive function ($r = -0.22$, $p < 0.05$); no correlation with attention, language, or visuoconstruction

Abbreviations: FIM = Functional Independence Measure; NUCOG = Neuropsychiatry Unit Cognitive Assessment Tool; SCI = spinal cord injury.

Table 6 Studies examining the correlation with lesion level

Author, year	Participants/lesion characteristics	Correlation
Wilmot et al., 1985 ¹⁰	67 SCI; C2–4 (26.9%), C5–8 (49.1%), T1–7 (12%), below T8 (12%)	No correlation was observed
Richards et al., 1988 ⁴⁵	150 SCI (48.7% with paraplegia, 51.3% with tetraplegia)	Tetraplegic individuals performed similar to those with paraplegia with a few exceptions (exact number not specified); overall, no correlation was observed
Copes et al., 1996 ⁸⁴	94 SCI (53.2% with paraplegia, 46.8% with paraplegia)	No correlation was observed
Tun et al., 1997 ⁵¹	23 Younger adults (4 cervical, 19 thoracolumbar) and 23 elderly adults (9 cervical, 14 thoracolumbar) with SCI	No correlation was observed
Middleton et al., 1998 ⁸⁵	112 SCI; C1–4 (11), C5 (19), C6 (24), C7–8 (7), T1–6 (13), below T7 (38)	No correlation was observed
Hall et al., 1999 ²⁹	3,971 SCI; C1–3 (156), C4 (517), C5 (578), C6 (313), C7 (177), C8 (55), thoracic (1718), lumbar/sacral (457)	No correlation was observed
Masedo et al., 2005 ³⁷	84 SCI; cervical (53.6%), thoracic (38.1%), lumbar/sacral (7.1%)	No correlation was observed
Samuelkamleshkumar et al., 2010 ⁸⁶	104 SCI; T6 and above (30), T7 and below (74)	No correlation was observed
Macciocchi et al., 2012 ⁴⁶	189 SCI (93 with paraplegia, 96 with tetraplegia)	No correlation was observed
Wecht et al., 2012 ⁶⁷	13 SCI; C4–8 (7), T2–10 (6)	Paraplegic individuals were more impaired than tetraplegic ones
Lazzaro et al., 2013 ⁸⁷	37 SCI (27 with paraplegia and 10 with tetraplegia) and 37 controls	Response time in the tetraplegic group was significantly more delayed than in the paraplegic group
Barbetta et al., 2014 ⁸⁸	218 SCI; cervical (62), thoracic (127), lumbar (29)	No correlation was observed
Zonfrillo et al., 2014 ³⁸	2,190 SCI; paraplegic (1,244), quadriplegic (946)	No correlation was observed
Craig et al., 2017 ¹⁴	150 SCI (42% with paraplegia, 58% with tetraplegia)	No correlation was observed

Abbreviations: C = cervical spinal level; SCI = spinal cord injury; T = thoracic spinal level.

cognitive test appears to play a major role in determining the outcomes in this category.

Association with psychological and somatic comorbidities

SCI is associated with an elevated risk of psychological morbidities in contrast to a normal process of grief because of the devastating nature of the event or simply a stage in the adjustment process.^{48,49} The association of SCI with psychological morbidities such as anxiety, depression, distress, and posttraumatic stress disorder has been extensively reviewed^{2,11,12} but their comorbid effect on cognitive capacity has not yet been discussed. This section reviews the effect of psychological disorders on cognitive functions after SCI. Studies examining psychological disorders after SCI were excluded if they did not include a cognitive assessment or an assessment of correlation. A total of 9 studies are discussed here (table 3).^{14,27,50–56}

Six studies examined the association with depression.^{50,51,53–56} While 3 studies showed no correlation,^{51,53,54} the other 3 showed significant negative correlation between severity of depression and cognitive capacity.^{50,55,56} Most striking among the latter 3 was the study by Craig et al.⁵⁵ that showed cognitive capacity was a strong predictor of psychological disorders

postdischarge; i.e., participants with higher cognitive capacity were 6.3 times less likely to experience a psychological disorder 6 months postdischarge.

Three studies showed correlation between pain and decline in self-perceived cognitive ability based on Ruff Neuro-behavioral Inventory,⁵² NUCOG,¹⁴ or a comprehensive neuropsychological battery.²⁷

Three studies examined the association with fatigue. Dowler et al.²⁷ reported fatigue to be associated with poorer processing speed based on the somatic complaints subscale of the Minnesota Multiphasic Personality Inventory. The other 2 studies were from Craig et al.^{14,56}: one demonstrated cognition-related fatigue after SCI (Iowa Fatigue Scale) and the other showed no interaction between fatigue (Fatigue Severity Scale) and cognitive function (NUCOG).

For psychological comorbidities, despite the numerous reports of presence of psychological comorbidities after SCI,^{2,12} their association with cognitive decline is investigated by only 6 studies and is supported by only 3 of them. Further, since 2 of the 3 studies included a considerable proportion of individuals with concomitant TBI^{55,56} and only one had excluded participants with severe TBI,⁵⁰ the contribution of TBI

cannot be dismissed. For somatic comorbidities, 3 of the 4 studies show an association between cognitive sequelae and somatic abnormalities such as pain and fatigue. Only one of the studies excluded participants with TBI,⁵² hence the effect of TBI on these associations cannot be completely ruled out.

Effect of decentralized cardiovascular control

Spinal injuries that damage the sympathoregulatory pathways result in impaired vasomotor tone and disordered cardiovascular control.^{1,5} In able-bodied individuals, there is an abundance of literature linking cognitive impairment to altered cardiovascular control,⁵⁷ systemic hypotension,⁵⁸ hypertension,⁵⁹ cerebral hypoperfusion^{60,61} (references 61–123 available from Dryad: doi.org/10.5061/dryad.rj74424), and increased arterial stiffness.^{62,63} It is conceivable that similar mechanisms that are frequent after SCI^{64–66} may contribute to cognitive impairment. Interestingly, we identified 5 studies investigating the contribution of altered cardiovascular and cerebral vascular control in cognitive impairment after SCI (table 4).^{53,67–70}

Jegede et al.⁵³ classified participants with SCI (matched for TBI incidence) as hypotensive and normotensive based on 24-hour observation of blood pressure. The hypotensive group was significantly impaired in memory, attention, and processing speed. A follow-up study compared cerebral hemodynamics among paraplegic, tetraplegic, and able-bodied individuals during a Stroop test⁶⁷ (doi.org/10.5061/dryad.rj74424). Surprisingly, this study reported reduced test performance in the paraplegic (and not tetraplegic) group compared to controls without SCI. This unexpected finding was attributed to small sample size, variability in results, and possibly co-occurring TBI. Interestingly, both SCI groups showed increased cerebrovascular resistance and decreased cerebral blood flow (CBF) during the task in contrast to increased CBF in the controls without SCI, suggesting abnormal cerebral hemodynamics and impaired neurovascular coupling after SCI. Based on these findings, this group further showed that although antihypotensive drugs increased mean arterial pressure and CBF velocity during cognitive tasks in participants with SCI, the test performance did not improve, suggesting the need for further optimization of pharmacotherapy.⁶⁸

Contrary to these findings, our work shows that SCI-associated impairments in systemic and cerebral hemodynamics as well as cognitive function are partially mitigated by the antihypotensive agent midodrine hydrochloride⁶⁹ (doi.org/10.5061/dryad.rj74424). Finally, a recent study by Diaz et al.⁷⁰ reported a lack of correlation between SCI-associated cognitive impairment and various cardiovascular measures.

Relatively recent (2010–2017) evidence suggests there is a correlation between sympathetic cardiovascular decentralization and impaired cognitive outcomes. However, the limited number of studies as well as the considerable dissonance across findings warrant further clarification to

delineate the consequences of impaired cardiovascular function on cognitive functioning after SCI. More importantly, the majority of studies did not employ rigorous controls for a head injury (table 4); therefore the contribution of TBI cannot be ruled out.

Effect of sleep apnea

Obstructive sleep apnea (OSA) is the most common form of sleep breathing disorder among individuals with tetraplegia⁷¹ (doi.org/10.5061/dryad.rj74424). Arterial oxygen desaturation and sleep disruption cause patients with OSA to present with daytime sleepiness.^{72–74} In able-bodied individuals, hypoxia (e.g., in hypoxemic lung disease)⁷⁵ as well as untreated cases of OSA have been associated with neuropsychological disorders. Moreover, decreased glymphatic clearance of neuronal metabolites due to OSA has also been linked to cognitive decline.⁷⁶ Interestingly, neuropsychological disorders are mitigated upon successful treatment of sleep apnea.^{77,78} It is therefore possible that individuals with SCI and OSA are prone to cognitive impairment.

We identified 2 studies that examined the association between sleep apnea and cognitive deficits after SCI^{79,80} (doi.org/10.5061/dryad.rj74424). Sajkov et al.⁷⁹ administered a neuropsychological test battery on participants with tetraplegia while excluding the cases with a co-occurring TBI. Although no direct relationship was found between sleep apnea and cognitive impairment, severe oxygen desaturation (SaO₂ <80%) was associated with impaired attention, concentration, immediate and short-term memory, cognitive flexibility, internal scanning, and working memory. More recently, Schembri et al.⁸⁰ classified participants with tetraplegia (with no TBI) based on the severity of sleep apnea and administered a similar battery of tests. Participants with more severe sleep apnea performed worse on the attention, information processing, and immediate recall tasks compared to mild/moderate groups.

Both studies suggest that sleep-disordered breathing is common after SCI and is associated with oxygen desaturation. While one study reports a direct association between severities of sleep apnea and cognitive impairment⁸⁰ (doi.org/10.5061/dryad.rj74424), the other suggests that nocturnal oxygen desaturation could impair daytime cognitive functioning.⁷⁹ A major strength of both studies was the exclusion of individuals with TBI.

Effect of age

Medical and technological advancements over decades have led to substantially increased life expectancy of individuals with SCI⁸¹ (doi.org/10.5061/dryad.rj74424). Yet with this increase, individuals' SCI-associated impairments are prone to be compounded by the numerous physiologic and psychological changes experienced in the general population. Therefore, it is of clinical significance to understand the effect of age on cognitive impairment after SCI.

Five studies reported the investigation of age in cognitive impairment following SCI (table 5)^{14,51,53,80,82} (doi.org/10.5061/dryad.rj74424). While one study did not show a correlation between age and any of the tests from a neuropsychological test battery,⁵³ a further 3 studies showed significant cognitive decline in elderly participants (>60 years) compared to younger ones (<40 years) across a cognitive test battery^{51,80} as well as on the FIM instrument.⁸² Finally, one study using the NUCOG test reported that age was negatively correlated with memory and executive functions but not with attention, language, or visuconstruction function.¹⁴

Four out of five studies support a greater prevalence of increase in SCI-associated cognitive impairment with increasing age.

Correlation with neurologic level of injury

It is generally accepted that physical and physiologic disability increases as a function of higher neurologic level of spinal lesion⁸³ (doi.org/10.5061/dryad.rj74424). Moreover, with newer studies highlighting the effect of higher-level SCI-related issues (e.g., cardiovascular dysfunction) on cognitive impairment, it is imperative to review the association between level of lesion and cognitive impairment.

Of the 14 studies analyzing the severity of cognitive impairment in relation to injury level (table 6)^{10,14,29,37,38,45,46,51,67,84–88} (doi.org/10.5061/dryad.rj74424), 12 studies showed no effect of injury level on the extent of cognitive impairment.^{10,14,29,37,38,45,46,51,84–86,88} One study showed that response time was delayed in quadriplegic individuals compared to paraplegics on auditory button-press oddball discrimination paradigm.⁸⁷ In contrast, Wecht et al.⁶⁷ showed that quadriplegic individuals performed better on the Stroop test than paraplegic individuals.

The majority of studies show no correlation between injury level and cognitive decline.

Limitations of the existing literature and research implications

This review revealed that individuals with SCI have significant cognitive impairment. However, substantial variability across the studies makes it challenging to conclude the incidence rates of cognitive impairment in this population. One such variation is the number of participants across the studies, which ranged between 9 and 233,778. This needs to be taken into consideration before concluding and interpreting the findings. Another factor contributing to variable results is the choice of test administered, i.e., FIM vs comprehensive neuropsychological testing. When using FIM to test cognitive functioning after SCI, researchers and practitioners need to consider that the FIM instrument was developed to assess impairment across diverse disability groups. Moreover, cognition subscales of FIM are largely based on bedside observations of patient behavior, which arguably lacks the

sensitivity of a systematic neuropsychological evaluation. This argument was supported by a blinded study by Davidoff et al.,²⁶ which showed that cognition scores on FIM did not correlate with any of the test scores from a neuropsychological battery within the same set of participants. Unsurprisingly, this apparent lack of sensitivity resulting in a ceiling effect (i.e., most patients scoring near maximum range on the FIM scale) was also reported by many other studies (table 1). This warrants the need for a wider scientific community to establish a standardized testing protocol, which is not only sensitive to various domains of cognition, but is also easy to implement in a clinical setting. Moreover, these tools need to be tested for reliability in this specialized population of interest.

Another major limitation is the inadequate control for a concomitant TBI. Owing to the etiologic similarities, the co-occurrence of TBI and SCI is inevitable, reported in up to 60% of SCI cases.^{42,43} Although TBI explains the cognitive impairment after SCI, it also confounds the contribution of other potential factors. Many studies attempting to examine the role of confounding factors are plagued by the lack of adequate controls for TBI. For example, the contribution of TBI could not be ruled out in the majority of studies investigating the association with psychological/somatic comorbidities (table 3) or the effect of decentralized cardiovascular control (table 4). This appears to be a major methodologic limitation in otherwise well-designed studies. We hope that this review encourages future studies to use stringent inclusion criteria for participants and meticulous analyses of individuals with spinal cord pathologies where TBI is less likely, e.g., motor vehicle accidents vs gunshot wound injuries as well as nontraumatic cases (e.g., neoplasia, stroke, infection, inflammation).

Finally, some other limitations of current studies can be addressed by future research. For instance, potential interactions between one or more comorbidities needs further examination, e.g., patterns of psychological impairment and its interaction with TBI or sleep apnea. In addition, given the effect of cardiovascular and cerebrovascular dysfunction, more sensitive noninvasive diagnostic methods, e.g., arterial spin labeling–MRI, could be used to investigate small vessel disease burden and white matter abnormalities, which may play a role in cognitive decline post SCI.

Clinical implications

Successful SCI rehabilitation relies heavily on the patient's acquisition of novel skills that are crucial for survival, self-care, mobility, and overall well-being following discharge. Quick and reliable learning of these skills can be a major challenge if the patient has cognitive impairment. Evaluation of cognitive problems may allow the patient education to be tailored accordingly. For instance, single demonstration of a task may be adequate for a cognitively intact individual, but those with cognitive impairment may require frequent repetitions of the task, simpler instructions, and auditory/visual reminders.

Other factors to be considered may include the consistency of instructions given, format of instructions (e.g., in group settings vs one-on-one sessions), and the patient's ability to understand supplemental literature if provided.³

In addition to modifying existing rehabilitation programs, novel specialized therapies may be implemented to improve cognitive health. Encouraging results from TBI rehabilitation programs show improvement not only in memory, attention, and problem-solving, but also in mood disturbances and anger management^{89,90} (doi.org/10.5061/dryad.rj74424). Moreover, specialized psychological treatment programs (e.g., cognitive behavioral therapy) in individuals with SCI have also shown both short- and long-term effects in immunizing against anxiety and depression.^{91,92} Broader application of similar therapies may improve cognitive well-being and overall quality of life after SCI.

It has been acknowledged that SCI has far-reaching effects and can pose considerable emotional stress for family members and rehabilitation staff.² Caregiving spouses report more physical and emotional stress, burnout, fatigue, anger, and resentment compared to spouses who were not caregivers⁹³ (doi.org/10.5061/dryad.rj74424). Similar psychological effects have also been reported for the nursing staff.^{94,95} It is therefore of great importance for family members to be educated about these consequences of SCI, as they often tend to focus on more overt physical outcomes of SCI and are unaware that cognitive impairment may reduce independence and require more care. It is also vital for the rehabilitation staff to recognize that SCI is associated with mood/personality issues and impaired learning ability. Having a realistic view of expectations may lower the stress levels for family members and staff.

Discussion

This systematic review offers a broad picture of negative cognitive sequelae following SCI and highlights various contributing factors. We also attempt to underline some of the major methodologic issues responsible for discrepancies across studies, which confound the synthesis of broader conclusions from the currently available evidence base. Nevertheless, there is a substantial amount of evidence portraying the severity of the cognitive problems in individuals with SCI. Consequently, there is an urgent need for further research in this area. Future research should consider adopting more rigorous controls to account for TBI when examining participants with SCI. Clinical implications encompass superior rehabilitation standards or dedicated neuropsychological therapies that will likely benefit the patients as well as the caregivers.

Author contributions

R. Sachdeva: study design, literature search, analysis, manuscript writing and editing. F. Gao: study design, manuscript

editing. C.C.H. Chan: study design, manuscript editing. A.V. Krassioukov: study design, literature search, analysis, manuscript writing and editing.

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