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## Is there an association between traumatic peripheral lesions and cognitive impairments in adults? A scoping review

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### Abstract

The aim of this scoping review was to critically review and synthesize the evidence concerning the relationship between traumatic peripheral lesions and cognitive impairments.

Five electronic databases (Medline, Cinahl, Psycinfo, Embase, and Cochrane Library) were searched in their entirety using the two key words “cognition” and “trauma”. An additional manual search was conducted. All inclusion criteria comprised English language, an assessment of cognition, and the study participants experienced acute peripheral lesion or physical trauma and were aged between 18 and 65 years. The articles were screened for eligibility by two independent reviewers. Disagreements were resolved by discussion or consensus with a third author.

A total of 11737 records were identified, of which 10 met the inclusion criteria. Whiplash injury, brachial plexus injury, soft tissue injury around the cervical spine, and fracture were found to be associated with cognitive impairments. The earliest cognitive assessment time point was one-month post injury, while the latest counterpart was 444 months. Cognition was assessed using 20 unique instruments, targeting nine distinct cognitive domains.

An overall positive association was found between traumatic peripheral lesions and cognitive impairments. Therefore, further longitudinal research is needed to monitor the changes in cognitive functions post physical trauma.

**Keywords:** cognition, cognitive impairments, injury, peripheral lesions, physical trauma

### Introduction

Traumatic peripheral lesions, a severe bodily injury, has traditionally been a prominent cause of disability across the globe [1,2], and it is responsible for around 4.4% of all hospital admissions [1]. Worse still, 34% of all patients suffer from recurring injuries [3], resulting in a growing financial burden associated with caring for patients. There is hence a need to prevent such trauma from recurring. It is suggested that cognitive function [4,5] might influence

the risk of subsequent injury within a short period of time [3], particularly in jobs that require a high level of concentration, memory, and executive function.

Although the correlation between cognitive impairments and traumatic peripheral lesions is less well established, an increasing number of reports suggest that patients develop cognitive impairments following traumatic peripheral lesions [6–17]. For instance, a variety of significant cognitive impairments have been detected in patients with peripheral nerve injury [11,16,17],



fibromyalgia syndrome [6–9] musculoskeletal injuries [10,12–14], and even burn injury [15]. These impairments referred to a wide range of cognitive domains, such as attention [11], memory [7], language [12], visuospatial capacities and cognitive flexibility [17]. The potential mechanisms were intricate, being found to be associated with pain [11,13], sensory recovery [17], exhaustion [8], emotions [8,9,13], and sleeplessness [9]. The fact that these factors may mediate the association between traumatic peripheral lesions and memory impairment is significant because they can impair cognitive function by altering neuroplasticity or dysregulating neurochemistry in the brain [18].

In contrast, no significant differences in attention or memory were observed on patients who had suffered burns [19]; however, it was unclear whether this was related to the evaluation time point in the study design or not. Therefore, additional research and reviews are necessary to shed light on the possible association between traumatic peripheral lesions and cognitive impairments in patients. This is very important as it can affect the treatment plan following the occurrence of traumatic peripheral lesions.

The aim of this scoping review was to determine whether an association exists between cognitive impairments and traumatic peripheral lesions using the scoping review framework presented by Arksey and O'Malley [20].

## Materials and methods

The protocol was registered with the Open Science Framework in September (Registration DOI: 10.17605/OSF.IO/7HV9W). More detail is given at: [https://osf.io/rp8nd/?view\\_only=7e9e5a87233b4b3bac6b37caeb73d28d](https://osf.io/rp8nd/?view_only=7e9e5a87233b4b3bac6b37caeb73d28d)

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### Search strategy

As the evidence base is relatively new and small, a broad search strategy was employed which included a wide range of study designs including observational, interventional, retrospective, and case studies. Five databases, *viz.* MEDLINE, CINAHL, PSYCINFO, EMBASE and COCHRANE LIBRARY, were searched to identify relevant studies, in addition to hand searches. The searches were performed on the entirety of the databases, *i.e.* from inception until 4 August 2022, using the concepts of trauma and cognitive impairments in adults. Various combinations of Medical Subject Headings (MeSH) and keyword terms were used as search terms. Subject headings and synonyms were used to expand the search, along with wildcards (*i.e.* ‘?’), truncations (*i.e.* cognit\*), and Boolean operators (*i.e.* AND, OR). Animal studies and studies on children (*e.g.* congenital or developing diseases) were excluded from the study. Additionally, cognitive impairments that were caused by other factors, such as aging, psychological and emotional problems, substance addiction, chronic disease, chronic pain, and post-injury with any damage to human sight, hearing, smell, or taste were excluded, as well as trauma or disease of the central nervous system. Also, visceral nociception and burn were eliminated (Tab. 1).

If a full-text paper was not available, the corresponding author was contacted. If no response was received within one month, those studies were excluded. To allow collaboration between all study team members, only studies published in English were included in the search.

**Tab. 1.** Inclusion and exclusion criteria

Criteria	NO.	Details
Inclusion criteria	1	Types of studies: observational, interventional, retrospective, and case studies
	2	Age: 18–65
	3	Cognitive impairments due to acute traumatic peripheral lesions
	4	Full text available in English
Exclusion criteria	1	Animal studies
	2	Trauma or disease in the central nervous system
	3	Chronic injuries without a definite timepoint of trauma
	4	Congenital or developing diseases
	5	Cognitive impairments due to aging, psychological, emotional problems, or substance addiction
	6	Damage to sight, hearing, smell or taste
	7	Visceral nociception or burn
8	Study protocols	

### Data extraction

Titles, abstracts, and full texts were screened by two independent reviewers using Covidence [21]. Conflicts were resolved through discussion after being reviewed in full, or by the third author, who made the final decision. This stage was followed by data extraction.

Two reviewers independently extracted the data using a predefined data extraction form. Disagreements were resolved by discussion or consensus with a third author. The extracted data included general information (i.e. title, authors, year, country, aims, key findings), participant characteristics (i.e. type of trauma, total number of participants, sex, mean age, earliest cognitive assessment time point post-injury, latest cognitive assessment time point post injury), the cognitive assessment tools used in these studies, and the distribution of domains evaluated. For studies with insufficient information, the team of reviewers contacted the corresponding authors, where possible, to acquire and verify the data.

### Collating and summarizing results

Firstly, general information and other characteristics were collected and summarized in tables and figures. The earliest and latest cognitive assessment time point post-injury were recorded, as well as the average value.. Two reports only provided a mean time point [22,23]; as both articles were published more than two decades ago, no email or phone number was recorded, leading to partial data loss.

Outcome measurement of cognitive function were determined using either full assessments or subtests used as stand-alone assessments. One such stand-alone assessment tool was the *Logical Memory* subtest [24], derived from parts of the Wechsler Adult Intelligence Scale [25], which was used in isolation to evaluate a specific cognitive domain. However, different versions of the same assessment tool were considered the same assessment tool for the sake of the study. For instance, the Wechsler Adult Intelligence Scale-Revised [26,27] and the Wechsler Adult Intelligence Scale-Third Edition [28] were considered the same evaluation, named the *Wechsler Adult Intelligence Scale* [25].

Additionally, cognitive domains were classified according to the International Classification of Functioning, Disability, and Health (ICF) [29], as indicated previously [30]. First, the raw domains reported by authors in each study were extracted. They were then mapped to certain categories by two reviewers. Any disagreement was discussed by the two reviewers, or was decided by the third author. The types of cognitive domain content included ICF functions (b110–b139) and specific mental functions (ICF functions b140–b189). Also, if the same field of cognition was evaluated repeatedly

by different scales in a single study, the total number of times involved would be calculated.

The entire flow of articles through identification to inclusion was operated in Covidence, and the data available in the studies were documented and processed using Excel.

## Results

The original search yielded 11737 potentially relevant articles. After removing duplicates, 10900 studies remained. Independent screening of the titles and abstracts identified 67 studies, which were included in the full-text screening. Studies were excluded due to the following reasons: including participants aged over 65 years (15 studies), no physical trauma (nine studies), not relevant to the research topic (seven studies), no cognitive function or related brain area evaluated (six studies), chronic conditions such as lumbar disc herniation with no information about the onset of the injuries (five studies), trauma or disease in the central nervous system (five studies), visceral nociception (two studies), burns (two studies). The results are presented in more detail in Figure 1. Following screening, 10 studies met the inclusion criteria and were included in this review. The flow of articles from identification to inclusion is shown in Figure 1.

### General study characteristics

It was found that the frequency of studies assessing cognitive functions after traumatic peripheral lesion has increased over time. From the 10 included papers in the final review, seven were published after 2001. Moreover, all the studies were observational, i.e. seven case-control studies and three cohort studies. In total, the complete group of evaluated studies included 354 patients with traumatic peripheral lesions. The cohort size of each study ranged from 6 to 109 patients. Most study samples came from Europe (47.7%, including Belgium, Sweden, Switzerland, Denmark), followed by the United States (30.8%), Oceania (15.5%, Netherlands), and Asia (5.9%, China) (Tab. 2).

The complete selection of reports was divided into two groups based on the location of trauma: soft tissue injury (nine reports – including six whiplash injury, two brachial plexus injury, one soft tissue injury of the cervical spine) and fracture (one report). Accordingly, patients with soft tissue disorders of the cervical spine and upper limb, as well as those with fracture fixation, developed significant cognitive impairments following trauma. These cognitive impairments lasted from around one month to over 30 years post injury, and they were not related to the length of the post-traumatic interval. (Table 3).

**Tab. 2.** Summary data from the studies included in the present scoping review of cognition and peripheral trauma

Lead author	Year	Sample size	Country	Aims	Key findings
Coppieters [31]	2017	32	Belgium	To examine differences in disability, cognitive impairments, and central sensitization between women with traumatic and idiopathic (nontraumatic) neck pain and women who were healthy.	1. Cognitive impairments in memory and executive function were present in participants with whiplash associated disorders. 2. Strong correlations between disability and cognitive impairments were observed in participants with whiplash associated disorders.
Ickmans [32]	2016	27	Belgium	To examine postexercise cognitive performance in people with chronic Whiplash-Associated Disorders.	People with whiplash-associated disorders displayed significantly lower scores on attention and psychomotor, compared with healthy controls.
Jun-Tao [33]	2016	15	China	To explore the higher-level brain functional abnormality pattern of BPI patients from a large-scale network function connectivity dimension in right-handed BPI patients.	Brain functional disturbance in BPI patients extends in the executive-control network, as revealed by functional MRI analysis, and this may lead to cognitive alterations in complex tasks post BPI.
Richards [34]	2011	109	USA	To examine the association between reamed IMN and long-term cognitive impairment in trauma intensive care unit survivors.	Fracture fixation with a reamed IMN is associated with cognitive impairment of Global (ICF-ch1), memory, attention, HLCF in multiple trauma patients at one year post injury.
Chen [35]	2008	6	China	To investigate the brain regions involved in chronic spontaneous pain due to BPA, to determine the glucose metabolic changes in patients with pain due to BPA.	Brain areas involved in attention and internal modulation of pain had significant glucose metabolism decreases in patients with BPA.
Antepohl [36]	2003	30	Sweden	To verify the occurrence of cognitive impairments in patients with WAD and to provide a more detailed description of the impairment character and context.	Compared to healthy controls, patients with whiplash-associated disorder performed worse in psychomotor and memory.
Bosma [37]	2002	31	Netherlands	To investigate underlying mechanisms of cognitive impairments in whiplash syndrome.	Patients with whiplash performed worse on memory and attention tasks compared with the control group.
Kessels [22]	1998	24	Netherlands	To compare attentional dysfunctions in whiplash patients with age-matched controls.	Whiplash patients had lower scores on the attention identified by PASAT.
Smed [38]	1997	29	Denmark	To address which factors lead to the chronic syndrome of whiplash injury.	Patients with whiplash injury showed deficiencies in the score of Cognitive Function Scan. The performances of basic learning of the whiplash patients coping with stressful life events in addition to the accident were significantly worse than patients without, whereas memory was unaffected.

Tab. 2. Cont.

Lead author	Year	Sample size	Country	Aims	Key findings
Radanov [23]	1992	51	Switzerland	To assess cognitive functions after soft tissue injury of the cervical spine.	1. Those suffering from cervicoencephalic syndrome had poorer results when tested for attention and HLCF. 2. All the findings above were not related to the length of the post-traumatic interval.

BPA – brachial plexus avulsion, BPI – brachial plexus injury, HLCF – higher-level cognitive functions, IMN – intramedullary nailing, PASAT – Paced Auditory Serial Addition Task [38], WAD – whiplash-associated disorder.

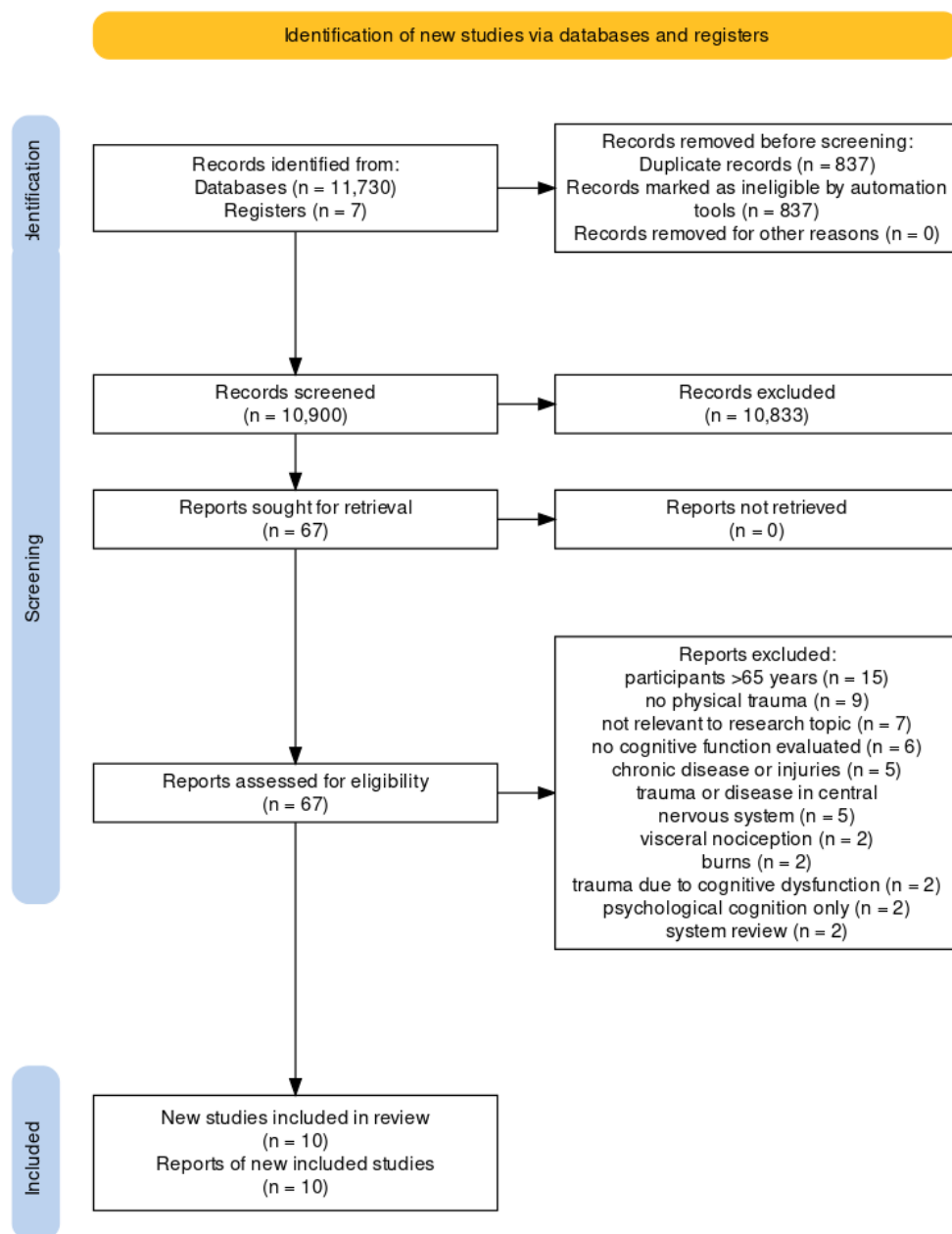


Fig. 1. Included studies and reasons for exclusion

**Tab. 3.** Summary of study participants pooled data grouped into three trauma/lesion types

Trauma/lesion	Number of participants	Gender		Mean age	Earliest cognitive assessment time point post injury	Latest cognitive assessment time point post injury
		male	female			
Soft tissue injury	245	79	166	36.6	1 month	444 months
a. Whiplash injury	173	45	128	37.0	1 month	444 months
b. Brachial plexus injury	21	19	2	32.9	1 month	240 months
c. Soft tissue injury around cervical spine	51	15	36	36.9	*	*
Fracture	109	62	47	42.7	12 months	12 months
Total	354	141	213	38.5		

\* – Not mentioned in corresponding reports.

**Tab. 4.** Cognitive assessment tools used in these studies

NO.	Scale	Frequency
1	Trail Making Test	3
2	Paced Auditory Serial Addition Task (PASAT)	3
3	Stroop Test	2
4	Rey Osterreith Complex Figure Test	2
5	Mini Mental State Exam	2
6	Rey Auditory Verbal Learning Test	1
7	Psychomotor vigilance task (PVT)	1
8	Digit Symbol Coding	1
9	FAS Test	1
10	Verbal Reaction time task	1
11	Spatial Reaction time task	1
12	Reading Span Task	1
13	Matrix Test	1
14	Dutch adaptation of the California Verbal Learning Test (CVLT)	1
15	Bourdon-Wiersma cancellation task	1
16	Cognitive Function Scanner (CFS)	1
17	Wisconsin Card Sorting Test (WCST)	1
18	Number connection Test	1
19	Drawings and Rey Complex Figure	1
20	Bourdon – Wiersma Test	1
Total		33

#### Assessment tools and evaluated domains

Two types of assessment tools were used to evaluate cognitive functions: cognitive scales, and acquisition of data concerning cognitive regions in the brain by magnetic resonance imaging (MRI). Nine domains of cognition were involved, including HLCF (b164), memory (b144), attention (b140), psychomotor

(b147), language (b167), global (ICF-ch1), basic learning (d130-159), consciousness (b110) and perception (b156).

As for the cognitive scales, the most common examples included the Trail Making Test (TMT) [40] and the Paced Auditory Serial Addition Task (PASAT) [39] (Table 4).



In total, nine areas related to the cognitive domain were assessed in the studies. Of these, the most frequently covered were *higher-level cognitive functions (HLCF)(b164)*, *memory (b144)*, and *attention (b140)* ('b' stands for *body functions* in ICF), almost reaching 71.9% (Tab. 5).

**Tab. 5.** Distribution of Domains Evaluated

NO.	Domain	Frequency
1	HLCF (b164)	18
2	Memory (b144)	14
3	Attention (b140)	11
4	Psychomotor (b147)	4
5	Language (b167)	3
6	Global (ICF-ch1)	2
7	Basic learning (d130-159)	1
8	Consciousness (B110)	1
9	Perceptual (b156)	1
Total		55

## Discussion

The purpose of this scoping review was to identify whether traumatic peripheral lesions could be associated with developing cognitive impairments following physical injuries. Its findings, based on 10 studies, allow a preliminary understanding of cognitive impairments after acute trauma. All these studies showed that cognitive impairments could develop following injury causing traumatic peripheral lesions.

Most importantly, even though all the samples of the included studies had excluded the cases with original head injuries, cognitive impairments could still be detected due to the presence of secondary brain injury post-traumatic peripheral lesions [34]. The term 'secondary brain injury' is used to explain the cerebral damage caused indirectly by peripheral lesions [34], which can be missed by therapists. However, an MRI study of participants with brachial plexus injury found the evoking activation of higher-level cognitive functions in the brain to be deactivated consistently in the executive-control network [33,35].

### Possible explanations of the underlying mechanisms

Those possible reasons that may lead to the 'secondary injury' of the brain following traumatic peripheral lesions includes the following:

An important assumption is related to cerebral anoxia and/or hypoxia; the brain requires a constant and

abundant blood supply to provide oxygen and other nutrients, and any deterioration of the blood supply can have an impact on cerebral functions, including cognitive functions [41,42]. It has been proposed that soft tissue injuries or fractures could lead to suboptimal oxygen delivery to the brain [43,44]. Soft tissue injuries or fractures result in increased blood flow in the injured area as an emergency response to the injury, which will continue during subsequent repair and regeneration period; this might result in suboptimal oxygen delivery to the brain [45]. This alteration in oxygen supply may cause transient or long-term changes in brain functions and result in various degrees of neuropsychological change [41,42].

Another possible reason is pain perception associated with the injuries [31,35,36]; this which is one of the common symptoms after acute trauma and has a potentially deleterious direct or indirect impact on cognitive tasks [46]. Pain in one of the most effective alarm systems in the body and can increase cerebral activity [36]. This creates a state of central functional remodeling [35], such as the dynamic epigenetic reprogramming of the prefrontal cortex, which appears to affect cognitive functions, and has been identified as much as one year after peripheral nerve injury [47,48]. This phenomenon indicates neuroplastic changes in the brain due to pain. Additionally, pain can cause distraction and decrease the level of attention and concern when the participants are performing complex mental tasks, especially during the verbal reaction time task [36].

The third possible contributing factor is pharmacological management during the recovery process following injury or surgery, which has been reported as a critical contributing element in several studies [49-51]. Among these medications, the side effects of strong analgesic medications and anaesthetics on cognitive functions have been clearly established, and they are not recommended as the first choice for pain management [52]. Furthermore, other anti-inflammatory analgesic drugs can have negative effects. For instance, a double-blind, randomized, placebo-controlled, repeated-dose clinical trial found that patients taking hydrocodone bitartrate plus ibuprofen performed significantly worse on a simple tracking task and reaction-time task compared with patients in the placebo group [53]. Additionally, caution should be taken when prescribing drugs that could affect the cerebral blood supply, as side effects as it can affect the supply of oxygen and other nutrients to the brain [52].

Fat embolism (FE) may occur frequently after traumatic peripheral lesions or during orthopaedic procedures; this can result in mechanical blockage of vessels or in biochemical changes, such as the catabolism of fat molecules to free fatty acids, contributing to an

inflammatory response [54]. However, the classical clinical entity of FE syndrome, such as pulmonary distress, neurologic symptoms and petechial rash, is much less common [55]. The capillaries in brain tissue can also experience embolism; while this may be overlooked if the symptoms are not obvious, they can be identified by cognitive impairments in patients [56,57]. In other words, an atypical FE can affect the brain and result in cognitive impairments.

Another potential hypothesis is that an elevated systemic inflammation could be associated with cognitive impairments [58]. A growing body of evidence has recently indicated a possible association between inflammation and neurocognitive functions. Even low-grade inflammation appears to play an etiological role in cognitive impairments [59]. Within 15 minutes of an acute traumatic peripheral lesion, the damaged tissues, comprising disrupted extracellular tissue and dead cells, platelets and plasma, release powerful enzymes, thereby setting off an inflammatory cascade [45]. Inflammatory chemicals then travel with the circulatory system and invade the brain tissue, exerting a negative influence on cerebral functions.

Another possible contributing factor is psychological distress following a traumatic event, common after severe musculoskeletal injury [37,60,61]. Patients with stress and distress seemed to perform unstably and worse in cognitive assessments compared with those without any psychological distress [38]. Psychological distress also causes sleep deprivation, which in turn prevents corticosterone and interleukin 1 $\beta$  signalling cell proliferation, which will affect the hippocampal neurogenesis [62].

In summary, the review discusses several possible contributing factors that may affect the development of cognitive impairments following traumatic peripheral lesions: cerebral anoxia / cerebral hypoxia, pain, analgesic medications, fat embolism, inflammatory responses, and psychological distress. Undoubtedly, other factors may exist but they remain to be investigated. As these contributing factors may overlap and are hence difficult to be tested in isolation, further multi-dimensional studies are needed to better understand them.

### Time course

A month after whiplash or brachial plexus injuries was the earliest time point for cognitive assessment. Consequently, it is impossible to determine whether cognitive impairments occur earlier than one month after peripheral injury in adults. However, some insight may be provided by animal studies. Several adult rat studies have evaluated cognitive assessment at seven days post trauma [63,64], yet for those laboratory rats, seven days are equivalent to about seven months for an

adult human with regard to lifespan [65]. Hence, to determine when cognitive impairments appear following traumatic peripheral lesions, further studies should be conducted as soon as possible following the initial trauma in humans.

According to the latest cognitive assessment time point post trauma, cognitive impairments were still detected 444 months after whiplash injury. Moreover, a whiplash trauma study indicated that cognitive performance declined, and this decline did not correlate with the duration between the actual accident and the time of testing [15]. This may suggest recovery of cognitive functions becomes poorer in the years following traumatic peripheral lesions; however further research and monitoring of cognitive functions after trauma is needed to confirm this. As there is no data available about the progression of cognitive impairments, it is unclear whether the symptoms get worse, improve, or return to normal over time. This information is needed to decide whether a rehabilitation program should include interventions based around cognitive functions.

### Cognitive assessment tools and domain

The findings identified a wide range of cognitive assessment tools that were used in the included studies; in total, 20 different measurement tools were identified in the 10 reports and among them, the most frequently used scales were the Trail Making Test (TMT) and the PASAT. Many cognitive measures are available, and they assess different domains of cognitive functions at different levels [66]. Although the TMT and the PASAT were the most frequently used tools of cognition, further research is needed to confirm whether that are the best tools for assessing patients with traumatic peripheral lesions. It could be that such assessment needs more sensitive tools, since the cognitive impairments are not as obvious as those of brain injury.

A wide range of cognitive domains were evaluated. *Higher-level cognitive functions (HLCF)* (*b164*) ranked first, at 18 times, followed by *memory* (*b144*) at 14 times, and *attention* (*b140*) at 11 times; other areas were of less concern. A review of cognitive assessment tools will allow the selection of the most appropriate and efficient scales for further study. Particularly those tools that target vulnerable cognitive areas and require close attention. In addition, cognitive domains represent relatively unexplored territory, and these should be investigated to determine whether they tend to be less affected or simply less studied by researchers.

### Study limitations

The studies included in this review were all published in English, which ruled out a number of other potentially valuable studies.



### Future directions

The findings of this scoping review suggest there may be an association between cognitive impairments and traumatic peripheral lesions in adults, but more high quality studies need to be conducted. Future studies should focus on a well defined population with one single type of peripheral injury. In future, assessments of cognition ought to be commenced as soon as possible after injury and should follow the study participants over time to track any changes in cognitive function.

### Conclusions

An overall positive association was noted between the occurrence of traumatic peripheral lesions and cognitive impairments. Peripheral injuries could cause cognitive impairment in both the acute and chronic phases of recovery. Further research is needed to identify more sensitive cognitive tools for assessment and evaluate hitherto unexplored domains.

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### Conflicts of Interest

The authors have no conflict of interest to declare.

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