Utility of transcranial magnetic stimulation in the assessment of spinal cord injury: Current status and future directions

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Comprehensive assessment following traumatic spinal cord injury (SCI) is needed to improve prognostication, advance the understanding of the neurophysiology and better targeting of clinical interventions. The International Standards for Neurological Classification of Spinal Cord Injury is the most common clinical examination recommended for use after a SCI. In addition, there are over 30 clinical assessment tools spanning across different domains of the International Classification of Functioning, Disability, and Health that have been validated and recommended for use in SCI. Most of these tools are subjective in nature, have limited value in predicting neurologic recovery, and do not provide insights into neurophysiological mechanisms. Transcranial magnetic stimulation (TMS) is a non-invasive neurophysiology technique that can supplement the clinical assessment in the domain of body structure and function during acute and chronic stages of SCI. TMS offers a better insight into neurophysiology and help in better detection of residual corticomotor connectivity following SCI compared to clinical assessment alone. TMS-based motor evoked potential and silent period duration allow study of excitatory and inhibitory mechanisms following SCI. Changes in muscle representations in form of displacement of TMS-based motor map center of gravity or changes in the map area can capture neuroplastic changes resulting from SCI or following rehabilitation. Paired-pulse TMS measures help understand the compensatory reorganization of the cortical circuits following SCI. In combination with peripheral stimulation, TMS can be used to study central motor conduction time and modulation of spinal reflexes, which can be used for advanced diagnostic and treatment purposes. To strengthen the utility of TMS in SCI assessment, future studies will need to standardize the assessment protocols, address population-specific concerns, and establish the psychometric properties of TMS-based measurements in the SCI population.

KEYWORDS
spinal cord injury, transcranial magnetic stimulation, clinical assessment, neurophysiology assessment, international standards for neurological classification of spinal cord injury
Introduction

Spinal cord injury

Spinal cord injury (SCI) is a life-altering event with impairment of various neurological functions including motor, sensory, and autonomic dysfunction. These changes almost invariably result in a reduced quality of life. In the United States, SCI affects over 17,000 individuals each year and it has a prevalence of approximately 294,000 (1–3). The most common cause for SCI is motor vehicle crashes, and males account for 78% of new SCI cases (3). Recovery of upper and lower extremity function is a top priority for individuals with SCI (4, 5); however, the neurophysiological mechanisms underlying movement impairments are poorly understood (6, 7). A better understanding of the neurophysiological mechanisms underlying movement impairments and recovery can help in better prognostication and allow for more targeted and individualized therapies to improve motor recovery.

Following acute traumatic SCI, clinical examination remains the first and most important diagnostic approach to determine the extent of motor and sensory deficits, and the level and severity of injury, which can be used to characterize natural neurological recovery (8). The information gleaned from the examination and classification can inform the planning of rehabilitation strategies (9). In the chronic stages of traumatic SCI, usually defined as greater than 1-year post-injury, spontaneous recovery is rare; however, newer rehabilitation techniques (e.g., neuromodulation) are showing potential for neurologic recovery in individuals with chronic SCI (10, 11). There is a growing interest in advancing the use of electrophysiology (e.g., transcranial magnetic stimulation, somatosensory evoked potential, spinal reflexes) (12) and neuroimaging (diffusor tensor imaging, spinal tractography) (13) techniques to supplement the clinical assessments for characterizing residual connectivity and neurological recovery following SCI. Transcranial Magnetic Stimulation (TMS) is one of the non-invasive electrophysiology techniques that has been repeatedly proposed as a method to supplement clinical assessment in individuals with SCI (12, 14, 15). TMS-based measures assess the body structure and function domain of the International Classification of Functioning, Disability, and Health. Specifically, the TMS-based outcomes allow objective assessment of corticomotor neurophysiology to help monitor neurological changes following SCI.

In this review, we will briefly discuss the current best practice clinical assessment tools within the body structure/function and activity domains of the International Classification of Functioning, Disability, and Health and provide an in-depth review of the TMS-based measures that may potentially aid better prognostication and advance the understanding of neurophysiologic mechanisms underlying impairments and functional recovery.

Clinical assessments after spinal cord injury

Clinical assessments in rehabilitation settings are often used to guide the progression of therapy post SCI. Several outcome assessment tools are designed to measure different domains under the International Classification of Functioning, Disability, and Health framework. Whereas these measures are important for devising patient’s plan of care based on prognosis for recovery, the individual measures usually do not have any predictive value for long-term motor recovery. Clinical prediction rules (CPR) have been developed by researchers by combining clinical features, such as demographics, symptoms, physical examination findings, imaging results, and assessment scores (16–20). CPR may provide an estimate of the probability of the presence of disease (diagnostic CPR), the outcome (prognostic CPR), or response to treatment (prescriptive CPR) in a given patient (16, 17). A few prognostic CPR using logistic regression analysis have been developed in SCI, more notably to predict lower extremity/ambulatory recovery (18, 21–23). CPR may assist in planning for lifestyle changes, treatment decisions or help manage patient expectations and stratify patients for therapeutic intervention trials (24). There are some CPR methods that have prognostication value; however, they do not identify the neurophysiological basis of the prognosis of individuals with SCI (16). With a shift towards individualized treatment plans, it becomes important to identify individual patient’s prognosis in the acute stages, so that treatment plans can be developed accordingly, and during chronic stages to monitor improvements with newer therapies targeted at neuro-restoration.

The Spinal Cord Injury Research Evidence (SCIRE) team published a standardized set of outcome measures developed in consultation with experts in SCI, for use in SCI clinical practice (25). This set consists of 32 measures that have been psychometrically validated in SCI population. Below we discuss some of the outcome measures that are commonly used both in clinical practice as well as in research in SCI population.

International standards for neurological classification of spinal cord injury

The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) in association with the American Spinal Injury Association (ASIA) Impairment Scale (AIS) is the most commonly used neurological examination and classification of severity of injury following traumatic SCI (8). The ISNCSCI has evolved over time with many revisions (26–28) and in its current form, offers clear instructions and consistent terminologies related to the level and completeness of SCI. The most recent revision from 2019 (28) incorporates...
two main changes including (a) a new taxonomy for systematic documentation of clinical judgment in the presence of non-SCI related conditions, and (b) a new definition of the zone of partial preservation, which applies not only to neurological complete but also to incomplete injuries with missing motor or sensory functions in the lowest sacral segments (28–30). The ISNCSCI is an impairment-based measure and assesses function in the body structure/function domain of the International Classification of Functioning, Disability, and Health. It involves sensory and motor impairment assessments in segments above and below the level of injury to define the neurological level of injury and the neurological “completeness” of injury based upon the sacral sparing definition. In addition, the motor and sensory scores are also used for stratification and prognostication purposes (14, 31).

Although the ISNCSCI is the most widely used standardized clinical neurological assessment in SCI and has shown relatively good psychometric properties, there are challenges in its use for neurological classification and prognostication (30, 32), and its utility as a measure to estimate prognosis is debatable (33). The assessment is subjective and depends on the experience and training of the assessor (34).

Other than ISNCSCI, there are specific tools for the assessment of upper and lower extremity functional outcomes (Tables 1, 2). The SCIRE published a set of measures specifically designed for measuring upper and lower extremity assessment (25). Tables 1, 2 include psychometric properties of some of the upper and lower extremity measures that have been used in individuals with SCI. There are other outcome measures in Table 1:

| Outcome measure | Primary construct | Psychometric properties |
|-----------------|-------------------|-------------------------|
| Spinal Cord Independence Measure version III (SCIM III)—self-care and grooming sub-scale | Independence level in ADLs, ICF domain: Activity | Inter-rater reliability: 71.6%–97.5% depending on item (100) Construct validity: Correlated with the Functional Independence Measure (r = 0.85) (104) |
| Capabilities of Upper Extremities Questionnaire (CUE) | Proximal and distal upper extremity function, ICF domain: Activity | Internal consistency: High (Cronbach’s α = 0.96) (101) Validity: High Spearman’s ρ correlation with the Graded Redefined Assessment of Strength, Sensibility, and Prehension measure ρ = 0.77–0.83 (102); high correlation with ASIA Upper Extremity Motor Score: r = 0.78 (105) |
| Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) | Multidimensional—hand impairment and function, ICF domain: Body structure/Function, Activity | Inter-rater reliability: 0.84–0.96; test-retest reliability: 0.86–0.98 (102) Construct validity: 50% more sensitive than the ISNCSCI when defining sensory and motor integrity of the upper limb (102) Concurrent validity: significantly correlated with the SCIM, SCIM-s, self care, and CUE (103) |
| Grasp and Release test | Designed to measure function following FES and tendon transfer surgeries, assess lateral and palmar grasp, ICF domain: Activity. | Test-retest reliability is high for all 6 items (ICC = 0.87–1.00) (104, 105) Validity: statistically significant and moderate to high correlations between the 12-month Functional Independence Measure and the forklift item (r = 0.624), the can item (r = 0.700) and the videotape item (r = 0.503) (104, 105) |
| Ashworth and Modified Ashworth | Used to assess spasticity in SCI, ICF domain- Body structure and function | Reliability: moderate inter-rater reliability (for MAS): ICC = 0.56 (106) Validity: moderate to high correlation of Ashworth (hip, knee, ankle) with SCATS (clonus, flexion, extension); moderate correlation between Ashworth (hip, knee, ankle) and Penn Spasm Frequency Scale (PSFS) (107) |
| Sollerman Hand Function Test | Designed to measure grips that are needed for certain ADLs and considers the quality and level of difficulty, ICF domain- Activity | Reliability: high inter-rater reliability (r = 0.98) (108, 109) Validity: high correlation of the Sollerman Hand Function test with the International Classification for Surgery of the Hand in Tetraplegia (Pearson’s r = 0.88) and the Motor Capacities Scale (Spearman’s r = 0.959) (108, 109) |

ADLs, activities of daily living; ASIA, American Spinal Injury Association; ICF, International Classification of Functioning, Disability and Health; MAS, Modified Ashworth Scale; ISNCSCI, The International Standards for Neurological Classification of Spinal Cord Injury; FES, functional electrical stimulation; SCATS, Spinal Cord Assessment Tool for Spastic Reflexes; SCIM, Spinal Cord Independence Measure version.
Transcranial magnetic stimulation-based assessment of spinal cord injury

Transcranial magnetic stimulation is a non-invasive brain stimulation technique that uses a rapidly changing magnetic field to induce currents in the cortical structures (38). The induced current can depolarize the cortical neural structures and activate target muscles leading to motor evoked potentials (MEP) or inhibit the ongoing muscle activity to a silent period in the electromyographic (EMG) recordings (Figure 1). The MEP and silent period provide useful information on the excitatory and inhibitory pathways underlying motor impairments and recovery after SCI. The TMS-based metrics are associated with the extent of injury, and clinical-based assessment of impairments and activity (14, 39, 40).

Residual corticospinal connectivity

In the simplest form, TMS can detect the presence or absence of MEP in the muscles affected by SCI. Despite being diagnosed as a motor complete SCI, presence of MEP has been reported in the muscles with no detectable motor function, including abdominal, lower extremity and pelvic floor muscles (41–43). The presence of MEP in these muscles confirms residual connectivity in the corticospinal pathways, which may otherwise go undetected using clinical examination alone. MEP measurements can detect changes in the residual function and recovery of SCI over time. For example, a longitudinal study monitored MEPS from abductor digiti minimi muscles in 305 individuals with complete and incomplete SCI at 15 days, 1 month, 3 months, 6 months and 12 months following an acute traumatic SCI (C2-C8/T1; AIS A–E) (14). On the basis of MEP deterioration and evolution, the authors categorized MEPS as Abolished (absent in all assessments; 34%), Reappearing (absent initially, but consistent reappearance in at least 1/4 sessions; 25%), Inconsistent (occasionally present in at least 1/5 sessions; 4%), and Mildly (always present with normal latencies; 19%) or Severely deteriorated (always present with delayed latencies; 18%) (14). Out of these 305 individuals, ∼16% were diagnosed with clinically complete injuries (AIS A). Amongst those with AIS A, only 37% had fully abolished MEPS, remaining 63% had some presence of MEPS throughout the study. The findings suggest MEP can be present below the level of lesion, and in cases when absent, may evolve over time with spontaneous motor recovery even in those with clinically complete injuries.

The motor threshold, defined as TMS intensity (expressed as % maximum stimulator output; MSO) for eliciting consistent MEP, is typically higher in muscles impaired from SCI (40, 44–48). In some cases, the thresholds can be too high to elicit MEP even with the maximum intensity (i.e., 100% MSO). In some of these cases, there may be residual connectivity which may go undetected, leading to false-negative interpretation. In case of the absence of MEP with the 100% MSO, neurological reinforcement such as target and remote muscle contractions has been recommended to minimize the risk of false-negative interpretations (43, 49). For example, Williams et al. (2020) were able to obtain MEPs

| Measure | Primary construct | Psychometric properties |
|---------|------------------|-------------------------|
| Walking Index for Spinal cord injury II (WISCI II) | Amount of physical assistance, braces or devices needed to walk 10 m, ICF domain- Body structure/function | Reliability: very good inter-rater reliability (110); intra-rater reliability: >0.97 (111) Validity: concurrent validity: sensitive in patients with more impaired gait, however superior to 6MWT and 10MWT in patients with good ambulatory function; poor correlation in patients with SCI who have poor ambulatory function (WISCI II scores <10); positively correlated with 10MWT, 6MWT, TUG (111) |
| Spinal cord injury functional ambulation inventory (SCI-FAI) | Gait is assessed in terms of gait parameters, assistive device use, walking mobility, ICF domain- Body structure/function | Reliability: inter-rater reliability: 0.703–0.840; intra-rater reliability: 0.850–0.960 (112) Validity: construct validity: gait score positively correlated with change in lower extremity strength (Pearson r = 0.58) (112); concurrent validity: highly correlated with the BBS (113) |
| Spinal cord assessment tool for spastic reflexes (SCATS) | Measures the primary spastic reaction in the SCI population, ICF domain- Body function | Reliability: high inter-rater and test-retest reliability (114) Validity: high correlation range with kinematic and electromyography = 0.69–0.94 (P < 0.01) (114) |
| Spinal Cord Independence Measure SCIM III: Mobility subscore | Measures the independence with transfers and household as well as community ambulation | Reliability: inter-rater reliability: adequate to excellent for the motor function in room and toilet transfers and excellent for the indoor and outdoor mobility (kappa values: 0.631–0.832) (115) |

| Outcome measure | Primary construct | Psychometric properties |
|-----------------|------------------|-------------------------|
| 6MWT, 6-minute walk test | | 6MWT, 6-minute walk test; 10MWT, 10-minute walk test; BBS, berg balance scale; ICF, international classification of functioning, disability and health; TUG, timed up and go test |

Measures that were developed for other clinical populations, have excellent validity, and have been recommended for use in SCI population (e.g., berg balance scale, 10 MWT). It is beyond the scope of this paper to discuss all the clinical measures currently being used in SCI population. While these clinical measures have been validated for the assessment of upper and lower extremity function in individuals with SCI, they are still limited in terms of subjectivity, insufficient prognostic information, and lack of insight into the neurophysiological mechanisms.
in pelvic floor muscles of all nine participants with chronic motor complete SCI (C6–T10 level) upon reinforcement using six different maneuvers involving isolated or combined contraction of abdominal, paraspinal, gluteal and pelvic floor muscle contraction. Another way of studying residual connectivity after SCI is through modulation of spinal reflexes by TMS (49–51). For example, TMS can facilitate plantar (50) or pudenda-anal reflexes (51), confirming preservation of descending pathways in some individuals with SCI. The above methods show that TMS is a useful tool to test the status of corticospinal tracts and other descending inputs in individuals with SCI. This is helpful in identifying “discomplete” SCI, which refers to clinically complete injuries with neurophysiological evidence of residual brain influence on spinal cord function below the lesion (52).

**MEP latency and central motor conduction time**

MEP latencies (time from TMS to the earliest deflection of the MEP) in individuals with SCI are typically delayed (Table 3). A longitudinal study evaluated MEPs in thenar muscles of individuals with SCI (C3–C7; AIS A–D) on multiple occasions from 19 to 1,109 days post-injury and found prolonged MEP latency throughout the follow-up period (45). Similar results have been reported in several studies for upper extremity (46, 53), lower extremity (39, 53, 54), and core muscles (42, 55) in individuals with SCI. Changes in the MEP latency are thought to result from axonal damage, demyelination and degeneration of the fast-conducting corticospinal tracts (56).

Although MEP latency is indicative of central and peripheral conduction, it can be combined with peripheral nerve conduction measurements to calculate the central motor conduction time (CMCT), which is an estimate of the conduction time of corticospinal fibres from the motor cortex and spinal motor neurons (57, 58). The CMCT is estimated by subtracting the spinal motor neuron to muscle latency ( peripheral conduction time) from the cortex to muscle latency (MEP latency). The peripheral conduction time can be calculated by using M-wave and F-wave latencies that are elicited by stimulation of the peripheral nerves (57, 58). M-wave is an early response to peripheral stimulation resulting from a direct activation of the target muscle, whereas F-wave is a smaller and more variable later response resulting from activation of the α-motoneuron by the antidromic volley (58). 1 ms is the estimated turnaround
time for the stimulus through the cell body of the spinal motor neuron (58) (see below Equation 1).

Central Motor Conduction Time (CMCT)  
= (MEP Latency – Peripheral Conduction Timec)  
(1)

PeripheraConduction Time  
= [(M – max latency + F – wave latency – 1)/2].

CMCT is delayed in individuals with SCI compared to healthy controls (Table 4). A study found delayed CMCT for the first dorsal interosseous muscle in about half of the individuals (55/113) who had consistent MEPs (14). The CMCT values were delayed after acute SCI and remained delayed for at least 12 months (14). These findings confirm that TMS can be used to objectively measure the delay in conduction time of corticospinal fibres. TMS in combination with peripheral nerve stimulation has also been used to study the influence of afferent input on motor cortex excitability in individuals with SCI (54, 59). A study on 8 individuals with tetraplegia (C3–C7; AIS B–D) reported reduced short-latency afferent inhibition in the flexor carpi radialis muscle, which is typically seen in healthy subjects at ~15–18 ms following median nerve stimulation (59). Another study in 22 individuals with SCI (C3–L5; AIS C–D) reported loss of MEP facilitation in the tibialis anterior muscle by prior (~50–60 ms) conditioning stimulation of the tibial nerve, but intact facilitation with conditioning stimulation of the common fibular nerve (54). In addition, precise calculations of the CMCT have been used to design targeted paired-associative stimulation neuromodulation approaches to facilitate functional recovery after SCI (Figure 2) (60–64). The paired-associative stimulation approaches are based on the Hebbian principle of associative plasticity, i.e., “neurons that fire together, wire together” (65, 66). These studies support the use of TMS in developing highly precise and targeted non-invasive neuromodulation for rehabilitation.

### Corticomotor output and gain: MEP amplitude, area, and recruitment curve

The MEP amplitude (14) and area (48) are commonly used measures of corticomotor output. Typically, MEP amplitude is measured “peak-to-peak”, from negative to positive peak in EMG activity. However, some studies have measured amplitude from the baseline to the negative peak (14). The MEP amplitudes at multiple TMS intensities from subthreshold to suprathreshold levels result in sigmoid-shaped stimulus-response, input-output, or recruitment curve (48, 54, 59).

| Reference           | Muscle                      | Test side                                      | Number of participants | SCI (ms) | Healthy controls (ms) |
|---------------------|-----------------------------|------------------------------------------------|------------------------|----------|-----------------------|
| Davey et al., 1998  | Thenar Muscles              | More Affected Side (lateralized symptoms) OR ELSE Dominant Side (Right) | SCI = 10 AB = 10       | Rest = 27.7 (SE = 1.3) Active = 27.6 (SE = 1.3) | Rest = 21.3 (SE = 0.5) Active = 19.8 (SE = 0.5) |
| Alexeeva et al., 1998 | Soleus                      | SCI: Stronger Side AB: Left Side               | SCI = 10 AB = 20       | 42.5 (18.4) | 34.0 (14.5)           |
| Alexeeva et al., 1998 | Abductor Halluces           | SCI: Stronger Side AB: Left Side               | SCI = 10 AB = 20       | 48.2 (24.1) | 38.2 (19.0)           |
| Smith et al., 2000  | Thenar Muscles              | More Affected Side (lateralized symptoms) OR ELSE Dominant Side (Right) | SCI = 21 AB = 10       | 51–100 days post injury: Rest = 27 (SE = 1.2) Active = 26 (SE = 0.8) | 51–100 days post injury: Rest = 21 (SE = 0.6) Active = 20 (SE = 0.5) |
| Barthelemy et al., 2015 | Tibialis Anterior          | More impaired side based on LEMS               | SCI = 24 AB = 15       | 40.0 (6.0) | 32.0 (2.0)            |
| Squair et al., 2016 | External/Internal Oblique   | Right and Left side values collapsed           | SCI = 13 AB = 13       | 23.6 (3.2) | 21.8 (2.9)            |
| Squair et al., 2016 | Sartorius                   | Right and Left side values collapsed           | SCI = 14 AB = 14       | 27.8 (7.1) | 23.4 (2.5)            |
| Squair et al., 2016 | Rectus Femoris              | Right and Left side values collapsed           | SCI = 5 AB = 5         | 31.3 (6.9) | 22.8 (1.7)            |
| Squair et al., 2016 | Tibialis Anterior           | Right and Left side values collapsed           | SCI = 1 AB = 1         | 48.3       | 33.3                  |
| Squair et al., 2016 | Soleus                      | Right and Left side values collapsed           | SCI = 2 AB = 2         | 52.7 (9.1) | 34.5 (3.3)            |

Table 3: Motor evoked potential latency in individuals with and without spinal cord injury.

| Reference | Muscle                          | Test side                                      | Number of participants | SCI (ms) | Healthy controls (ms) |
|-----------|---------------------------------|------------------------------------------------|------------------------|----------|-----------------------|
| Alexeeva et al., 1998 | Soleus                      | SCI: Stronger Side AB: Left Side               | SCI = 10 AB = 20       | 42.5 (18.4) | 34.0 (14.5)           |
| Alexeeva et al., 1998 | Abductor Halluces           | SCI: Stronger Side AB: Left Side               | SCI = 10 AB = 20       | 48.2 (24.1) | 38.2 (19.0)           |
| Smith et al., 2000  | Thenar Muscles              | More Affected Side (lateralized symptoms) OR ELSE Dominant Side (Right) | SCI = 21 AB = 10       | 51–100 days post injury: Rest = 27 (SE = 1.2) Active = 26 (SE = 0.8) | 51–100 days post injury: Rest = 21 (SE = 0.6) Active = 20 (SE = 0.5) |
| Barthelemy et al., 2015 | Tibialis Anterior          | More impaired side based on LEMS               | SCI = 24 AB = 15       | 40.0 (6.0) | 32.0 (2.0)            |
| Squair et al., 2016 | External/Internal Oblique   | Right and Left side values collapsed           | SCI = 13 AB = 13       | 23.6 (3.2) | 21.8 (2.9)            |
| Squair et al., 2016 | Sartorius                     | Right and Left side values collapsed           | SCI = 14 AB = 14       | 27.8 (7.1) | 23.4 (2.5)            |
| Squair et al., 2016 | Rectus Femoris                | Right and Left side values collapsed           | SCI = 5 AB = 5         | 31.3 (6.9) | 22.8 (1.7)            |
| Squair et al., 2016 | Tibialis Anterior             | Right and Left side values collapsed           | SCI = 1 AB = 1         | 48.3       | 33.3                  |
| Squair et al., 2016 | Soleus                         | Right and Left side values collapsed           | SCI = 2 AB = 2         | 52.7 (9.1) | 34.5 (3.3)            |

Table 4: Motor evoked potential latency in individuals with and without spinal cord injury.

AB, Able-bodied; LEMS, lower extremity motor score; ms, milliseconds; SCI, spinal cord injury; SE, standard error of the mean.
This curve may be plotted with Boltzmann function, and characteristics such as slope (rate of increase in MEP amplitude with increasing TMS) and highest MEP amplitude (MEPmax) are evaluated. The amplitudes at the suprathreshold intensities including the MEP max are smaller in individuals with SCI compared to healthy individuals in the affected upper (48, 68) and lower limb (54) muscles. These studies show that TMS can be used to capture reduced corticomotor output in individuals with SCI.

Silent period

TMS can suppress ongoing muscle activities in the target muscles, causing electrical silence in the surface EMG (Table 5). This brief interruption can be observed at subthreshold (45, 46) and suprathreshold (40, 44, 69) intensities and is termed the contralateral silent period (cSP). The early part of cSP is thought to involve spinal inhibitory networks (70), whereas the later part involves intracortical circuits (71). The onset of cSP obtained using subthreshold TMS is delayed in muscles impaired from SCI compared to those without SCI (45, 46). A study found delayed cSP onset latencies in the thenar muscles of individuals with SCI (C3–C7; AIS A–D) over multiple occasions from 19 to 1,109 days post-injury (45). The authors suggested the delay in cSP onset latency to be reflective of reduced intracortical inhibition to facilitate movement recovery (45). However, the delay in cSP onset may also be reflective of changes in the early part of cSP, which involves the spinal inhibitory mechanisms (70, 72, 73). The duration of cSP...
is another parameter that changes following SCI. A study used suprathreshold TMS intensities and reported prolonged cSP in extensor digitorum communis muscle of 9 individuals with chronic SCI at C5-C8 level (40). There are different explanations for prolonged cSP duration after SCI. Firstly, SCI leads to impairments in the corticospinal tracts leading to higher motor thresholds, but the cortical inhibitory interneurons are spared. Use of suprathreshold TMS requires higher absolute TMS thresholds, but the cortical inhibitory interneurons are spared. The changes in cSP duration were due to reorganization of neural structures at a supraspinal level. The above findings show that the TMS-based silent period measurements provide an objective assessment of the inhibitory networks after SCI.

### Cortical muscle representations

There is spontaneous and treatment-induced corticospinal reorganization following SCI (see reviews by Brown and Martinez, 2019 (76); Oudega and Perez, 2012 (56)). TMS-based motor maps have been used to study the corticospinal reorganization following SCI (40, 77–81). For example, the center of gravity (COG; the region thought to approximate the location of the highest density of corticospinal projections) of the cortical map for extensor digitorum communis muscle shifted posteriorly towards the hand representation in the anatomically defined hand knob in the central sulcus in individuals with chronic SCI (40). A case study in an individual with a transient (lasting ~5 h) episode of complete SCI at the C5 level found a posterior shift of the COG for another hand muscle (abductor pollicis brevis) at 1-day post-injury (79). Interestingly, there was a partial reversal in the shift of COG within 10-days of the injury, and complete reversal at a 2-year follow-up that corresponded with functional recovery (79). The changes in motor map from the resting state to an active state (during voluntary contraction) also differ in individuals with SCI in comparison to able-bodied people, with a shift towards the contralateral hand representation in SCI.

### Table 5: Contralateral silent period latency and duration findings in individuals with and without spinal cord injury.

| Reference                | Muscle                  | Test side                     | Number of participants | Metric                  | SCI (ms) | Healthy control (ms) | CSP definition + findings                                                                 |
|--------------------------|-------------------------|-------------------------------|------------------------|-------------------------|----------|----------------------|------------------------------------------------------------------------------------------|
| Davey et al., 1998 (46)  | Thenar                  | More Affected Side (lateralized symptoms) OR ELSE Dominant Side (Right) | SCI = 10 AB = 10      | Onset Latency           | 51.8 (SE = 1.8) | 33.4 (SE = 1.9)      | From the stimulus to the point in the record where the EMG fell consistently below mean background levels using sub-threshold TMS intensity |
| Smith et al., 2000 (45)  | Thenar                  | More Affected Side (lateralized symptoms) OR ELSE Dominant Side (Right) | SCI = 21 AB = 10      | Onset Latency           | 50 (SE = 2.2)    | 32 (SE = 1.5)        | From the stimulus to the point in the record where the EMG fell consistently below mean background levels using sub-threshold TMS intensity |
| Freund et al., 2011 (40) | Extensor Digitorum Communis | Dominant side (9 = right, 1 = left) | SCI = 9 AB = 14      | Duration                | Median = 130 (IQR = 60) | Median = 96 (IQR = 30) | From the time-point of TMS stimulus artefact to the resumption of sustained EMG activity + CSP duration negatively correlated with cervical cross-sectional area |
| Sfreddo et al., 2021 (44) | Abductor Pollicis Brevis | Side with lower motor thresholds and more consistent central and peripheral electrophysiological responses | SCI = 9 AB = 12      | Duration                | Median = 102.5 (IQR = 76.3–148.6) | Median = 95.4 (IQR = 86.6–110.2) | From the end of MEP to the earliest resumption of pre-TMS EMG activity Differences between groups not significant |
| Nardone et al., 2008 (74)| Interossei              | Both sides                    | SCI = 1 AB = 10      | Duration                | Right = 245 (95% CI = 82.2) | Left = 165.2 (95% CI = 83.4) | From the end of the MEP response to the return of sustained poststimulus EMG activity |

**Notes:** AB, Able-bodied; CI, confidence intervals; CSP, contralateral silent period; EMG, electromyography; IQR, Interquartile range; MEP, motor evoked potential; ms, milliseconds; SCI, spinal cord injury; SE, standard error of the mean; TMS, transcranial magnetic stimulation.
to healthy controls. A study of 22 individuals with chronic SCI (C2–C8; AIS A–D) found the motor map area reduced upon voluntary contraction of the target muscle (first dorsal interossei) and other proximal muscles (biceps brachii), whereas in healthy controls map areas increased upon contraction of the same muscles (81). Another study reported smaller motor map areas for severely impaired (motor power 1/5) forearm muscles in three (out of 10) participants with chronic SCI (C4–C6; AIS A–C), whereas the remaining seven participants had values comparable to healthy controls (47). The authors suggested that severely impaired muscles with normal motor maps (along with other TMS metrics) may benefit from targeted rehabilitation programs even in the chronic stage after SCI (47). These studies showed that the TMS can be used to study corticomotor reorganization with changes in cortical muscle representations following SCI.

Intracortical circuits

Paired-pulse TMS can be used to study the intracortical circuits after SCI. Paired-pulse TMS paradigms involve delivering a conditioning TMS pulse before a test TMS pulse (see review by Chen, 2004) (82) (see Table 6 for common protocols). Some of these measures such as short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), intracortical facilitation (ICF), and short-interval intracortical facilitation (SICF) have been used in individuals with SCI to study changes at the cortical level (48, 83–85). A study found reduced SICI in the tibialis anterior muscle in individuals with incomplete chronic SCI (C3–T12) compared to healthy controls (83). Moreover, SICI recorded from the first dorsal interossei muscles was greater than that from the tibialis anterior muscle (83). Another study reported reduced SICI and LICI in the flexor carpi radialis muscle in individuals with incomplete chronic SCI (C3–C7 level) (48). However, when individuals with motor thresholds similar to healthy controls were included to control for the differences in motor threshold, SICI was not different between the groups (48) but LICI remained different, suggesting that changes in LICI were not due to excitability differences (48). Another study reported distinct modulation of different SICF peaks following chronic incomplete SCI with reduced magnitude for all SICF peaks, delayed latencies for second and third peaks, and a longer duration for only the third peak in individuals with chronic incomplete SCI (85). Using various TMS coil orientations to induce current in different directions, a study demonstrated that corticospinal responses elicited by targeting different cortical circuits are affected to varying extent by SCI (86). In a follow-up study that involved TMS during precision and power grips, the authors found these cortical circuits were engaged to a different extent in individuals with and without SCI (87). These studies show that TMS can be used to study the changes in the intracortical excitatory and inhibitory networks in individuals with SCI.

### Discriminative and predictive ability, and clinical correlations of TMS measures

TMS-based measurement can differentiate between individuals with different extent of motor impairments. For example, a study found that individuals with greater severity
of cervical SCI had smaller abductor digitii minimi MEP amplitudes (14). In addition, the upper extremity motor scores were different between the five categories (Abolished, Reappearing, Inconsistent, Mildly deteriorated, or Severely deteriorated) based on the consistency of MEP (14). In individuals with consistent MEPs, the MEP amplitude correlated with the upper extremity motor scores (14). Using SICF, a study reported correlations between the upper extremity reaction time (latency and its variability) and amplitudes and latencies of later peaks of MEPs from the first dorsal interosseous muscle (85). Another study found negative correlations between the cross-sectional area of the spinal cord at the cervical level and TMS-based motor threshold and cSP duration (40). These results suggest that greater atrophy of the cervical cord is associated with reduced corticospinal excitability and prolonged inhibition (40). In the lower extremities, the MEP amplitude of the tibialis anterior muscle showed good correlation with better performance in clinical measures of gait including the Walking Index for Spinal Cord Injury, the Timed-Up and Go, the 6-Min Walking Test, and the maximal treadmill gait speed (39). In addition, smaller MEP amplitudes were associated with greater atrophy in the lateral–ventral quadrant of the spinal cord on the more impaired side (39). TMS-based assessment of residual connectivity after SCI has also shown to be correlated with spasticity in the lower extremity muscles (88, 89). TMS metrics are also sensitive to neurophysiological changes following rehabilitation training. For example, rehabilitation training was associated with anterior shift in COG, along with an increase in the map area and volume for the biceps brachii muscle in an individual with chronic complete C6 SCI (80). Moreover, voluntary contraction-related decrease in motor map area of the first dorsal interosseous muscle was associated with the sensory deficits in the hand, and 10 min of vibration over hand muscle-tendon increased the motor map area during voluntary contraction (81). Improvements in upper extremity strength following intensive training has shown to correlate with excitability and motor map changes in muscles with different extent of impairments following SCI (90). Similarly, intensive locomotor training led to increased MEP amplitudes and the slope of the recruitment curve in individuals with SCI (91).

Conclusion and future directions

Currently, clinical assessments are the main forms of evaluations during acute and chronic phases of SCI rehabilitation. ISNCSCI is the most standardized and commonly used clinical assessment following SCI. There are over 30 other outcome measures that have been validated and recommended for use in SCI. In addition, there are clinical prediction rules that combine clinical features, such as demographics, symptoms, physical examination findings, imaging results, and assessment scores for better prediction of outcomes. Clinical assessments are valuable in understanding recovery profiles and functional gains over the course of rehabilitation. However, they are subjective and do not provide information about the neurological processes underlying SCI, which limits their prognostication value.

TMS is an objective neurophysiological assessment tool and its different measures offer extensive information on corticomotor function. TMS offers a better insight into residual corticomotor connectivity, which may go undetected with the clinical scores of sensory and motor assessment. Due to this, TMS can be used to identify discomplete SCI. The TMS-based insights into neurophysiology can also be combined with the anatomical findings that are obtained using other techniques, such as diffusor tensor imaging or spinal tractography for more comprehensive understanding of corticomotor impairments and residual connectivity. However, whether the individuals with discomplete injuries would benefit from a different course of rehabilitation than those with complete injuries is a topic that needs to be investigated by future studies. TMS-based investigation of MEP and cSP characteristics (amplitude, latency, duration) provides insights into excitatory and inhibitory pathways following SCI. TMS-based motor maps allow study of corticomotor reorganization following SCI. Displacement of motor map COG or changes in its size following SCI or rehabilitation reflect neuroplastic changes following SCI. Paired-pulse TMS measures (SICI, LICI, ICF, SICF) help understand the compensatory reorganization of the cortical circuits following SCI. TMS can be combined with peripheral stimulation to study the central motor conduction time and modulation of spinal reflexes, that can be used for more advanced diagnostic and treatment purposes. Different TMS-based measures are able to differentiate between individuals with different severity levels of SCI, and correlate with the extent of injury and clinical scores. Lastly, TMS requires lesser time and training, has a higher temporal resolution and is more cost-effective than many neuroimaging techniques. Based on the above discussed advantages, TMS can be used to supplement clinical assessments in acute and chronic stages of SCI.

Future studies are needed to strengthen the use of TMS for clinical assessments in individuals with SCI. There are discrepancies in the findings of TMS studies, for example, delayed (41, 45) vs. non-delayed (42, 47) MEP latencies, smaller (14, 48) vs. larger (67) MEP amplitudes, absent (75) vs. similar (44) vs. prolonged (40) cSP, smaller (47) vs. large motor maps (81). The factors leading to these discrepancies need to be addressed. Methodological differences (e.g., sample size, target muscles, active vs. resting muscle state, extent of background contraction, type of TMS coils, coil orientation, stimulation intensities, definitions for MEP/cSP onset and offset) can contribute to these differences. Some of the
differences can be addressed by standardizing the protocols. For example, selecting and reporting the appropriate coil orientation to target different cortical pathways (86, 87). Similarly, selecting suitable coil type for targeting of different muscles, for example double-cone (39, 92) or specialized batwing coil (54) for the lower extremity muscles and figure-of-eight coil (60) for the upper extremity muscles. Issues related to the study population may be more challenging to address. For example, early fatigue in muscles affected by SCI may make it challenging to maintain sustained background contraction throughout the testing, especially in severely impaired muscles. Antispastic medications (e.g., baclofen) that are commonly prescribed in individuals with SCI may affect TMS measures (93, 94). It has been suggested that the effects of antispastic medications on MEP are overridden by the volitional excitatory drive when testing the actively contracting muscle (49), but this needs to be tested with more extensive studies. Peripheral afferents input affect cortical excitability, and hence TMS measures (54, 59). Therefore, it is important to understand that changes in TMS measures may not always reflect changes in corticomotor transmission, but may also result from other sources such as afferent-based modulation of cortical pathways. Lower motor neuron lesions influence TMS measures and should be taken into consideration by use of F-waves (14), H-reflexes or lower motor neuron integrity tests (95). The psychometric properties of any technique are population specific, and currently only a few studies have investigated the psychometric properties of TMS-based measures in individuals with SCI (44, 96, 97). The smallest detectable change (SDC; the smallest change that is above the inherent measurement error and can be reliably detected) of TMS-based measures in proximal arm muscles is typically high for individuals with SCI (96). Changes in TMS measures should exceed these high SDC values to be considered as real change, which makes it challenging to use TMS measures as individual biomarkers. There is an upcoming work addressing the feasibility and relevance of TMS-based assessment after SCI in the rehabilitation settings, and validating their use (along with imaging assessments) as predictive markers (98). The clinically meaningful difference of TMS-based metrics have yet to be established for individuals with SCI.

In conclusion, TMS allows detection of residual corticospinal connectivity following SCI. The measurement of MEP, cSP, cortical muscle representations, and intracortical circuits allows better understanding of the neurophysiology of corticomotor impairments and recovery following SCI. Due to its objectivity and ability to probe into neurophysiological mechanisms, TMS can supplement clinical assessments after SCI and help in devising targeted and individualized therapies for movement recovery. Studies with larger sample size and standardized protocols are needed to improve consistency in TMS-based findings in individuals with SCI. More research is needed to establish the psychometric properties of TMS-based measurements in the SCI population.

Author contributions

TA conceptualized the research aims and design in consultation with ND, SK and RC. TA and ND reviewed the literature and wrote the original draft. All authors reviewed and edited the original draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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