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Supraspinal Control Predicts Locomotor Function and Forecasts Responsiveness to Training after Spinal Cord Injury

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Abstract

Restoration of walking ability is an area of great interest in the rehabilitation of persons with spinal cord injury. Because many cortical, subcortical, and spinal neural centers contribute to locomotor function, it is important that intervention strategies be designed to target neural elements at all levels of the neuraxis that are important for walking ability. While to date most strategies have focused on activation of spinal circuits, more recent studies are investigating the value of engaging supraspinal circuits. Despite the apparent potential of pharmacological, biological, and genetic approaches, as yet none has proved more effective than physical therapeutic rehabilitation strategies. By making optimal use of the potential of the nervous system to respond to training, strategies can be developed that meet the unique needs of each person. To complement the development of optimal training interventions, it is valuable to have the ability to predict future walking function based on early clinical presentation, and to forecast responsiveness to training. A number of clinical prediction rules and association models based on common clinical measures have been developed with the intent, respectively, to predict future walking function based on early clinical presentation, and to delineate characteristics associated with responsiveness to training. Further, a number of variables that are correlated with walking function have been identified. Not surprisingly, most of these prediction rules, association models, and correlated variables incorporate measures of volitional lower extremity strength, illustrating the important influence of supraspinal centers in the production of walking behavior in humans.

Keywords: human studies; locomotor function; outcome measures; recovery; rehabilitation

Introduction

Today in the United States, a person who sustains a spinal cord injury (SCI) at the age of 20 can expect to live with disability for 25–53 years after surviving the first post-injury year.[1] Consequently, in terms of disability-years, the potential long-term impact of rehabilitation for persons with SCI is even larger than in other neurologic conditions such as adult stroke.

Restoration of walking function is cited as a priority among persons with SCI of all degrees of severity, chronicity, or age at injury.[2] Given the functional, health, and fitness related value of standing and walking (and for many the relatively young age of injury), walking can have a significant impact on health, quality of life, and social participation after SCI.[3,4] Being able to stand and walk through a narrow doorway, to negotiate confined spaces inaccessible to a wheelchair, or simply to get out of a wheelchair to sit in a ''regular'' chair at a table with friends, provides opportunities to participate in ways that might otherwise be unattainable.

The development of interventions that extract the greatest improvement from the limited time and resources available for rehabilitation is essential for optimizing rehabilitation outcomes related to walking function. When selecting a rehabilitation approach with the goal of improving walking function, the theoretical basis for the approach, in terms of the underlying neurophysiologic mechanisms being targeted, bears consideration. The rich history of the neuroscience of walking in mammals has been especially influential in the development of intervention strategies for restoring walking after SCI (for review, see Rossignol and Frigon[5]).

Because there are excellent published reviews of the control of vertebrate locomotion,[6,7] we will offer only brief overviews of

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work in animal models of locomotion, except where work on humans is limited, and focus on what is currently known about control of locomotion in humans. In addition, for an overview of the available published locomotor training studies in persons with SCI, the reader is referred to a systematic review on this topic.[8]

While there is great interest in the potential of pharmacological, biological, and genetic interventions to improve walking function in persons with SCI,[9] at this time the efficacy of these approaches in humans has not been established. A recent systematic review of the experimental strategies aimed at improving motor function in persons with SCI concluded that multi-intervention approaches that contain a rehabilitation component currently have the best evidence to support their value.[9] While early training approaches to improve locomotor function in persons with SCI focused on activating spinal central pattern generator (CPG) circuits associated with locomotor behavior,[10,11] there has been growing recognition of the role of spared supraspinal pathways in locomotor function. For this reason, recent studies have begun to target supraspinal control mechanisms in both animal models[12,13] and humans.[14–18]

The increasing appreciation for the importance of supraspinal contributions to locomotor function in persons with SCI derives from studies that have shown the influence of volitional control on walking. Evidence is accumulating for the value of clinical measures of volitional control in predicting future walking function, in forecasting responsiveness to training, and delineating the variables that correlate with walking capacity. There is great interest in imaging and electrophysiological biomarkers of future walking function; however, to be of greatest value, they must be shown to be superior to widely accessible clinical measures that require fewer technical resources.

Neural Contributions to Locomotor Behavior

Spinal contributions

While to the uninitiated, the spinal cord is most frequently associated with the role of transmitting information between the brain and the periphery (i.e., muscles or peripheral sensory receptors), or producing simple reflex responses to sensory stimuli, it has long been known that the spinal cord subserves much more complex motor behaviors. Over the past century, the mammalian spinal CPGs that provide the basic rhythm and pattern of innate locomotor behaviors have been the subject of extensive research.

Animal studies have shown that the spinal CPGs are an important component of the distributed neural control of locomotor behavior. In these models, CPGs produce stepping behavior even after complete spinal transection that isolates the spinal circuits from supraspinal centers, and in addition they show remarkable adaptation to sensory input (for review, see Hultborn and Nielsen[19]), particularly inputs related to limb load and position.[20] Intermediate interneurons in lamina VII comprising CPGs of the lumbar cord are the post-synaptic site for descending motor systems (for review, see Jankowska[21]), and serve the important function of integrating phasic afferent signals and descending supraspinal input. The net result conveys synaptic drive to lumbar motor neurons and modulates reflex and locomotor function.

In cat locomotion, task-specific characteristics were defined using an innovative comparison of backward and forward treadmill walking.[22,23] Similar kinematic and muscle activation patterns between the walking conditions showed the baseline contributions of CPGs. These CPG contributions included ankle control, limb extensor activity, temporal characteristics, and interlimb joint coordination.[22]

Differences between forward versus backward walking indicated a primary role for afferent or supraspinal drive in stepping. Two discriminating features were found in backward walking—postural changes and loss of dual-burst muscle activation during stepping. Postural changes were attributed to altered brainstem input, while the muscle activation patterns reflect differences in afferent drive.[23] Afferent drive, conveying cutaneous input and force feedback from proprioceptors through the CPGs interneurons, modulates stance/swing transitions, paw placement onto the plantar surface, locomotor precision, and obstacle avoidance.[24–26]

Although early on there were questions regarding whether CPG circuits were preserved at the level of the spinal cord in primates, there now exists considerable evidence from both non-human primates[27] and humans[28–30] that the pattern-generating circuits that subserve some aspects of locomotor behavior exist at the level of the spinal cord. Yet these circuits are more difficult to activate and sustain in both non-human primates and humans after SCI, so effective ways to engage these circuits after injury remain a challenge.

Supraspinal contributions

Animal studies have revealed that locomotion emerges from a distributed neural control system including descending supraspinal systems that extend throughout the length of the spinal cord. Reversible cooling studies of the primary motor cortex in cats established that cortical neurons produce precise paw placement onto narrow rungs, as inactivation precluded correct placement.[31] Corticospinal inputs further serve to modify the pattern of spinal locomotor output in situations where there is a need for control of foot placement, such as when there are constraints on the walking pattern[32] or a need to adapt gait to environmental obstacles.[33,34]

Activation of red nucleus neurons and the rubrospinal tract coincides with maximal hindimb flexor electromyographical (EMG) activity and is associated with the extent of hip flexion during swing phase.[35–37] The lateral vestibular nucleus neurons exhibit high resting discharge rate, which establishes tonic muscle tone of paraspinal muscles extending to the lumbar cord, providing static posture and balance control. In addition, descending vestibular drive appears to be polysynaptic, stimulating extensor motor neurons during stance while triggering concurrent dynamic paraspinal responses.[38,39]

The reticulospinal neurons, especially those located in the ventral medulla and pons, produce position-dependent motor responses, with increased limb flexor EMG occurring in the swing limb and simultaneous excitation of the extensors of the stance limb. The reticular formation also contributes to postural control during locomotion so that stepping is sustained.[40–42] These descending systems appear to exact precise coordinated control of stepping, posture, and balance through both monosynaptic inputs to motor neurons and through integration with afferent inputs within the interneuronal networks making up the spinal CPGs.

Our understanding of the supraspinal control of walking in humans is limited in comparison to what is known based on studies of animal models. Besides the control of cyclic alternating limb movement and initiation of stepping that are required for quadrupedal locomotion, bipedal locomotion has additional requirements for control of balance and upright posture. These functions are subserved by supraspinal reticular, vestibular, and cerebellar inputs.[43]

As was first described in the 1970s,[44] the strong relationship between volitional control of the lower extremity muscles and walking ability[44–56] attests to the importance of supraspinal contributions to human walking. During human walking, neuronal activity related to lower extremity movement is represented in the primary motor and sensory cortices.[57,58] The primary motor cortex and corticospinal pathway have received the greatest amount of

attention, with studies showing direct contributions to the ankle dorsiflexors,[59,60] including activation on a step-to-step basis.[59]

The role of the motor cortex in human walking has been elucidated by studies in humans showing that: (1) subthreshold transcranial magnetic stimulation (TMS) to activate inhibitory interneurons in the motor cortex suppresses the locomotor EMG in the ankle dorsi - and plantar flexor muscles,[61] (2) suprathreshold TMS activates dorsiflexors to the same extent as during volitional contractions in sitting,[62] and (3) electroencephalographic (EEG)-EMG coherence shows synchrony in the frequency domain between the primary motor cortex and the dorsiflexors during walking.[59] Most of the evidence related to corticomotor control of walking in humans has focused on the dorsiflexor muscles, in which there is step-to-step modulation of muscle activity during level overground walking (or at least a constant drive to facilitate spinal circuitry).[59,61] The role of the motor cortex in other locomotor muscles remains to be elucidated, as does a potentially modified role of supraspinal inputs following injury wherein walking speeds are slower and the task of walking requires more cognitive attention.[63]

Step initiation is another critical aspect of locomotor function that appears to be under supraspinal control. There is evidence from human studies that step initiation is subserved by the peduncuolopontine nucleus (located in the mesencephalic locomotor region), which has extensive connections with the basal ganglia.[64] Given the slow walking speed of persons with SCI, these supraspinal centers may be even more important after SCI than in intact humans. Rather than being an automatic behavior generated by the entrainment of spinal circuits, stepping after SCI may represent a series of voluntary steps, each initiated by supraspinal centers.

While evidence regarding the role of supraspinal centers during human walking is less detailed than that for other vertebrates, all testable pathways suggest they are strong contributors in the absence of SCI. Hence, studying how these circuits change after SCI and with training-induced improvements in walking is essential to understand their potential role in supporting walking after SCI. Beyond providing information that is of value for informing the development of locomotor training strategies, understanding supraspinal contributions to walking in humans may have future value for the development of brain-machine interface systems to support walking.[65,66] For example, because the pedunculopontine nucleus reflects the intention to walk, recordings from this area might be linked with control of step initiation in a robotic gait orthosis. The exploration of brain-machine interfaces to drive functional electrical stimulation devices for walking function in persons with paraplegia is in the early stages.[67,68]

Modulation of Neural Circuits by Locomotor Training

Training-related modulation of spinal circuits

While spinal circuits were once thought to be hardwired, in recent decades it has become clear that even in humans, simple segmental reflex circuits respond to training.[69,70] There is evidence that movement is necessary for the maintenance of normal activity in spinal reflex circuitry. As an example, in non-disabled human subjects, joint immobilization is associated with loss of normal modulation.[71] Persons with SCI who participate in locomotor training demonstrate more typical modulation of spinal reflex excitability after training compared with their pre-training levels.[72–75]

The importance of changes in reflexes should be considered in conjunction with observable improvements in overground walking; for example, improvement in overground walking speed is correlated with reduction in clonus and H-reflex magnitude.[73,76] The observation that reflex modulation can change in the absence of measurable change in the walking outcome,[77] however, suggests either that the reflex modulation is an epiphenomenon unrelated to walking performance or that the walking measures are not sufficiently sensitive to the changes in gait that accompany improved reflex modulation. For this reason, it is critical to have sensitive measures of walking outcomes and to link these training-related changes in walking function with the associated neuroplastic changes. It has been suggested in studies of participants with SCI that intralimb coordination provides such a measure, because the capacity of the nervous system to regulate the timing relationships between limb segments is the hallmark of motor control.[78,79]

In converse to questions about how locomotor training influences reflex modulation, some preliminary work has been performed to answer the question regarding how training to improve reflex modulation may influence walking-related variables.[69,70] Beyond the ''learning'' in simple segmental reflexes described earlier, the more complex spinal circuits associated with locomotor central pattern generators also learn in response to training.[5,80,81] In particular, there is increased inhibition of polysynaptic spinal reflexes with improvements in walking, suggesting better inhibitory control of spinal circuits.[82] Adaptation and plasticity in these circuits is thought to contribute significantly to the improvements in walking function observed after locomotor training in persons with SCI.[83]

Training-related modulation of supraspinal circuits

Improvements in motor function after SCI, spanning the acute, subacute, and chronic phases, are associated with increased strength of corticospinal connectivity, as evidenced by increased amplitude of motor evoked potentials elicited by TMS over the motor cortex.[84] In a longitudinal study, persons with motor-incomplete SCI demonstrated increased amplitude of motor evoked potentials over the course of the first post-injury year (with no associated change in latency).[85] While the sample sizes in some subgroups were too small to reach statistical significance, the mean change in motor evoked potentials suggests a parallel between cortical connectivity and motor scores.

In persons with motor-incomplete, chronic (>1 year post-injury) SCI, motor evoked potentials in the ankle dorsiflexor and knee extensor muscles are larger after locomotor training, indicating increased corticospinal or corticoreticulospinal pathway connectivity.[86] A small imaging study with four subjects indicated increased activation in the cortical sensorimotor and cerebellar regions after locomotor training in both subacute and chronic, motor-incomplete SCI.[87] In a case report of an individual with chronic, motor-incomplete SCI, locomotor training that emphasized feedback-error learning was associated with increases in somatosensory and corticospinal excitability, as well as radiographic evidence of increased corticospinal connectivity.[88]

Targeting Neural Circuits to Enhance Locomotor Function

Targeting spinal structures

Beginning in the late 1980s,[89] body weight supported locomotor training received significant attention in the SCI literature. Studies of body weight supported treadmill training in animals with spinal transection (for review, see Duysens and Van de Crommert[90]) gave rise to interest in similar approaches for persons with motor-incomplete SCI.[10,11,89,91–93] These approaches were based on elements considered essential in the training

approaches developed for animal models of SCI, and for this reason incorporated tenets such as assistance for stepping, partial support of body weight to adjust limb loading, attention to hip position for the swing-stance transition.

While derived from studies of animal models, support for the translation of these tenets to humans was evidenced by studies of stepping in human infants.[94,95] Other training approaches also targeted spinal circuits; for example, evidence that the flexor reflex response is closely tied to the locomotor central pattern generator[96] influenced the development of training approaches that incorporated stimulation to elicit stepping by activating reflex circuits.[97,98]

Also beginning in the 1980s, there were published reports of spinal cord stimulation with implanted epidural electrodes to improve motor function in persons with neurological conditions,[99] to elicit step-like behavior in persons with SCI,[30] and facilitate walking in persons with motor-incomplete injuries.[100] More recently, there have been reports wherein epidural stimulation has been used to increase the excitability of spinal circuits to a level that allows some volitional movement in persons with injuries clinically classified as motor complete.[101]

While epidural spinal cord stimulation requires an invasive surgical procedure for the implantation of electrodes into the epidural space, more recent evidence indicates that transcutaneous spinal cord stimulation provides a non-invasive alternative for the stimulation of the spinal cord, using electrodes placed on the skin over the spine.[102,103] Modeling of both epidural[104–106] and transcutaneous spinal cord stimulation[107] shows that large diameter afferent fibers in the dorsal roots are the likely sites of neural activation, suggesting that both stimulation approaches act through a common mechanism to modulate excitability within the spinal circuits.

While patterned peripheral nerve stimulation also has been shown to modulate spinal reflex excitability,[108,109] because transcutaneous spinal cord stimulation electrodes span multiple spinal roots, this approach has the advantage of being able to influence the excitability of multiple spinal segments simultaneously, bringing spinal motoneurons closer to threshold so that weak, descending inputs become functional. Multi-site transcutaneous spinal cord stimulation with a customized stimulator elicits involuntary step-like behavior in non-disabled subjects when positioned in sidelying with the legs suspended to counteract the effects of gravity.[110]

Involuntary stepping similar to that described for multi-site transcutaneous spinal cord stimulation has also been observed with vibration to the muscles of the thigh in non-disabled subjects,[111,112] as well as in subjects with motor-incomplete and with motor-complete SCI.[112] These responses are thought to be attributed to activation of the spinal pattern generating circuits.[111–113] Based on evidence for the influence of vibration on circuitry related to locomotor behavior, whole body vibration has been used as an intervention to improve walking in participants with motor-incomplete SCI.[114] Moreover, in a proof of concept study, time-organized vibration to multiple lower extremity muscles has been shown to be capable of inducing small amplitude, gait-like movements in one non-disabled participant and one participant with SCI.[115]

These studies of body weight supported locomotor training, spinal cord stimulation, and vibration are intended to facilitate the activation of locomotor circuits in the spinal cord. The focus on spinal mechanisms underlying locomotion has dominated training approaches for persons with SCI for well over 20 years. New evidence is emerging, however, that seems to support a broader consideration of neuroplasticity at many sites in the neuraxis including supraspinal centers.

Targeting supraspinal structures

Recent evidence in rodent models of SCI indicates that recovery of locomotor function depends largely on activation of spared supraspinal pathways.[116] For this reason, there are new approaches that aim to improve locomotor function by increasing effectiveness of the spared corticospinal or corticoreticulospinal pathways.[117] This premise has been tested in an operant conditioning training program in humans targeting improved volitional control of ankle dorsiflexion.[70] The focus on ankle dorsiflexion arose from evidence that corticospinal drive to the ankle dorsiflexors is impaired in persons with SCI,[118] and control of ankle dorsiflexion represents a physiologic assay of locomotor control.[119] In comparison with a training intervention targeting reduction of reflex amplitude in the ankle plantar flexors, training to increase volitional control of dorsiflexors was associated with meaningful effects in a greater number of outcome measures including walking speed and step height.[70]

Several locomotor training studies support the concept that targeting supraspinal control is a valuable approach for persons with SCI. In a study that compared treadmill-based training with overground training, larger effect sizes for improvements in walking speed and distance were observed in persons who trained with overground training.[51] The authors attributed these findings to greater engagement of the entire neuraxis with overground training compared with treadmill-based training.[51] Evidence from a small crossover study of four participants suggests that training walking function in the real-world environment is associated with greater functional improvement than is treadmill-based training.[14]

In a larger follow-up study, participants were randomized to an endurance group whose members received treadmill-based training, or to a precision group wherein subjects walked over ground. Precision training required that participants step over objects and that they attend to precise foot placement during stepping. Between-groups differences were indentified only in the 6-min walk test, for which participants in the endurance group improved significantly more than participants in the precision group.[15] While attention to foot placement may engage the supraspinal centers, a confounding effect of the attention to precision was that the subjects in this group had a significantly lower dose of training (i.e., number of steps per session) because of the necessarily slower movements when precision is emphasized compared with the treadmill group. Interestingly, motor evoked potentials were strengthened by both mass practice of walking on the treadmill and by precision training over ground,[82] even though precision training was hypothesized to engage the corticospinal system more. Hence, it is possible that targeting one or another type of training is less important than including the key ingredients that induce neuroplasticity in the walking training.

Studies to assess the value of different forms of cortical stimulation for improving walking function in persons with SCI are in the early stages. To date, three studies of this type have been published related to walking,[16–18] as well as a case study related to lower extremity muscle activity.[120] Two studies using transcranial direct current stimulation (tDCS) followed by locomotor training showed mixed results.[16,17] In nine subjects who received 36 sessions of tDCS, improvements in lower extremity motor scores of the right lower extremity were observed compared with six subjects who received sham-tDCS.[16] There were mixed results, however, with other outcomes; participants in the sham group had greater change in some measures, including significantly greater improvements on the outcome measure related to functional independence.[16]

A second study of 24 subjects, wherein outcomes associated with four weeks of daily tDCS and robotic gait training were assessed, showed no differences in walking outcomes in the 12 subjects who received tDCS compared with the 12 who received sham-tDCS.[17] In a study of repetitive TMS (rTMS) applied over the leg motor area in persons with American Spinal Injury Association Impairment Scale (AIS) D injury classification, 17 subjects were randomized to either rTMS or sham-tTMS.[18] Both groups also received locomotor training. The study concluded that rTMS was associated with improvements in walking speed, lower extremity motor scores, and spasticity that were not observed in the sham-rTMS group.

Finally, a case series that included a subject with chronic motor-incomplete paraplegia documented change associated with a multi-session intervention of paired associative stimulation (PAS).[120] In this form of stimulation, single-pulse TMS was paired with peripheral nerve stimulation, and timing of stimulation was configured such that the corticospinal and peripheral impulses arrived at the spinal cord simultaneously. Before the PAS sessions, the subject had motor scores of 0 out of 5 for both dorsiflexors (key muscle for L4 motor level) and plantar flexors (key muscles for L5 motor level) and no observable EMG in these muscles. After 21 weeks of PAS, the EMG record indicated volitional activity in the plantar and dorsiflexors. Post-intervention lower extremity motor scores were not reported, and no gait-related measures appear to have been tested. Future studies with sufficient sample sizes are needed to assess the value of augmenting locomotor training with cortical stimulation.

Key ingredients of training

Critical ingredients of training for humans with chronic SCI are starting to emerge, particularly from studies that have contrasted different forms of training, in which some key components of training are different. First, volitional effort of the participant is essential. Robotic assisted training wherein full assistance is provided, such that stepping is produced regardless of whether the participant exerts volitional effort, is less effective than methods requiring volitional effort.[51,121] Further, the changes in walking speed associated with full robotic assistance in the chronic phase after injury produced changes in walking speed below the level of minimal detectable change (MDC; amount of change that is greater than the error of the measurement),[51] which has been identified as $\sim$0.05 to 0.1 m/sec.[122,123] We speculate that volitional effort engages the important neural circuits required for walking, which in turn induces neural plastic change. Based on what is known about the way the nervous system responds to training, it seems likely that this applies equally to training for persons with chronic SCI, as well as to those with acute/subacute SCI.

Second, interventions that are intended to improve locomotor function are most effective when they incorporate locomotor training. For example, training of walking-related tasks, such as increasing volitional control of dorsiflexors or reducing H-reflex excitation of the soleus, without the addition of walking training itself resulted in improvements in walking speed that were below the MDC for persons with chronic SCI.[69,70] Both operant conditioning training to improve volitional control of dorsiflexion and training to decrease reflex excitability, however, were each associated with improvements in walking distance[70] that reached the minimal important difference for 2-min walk test distance in persons with SCI.[51] Thus, while training of walking-related tasks is helpful, engagement of the circuits directly required for walking will likely have a greater impact on enhancement of walking speed.

Third, training intensity as measured by the number of steps executed in training within a specific time may be important. Comparing methods in which the total duration of training (i.e., time) is the same while the number of steps executed is different indicated that repetition of the motion within a certain time frame may be a critical ingredient to induce improvement.[15] Indeed, studies of neuroplasticity in rodents also point to the importance of quantifying a similar measure of training intensity (i.e., number of attempts in a pellet grasping task in a day).[124]

Predicting Future Walking Function and Forecasting Responsiveness to Training

An important starting place for planning a locomotor rehabilitation program is the ability to predict likely future walking ability, as well as to anticipate responsiveness to training, Because AIS conversion between the acute and chronic phases of SCI appears to have little relationship with improvement in walking capacity,[125] a focus on prediction of walking related outcomes is more clinically meaningful than predicting AIS conversion. Of the various measures available to assess walking function, walking speed and distance have been identified as the measures most responsive to change.[53]

Walking speed is an objective and sensitive measure of walking function and is among the primary outcome measures recommended by several expert groups for assessment of walking function after SCI.[126–128] Average walking speed can be used to classify level of functional walking ability in persons with SCI according to: (1) wheelchair-dependent (0.01 m/sec), (2) walks using assistive device with supervision indoors but dependent on a wheelchair outside (0.34 m/sec), (3) walks independently indoors but dependent on a wheelchair outside (0.57 m/sec), (4) walks with assistive device inside and outside (0.88 m/sec), and (5) walks without assistive device (1.46 m/sec).[129] Because of its practicality for use in both the clinical and research settings, walking speed is widely used as a primary index of walking function in both clinical and research settings.

There are a number of clinical prediction rules to predict future walking function based on early clinical presentation, along with association models that delineate the characteristics associated with responsiveness to training, as well as correlated variables that have been found to be related to walking ability. With knowledge of the predicted future walking function, training programs can be designed to achieve the maximum potential for standing and walking function, and possibly to exceed expectations based on the prediction rules. Likewise, being able to forecast the outcomes of locomotor training based on pre-training characteristics can assist with clinical decision-making and discharge planning.

While clinical prediction rules and association models are useful for guiding rehabilitation strategies, these estimates are most valuable when they are based on large datasets containing information from many subjects. The larger the number of subjects in the dataset, the more likely the dataset will accurately represent the population of persons with SCI in the larger community.[130]

Clinical prediction rules/prognostic studies to predict locomotor outcomes

We identified six clinical prediction rules for predicting locomotor outcomes based on early presentation (Table 1). Among the prediction rules, there were differences in the timing of the early test, as well as differences in the time post-injury for which walking outcomes were predicted. Some studies acquired the initial measures within the

Table 1. Observational Prognostic Studies Forming the Basis for Clinical Prediction Rules for Walking Outcomes Based on Measures Obtained in the Acute/Subacute Phase after Traumatic Spinal Cord Injury

Source	N	*Age (yr)*	*AIS*	*Level of injury*	*Best prognostic variables*	*Time prognostic variables measured*	*Outcome predicted*	*Time outcome measured*	*Prediction accuracy*
Crozier et al[46]	17	17–59	C (MMT quad ≤2/5 @ <1 wk)	C4-T10	MMT quad of stronger side >3/5	2 mo	Functional vs. non-functional walker	6–12 mo	88%
Waters et al[47]	36	29 ± 10.1	Able to walk 5 min with or without braces	All	LEMS	0.5 ± 0.7 y	Walking speed, cadence, O_2 consumption	0.5 ± 0.7 y	–
Zörner et al[49]*	51	≥18	C & D @ (subacute)	Tetra	LEMS+AIS	≤6 mo	6MWT (functional vs. non-functional walker)	≥6 mo	100%
	39		C & D @ (subacute)	Para	LEMS+age	≤6 mo			84%
Van Middendorp et al[45]*	492	≥18	All	All	LEMS (L3 & S1) + light touch (L3 & S1) + age	≤15 d	Dependent (0–3 SCIM mobility), or Independent (4–8 SCIM mobility)	6–12 mo	0.956 (area under ROC)
Teeter et al[48]	1032	≥12 (37.7 ± 16.7)	All	C1-T9	AIS, age, TSI, BMI, work, PT Rx	Admission to rehab	Motor FIM	Discharge from rehab	$R^2 = 0.77$
Oleson et al[132]	249	≥18	B	All except sacral levels	Age + pin prick (L2–S1)	<30 d	Primary mode of locomotion	1 y	–

All times refer to time since injury (TSI).

N, sample size; AIS, American Spinal Injury Association Impairment Scale; MMT, manual muscle test; LEMS, lower extremity motor score (from AIS); 6MWT, 6-min walk test; SCIM, Spinal Cord Independence Measure; ROC, Receiver Operating Characteristics curve BMI, body mass index; PT Rx, physical therapy treatment; FIM, Functional Independence Measure.

*These studies contained overlapping participants from the European Multicenter Study on Human SCI.

first few days post-SCI, while others acquired the initial measures within the first weeks post-injury. Likewise, while most studies attempted to predict walking-related outcomes at one year post-injury, other studies attempted to predict short-term walking-related outcomes at discharge from inpatient rehabilitation or at six months post-SCI.

A clinical prediction rule for walking function after SCI with high discriminatory ability was developed based on the European Multicenter Study on Human Spinal Cord Injury (EM-SCI). This prediction rule is based on clinical measures obtained within the first 14 days post-injury in 492 persons with SCI from whom one-year ambulation outcomes were available. The EM-SCI clinical prediction rule is able to accurately predict the one-year indoor walking status of independent walkers, dependent walkers, and non-walkers, based on the clinical measures including motor scores from knee extensor (key muscle for spinal level L3) and plantar flexor (key muscle for spinal level S1) muscles, and light touch sensation of L3 and S1 dermatomes. The discriminative ability (defined as the area under the receiver-operating-characteristics curve [area under the curve, AUC]) of this clinical prediction rule was 0.956, 95% confidence interval (CI): 0.936–0.976 ($p < 0.0001$).

The discriminative ability of the EM-SCI clinical prediction rule value was significantly greater than the clinical prediction rule based on the AIS classification of motor and sensory function below the level of injury. Moreover, the EM-SCI clinical prediction rule had additional value for predicting ability to walk independently based on each of the AIS grades.[45] However, despite the greater discriminative ability of the EM-SCI clinical prediction rule, this study showed that the AIS classification has excellent ability to serve as a clinical prediction rule with an AUC of 0.898, 95% CI: 0.867–0.928 ($p < 0.0001$).[45]

There are other studies that have based predictions about future walking status on muscle test scores of single muscles or composite lower extremity motor score (LEMS) of the AIS.[131] In agreement with the EM-SCI clinical prediction rule, an earlier study of 17 persons with SCI who had initial evaluation within 72 h to one week post-SCI also showed the predictive value of knee extensor strength. All participants had knee extensor motor scores of ≤2/5 in both legs on initial evaluation; a knee extensor motor score of ≥3/5 at by two months post-SCI was predictive of household or community ambulation by six months post-injury.[46] Likewise in a study of 54 persons with LEMS of >10 at one month post-SCI, regardless of level of injury, those with hip flexor or knee extensor motor score of ≥2/5 were likely to be community ambulators at one year post-injury.[47]

Beyond the predictive ability of individual lower extremity muscles, composite LEMS have also been shown to have predictive value. In a study of 1376 persons with SCI admitted to the Spinal Cord Injury Model Systems Centers, LEMS on admission to inpatient rehabilitation and change in LEMS during inpatient rehabilitation were the factors found to be most highly predictive of walking ability at discharge[48]; unfortunately, only this short-range outcome was investigated in this study.

A study that included 90 persons with AIS C or D injury classification with initial measures available from the subacute phase (within 16–40 days of injury) concluded that the LEMS was the single factor that best predicted walking capacity at six months post-injury.[49] The LEMS was the single best predictor of walking outcome, correctly classifying non-functional (<0.6 m/sec) and functional (>0.6 m/sec) walkers with 90% correct prediction for both persons with tetraplegia and persons with paraplegia. LEMS in combination with other measures (tetra- vs. paraplegia, age, AIS classification) further improved prediction. Motor scores indicate ability to voluntarily activate a muscle or muscles; the value of these scores for predicting walking outcomes illustrates the important contribution of supraspinal contributions to locomotor function in humans.

Aside from LEMS as a predictor, a recent retrospective analysis of data obtained within the first 2–4 weeks from 249 persons with AIS grade B SCI assessed the value of pinprick scores for predicting walking outcomes.[132] The likelihood of attaining household ambulation at 1 year post-injury was more than five times greater in those persons in whom pinprick was present in at least one-half of the lower-extremity dermatomes (AIS L2–S1) in the subacute stage. The results, however, were strongly influenced by age, because pinprick score was not significantly related to walking outcomes in persons over age 50 years.

Further illustrating the importance of age as a predictor, in addition to the six clinical prediction rules described above that are based on clinical measures, age has also emerged as an important predictive variable. Older persons (variously defined as >50 or >65) generally have poorer recovery compared with younger persons.[48,49,133] With the increase in the average age at time of injury in the past two decades,[134–136] age of injury will become increasingly important. Nonetheless, older persons continue to respond to rehabilitation,[137] and the influence of age on selection of the most effective types of interventions will also be important.

Association models of characteristics that forecast locomotor training outcomes

Beyond predicting future walking capacity in persons with acute/subacute SCI, there is also value in association models that identify factors associated with responsiveness to locomotor training. Many persons with SCI engage in training after the subacute phase of injury and make meaningful improvements in function. These models provide a forecast of the possible outcomes, which can be useful for making informed decisions about how to most effectively allocate interventions. Studies of this type are costly and time-intensive, and for these reasons they often involved smaller numbers of participants. Nevertheless, the information gained from these studies is essential to distinguish the elements of training that are most valuable, without the influence of natural recovery that confounds the interpretation of outcomes in studies of persons with acute/subacute studies.

Despite their potential value, it is important to be aware of the limitations of currently available association models (many of which are described by the authors as prediction models) that forecast training-related outcomes based on pre-training characteristics. First, some of the available association models are based on studies that included both participants with subacute SCI and participants with chronic SCI. While improvements continue to be possible even in the chronic phase regardless of training approach,[51] there is evidence that training responsiveness is greatest early after SCI.[52,138] During chronic stages, 1–5 years after SCI, recovery of muscle strength slows or regresses.[139] For this reason, studies that include both participants with subacute SCI and those with chronic SCI may offer limited ability to forecast training-related outcomes in either group alone.

Second, it is important to distinguish between studies that describe variables associated with responsiveness to training—that is, variables that forecast amount of change versus studies that identify variables associated with outcomes of training. We contend that forecasting responsiveness to training rather than final outcome of training is the more valuable focus, because unsurprisingly, final

Table 2. Intervention Studies Forming the Basis for Association Models to Forecast Responsiveness to Locomotor Training in the Subacute and Chronic Phases after Spinal Cord Injury

Source	N	*Age (y)*	*AIS*	*Level of injury*	*Time since injury (y)*	*Best variables for prediction*	*Intervention (Rx)*	*Duration of Rx*	*Outcome predicted*	*Accuracy of prediction*
Field-Fote & Roach[51]	64	≥18	C & D	T10 and above	≥1.0	LEMS	4 types of locomotor training	60 sessions	Δ10MWT	–
Yang et al[50]	19	20–77	C & D	C1 – L1	0.6–28.2	MMT (knee ext + knee flex + ankle plantar + hip abd)	BWSTT manual	5x/wk for 18 ± 10 wk	Δ10MWT	r = 0.82
Buehner et al[140]	144	17–86	C & D	All with no LMN signs	0.09–25.8	LEMS = 20 to 50	NRN locomotor training	60 ± 53 sessions	Δ10MWT	–
Jones et al[52]	38	22–63	C & D	All	≥1.0	AIS D + TSI (<3 y)	Activity-based therapy	9 h/wk for 24 wk	Δ6MWT	$p < 0.05$

N, sample size; AIS, American Spinal Injury Association Impairment Scale; LEMS, lower extremity motor score (from AIS); 10MWT, 10-min walk test; MMT, manual muscle test; BWSST, body-weight supported treadmill training; LMN, lower motor neuron; NRN, Neural Recovery Network; TSI, time since injury.

outcomes of training are invariably tied to initial values; i.e., participants with the fastest pre-training walking speed typically have the fastest post-training walking speeds.[138] Conversely participants with very slow pre-training walking speeds can make large gains relative to initial values, but still walk very slowly after training.[92,140]

Third, association models are often based on relatively small samples; forecasts based on small samples may not be representative of the responsiveness or outcomes of persons with SCI in the population as a whole.[130] Fourth, the models are based on outcomes from specific training programs with great variability in total number of training sessions and training approaches; therefore, the models may not be generalizable to all persons with SCI, or to similar participants receiving other types of locomotor training.

We identified four studies that described the characteristics associated with responsiveness to training in persons with SCI classified as AIS C or D, and one additional study that described the characteristics associated with outcomes of training (Table 2). Of the studies of responsiveness to training, two studies included only persons with chronic SCI (i.e., at least one year post-injury), and two studies included both participants with subacute SCI and participants with chronic SCI. The study that assessed characteristics associated with outcomes of training also included both participants with subacute SCI and participants with chronic SCI.

Of the two studies that assessed responsiveness to training exclusively in participants with chronic SCI, one was a randomized clinical trial comparing different training approaches[51] and the other study involved a training approach that included both locomotor and non-locomotor training activities.[52] The randomized clinical trial included findings from 64 participants, all with chronic SCI (at least one year post-injury) who completed training using one of four different training approaches and a training target of 60 sessions. Across all training groups, participants with higher LEMS (i.e., ≥15 in one leg and ≥10 in the other leg) were more likely to achieve an improvement in walking speed that exceeded the MDC.[51]

Another of study of responsiveness to training in participants with chronic SCI incorporated locomotor training along with other functional and strengthening activities. Of the 38 participants, responsiveness to the 72-session training program was greatest in persons with AIS D grade SCI who were within the first three years of injury.[52] Despite the relationship between LEMS and walking function as identified by clinical prediction rules, there does not appear to be a direct relationship between training-related change in lower extremity strength and change in walking speed.[141]

Of the locomotor training studies that assessed responsiveness and included both participants with subacute and with chronic SCI, one study reported findings from 144 participants, of whom more than 50% had chronic SCI and who participated in an average of 60 training sessions. Absolute values of increases in walking speed were greater in participants with AIS D injury classification. Because of slower initial walking speeds, participants with AIS C injury classification had gains that were lower relative to the overall group, but when compared with their baseline walking speeds, the proportional gains were larger.[140]

A second study assessed responsiveness in 19 participants with either subacute or chronic SCI (at least seven months post-injury) who completed an average of 90 sessions. Lower extremity manual muscle test scores at baseline had good correlation with change in walking speed after locomotor training.[50] Only those participants with a composite initial lower extremity manual muscle test score of >30/80 (eight muscle groups from both legs) were responsive to

locomotor training. Moreover, ability to forecast responsiveness to training was improved by focusing on the summed manual muscle test scores of four key muscles: knee extensors, knee flexors, ankle plantar flexors, and hip abductors (the latter of which is not included in the AIS LEMS).

A final study assessed the variables associated with final walking speeds obtained after training, rather than variables associated with responsiveness to training. In 30 participants with subacute or chronic SCI who took part in a 36-session locomotor training program, the factors associated with fastest post-training walking speeds were pre-training walking speed, voluntary bowel/bladder function, time since injury, and spasticity as assessed by resistive forces generated during robotic stepping.[138] Given that voluntary bowel/bladder function is an indication of supraspinal control over circuits in the lower levels of the spinal cord, as with the studies showing the contribution of LEMS to walking function, this finding supports the role of supraspinal centers in walking after SCI in humans.

Variables associated with walking function

Beyond the ability to predict future walking capacity based on early clinical presentation and pre-training characteristics that are associated with responsiveness to locomotor training, a number of studies have identified clinical measures that have a strong relationship with walking function. Several studies have shown that there is a strong correlation between LEMS and walking ability, adding support to the premise that volitional supraspinal control is essential for walking after SCI in humans. LEMS are highly correlated with walking speed, and LEMS of 20/50 or less are associated with limited walking ability, while scores of 30/50 or greater are associated with capacity to walk in the community.[142]

In addition, LEMS have been found to be well correlated with measures of walking outcomes including the 10-m walk test,[53] and the 6-min walk test.[53,54] While some studies have suggested that performance on the Walking Index for Spinal Cord Injury II (WISCI II) is associated with LEMS.[54,143] Other studies have indicated that the WISCI II is not strongly correlated with muscle strength and is less responsive to change in walking function than are speed and distance measures.[53]

Interestingly, two studies have shown that the strength of muscle groups that are not included in the AIS contributes meaningfully to walking ability. A study of 22 subjects with motor-incomplete SCI found that hip extensor strength of the less affected limb explained 64% of the variability in home and community walking capacity.[55] The strength of the hip flexors, hip extensors, and hip abductors of the less affected lower extremity had the highest correlations with measures of functional walking performance, leading to the conclusion that strength of the less affected limb is an important determinant of functional walking performance. Another study found that the summed values of maximal force production (obtained with hand-held dynamometry) in the hip flexors, extensors, and abductors, knee flexors and extensors, and ankle dorsiflexors and plantar flexors was moderately correlated with walking speed, and strongly correlated with daily step activity.[56]

Imaging and electrophysiological measures associated with walking capacity

In recent years, there has been growing interest in identifying electrophysiological and radiographical biomarkers that can predict locomotor outcomes.[60,144,145] Recent evidence from studies of TMS[146] and EMG coherence[60,144] have provided additional support for the importance of corticospinal pathways in human walking. More generally, there is some evidence that magnetic resonance imaging (MRI)-based measures are correlated with impairment. Cross-sectional area of spinal tracts measured using MRI correlates with motor and sensory scores[147] and some diffusion tensor imaging have also been found to be correlated with motor and sensory function.[148] As yet, however, no studies have described the relationship between walking function and measures obtained via imaging.

These studies show that the corticospinal pathways are an important driver of human locomotion, and the anatomical and functional integrity of corticospinal pathways are correlated to clinical measures of walking function.[59] As noted in a recent systematic review, however, the clinical usefulness of these approaches for prediction of outcomes and forecasting responsiveness to training has yet to be established.[149]

To justify the greater time and resource requirements needed to acquire these state-of-the-art measurements, in order to have true value as biomarkers for recovery, they will need to provide a more accurate picture of future walking status than do prediction rules based on clinical measures. While the electrophysiological, imaging, and clinical prediction rules all indicate that supraspinal control is the most valuable predictor of walking function, to date the electrophysiological and imaging biomarkers have not been rigorously compared with prediction rules based on common clinical measures.

Summary and Future Directions

A solid understanding of how locomotor behavior is produced by the intact nervous system, how the role of the nervous system in production of locomotion changes after SCI, and how the injured nervous system responds to therapeutic interventions all serve as the bases for the development of effective locomotor training approaches. There is a long history of attention to spinal contributions to locomotor function and interventions that have focused on activating spinal mechanisms.

Of late, greater attention has been given to supraspinal mechanisms that contribute to locomotor function, and it is possible that these supraspinal pathways are even more important after SCI, when walking speeds may too slow to engage spinal mechanisms. Moreover, this recent focus on supraspinal contributions to locomotion can inform the development of rehabilitation approaches directed at strengthening these supraspinal pathways and represents an acknowledgment that engaging the entire nervous system in training approaches is likely to result in the most robust outcomes of training. By careful consideration of all the factors that contribute to walking and to improvement of walking after injury, future studies may be able to tailor interventions to meet the specific needs of each person with SCI.

The strong influence of supraspinal centers on walking after SCI is illustrated by clinical prediction rules/prognostic studies showing how early measures of volitional control predict future walking function, by association models showing the association between clinical measures of volitional control and outcomes of locomotor training, and by correlations between variables indicative of volutional control and walking function

The usefulness of identifying individuals who will respond to walking interventions depends on the subsequent provision of effective locomotor training and other physical therapy to promote walking. These represent necessary pieces of the puzzle that will facilitate identification of the most effective forms of training and

possibly strategies that combine training with other types of physical therapeutic intervention such as peripheral nerve, spinal cord, or cortical stimulation.

Viable clinical prediction rules, based on combinations of clinical measures obtained in the acute phase after SCI, are available to forecast likely locomotor-related outcomes in the chronic phase. Beyond predicting walking function in the chronic stage based on measures obtained in the acute phase, a number of association models have been developed that attempt to identify variables that can be used to forecast outcomes of locomotor training. The ability to predict in the acute/subacute phase which patients would be most responsive to training, or which training approach would be most effective, however, would require information from studies that have randomized participants with different acute/subacute presentation to different forms of training. Studies of this type have not yet been performed and thus represent a worthy focus of future research.

Finally, there are several studies that report the characteristics exhibited by persons in the various categories of walking function. Biomarkers based on electrophysiological and radiographical measures are in the early stages of development, and it remains to be seen whether these measures are able to provide superior predictive value compared with clinical measures, and if so whether the additional expense and technical resources are justified by the added predictive accuracy.

Author Disclosure Statement

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