

Physiological methods to measure motor function in humans and animals with spinal cord injury

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Abstract—This article compares some physiological methods commonly used to measure the functional capability of the motor system in humans and animals after spinal cord injury. Some of the differences between animal and human experimentation are considered first. Then we discuss how to measure the effectiveness of conduction through the motor system. We describe ways to assess the integration of different inputs at the spinal cord and to measure the responsiveness of the neuromuscular system. We conclude that comparisons across species are invaluable to understand the control of movement, both before and after injury.

Key words: central nervous system regeneration, control of movement, electromyography, motor-evoked potential, neuromuscular adaptation, neuron excitability.

INTRODUCTION

The neural responses to spinal cord injury (SCI) depend on the nature of the injury. A thorough understanding of the mechanisms that contribute to these responses, either in the short- or long-term, has important implications for neurological recovery, the optimal care and management of the injured person, and the design and implementation of therapeutic strategies that aim to promote repair and functional recovery. Our knowledge, furthermore, rests on the availability of clearly defined

and reproducible methods to assess the neurological response to injury. In this article, our aim is to compare some of the physiological methods commonly used to measure function of the motor system in humans and animals after SCI. However, recovery of function, whether it occurs spontaneously or as a result of an intervention, is best understood when it is evaluated with a principled approach that includes different assessments (e.g., physiological, anatomical, behavioral) of both motor *and* sensory function. In this regard, other recent reviews provide important information on the motor neurobiology of the spinal cord, ways to restore motor function after injury, and behavioral assessments of functional recovery following SCI [1–5].

Abbreviations: EMG = electromyogram, MEP = motor-evoked potential, SCI = spinal cord injury.

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DIFFERENCES BETWEEN SPECIES, THE NATURE OF INJURY, AND EXPERIMENTAL CONDITIONS ALL INFLUENCE COMPARISONS BETWEEN ANIMAL AND HUMAN DATA

When comparing methods to evaluate motor function in humans and animals with SCI, one must consider many factors. First, the function of descending tracts in motor control may differ across species. For example, the corticospinal tract is fundamental for the production of fine voluntary movements in humans, but less so in rats, a species commonly used to model SCI. Second, there is always the question of whether an animal model adequately mimics the human injury. Assuming that it does, there is greater flexibility to test the mechanisms that underlie the control of movement in animals than in humans, in part because the physiological observations made in animals are commonly interpreted in view of subsequent, direct anatomical investigations of the nature of the central lesion and its consequences (e.g., on muscle properties). However, in some situations the reverse is also true. The study of voluntary motor control is easier in human studies, because one can simply ask the person to perform a given movement, a task that is more problematic when dealing with animals. In addition, comparisons between human and animal data must be interpreted in relation to the experimental conditions under which they were obtained. For example, individuals with SCI usually take various medications, and many animal experiments are conducted under anesthesia. The effects of these substances on motor function are poorly understood.

HOW CAN THE EFFECTIVENESS OF CONDUCTION THROUGH MOTOR SYSTEMS BE MEASURED?

Voluntary Contractions

In a clinical setting, manual examination is a common way to assess whether a particular muscle remains under some voluntary control after injury to the human spinal cord. Muscles are typically scored on a six-point ordinal scale (0: complete muscle paralysis; 1: trace muscle contraction; 2: movement of the muscle through its range without gravity; 3: movement of the muscle through its range against gravity; 4: movement of the muscle through its range against gravity and resistance;

5: normal muscle function) [6]. Clinicians often express these scores as measures of muscle strength, but maximum voluntary force-generating capacity can differ widely, both within and across muscles of different people [7,8]. While comparisons between muscle scores and isometric force are positively related after chronic SCI, muscles with quite different force-generating capacities can be assigned the same score [9–11]. Thus, the sensitivity of this scoring method as an outcome measure in a clinical trial needs to be questioned. Equally important, considerable care must be exercised when performing force evaluations. The limb must be restrained adequately so that the force primarily arises from the test muscle or muscle group. Simultaneous measures of electromyographic activity from various muscles are also advisable, since these can provide insight into the source of the generated forces; for example, by detecting the presence of cross-talk or coactivation of synergists and antagonists [12,13]. Comparisons between the maximal voluntary forces produced by contractions of muscles influenced by SCI with those produced by uninjured subjects can provide an overall estimate of injury severity. However, these force measures do not distinguish whether any weakness results from disruption of descending inputs to spinal motoneurons, as opposed to muscle denervation from motoneuron death and/or ventral root damage.

This issue is crucial, for example, when there is no voluntary contraction (manual muscle score of 0). A zero score does not reveal the caudal extent of the damage or the cause of the muscle paralysis, yet the nature of the injury will strongly influence what interventions are necessary and their potential benefit. For example, after a cervical injury, motor deficits in arm muscles are likely to involve a combination of upper and lower motoneuron damage, whereas deficits to lumbar spinal segments of the same cord are likely to involve only destruction of the descending inputs to lumbar motoneurons. Supramaximal electrical stimulation of the appropriate peripheral nerve, coupled with records of evoked electromyogram (EMG) and muscle force, could be used to show disruption of descending inputs to the spinal cord, whereas an absence of any evoked EMG and force would show complete muscle denervation [14]. Evoked EMG and force of small magnitude, compared to data recorded from intact subjects, may indicate some combination of upper and lower motoneuron damage. Coupling these score and force assessments with imaging of the spinal cord [15]

would be particularly useful in resolving the extent and nature of the damage.

When assessing voluntary muscle function, it is equally important to encourage patients to make their best efforts during every evaluation. This is particularly critical for interpreting motor recovery that occurs over time or after intervention, if spurious conclusions are to be avoided. The ability of SCI subjects to maximally activate their muscles by voluntary effort can be assessed by comparing the maximum voluntary force to that elicited by cortical stimulation [16]. If voluntary drive is maximal, no additional force should be evoked in the test muscle or muscle group in response to magnetic stimulation of the appropriate motor cortical area. Any disparity between voluntary and evoked forces, a common feature after cervical SCI, must reflect a lack of voluntary drive and/or possible deficits in sensorimotor integration [16,17]. It is not possible to test central motor drive with peripheral nerve stimulation (below-lesion stimulation), as is customary in control subjects [18–20], since this stimulation maximally excites not only motoneurons that remain intact centrally, but also those that have been denervated from higher brain centers. The force evoked by peripheral nerve stimulation does provide an estimate of muscle atrophy, however (assuming that any denervated muscle has been reinnervated from intact axons), if the SCI data are compared to the intrinsic strength of muscles of uninjured control subjects. Different rehabilitation strategies will be required, depending on the reason for the atrophy. Atrophy from alterations in use should be amenable to physical therapy, whereas recovery from denervation-induced atrophy will require muscle reinnervation.

The difficulties associated with assessment of voluntary contractions in humans are compounded further when studying animal models of SCI. In animal studies, it is crucial to know whether the initiated movement requires input from centers above the lesion, not just the reflex activation of spinal circuitry below the lesion [21]. The same issue must be considered with regard to sustaining the behavior, especially in tasks such as locomotion, which can be maintained entirely by a spinal locomotor generator. In contrast, movements such as target reaching require integration in descending motor pathways, even though spinal neurons are required to mediate the movement [22,23]. To distinguish between nonspecific facilitation of reflexes and intrinsic spinal networks (functional compensation or adaptation) versus central nervous system regeneration, it is important to

demonstrate *functional* connectivity (spared or reestablished) across the lesion before conclusions are drawn about what structures underlie movement initiation or patterning.

Evoked Contractions

Measurement of responses evoked by stimuli that are delivered above a lesion offers an alternative strategy to examine conduction through central motor pathways. In both humans and animals, motor-evoked potentials (MEPs) can be examined from surface or intramuscular EMG recordings. In animals, recordings can also be made from a peripheral nerve, the surface of the spinal cord, and/or from individual neurons using intracellular or extracellular methods.

A distinct advantage in animal studies is the opportunity to assess function in a number of different pathways following SCI. Pathways that have been studied include the corticospinal [24,25], rubrospinal [26,27], vestibulospinal [28], reticulospinal [29–31], and propriospinal tracts [32]. In contrast, relatively fewer pathways can be selectively activated in humans. The easiest pathway to stimulate in humans is the corticospinal tract, through magnetic stimulation of the motor cortex [33–35].

In general, the size of the MEP gives an estimate of the degree of preservation of the pathway stimulated [36,37,27] and an evaluation of spinal cord function after injury [38–40,16]. However, the size of the MEP is influenced by a number of factors, both practical and biological. For example, animal studies have shown that cortically evoked MEPs are often contaminated by responses produced by the concurrent activation of extrapyramidal pathways [27]. Thus the analysis of evoked responses following injury must take into account the possibility that other pathways are activated either directly via the spread of stimulation or indirectly via afferent projections to other target neurons [41]. Second, these stimuli sometimes elicit responses that are not apparent from clinical or behavioral assessments of motor function [42,27], possibly because the behaviorally generated impulses are too weak or less synchronized than the evoked responses. Alternatively, the pathways that mediate the evoked responses may differ from the pathways responsible for the behavior but colocalize to the site of the lesion [27]. Thus, an absence of transcortically evoked MEPs and loss of locomotor function may simply be coincidental, because the lesion encompasses all the responsible pathways [43]. Lastly, it

is important to consider that the size of the MEP can vary substantially between subjects, depending on a number of experimental factors, such as the proximity of the stimulating electrodes to the targeted nucleus, the stimulus intensity, and the interpolar distance of the recording electrode (number of depolarized neurons between the recording electrode) [27].

The stimulus intensity needed to evoke an MEP provides some indication of the excitability of the descending tracts. The latency and the duration of the MEP give an indication of the fastest and slowest conducting motor axons, provided that one also verifies that conduction along peripheral axons is unimpaired. The latency of the response to stimulation, which typically slows after injury [26,16], probably reflects slowing through the injury site, since similar conduction delays are reported irrespective of the level of the injury [38]. Changes in latency could reflect a number of different pathophysiological consequences of injury. For example, selective destruction of large-diameter fibers following injury [44] could result in an apparent slowing of the response to stimulation. Changes in the path that the signals take (e.g., disynaptic versus monosynaptic connections) may also delay the response [45]. In addition, demyelination or incomplete remyelination of central pathways will result in the slowing or failure of conduction along surviving axons, resulting in diminished and temporally dispersed responses [46]. The duration of an MEP may also depend on the extent to which it was polysynaptically mediated and/or may include a repetitive component (afterdischarge). In animals, slowing of conduction through central pathways can be studied readily in single fibers. In humans, the relative importance of these factors in conduction slowing can be examined by assessing changes in the firing patterns of different single motor units during voluntary contractions in response to stimulation of the motor cortex [35]. The practical consequences of any slowing of conduction through central pathways could be a failure to initiate, coordinate, and/or maintain a certain movement. This is particularly evident for the initiation of locomotion in decerebrate animals with stimulation of the midbrain locomotor region, where the parameters of stimulation determine whether locomotion will be generated, as well as the frequency and amplitude of the response [47].

HOW CAN INTEGRATION OF DIFFERENT INPUT SYSTEMS AT THE SPINAL CORD LEVEL BE EXAMINED?

Integration of many descending, intraspinal, and afferent inputs has to occur at the spinal level for smooth, refined control of skeletal muscles [48]. With SCI, the descending and ascending communication between the brain and spinal cord is disrupted, denervating spinal neurons to various extents. However, with time the spinal cord adapts: vacated synapses may be replaced, existing synapses may be strengthened or unmasked, and the excitability of neurons (interneurons or motoneurons) may change because of modifications in their intrinsic membrane properties [49]. All these changes may alter the balance between spinal excitation and inhibition, as is evident after human SCI by a loss of voluntary control of skeletal muscles, ongoing spontaneous motor unit activity at rest, the appearance of spasticity (including changes in muscle tone and reflex strength, involuntary muscle contractions, or spasms), and the ability to evoke novel reflexes [50–56].

At the level of the spinal cord, the physiological responses to voluntary inputs or stimulation depend on descending modulatory influences and the excitability of spinal neurons, both of which are state-dependent [57–59]. For example, inputs from cortical centers can reset the locomotor rhythm and influence posture [60,61]. Similarly, it is well known that behavior such as locomotion results in the widespread modification of transmission in reflex pathways [62]. Excitation of Ib afferents with peripheral stimulation results in inhibition of extensor motoneurons at rest, but during locomotion the same stimulation results in excitation [63,64,58]. The emergence of these new excitatory reflex pathways during locomotion likely involves suppression of the interneuronal pathways that operate at rest, augmentation of afferent influences on central pattern generator interneurons, reductions in presynaptic transmission from afferents, and changes in the membrane currents of motoneurons and their firing properties [62,65].

In terms of interneuron function, either at rest or during behavior, assessments can be made in animals by measuring states of excitation and inhibition in interneurons, motoneurons, or muscles. In humans, interneuron function is surmised from measures of motoneuron activity in muscles. If possible, it is important to distinguish whether the change in interneuron activation is a result of

presynaptic or postsynaptic mechanisms [66]. Reflex activity may be evoked by stimulation of peripheral afferents or descending pathways and modulated by conditioning stimuli. For example, in humans and animals, different interneurons could be engaged by head tilt, incline plane walking, or startle to monitor possible changes in vestibulospinal or reticulospinal pathways [67–70]. The importance of afferents could be examined by assessing reflex modulation during locomotion [21,62,71]. These data may indicate the magnitude of damage or preservation, as well as adaptive changes. Thus, data interpretation requires careful comparisons of the responses of the uninjured system to those of the injured spinal cord [72].

Changes in neuron excitability may also underlie poor coordination of movements after SCI. In animals it is possible to record intracellularly to measure intrinsic properties of motoneurons, such as the rheobase current to evoke action potentials or the input resistance of the cell. These parameters have been used to show either no change or an increase in the voltage threshold of different motoneurons after injury [73–75]. Other studies have shown that the membrane properties of motoneurons are altered after chronic cord section, with sustained depolarization occurring in response to current injection, behavior that can be altered immediately after cord section by descending modulatory influences [76,77]. This sustained firing is consistent with the exaggerated reflexes and sustained motor unit activity seen in rats and humans with spasticity following SCI [78–81]. Alternative mechanisms underlying this excessive muscle activity may include reduced inhibition or altered fusimotor control.

In humans, changes in the excitability of motoneurons are usually examined by monitoring F-waves (the antidromic response to peripheral nerve stimulation sometimes elicits a second, smaller orthodromic EMG potential, termed an F-wave) [82]. A higher incidence of F-waves and F-waves of greater magnitude relative to the maximal motor response from a muscle are considered to be a reflection of greater motoneuron excitability [83–85]. Although F-wave studies at the single motor unit or muscle fiber level [86–89] are more difficult to perform, these data can be used to estimate the conduction velocity of the proximal segment of the peripheral axon, a particularly useful feature when ventral root damage is suspected.

HOW CAN THE RESPONSIVENESS OF THE NEUROMUSCULAR SYSTEM BE MEASURED?

Following SCI, muscle weakness and fatigue are common, factors that will influence motor performance. While measurements of whole muscle performance can provide valuable insight into why a particular outcome measure does or does not change, as described earlier, more detailed understanding will come from analysis at the single motor unit level. The major drawback with motor unit stimulation and/or recording techniques is that they are much more challenging technically, and the data analyses are time consuming. Furthermore, it is often only possible to record data during weak contractions because the simultaneous activation of many motor units makes it difficult to distinguish the activity of a single motor unit as force increases.

In terms of force production, it is important to determine the order in which motor units are recruited, the range of whole muscle force over which recruitment occurs, the rates at which the motor units fire, and the variability in the motor unit firing pattern. Before SCI, the contribution of these factors to force generation differs between muscles, across force levels, with different inputs, and as muscles fatigue [90–94]. Following SCI, other factors such as adaptation and muscle reinnervation may become important [95,96,81].

With respect to motor unit properties, measurements can be made during different conditions. In animal studies, measurement of motor unit contractile properties has relied on selective stimulation of the motor unit, either via the motoneuron or a ventral root filament, or from within the axon. Apart from activation of the test unit, measurement of parameters such as peak force, contraction, and half relaxation times, as well as fatigability, are performed in an otherwise relaxed muscle. Human motor unit contractile properties can also be examined under similar conditions by employing intraneural stimulation of motor axons [97], intramuscular microstimulation [98], or percutaneous nerve stimulation [99,100]. Thus, direct comparisons between human and animal data can be made. For measurement of motor unit twitch properties during voluntary contractions, it is possible to use the method of spike-triggered averaging [101,102] to examine issues such as muscle disuse and reinnervation after SCI [95]. However, the twitch force data obtained depend on the motor unit being activated at a low rate (<12 Hz) to avoid twitch fusion. Thus, the method of spike-triggered

averaging may prove problematic in cases where voluntary motor control is deficient (e.g., high motor unit firing rates would result in complete twitch fusion). In contrast, spike-triggered averaging may be useful for those muscles innervated by a peripheral nerve that is not readily accessible for stimulation.

CONCLUSIONS

The different physiological responses that are typically seen at rest or during movement emphasize the importance of examining function in different contexts after SCI. These physiological assessments are essential to determine whether regenerated axons are functional and whether behavioral improvements arise from central axon regeneration, plasticity, or both of these possibilities. Furthermore, considerable insight into movement and the consequences of SCI can be obtained by comparing data across species using different techniques.

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