SPECIAL COMMUNICATION

Basic Concepts of Activity-Based Interventions for Improved Recovery of Motor Function After Spinal Cord Injury

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Spinal cord injury (SCI) is a devastating condition that affects a large number of individuals. Historically, the recovery process after an SCI has been slow and with limited success. Recently, a number of advances have been made in the strategies used for rehabilitation, resulting in marked improved recovery, even after a complete SCI. Several rehabilitative interventions, that is, assisted motor training, spinal cord epidural stimulation, and/or administration of pharmacologic agents, alone or in combination, have produced remarkable recovery in motor function in both humans and animals. The success with each of these interventions appears to be related to the fact that the spinal cord is smart, in that it can use ensembles of sensory information to generate appropriate motor responses without input from supraspinal centers, a property commonly referred to as central pattern generation. This ability of the spinal cord reflects a level of automaticity, that is, the ability of the neural circuitry of the spinal cord to interpret complex sensory information and to make appropriate decisions to generate successful postural and locomotor tasks. Herein, we provide a brief review of some of the neurophysiologic rationale for the success of these interventions.

Key Words: Rehabilitation; Spinal cord injuries.

THE CONCEPTS OF neural control of locomotion that underlie the activity-based therapy locomotor training include (1) the level of automaticity of the spinal cord networks; (2) the importance of sensory input to the spinal cord automaticity; (3) neuromodulation of the physiologic state and the learning capacity of the spinal cord locomotor circuitry; and (4) the role of descending pathways in the control of locomotion.

AUTOMATICITY OF THE SPINAL CORD NETWORKS

The overriding general concept of the neural control of locomotion that makes locomotor training an effective therapeutic strategy is the high level of automaticity of the nervous system.[1-12] The automaticity of the spinal networks is identified by the properties of self-regulation and functioning without volition or conscious control. An essential component of automaticity of motor control is central pattern generating networks that elicit neural activity in response to sensory input that is task specific for posture and locomotion.[2,3,13-25] Effective standing and walking occurs with considerable precision and discrimination without conscious thought, suggesting that there is significant potential for recovery if these networks or their residual components are optimized functionally, even after a severe spinal cord injury (SCI).

Evidence of Automaticity in Biological Systems

The idea that networks of neurons within biological systems could generate a cyclic motor output is centuries old, as key experiments demonstrating automaticity in the mammalian spinal cord were performed by Brown in 1911.[26] Orlovsky et al[27] hypothesized that each limb is modulated by supraspinal input via groups of spinal neurons called controllers. These controllers respond to a tonic drive from the brain by generating a relatively complex rhythmic pattern that activates the limb musculature in a coordinated pattern to generate locomotion. Shik and Orlovsky[12] proposed a 2-level automatism control system for locomotion. One level provides nonspecific tonic input that determines the intensity of locomotion (speed and grade), while the other is responsible for making fine adjustments in the control of the limbs, including maintaining equilibrium. This fine control system normally interacts with sources of sensory information, such as proprioceptive and visual inputs, to execute fine adjustments in the locomotor pattern (fig 1). These observations[6,7,28,29] were followed by an explosion of studies attempting to define the mechanisms underlying the phenomenon of central pattern generation (CPG).[3,8,30-37]

From a teleological perspective, one might question the concept of automaticity with respect to its usefulness. Similar sensory and motor components among a wide range of animals with vastly different musculoskeletal structures have evolved in a 1G environment in a manner that has enabled postural and locomotor tasks to occur quite automatically among all complex animals.[38] The automatic aspects of these functions reflect successful evolution that enables postural and locomotor responses to be generated by the lower nervous system without relying on more complicated, and probably more unpredictable, delayed decision-making by higher neural centers. A greater reliance on the brain would require additional time and would impose disadvantages in the execution of a variety of postural and locomotor tasks, particularly when the response time is critical for survival. In this sense, evolutionary learning has played a key role in the automaticity of neural control exhibited during the execution of motor tasks. Thus, the nervous system, even without conscious control, demonstrates

List of Abbreviations

CPG	central pattern generation
EMG	electromyogram
SCI	spinal cord injury

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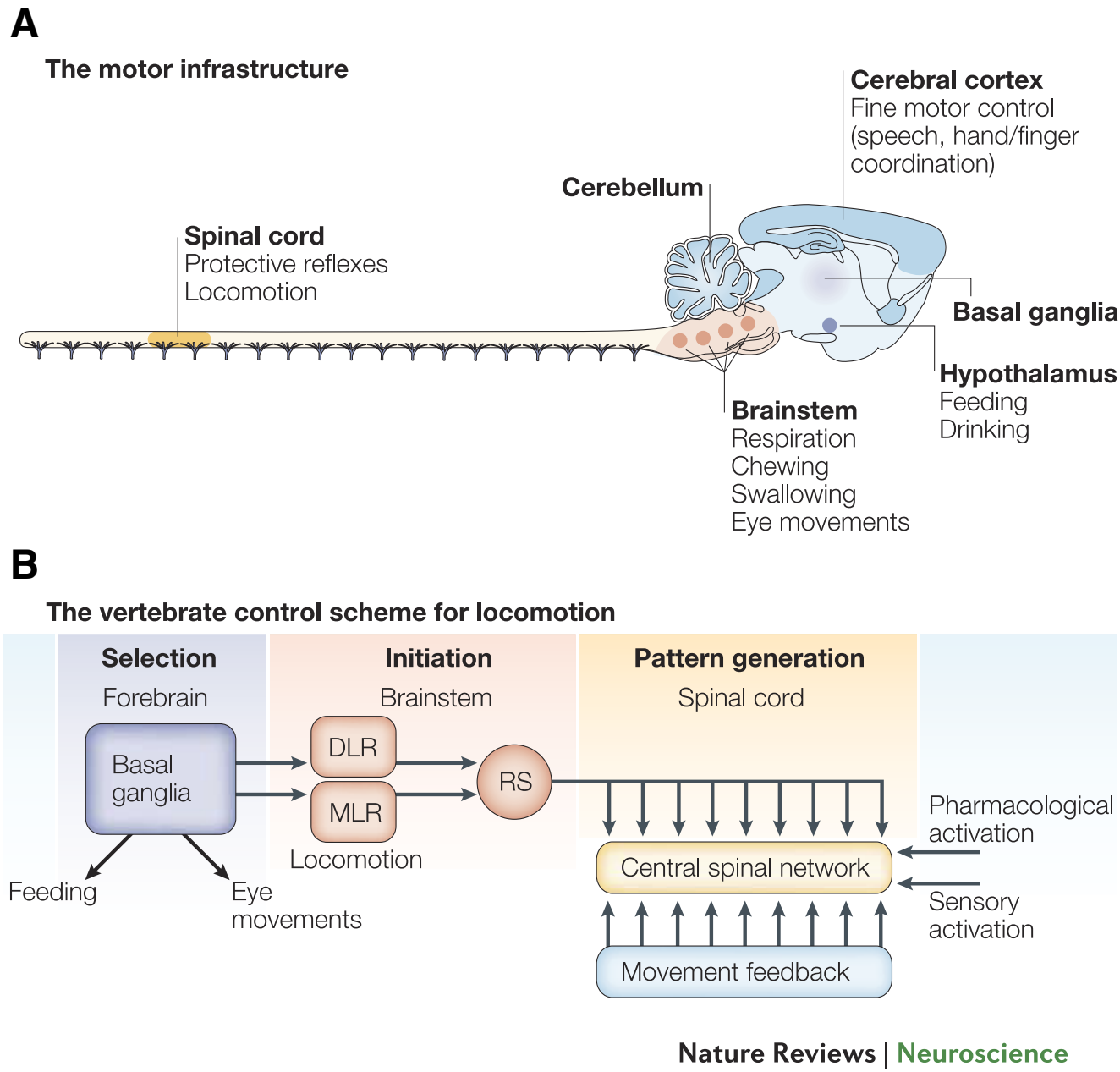

Fig 1. The motor infrastructure. (A) Location of different networks (CPGs) that coordinate different motor patterns in vertebrates. These areas can coordinate the activation of different CPGs in a behaviorally relevant order. For instance, if the fluid intake area is activated, an animal will look for water, walk toward it, position itself, and start drinking. The cerebral cortex is important in particular for fine motor coordination involving hands and fingers and for speech. (B) General control strategy for vertebrate locomotion. Locomotion is initiated by activity in RSs of the brainstem locomotor center, which produces the locomotor pattern in close interaction with sensory feedback. With increased activation of the locomotor center, the speed of locomotion increases and interlimb coordination can change (eg, from a walk to a gallop). The basal ganglia exert a tonic inhibitory influence on motor centers that is released when a motor pattern is selected. Experimentally, locomotion can also be elicited pharmacologically by administration of excitatory amino-acid agonists and by sensory input. Abbreviations: DLR, diencephalic locomotor area; MLR, mesopontine locomotor area; RS, reticulospinal neuron. Reprinted with permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience. Grillner S. The motor infrastructure: from ion channels to neuronal networks. Nat Rev Neurosci 2003;4:573-86.[39] Copyright 2003.

a sophisticated level of automaticity and also is smart and highly adaptable or plastic.

Spinal Cord Automaticity and Plasticity in the Control of Locomotion

Historically, the spinal cord's level of control over postural and locomotor tasks has been substantially underestimated. New insights continue to be gained into the properties of the spinal cord that enable it to execute these tasks, often with minimal conscious supraspinal control. The phenomenon of CPG within the spinal cord has magnified the importance of the concept of spinal automaticity, that is, the ability of the neural circuitry of the spinal cord to interpret complex sensory information and to make appropriate decisions to generate successful postural and locomotor tasks.[38,40] There is a high predict-

ability of the activity patterns and the kinematics patterns of the limbs during locomotion from the electromyography of a single muscle. These observations suggest that individual muscles and joints are controlled by the nervous system, not as distinct components, but as a highly interactive system with interdependent components, allowing the variation of individual parameters to achieve locomotion over a range of speeds. This greatly simplifies neural control by reducing the degrees of freedom that must be controlled to execute very complex but largely stereotypical movements, at least in a constant environment. It is this type of control that has led to the evolution of the concept of automaticity or the automatism of stepping.

Another series of studies originating in the laboratory of Grillner and Zangger[7] and Forssberg et al[41,42] demonstrated that complete, low thoracic spinal kittens could regain full weight-bearing locomotion by using the combined concepts of CPG and the ability of this network to process sensory input in a meaningful way. Initially, most scientists believed that it would be necessary to spinalize animals during the neonatal stage for them to have the capacity to recover weight-bearing stepping, a view that was upheld through the early 1990s. After a few initial studies demonstrating that adult spinal cats could be trained to step, the outstanding potential of the plasticity within the adult spinal locomotor circuitry became clear.[43-49] We now know that the spinal circuitry can learn a task, that it learns the task that is taught (practiced),[50,51] and that it can forget the task if it is not practiced.[52,53] For example, when spinal cats are trained to step their stepping ability improves,[51] whereas when they are trained to stand their standing ability improves.[50] This specificity of training is further demonstrated by the finding that standing ability, but not necessarily stepping ability, is improved after stand training.[50] In fact, in some instances spinal cats trained to stand will step more poorly than spinal cats that are not trained at all. Furthermore, when spinal cats are trained to step, their stepping, but not their standing, ability is improved.[54] These and similar observations of spinal locomotor circuitry plasticity provided the fundamental concept that forms the basis of the Neuro-Recovery Network strategy for locomotor recovery.

Automaticity and Spinal Cord Control of Locomotion in Humans

Several laboratories and/or clinics began to explore in humans those properties observed in laboratory animals, each with a slightly different strategy and objective. Although many of these efforts have produced insights into the neurophysiology of locomotion, the enthusiasm of the general field of SCI has been limited because of the very strong perception that the fundamental features of automaticity, while so clearly demonstrated in a number of studies in cats, rats, and mice, are not applicable to humans. There has been striking rigidity in the widely held viewpoint that human locomotion is under cortical control and that CPG within the spinal cord has long been abandoned and taken over by the cortex throughout evolution. A plethora of studies have demonstrated otherwise and led to the development of locomotor training as a therapeutic strategy with many of the clinical outcomes reported in this issue.

The most poignant example of the field's focus on the dominance of human cortical and supraspinal control over spinal circuitries that control movement are the studies of human clonus. An early series of publications addressed this issue with 2 prominent, albeit opposing, interpretations. One asserted that clonus was an intrinsic oscillating circuit, possibly even a component of CPG, and the other asserted that the absence of supraspinal input simply brings about the loss of supraspinal control over the stretch reflex.[55-62]

Eventually, attempts were undertaken to apply the same step training that evolved for the cat experiments to humans with an SCI.[63-86] For instance, experiments have been conducted in individuals with an incomplete injury, hence with a spinal locomotor system having a reduced influence from supraspinal input.[65,67,71,87-95] Studying individuals with a complete SCI showed that the functionally isolated human spinal cord has properties of automaticity including oscillatory locomotor-like activity, neuromodulation to loading and other afferent input to the circuitry that controls interlimb coordination, coordination of flexors and extensors within a leg,[4,10,96-106] control of speed and direction of stepping, and control of balance during locomotion.[3,107-112]

IMPORTANCE OF SENSORY INPUT TO THE SPINAL CORD AUTOMATICITY

The circuitries responsible for CPG receive and interpret sensory information in a highly dynamic way. Whether a group of muscles is excited or inhibited by a given afferent input during locomotion often depends on the stage of the step cycle. For example, a stimulus applied to the dorsum of a cat's paw (as in a stumbling response) will excite the flexor muscles of the ipsilateral

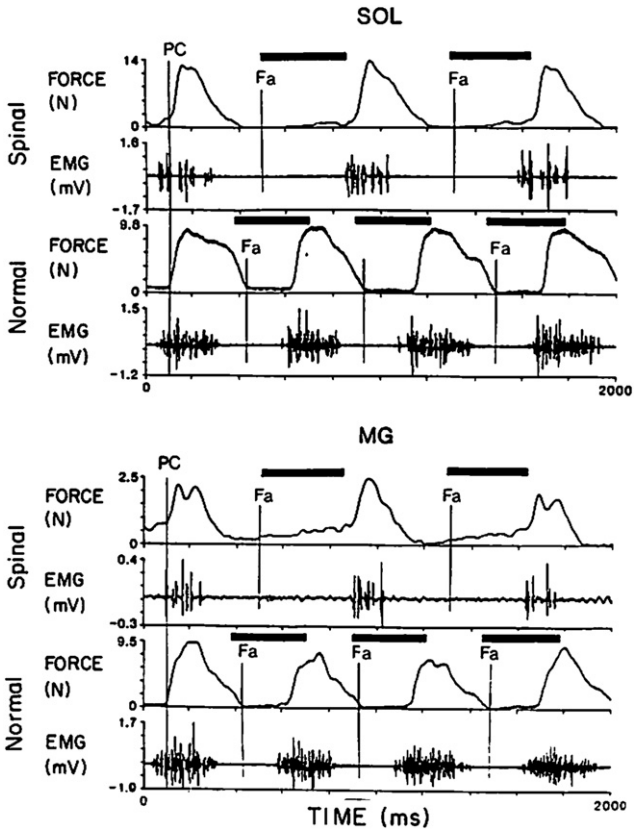

Fig 2. Force and EMG records from the soleus and medial gastrocnemius muscles of a spinal (complete transection at T12) and a control (normal) cat stepping on a treadmill belt moving at a moderate speed. The force was recorded using implanted strain gauges on the tendons of the muscles. Note that the timing of the EMG and force patterns are similar for the spinal and control cats. However, there are some obvious differences as well. For example, the force pattern in the soleus is shorter in the spinal cat. Also note that although the peak force levels are similar in the soleus, the peak force in the MG of the spinal cat is much less than in the control. This reflects a limitation in the level of recruitment of the motor pools consisting of the larger, less excitable motor units. This is also indicated in the intensity of the EMG signals of the MG of the spinal versus control cat. Abbreviations: Fa, point of ankle flexion; MG, medial gastrocnemius; PC, time of paw contact; SOL, soleus. The thick horizontal line indicates time for stance in the contralateral limb.[113]

limb when applied during the swing phase, whereas the same stimulus will excite the extensor muscles when applied during the stance phase of the step cycle.[114] This observation, and a series of other experiments demonstrating qualitatively similar capabilities of the spinal cord, has led to the concept that the spinal cord is smart.[115,116] The spinal cord receives sensory information and makes decisions as to what the appropriate response is at that time. In this context, it is logical to think of the spinal cord as interpreting the total ensemble of afferent information at any given time, as opposed to receiving input from each sensory receptor and responding to each receptor in a stereotypical, reflexive manner.[117] An analogy is the way we interpret a visual image. When we are observing an artistic painting, it is the total visual field of the painting that our brain interprets, as opposed to processing each individual pixel of information independently and then deriving a final image. Similarly, at any given instant in time, the spinal cord is receiving information from all receptors throughout the body and then deciding which neurons to excite.

The smart and integrative features of CPG provide a basis for the automaticity in the neural control of posture and locomotion. For example, in the complete spinal animal, spinal interneurons can predict the next logical sequence of neurons to activate based on the specific groups of neurons that were activated immediately prior to that point. The more critical property is not that CPG can continuously generate repetitive cycles, but that it can coordinate motor pools based on the sensory input received and then predict the next logical sequence of action. It is perhaps useful to think of the neurons that produce locomotor activity as basically modulating the probability of a given set of neurons being active at any given time, while the peripheral sensory input modulates the probabilities of completing each component of a motor task successfully. The degree of detail in motor output that can be generated by the spinal cord in combination with the information from the periphery is readily evident when comparing the electromyogram (EMG) and force signals from a battery of muscles from a cat before and after a complete spinal cord transection at a midthoracic level (fig 2). Although there are some differences in the EMG signals in chronic spinal cats during bipedal stepping relative to those in intact controls, they are relatively minor and may be associated with only slight differences in the biomechanics of the hindquarters. Even nonspecific afferent signals are interpreted by CPG neurons, that is, they can provide the information needed to generate effective stepping in the complete absence of supraspinal input.[40,118]

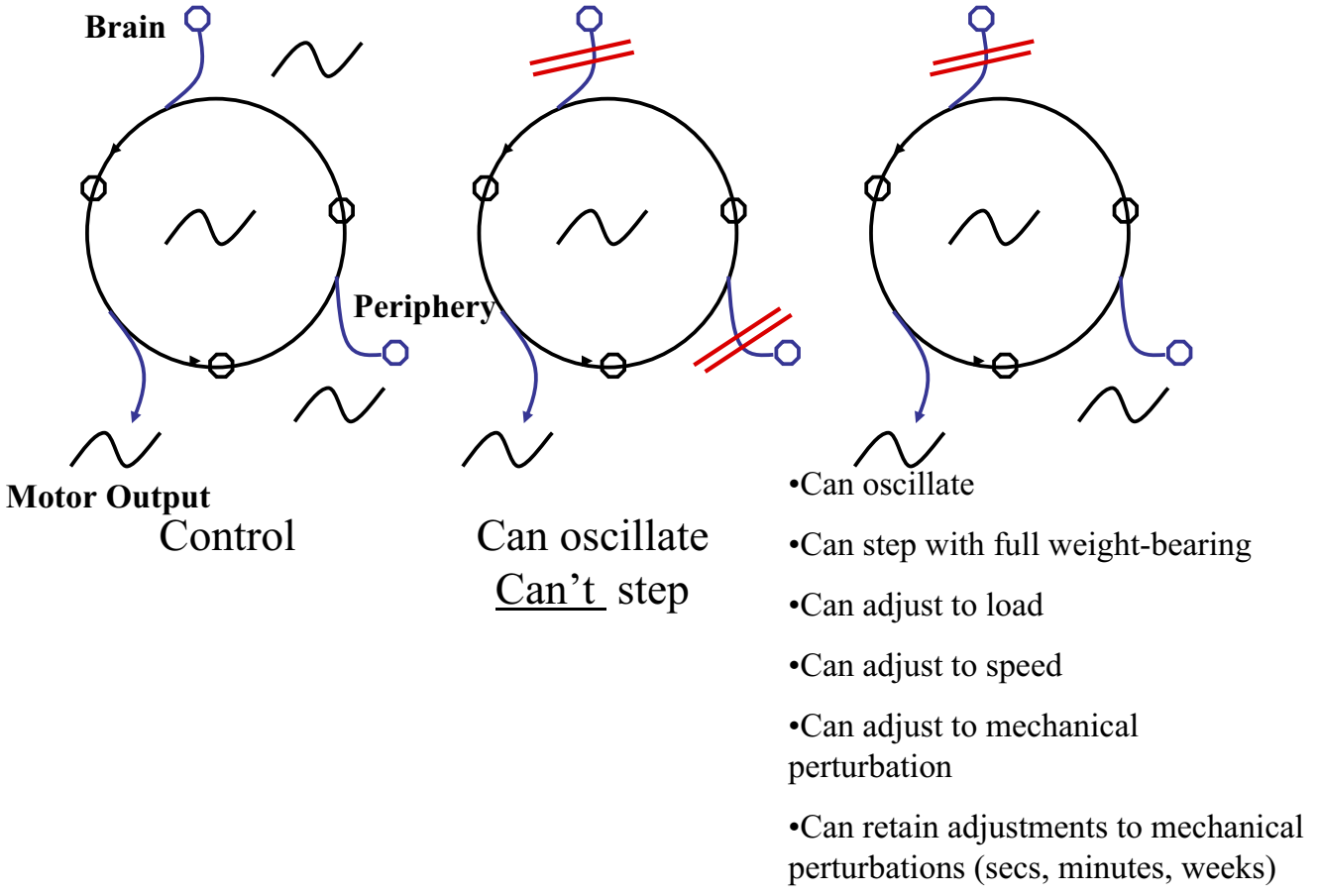

Fig 3. The motor output capabilities of the spinal cord are illustrated under 3 conditions. On the left, the control situation is shown whereby the spinal cord is able to receive normative input from the brain and the peripheral nerves transmitting proprioceptive input largely from mechanoreceptors. Movement capability in this case would be normal. The figure in the center represents the output potential when both brain and peripheral input are eliminated. The spinal cord can generate oscillating efferent patterns that approximate those properties observed during actual locomotion. On the far right, the motor capacity of the spinal cord without input from the brain but with the peripheral input preserved has a greatly enhanced capability, including the ability to step over a range of speeds and loads, and can even make adjustments when the legs are tripped. The spinal cord also can learn motor tasks, as described in the text. From Farrell PA, Joyner MJ, Caiozzo VJ, editors. ACSM's advanced exercise physiology. 2nd ed.[119] Lippincott Williams and Wilkins; 2012. Reprinted with permission.

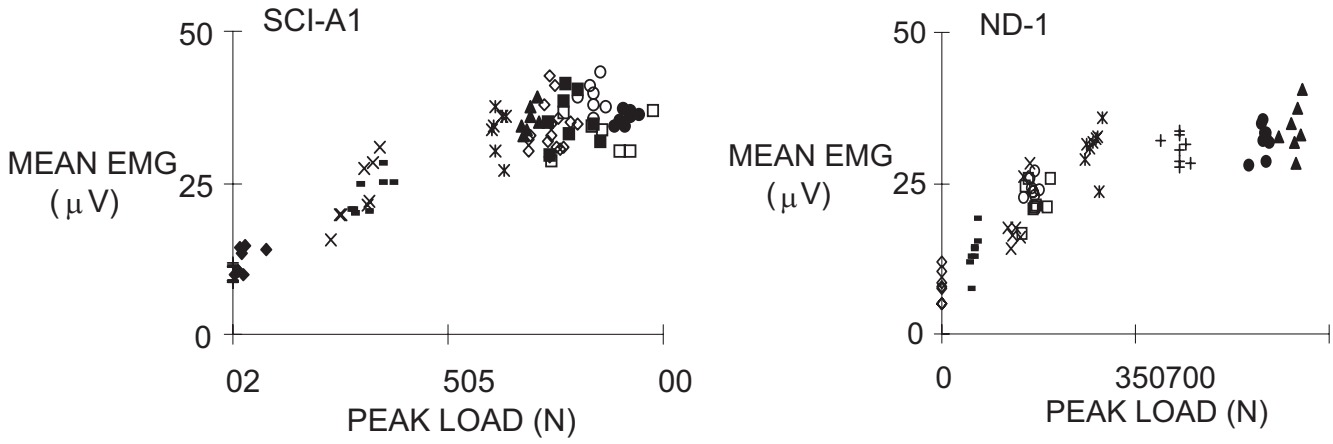

Fig 4. Relationships between soleus EMG mean amplitude (mV) and limb peak load (N) for an SCI-A1 and an ND-1 subject stepping on a treadmill with a harness suspended from overhead to provide a range of loading conditions are shown. An ASIA grade A SCI subject is one commonly called complete, that is, there is no clinical evidence of any motor control below the lesion site or sensory information from below the lesion. Each data point represents 1 step and each symbol represents a series of consecutive steps at 1 level of body weight support. Note that as the subjects bear more body weight the EMG amplitude increases similarly in both the SCI and ND subjects. Abbreviations: ASIA, American Spinal Injury Association; ND-1, nondisabled subject; SCI-A1, ASIA grade A spinal cord injured subject. Adapted with permission from the American Physiological Society.[23]

CPG is a physiologic phenomenon in which an oscillatory motor output is generated in the absence of any oscillatory input.[120] In mammalian systems, CPG represents an important component of the neural circuitry located in the lumbosacral spinal cord that generates and controls posture and locomotion. Without sensory input providing environmental cues, the functional significance of the CPG by itself would be limited. Because the spinal cord has access to sensory information from peripheral receptors, a wide range of useful and highly adaptable motor tasks can be performed without input from the brain (fig 3). This stepping ability results from a combination of the processing of the sensory input and the CPG itself.

An example of the human spinal cord's ability to receive complex proprioceptive input and to use this information in a functional way was shown by Harkema et al.[23] The level of activation of an extensor muscle, the soleus, was modulated according to the amount of load that was placed on the lower limbs of a human uninjured subject (fig 4). In the example on the right of the figure, the increase in the level of activation, as illustrated by the EMG amplitude, is directly related to the load imposed on the limb. The results of a similar experiment on a subject who had a complete SCI (no voluntary control of any muscles below the lesion and no sensation from tissues below the lesion) are shown on the left. The similarity of the relationship between the level of loading and the level of activation of the motor pool (EMG amplitude) in the uninjured and the complete spinal cord injured subject demonstrates that the spinal cord circuitry is able to sense the level of load and activate the soleus and other motor pools accordingly. There are several possible deductions regarding how the spinal cord senses load online including that (1) sensory receptors in the limbs (eg, soles of the feet, tendons, muscles, and joints) specifically sense the load; and (2) an ensemble of many types of sensory receptors at multiple locations within the limbs generate a highly recognizable image to inform the spinal circuitry of the biomechanical status of the weight bearing. We favor the second interpretation, as it is consistent with the concept that meaningful sensory input can be interpreted by the spinal cord circuitry so that an appropriate motor pattern can be generated.[38,121] These data also demonstrate that the spinal cord can activate the motor pools in a precise and highly coordinated manner. Thus, contrary to a pervasive perception, the spinal cord is not hard-wired, but can interpret the combination of intrinsic activity and sensory input to readily adjust parameters such as stepping speed, the level of load imposed on the limbs, and a wide range of unpredictable patterns of sensory anomalies.[44] This plasticity and adaptability can occur over milliseconds and through months.

Some key points related to sensory processing by the spinal cord are as follows: (1) within the musculoskeletal and cutaneous tissues is an extensive network of mechanoreceptors and metaboreceptors that continuously update the spinal cord on the physiologic state of the peripheral tissues; (2) these receptors provide an ensemble of highly integrated and perceptually meaningful information to the spinal cord; (3) the spinal cord is smart, as demonstrated by its ability to interpret and appropriately respond to highly complex and meaningful sensory ensembles; and (4) the human spinal cord demonstrates this smartness and automaticity.

Supraspinal systems can modulate different muscle groups, for example, extensors versus flexors, during stepping using strong gating functions to time its input closely with the phase of the step cycle. In addition, specific regions within the brainstem can initiate and control very complex motor behaviors, apparently with little to no conscious control, resulting in the generation of largely automatic responses.

It is often assumed that the initiation of a movement, even the more automatic ones such as stepping, is triggered by a conscious event in the motor cortex. Even a superficial examination of this assumption raises difficult questions concerning the nature of consciousness. To simplify the issue, we suggest conceptualizing a continuum of consciousness ranging from simple reflexes absent of any conscious awareness or control, to task modulation with full and continuous awareness. Therefore, even the efficacy of a monosynaptic response can be modulated by conscious control in rats, monkeys, and humans. An individual with a low-thoracic SCI, and a corresponding lack of supraspinal control below the lesion, can learn to stand and initiate steps using sensory informa-

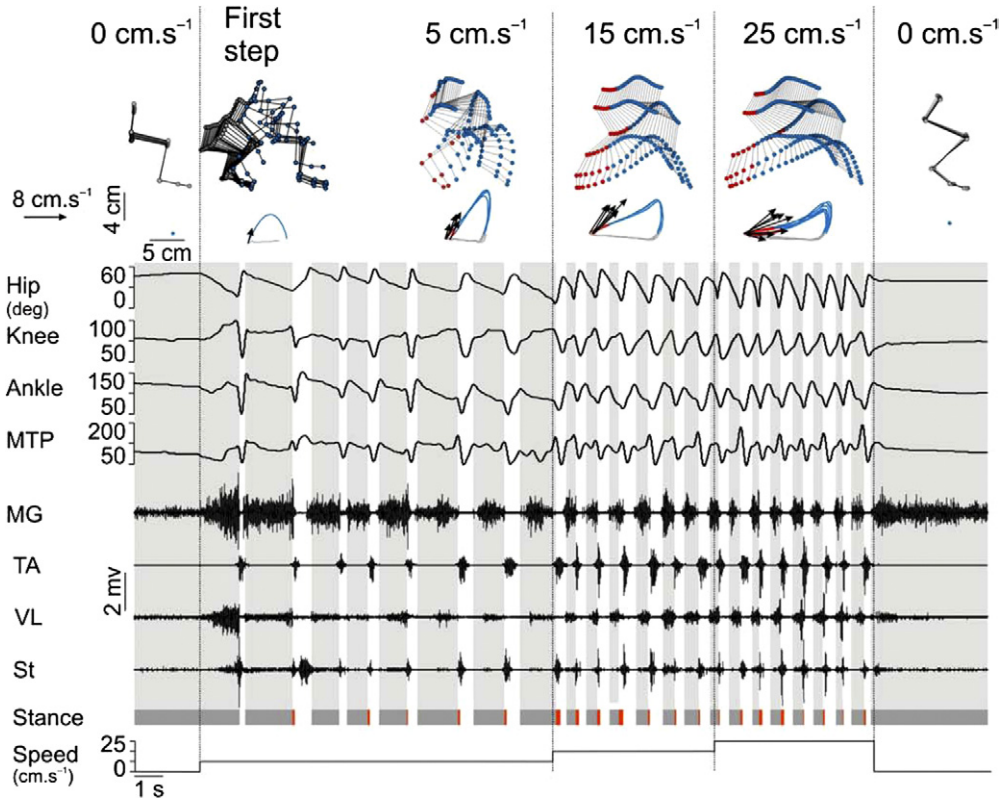

Fig 5. Representative example of hindlimb kinematics and EMG activity recorded from a continuous sequence of steps during which the speed of the treadmill was increased incrementally from 0 to 25 cm/s and then the treadmill stopped. Stick diagram decomposition of the first step is shown to demonstrate the transition from standing to stepping as the treadmill belt began to move. Color-coded trajectories (drag, red; swing, blue) at each joint are shown for a representative step at each treadmill speed. Shown immediately below are the swing trajectories (including drag) for 10 steps with vectors representing the direction and intensity of the limb endpoint velocity at swing onset. Hindlimb joint angles and EMG activity for a series of steps at each treadmill speed also are shown (gray and red bars indicate the duration of stance and drag, respectively). Abbreviations: MG, medial gastrocnemius; MTP, metatarsophalangeal; St, semitendinosus; TA, tibialis anterior; VL, vastus lateralis. Adapted with permission from Nature America.[122]

tion associated with unilaterally bearing weight and manipulating the hip position.[74] This spinal stepping can be initiated consciously and voluntarily although the subject initiates the process reflexively. Thus, the subject manipulates the afferent inflow by controlling critical biomechanical and neurophysiologic signals via manipulation of other parts of the body into a load-bearing position.[80]

NEUROMODULATION OF THE PHYSIOLOGIC STATE AND THE LEARNING CAPACITY OF THE SPINAL CORD LOCOMOTOR CIRCUITRY

After a complete midthoracic spinal cord transection in adult cats, a significant level of weight-bearing and coordinated bipedal stepping can recover with step training alone. In rats spinalized as adults, however, little recovery of weight-bearing stepping is achieved with step training alone. The recovery of full weight-bearing bipedal stepping is possible, if a combination of postinjury interventions having complementary effects are applied.[117,122,123] These interventions capitalize on the automaticity of the spinal circuitry and acutely modulate the physiologic state of the spinal circuitry using (1) tonic epidural stimulation, (2) selected pharmacologic agonists (eg, serotonergic agonists of 5-HT1, 2, and 7 receptors), and/or (3) chronic modulation of the physiologic state of the spinal circuitry via step and/or stand training for weeks. As previously noted, the automaticity of the locomotor circuitry, at least in complete spinal animals, can be attributed to its CPG potential to generate rhythmic and coordinated motor output and to the ability of the CPG circuitry to receive and interpret the ensemble of proprioceptive input derived from the load-bearing hindlimbs. In fact, once an appropriate physiologic state of the circuitry is achieved, the sensory input from the hindlimbs to the locomotor circuitry actually serves as the primary source of control of the stepping (fig 5). The following observation demonstrates this source of control. No stepping is observed as long as the treadmill belt is stationary, even in the presence of epidural stimulation and serotonergic agonists. As soon as the treadmill belt starts to move backward, however, the animal begins to step forward with the rate of stepping depending on the speed of the treadmill belt. When the movement of the treadmill belt is stopped, the hindlimbs stop stepping. By positioning the rat hindlimbs so that they would have to step sideways or backwards when the treadmill belt was moving, this concept of sensory control of stepping was tested further. Under these conditions, the kinematics of the hindlimbs readily adapt to the direction of the treadmill belt.[122]

As noted previously, effective weight-bearing stepping can be induced in a decerebrated cat by tonically stimulating areas of the brainstem, such as the mesencephalic locomotor region. We now know that tonic stimulation of the lumbo-

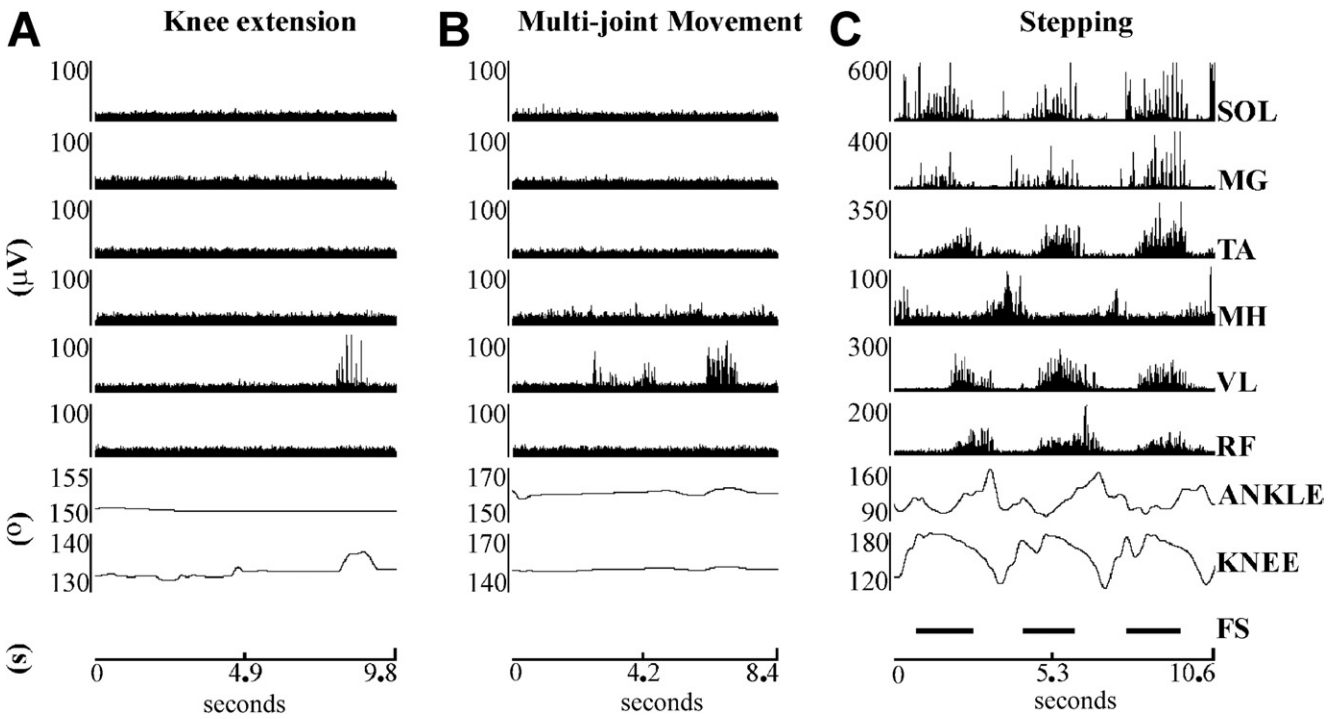

Fig 6. Single- and multijoint movements and stepping from a clinically incomplete, but severely injured, SCI subject. When the subject is asked to extend the knee, little movement occurred (lower left of A) and EMG was observed in 1 muscle. The subject was slightly more successful when instructed to move the limbs in a cycling motion. EMG activity (mV) from the SOL, MG, TA, MH, VL, and RF; knee and ankle angles (degrees); and foot switches (black bars indicate stance phase) during an attempted (A) single-joint movement, (B) multijoint movement, and (C) during weight-bearing stepping at .28m/s with 56% body weight support. Minimal EMG was observed only in the VL during attempted knee extension (A), and only the MH became more active (although no clear EMG burst) during multijoint effort (B). Minimal movement of the knee or ankle occurred. This EMG pattern contrasts with the alternating bursts in each muscle during stepping (C). These results emphasize the fact that voluntary control from the brain is not essential for generating stepping. The TA was largely synchronized with the SOL and MG, while the MH EMG was reciprocal to that in the VL and RF and with ankle muscles. Abbreviations: FS, foot switch; MG, medial gastrocnemius; MH, medial hamstrings; RF, rectus femoris; SOL, soleus; TA, tibialis anterior; VL, vastus lateralis. Used with permission from Mary Ann Liebert, Inc.[124]

sacral spinal cord in laboratory animals and humans can accomplish a similar effect. Grillner and Zangger[7] demonstrated that tonic stimulation of the dorsum of the spinal cord could induce fictive locomotion, that is, movement in the absence of supraspinal and sensory input to the spinal circuitry, and rhythmic stepping like motions.

At first, these results may lead to the assumption that the movements are reflexive and therefore relatively nonfunctional, at least with respect to support and effective standing and stepping. However, this is not, in fact, the case. First, the spinal circuitry responds to complex ensembles of sensory input in precise state-dependent conditions and thereby makes appropriate (smart) decisions as to the correct circuitry to activate at any given point in time within a step cycle or during standing. Second, individuals diagnosed as having a complete SCI can exert control by manipulating sensory (proprioceptive) information combined with epidural stimulation. Thus, motor control can be enabled by electrical stimulation and pharmacologic interventions that we now identify as electrical enabling motor control and pharmacologic enabling motor control.

ROLE OF DESCENDING PATHWAYS IN THE CONTROL OF LOCOMOTION

Locomotion can be initiated by supraspinal centers to activate limb controllers when some descending pathways remain functional, with the reticulospinal neurons and the mesencephalic locomotor region playing important roles. The relationship between the neural control of posture and locomotion, however, still remains uncertain and undoubtedly the sources of the level of control will change after an SCI. It seems highly likely that any residual descending input can be amplified given the spinal automaticity in the control of locomotion and posture combined with its ability to learn.[50,51]

In quadrupeds, the motor cortex may play a minimal role in generating the details of basic locomotor patterns and it is clear that the basic locomotor patterns can be achieved without corticospinal input[39] (fig 1). For less automatically executed movements, such as reaching and grasping in primates, cortical control may be more essential and lesions of the motor cortex or spinal cord may produce a greater disruption of the basic locomotor patterns than in lower mammalian species.[125]

Stimulation of the mesencephalic locomotor region (a 1-mm long strip of cells in the nucleus cuneiformis) can elicit locomotion by activating reticulospinal neurons that, in turn, stimulate the spinal centers that produce locomotion. Accordingly, reticulospinal neurons become more active during locomotion than when the animal is at rest, and the activity of neurons in the mesencephalic locomotor region increases during locomotion. Additionally, if the ventrolateral funiculi of the spinal cord are cut, a coordinated locomotor pattern cannot be initiated. A second area in the brainstem that can initiate locomotion and that also projects to reticulospinal neurons is the

subthalamic locomotor region.[27] The exact manner in which these neurons induce locomotion is not known. There is some evidence that the mesencephalic locomotor region is controlled by inhibition and that the initiation of stepping may be induced by disinhibition.[27] Neurons that form the reticulospinal, vestibulospinal, and rubrospinal tracts are rhythmically active during locomotion. Most of the vestibulospinal neurons are active at the beginning of stance. Most of the neurons forming the rubrospinal and reticulospinal tracts are maximally active during the swing phase of a step cycle. Thus, the vestibulospinal tract seems to facilitate extensor motoneurons, whereas the reticulospinal tract mainly facilitates flexor and inhibits extensor motoneurons. The rubrospinal and corticospinal tracts mainly facilitate flexor motoneurons.[27]

Thus, these descending tracts seem to have a modulatory effect on the motoneurons during specific phases of the step cycle. The rhythm and firing of these descending tracts are due, in large part, to influences from ascending input derived from the spinal cord circuitry. This phasic input (cyclic input associated with stepping) can occur independent of the afferent input from the periphery. For example, in paralyzed and decerebrated cats in which phasic afferent inflow from the periphery is precluded, phasic descending and ascending activity between the spinal cord and supraspinal centers is still present during spontaneous motor activity.

The combination of research on CPG and stimulation of the mesencephalic locomotor region have provided a solid basis for general neural control strategies and the level of automaticity within these regions. Shik et al[12,126] conducted a series of groundbreaking studies demonstrating that tonic electrical stimulation within the mesencephalon could induce stepping in acutely decerebrate cats. Subsequent experiments have revealed considerable detail about this phenomenon, but the essential conceptual elements from these studies suggest that nonspecific signals can induce very complex motor patterns, as different sites within the mesencephalon can be stimulated to induce remarkably well-coordinated stepping.[127-134]

CONCLUSIONS

The concept that a nonspecific tonic stimulation can be applied to the brainstem to induce complex motor tasks, as shown by Shik et al,[126] emphasizes that much of the detail in generating coordinated stepping lies within the spinal circuitry. The introduction of the phenomenon of CPG demonstrated how the spinal circuitry could generate well-coordinated activity of the motor pools to generate stepping. These observations, combined with those showing that the spinal circuitry can learn as it receives sensory input associated with posture and locomotion, form the basis for the evolving optimism for regaining significant motor function after an SCI. If we consider that the human spinal cord circuitry, even with either compromised or complete loss of supraspinal influence, has (1) a sufficient level of automaticity for locomotion, (2) responsiveness to task-specific sensory cues, and (3) plasticity with repetitive training, then our approach to rehabilitation after neurologic injury can be expanded (figs 4 and 6). These principles form the conceptual core for the rehabilitation intervention of locomotor training. This intervention has been standardized and is being implemented in 7 rehabilitation centers in the United States.

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