The Spinal Cord, Not to Be Forgotten: the Final Common Path for Development, Training and Recovery of Motor Function

Michele R. Brumley¹ · Misty M. Strain² · Nancy Devine³ · Aimee L. Bozeman¹

Published online: 13 November 2018

© Association for Behavior Analysis International 2018

Abstract

Research on learning, memory, and neural plasticity has long focused on the brain. However, the spinal cord also exhibits these phenomena to a remarkable degree. Following a spinal cord injury, the isolated spinal cord in vivo can adapt to the environment and benefit from training. The amount of plasticity or recovery of function following a spinal injury often depends on the age at which the injury occurs. In this overview, we discuss learning in the spinal cord, including associative conditioning, neural mechanisms, development, and applications to clinical populations. We take an integrated approach to the spinal cord, one that combines basic and experimental information about experience-dependent learning in animal models to clinical treatment of spinal cord injuries in humans. From such an approach, an important goal is to better inform therapeutic treatments for individuals with spinal cord injuries, as well as develop a more accurate and complete account of spinal cord and behavioral functioning.

Keywords Spinal learning · Rodent · Behavior · Locomotion · Central pattern generator · Physical therapy · Rehabilitation

✉ Michele R. Brumley
brummich@isu.edu

¹ Department of Psychology, Idaho State University, 921 South 8th Avenue, Stop 8112, Pocatello, ID 83209-8112, USA

² United States Army Institute of Surgical Research, JBSA-Fort Sam Houston, San Antonio, TX, USA

³ Department of Physical and Occupational Therapy, Idaho State University, Pocatello, ID, USA

This last link in the chain, e.g. the motor neurone . . . is the sole path which all impulses, no matter whence they come, must take if they are to act on the muscle-fibres to which it leads.

—Charles Sherrington (1906, p. 117)

Sir Charles Sherrington, one of the fathers of modern neuroscience and corecipient of the Nobel Prize for Physiology or Medicine in 1932, referred to motoneurons in the spinal cord as the “final common path,” whose activity leads to skeletal muscle action (Sherrington, 1906). Activity within this final common path to movement are influenced by multiple inputs from sensory afferents, interneurons, and descending pathways from the brain. Of course, motoneurons exist in cranial motor nuclei as well, and thus produce activity of muscles of the head, including permitting verbal behavior. Therefore, the final common path to any behavior expressed by animals, whether of the head, trunk, or limbs, ultimately relies on a functioning central nervous system (CNS) that is able to coordinate motor output.

In psychology and neuroscience, we often think of the brain as the main organ that is active when the environment controls our behavior. There is no doubt that the brain is a complex, amazing product of evolution, accomplishing sophisticated computations of neural integration that support processes such as learning, memory, and responsiveness to the environment. Yet in this analysis, the spinal cord is often overlooked, and relegated to a simple highway system that provides inputs to and outputs from the brain. A highway system, where there is nothing sophisticated or amazing happening, like there is happening in the brain. Although it is the case that the spinal cord and brain are in constant communication with each other, available evidence suggests that the spinal cord is capable of much more than only supplying signals to and from the brain. The spinal cord can learn! It is able to integrate information, adapt and respond to experience, and shows evidence of classical and instrumental conditioning. Such learning often happens in the context of an intact CNS; however, the spinal cord isolated from the brain also can exhibit such phenomena to an impressive degree. Hence the spinal cord’s potential to adapt to the environment and benefit from training becomes paramount after a spinal cord injury (SCI), when recovery of lost motor functions is a high priority.

Following an SCI, physical therapists are often on the frontlines of helping and training individuals to recover lost or impaired motor behaviors, such as independent walking. Such physical therapy arguably relies on training, or retraining, the damaged spinal cord. Yet physical therapists typically do not receive formal education in behavior analysis, or psychology, even though a large part of their practice relies on methods used to facilitate what is essentially learning new behaviors. Despite this, it is clear that many of the most successful therapeutic approaches for helping individuals regain or improve motor function involve behavioral and learning/training paradigms (although not in the traditional psychology sense) with a regard for tapping into the neuroplasticity of the spinal cord.

It is our view that here—in the understanding of the spinal cord—lies a rich opportunity to increase knowledge of the mechanisms of behavior and improve outcomes after SCI. This entails developing an integrated approach to the spinal cord, one that combines basic and experimental information about learning (i.e., behavior

analysis), neuroscience, and development and clinical treatment of SCIs (i.e., physical therapy). From such an approach, an important goal is to better inform therapeutic treatments for individuals with SCI, as well as developing a more accurate and complete account of spinal cord and behavioral functioning.

Moving towards this goal, in the present article we discuss learning in the spinal cord, including associative conditioning, neural mechanisms, development, and applications to clinical populations. Classical and operant conditioning paradigms of spinal cord learning in animal models are discussed with a focus on mechanisms of spinal learning. Next, demonstrations of spinal learning and responses to environmental conditions in developing animals are discussed. Finally, implications of this work for informing therapeutic treatments for individuals with SCI in humans are explored. Overall, a natural alliance among the areas of psychology, neuroscience, and the clinical sciences will most likely yield the most successful approach for understanding the relationship between the spinal cord and behavior. Although the spinal cord may be the final common path to behavior, it is anything but simple.

Learning and Memory in the Isolated Spinal Cord

Circuits in the spinal cord have been shown to exhibit many forms of learning, including more complicated forms of learning once thought to be dependent on the brain, such as classical and instrumental conditioning (for detailed reviews, see Edgerton, Tillakaratne, Bigbee, de Leon, & Roy, 2004; Grau, 2014; Huie, Morioka, Haefeli, & Ferguson, 2017; Wolpaw, 2010). In this section, we focus on recent research examining the mechanisms underlying learning and memory in the isolated spinal cord *in vivo*. Here we focus on animals that have received a complete transection of the spinal cord in order to highlight how spinal circuits learn to adapt and change without brain input.

Classical Conditioning

Establishing a valid model of classical conditioning in the isolated spinal cord took many years to develop, as many early studies proved controversial and difficult to replicate (for review, see Grau, 2014). Despite some setbacks, methods have been established for studying classical conditioning within the spinal cord that has been isolated from descending brain input. An important consideration in the development of a paradigm for studying learning in the isolated spinal cord entails identifying sensory stimuli that nerves innervating the isolated spinal cord can detect (i.e., tactile, thermal, nociceptive) and measuring behavior that does not require a brain *per se*, such as limb movements.

Methodologies An early model of classical conditioning in the spinal cord involved pairing electrical stimulation of the thigh or saphenous nerve (conditioned stimulus [CS]) to stimulation of the superficial peroneal nerve or the paw (unconditioned stimulus [US]), in spinal transected adult cats. In these experiments, cats received a complete high thoracic/low thoracic spinal cord transection. Electrical stimulation of the US produced a leg flexion, whereas stimulation of the CS did not (Beggs,

Steinmetz, & Patterson, 1985; Durkovic, 1975; Patterson, Cegavske, & Thompson, 1973). During training, the CS and US were paired together. Learning was measured by the strength of the flexion response produced by the pairing of stimuli, also known as the conditioned response [CR]. In animals that received pairing of the CS and US, the strength of the CR increased across trials. In the control group that received both the CS and US stimulation in an explicitly unpaired fashion, animals did not show an increase in CR magnitude. Furthermore, exposure to the CS alone produced habituation of the CR (i.e., the magnitude of the CR decreased over time). In addition, it was found that the order of presentation of the CS and US was critically important, with retention of the CR during extinction trials only being seen when the CS preceded the US (forward conditioning) (Durkovic & Damianopoulos, 1986). No retention of the CR was seen when the US preceded the CS (backward conditioning).

Other models of classical conditioning, such as in rats, have been developed that use electrical stimulation of the tail as the US (Illich, Salinas, & Grau, 1994; Joynes, Illich, & Grau, 1997). These models tend to be a little more controversial, since stimulation of the tail can elicit a weak CR. However, many stimuli widely used in traditional classical conditioning paradigms are not neutral as well (e.g., a light can cause a startle or an orienting response in rats). Using this model, many important properties of classical conditioning, such as overshadowing, latent inhibition and blocking have been observed in the isolated spinal cord (Illich et al., 1994).

Underlying Mechanisms Examination of the underlying mechanisms of classical conditioning in the isolated spinal cord has been limited. In one study, the role of glutamate receptors in mediating acquisition of the CR was examined using a competitive NMDA receptor antagonist (APV) applied to the spinal cord during training. This study found that blocking NMDA receptors did not block acquisition of the CR. Instead, it blocked the consolidation of the memory, leading to a lack of retention of the CR (Durkovic & Prokowich, 1998).

Parameters of Learning Although little is known about the underlying mechanisms of classical conditioning in the isolated spinal cord, relatively more is known about the conditions needed to promote learning. For example, classical conditioning after spinal injury occurs only very soon after injury (Patterson, 2001). In addition, the stimulation intensity needs to recruit Group A (sensory) nerve fibers, in order for the animal to exhibit a learned response (Durkovic & Light, 1975). Finally, examination of the optimal interstimulus interval (ISI) in cats has been found to be around 1 s for forward conditioning and -0.25 s for backward conditioning (Durkovic & Damianopoulos, 1986). More work is needed to better understand the spinal circuits involved in the acquisition and maintenance of the CR.

Instrumental Conditioning

Much like research examining classical conditioning within the spinal cord, early experiments examining instrumental learning in the isolated spinal cord were highly criticized and controversial (for review, see Grau, Barstow, & Joynes, 1998). However, rigorous studies and replications of the findings across different laboratories have

provided strong evidence that the isolated spinal cord is capable of exhibiting instrumental learning when isolated from brain circuits. Two models of instrumental learning have been examined within the isolated spinal cord—one in rats (Grau et al., 1998), and the other in mice (Jindrich et al., 2009).

Methodologies In both rodent models, mid-thoracic spinal transected subjects are trained to avoid a shock to the hind leg by maintaining a flexed hind leg position. During training, an electrode is placed in the tibialis anterior (TA) muscle, which is an ankle flexor. Whenever the leg extends below a set level, the animal receives a shock to the TA muscle, which causes the leg to flex. These animals are called Masters because they have control over whether or not they receive shock stimulation. Without brain input, Masters easily learn over a 30-min training period to maintain their hind leg in a flexed position (response) in order to minimize shock exposure (outcome; Grau et al., 1998; Jindrich et al., 2009).

To ensure that shock alone does not cause the hind leg to maintain a flexed posture and to show that the contingency between the response–outcome matters, control animals (Yoked) are tested as well. These Yoked controls receive the same number of shocks to the TA muscle, and in the same sequence as the Masters. However, for these Yoked controls, shock is not contingent on leg position. Instead, they receive shock stimulation whenever the other rat (Master) receives stimulation, regardless of their leg position; thus, the shock stimulation for Yoked controls is uncontrollable. In Yoked animals, shock fails to cause an increase in leg flexion (Grau et al., 1998; Jindrich et al., 2009). This failure to increase the leg flexion response is not the result of a lack of response, as response number is similar for both Master and Yoked animals (Grau et al., 1998; Jindrich et al., 2009). Together, this shows that only animals that are trained with *contingent* shock (i.e., hind leg extension → shock) learn to maintain a flexed hind leg position. Thus, rodents are able to learn response–outcome relationships, with only the lower portion of the spinal cord.

In addition, all animals can be trained again under common environmental conditions. This time, all subjects (Masters and Yoked controls) receive shock stimulation that is contingent upon positioning of the hind leg. In this scenario, subjects that had previously received contingent shock (Master subjects) show a savings effect (Grau et al., 1998). In other words, these subjects learn to maintain a flexed hind leg posture faster than rats that had not previous training. In subjects that had previously been given Yoked training, they fail to learn (i.e., they do not maintain flexion of the hind leg) despite now having control over the stimulation (Grau et al., 1998). Thus, previous exposure to noncontingent shock appears to produce a learning deficit or a type of learned helplessness in the spinal cord, for which later training with contingent shock fails to produce learning. This learned helplessness has been reported to last for up to 48 h (Joynes & Grau, 2004).

Underlying Mechanisms The circuitry for learning of this instrumental response has been found to be centrally located and to rely on neural circuits within the lower lumbar and upper sacral spinal cord, between the L4 and S2 segments (Crown, Ferguson, Joynes, & Grau, 2002b; Grau et al., 2006). Much like hippocampus-dependent learning, instrumental learning in the spinal cord also relies on the induction of long-term potentiation (LTP). LTP is when synaptic strength increases between two active

synapses. This process is regulated by glutamatergic receptors (i.e., NMDA and AMPA receptors) and can lead to long-term changes in gene expression. When AMPA or NMDA receptors are blocked before instrumental training of the leg flexion response, subjects show a dose-dependent reduction of the acquisition of the learned response (Ferguson, Crown, & Grau, 2006; Hoy, Huie, & Grau, 2013; Joynes, Janjua, & Grau, 2004). Further, blocking both AMPA and NMDA receptors eliminates maintenance of the learned response (hind leg flexion) (Hoy et al., 2013; Joynes et al., 2004). Thus, synaptic mechanisms of learning in the spinal cord are similar to synaptic mechanisms of learning in the brain, in that both use activity-dependent changes at glutamatergic receptors.

Facilitators of Learning There are a number of factors that have been shown to facilitate learning in the spinal cord, using this paradigm. One that has already been alluded to earlier is previous training with contingent shock. Thus, previous training with contingent shock produces faster learning of the limb flexion response. In addition, previous experience with contingent shock has been shown to facilitate learning at a higher limb flexion criterion, that is unobtainable by rats that have not experienced contingent shock (Crown et al., 2002b). This effect (training at a higher criterion) shows contralateral transfer, meaning that if one hind leg is trained, the contralateral hind leg will show a facilitation effect as well as the originally trained hind leg (Crown et al., 2002b). Facilitation of learning of this response has been shown to depend on BDNF (brain-derived neurotrophic factor) and CaMKII (calmodulin-dependent protein kinase II). It is interesting that the levels of BDNF, CaMKII, and CREB (cAMP response element-binding protein) in the spinal cord are proportionate to learning performance (Gomez-Pinilla et al., 2007).

In addition to facilitating learning, previous training with contingent shock also has been shown to prevent the induction of the learning deficit caused by uncontrollable shock (as in the Yoked control condition) and can be used to prevent tactile reactivity (a marker of central sensitization) produced by an intradermal formalin or capsaicin injection (Crown & Grau, 2001; Ferguson, Huie, Crown, & Grau, 2012b; Hook, Huie, & Grau, 2008). Training with contingent shock also can reverse the effect of the learning deficit when training is accompanied by naltrexone, an opioid antagonist shown to temporarily block the expression of the learning deficit (Crown & Grau, 2001).

Another factor that has been found to foster learning in the isolated spinal cord is extended training with fixed-spaced shock stimulation. For example, extended training with fixed-spaced stimulation (i.e., 540–900 shocks) promotes spinal cord learning and has even been shown to protect and reverse the learning deficit produced by Yoked control conditions, capsaicin, or variable shock (Baumbauer & Grau, 2011; Baumbauer et al., 2008, 2012; Lee et al., 2015). Such facilitation of learning has been shown to last for up to 24 h (Baumbauer, Huie, Hughes, & Grau, 2009b).

The protection produced by fixed-spaced stimulation is dependent on circuitry located in the T12 to L3 region of the spinal cord (Lee, Huang, & Grau, 2016). Many of the properties of fixed-spaced stimulation point to an underlying oscillator mediating these effects. For example, fixed-spaced stimulation can still be beneficial even when shocks are randomly skipped, as long as the rhythm stays in time (Lee et al., 2015, 2016). It is interesting that, the protective effects of fixed-spaced stimulation are only

seen when animals are given extended training of at least 540 shocks (Lee et al., 2015). Further, the frequency must be between 0.5 and 5 Hz (Baumbauer, Turtle, & Grau, 2017). The mechanisms that underlie fixed-spaced stimulation are similar to instrumental learning in that the protective effects are mediated by NMDA, BDNF, CAMKII, and neurokinins (Baumbauer et al., 2009b; Baumbauer, Young, Hoy, Abood, & Joynes, 2007; Baumbauer, Young, Hoy, & Joynes, 2007a, b; Patton, Hook, Ferguson, Crown, & Grau, 2004).

Inhibitors of Learning As mentioned previously, Yoked control subjects that receive the same number of shock stimulations in the same sequence as Master subjects, but in a noncontingent fashion, fail to learn (i.e., maintain a flexed hind leg position) when later tested with contingent stimulation. This learning deficit caused by noncontingent stimulation also has been found to be centrally mediated and shows contralateral transfer (Joynes, Ferguson, Crown, Patton, & Grau, 2003). The learning deficit induced by noncontingent stimulation is κ -opioid receptor mediated and can be blocked and reversed by treatment of an opioid antagonist (Joynes & Grau, 2004).

Another well-studied inhibitor of instrumental learning in the spinal cord is preexposure to inescapable variable-spaced stimulation that engages Group C-fibers. Studies have shown that just 6 min of noncontingent stimulation is enough to inhibit learning for up to 48 h and enhance tactile reactivity (a marker of central sensitization) (Baumbauer et al., 2008; Chopin & Bennett, 1975; Crown, Ferguson, Joynes, & Grau, 2002a; Ferguson et al., 2012a). The same effect is not seen when continuous stimulation is given. GABA_A receptors are thought to play a role in the inhibition seen after noncontingent stimulation, as the GABA_A receptor antagonist, bicuculline, blocks learning in a dose-dependent fashion and blocks development and expression of the deficit (Ferguson, Washburn, Crown, & Grau, 2003). This uncontrollable shock stimulation (as in the Yoked control condition) also engages group I metabotropic receptors (mGluRs), which activate protein kinase C (PKC) to inhibit learning, thus demonstrating an important role of NMDA in mediating the development and expression of the deficit (Ferguson et al., 2006, 2008). As well as playing a role in the learning deficit, over activation of NMDA receptors alone can cause a learning impairment (Ferguson et al., 2012b). Other pathways affected by uncontrollable stimulation are BDNF-TrkB signaling (which decreases in animals given uncontrollable shock), and the 5-HT_{1A} pathway (which produces a deficit when blocked pharmacologically and physically with a dorsolateral funiculus lesion; Crown & Grau, 2005; Garraway et al., 2011). Neurokinins also are involved in the induction and maintenance of the learning deficit (Baumbauer et al., 2007b), as neurokinins have been shown to play a key role in nociceptive processing and LTP. The learning deficit is known to require protein synthesis as evidenced from studies using protein-synthesis inhibitors such as cycloheximide and anisomycin (Baumbauer, Young, Hoy, France, & Joynes, 2006; Patton et al., 2004).

Like variable-spaced stimulation and Yoked control training, tissue damage and exposure to capsaicin, carrageenan, lipopolysaccharide (LPS), or formalin have been shown to inhibit the ability to learn an instrumental response for 24–48 h and share similar pathways (Ferguson et al., 2006, 2012b; Hook et al., 2008; Vichaya, Baumbauer, Carcoba, Grau, & Meagher, 2009; Young, Baumbauer, Elliot, & Joynes, 2007).

Role of the Brain Work investigating the associative conditioning of spinal reflexes in intact animals has shown that the brain can have lasting effects on spinal circuits as well. For example, if intact rats are trained with electrical stimulation of the tail as the US and vibrotactile stimulation to a hind leg as the CS, subjects continue to exhibit differential conditioning to the stimuli after the spinal cord has been transected (Joynes et al., 1997). Likewise, work examining the conditioning of the H-reflex has provided insight on how the brain influences spinal cord circuits (for review, see Wolpaw, 2010).

Motor Learning

Promoting motor learning after a complete spinal cord transection has gained much evidence throughout the years (for review, see Cai et al., 2006; Edgerton et al., 2004). Using methods such as physical therapy (e.g., treadmill, bicycle, and step training), electrical stimulation and pharmacological treatments, fully transected adult animals have been able to regain some locomotor behaviors. Most often, the retraining of locomotor behaviors has been shown to be task specific. For example, training cats to stand does not improve their stepping behavior and vice versa (de Leon, Hodgson, Roy, & Edgerton, 1998). In addition, motor training does not necessarily lead to improved associative spinal cord learning. For example, work in rats transected as neonates that were later given either stand or step training as adults showed differences in their ability to learn the instrumental response: rats trained to stand showed an inability to learn, whereas rats trained to step or that were untrained showed good learning (Bigbee et al., 2007).

An important part of motor learning is the ability to use environmental input/sensory feedback to update motor commands. Circuits in the spinal cord have been shown to use sensory information to adapt motor output and locomotor behavior to sensory inputs from the environment. For example, if the speed of the treadmill is changed, spinal transected animals can adjust their walking pattern (Forssberg, Grillner, & Halbertsma, 1980b; Forssberg, Grillner, Halbertsma, & Rossignol, 1980a). Further, if a perturbation is placed in front of the paw, spinal transected animals will change their kinematics to step over the obstacle (Forssberg, Grillner, & Rossignol, 1975). Exposure to the perturbation can cause long-term changes in limb kinematics that persist after the perturbation is removed (de Leon et al., 2002; Hodgson, Roy, de Leon, Dobkin, & Edgerton, 1994; Timoszyk et al., 2002).

Many of the same mechanisms involved in spinal learning also underlie motor learning. For example, GABA_A receptors play a role in improving locomotor training (Edgerton et al., 1997). After an SCI in adults, GABA levels are altered leading to a high level of inhibition (de Leon et al., 1998). Training has been shown to restore activity to normal levels (Edgerton et al., 2001). In addition, BDNF has been shown to improve locomotor training and is up-regulated after locomotor training, compared to untrained control animals (Gomez-Pinilla, Ying, Roy, Molteni, & Edgerton, 2002).

Electrical stimulation has often been used to activate locomotor patterns in spinal animals. This stimulation is usually provided as continuous stimulation to the muscles, nerves, or spinal cord (Edgerton et al., 2004). The location, frequency, and pattern of stimulation are important for targeting different motor patterns (Edgerton et al., 2004). In particular, epidural stimulation over the lumbosacral spinal cord has been shown to

evoke hind leg stepping behavior in adult spinal transected rats (Ichiyama, Gerasimenko, Zhong, Roy, & Edgerton, 2005; Lavrov et al., 2008).

Pharmacological stimulation of spinal circuits also is used to activate and train spinal cord circuitry in animals with SCI. Furthermore, pharmacological stimulation is often used in conjunction with physical therapy or electrical stimulation (Brumley, Guertin, & Taccola, 2017). Administration of drugs that activate glutamatergic, dopamine, and serotonin systems have been shown to facilitate locomotor outputs that resemble uninjured animals (Edgerton et al., 2004).

Summary

Research examining the capabilities of the isolated spinal cord *in vivo* has provided evidence that the spinal cord is capable of associative learning, and has pointed to a number of important mediators and mechanisms of this learning. These include the glutamatergic system, the serotonin system, and BDNF signaling. In addition, this work points out the importance of previous experience on spinal cord plasticity. In the next section, we discuss how early experience (or training) shapes the developing spinal cord, and how plasticity of the spinal cord and behavioral recovery is influenced by the age at which a spinal injury occurs.

Developmental Plasticity of the Spinal Cord

The dynamic and interacting relationship between all systems in an organism (i.e., at the cellular, organ, and behavioral levels of analysis) during development illuminates the complexity and flexibility of motor behaviors that often appear rigid and reflexive, and are to a large extent controlled by the final common path that Sherrington identified. In fact, plasticity and behavioral potential of the spinal cord in the absence of supraspinal input underlies some of the most seemingly stereotypical motor behaviors in developing animals (Brumley, Kauer, & Swann, 2015). Moreover, changes in one system (i.e., lesion of the spinal cord) of the organism may lead to a cascade of changes across other systems (i.e., behavioral, adaptations in the nervous system) and influence developmental trajectories, as occurs in neurodevelopmental disorders. Although it is unclear if one system has priority over the others, the integration of these systems or levels is important to consider (Brumley et al., 2017) when discussing how developmental changes affect the amount of recovery possible following SCI.

The Infant Lesion Effect

Spinal plasticity has been shown to occur to a greater degree during early development than in adulthood. Referred to as the “infant lesion effect,” neonates with an SCI show a greater sparing and restoration of spinal and motor function compared to adults with the same injury (Goldberger, 1986; Robinson & Goldberger, 1986). These differences in the amounts or degrees of spinal and behavioral plasticity between immature and mature animals are thought to be due to the continuance of normal physiological processes, which typically occur during early developmental time periods. For instance, increased synaptogenesis and decreased denervation in the spinal cord contribute

greatly to the differences in recovery of function following SCI in neonates compared to adult rats (Cummings & Stelzner, 1988). Furthermore, research has shown that recovery of function in rats with SCI is not due to the regrowth of axons across the lesion site, but is due instead to adaptations made by the spared fibers and local spinal circuitry (Weber & Stelzner, 1980; Cummings & Stelzner, 1988; Tillakaratne et al., 2010). This evidence also suggests that the immature spinal cord is better able to adapt isolated spinal circuitry to the demands of the environment.

Physiological Mechanisms The heightened recovery of spinal function in young animals is driven by, to some extent, the processes that occur during normal development in the absence of an SCI. When the spinal cord is injured during development, typical neurophysiological processes continue to occur, in addition to adaptations made by the developing nervous system in response to the injury or defect. The amount of change occurring within local spinal circuits (i.e., synaptogenesis, spinal shock, denervation supersensitivity) during the time of injury contributes greatly to the amount of recovery possible. In addition, the use of motor training paradigms (i.e., treadmill training) has been shown to increase the quantity and quality of motor behavior in neonatal-transected animals (Cha et al., 2007; Tillakaratne et al., 2010).

Neural plasticity and learning is displayed in the spinal cord throughout the lifetime (Wolpaw, 2006, 2018). When plasticity occurs during critical periods of development and leaves a lasting influence on the trajectory of that system(s), we call this *developmental plasticity*. Hence a large part of the infant lesion effect for SCI is due to developmental plasticity of the spinal cord.

During early development, such as the fetal and early postnatal periods, the CNS undergoes incredible change. The spinal cord grows in size and complexity, and synapses become more organized (Gramsbergen, 1998). In rats, synaptogenesis in the lumbosacral spinal cord, the location of the central pattern generator (CPG) circuits supporting hind leg locomotion and stepping, is highest at birth (Chemiak, Etlin, Strauss, Anglister, & Lev-Tov, 2014). Descending neural pathways from the brain, such as the reticulospinal, rubrospinal, and corticospinal tracts, begin to reach the lumbar spinal cord at E15 (embryonic day 15; birth occurs on E22), E18, and P6 (postnatal day 6), respectively (reviewed in Clarac, Vinay, Cazalets, Fady, & Jamon, 1998; and Vinay et al., 2002). During the early postnatal period, progressive changes are observed in spinal cord motoneuron morphology following SCI. Rats that received a spinal cord transection as weanlings or adults exhibited regressive changes in motoneurons, such as displaying an irregular number of somatic spines, abnormal varicose swellings in primary dendrites, and a decreased expanse of the dendritic tree (Cummings & Stelzner, 1988). However, rats that received a spinal transection as neonates showed motoneuron development comparable to neonates without a lesion (Cummings & Stelzner, 1988). Thus, it is clear that age and developmental stage plays a pivotal role in the physiological adaptations of the spinal cord following injury and contributes to differences in the quality and quantity of locomotor behavior. In general, the neurophysiological changes that occur following SCI in developing animals are perhaps less extreme compared to what occurs in mature animals. But what about behavior?

Behavioral Differences A complete spinal cord transection in adulthood typically leaves the animal with very limited motor function caudal to the lesion site, and typically results in complete loss of function or paralysis. However, neonatal rats with a complete

spinal cord transection continue to show spontaneous limb activity, which is characteristic of mammalian perinatal development, caudal to the lesion (Robinson & Smotherman, 1990; Robinson, Blumberg, Lane, & Kreber, 2000). Furthermore, although their locomotor behavior is definitely impaired, rats that received a neonatal spinal transection do develop some functional locomotor behavior as they mature (Yuan, Su, Chiu, & Lin, 2013). Even with the use of stimuli (e.g., pharmacological or sensory) to stimulate or induce locomotion, animals transected as adults display a lower frequency and quality of locomotor behavior compared to animals transected as neonates. It has been determined that the time from birth to P15 is a critical period for recovery of motor function following SCI in rats (Weber & Stelzner, 1977). Thus, up until 2 weeks postnatally, developmental plasticity of the spinal cord is able to continue with typical developmental processes to a degree, and preserve motor function and typical responsiveness to the environment. Such findings highlight how developmental changes are an integral aspect in the recovery of lost motor function, such as locomotion, following an SCI.

Work has shown that rats given a spinal cord transection as neonates (P5) can exhibit associative learning as adults (Bigbee et al., 2007). However, a comparison of the differences in associative learning in the isolated spinal cord between a neonatal or adult SCI, has not been determined. Examination across studies done in adults and the study examining adults transected as neonates suggests that differences might exist between the developmental stages, as the shock intensity required to exhibit a 0.4 N force in adults is typically 0.5 mA, however in the adults transected as neonates the intensity was 0.16 mA (Bigbee et al., 2007; Grau et al., 1998). Thus, it would be interesting to examine how parameters and performance indicators of learning might differ based on the age that the SCI was incurred, as well as the age of testing. Although associative conditioning paradigms have not been used to test learning ability during development, paradigms of motor learning have demonstrated that the immature spinal cord is responsive and adapts to sensory input from the environment, suggesting some learning abilities.

Motor Learning During Development

In all vertebrates, motor behavior begins during the prenatal period. Fetal behavior in rats starts out as spontaneous or nonevoked, and becomes more organized over the course of perinatal development. For example, in vivo rodent fetuses show spontaneous limb activity that increases in both temporal and spatial organization during prenatal development (Kleven, Lane, & Robinson, 2004; Robinson & Smotherman, 1987). In rats, spontaneous limb movements begin to occur on E16 (Robinson & Smotherman, 1987). It is interesting that spontaneous limb movements continue to be expressed in immature rats after a complete severing of the spinal cord. The occurrence of spontaneous limb activity, as well as spatial and temporal organization, is preserved following a cervical (Robinson et al., 2000) or mid-thoracic (Robertson & Smotherman, 1990) spinal transection, demonstrating that the isolated spinal cord can both generate and regulate spontaneous motility. Just a few days after the inception of spontaneous activity, rat fetuses are capable of showing several coordinated action patterns, including alternating stepping (Bekoff & Lau, 1980; Brumley & Robinson, 2005), the leg-

extension response (Smotherman & Robinson, 1988), facial wiping (Brumley & Robinson, 2004), and the stretch response to milk (Robinson & Smotherman, 1992). Rat fetuses are also capable of motor learning, as has been shown using an interlimb yoke training paradigm.

Interlimb Training During interlimb yoke training, the hind legs are yoked together by a fine thread looped around each ankle with a small piece of tubing separating the limbs (Robinson, 2005). In this paradigm, when one hind leg moves, it moves/pulls the other hind leg along with it, because the legs are physically yoked. During the course of 30 min, E19–E21 fetuses show a gradual and significant increase in conjugate limb movements (CLM) of the hind legs (Robinson, Kleven, & Brumley, 2008). CLMs are movements of the limbs that occur at the same time and in the same trajectory. Note that increases in CLM occur without any explicit reinforcement. Particular rewards or punishments are not administered to the subjects. Instead, any contingent sensory feedback that is experienced during spontaneous limb movements in the context of the interlimb yoke (e.g., biomechanical constraint of movement, pulling of a limb) must be shaping the acquisition of CLM.

Following a mid-thoracic spinal cord transection, E20 rat fetuses show an increase in hind leg CLMs (Robinson, 2015), indicating that the isolated spinal cord can support this form of motor learning. Even more, if subjects are first exposed to the interlimb yoke training task while intact, and then afterwards given a spinal cord transection, they show faster acquisition or savings of the CLM pattern of movement (Robinson, 2015). Other work shows that neonatal spinal transected rats are able to adapt patterns of intralimb coordination to environment conditions (i.e., range of motion restriction) as well (Strain, Kauer, Kao, & Brumley, 2014). These findings strongly suggest that the developing spinal cord is able to learn and remember specific patterns of motor coordination in response to environmental perturbations.

Developing a Reflex Just as animals appear to use sensory feedback generated from spontaneous movements to demonstrate interlimb motor learning, they also use this feedback to shape the development of spinal circuits controlling the withdrawal reflex. Research has shown that proper development of the nociceptive withdrawal reflex of the hind legs and tail (i.e., where the appendage moves in the opposite direction of a noxious stimulus) is dependent upon sensory feedback following spontaneous movement during the first two postnatal weeks (Pettersson, Waldenstrom, Fahreus, & Schouenborg, 2003; Waldenstrom, Thelin, Thimansson, Levinsson, & Schouenborg, 2003). Although this reflex is controlled at the level of the spinal cord (Schouenborg, 2002, 2010) and the spinal cord is capable of generating the spontaneous activity, the brain is required for the proper tuning of the spinal reflex circuitry. Thus, animals that have received a spinal cord transection as neonates do not develop the proper reflex behavior (i.e., they are just as likely to move towards or away from the noxious stimulus; Levinsson, Luo, Homberg, & Schouenborg, 1999). Likewise, work examining operant conditioning of the H-reflex in adult animals has shown that the brain mediates changes in the spinal stretch reflex circuitry, which also remain after a spinal cord transection (Thompson & Wolpaw, 2014). Therefore, this is an interesting case where the brain helps to develop spinal cord reflex circuitry and behavioral responses to the environment. Considering this, it becomes clear that a strict dichotomy of separating behaviors as wholly activated by the brain or spinal cord becomes quite murky.

Training the Injured Human Spinal Cord to Walk

Some of the discoveries achieved through basic and applied research about the capability of the spinal cord to display plasticity have influenced rehabilitation practice with humans following a neurologic injury. The application of these discoveries has included new interventions to restore or improve walking, treat chronic pain, and develop more sensitive, functionally relevant assessment tools. Although more human clinical research is needed, the impact of the improved understanding of the spinal cord, and ways to better promote adaptive plasticity, has already had a positive impact on rehabilitation outcomes.

Historical Rehabilitation Interventions: The Spinal Cord Is Hardwired

Most of the rehabilitation interventions used by physical and occupational therapists for people with a neurologic pathology were developed based upon the model of the nervous system as a hierarchy in which the higher (brain) centers controlled middle and lower centers (Basso, 2000a, b; Behrman, Ardolino, & Harkema, 2017; Grau et al., 2006; Harkema, Dobkin, & Edgerton, 2000). In this view, the spinal cord was considered to be a part of the lower centers and was understood to be hardwired and unable to undergo experience-dependent changes. Rehabilitation interventions based upon the hierarchical model of the nervous system therefore emphasized improving the strength and endurance of intact muscle groups, bracing of joints surrounded by impaired or absent muscle groups, and training to use assistive devices such as wheelchairs, walkers, and crutches in order to compensate for the effects of the damaged nervous system (Basso, 2000b; Craik, 2000; Harkema et al., 2000). Such interventions were consistent with the scientific understanding in which *compensation* was the only option available in the presence of neurologic pathology, including an SCI.

Differences in Clinical Manifestations Following SCI in Animals and Humans

As research with nonhuman animal models provided evidence of the spinal cord's capacity to learn and modify connections based upon experience, new clinical interventions were developed for people with neurologic pathology. However, it should be noted that there are some important differences in animals' and humans' response to neurologic injuries (Deitz & Schwab, 2017). For example, following an injury to the spinal cord, humans typically experience spinal shock. Spinal shock is the general suppression of neurological activity at and below the level of the lesion. Spinal shock typically lasts for 4–6 weeks and is manifested by a lack of deep tendon reflexes, flaccid muscle paralysis, and no voluntary active movement. Following resolution of spinal shock, humans typically develop hyperreflexia and spasticity below the lesion. Rats and cats do not display the same severity or duration of spinal shock and may display no changes in deep tendon reflexes following, or long after, the spinal injury. Animal models also do not always display signs or symptoms of spasticity below the level of the lesion (Deitz & Schwab, 2017). Despite these differences, new understanding of the spinal cord has prompted development of clinical interventions that provide repeated exposure in a task-specific context to promote functional use of the intact

portions of the spinal cord below the lesion. In this way, we can see the direct applications of basic research in spinal cord learning and plasticity affecting clinical research and interventions for recovery of function with human clinical populations.

New Rehabilitation Interventions: the Spinal Cord Is Plastic

The most direct clinical application of the basic and applied research revealing the capacity of the spinal cord to learn, with and without supraspinal input, is the change in locomotor training for people with an SCI to emphasize *recovery* instead of just compensation. It is estimated there are approximately 285,000 people living in the United States who have sustained an SCI and an additional 17,500 people who survive an SCI each year (National Spinal Cord Injury Statistical Center, 2017). Due to technological advances in the safety of motor vehicles, emergency care, and acute medical management (Craik, 2000), the majority (66.7%) of people sustain an incomplete spinal cord lesion (National Spinal Cord Injury Statistical Center, 2017) in which there is sparing of ascending and descending pathways across the level of the lesion. Despite the capacity for locomotor training to produce independent weight support and stepping for people with a complete SCI (Edgerton et al., 2001), the stepping produces no functional change since it does not generalize to training for over-ground ambulation. Therefore, locomotor training is most often used as a rehabilitation intervention for people with an incomplete SCI, where the pathways to the brain and other spinal areas are not completely severed.

The clinical application of locomotor training for people with incomplete SCI typically begins with body-weight supported treadmill training (BWSTT). This requires equipment to suspend the person in a harness over a treadmill and adjust the amount of body weight the person bears through the legs. Rehabilitation equipment companies have been developing, improving, and providing clinically applicable BWSTT equipment for over a decade (Behrman et al., 2005). Specialized treadmills that can move at slower speeds and have motors that can withstand forces on the belt in opposition to the direction of movement may be used. The amount of weight on the legs, speed of the treadmill, and amount of physical assistance given to assist normal stance and swing phase of the legs are variables that are adjusted and altered based upon the individual's performance during step training.

Research in this area has provided general guidelines to direct the application of BWSTT (Harkema et al., 2000). The general guidelines recommend using a normal walking speed (.75 to 1.25 m/s), bearing as much weight on the legs while still allowing stepping to occur, preventing weight bearing through the arms, encouraging an upright trunk and head posture, avoiding any conflicting sensory inputs (e.g., touching a flexor surface of the leg during stance phase), and encouraging contralateral arm swing during leg advancement (Harkema et al., 2000). During initial sessions, therapists will often physically assist in moving the legs through the swing phase of gait by contacting only flexor surfaces of the limb and timing the advancement of the leg with weight acceptance of the other limb. As stepping improves, less and less assistance is provided until stepping occurs independently. After achieving independent stepping, the amount of body weight support may be reduced and/or the speed of the treadmill may be increased. Behrman et al. (2005) provided a decision-making algorithm listing the components to consider when working on standing, initiating step training, and

progressing to over-ground gait training. There is no evidence-based protocol for the clinical manipulation of the variables to best promote the acquisition of step training on the treadmill for people with an SCI.

Published patient cases of people with incomplete SCI who participated in BWSTT indicate successful changes in walking distance, speed, and kinematics were achieved using a range of 60–90-min sessions, 3–5 times per week, for 15–85 sessions over an 8–15-week period (Behrman & Harkema, 2000; Behrman et al., 2005, 2008; Holleran et al., 2018). These dosage parameters demonstrate a wide range of duration and intensity applied to meet the desired outcome. The dosage parameters appear to be consistent with animal models in that there must be a sufficient duration and intensity of stepping practice to produce the neuroplastic changes. There was substantial variability in the level of SCI, extent of spinal cord damage, length of time since the injury, and age of the patient within the cited published cases that could influence the effectiveness and success of BWSTT dosage parameters. More research is needed to further guide the minimum and ideal dosage parameters in order to ensure an efficient and feasible application of BWSTT as a clinical intervention.

The application of animal research also has influenced clinical practice with people with incomplete SCI in another way beyond just locomotor training. Conventional practice typically recommended people with an SCI use a standing frame daily for 30–60 min. Because evidence indicates the spinal cord displays neuroplastic changes in a task-specific manner, training to stand interrupts training to step. Therefore, those with SCI who are receiving locomotor training no longer use the standing frame. Evidence indicates the benefits of step training exceed the benefits of passive standing for the skin, muscle length, bone density, and the urologic, digestive, and cardiovascular systems (Edgerton et al., 2001).

One potential barrier to the clinical implementation of BWSTT as a clinical intervention is the high cost due to the required equipment, increased staff, and frequency and duration required to implement it successfully (Morrison & Backus, 2007). Many of the published cases describing the success of BWSTT to restore walking ability were conducted as research case studies or clinical trials that did not require reimbursement (Behrman & Harkema, 2000; Behrman et al., 2005; Field-Fote, Lindley, & Sherman, 2005; Gandhi, Chan, Verrier, Pakosh, & Musselman, 2017). However, Morrison & Backus, (2007) conducted a retrospective cost analysis covering the years 2003–2005 and found it was profitable for patients with private insurance. For the 28 patients provided BWSTT at a single facility, there were a total of 267 visits and a 19% profit for those with private insurance counterbalanced by a 50% loss for those patients with Medicare and Medicaid (Morris & Backus, 2007). This suggests it is possible for the high cost of implementing BWSTT to be profitable if enough patients attend the facility that have private insurance within the standard revenue cycle.

Consistent with the evidence from animal models of step training following an SCI, BWSTT alone will not provide a human the functional ability to ambulate over-ground (de Leon & Dy, 2017). Task-specific training over-ground is required to adapt the spinal networks trained for stepping on the treadmill to function in a more variable and functional environment. Physical therapists readily incorporate over-ground training as part of locomotor training during inpatient and outpatient services (Behrman & Harkema, 2000; Behrman et al., 2005; Morrison & Backus, 2007; Field-Fote, Lindley, & Sherman, 2005; Gandhi et al., 2017; Holleran et al., 2018), despite the lack of an

evidence-based protocol to indicate when to initiate over-ground training. The sole source of guidance on this issue is Behrman et al. (2005) decision-making algorithm.

Due to the high cost of implementing BWSTT, the need to include over-ground training, and the physical demands on staff of providing manual assistance during the intervention, additional strategies for promoting task-specific spinal cord plasticity have been developed. These include the use of functional electrical stimulation (FES; Field-Fote & Roach, 2011; Sharif, Gammage, Chun, & Ditor, 2014) to activate the muscle groups in the legs to contract to produce the correct timing and kinematics for gait; the use of robot-assisted devices (Edgerton et al., 2001; Field-Fote & Roach, 2011) worn on the legs to mechanically produce the proper gait sequence; and an EEG-based brain-machine interface gait protocol that delivers tactile feedback below the lesion site during production of motor imagery (Donati et al., 2016). These options have been used in addition to BWSTT as well as directly with over-ground ambulation with and without body weight support (e.g., Field-Fote & Roach, 2011). There is a question regarding whether there are differences in training spinal cord networks through passive manual assistance and robotic-assisted devices versus active contraction through BWSTT and FES. The current evidence suggests the FES, robot-assisted, and traditional BWSTT all produce consistent outcomes as long as over-ground training is included in the intervention (Field-Fote & Roach, 2011). This suggests that providing task-specific training to purposefully influence the development of neurologic connections below the level of the lesion through experience-dependent learning is an effective clinical intervention and may be accomplished through multiple methods.

Clinical Applications to Other Neurologic Pathologies Although the initial application of locomotor training to improve spinal cord networks in people with neurologic injury was applied to people with SCI, BWSTT has also been clinically applied as a rehabilitation intervention for people post-stroke (Dean et al., 2010; Middleton et al., 2014; Takao et al., 2015), with Parkinson's disease (Evans & Cook, 2007), and with cerebral palsy (Cherng, Liu, Lau, & Hong, 2007; Day, Fox, Lowe, Swales, & Behrman, 2004; Mattern-Baxter, 2009). The evidence that task-specific training improves connections of spinal networks through activity-dependent use and training, and the presence of the equipment in the rehabilitation centers, provided the opportunity to implement the intervention as a means for assisting those with other sources of neurologic disability. BWSTT essentially became a task-specific exercise to build an improved neural network within the spinal cord to provide a resource to support and improve walking when other aspects of the nervous system are impaired (Evans & Cook, 2007; Takao et al., 2015; Mattern-Baxter, 2009).

Spinal cord plasticity also has been implicated in central pain syndromes, in particular after SCI (Baumbauer, Young, & Joynes, 2009a; Ferguson et al., 2012a, 2012b; Mercier, Roosink, Bouffard, & Bouyer, 2017). Based upon animal models, the same mechanisms that lead to spinal plasticity following locomotor training occur due to the nociceptive (pain pathway) input that occurs during a traumatic spinal injury. If the nociceptive input occurs below the level of the lesion, the lack of descending control on spinal cord processing of nociceptive inputs drives changes in spinal cord networks that can produce enhanced responses to future stimuli. The response of the spinal cord nociceptive processing is influenced by learning paradigms such as contingent or noncontingent stimulation and has broad effects on the susceptibility to

plasticity in related areas of the spinal cord (Ferguson et al., 2012). Therefore, spinal cord plasticity may be helpful, such as building a central pattern generator to support stepping of the lower limbs, but may also be detrimental, such as producing long-term sensitization to nociceptive input.

It is interesting that it appears there is an interaction between developing spinal cord locomotor pattern generators and maladaptive nociceptive processing, given that locomotor training reduces the sensitization to nociceptive stimuli (Ferguson et al., 2012; Mercier et al., 2017). However, the timing of training may be important because well-established, untreated, uncontrolled nociceptive input may also reduce the capacity to build central pattern generating circuitry through locomotor training (Ferguson et al., 2012). Overall, these findings suggest that another benefit to understanding what impacts the connections made in the spinal cord may allow the development of clinical interventions specifically directed to promote advantageous adaptations during recovery and rehabilitation. BWSTT and other forms of locomotor training for people with incomplete SCI may be influencing the presence and severity of centralized pain syndromes, but there is no published research providing evidence of this in humans.

Conclusions: an Integrated Approach to Spinal Cord Plasticity

Recognition of the fact that the spinal cord is capable of learning beckons for combining a behavior analytic approach with current neuroscientific understanding and physical therapy techniques in the area of SCI. It is our view that integrating information about behavioral principles of learning, spinal cord function and physiology, and developmental plasticity of the spinal cord, will lead to additional evidence-based clinical interventions to improve outcomes and recovery of function following an SCI. Of course, incorporating additional aspects and disciplines (e.g., biomedical engineering) into this approach should yield even better outcomes; however, these are beyond the scope of the current article. Although it is clear that basic and applied research on spinal cord learning and plasticity currently is being used to inform rehabilitation practice for humans with an SCI to some degree, there remains room for additional research.

In particular, regarding animal studies, there are outstanding questions that have yet to be answered about the relationship between associative and motor learning abilities in the spinal cord. Although it has been shown that motor training does not necessarily improve associative spinal cord learning (Bigbee et al., 2007), it is unclear if associative training facilitates motor learning or functional movement recovery. For example, can particular responses or kinematic patterns that are difficult to reestablish with motor learning strategies alone be associatively conditioned (in full or in part)? Can associative training induce spinal cord plasticity that is more conducive to different forms of motor learning to more quickly be able to recover functional movement? In addition, it is unclear how clinical interventions for humans with SCI that are designed to get individuals moving may facilitate or inhibit mechanisms of learning and plasticity in the spinal cord.

In humans, behavior analytic approaches also could be used to help determine optimal parameters of physical therapy treatments for SCI, such as BWSTT. In a recent

single-subject design study, it was shown that BWSTT that involved both forward and backward stepping on a treadmill in an individual with SCI improved performance on a sit-to-stand test (Moriello et al., 2014). The improvement was thought to be due to differences in muscle activation and difficulty between the two stepping conditions. Because there is wide variability in the presentation of SCI, research studies utilizing applied behavior analysis paradigms, such as single-subject designs, may be useful in establishing evidence-based practices (Haegele & Hodge, 2015).

In addition, behavioral techniques could be used to reinforce physical activity and promote healthy behaviors following an SCI. Following inpatient rehabilitation, individuals with SCI often decrease their physical activity levels to severely low rates (van den Berg-Emons, Bussman, & Stam, 2010), to a level that may compromise overall health. Yet when individuals with an SCI underwent an intervention that involved individual coaching sessions in a randomized controlled trial, they maintained physical activity for at least 6–12 months following inpatient discharge (Nooijen et al., 2016). Moreover, their health also improved, as measured by significant changes in blood pressure, total cholesterol, low-density lipoprotein cholesterol, and social participation (Nooijen et al., 2017).

Likewise, behavior analysts are skilled at changing people's behavior, and promoting healthier behavior. Although such interventions are usually used to promote healthier behaviors in the context of substance use disorders (Rash, Stitzer, & Weinstock, 2017), contingency management interventions (i.e., token reinforcement) have been shown to be successful in promoting physical activity in adults with intellectual disabilities (Krentz, Miltenberger, & Valbuena, 2016). Thus, contingency management interventions specifically designed for individuals with SCI might not only lead to improved health outcomes, but may also help to induce and promote spinal plasticity and recovery of function well after inpatient rehabilitation efforts cease. A key aspect in the development of such an approach regarding SCI recovery would require careful arrangement of the environment and monitoring of the behavior in a way that is well-suited for an individual living with SCI, and would likely need to be informed by some of the issues (e.g., physical therapy, spinal plasticity) discussed in the current article.

A final area of intersection, where there is also room for improvement, is in the understanding and treatment of infants and children with SCI or other neurological pathology (e.g., stroke, spina bifida, Down's Syndrome). Most SCI research uses adult animals, even though neonatal animals exhibit significantly more recovery of function following injury (Murray, Fischer, Smeraski, Tessler, & Giszter, 2004). Basic animal research into the mechanisms of spinal learning and recovery of function should continue to examine the factors that influence this developmental plasticity in the spinal cord. In addition, therapeutic interventions designed for adults with SCI are not necessarily generalizable to pediatric populations. In young children, bones are still growing, cartilage is softer, and histochemical properties of muscles change dramatically (Ulrich, 2010). These considerations must be incorporated into treatment interventions. None the less, infants with spina bifida, Down Syndrome, and stroke-induced hemiplegia have been shown to respond to treadmill training (Teulier et al., 2009; Ulrich, Ulrich, Collier, & Cole, 1995; Yang et al., 2013) before mature walking has developed. Such evidence has prompted a call for more empirically based protocols for children that are grounded in basic neuroscience and activity-based approaches (Ulrich, 2010).

Research and clinical practice activities are becoming increasingly more collaborative and team-based, often involving scientists and professionals from multiple disciplines. The area of spinal cord plasticity and SCI is no exception. We hope that one day soon it will be the case that behavior analytic scientists will be at the forefront of activities in this area, as they lend their expertise to yield a better understanding and management of spinal cord learning, plasticity, and recovery of function following SCI.

Funding Information MRB is supported by the National Science Foundation under grant number BCS-1748986.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- Basso, D. M. (2000a). Neuroanatomical substrates of functional recovery after experimental spinal cord injury: implications of human spinal cord injury. *Physical Therapy*, 80, 808–817.
- Basso, D. M. (2000b). Recovery of walking after central nervous system insult: basic research in the control of locomotion as a foundation for developing rehabilitation strategies. *Neurology Report*, 24, 47–54.
- Baumbauer, K. M., & Grau, J. W. (2011). Timing in the absence of supraspinal input III: regularly spaced cutaneous stimulation prevents and reverses the spinal learning deficit produced by peripheral inflammation. *Behavioral Neuroscience*, 125, 37–45.
- Baumbauer, K. M., Hoy Jr., K. C., Huie, J. R., Hughes, A. J., Woller, S. A., Puga, D. A., Setlow, B., & Grau, J. W. (2008). Timing in the absence of supraspinal input I: variable, but not fixed, spaced stimulation of the sciatic nerve undermines spinally-mediated instrumental learning. *Neuroscience*, 155, 1030–1047.
- Baumbauer, K. M., Huie, J. R., Hughes, A. J., & Grau, J. W. (2009b). Timing in the absence of supraspinal input II: regularly spaced stimulation induces a lasting alteration in spinal function that depends on the NMDA receptor, BDNF release, and protein synthesis. *Journal of Neuroscience*, 29, 14383–14393.
- Baumbauer, K. M., Lee, K. H., Puga, D. A., Woller, S. A., Hughes, A. J., & Grau, J. W. (2012). Temporal regularity determines the impact of electrical stimulation on tactile reactivity and response to capsaicin in spinally transected rats. *Neuroscience*, 227, 119–133.
- Baumbauer, K. M., Turtle, J. D., & Grau, J. W. (2017). Fixed spaced stimulation restores adaptive plasticity within the spinal cord: identifying the eliciting conditions. *Physiology & Behavior*, 174, 1–9.
- Baumbauer, K. M., Young, E. E., Hoy Jr., K. C., Abood, A., & Joynes, R. L. (2007). Administration of a Casuper(2+)/calmodulin-dependent protein kinase II (CaMKII) inhibitor prevents the learning deficit observed in spinal rats after noncontingent shock administration. *Behavioral Neuroscience*, 121, 570–578.
- Baumbauer, K. M., Young, E. E., Hoy Jr., K. C., France, J. L., & Joynes, R. L. (2006). Intrathecal infusions of anisomycin impact the learning deficit but not the learning effect observed in spinal rats that have received instrumental training. *Behavioral Brain Research*, 173, 299–309.
- Baumbauer, K. M., Young, E. E., Hoy Jr., K. C., & Joynes, R. L. (2007a). Intrathecal administration of neurokinin 1 and neurokinin 2 receptor antagonists undermines the savings effect in spinal rats seen in an instrumental learning paradigm. *Behavioral Neuroscience*, 121, 186–199.
- Baumbauer, K. M., Young, E. E., Hoy Jr., K. C., & Joynes, R. L. (2007b). Neurokinin receptors modulate the impact of uncontrollable stimulation on adaptive spinal plasticity. *Behavioral Neuroscience*, 121, 1082–1094.
- Baumbauer, K. M., Young, E. E., & Joynes, R. L. (2009a). Pain and learning in a spinal system: contradictory outcomes from common origins. *Brain Research Reviews*, 61, 124–143.
- Beggs, A. L., Steinmetz, J. E., & Patterson, M. M. (1985). Classical conditioning of a flexor nerve response in spinal cats: effects of tibial nerve CS and a differential conditioning paradigm. *Behavioral Neuroscience*, 99, 496–508.
- Behrman, A. L., Ardolino, E. M., & Harkema, S. J. (2017). Activity-based therapy: from basic science to clinical application for recovery after spinal cord injury. *Journal of Neurologic Physical Therapy*, 41, S39–S45.

- Behrman, A. L., & Harkema, S. J. (2000). Locomotor training after human spinal cord injury: a series of case studies. *Physical Therapy*, 80, 688–700.
- Behrman, A. L., Lawless-Dixon, A. R., Davis, S. B., Bowden, M. G., Nair, P., Phadke, C., Hannold, E. M., Plummer, P., & Harkema, S. J. (2005). Locomotor training progression and outcomes after incomplete spinal cord injury. *Physical Therapy*, 85, 1356–1371.
- Behrman, A. L., Nair, P. M., Bowden, M. G., Dauser, R. C., Herget, B. R., Martin, J. B., Phadke, C. P., Reier, P. J., Senesac, C. R., Thompson, F. J., & Howland, D. R. (2008). Locomotor training restores walking in a nonambulatory child with chronic, severe, incomplete cervical spinal cord injury. *Physical Therapy*, 88, 580–590.
- Bekoff, A., & Lau, B. (1980). Interlimb coordination in 20-day-old rat fetuses. *Journal of Experimental Zoology*, 214, 173–175.
- Bigbee, A. J., Crown, E. D., Ferguson, A. R., Roy, R. R., Tillakaratne, N. J., Grau, J. W., & Edgerton, V. R. (2007). Two chronic motor training paradigms differentially influence acute instrumental learning in spinally transected rats. *Behavioral Brain Research*, 180, 95–101.
- Brumley, M. R., Guertin, P. A., & Taccola, G. (2017). Multilevel analysis of locomotion in immature preparations suggests innovative strategies to reactivate stepping after spinal cord injury. *Current Pharmaceutical Design*, 23, 1764–1777.
- Brumley, M. R., Kauer, S. D., & Swann, H. E. (2015). Developmental plasticity of coordinated action patterns in the perinatal rat. *Developmental Psychobiology*, 57, 409–420.
- Brumley, M. R., & Robinson, S. R. (2004). Facial wiping in the rat fetus: variation of chemosensory stimulus parameters. *Developmental Psychobiology*, 44, 219–229.
- Brumley, M. R., & Robinson, S. R. (2005). The serotonergic agonists quipazine, CGS-12066A, and alpha-methylserotonin alter motor activity and induce hindlimb stepping in the intact and spinal rat fetus. *Behavioral Neuroscience*, 119, 821–833.
- Cai, L. L., Courtine, G., Fong, A. J., Burdick, J. W., Roy, R. R., & Edgerton, V. R. (2006). Plasticity of functional connectivity in the adult spinal cord. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 361, 1635–1646.
- Cha, J., Heng, C., Reinkensmeyer, D. J., Roy, R. R., Edgerton, V. R., & de Leon, R. D. (2007). Locomotor ability in spinal rats is dependent on the amount of activity imposed on the hindlimbs during treadmill training. *Journal of Neurotrauma*, 24, 1000–1012.
- Cherng, R. J., Liu, C. F., Lau, T. W., & Hong, R. B. (2007). Effect of treadmill training with body weight support on gait and gross motor function in children with spastic cerebral palsy. *American Journal of Physical Medicine & Rehabilitation*, 86, 548–555.
- Cherniak, M., Etlin, A., Strauss, I., Anglister, L., & Lev-Tov, A. (2014). The sacral networks and neural pathways used to elicit lumbar motor rhythm in the rodent spinal cord. *Frontiers in Neural Circuits*, 8, 1–8.
- Chopin, S. F., & Bennett, M. H. (1975). The effect of unavoidable shock on instrumental avoidance conditioning in spinal rats. *Physiology & Behavior*, 14, 399–401.
- Clarac, F., Vinay, L., Cazalets, J. R., Fady, J. C., & Jaxon, M. (1998). Role of gravity in the development and posture and locomotion in the neonatal rat. *Brain Research*, 28, 35–43.
- Craik, R. L. (2000). Spinal cord injury: the bridge between basic science and clinical practice. *Physical Therapy*, 80, 671–672.
- Crown, E. D., Ferguson, A. R., Joynes, R. L., & Grau, J. W. (2002a). Instrumental learning within the spinal cord: IV. Induction and retention of the behavioral deficit observed after noncontingent shock. *Behavioral Neuroscience*, 116, 1032–1051.
- Crown, E. D., Ferguson, A. R., Joynes, R. L., & Grau, J. W. (2002b). Instrumental learning within the spinal cord. II. Evidence for central mediation. *Physiology & Behavior*, 77, 259–267.
- Crown, E. D., & Grau, J. W. (2001). Preserving and restoring behavioral potential within the spinal cord using an instrumental training paradigm. *Journal of Neurophysiology*, 86(2), 845–855.
- Crown, E. D., & Grau, J. W. (2005). Evidence that descending serotonergic systems protect spinal cord plasticity against the disruptive effect of uncontrollable stimulation. *Experimental Neurology*, 196(1), 164–176.
- Cummings, J. P., & Stelzner, D. J. (1988). Effect of spinal cord transection in the newborn, weanling, and adult rat on the morphology of thoracic motoneurons. *Experimental Neurology*, 100, 381–393.
- Day, J. A., Fox, E. J., Lowe, J., Swales, H. B., & Behrman, A. L. (2004). Body weight support on a treadmill in a nonambulatory child with spastic tetraplegic cerebral palsy: a case report. *Pediatric Physical Therapy*, 16, 106–113.
- de Leon, R. D., & Dy, C. J. (2017). What did we learn from the animal studies of body weight-supported treadmill training and where do we go from here? *Journal of Neurotrauma*, 34, 1744–1750.

- de Leon, R. D., Hodgson, J. A., Roy, R. R., & Edgerton, V. R. (1998). Full weight-bearing hindlimb standing following stand training in the adult spinal cat. *Journal of Neurophysiology*, 80, 83–91.
- de Leon, R. D., Kubasak, M. D., Phelps, P. E., Timoszyk, W. K., Reinkensmeyer, D. J., Roy, R. R., & Edgerton, V. R. (2002). Using robotics to teach the spinal cord to walk. *Brain Research Reviews*, 40(1–3), 267–273.
- Dean, C. M., Ada, L., Bampton, J., Morris, M. E., Katrak, P. H., & Potts, S. (2010). Treadmill walking with body weight support in subacute non-ambulatory stroke improves walking capacity more than overground walking: a randomised trial. *Journal of Physiotherapy*, 56, 97–103.
- Deitz, V., & Schwab, M. E. (2017). From the rodent spinal cord injury model to human application: promises and challenges. *Journal of Neurotrauma*, 34, 1826–1830.
- Donati, A. R. C., Shokur, S., Morya, E., Campos, D. S. F., Moiola, R. C., Gitti, C. M., Augusto, P. B., Tripodi, S., Pires, C. G., Pereira, G. A., Brasil, F. L., Gallo, S., Lin, A. A., Takigami, A. K., Aratanha, M. A., Joshi, S., Bleuler, H., Cheng, G., Rudolph, A., & Nicolelis, M. A. L. (2016). Long-term training with a brain-machine interface-based gait protocol induces partial neurological recovery in paraplegic patients. *Scientific Reports*, 6, 30383.
- Durkovic, R. G. (1975). Classical conditioning, sensitization and habituation in the spinal cat. *Physiology & Behavior*, 14, 297–304.
- Durkovic, R. G., & Damianopoulos, E. N. (1986). Forward and backward classical conditioning of the flexion reflex in the spinal cat. *Journal of Neuroscience*, 6, 2921–2925.
- Durkovic, R. G., & Light, A. R. (1975). Spinal conditioning: unconditioned stimulus intensity requirement. *Brain Research*, 98, 364–368.
- Durkovic, R. G., & Prokovich, L. J. (1998). D-2-Amino-5-phosphonovalerate, and NMDA receptor antagonist, blocks induction of associative long-term potentiation of the flexion reflex in spinal cat. *Neuroscience Letters*, 257, 162–164.
- Edgerton, V. R., de Leon, R. D., Tillakaratne, N., Recktenwald, M. R., Hodgson, J. A., & Roy, R. R. (1997). Use-dependent plasticity in spinal stepping and standing. *Advances in Neurology*, 72, 233–247.
- Edgerton, V. R., Leon, R. D., Harkema, S. J., Hodgson, J. A., London, N., Reinkensmeyer, D. J., et al. (2001). Retraining the injured spinal cord. *Journal of Physiology*, 15, 15–22.
- Edgerton, V. R., Tillakaratne, N. J., Bigbee, A. J., de Leon, R. D., & Roy, R. R. (2004). Plasticity of the spinal neural circuitry after injury. *Annual Review of Neuroscience*, 27, 145–167.
- Evans, E. A., & Cook, D. P. (2007). Case study evaluation of body weight-supported treadmill training for parkinsonian gait. *International Journal of Therapy and Rehabilitation*, 14, 364–371.
- Ferguson, A. R., Bolding, K. A., Huie, J. R., Hook, M. A., Santillano, D. R., Miranda, R. C., & Grau, J. W. (2008). Group I metabotropic glutamate receptors control metaplasticity of spinal cord learning through a protein kinase C-dependent mechanism. *Journal of Neuroscience*, 28, 11939–11949.
- Ferguson, A. R., Crown, E. D., & Grau, J. W. (2006). Nociceptive plasticity inhibits adaptive learning in the spinal cord. *Neuroscience*, 141(1), 421–431.
- Ferguson, A. R., Huie, J. R., Crown, E. D., Baumbauer, K. M., Hook, M. A., Garraway, S. M., et al. (2012a). Maladaptive spinal plasticity opposes spinal learning and recovery in spinal cord injury. *Frontiers in Physiology*, 3, 399.
- Ferguson, A. R., Huie, J. R., Crown, E. D., & Grau, J. W. (2012b). Central nociceptive sensitization vs. spinal cord training: opposing forms of plasticity that dictate function after complete spinal cord injury. *Frontiers in Physiology*, 3, 396.
- Ferguson, A. R., Washburn, S. N., Crown, E. D., & Grau, J. W. (2003). GABA(A) receptor activation is involved in noncontingent shock inhibition of instrumental conditioning in spinal rats. *Behavioral Neuroscience*, 117, 799–812.
- Field-Fote, E. C., Lindley, S. D., & Sherman, A. L. (2005). Locomotor training approaches for individuals with spinal cord injury: a preliminary report of walking-related outcomes. *Journal of Neurologic Physical Therapy*, 29, 127–137.
- Field-Fote, E. C., & Roach, K. E. (2011). Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. *Physical Therapy*, 91, 48–60.
- Forssberg, H., Grillner, S., & Halbertsma, J. (1980b). The locomotion of the low spinal cat. I. Coordination within a hindlimb. *Acta Physiologica Scandinavica*, 108, 269–281.
- Forssberg, H., Grillner, S., Halbertsma, J., & Rossignol, S. (1980a). The locomotion of the low spinal cat. II. Interlimb coordination. *Acta Physiologica Scandinavica*, 108, 283–295.
- Forssberg, H., Grillner, S., & Rossignol, S. (1975). Phase dependent reflex reversal during walking in chronic spinal cats. *Brain Research*, 85, 103–107.

- Gandhi, P., Chan, K., Verrier, M. C., Pakosh, M., & Musselman, K. E. (2017). Training to improve walking after pediatric spinal cord injury: a systematic review of parameters and walking outcomes. *Journal of Neurotrauma*, 34, 1713–1725.
- Garraway, S. M., Turtle, J. D., Huie, J. R., Lee, K. H., Hook, M. A., Woller, S. A., & Grau, J. W. (2011). Intermittent noxious stimulation following spinal cord contusion injury impairs locomotor recovery and reduces spinal brain-derived neurotrophic factor-tropomyosin-receptor kinase signaling in adult rats. *Neuroscience*, 199, 86–102.
- Goldberger, M. E. (1986). Mechanisms contributing to sparing of function following neonatal damage to spinal pathways. *Neurochemical Pathology*, 5, 289–307.
- Gomez-Pinilla, F., Huie, J. R., Ying, Z., Ferguson, A. R., Crown, E. D., Baumbauer, K. M., et al. (2007). BDNF and learning: evidence that instrumental training promotes learning within the spinal cord by up-regulating BDNF expression. *Neuroscience*, 148, 893–906.
- Gomez-Pinilla, F., Ying, Z., Roy, R. R., Molteni, R., & Edgerton, V. R. (2002). Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. *Journal of Neurophysiology*, 88, 2187–2195.
- Gramsbergen, A. (1998). Posture and locomotion in the rat: independent or interdependent development? *Neuroscience & Behavioral Reviews*, 22, 547–553.
- Grau, J. W. (2014). Learning from the spinal cord: how the study of spinal cord plasticity informs our view of learning. *Neurobiology of Learning and Memory*, 108, 155–171.
- Grau, J. W., Barstow, D. G., & Joyner, R. L. (1998). Instrumental learning within the spinal cord: I. Behavioral properties. *Behavioral Neuroscience*, 112, 1366–1386.
- Grau, J. W., Crown, E. D., Ferguson, A. R., Washburn, S. N., Hook, M. A., & Miranda, R. C. (2006). Instrumental learning within the spinal cord: underlying mechanisms and implications for recovery after injury. *Behavioral and Cognitive Neuroscience Reviews*, 5, 191–239.
- Haeghele, J. A., & Hodge, S. R. (2015). The applied behavior analysis research paradigm and single-subject designs in adapted physical activity research. *Adapted Physical Activity Quarterly*, 32, 285–301.
- Harkema, S. J., Dobkin, B. H., & Edgerton, V. R. (2000). Pattern generators in locomotion: implications for recovery of walking after spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, 6, 82–96.
- Hodgson, J. A., Roy, R. R., de Leon, R., Dobkin, B., & Edgerton, V. R. (1994). Can the mammalian lumbar spinal cord learn a motor task? *Medicine & Science in Sports & Exercise*, 26, 1491–1497.
- Holleran, C. L., Hennessey, P. W., Leddy, A. L., Mahtani, G. B., Brazg, G., Schmit, B. D., & Hornby, T. G. (2018). High-intensity variable stepping training in patients with motor incomplete spinal cord injury: a case series. *Journal of Neurologic Physical Therapy*, 42, 94–101.
- Hook, M. A., Huie, J. R., & Grau, J. W. (2008). Peripheral inflammation undermines the plasticity of the isolated spinal cord. *Behavioral Neuroscience*, 122, 233–249.
- Hoy, K. C., Huie, J. R., & Grau, J. W. (2013). AMPA receptor mediated behavioral plasticity in the isolated rat spinal cord. *Behavioral Brain Research*, 236, 319–326.
- Huie, J. R., Morioka, K., Haefeli, J., & Ferguson, A. R. (2017). What is being trained? How divergent forms of plasticity compete to shape locomotor recovery after spinal cord injury. *Journal of Neurotrauma*, 34, 1831–1840.
- Ichiyama, R. M., Gerasimenko, Y. P., Zhong, H., Roy, R. R., & Edgerton, V. R. (2005). Hindlimb stepping movements in complete spinal rats induced by epidural spinal cord stimulation. *Neuroscience Letters*, 383, 339–344.
- Illich, P. A., Salinas, J. A., & Grau, J. W. (1994). Latent inhibition, overshadowing, and blocking of a conditioned antinociceptive response in spinalized rats. *Behavioral and Neural Biology*, 62, 140–150.
- Jindrich, D. L., Joseph, M. S., Otoshi, C. K., Wei, R. Y., Zhong, H., Roy, R. R., Tillakaratne, N. J. K., & Edgerton, V. R. (2009). Spinal learning in the adult mouse using the Horridge paradigm. *Journal of Neuroscience Methods*, 182, 250–254.
- Joyner, R. L., Ferguson, A. R., Crown, E. D., Patton, B. C., & Grau, J. W. (2003). Instrumental learning within the spinal cord: V. Evidence the behavioral deficit observed after noncontingent nociceptive stimulation reflects an intraspinal modification. *Behavioral Brain Research*, 141, 159–170.
- Joyner, R. L., & Grau, J. W. (2004). Instrumental learning within the spinal cord: III. Prior exposure to noncontingent shock induces a behavioral deficit that is blocked by an opioid antagonist. *Neurobiology of Learning and Memory*, 82(1), 35–51.
- Joyner, R. L., Illich, P. A., & Grau, J. W. (1997). Evidence for spinal conditioning in intact rats. *Neurobiology of Learning and Memory*, 67, 64–68.
- Joyner, R. L., Janjua, K., & Grau, J. W. (2004). Instrumental learning within the spinal cord: VI. The NMDA receptor antagonist, AP5, disrupts the acquisition and maintenance of an acquired flexion response. *Behavioral Brain Research*, 154, 431–438.

- Kleven, G. A., Lane, M. S., & Robinson, S. R. (2004). Development of interlimb movement synchrony in the rat fetus. *Behavioral Neuroscience*, *118*, 835–844.
- Krentz, H., Miltenberger, R., & Valbuena, D. (2016). Using token reinforcement to increase walking for adults with intellectual disabilities. *Journal of Applied Behavior Analysis*, *49*, 745–750.
- Lavrov, I., Dy, C. J., Fong, A. J., Gerasimenko, Y. P., Courtine, G., Zhong, H., Roy, R. R., & Edgerton, V. R. (2008). Epidural stimulation induced modulation of spinal locomotor networks in adult spinal rats. *Journal of Neuroscience*, *28*, 6022–6029.
- Lee, K. H., Huang, Y. J., & Grau, J. W. (2016). Learning about time within the spinal cord II: evidence that temporal regularity is encoded by a spinal oscillator. *Frontiers in Behavioral Neuroscience*, *10*, 14.
- Lee, K. H., Turtle, J. D., Huang, Y. J., Strain, M. M., Baumbauer, K. M., & Grau, J. W. (2015). Learning about time within the spinal cord: evidence that spinal neurons can abstract and store an index of regularity. *Frontiers in Behavioral Neuroscience*, *9*, 274.
- Levinsson, A., Luo, X. L., Homberg, H., & Schouenborg, J. (1999). Developmental tuning in a spinal nociceptive system: effects of neonatal spinalization. *Journal of Neuroscience*, *19*, 10397–10403.
- Mattern-Baxter, K. (2009). Effects of partial body weight supported treadmill training on children with cerebral palsy. *Pediatric Physical Therapy*, *21*, 12–22.
- Mercier, C., Roosink, M., Bouffard, J., & Bouyer, L. J. (2017). Promoting gait recovery and limiting pain after spinal cord injury: two sides of the same coin? *Neurorehabilitation and Neural Repair*, *31*, 315–322.
- Middleton, A., Merlo-Rains, A., Peters, D. M., Greene, J. V., Blanck, E. L., Moran, R., & Fritz, S. L. (2014). Body weight-supported treadmill training is no better than overground training for individuals with chronic stroke: a randomized controlled trial. *Topics in Stroke Rehabilitation*, *21*, 462–476.
- Moriello, G., Pathare, N., Cirone, C., Pastore, D., Shears, D., & Sulehri, S. (2014). Comparison of forward versus backward walking using body weight supported treadmill training in an individual with a spinal cord injury: a single subject design. *Physiotherapy Theory and Practice*, *30*, 29–37.
- Morrison, S. A., & Backus, D. (2007). Locomotor training: is translating evidence into practice financially feasible? *Journal of Neurologic Physical Therapy*, *31*, 50–54.
- Murray, M., Fischer, I., Smeraski, C., Tessler, A., & Giszter, S. (2004). Towards a definition of recovery of function. *Journal of Neurotrauma*, *21*, 405–413.
- National Spinal Cord Injury Statistical Center. (2017). *Spinal cord injury facts and figures at a glance*. Birmingham, AL: University of Alabama at Birmingham <https://www.nscisc.uab.edu>.
- Nooijen, C. F., Stam, H. J., Bergen, M. P., Bongers-Janssen, H. M. H., Valent, L., van Langeveld, S., Twisk, J., & van den Berg-Emons, R. (2016). A behavioural intervention increases physical activity in people with subacute spinal cord injury: a randomised trial. *Journal of Physiotherapy*, *62*, 35–41.
- Nooijen, C. F., Stam, H. J., Sluis, T., Valent, L., Twisk, J., & van den Berg-Emons, R. J. (2017). A behavioral intervention promoting physical activity in people with subacute spinal cord injury: secondary effects on health, social participation, and quality of life. *Clinical Rehabilitation*, *31*, 772–780.
- Patterson, M. M. (2001). Classical conditioning of spinal reflexes: the first seventy years. In J. E. Steinmetz, M. A. Gluck, & P. R. Solomon (Eds.), *Model systems and the neurobiology of associative learning* (pp. 1–22). Mahwah, NJ: Lawrence Erlbaum Associates.
- Patterson, M. M., Cegavske, C. F., & Thompson, R. F. (1973). Effects of a classical conditioning paradigm on hind-limb flexor nerve response in immobilized spinal cats. *Journal of Comparative & Physiological Psychology*, *84*, 88–97.
- Patton, B. C., Hook, M. A., Ferguson, A. R., Crown, E. D., & Grau, J. W. (2004). The behavioral deficit observed following noncontingent shock in spinalized rats is prevented by the protein synthesis inhibitor cycloheximide. *Behavioral Neuroscience*, *118*(3), 653–658.
- Petersson, P., Waldenstrom, A., Fahreus, C., & Schouenborg, J. (2003). Spontaneous muscle twitches during sleep guide spinal self-organization. *Nature*, *424*, 72–75.
- Rash, C. J., Stitzer, M., & Weinstock, J. (2017). Contingency management: new directions and remaining challenges for an evidence-based intervention. *Journal of Substance Abuse Treatment*, *72*, 10–18.
- Robertson, S. S., & Smotherman, W. P. (1990). The neural control of cyclic motor activity in the fetal rat (*Rattus norvegicus*). *Physiology & Behavior*, *47*, 121–126.
- Robinson, G. A., & Goldberger, M. E. (1986). The development and recovery of motor function in spinal cats. I. The infant lesion effect. *Experimental Brain Research*, *62*, 373–386.
- Robinson, S. R. (2005). Conjugate limb coordination after experience with an interlimb yoke: evidence for motor learning in the rat fetus. *Developmental Psychobiology*, *47*, 328–344.
- Robinson, S. R. (2015). Spinal meditation of motor learning and memory in the rat fetus. *Developmental Psychobiology*, *57*, 421–434.
- Robinson, S. R., Blumberg, M. S., Lane, M. S., & Kreber, L. A. (2000). Spontaneous motor activity of fetal and neonatal rats is organized into discrete multilimb bouts. *Developmental Psychobiology*, *114*, 328–336.

- Robinson, S. R., Kleven, G. A., & Brumley, M. R. (2008). Prenatal development of interlimb motor learning in the rat fetus. *Infancy*, 13, 204–228.
- Robinson, S. R., & Smotherman, W. P. (1987). Environmental determinants of behaviour in the rat fetus. II. The emergence of synchronous movement. *Animal Behaviour*, 35, 1652–1662.
- Robinson, S. R., & Smotherman, W. P. (1990). The prenatal origins of behavioral organization. *Psychological Science*, 1, 97–106.
- Robinson, S. R., & Smotherman, W. P. (1992). Organization of the stretch response to milk in the rat fetus. *Developmental Psychobiology*, 25, 33–49.
- Schouenborg, J. (2002). Modular organisation and spinal somatosensory imprinting. *Brain Research Reviews*, 40, 80–91.
- Schouenborg, J. (2010). Role of spontaneous movements in imprinting an action-based body representation in the spinal cord. In M. S. Blumberg, J. H. Freeman, & S. R. Robinson (Eds.), *Oxford handbook of developmental behavioral neuroscience* (pp. 254–261). New York, NY: Oxford University Press.
- Sharif, H., Gammage, K., Chun, S., & Ditor, D. (2014). Effects of FES-ambulation training on locomotor function and health-related quality of life in individuals with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, 20, 58–69.
- Sherrington, C. S. (1906). *The integrative action of the nervous system*. New Haven, CT: Yale University Press.
- Smotherman, W. P., & Robinson, S. R. (1988). Fetal expression of the leg extension response to anogenital stimulation. *Physiology & Behavior*, 43, 243–244.
- Strain, M. M., Kauer, S. D., Kao, T., & Brumley, M. R. (2014). Inter- and intralimb adaptations to a sensory perturbation during activation of the serotonin systems after a low spinal cord transection in neonatal rats. *Frontiers in Neural Circuits*, 8, 1–13.
- Takao, T., Tanaka, N., Iizuka, N., Saitou, H., Tamaoka, A., & Yanagi, H. (2015). Improvement of gait ability with a short-term intensive gait rehabilitation program using body weight support treadmill training in community dwelling chronic poststroke survivors. *Journal of Physical Therapy Science*, 27, 159–163.
- Teulier, C., Smith, B. A., Kubo, M., Chang, C. L., Moerchen, V., Murazko, K., & Ulrich, B. D. (2009). Stepping responses of infants with myelomeningocele when supported on a motorized treadmill. *Physical Therapy*, 89, 60–72.
- Thompson, A. K., & Wolpaw, J. R. (2014). The simplest motor skill: mechanisms and applications of reflex operant conditioning. *Exercise and Sport Sciences Reviews*, 42, 82–90.
- Tillakaratne, N. J. K., Guu, J. J., de Leon, R. D., Bigbee, A. J., London, N. J. L., Zhong, H., et al. (2010). Functional recovery of stepping in rats after complete neonatal spinal cord transection is not due to regrowth across the lesion site. *Neuroscience*, 166(1), 23–33.
- Timoszyk, W. K., De Leon, R. D., London, N., Roy, R. R., Edgerton, V. R., & Reinkensmeyer, D. J. (2002). The rat lumbosacral spinal cord adapts to robotic loading applied during stance. *Journal of Neurophysiology*, 88, 3108–3117.
- Ulrich, B. D. (2010). Opportunities for early intervention based on theory, basic neuroscience, and clinical science. *Physical Therapy*, 90, 1868–1880.
- Ulrich, B. D., Ulrich, D. A., Collier, D. H., & Cole, E. L. (1995). Developmental shifts in the ability of infants with Down syndrome to produce treadmill steps. *Physical Therapy*, 75, 14–23.
- van den Berg-Emons, R. J., Bussman, J. B., & Stam, H. J. (2010). Accelerometry-based activity spectrum in persons with chronic physical conditions. *Archives of Physical Medicine and Rehabilitation*, 91, 1856–1861.
- Vichaya, E. G., Baumbauer, K. M., Carcoba, L. M., Grau, J. W., & Meagher, M. W. (2009). Spinal glia modulate both adaptive and pathological processes. *Brain, Behavior, and Immunity*, 23, 969–976.
- Vinay, L., Brocard, F., Clarac, F., Noreel, J. C., Pearlstein, E., & Pflieger, J. F. (2002). Development of posture and locomotion: an interplay of endogenously generated activities and neurotrophic actions by descending pathways. *Brain Research Reviews*, 40, 118–129.
- Waldenstrom, A., Thelin, J., Thimansson, E., Levinsson, A., & Schouenborg, J. (2003). Developmental learning in a pain-related system: evidence for a cross-modality mechanism. *Journal of Neuroscience*, 23, 7719–7725.
- Weber, E. D., & Stelzner, D. J. (1977). Behavioral effects of spinal cord transection in the developing rat. *Brain Research*, 125, 241–255.
- Weber, E. D., & Stelzner, D. J. (1980). Synaptogenesis in the intermediate gray region of the lumbar spinal cord in the postnatal rat. *Brain Research*, 185, 17–37.
- Wolpaw, J. R. (2006). The education and re-education of the spinal cord. *Progress in Brain Research*, 157, 261–280.

- Wolpaw, J. R. (2010). What can the spinal cord teach us about learning and memory? *Neuroscientist*, *16*, 532–549.
- Wolpaw, J. R. (2018). The negotiated equilibrium model of spinal cord function. *Journal of Physiology*, *596*, 3469–3491.
- Yang, J. F., Livingstone, D., Brunton, K., Kim, D., Lopetinsky, B., Roy, F., & Gorassini, M. (2013). Training to enhance walking in children with cerebral palsy: are we missing the window of opportunity? *Seminars in Pediatric Neurology*, *20*, 106–115.
- Young, E. E., Baumbauer, K. M., Elliot, A., & Joynes, R. L. (2007). Neonatal hind-paw injury disrupts acquisition of an instrumental response in adult spinal rats. *Behavioral Neuroscience*, *121*, 1095–1100.
- Yuan, Q., Su, H., Chiu, W., & Lin, Z. (2013). Changes in serotonin-induced potential during spinal cord development. *Neuroscience Bulletin*, *29*, 509–516.