

# Promoting Gait Recovery and Limiting Neuropathic Pain After Spinal Cord Injury: Two Sides of the Same Coin?

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## Abstract

Most persons living with a spinal cord injury experience neuropathic pain in the months following their lesion, at the moment where they receive intensive gait rehabilitation. Based on studies using animal models, it has been proposed that central sensitization in nociceptive pathways (maladaptive plasticity) and plasticity related to motor learning (adaptive plasticity) share common neural mechanisms and compete with each other. This article aims to address the discrepancy between the growing body of basic science literature supporting this hypothesis and the general belief in rehabilitation research that pain and gait rehabilitation represent two independent problems. First, the main findings from basic research showing interactions between nociception and learning in the spinal cord will be summarized, focusing both on evidence demonstrating the impact of nociception on motor learning and of motor learning on central sensitization. Then, the generalizability of these findings in animal models to humans will be discussed. Finally, the way potential interactions between nociception and motor learning are currently taken into account in clinical research in patients with spinal cord injury will be presented. To conclude, recommendations will be proposed to better integrate findings from basic research into future clinical research in persons with spinal cord injury.

## Keywords

nociception, central sensitization, motor learning, plasticity, locomotion, rehabilitation

## Introduction

Pain is highly prevalent in the chronic phase after spinal cord injury (SCI), affecting one half to two thirds of individuals.<sup>1</sup> Prevalence is particularly high at the subacute stage, with close to 80% of individuals reporting at least moderate neuropathic pain at 1 and 6 months postinjury,<sup>2</sup> corresponding to the time period during which they receive intensive rehabilitation services. As a consequence, a large proportion of patients will receive motor rehabilitation in the presence of pain. Surprisingly, very limited attention has been devoted to understanding the potential influence of pain on motor recovery, and in particular on gait retraining, during rehabilitation. Pain and motor recovery are typically considered as 2 independent problems in clinical research and practice, although both are ultimately recognized as having an impact on community reintegration and quality of life.<sup>3</sup> This dichotomic view probably results from the fact that for a long time pain was considered and treated simply as a symptom of injury (ie, a “secondary complication”) and considered solely as a sensory phenomenon.

In contrast to this view, researchers in basic science have proposed the existence of strong interactions between

nociception and learning within the spinal cord. On the one hand, locomotor recovery following a spinal lesion is known to involve adaptive plasticity in the spinal cord.<sup>4-7</sup> Since the late 1990s, several studies have shown that motor training after spinal cord transection can lead to improvement in performance (training-induced walking recovery<sup>8</sup>), be very specific (eg, stand vs walk<sup>9,10</sup>), and involve spinal circuits reorganization.<sup>4,11,12</sup> On the other hand, sustained exposure to nociceptive input is known to result in central sensitization, a phenomenon defined as *an amplification of neural signaling within the CNS eliciting pain hypersensitivity*, including increased synaptic efficacy in nociceptive neurons in the dorsal horn of the spinal cord.<sup>13</sup> Central sensitization is considered as a form of maladaptive plasticity

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as it is an important feature in many patients with chronic pain, and especially in “unexplained” chronic pain disorders.<sup>14</sup> It has been proposed that spinal plasticity associated with central sensitization and with motor learning share similar neural mechanisms and may therefore interact with each other.<sup>15,16</sup>

## The Problem

This article aims to address the discrepancy between the general belief in clinical research and practice that pain and gait rehabilitation represent 2 independent challenges, on the one hand, and current evidence from animal research suggesting competition between central sensitization associated with nociception and plasticity related to motor learning on the other. The main findings from basic research showing interactions between nociception and learning in the spinal cord will first be summarized, focusing both on evidence showing impact of nociception on motor learning and impact of motor learning on central sensitization. Second, how and to what extent these observations in animal models translate to humans will be discussed. Third, the manner in which these potential interactions are currently taken into account in clinical research in patients with SCI will be described. Finally, recommendations for future clinical research in patients with SCI will be proposed.

## Lessons From Animal Studies

**Impact of Nociception on Motor Learning.** In the animal model literature, interactions between nociceptive input and motor learning after SCI have been mainly studied by an instrumental learning paradigm developed by Grau and collaborators.<sup>17</sup> Briefly, spinal rats (ie, complete transection at T2) can be trained to keep their hindlimb flexed if systematically exposed to ipsilateral noxious stimuli when their hindlimb is extended (controllable shocks). However, if the noxious stimulation is randomly applied (uncontrollable shocks), rats do not acquire this motor behavior. In addition, when retrained on a subsequent day, rats that were previously trained with controllable shocks reacquire the flexion response much faster than previously untrained rats, indicating some consolidation of the previous learning. In contrast, rats previously exposed to uncontrollable shocks perform worse than untrained rats, thereby providing evidence of a long-term interaction between nociception and motor learning. Strikingly, as little as 6 minutes of uncontrolled nociceptive stimulation can induce a learning deficit that remains for 48 hours.<sup>18</sup> Similar interference with motor learning has been demonstrated for stimuli inducing peripheral inflammation, such as capsaicin or formalin.<sup>19,20</sup> Further studies with this model have also shown nociception-induced motor learning impairment on the contralateral side, suggesting a strong central component.<sup>21</sup> In addition, interference has

been observed when stimulation is applied to the tail rather than to the leg.<sup>18</sup> As such, spinal interference does not appear to be highly dependent on specific localization of nociceptive stimuli, which has important consequences for motor recovery during rehabilitation.

Results from experiments in animals with complete cord transection have been replicated and extended to incomplete spinal lesions (ie, contusion model; 12.5 mm weight drop).<sup>22</sup> The deleterious effect of uncontrollable noxious stimulation on locomotor recovery (measured with the BBB [Basso, Beattie, Bresnahan] scale<sup>23</sup>) over the 6 weeks following the injury was evident within 3 days and was maintained over the next 6 weeks. Stimulation applied early after the lesion had more impact on recovery, and only uncontrollable stimulation had an effect.

Interestingly, blocking the *perception* of pain does not necessarily protect from these learning deficits if the nociceptive input is still present. Indeed, systemic morphine injections in contused rats eliminated behavioral signs of pain, but did not counter the learning deficits induced by uncontrollable stimulation.<sup>24,25</sup> The glutamergic system seems to mediate such learning deficits induced by nociceptive input, opening alternative avenues for future pharmacological manipulation (for more details and discussion, see Ferguson et al<sup>26</sup> and Grau et al<sup>27</sup>).

*Together, these observations suggest that nociceptive input can have long-term effects on motor recovery after spinal cord injury by modulating the ability of the spinal cord to learn.*

**Impact of Motor Learning on Pain.** The interactions between pain and motor systems are quite complex. Indeed, in addition to nociception and pain having a deleterious effect on motor learning, motor learning can also influence nociception and pain perception. For example, it has been shown that spinal learning (using the instrumental learning paradigm described in the preceding section) *prior* to capsaicin or formalin application blocks the development of tactile hyperreactivity in completely spinalized rats.<sup>16,19</sup> Tactile hyperreactivity, the triggering of a withdrawal response from normally innocuous tactile stimuli, is generally considered to be related to tactile allodynia measured in humans (perception of pain in response to normally innocuous tactile stimuli); this response is present in spinally transected animals, even though they cannot perceive pain. In addition, results obtained in rats with incomplete lesions suggest that an early exercise regimen (starting at Day 1 postcontusion vs Day 8) is associated with better motor recovery (BBB scale) and with less tactile hyperreactivity.<sup>28</sup> Importantly, tactile hyperreactivity is not reversed by exercise in the Day 8 group, suggesting that the timing of the intervention is important. A subsequent study showed that exercise initiated at Day 14 or Day 28 was ineffective at attenuating tactile hyperreactivity, and could even lead to the development of

hyperreactivity and aberrant afferent plasticity in previously pain-free rats.<sup>29</sup> In contrast, another study showed that intensive locomotor training both prevented (training initiated Day 5 postcontusion) and reversed (training initiated 3 weeks postcontusion) the development of tactile hyperreactivity.<sup>30</sup> Other recent studies have provided evidence that exercise can prevent (automated running wheels starting at Day 5 postcontusion)<sup>31</sup> or reverse (quadrupedal step training beginning at Day 14 postcontusion)<sup>32</sup> tactile hyperreactivity in rats. Similar results have also been reported in a mouse model, treadmill training starting at Day 7 postcontusion reversing the development of mechanical (but not thermal) tactile hyperreactivity.<sup>33</sup> While the results of these studies globally advocate for early intervention in order to prevent the development of tactile hyperreactivity, it should be pointed out that potential negative impacts of very early training following SCI have been reported. For instance, swim training initiated at Day 3 after a thoracic injury was reported to be less effective at improving swimming than a training initiated at Day 14, and this was paralleled by an increase in extravasation in and around the lesion site.<sup>34</sup>

Finally, some training modalities seem to be more efficient than others at decreasing tactile hyperreactivity; for example, treadmill training has been reported to be superior to stand or swim training.<sup>35</sup> A possible interpretation of such a finding is that the coherent pattern of sensory feedback returning to the spinal cord during training (ie, multisensory, multijoint, coordinated inputs) might be involved in mediating the inhibitory effect of motor training on central sensitization. This hypothesis is consistent with a model proposed by Grau et al, suggesting that the relationship between the nociceptive stimuli and proprioceptive signals determines how stimulation affects spinal systems.<sup>36</sup>

*Taken together, these results confirm that pain/nociception and motor learning share some neural circuitry at the spinal level and that the mechanisms underlying pain/nociception and motor learning interact bidirectionally.<sup>16</sup> Therefore, a better understanding of the interactions between pain and motor learning mechanisms could be used to promote or develop rehabilitation strategies that may lead simultaneously to better motor recovery and reduced chronic neuropathic pain.*

### **How Do Findings From Animal Models Translate to Humans?**

While the results on the effects of nociceptive input on spinal learning are very important, they cannot be directly transferred to clinical practice for 2 main reasons: (1) the instrumental learning paradigm used in most animal studies is very different (involving nociceptive stimuli) from locomotor training performed in rehabilitation; (2) the experimental pain model employed (and particularly uncontrollable electrical stimulation) is difficult to relate to what is experienced

by patients with SCI. Human studies are therefore needed to bridge the gap between basic science research and potential clinical applications. In the human acute pain model, several studies have investigated the effect of nociceptive inputs on gait kinematic, kinetic, and muscle activation patterns, but focusing mainly on muscle or joint pain models that are more relevant for musculoskeletal than for neuropathic pain.<sup>37-42</sup> Moreover, only one study so far looked at the effect of pain on locomotor learning. In this study, pain was induced only during initial training (motor acquisition) and subjects were retested pain-free on the following day, to assess retention,<sup>43</sup> thereby using an experimental design similar to that of animal studies (eg, see Hook et al<sup>19</sup>). The locomotor learning task required that participants adapt to the presence of a perturbing force applied to the ankle by a robotized orthosis during the swing phase of gait. Results showed that pain induced by topical application of capsaicin (a model of neuropathic pain) around the ankle impairs next-day motor retention despite normal performance during the motor acquisition phase. This study is the first to show that *results obtained in animal studies regarding the interfering effect of nociceptive input on motor learning translate to humans in a task relevant to human motor rehabilitation*. It also shows that such interference is present even in the absence of a spinal cord lesion, an aspect that has been put into question in animal studies. Indeed, as applying uncontrollable stimulation *prior* to SCI in rats does not induce a learning deficit, it was previously suggested that brain-dependent processes exerted a modulatory effect that could counter the development of the learning deficit at the level of the spinal cord.<sup>44</sup>

To the best of our knowledge, the protective impact of motor training against the *development* of central sensitization that has been described in animal studies has not been addressed in the human acute pain model, despite a significant body of literature on the positive impact of exercise, including walking, in various chronic pain populations.<sup>45</sup> While the acute effect of exercise on pain perception is generally explained by exercise-induced endogenous analgesia,<sup>46</sup> exercise might also exert longer-term, anti-central sensitization effects by influencing neurotrophic factors levels, including brain-derived neurotrophic factor.<sup>14</sup> However this remains speculative at the moment, and thus *the potential impact of motor training on the development or the reversal of central sensitization and pain perception in humans remains to be investigated*. It should be kept in mind that a limitation of animal models is the possibility to translate the results to pain measures employed to the human condition as assessing the perception of pain is impossible, and examining behavioral evidence of nociception is still very difficult. Consequently, studies on animal models focused almost exclusively on tactile hyperreactivity. More recently, some studies have attempted to use complementary measures that might better reflect spontaneous pain (or evoked pain in a natural context). In the mouse SCI

contusion model, for example, in addition to reducing mechanical tactile hyperreactivity, treadmill training was recently shown to significantly reduce the number of freezing episodes, a measure of fear or anxiety that is a frequent comorbidity of pain.<sup>33</sup> However, such measures are obviously difficult to directly link to actual pain perception; this likely explains why most studies only measure tactile hyperreactivity as a proxy for the allodynia observed in humans.

In patients with SCI, presence of allodynia or dysesthesia at 1 month postinjury has been shown to predict an increased risk of reporting chronic, below-level (but not at-level) pain at 12 months postinjury (odds ratio of 5.7).<sup>2</sup> That being said, the majority (64%) of patients that will eventually develop chronic pain do not exhibit allodynia at 1 month postinjury.<sup>2</sup> The different pain phenotypes observed after SCI suggest that several underlying mechanisms might coexist, and therefore studies in humans are needed to better understand the extent to which results obtained in animal models represent the complexity observed in persons with SCI and can translate into reduction in clinical pain.

### **How Are Interactions Between Pain and Motor Learning Currently Taken Into Account in Human Rehabilitation Research?**

To answer this question, it is important to consider 2 aspects: (1) the recognition of interactions between pain and motor learning as being relevant for rehabilitation outcomes and (2) the practical approach toward the inclusion, exclusion, and assessment of pain in individuals with SCI in clinical research studies. For the purpose of this article, we have explored these aspects for lower limb interventions after SCI based on existing syntheses of original research studies ([www.scireproject.com](http://www.scireproject.com); “Pain Management,” “Physical Activity,” and “Lower Limb” reviews), registered clinical trials (<http://www.clinicaltrials.gov>; search terms [spinal cord injury] AND [gait]; search performed on January 21, 2016; studies with status withdrawn or unknown excluded), and a convenience sample of 2 recent lower limb intervention studies that explicitly included individuals with SCI and pain and in which both gait and pain were considered relevant outcome parameters.<sup>47,48</sup> This exploration unraveled several important issues.

*First, there seems to be limited recognition of the (bidirectional) interactions between pain and motor learning after SCI, in particular with respect to the potential impact of pain on motor recovery.* While the SCIRE syntheses clearly recognize that pain coincides with intensive motor rehabilitation after SCI, and that physical activity can reduce musculoskeletal and neuropathic pain, the presence of pain is hardly taken into account when studying the effectiveness of lower limb interventions. In fact, of the 93 listed studies (“Lower Limb” review paragraph 4, 4.10

excluded) that focused on the effectiveness of lower limb interventions (eg, overground/treadmill training, functional electrical stimulation [FES], bracing interventions) on functional ambulation after SCI, pain was assessed as an outcome parameter in 2 studies only.<sup>49,50</sup> Likewise, of the 36 clinical SCI gait trials registered on <http://www.clinicaltrials.gov>, only 6 assessed (or are planning to assess) pain as an outcome parameter (NCT01087918,<sup>7</sup> NCT01740128, NCT02104622, NCT02441179, NCT02562001, NCT02600013). In these studies, pain assessment is generally limited to pre-post assessments of pain intensity. This neglects the multidimensionality of pain as well as its heterogeneous presentation after SCI,<sup>51</sup> but represents a first step that can be implemented without adding too much burden to the assessment battery performed in clinical trials.

*Second, the lack of documentation on pain in lower-limb intervention studies might have an impact on their internal validity.* For example, when focusing on the inclusion and exclusion criteria of the more recent intervention studies (2012-2013) included in SCIRE investigating gait training ( $\pm$  body-weight support or FES) after SCI (“Lower Limb” review paragraphs 4.2 and 4.6.2), none of the 11 retrieved studies explicitly reported pain as an exclusion criteria,<sup>49,52-61</sup> and only 1 study explicitly included and assessed patients with pain.<sup>49</sup> Did the other 10 studies also include individuals with pain? Considering that pain is reported to affect one half to two thirds of persons with SCI,<sup>1</sup> it is very likely that these studies included individuals with one or more types of pain. Indeed, 2 studies hinted toward the inclusion of individuals with pain by reporting gabapentin use (a drug prescribed for neuropathic pain management)<sup>56</sup> or having lost a patient at follow-up due to increased knee and low back pain.<sup>59</sup> Still the prevalence and distribution of individuals with pain in controlled trials currently remains unknown, thereby making it difficult to determine whether, as suggested by animal studies, pain affects motor recovery in humans with SCI. Explicit inclusion of individuals with pain and assessment of their pain at admission would help answer this question.

*Third, the explicit exclusion of (certain) patients with pain in lower-limb intervention studies reduces the external validity of these studies.* Four out of the 36 clinical SCI trials registered on <http://www.clinicaltrials.gov> explicitly excluded certain patients with pain with variable criteria, for example, exclusion of any pain in the affected limbs (NCT01498991), excessive pain in the lower limbs as measured by a score of  $>5/10$  on a Visual Analog Scale (NCT01302522), pain precluding full weight bearing and ambulation (NCT02104622), and pain limiting participation (NCT01438671). Only 1 of these 4 studies subsequently assessed pain in the final study sample (NCT01438671).

*Fourth, lower limb training interventions targeting motor improvement can sometimes alleviate pain, although both outcomes are not necessarily related.* For example,

**Table 1.** Synthesis of Key Evidence Supporting the Presence of Interactions Between Pain and Gait Rehabilitation<sup>a</sup> After Spinal Cord Injury (SCI).

	Effect of Nociception/Pain on Motor Learning/Recovery	Effect of Motor Training/Learning on Central Sensitization/Pain
Animal studies	Nociceptive stimulation (various modalities) interferes with spinal learning (complete SCI) and motor recovery (incomplete SCI).  Learning deficit exceeds the period of nociceptive stimulation.	Early motor training can <i>prevent</i> the development of tactile hyperreactivity. Whether motor training can <i>reverse</i> tactile hyperreactivity once established remains more controversial.
Experimental human studies	The presence of cutaneous pain during training interferes with retention of locomotor learning tested in the absence of pain.	No evidence available.
Clinical human studies	No direct evidence as the presence of pain is very rarely documented in clinical trials targeting gait rehabilitation.  An observational study showed that pain treatment might impact on recovery, but no direct relationship was established.	No direct evidence on central sensitization or allodynia. However, results of a few small trials suggest that lower limb training can decrease clinical pain.

<sup>a</sup>Only studies on gait/lower limb were considered.

whereas previous studies have reported improvements in gait parameters,<sup>62-65</sup> mobility,<sup>63,64</sup> and muscle strength<sup>63,64</sup> after robot-assisted gait training (RAGT) in patients with chronic incomplete SCI, a recent cross-over study by Labruyère and colleagues did not find any significant effects of RAGT on motor functions (gait and balance).<sup>47</sup> However, unlike previous studies, the study by Labruyère and colleagues explicitly included patients with various types of concomitant pain (ie, neuropathic and musculoskeletal pain). Interestingly, they showed that despite a lack of effects on motor functions, RAGT was associated both with immediate (pre-post training sessions) and long-term (pre-post intervention) reductions in general pain intensity.<sup>47</sup> In contrast, in the same sample, strength training did improve motor functions, but was not associated with longitudinal reductions in general pain intensity.<sup>47</sup> Another recent study by Villiger and colleagues assessed the impact of lower limb training by means of interactive virtual reality in individuals with chronic incomplete SCI with and without neuropathic pain.<sup>48</sup> In this case, stable improvements (up to 16 weeks after training completion) were observed both for motor functions (gait, balance, and strength) and the intensity and unpleasantness of neuropathic pain. This supports the view that interactive virtual feedback interventions could potentially affect simultaneously on motor functions and pain.<sup>66,67</sup>

In conclusion, there is only limited recognition of possible interactions between pain and motor learning/recovery in current rehabilitation research. As a result, clinical lower limb intervention studies have largely ignored or neglected pain after SCI, leading to internal and external validity

problems. Unfortunately, this prevents an appropriate evaluation of the actual impact of the interaction between pain and motor learning on motor recovery after SCI. Such interactions are not expected to be straightforward, as both differential and simultaneous effects of training on motor functions and pain have been reported.

### The Solution: Recommendations for Strategies to Try to Resolve the Controversy

Studies on animal models of complete and incomplete SCI have provided compelling evidence that pain can interfere with motor learning/recovery and, conversely, that early motor training might help preventing the development of neuropathic pain. A single study in the human acute pain model (in the absence of SCI) confirmed that tonic pain can interfere with locomotor learning, but the impact of locomotor training on central sensitization remains unexplored in humans. A synthesis of key evidence supporting the presence of interactions between pain and gait rehabilitation after SCI is presented in Table 1. Unfortunately, to date, pain after SCI has been largely ignored or neglected in clinical trials targeting gait retraining. In order to better understand the implications of these basic science results for the SCI population, future intervention studies should:

1. Include patients with pain to ensure external validity of the results;
2. Document pain adequately before, during, and after the intervention, to clarify:

- a. The potential impact of pain on the response to motor rehabilitation;
  - b. The potential impact of motor training on pain;
3. Consider implementing neuromodulation strategies that could mitigate the negative impact of pain on motor learning, keeping in mind that *nociceptive input*, and not only pain *perception*, could alter adaptive plasticity (ie, drugs like morphine could be deleterious rather than beneficial).

Observational studies might also help to shed some light on these interactions and to identify potential targets for intervention. For example, a recent study examined whether pain characteristics and management through medication affect the course of recovery in patients with SCI.<sup>68</sup> While pain characteristics had no effect on neurological outcomes, receiving anticonvulsant medication early after injury both significantly reduced pain intensity and enhanced motor recovery. Despite the fact that no direct relationship was established between the improvement on both outcomes, this is a nice example of how a single intervention (in this case initially oriented toward the treatment of pain) might provide benefits both for pain management and motor recovery. It also emphasizes the need for clinical studies to assess pain and motor recovery in a more integrated manner in order to populate the clinical literature with information that will later lead to better clinical recommendations.

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