

Targeting the motor cortex to restore walking after incomplete spinal cord injury

Marina Martinez*

Spinal cord injury (SCI), second only to stroke, is the leading cause of paralysis. The ability to walk is often lost after SCI, reducing independence and quality of life. Restoration of walking is cited as a priority among persons with SCI of all degrees of severity, chronicity, or age at injury. As 70% of SCIs are anatomically incomplete, some neural connections relaying information to and from the brain are spared. Even in severe SCI, clinically deemed motor complete, these residual descending pathways might participate in the recovery of motor function. Specifically, direct and indirect pathways originating from the motor cortex are crucial for planning, controlling, and executing voluntary movements. Studies performed by my team in rats (Brown and Martinez, 2018, 2021; Bonizzato and Martinez, 2021) and by others in humans (Smith et al., 2000; Thomas and Gorassini, 2005; Pulverenti et al., 2021) indicate that recovery of walking following incomplete SCI depends largely on activation, strengthening, and plasticity of these pathways. Directly engaging these spared connections through targeted cortical neurostimulation led to previously unseen acute alleviation of locomotor deficits and long-term improvement of voluntary control of movements in rats (Bonizzato and Martinez, 2021).

Knowledge of the cortical mechanisms of functional recovery has informed neurostimulation strategies that we have recently developed (Bonizzato and Martinez, 2021). In our studies, we have used a rat model of incomplete SCI consisting of a unilateral hemisection at T9 that produces highly reproducible lesions and locomotor deficits (Brown and Martinez, 2019). Unilateral disruption of sensorimotor pathways induces unilateral deficits in foot control that chronically persist, impeding the ability of rats to perform complex voluntary motor tasks (such as crossing a ladder) (Brown and Martinez, 2018) (**Figure 1A**). Hemisection SCI maximizes the loss of connectivity from the contralesional cortex to the paralyzed leg while preserving the opposite half of the spinal cord, allowing spared fibers to participate in the locomotor recovery. Using this lesion model, we first examined the link between changes in the cortical representation of hindlimb movements and locomotor recovery. We identified the time-course by which the contralesional motor cortex recovers access to sublesional spinal circuits by collecting motor maps in awake rats along the recovery process (Bonizzato and Martinez, 2021). As opposed to classic cortical mapping, tested under ketamine anesthesia and during terminal experiments, we chronically implanted 32-channel electrode arrays within the motor cortex of rats and monitored the changes in cortico-spinal connectivity by recording hindlimb movements evoked by intracortical stimulation. The main advantages of awake mapping are twofold: first, this technique allows to longitudinally track motor cortex plasticity in the same

animal; second, awake mapping unveils non-pyramidal transmission, which is suppressed by ketamine anesthesia (Bonizzato and Martinez, 2021). Typically, intact rats' motor maps are characterized by contralateral hindlimb motor responses, but bilateral responses are also frequent. During the first week after spinal hemisection, contralesional motor cortex stimulation failed to evoke movements of the paralyzed hindlimb, but responses were visible in the less-affected hindlimb, ipsilateral to the stimulated cortex. This early stage is associated with complete foot drag. As soon as the rats recover alternating stepping (from week 1), bilateral motor evoked responses re-emerge, and keep increasing in the following weeks as rats recover. In line with human studies (Smith et al., 2000; Thomas and Gorassini, 2005), our findings show that the re-establishment of cortico-spinal transmission parallels locomotor recovery.

We next tested whether residual activity in the contralesional motor cortex participates in locomotor recovery (Brown and Martinez, 2021). The contralesional motor cortex was inactivated for 3 weeks with a continuous infusion of muscimol (GABA_A agonist) delivered via an implanted osmotic pump from the time of spinal hemisection. We evaluated global locomotor and postural abilities in an open field arena, hindlimb locomotor kinematics on a treadmill, and skilled paw placement on a horizontal ladder before, and for three weeks after hemisection. We found that inactivating the contralesional motor cortex for 3 weeks after SCI significantly impedes locomotor recovery. Specifically, contralesional cortical inactivation decreased the ability of rats to initiate proper flexion of the affected hindlimb, leading to increased toe drag and reduced step height by comparison to hemisected controls. Additionally, cortical inactivation impaired skilled walking during ladder crossing, increasing the percentage of foot-faults by almost twice. These results provide evidence that residual cortical activity in the contralesional motor cortex contributes to the spontaneous recovery of hindlimb locomotor function after SCI. Based on these results, we hypothesized that targeted cortical stimulation approaches could be used to drive recovery.

We developed a novel neurostimulation approach that directly targets the motor cortex, intending to recruit spared connections between the motor cortex and sublesional spinal circuits. Intracortical electrode arrays were used to deliver electrical stimulation within the hindlimb motor cortex in behaving rats (Bonizzato and Martinez, 2021) (**Figure 1B**). The innovation here is that electrical stimulation is delivered to the motor cortex with timing coinciding with the predicted phase of the intended movement. Instead of tonic stimulation, the neuroprosthetic system uses retroactive control based on the functional parameters of walking to enhance leg flexion.

Intracortical stimulation is real-time controlled to be delivered within a specific area of the cortex that controls leg flexion, and with precise time resolution during the leg flexion phase of gait (in "phase-coherence" with walking). The concept is readily explained: different cortical stimulation sites can elicit selective flexor/extensor synergies. For finer facilitation of walking, the appropriate synergy (spatial choice of stimulation site) should be activated in synchrony with the appropriate walking phase (temporal choice).

We first tested this stimulation approach in intact rats during treadmill walking. Short-train intracortical microstimulations (40 ms, 330 Hz) were delivered at different time points of the step cycle through the electrode array that produced the strongest flexion of the left ankle. The maximal increase in foot trajectory was obtained when stimulation was delivered in phase with the contralateral hindlimb lift. Stimulation delivered at other time points of the step cycle disrupted locomotor behavior. Thus, we defined cortical stimulation to be "phase-coherent" with walking when delivered during the contralateral hindlimb swing preparation phase. We next tested the effect of increasing stimulation amplitude and found that step height and flexion velocity were modulated linearly with increasing stimulation amplitudes. These data show that the motor cortex modulates walking in a phase- and amplitude-dependent manner.

We next tested the effects of delivering phase-coherent cortical stimulation over immediate modulation of walking in rats submitted to a spinal hemisection. As early as one week after spinal hemisection, phase-coherent stimulation applied to the contralesional motor cortex immediately alleviated the lack of leg flexion and foot drag, re-establishing control of the paralyzed hindlimb and acting as a neuroprosthesis. This can appear surprising since movements of the paralyzed leg were not present in cortical motor maps one week after injury. Despite our SCI model disrupting crossed corticospinal fibers originating from the contralesional cortex, cortical stimulation was efficient in conveying motor outputs to sublesional spinal circuits through other residual channels, a promising result considering the variability of spinal white matter damages observed in the clinic.

Because phase-coherent intracortical stimulation was effective in acutely alleviating locomotor deficits after SCI, we next tested whether the daily neuroprosthetic intervention could facilitate locomotor recovery after SCI. We imbedded this neurostimulation strategy into locomotor training on a treadmill, from week one to four after SCI. Because treadmill walking is primarily modulated by subcortical and spinal circuits (Barbeau and Rossignol, 1987), introducing cortical stimulation was expected to help the brain to regain high-level control over spinal circuits. Voluntary locomotor control was evaluated on an untrained task, the horizontal ladder, which requires cortical control to correctly position the foot on the rungs. After three weeks of daily neurostimulation (30 min/d during treadmill walking), rats improved voluntary control of their foot. Such improvement in voluntary motor skills was not observed in rats submitted to cortical stimulation in the cage and additionally trained to walk on the treadmill. These rats did not display better performance than rats trained to treadmill walking without cortical

stimulation or rats that were allowed to recover spontaneously in the cage (Figure 1C). These data show that neurostimulation strategies that involve coherent stimulation of cortical motor circuits, while the subject is involved in a locomotor task, are more efficient in restoring voluntary control of walking than continuous, unmodulated stimulation protocols. In addition, the transfer of motor skills observed with phase-dependent cortical stimulation strongly suggests that engaging the whole brain-spinal commands into rehabilitation training has the potential to further facilitate the return of voluntary motor control.

An important result of our study was the long-term persistence of performance after neurostimulation was discontinued. After rats were submitted to cortical stimulation for 3 weeks, we interrupted the therapy and re-evaluated the animals on the ladder task after 4 weeks of inactivity. We found that early gains were maintained after cortical stimulation was discontinued (Figure 1C). We next evaluated whether a shorter period of cortical stimulation (1 week) would be sufficient to promote long-term locomotor recovery. However, short-term stimulation (1 week) was not sufficient to retain the acquired performance, which dropped immediately after therapy was discontinued, contrary to rats stimulated for longer periods (3 weeks). Determining the window of opportunity for delivering cortical stimulation will represent an important milestone for optimizing neurorehabilitation paradigms.

In conclusion, we have developed a novel stimulation strategy to foster locomotor recovery after SCI in rats. The phase-coherent intracortical stimulation paradigm represents a complete novelty in the field of neuroprosthetics. It couples the potential benefits of supraspinal approaches (Bachmann et al., 2013), a current important trend in clinical translational proposals, and patterned stimulation techniques, which is recently radically changing the field of neurostimulation (Wenger et al., 2016). Clinical translation of such approaches is still challenging; nevertheless, supraspinal brainstem (Bachmann et al., 2013) and spinal (Wenger et al., 2016; Wanger et al., 2018) neuroprostheses have been rapidly translated to ongoing clinical trials (ClinicalTrials.gov ID NCT03053791 and NCT02936453). Similar to deep brain stimulation approaches, available for decades to alleviate Parkinson's tremors, a potential limitation of our approach is the procedure invasiveness. Immediate next steps will focus on determining the trade-off between neurostimulation efficacy and interface invasiveness. Since less invasive electrical stimulation protocols can be potentially subject to different and less specific cell recruitment mechanisms, the level of controllability of leg motor output allowed by surface cortical stimulation will be characterized. The impact of implantation procedure and chronic delivery of current over long-term recovery, brain inflammatory processes and tissue damage will be thoroughly assessed in a biocompatibility study. While the work on the rat model progresses, we will test similar solutions on larger animal models, including the cat, to validate our findings across dimension scaling and clinically applicable technology. Alternative stimulation protocols to increase cortico-spinal excitability are also envisioned. Transcranial magnetic stimulation is already part of experimental clinical protocols and has the potential to provide long-term functional

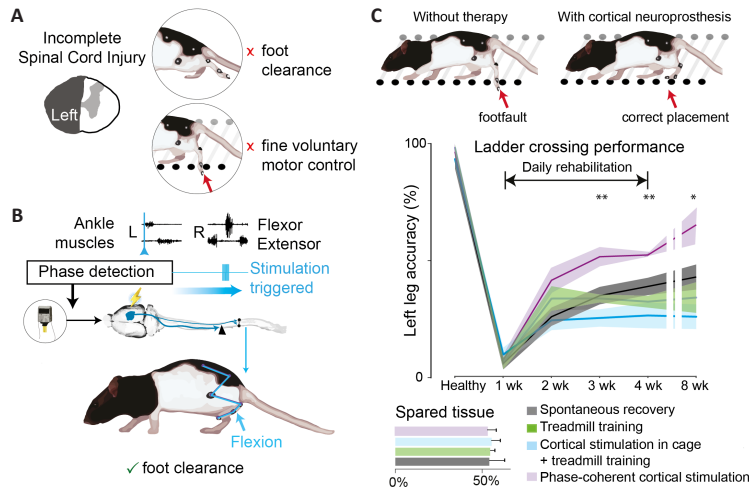


Figure 1 | Phase-coherent cortical stimulation improves recovery of skilled walking after incomplete spinal cord injury.

(A) Unilateral spinal cord injury at the thoracic level induces unilateral deficits in foot clearance and impedes the ability of rats to perform complex voluntary motor tasks. (B) Electrical stimulation was applied to the contralesional motor cortex during treadmill walking. When delivered in phase-coherence with the movement, i.e. just before foot lift, cortical stimulation immediately increased leg flexion and alleviated foot drag. (C) When embedded into rehabilitation training, phase-coherent cortical stimulation promoted long-term recovery of skilled walking, by comparison to groups of rats submitted to treadmill training, in conjunction or not with cortical stimulation delivered in the cage, or spontaneous recovery ($n = 6$ per group). $*P < 0.05$, $**P < 0.01$. Such a result is not related to different lesion damages, since all groups displayed a similar amount of spared spinal tissue. Data are displayed as group mean \pm SD. Data from the group cortical stimulation in cage + treadmill training (in blue) are unpublished. Data from the other groups have been re-analyzed for the purpose of this perspective, but these groups have been used in our published work (Bonizzato and Martinez, 2021).

improvements (Jo and Perez, 2020; Pulverenti et al., 2021). This work will provide a strong framework for using cortical stimulation in motor rehabilitation.

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Marina Martinez*

Département de Neurosciences, Groupe de recherche sur la Signalisation Neurale et la Circuiterie and Centre Interdisciplinaire de Recherche sur le Cerveau au service de l'Apprentissage, Université de Montréal; CIUSSS Nord-de-l'Île-de-Montréal, Montréal, QC, Canada

*Correspondence to: Marina Martinez, PhD, marina.martinez@umontreal.ca. <https://orcid.org/0000-0002-3294-3017> (Marina Martinez)

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