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A Transcutaneous Spinal Cord Stimulation protocol for motor facilitation during cycling: a proof-of-concept study with Spinal Cord Injury subjects

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Abstract: Spinal Cord Injury (SCI) can lead to the loss of movement control in the upper and lower limbs, significantly reducing the independence of those affected. Spinal cord stimulation (SCS) has emerged in the past decades as a SCI motor-rehabilitation technique, showing reinstatement of volitional motor control in previously completely paralyzed subjects in its epidural, invasive version. Transcutaneous Spinal Cord (tSCS) stimulation is a non-invasive, accessible and cost-effective alternative to the epidural approach. Despite significantly lacking selectivity, tSCS has shown promising results and high efficacy in SCI neurorehabilitation. It has been shown that combining spinal stimulation with volitional intent and movement-based therapy is more effective for improving motor outcomes than stimulation alone. Although most of the SCI motor-rehabilitation research is focused on walking-based protocols, passive cycling removes the weight-bearing- and falling-related risks of walking. Here, we suggest an integrated protocol of tSCS and cycling for motor rehabilitation in people with SCI.

Methods A study with four SCI participants was conducted to evaluate the feasibility and the motor-facilitating effects of tSCS and tSCS combined with volitional effort during cycling. They underwent 30-minute spinal stimulation and cycling sessions on a motor-assisted trike. Stimulation electrodes were placed on the T11-T12 and L1-L2 spinous segments and delivered continuous tSCS at 20, 50, and 80 Hz during consecutive cycling intervals. Data from lower-limbs electromyography (EMG) and forces on the trike's pedals were analyzed to evaluate the stimulation-related muscle activation and the possible effects on pedalling.

Results Gathered results proved the validity of the proposed approach and highlighted that tSCS modulates EMG activation in the lower limbs. Data from the trike pedals showed no direct correlation between higher muscle activation and improved forces during cycling. In one subject, stimulation combined with volitional effort improved force during pedalling compared to stimulation alone, highlighting SCS's potential amplification of residual volitional signals. EMG data showed a stretch reflex during cycling in participants with hypertonia, which was often reduced in amplitude by the stimulation, underlining the spasticity-related benefits of SCS. All participants reported no negative feelings during and after the stimulation and communicated that they experienced reduced muscle rigidity and improved bowel and bladder control in the days following the stimulation session.

Conclusions The study showed that tSCS combined with cycling is a feasible and promising approach for SCI motor rehabilitation and carries multiple interesting side benefits.

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1. State of the Art

Transcutaneous Spinal Cord Stimulation is a non-invasive spinal stimulation technique that engages spinal circuits [1]. In the past decades, spinal stimulation has been proposed as an effective rehabilitation tool in neurologically impaired subjects, in particular in the SCI scenario, showing significant results in walking and cycling [1–12], reinstating tactile sensations [13], spasticity reduction [14–16], pain management, cardiovascular normalization [17] and bladder control in rats [18]. The following literature review hence focuses on (i) the development of the spinal stimulation technique, (ii) its physiological background, (iii) the techniques and methods of tSCS and concludes by depicting (v) the applications of tSCS in SCI rehabilitation.

1.1. Overview of the historical development of Spinal Cord Stimulation

Spinal Cord Stimulation was developed in the second half of the twentieth century, starting as a chronic pain treatment in the 60s with epidural (invasive) stimulation and evolving to closed loop completely independent implantable systems in the last decades [19]. It is originally based on Melzack and Wall's (1965) gate control theory for peripheral neuromodulation of pain perception.
The first investigations of epidural stimulation-related motor effects were reported in the 70s, opening a new research line and highlighting the potential rehabilitation role of the technology for neurologically impaired subjects. While the first decades of research and development considered epidural stimulation only, in the late 90s, transcutaneous SCS (tSCS) was introduced, suggesting that there are low-threshold sites in the posterior structure of the human lumbosacral cord that could be accessed from the surface, that would cause muscle twitches [20]. In the following decade, the motor reflexes elicited by non-invasive stimulation have been studied and fully characterized [21], showing that tSCS can indeed access posterior root afferents. Alongside the rehabilitation discussion, and in its aid, multiple studies have investigated the neuroplasticity effects of both epidural and transcutaneous spinal stimulations [6, 22–24], highlighting its potential benefits and influences on the central nervous system (CNS) structures. Similarly, computational models have been developed starting from 1998 [25] and discussed alongside the experimental evaluations [25–29] proving effective in simulating the stimulation effects and offering a deeper understanding of the physiology underlying spinal stimulation.
In the past decade, both epidural and transcutaneous stimulation have reported significant results, with both clinical and technical improvements. Epidural stimulation has proven effective in both lower [6, 10] and upper limbs recovery [27, 30], with most of the research focusing on the rehabilitation of SCI subjects. Similarly, tSCS has reported significant results [9, 11, 12, 17, 29, 31, 32] in motor recovery and technological advancements allowed the technology to become a competitive alternative to the invasive epidural solution. Complications related to the epidural approach have been highlighted in the past years [33], contributing to increased attention towards tSCS, especially in the motor rehabilitation setting, where temporary and less invasive solutions are preferred. The following paragraphs discuss transcutaneous stimulation's physiological and technical aspects and their relevance within the SCI scenario.

1.2. Physiological background: the PRM reflex and motor facilitation

Spinal Cord Stimulation relies on the engagement of neural spinal circuits reached by an electrical stimulation current. While the electric current imposed by the electrodes reaches various neural structures and cell types, the primary motor response observed relies on the excitation of sensory afferent fibres (Ia) in the dorsal roots, which have the lowest activation threshold due to their large diameter and to the myelin sheet [34]. The sensory fibres elicit an action potential in the efferent motor fibres by inter-synaptic excitation within the spinal cord (Figure 1), and the activation of motor fibres causes a muscular contraction. The observed motor response to single pulses of current is named posterior root muscle (PRM) reflex, a distinctive element of spinal stimulation.

Anatomy of the posterior roots

Posterior root fibres are the proximal processes of the pseudo unipolar sensory neurons, with their cell bodies located in the dorsal root ganglia and their peripheral portion originating in the muscles, tendons, joints, and cutaneous and subcutaneous tissues of the body [34]. Within the dural sac, each posterior root fans out into rootlets, which enter the spinal cord in a longitudinal row. In the spinal cord, the afferent terminals make synaptic contacts with many homonymous and heteronymous spinal moto-neurons and interneurons, which integrate supraspinal information to generate the final motor output.

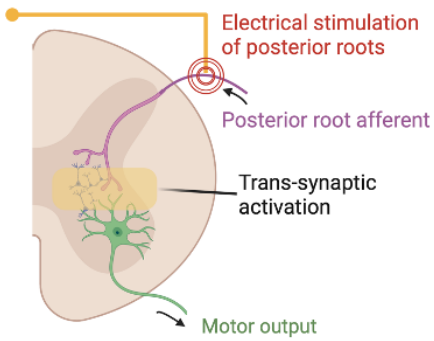

Figure 1: PRM reflex: the electrical stimulation causes an action potential in the sensory afferent fibres, which by trans-synaptic activation elicit the motor fibres, resulting in a short-latency muscular contraction (figure composed on `BioRender.com`)

Post activation depression (PAD)

PRM reflexes, caused by the transsynaptic activation from the sensory afferent to the motor efferent fibres, are distinguished from motor responses, which are instead evoked by direct activation of the motor fibres, by post-activation depression (PAD) [3]. It has been indeed observed that when two close stimuli are delivered to the spinal cord (with an interval around 50ms), the PRM reflex is characterized by an electromyographic (EMG) response to the second stimulus much smaller in amplitude with respect to the response to the first stimuli, hence post-activation depression (PAD) [21, 35]. PAD is also defined as a Monosynaptic Excitatory Postsynaptic Potential (EPSP) reduction. The decrease in the response amplitude to the second stimuli is not given by the refractory period of the fibres, which would characterize a direct motor stimulation as well but is caused by the dynamics of the trans-synaptic mechanisms involved in the PRM reflex generation.

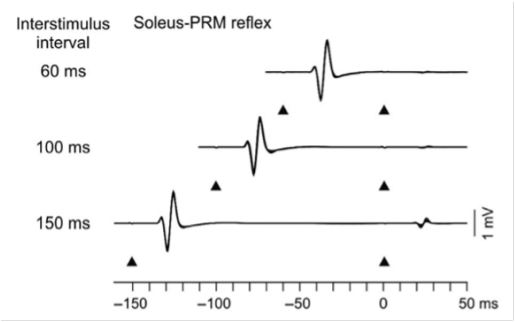

Figure 2: Post activation depression in the soleus muscle with PRM reflex elicited from transcutaneous SCS. The black triangles indicate the stimuli, and the wave represents the EMG response recorded on the soleus muscle. It is easily observed that the second stimuli do not generate a muscle response at all in the 60 ms interval or a very amplitude-limited response in the case of 100 and 150 ms intervals. Figure from Minassian et al., 2007 [21].

H-reflex vs. PRM reflex

The PRM reflex is very similar to the H-reflex, a monosynaptic reflex response that can be obtained on muscles after the stimulation of peripheral nerves. It's generally observed on the soleus muscle after tibial nerve stimulation. Both reflexes show PAD, are suppressed by tonic tendon vibration, and are modulated by passive leg movements or voluntary motor tasks. However, they differ in some ways, which have been thoroughly investigated by Minassian et al. in 2007 [21], recording the PRM and the H-reflex on the gastrocnemius:

1. Due to the more proximal site of proprioceptive afferent fibre depolarization, the PRM reflex has shorter latencies than the H-reflex, reflecting the higher time needed by the elicited action potentials to travel from the tibial nerve to the spinal cord. The H-reflex evoked by tibial nerve stimulation at the popliteal fossa has a latency of around 30ms. In comparison, a latency of about 19ms characterizes the PRM reflex in the same muscle.
2. In the tibial nerve excitation, both motor and sensory fibres are excited since it is a mixed nerve. Hence, a very short-latency M-wave due to the orthodromic stimulation of efferent fibres is observed a few milliseconds after the stimulation. Additionally, an antidromic volley is elicited on the motor fibres. The

latter collides with and annihilates the reflex volley in the same motor axon (caused by the orthodromic activation of sensory fibres and monosynaptic activation of motor ones), limiting the maximum size of the H-reflex. Differently, in the PRM reflex generation, SCS can be controlled to selectively activate afferent sensory fibres only.

3. Due to point (2), the maximal attainable proportion of the motoneuron pool in the reflex is larger in the PRM than in the H-reflex.
4. The recovery cycles of the two reflexes have been studied by Hofstoetter et al. in 2019 [36], both in healthy and in SCI subjects, showing that the PRM reflex has a stronger depression than the H-reflex and that while H-reflexes' recovery cycles do not differ between neurologically intact and SCI individuals, the PRM reflex depression is stronger in healthy subjects. This may depend on the different ways used to evoke the reflexes, with a larger pool of neurons being excited in the PRM reflex since the spinal cord is targeted. At the same time, with the H-reflex, only peripheral nerves are stimulated.

Hence, the PRM reflex offers the advantage of simultaneously testing the motoneuron excitability and the integrity of motor roots and peripheral nerves of all significant lower and upper limb muscles.

Methods for evoking PRM reflexes: epidural and transcutaneous SCS

PRM reflexes can be elicited with epidural or transcutaneous stimulation of spinal cord segments.

1. *Epidural stimulation*: uses implanted electrodes to deliver an electric current through percutaneous leads or an implanted device.
2. *Transcutaneous stimulation (tSCS)* is a non-invasive form of neuromodulation in which paravertebral and abdominal skin electrodes stimulate the spinal circuitries via an electrical current, generating a current flow through the lower trunk.

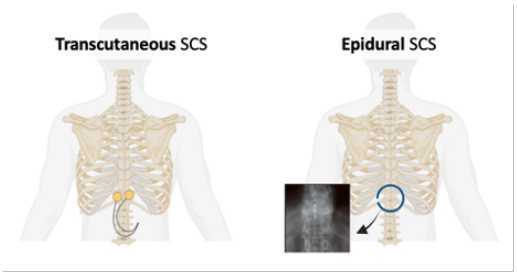

Figure 3: Transcutaneous vs epidural SCS setting: on the left, tSCS is represented, with two non-invasive electrodes; on the right, a CT scan from [37] shows implanted electrodes in the spinal cord (figure composed on `BioRender.com`).

The differences between the two methods were widely approached by Hofstetter et al. in 2018 [37], who compared the EMG responses of both methods for lumbar stimulation in SCI subjects. The PRM responses recorded were very similar (Figure 4): PAD was observed in both techniques; the bi- and tri-phasic EMG waveforms observed were very similar, and no statistical differences were found in the onset latencies. Only 3 out of the 16 parameters considered in the comparison showed statistical differences among the two methods.

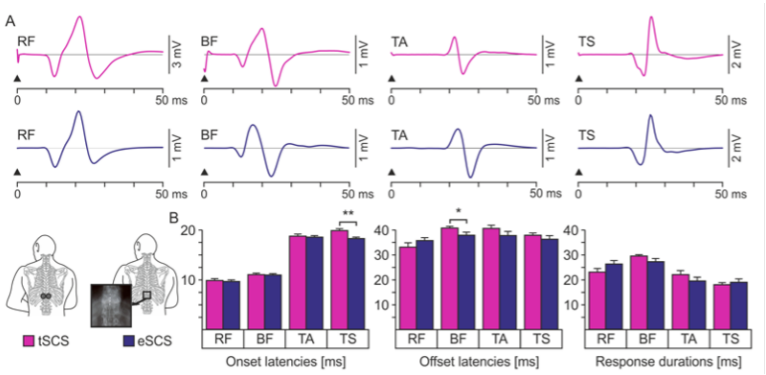

Figure 4: Transcutaneous vs epidural SCS motor responses: results from Hofstoetter et al. [37], showing motor responses recorded during tSCS and eSCS. Black triangles indicate single pulse stimulation. As discussed, the two techniques show very similar muscle responses.

While the reported results were very similar, the current flows and electric potentials induced by the two

methods are inherently different. In the epidural setting, 80 to 90% of the current flows in the highly conductive cerebrospinal fluid, in which the posterior roots are immersed, while in tSCS, the current flow is strongly influenced by the conductivity properties of the numerous tissue boundaries that are between the skin and the posterior roots. Hence, in the epidural technique, the stimulation is rather focused, and the recruitment of distal neurons is limited. Conversely, tSCS current flows first directly below the electrodes, sometimes causing brief contractions of paraspinal and abdominal muscles and then around the spine. Still, we must consider that some current crosses the spine via the soft tissues. The lowest threshold in the vertebral canal has been observed in myelinated large-diameter proprioceptive fibres within the posterior roots in both techniques and, once again for both methods, the largest depolarization is produced at the site where the second-order spatial derivative of the electric potential along the axons is at its maximum. Hofstoetter concluded that nearly identical EMG responses are observed in the two techniques, with an increased selectivity in epidural stimulation due to the more localized electrical field.
Complications with epidural SCS were reported by Taccola et al. in 2020 [33], highlighting the loss of efficacy of electrodes over time, the formation of masses around electrodes and the migration of the latter in 13 to 22% of implantation reports. These issues lead to a loss of therapeutic efficacy as well as to neurological complications and infections, hence requiring additional surgical and clinical interventions. While methods have been suggested to reduce the risk of complications, tSCS presents itself as a safe and more accessible modality of SCS. Furthermore, even in the absence of complications, tSCS is cheaper, much less invasive and better suited to temporary settings or situations that might need ongoing adjustment of electrode placement. Although the loss of selectivity is sometimes a burden, the transcutaneous approach is suggested when the experimental and clinical settings allow it [33].

Spinal stimulation mechanisms for motor facilitation

Until now, only single reflexes elicited with an over-threshold stimulation have been discussed. While the PRM reflexes demonstrate the ability to obtain a motor response by eliciting the spinal cord, reflexes elicited with single pulses do not necessarily produce movement and are not well suited to a rehabilitative setting. Instead been observed that under-threshold or threshold-level continuous stimulation allows SCI subjects with no residual motor ability to regain control of the targeted structures and immediately produce movement during the stimulation [35]. The neurological mechanisms allowing the facilitation of movement and the recruitment patterns during SCS are very complex and not entirely clear yet. They rely on various interacting mechanisms, including the modulation of spinal networks and activation of interneurons [35, 38]; but the complete electrophysiological picture is still to be understood entirely. To sum up the current state of the art, it can be said that the underlying idea is that an under-threshold stimulus modulates the excitability of spinal networks, moving the central state of excitability closer to the motor threshold so that the residual volitional signals are now enough to induce an action potential on motor neurons. This stands on the idea that there either are some residual descending fibres [35], see Figure 5 or that the other spinal circuits can be recruited to elicit motor neurons [38], see Figure 6.

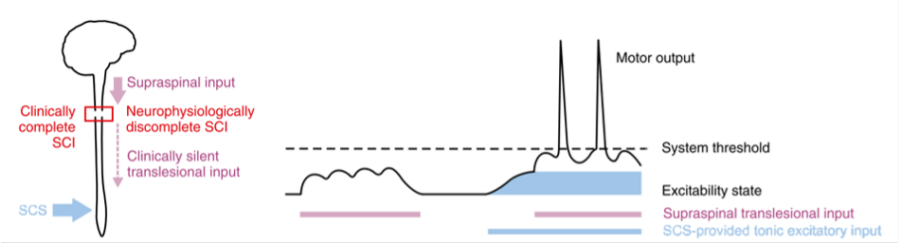

Figure 5: from Minassian et al., 2016 [35]; a possible explanation of the immediate enabling effects of tSCS: SCS-provided excitatory input moves the central state of excitability closed to the threshold and enables an otherwise ineffective supraspinal input to generate motor output.

The observed SCS-related assistive effect is distinct from the involuntary movements elicited by technologies such as Functional Electrical Stimulation (FES). FES applies the electrical stimulation to the nerves causing the muscles to contract and producing a functional movement. Rather than directly producing movement, SCS facilitates the ability of residual propriospinal and supraspinal inputs to activate spinal motoneurons, thereby enabling volitional movement in previously paralyzed subjects [30, 39]. In this scenario, multiple studies discussed spinal stimulation's ability to exploit residual spinal circuits' capability, unaffected by myelopathy and stroke damages [12, 40–42].
These mechanisms have been mainly investigated during walking movements. It has been known since the 70s (research on animals by Brown [43], and Shik [44]) that spinal locomotor neuronal circuitries, called central

pattern generators (CPGs), can induce stepping EMG patterns without supraspinal input and/or peripheral afferent input [12]. Complex neural interactions participate in walking, making the weight shift from one leg to another almost automatic for humans and controlling the oscillation of the arms during progression [42]. In the context of SCS for motor rehabilitation, these neuromechanical interactions are often unaffected by neurological injuries and the stimulation of spinal areas may engage them and exploit the residual functionality. Minassian et al. [35] showed that SCS at 22-50Hz can generate locomotor-like EMG activity and induce leg flexion-extension movements in individuals with chronic, motor-complete SCI lying supine and, in multiple studies, spinal neurostimulation during cyclic movements has shown increased activation of the circuits and perceived motor facilitation both in walking [8, 11, 12] and cycling [41, 45], proving efficient in motor rehabilitation of neurologically impaired subjects.

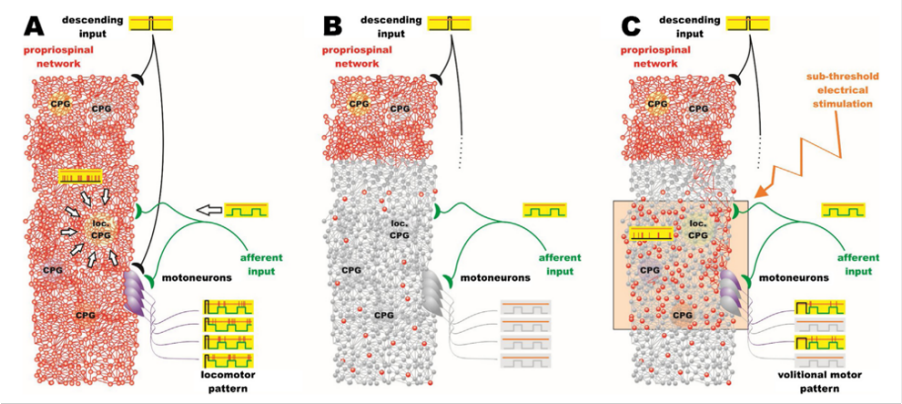

Figure 6: from Taccola et al., 2018 [38]; Neuromodulatory mechanisms for the recovery of voluntary control after SCI. The diagram illustrates some proposed mechanisms and targets. (A) reports a physiological healthy situation with all structures working properly; (B) shows an SCI setting, with an interruption in the descending pathway to the motor neurons, which makes the sublesional networks silent; (C) shows the effect of subthreshold stimulation applied to the SCI scenario, paired with specific motor training: although the direct descending fibres remain interrupted, descending input can now reach motoneurons through the polysynaptic pattern of propriospinal connections.

The collision issue in spinal cord stimulation

While SCS has shown significant results in SCI motor rehabilitation, these are remarkably less effective than those observed in other species. Formento et al. [46] hypothesized in 2019 that this discrepancy is due to the collision of the stimulation pulses with proprioceptive information during Epidural Spinal Cord Stimulation (EES). Their computer simulation shows that the antidromic recruitment of proprioceptive afferents during continuous EES blocks the propagation of naturally generated proprioceptive signals to the brain and spinal cord, disrupting the natural modulation of reciprocal inhibitory networks that is essential to produce alternating recruitment of antagonist motor pools during locomotion. To limit the collision extent, Formento proposes using high-frequency, low-amplitude stimulation that encodes the profile of proprioceptive feedback information, hence preserving it.

1.3. SCS effects on neural structures

The engagement and modulation of spinal circuits with electrical stimulation have shown multiple effects on neural structures in healthy and neurologically impaired subjects. The idea that engaging spinal circuits with spinal stimulation in rehabilitation-oriented protocols potentially carries neurological recovery benefits has been addressed and discussed by multiple studies [6, 22–24, 38], which reported significant results:

1. Wagner et al. [6] proposed in 2018 that the spatiotemporal contingency between residual supraspinal commands and proprioceptive circuit activations with epidural SCS increases the strength and number of terminals from the spared descending projections in SCI subjects through bidirectional spike-time-dependent-plasticity (STDP).
2. Spike time-dependent plasticity has also been described by Urbin et al. in their electrophysiological study [22]. In this case, Corticospinal-Motoneuronal Stimulation (PCMS) is caused by Long-Term Depression (LTD) and Long-Term Potentiation (LTP) in the spinal cord. Also, short-term plasticity within spinal inhibitory circuits was demonstrated [47], suggesting that there is room for plasticity benefits when targeting the spinal cord.

3. Benavides et al. [23] investigated in 2020 the cortical and subcortical effects of tSCS in tetraplegic individuals. Their results highlight that neuromodulation of spinal networks by tSCS boosts the excitability of motoneurons and cortico-moto-neuronal synapses, with an excitatory effect at the spinal level and an inhibitory effect at the cortical level. This aligns with reduced intracortical excitation observed after repeated practice and motor learning, suggesting that tSCS stimulation can mock, to some extent, physiological motor learning.
4. Al'joboori et al. [24] addressed in 2021 the immediate and short-term effects of tSCS on corticospinal excitability, showing that repeated coincidental input to motoneurons from descending corticospinal pathways (here induced with TMS) and afferent spinal (tSCS induced) volleys produced a short-term increase in corticospinal excitability, which positively influenced motor performance.

These results suggest that SCS rehabilitation has the potential to strengthen the residual spinal pathways at the spinal (points 1 and 2) through STDP and cortical (points 3 and 4) levels and aid in recovering independent volitional motor control [6, 10]. Pena Pino et al. [10] showed in 2020 that long-term (epidural) Spinal Cord Stimulation enables volitional movement in the absence of stimulation in complete SCI subjects. These findings suggest that complete SCI is less common than believed. It has been indeed observed that a large number of complete SCI subjects, with no motor or sensory residual abilities under the lesion level, preserves neural connections across the legion, resulting in an "anatomically incomplete" lesion [48, 49]. Even in the total absence of residual motor control, some neural pathways may have been preserved and are a suitable substrate for spinal stimulation. Supporting the latter notion, various studies report motor control improvements over time in neurologically impaired subjects, and some report the persistence of the obtained benefits in the absence of stimulation after the end of the protocol [6, 39, 41, 50, 51]. Inanici et al. reported in 2018 [51] that the functional gains obtained after four weeks of combined tSCS and task-oriented therapy on the upper limb were maintained at the 3-month follow-up. Similarly, in 2021 [5], they reported that the gains in movement and pinch force following a four-month protocol of cervical tSCS combined with upper limbs motor training were maintained for at least six months of follow-up without further treatment and improved functionality and motor abilities even without the stimulation.

It has been suggested that the combination of electrical stimulation with descending motor commands is essential for beneficial neuroplastic change, resulting in a Hebbian-type learning effect [2]. Hoover et al. reported maximum power production during assisted cycling in complete SCI subjects when the stimulation was combined with the voluntary drive [41].

Furthermore, the subcortical modulation [23] could have a significant role in a post-stroke scenario, where the corticospinal tract is the most commonly impaired anatomical district [52, 53].

While promising, the discussed findings fall within a complex scenario, where the exact neuromodulatory mechanisms in SCS are not yet entirely clear [35, 38], and more research is needed to define the rehabilitation benefits of SCS-induced neural plasticity and the related clinical applications.

1.4. Transcutaneous SCS: current scenario and stimulation parameters

tSCS is a non-invasive, accessible, and cost-effective alternative to the preceding invasive epidural approach. Despite significantly lacking selectivity, tSCS has shown promising results and demonstrated high efficacy in neurorehabilitation [1, 3]. It improved arm and hand function [5, 13, 31], stepping [12] and walking [8, 10, 12] performances and trunk stability [4] and effectively reduced spasticity [14–16] in neurologically impaired subjects. In the past decades, multiple research groups tackled the intrinsic issues of tSCS selectivity and successfully drove the technology to be a feasible alternative to the epidural approach; here we report some of the main results from the literature:

1. Minassian et al. in 2007 [21] were the first to show that transcutaneous pulses can depolarise posterior root afferents in the lumbosacral spinal cord (T11-T12).
2. Gerasimenko et al. [12] developed in 2015 a multielectrode surface array for independent Spinal Cord Stimulation (for lumbosacral stimulation in SCI subjects), addressing the selectivity issue of tSCS with respect to the epidural technique and showing in a later study that multisite activation with two or more active electrodes in the array improved significantly the motor outcomes [54].
3. Danner et al. [55] investigated in 2016 how the body position influences neural structures' recruitment during lumbosacral tSCS. They reported that responses obtained in the supine and standing positions likely resulted from selective stimulation of sensory fibres, while concomitant motor-fibre stimulation occurred in the prone position in healthy subjects.
4. Calvert et al. in 2019 [56] addressed the preferential activation of spinal networks via lateral tSCS, and their results were the first to suggest that lateral tSCS can selectively activate ipsilateral spinal sensorimotor networks, hence introducing the ability only to activate the left or right limbs. Lateral selectivity is very interesting in post-stroke applications, where hemiplegia and hemiparesis are particularly common.
5. Bryson et al. in 2023 [57] reported both lateral and rostro-caudal selectivity in lumbar tSCS, working on

the previous results by Calvert et al. (point d.) and De Freitas et al. [29].

6. Reviews by Taylor et al. in 2021 [1] and Megìa Garcìa et al. in 2020 [3] on tSCS applications and methods in SCI individuals defined to some extent standard parameters (excitation sites and electrode placement, waveform characteristics, etc.), both for upper and lower libs targeting, and discussed the reported effect of the stimulation.
7. Dalrymple et al. in 2023 [58] settled the issue of high-frequency (HF) carriers. Multiple previous tSCS studies reported that delivering the excitation current with an HF carrier would decrease discomfort and pain caused by the stimulation. On the other hand, other studies did not use a carrier and still obtained valid results. This study compared the two delivery methods and concluded an HF carrier for tSCS is equally as comfortable and less efficient as conventional stimulation at amplitudes required to stimulate spinal dorsal roots. Hence, it is suggested that future work not employ HF carriers.

tSCS parameters and stimulation settings

As a result of the advancements proposed by the research cited in the previous paragraph, the tSCS technique reached, if not a conclusive clinical setting, a standard framework. A variety of protocols, pulse sequences and electrode placements have been employed for tSCS. They are reported in the table in Appendix A, following the framework proposed by Malik et al. (2023, not published yet), that defines the minimum parameters to report SCS in spinal cord injury research, Figure 7. As depicted in the figure, the proposed framework identifies three parameters' categories: (1) SCS characteristics, which describe the pulse sequences imposed; (2) SCS intervention, which describes the intervention protocol followed; and (3) SCS hardware, which describes the stimulator and electrodes hardware.

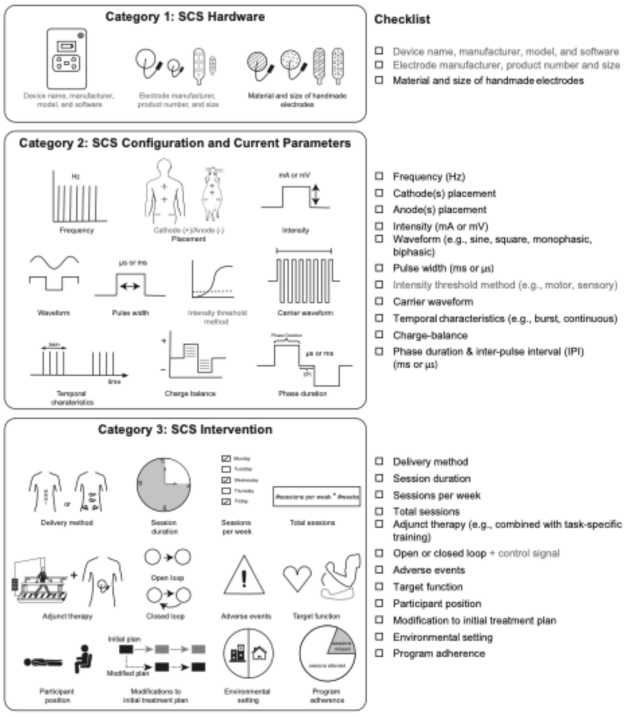

Figure 7: Minimum parameters framework to report SCS for SCI applications, by Malik et al. (not published yet)

Studies have reported the application of pulse trains with frequency bursts from 5 to 30Hz and a carrier frequency from 2.5 to 10kHz. There is no solid justification for the carrier's employment except for decreased noci-receptor sensitivity and recovery of muscle strength. However, the carrier issue was settled by Dalrymple et al. [58], as discussed in the previous point (g), who concluded that no benefit comes from employing HF carriers.

Current amplitudes span from 10-20 mA to 100- 200 mA, with the stimulation amplitude often chosen as the maximum bearable amplitude for the subject. While over-threshold current is used for PRM reflex identification and analysis, under-threshold (often around 80% of the threshold) or threshold-level current is used for continuous stimulation. The square waves' pulse width (PW) is usually around 1-2ms, and inter-pulse width depends on the stimulation frequency.

It has been observed that the bipolar electrode configuration generates a more localized electric field, affecting

spinal segments more selectively [1]. Both biphasic and monophasic waves have been used with multiple temporal characteristics (continuous trains of pules, sets of pulses alternated with rest intervals, etc.). Inanici et al. [5] compared the two modalities during cervical tSCS and reported that monophasic stimulation improved strength, whereas biphasic stimulation promoted fine motor skills.
Wave polarity is often not specified; Vienna's research group is the only one that consistently reports it, always stimulating with a biphasic wave starting with the positive, anodic front [9, 14, 36, 37]. Response to monophasic and biphasic waves has, indeed, been reported to be opposite, with nerve structures close to the anode responding at a significantly lower threshold than structures near the cathode when stimulating with a biphasic wave and vice versa when using a monophasic wave [59].
While the epidural approach allows for selective muscle targeting [60], tSCS electrodes are limited to upper or lower limb targeting, with some lateral and rostrocaudal selectivity in the case of multielectrode arrays [12, 13, 31, 61], representing are a growing approach in the field. Transcutaneous electrode placement is usually on T11-T12 or L1-L2 for lower limbs targeting and around C5-C6 for upper limbs targeting. Lumbar electrode placements have been compared by Skiadopoulos et al. in 2022 [62], who reported an increase in the resting motor threshold (RMT, minimum current to elicit a motor response) when moving from a single electrode centred on the spine to two electrodes on the sides of the spine (configuration similar to Calvert's [56] for lateral selection).
When part of a clinical or rehabilitation protocol, multiple sessions are performed, with durations spanning from 5 to 45 minutes, and often paired with rehabilitation therapy [5, 8, 41].
As for hardware, standard stimulators from Medtronic® and Digitimer® are commonly used with adhesive superficial electrodes, rectangular or square, in sizes from 5 to 10cm.

Alternative tSCS applications

While all the initial studies and discussions in the literature regard lumbosacral tSCS with lower limbs as the motor target, interest has grown towards cervical tSCS for upper limb motor rehabilitation and functional improvement in recent years. Stimulation of cervical roots is, in theory, more complex than lumbosacral stimulation since artificial recruitment of these fibres supplies synaptic inputs to multiple spinal segments [27], leading to a loss in selectivity. Nevertheless, various studies [5, 13, 29, 31, 61, 63] investigated cervical stimulation, showing that tSCS is also effective in upper limbs: distal and proximal joints can be elicited independently or synergistically and compared various electrodes configurations (from C5 to T1) and stimulation parameters for cervical tSCS. The lack of consensus around cervical electrode configuration reported in 2021 by Taylor et al. [1] has been addressed in the past years by a variety of multielectrode configurations, which have shown both rostrocaudal and mediolateral selectivity [13, 29, 61]. Significant results in upper limb rehabilitation were also reached with simple single electrode configurations: regain of motor control and increase of hand strength and dexterity were reported by Inanici et al. [5], within a combined protocol of cervical tSCS and intense activity training for SCI subjects. Remarkably, gains in movements and pinch force were maintained up to six months after the end of the stimulation protocol, providing significant evidence for the induction of neuroplasticity in the injured central nervous system through tSCS [6, 22, 23].
While traditionally stimulation has been performed in the lumbosacral and cervical regions individually, targeting lower and upper limbs respectively, some studies discussed the influence of SCS on multiple segments of the spinal cord and led to a new approach which combines simultaneous lumbosacral and cervical stimulation exploiting the coupling of spinal networks to improve the motor effects [32, 45, 64, 65]. The coupling of spinal networks is a bidirectional linkage between the cervical and lumbar segments of the spinal cord observed during rhythmic movement, and it is vital to human locomotion: lumbar and cervical networks influence each other during the performance of motor tasks [42]. It was hypothesized that combined cervical-lumbar tSCS might recruit these circuits and improve motor outcomes during cycling movement compared to single-site stimulation. Gerasimenko et al. showed in 2015 that multisite cervical and lumbar tSCS induces stepping movement in healthy subjects, while the lumbar stimulation alone does not [65]. Similarly, Barss et al. [45] reported in 2022 that combined tSCS increased PRM reflex amplitude compared to single-site stimulation. Another study [64] investigated the interlimb interaction with combined tSCS and compared it to the effects of peripheral stimulation of the fibular and ulnar nerves. Their results show that both forms of conditioning cause multisegmental facilitation of motor control with inter-limb effects. Also, they report that the magnitude of interlimb facilitation was more significant in participants with the least severe injuries, suggesting that the function of interlimb networks may play an important role in motor function after SCI.
These studies support the hypothesis that incorporating upper limb and bidirectional engagement of spinal pathways may be crucial in rehabilitation protocols and that cycling is a movement well suited to the application of SCS.

1.5. Spinal Cord Stimulation for Spinal Cord Injury recovery

SCS's main motor rehabilitation target and research focus is spinal cord injury (SCI), particularly in lower limb walking rehabilitation after SCI. SCI is a damage to the spinal cord resulting from trauma or from disease or tissues degeneration (WHO[1]). Symptoms may include loss of muscle function, sensation, or autonomic function in the parts of the body served by the spinal cord below the level of the injury. Depending on the location and severity of damage, the symptoms vary, from numbness to paralysis, including bowel or bladder incontinence. Complications can include muscle atrophy, loss of voluntary motor control, spasticity, pressure sores, infections, and breathing problems.
Transcutaneous spinal stimulation applied alone or in combination with activity-based rehabilitation programs to improve motor function for individuals with chronic spinal cord injury has been studied in the last decade, receiving considerable scientific, clinical, and media attention. The results of multiple studies highlight that tSCS is a viable option for increasing voluntary motor response of the upper and lower limbs, trunk stability, and improvement of function and quality of life of subjects with spinal cord injury [3, 5–7, 10, 12, 41]. It seems that electrical stimulation at the spinal level may modulate the functional status of the spinal network below the injury, hence improving the interaction between the motor drive from the cortex by an increase in spinal excitability mediated by stimulation of sensory afferents [2, 33].

Upper and lower limbs rehabilitation

Significant results have been observed in lower limb rehabilitation, from improving ankle control [7] and stepping performance [12] with tSCS to restoring walking, gaining voluntary control in previously paralyzed muscles, with eSCS [6] and tSCS [8]. The combination of voluntary drive and stimulation has shown better results in multiple cases, underlining the significant neuromodulatory effects of spinal stimulation [2, 9, 41].
On a side note, lower limb targeting often goes hand in hand with the inter-neuronal modulation of spinal circuits dedicated to cyclic movements (CPGs). Both walking and cycling are cyclic movements relying on CPG interactions, often unaffected by the injury, resulting in viable targets for the stimulation. Hoover et al. investigated eSCS during passive and assisted cycling in complete SCI subjects in 2023 [41], reporting the ability of all participants to pedal without motor assistance during stimulation and maximum power production when stimulation was combined with intention of movement. Cycling-based rehabilitation presents itself as an interesting alternative to walking since it eliminates the risk of falling and avoids the weight-bearing issues that characterized the early stages of walking-based therapy [2, 41]. In addition, passive cycling has shown beneficial changes across cardiovascular, musculoskeletal, and neurological systems in individuals with SCI [66]. Due to the decreased risks, the high engagement of spinal circuits and the potential side benefits, cycling might act as an early stage in SCS-based rehabilitation protocols.
While most of the research focuses on lower limb rehabilitation, cervical Spinal Cord Stimulation targeting upper limb motor rehabilitation in SCI subjects has been addressed by multiple studies showing promising results in the improvement of arm and hand functionality [5, 39, 51, 67]. Inanici et al. [5] reported in 2021 restored substantial and prolonged upper extremity function in six people with complete and incomplete SCI. Following the four-month protocol of alternating the sole training and the training paired with tSCS, the participants showed gains in movement and pinch force that were maintained for at least six months of follow-up without further treatment and improved functionality and motor abilities even without the stimulation.
Multiple studies have proposed rehabilitation protocols that combine Spinal Cord Stimulation with movement-based therapy, exploiting the benefits of physical activity (increased cardiovascular engagement, joint mobility etc.) during the stimulation [5, 8, 13, 17, 40]. Their results show that SCS is most effective when paired with physical activity and volitional intent [41], underlining the potential of combined protocols in clinical rehabilitation.

Spasticity control

Spasticity is characterized by abnormal muscle tightness due to prolonged muscle contraction, and it is one of the most prevalent impairments following spinal cord injury [16], increasing the motor impairment level and making rehabilitation more complex. SCI often affects descending fibres with a neuromodulatory role, causing the decrease of inhibitory effects and augmented muscular contraction. Common treatments range from oral medication and physical interventions to motor nerve block injections and intrathecal drug delivery [9]; however, the control of spasticity is still an issue in neurologically impaired subjects. The benefits of SCS on spasticity have been long investigated since Dimitrijevic [49] reported that epidural stimulation significantly reduced spasticity in more than half of the SCI participants in his study in 1986. In the 90s, Pinter's results showed a significant suppression of severe lower limb spasticity when the epidural electrodes were placed over the lumbar

[1] https://www.who.int/news-room/fact-sheets/detail/spinal-cord-injury

posterior roots [68] and suggested that the underlying mechanism was the modification of the excitability of spinal lumbar circuits through continuous activation of the posterior-roots. While the early studies approached epidural stimulation, in the last decade, transcutaneous techniques have been considered [14]. Hofstetter et al., [9, 15] showed a successful reduction of lower limb spasticity in incomplete SCI subjects through a 30-minute protocol of lumbar tSCS (continuous at 50 Hz). Reduced spasticity led to coactivation patterns and walking speed benefits, effectively improving the residual voluntary motor control. Alashram et al. reviewed the current state of the art on SCS for spasticity control in SCI in 2023 [16], and suggested that the observed reduction in spasticity is caused by the SCS recruitment of inhibitory spinal circuits through the continuous stimulation of afferent fibres, which hence causes the release of inhibitory neurotransmitters, usually reduced in the spastic pathophysiology. Supporting the results observed during spinal stimulation for spasticity-targeting, improvements in spasticity control have been observed as a side benefit in multiple studies with motor targets [5, 6, 15], reporting improvements in the subjects' functional levels.

SCS for SCI in targets other than motor rehabilitation

While most of the scientific attention is in the motor rehabilitation field, the application of spinal stimulation has been investigated for other targets as well, such as bladder function control in rats [18], trunk stability [4] and cardiovascular recovery after SCI [17]. These studies underline the broad applicability of SCS techniques. Phillips et al. [17] proposed in 2018 a cardiovascular-oriented, non-invasive SCS that showed normalized blood pressure, cardiac contractility, and cerebral blood flow. Hence, non-invasive transcutaneous electrical Spinal Cord Stimulation may be a viable therapy for restoring autonomic cardiovascular control after SCI.

SCS in the post-stroke scenario

While spinal cord stimulation research has been focused on SCI in the past decades, some interest has grown in recent years towards post-stroke (PS) applications. Motor impairments after a stroke occur due to the partial or complete loss of neural networks responsible for motor control. This results in the loss of voluntary motor control, strength, dexterity, and the introduction of aberrant synergies. In this scenario, SCS looks like a promising technique for restoring voluntary motor control by amplifying the residual capacity of the spinal circuits. The lower limbs PRM reflex in PS subjects was investigated in 2021 [69], showing increased motor threshold and reflex latency compared to healthy age-matched individuals. The study concluded that tSCS has the potential to aid PS lower limb motor recovery. Similarly, Powell et al. [50] hypothesized in 2023 that, since the damage to the CST is incomplete in most cases, voluntary motor control could be restored by amplifying the capacity of the residual CST, thereby restoring the ability of these supraspinal inputs to drive movement. They proposed a novel epidural stimulation of the cervical spinal cord for post-stroke upper limb rehabilitation, reporting successful results in two subjects with increased arm strength, arm motor control and tone and spasticity lasting effects. One of the two subjects could open her hand fully and volitionally for the first time in nine years after their stroke on the first stimulation session, suggesting SCS has a high potential in PS rehabilitation, even in chronically impaired subjects. However, the unique challenges of stroke-related pathophysiology and the translation of the widely discussed SCI stimulation into a post-stroke (PS) scenario have yet to be thoroughly investigated.

2. Aim of the Thesis

In light of the extensively discussed literature review, this thesis proposes an integrated transcutaneous spinal cord stimulation (tSCS) and cycling-based rehabilitation protocol for spinal cord injury subjects to evaluate the motor-facilitating effects of tSCS and tSCS combined with volitional effort. The work was conducted within the NearLab at the Polytechnic of Milan and in collaboration with Villa Beretta, the rehabilitation centre of the Valduce Hospital. The present study builds on the preliminary work on tSCS conducted during Federico Monterosso's master's thesis in the spring and summer of 2023. Monterosso determined the placement of the stimulation electrodes and the current values needed to elicit a motor response via tSCS and the reported findings have been instrumental in defining the current study.
The decision to adopt a cycling-centric approach stems from the robust literature support for cycling and the risk of syncope during standing tSCS identified in Monterosso's thesis. Moreover, the NearLab team has extensive experience in trike cycling for individuals with spinal cord injuries, having worked on FES-cycling in the past years. Therefore, the cycling setting is well-established, and the accumulated knowledge has been utilized to develop this protocol. While the proposed experimental protocol considers motor rehabilitation for Spinal Cord Injury (SCI) subjects, it may be extended to the post-stroke scenario in future applications, as the present literature review suggests.

3. Materials and Methods

This chapter presents the materials used for the experiments and the followed procedure. Transcutaneous Spinal Cord Stimulation (tSCS) was paired with motor-assisted trike-cycling in SCI subjects to evaluate the possible motor facilitation effects of the stimulation during cycling.
The experimental protocol was approved by Politecnico di Milano's ethical committee with protocol number 50/2023 on December 12th 2023, and conforms to the Helsinki Declaration of 1975, as revised in 2000.

3.1. Subjects and clinical data

After obtaining their informed consent, subjects with complete and incomplete SCI (classified as ASIA A and B) were recruited. The participants were otherwise male healthy adults with no prior experience with spinal stimulation. Medications were not changed during the study. The inclusion and exclusion criteria are summed up in Table 1.

Inclusion Criteria	**Exclusion Criteria**
• Age: 18-75 • Complete or incomplete spinal cord lesion (ASIA A or B) • Autonomous trunk motor control to allow independent sitting • Good response to spinal stimulation	• chronically denervated muscles • neurogenic paraosteoartropatia • cardiovascular diseases • fractures in the lower limbs in the last 12 months • absence of response to spinal cord stimulation • allergy to the stimulation electrodes • implanted pacemaker or other electrical devices • metal implants • inability to independently consent to the participation

Table 1: Inclusion and exclusion criteria of the presented experimental protocol

For safety reasons, each subject's clinical history was reviewed by Franco Molteni, MD, the study's clinical supervisor, who confirmed the absence of contraindications to spinal stimulation in the included individuals. Furthermore, anamnestic data were collected and double-checked by an on-site clinician to confirm the absence of metal implants in the subjects, their consent to the procedure and their health state at the time of the stimulation session.
The following basal data were acquired before each stimulation session: Heart Rate (HR), Arterial blood Pressure (AP), and blood oxygen saturation (SatO2 %). Their values were controlled against physiological ranges to confirm the subjects' health status.

3.2. Experimental Setup

The following experimental setup was defined to apply tSCS during motor-assisted cycling and to collect EMG and force data during the activity.

Trike

A trike model 700 (Catrike, US) with a cycling-assist motor was used; see Figure 8. It includes a pair of sensorised pedals (X-Power, SRM GmbH, Germany) and a motor controlled by a Raspberry central unit, which communicates with a custom Android app on a tablet. This app controls the motor state and cadence and allows real-time monitoring of the power produced by the subject. Orthesis are mounted on the pedals to keep the subject's legs in the correct position. The following data are provided: mean-cycle motor power, instantaneous motor power, instantaneous force on each pedal and the respective crankarm angle.
This trike setup was developed within the NearLab, PoliMi, in the scope of other projects. In particular, Davide Savona, PhD student, and Camilla Zanco, Master's Thesis student, developed the motor's control and app and assisted during the tSCS cycling trials.

Transcutaneous Spinal Cord Stimulation

tSCS was applied using self-adhesive electrodes (PALS Neurostimulation Electrodes, Axelgaard Manufacturing Co. Ltd., Fallbrook, USA). A pair of 5x5cm square stimulating electrodes were placed centrally along the spine,

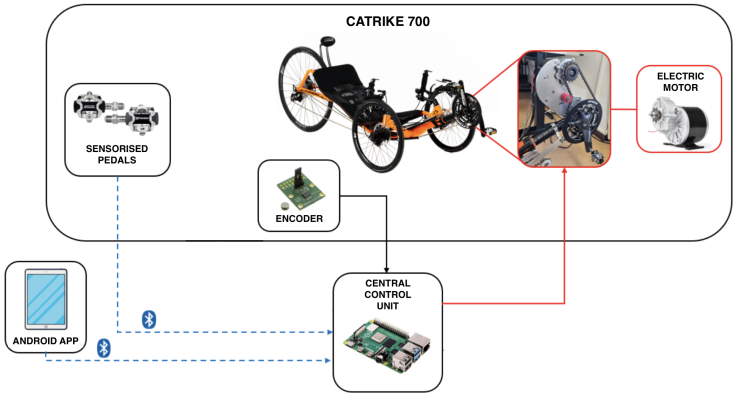

Figure 8: Trike setup for cycling

the anode over L1-L2 spinous processes and the cathode over T11-T12 spinous processes, as shown in Figure 10. Electrode placement was confirmed by eliciting posterior root-muscle reflexes (PRM reflexes) in the first phase of the stimulation protocol (*Calibration*).

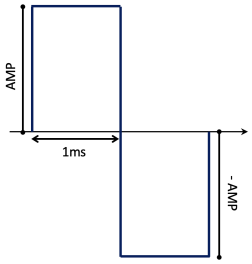

Figure 9: Single tSCS pulse

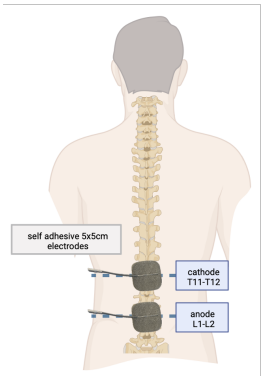

Figure 10: Electrode placement for tSCS (figure composed on `BioRender.com`)

A RehaMove Pro (Hasomed GmbH, Germany) stimulator delivered charge-balanced, biphasic square pulses with 2ms pulse width (1ms per phase), as shown in Figure 9, and amplitude and frequency adapted to the specific subject and test. The anode cable of the stimulator was identified with an oscilloscope test and used for anodic stimulation of the L1-L2 region since, as suggested in Mayr's publication [59], anodic stimulation is more effective when using a biphasic curve.
The simulator was programmed and controlled with a C++ Qt-based custom interface developed in QtCreator (version 4.5.2, 2018, based on Qt 5.9.5). The code runs on a Dell laptop (operative system Ubuntu 18.04.5 LTS) connected to the stimulator via USB cable. The interface, Figure 11, offers four different stimulation settings: *Single Stimuli, Close Stimuli, Ramp and Continuous Stimulation.* Each setting allows the control of the start and stop of the stimulation and the definition of some stimulation parameters (current amplitude, pulse width of the single phase, time between pulses or frequency depending on the type of stimulation). The four modalities are hereby detailed:

1. *Single Stimuli*: applies a series of ten single stimuli at a chosen time distance and current amplitude. It is used for the *Calibration* phase, during which the motor-threshold current amplitude is identified as the lowest current inducing a visible PRM reflex on the EMG signal. Once the series is completed, there is a one-minute pause, during which the *pause* progress bar on the interface fills. After the pause, another series of ten pulses is delivered, with the same time distance and current amplitude increased by a predefined value.
2. *Close Stimuli*: applies a series of ten coupled stimuli close to each other; the interface can set the time distance inside the doublet and between two consecutive doublets. This modality is used to identify Post-Activation Depression (PAD).
3. *Ramp*: applies a continuous stimulation at a chosen frequency, with amplitude increasing by a predefined increment after a set time interval. The ramp is used in a preliminary phase to investigate the effects of an increasing amplitude current during tSCS.
4. *Continuous stimulation*: applies a continuous stimulation at a chosen frequency and current amplitude.

The current amplitude gradually ramps up over a few seconds to reduce any discomfort caused by an abrupt start to the stimulation. This is the primary modality used during the experimental protocol to investigate motor facilitation.

The stimulation sequences provided during the four different modalities are shown graphically in Figure 12 for the default values set in the GUI.

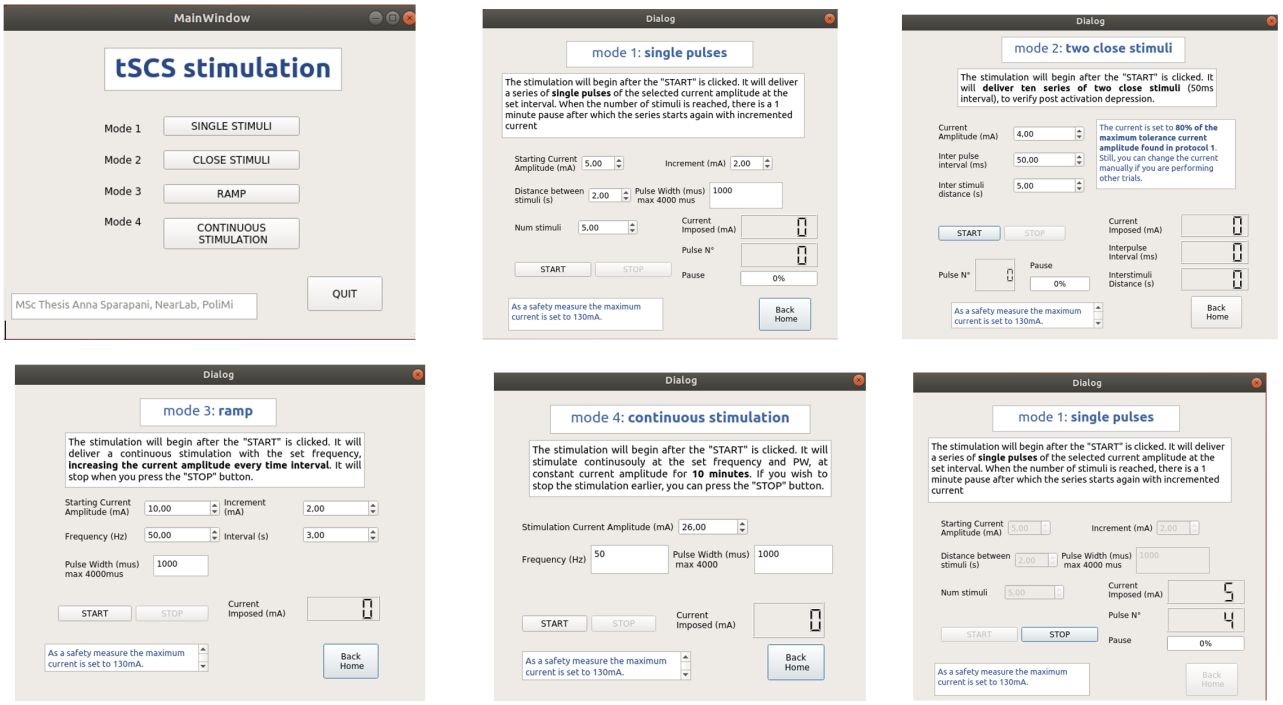

Figure 11: tSCS custom-developed Graphical User Interface (GUI). The GUI allows you to choose the stimulation mode, set the stimulation parameters, and start and stop the stimulation. Interfaces for all modes are shown, and in the bottom right figure, Mode 1 is shown when running. When the stimulation is running, the parameters settings and home button are disabled, and the current value and pulse number are shown on the display. The other modes have similar running interfaces.

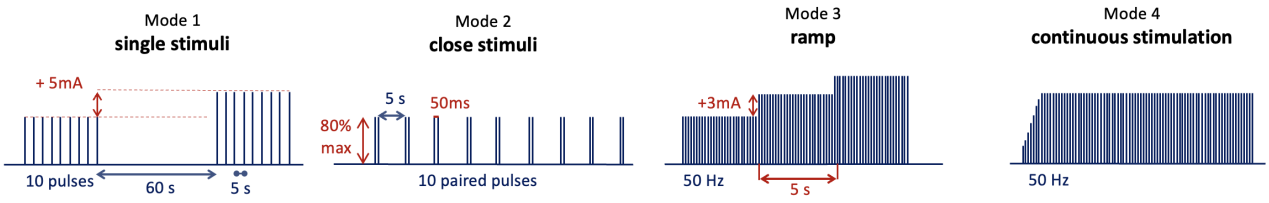

Figure 12: Time course of the stimulation modalities provided by the custom-developed GUI, with default parameters values

EMG system

Eight-channel surface electromyography (EMG) of lower limb muscles was acquired at 2000Hz sampling frequency with a TMSI SAGA 32+/64+ REV 2 (Twente Medical Systems International B.V., Netherlands) and its proprietary software SAGA, running on a Windows 11 (version 23H2) laptop. Sixteen monopolar channels were used to acquire data from four muscles on each leg: rectus femoris (quadriceps, QUAD), biceps femoris (hamstrings, HAMS), tibialis anterior (TA) and gastrocnemius (GAST). Self-adhesive hydrogel electrodes (Cardinal Health, Waukegan, USA) were placed with a 1cm inter-electrode distance as shown in Figure 13. An extra bipolar channel was connected to the trike's Raspberry trigger, which gives an impulse at the start of each pedalling revolution. This was later used in post-processing to align the trike data with the EMG activations. The entire setup is summarised and shown in Figure 14. The subject is sitting on the Catrike, and three laptops control the cycling-assist motor, the stimulation and the EMG acquisition, respectively.

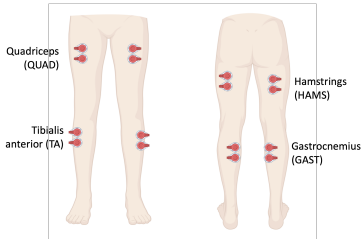

Figure 13: Position of EMG electrodes (figure composed on `BioRender.com`)

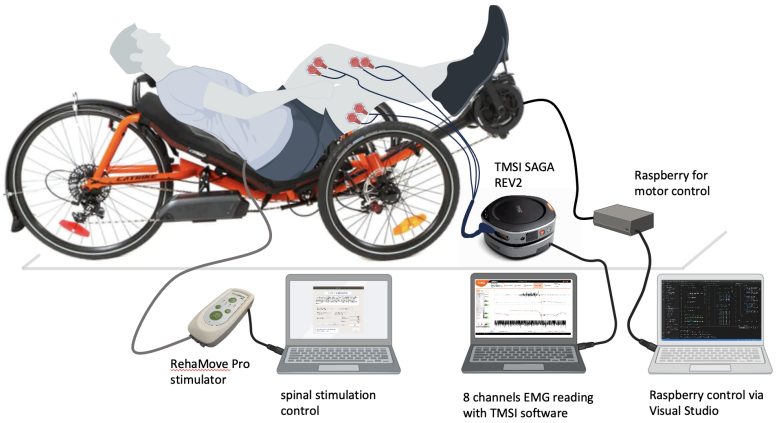

Figure 14: Experimental Setup. The RehaMove Pro stimulator provides transcutaneous spinal cord stimulation and is controlled from a laptop via the custom-developed GUI. EMG data is acquired with eight channels on the TMSI device and visualized in real-time on a laptop running the proprietary SAGA interface. The motor is controlled by a Raspberry, which is programmed via Visual Studio from a laptop (figure composed on `BioRender.com`).

tSCS questionnaire and feedback

To collect extra data on the tSCS-induced sensations, subjects were asked to complete a questionnaire on the stimulation experience at the end of each session. The questionnaire rates the *pain, burning, cramping* and *pressure* sensations on a 0-10 scale for all three stimulation frequencies and investigates if there are any perceptible motor facilitation effects. Participants were also asked to report any other relevant sensation they felt during the stimulation, and feedback calls were conducted about 24/48 hours after the stimulation session to take note of any stimulation-induced change the subjects may have noticed.

3.3. Experimental Protocol

The proposed experimental protocol aims to determine possible tSCS-induced motor facilitation during leg cycling. It lasts about 70 minutes per session. Once the subject has been selected for the study, he is initially asked to fill out the anamnestic form. Then basal data (heart rate, arterial pressure and oxygen blood saturation) are acquired, and if both the form and the data show no anomalies, the stimulation session can start.
The EMG and stimulation electrodes are placed on the legs and lower back, respectively; the subject is asked to sit on the trike, and his legs are fastened to the pedals' orthoses.

1. **Calibration**: the subject is seated on the trike, with the legs resting and the motor off; the pedals are placed in a standard position, with the right pedal up and the left pedal down. A series of ten single tSCS pulses are delivered (via the setup described in Figure 3.2) at a 5s time distance and with the amplitude increased by 5mA every ten pulses. The motor threshold current amplitude is identified by looking at the real-time EMG signal as the lowest value inducing a visible PRM reflex following the stimulation artefact on the signal trace.
2. **Passive cycling**: this phase consists of three minutes of passive cycling, meaning that the movement is completely generated by the trike's motor at a constant cadence while the stimulation is off. This serves as a baseline condition; EMG and trike data are compared to those from the following conditions.
3. **tSCS cycling**: this step comprises six minutes of cycling with both the motor on at a constant cadence and the continuous tSCS on. During the first three minutes, the subject is required to do nothing, while

during the following three minutes, he is asked to think about moving his legs voluntarily.
This test is repeated for three frequencies (20 Hz, 50 Hz and 80 Hz) in random order, and tSCS is switched off after each 6-minute block to change the stimulation frequency.

The protocol is summed up in Figure 15, showing each stage's state of stimulation, motor and voluntary effort. At the end of the experimental protocol, the subject is asked to fill out the questionnaire on the stimulation session.

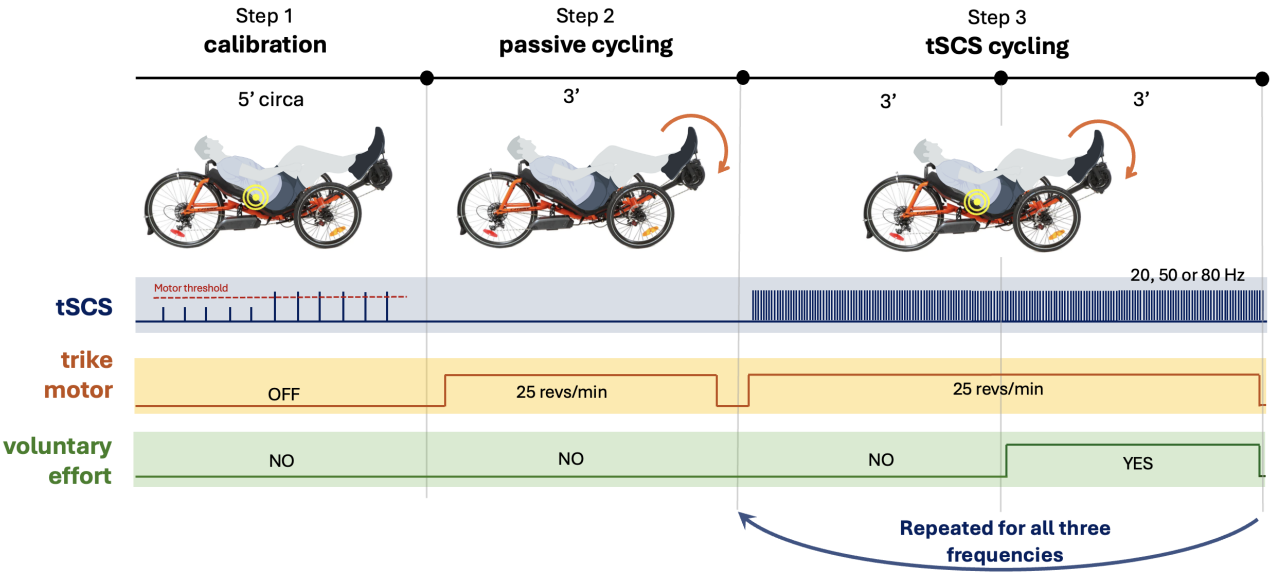

Figure 15: Experimental protocol. The protocol has three steps: *calibration*, *passive cycling* and *tSCS cycling*. The combination of stimulation, motor, and subject's voluntary effort in the three stages is shown in the diagram.

3.4. Data Analysis

Data analysis was performed in MATLAB (version R2023b) both for the EMG and the trike data.

EMG Data Analysis

EMG data was analysed to identify the PRM reflex and to study its amplitude and latency during the *Calibration* step. Then, it was used to compare the muscle activation during steps 2 *Passive Cycling* and 3 *tSCS Cycling*. For the muscle activation comparison, data were filtered with a 10-500Hz band-pass filter and a 50Hz notch filter to remove static noise from the trigger channel. Stimulation artefacts, superimposed on the recorded physiological EMG activities during cycling, were identified with the *findpeaks* MATLAB function. The *MinPeaksDistance* and *MeakPeaksHeight* parameters were adjusted to the considered stimulation frequency and muscle since, in distal muscles, the artefacts are significantly smaller. 2-5ms blanking intervals around the identified peaks were replaced with the artefacts to remove them. After artefact removal, offset subtraction and rectification were performed, and the pre-processing was concluded with envelope computation using a 5th-order low-pass Butterworth filter with a 10Hz cutoff frequency. Cycling revolutions were then segmented based on the trigger EMG channel and averaged to obtain a sample cycling revolution for each muscle and cycling condition. EMG average cycling revolutions were then rescaled based on the subject's baseline. The baseline was computed as the average EMG amplitude acquired for a few seconds before calibration in the standard position and passive conditions. Cycling revolutions were analyzed both individually and as averaged into a mean cycle.

Trike Data Analysis

Trike data were analysed to investigate possible force and power production changes during tSCS cycling and tSCS cycling paired with voluntary effort. The sensorised pedals and motor provided the average motor and pedal power during the session, as well as the instantaneous forces and crankarm angles. Instantaneous forces were averaged over the cycling revolutions for each session, obtaining an average cycle force for the right and left pedals.

4. Results

4.1. Included Subjects

The study included four male participants aged from 25 to 40 years old, three with complete motor and sensory spinal cord injury and one with incomplete SCI (Table 2). The participants were otherwise healthy adults.

	Lesion type	Lesion level	Time since lesion	Metal implants	BMI (kg/m^2)	Medication
Sub. 01	A	D4	52 months	D1-D7	19.11	baclofen, movicol, resolor
Sub. 02	A	D3	23 months	D3-D9	21.97	ossibutinine, urimesk
Sub. 03	B	D12	29 months	none	21.92	baclofen, lyrica
Sub. 04	B	D2	$\approx$ 12 months	none	25.18	ossibutinine, urivesch

Table 2: Included subjects' characteristics

Anamnestic data collected before each session confirmed the absence of metal implants and devices other than the spine stabilization devices reviewed by the study's clinical supervisor. Basal data acquired at the beginning of each session confirmed that the subjects were in healthy conditions.
All subjects, but subject 04, were used to FES-cycling as they had been consistently trained with a FES-bike in the past years but had never undergone spinal stimulation. Subjects 03 and 04 had lower limb muscle rigidity and hypertonia and presented some involuntary contractions and clonuses. Subject 03 exhibited some uncontrolled contractions on the left leg. Subject 04 scored one on the spasticity Ashworth scale in a clinical test six months before the study. He also presented a clonus on the right leg, triggered by the ankle joint at 90°; the trike's orthosis was adapted during his trial to avoid reaching this angle and inducing the clonus during cycling. Medication data shows that subjects 01 and 03 were undergoing anti-spasticity treatments and that all participants took medication to control urination and intestine functionality. Subjects 01, 02 and 03 underwent two stimulation sessions a week apart, while subject 04 underwent a single session.

4.2. PRM Reflex and Motor Threshold

The motor thresholds identified during the *Calibration* phase and the continuous tSCS current amplitudes used in the following *tSCS cycling* phase are reported in Table 3. The amplitude for the tSCS cycling phase was set to the minimum between the PRM threshold and the maximum amplitude tolerable by the participant. All participants but subject 03, who has preserved sensibility in the entire lower back region, tolerated the PRM threshold current.

	PRM threshold	tSCS cycling current
Sub. 01	60mA	60mA
Sub. 02	55mA	55mA
Sub. 03	70mA	50mA
Sub. 04	65mA	65mA

Table 3: PRM thresholds and currents used for the tSCS cycling phase

4.3. Questionnaire

The questionnaire was compiled after each stimulation block of *tSCS cycling*, collecting the user's feedback for each stimulation frequency. Subjects were asked to rate their feelings of pain, burning, cramping, tingling and pressure on a scale from 0 to 10. Any additional comments were also noted down. Sensations varied among participants, with those with lower lesions and more residual sensibility reporting feeling the stimulation both at the stimulation site and in their legs. Questionnaire answers are reported for each subject in Table 4.
Subject 01 consistently scored 0 in all categories, indicating no stimulation perception. However, during the

	Pain			Burning			Cramping			Tingling			Pressure		
Stim. frequency (Hz)	20	50	80	20	50	80	20	50	80	20	50	80	20	50	80
Subject 01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Subject 02	1	2	4	4	7	7	0	0	0	5	5	0	4	5	7
	2	4	0	5	5	3	0	0	0	0	0	0	2	4	0
Subject 03	3	4	0	0	0	0	3	5	0	5	7	5	5	8	4
	3	2	3	0	0	1	2	3	2	3	4	4	2	4	3
Subject 04	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 4: tSCS questionnaire's answers

second trial, he reported feeling a pressure sensation at the beginning of the continuous stimulation phase. In contrast, Subjects 02, 03 and 04 reported feeling the stimulation during the calibration and the tSCS cycling phases. They described the single pulse as a "push" on the lower back during the calibration. During the continuous stimulation, they reported experiencing a painful sensation at the beginning, which became less intense during the three-minute tSCS. No clear consensus was found among subjects regarding the stimulation type perceived as the most uncomfortable. Subject 02 declared increased discomfort with increasing frequencies. For subject 01, instead, the highest discomfort was experienced during the 50Hz tSCS, while similar sensations were felt for the 20 Hz and 80 Hz stimulations. Subject 03 communicated a significant increase in pain during the 20Hz stimulation with the voluntary effort; specifically, he said it was hard to maintain the voluntary motor intent because of the pain. He also reported a slight discomfort increase when adding the volitional intent to the 80Hz stimulation but no changes when adding it to the 50Hz stimulation. Subject 02 was the only one scoring non-null in the burning category, announcing intense heating in the lower back during the stimulation, which diffused to the proximal lower limbs. Subjects 02 and 03 reported tingling in the upper legs, which diffused, decreasing in intensity, to the feet. They described it as the primary sensation on their legs, similar to vascular tingling. Subject 02 also communicated an increased tingling sensation when pressure was applied by the study's physiatrist on his legs, together with a feeling of support under the front foot. Specifically, he detailed that the tingling in his toes felt as if he could move them. Subject 03 perceived a sensation of muscle contraction on the stimulation site, which was not as painful as cramping but still caused some discomfort. During the second session, he also reported feeling the right quadriceps contracted, like during FES-cycling. All subjects that tried FES-cycling before argued that the tSCS gave a similar sensation to that perceived during FES-cycling when stimulation is directly applied to the lower limb muscles. Subject 04 communicated feeling the stimulation intensively at the beginning of each block and much less in the later minutes, but he scored 0 in all categories, saying that the sensation was neither uncomfortable nor painful at all for him. During the second stimulation session, Subjects 02 and 03 scored lower values in all categories, and all participants experienced a reduction in discomfort over time during the single stimulation trials, indicating an adaptation phenomenon.

4.4. EMG and force results

The EMG and forces data were analyzed for each participant individually rather than as a population, given the participants' unique clinical histories and the low number of trials performed. Hence, the figures in this summary are relative to single trials. EMG and force results for the right biceps and rectus femoris muscles and right pedal during each protocol's session are summed up in Figures 16 to 22. Panel A reports on the left side the EMG data for the right rectus and biceps femoris normalized to the subject's baseline. On the right side, the RMS mean values and Standard Deviations (SD) of EMG amplitudes of the same trials are displayed. Hip and knee flexion and extension ranges for the specific experimental setup were measured and superimposed with grey and black lines to the plots. Panel B and C report force data, with panel B showing the absolute force of the considered tSCS test together with the passive one (left) and the active force computed as the difference between the force during tSCS and the passive trial (right). A positive active force indicates a functional participation of the subject in the movement. Panel C, instead, reports the mean active force with its SD for both sides and all performed tests. Each row is relative to a different tested frequency. EMG and force graphs consider an average cycling revolution starting at a null right crank angle, corresponding to the standard position.
The EMG data among all subjects shows that the stimulation does not consistently increase muscle activations compared to passive cycling, but it rather modulates them, both amplifying and reducing, depending on the

muscle and the session, with no particular scheme. Contrary to expectations, EMG during passive cycling was neither null nor inactive in multiple muscles and subjects. Although we could not identify a stimulation frequency consistently increasing the muscle activation over the passive level, the 80Hz tSCS showed reduced EMG amplitude in all participants and muscles. The 50 and 20 Hz stimulations often showed values over the passive range and sometimes slightly below, with the 50 Hz scoring as the most amplifying frequency on average. Although higher EMG activation did not consistently lead to a cycling force improvement, these results align with the literature, where a frequency from 30 to 50 Hz is usually employed in motor-oriented SCS studies [1]. The lack of motor outcomes in our study is probably due to the low number of trials, not to the stimulation frequency; indeed, studies reporting improved motor outcomes do so after months-long stimulation protocols. The muscle relaxation induced by 80Hz stimulation, on the other hand, suggests that it may be a viable option for spasticity reduction.
Forces on the pedals were analyzed, and those acquired during passive cycling were compared to those relative to sessions with tSCS to evaluate the motor-facilitating effects of the EMG modulation induced by tSCS.
Interestingly, subjects 01 and 02 showed similar behaviours for EMG activation and forces on pedals, which were clearly distinct from those common to subjects 03 and 04 during both passive and tSCS cycling. The two trends are discussed separately in *Case Studies* 01 and 02. We hypothesise that the difference between the two groups is caused by subjects 03 and 04's hypertonia and clonuses and by their lower level of spinal injury.

Case Study 01

EMG and force results for the right muscles and pedal during the tSCS cycling sessions of subjects 01 and 02 are summed up in Figures 16(A) to 19(A). In subject 01, EMG amplitude oscillates from 0.5 to 2 times the baseline level for both trials, showing less amplification with respect to the other participants. The 80Hz stimulation consistently reduced muscle activation, while the 50Hz tSCS increased the EMG amplitude. In addition, the 50Hz stimulation introduced a cyclic pattern, which is absent during passive cycling. This trend is, however, not in phase with a physiological activation. A peak up to 12 times the baseline is observed in the right biceps femoris during the second trial. This result deviates critically from what was observed in the other muscles and in the previous session, and it might be related to some acquisition error. Similarly, for participant 02 EMG data on the right rectus femoris shows a passive amplitude moderately over the baseline, which is slightly amplified and reduced by the 20 and 80Hz stimulations, respectively. The 50Hz stimulation amplifies the activation to three and seven times the baseline during the first and second trials respectively. The biceps femoris show a higher passive activation, which is reduced by all stimulation frequencies in the first trial and by the 20 and 80Hz tSCSs in the second session. In addition, the 50Hz stimulation introduces a cyclic trend on both muscles, clearly illustrated in Figure 17(A), which is absent in the passive condition. Interestingly, the 50Hz and the combined 50Hz plus voluntary intent conditions introduced opposite cyclic patterns. While neither one resembled a proper voluntary activation, the one without voluntary intent was closer to the expected behaviour, with rectus femoris activation at the beginning of knee extension and hip flexion.
Participants 01 and 02 showed small oscillations in amplitude with respect to the passive cycling force, as depicted in panels B of Figures 16 to 19. A minimum of cycling cooperation during *tSCS cycling* with respect to the passive condition can be observed around 200-300° during the pulling phase of each pedal's revolution. On the other hand, the negative active force peak around 0-50° shows a resistance introduced by tSCS at the beginning of the cycle in the majority of the sessions. The overall mean active forces, Figures 16 to 19(C), show an average increase for all tSCS conditions with respect to passive cycling, underlining that the positive phase in the active force during the pulling section of the revolution overcomes the negative phase at the push. The mean active force reveals similar values for all frequencies and no consistent difference between the tSCS+voluntary conditions and the tSCS-only ones. In subject 01, the 20 and 50Hz stimulations score slightly higher than the 80Hz tSCS, which remains around the passive level, with no consistent difference between tSCS only and the stimulation combined with voluntary intent. In subject 02 the 20 and 80Hz frequencies show a similar behavior, with the 50Hz scoring slightly higher and slightly lower in the first and second trials respectively.
While data for subjects 01 and 02 do not suggest noticeable motor facilitation during the stimulation, mean force data shows a promising preliminary result.

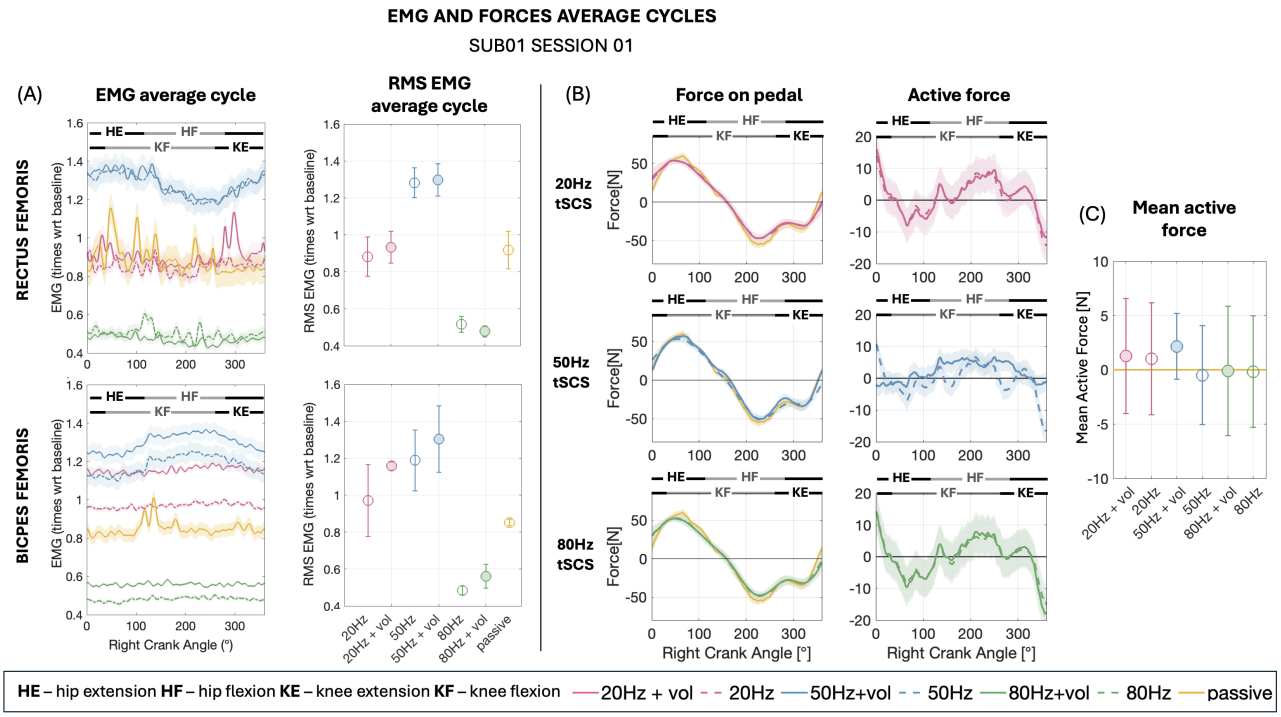

Figure 16: EMG and forces results for Subject 01 in the first session

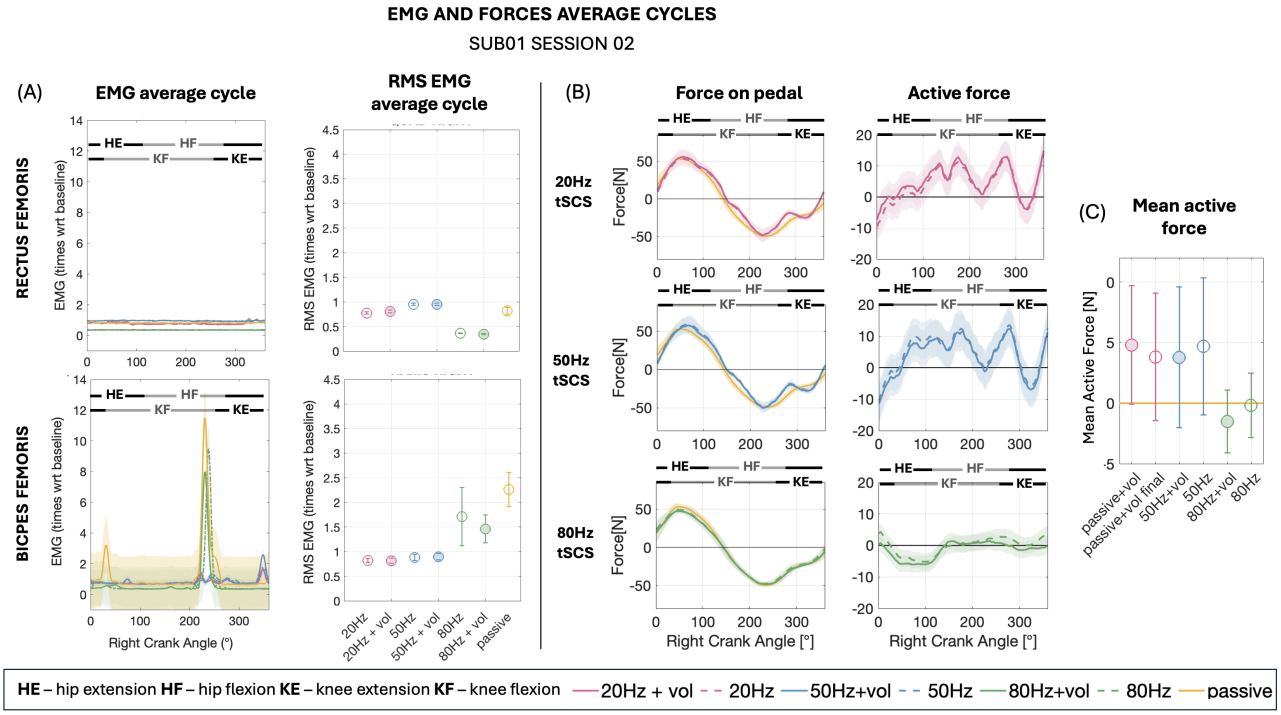

Figure 17: EMG and forces results for Subject 01 in the second session

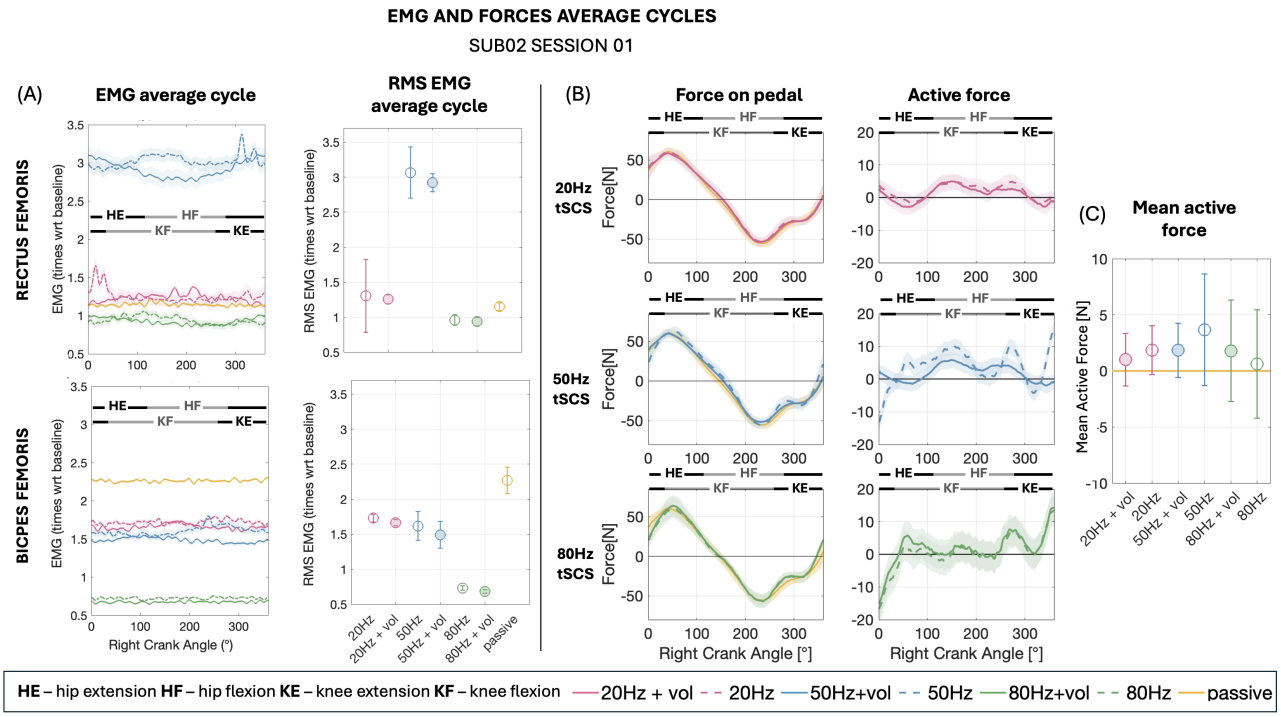

Figure 18: EMG and Forces results for Subject 02 in the first session

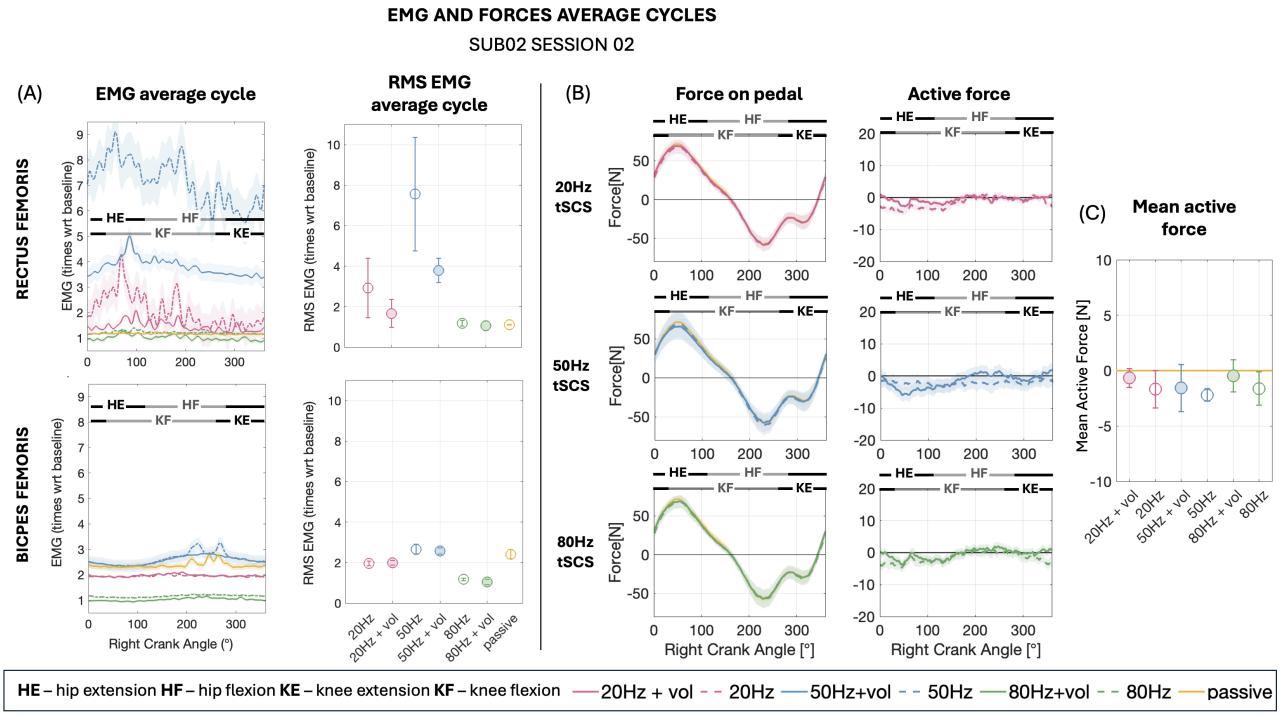

Figure 19: EMG and Forces results for Subject 02 in the second session

Case Study 02

Results for subjects 03 and 04 are reported in Figures 20 to 22 and considered in the discussion of the second *Case Study*'s results. Panels in the figure are organized as for the *Case Study 01*.
Subject 03 presents a passive EMG activation around the baseline in the rectus femoris, with the 80Hz stimulation moderately reducing it and the 20 and 50Hz tSCSs slightly amplifying or reducing it with opposite behaviours in the two trials, Figures 20(A) and 21(A). In addition, 50Hz stimulation introduced a clear cyclic component. While this behaviour is similar to the first *Case Study*, that on the biceps femoris reveals the critical

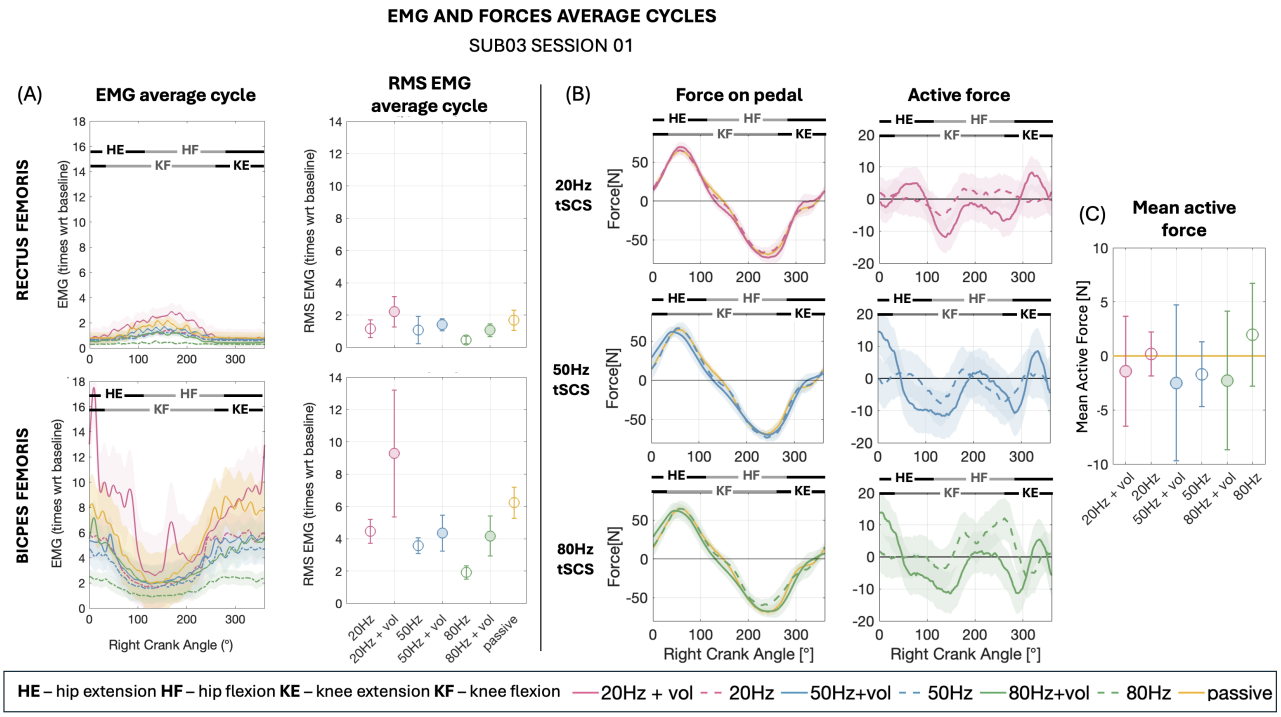

Figure 20: EMG and Forces results for Subject 03 in the first session

difference between the two groups. The EMG on the right biceps femoris shows a significant cyclic activation with amplitude up to 18 times the baseline, both during the passive- and the stimulation-cycling conditions. The stimulation did not affect the cyclic pattern and slightly modulated the amplitude, while the addition of volitional effort amplified the activation with respect to the same stimulation alone. A similar behaviour was observed on the left biceps femoris and in both the right rectus and biceps femoris of subject 04, Figure 22(A). Rectus femoris activation in participant 04 revealed a clear cyclic activation between 100° and 200° up to 20 times the baseline, which was significantly reduced amplitude by the stimulation, around 5 times the baseline. The participant has a minimum motor residual ability on the right leg, so passive trials with the addition of the voluntary effort were performed twice, before and after the *tSCS cycling* blocks (black dashed lines in Figure 22(A). In both muscles, the passive+voluntary trials caused an increased amplitude in the cyclic activation. A comparison of these cyclic activations of the knee and hip extension and flexion ranges revealed that they were not in phase with an expected physiological cycling contraction during trike cycling. To double-check the physiological muscle activity in the precise cycling setting, we collected EMG data during a healthy subject's voluntary cycling on the same trike. This was compared to subjects 03 and 04's cyclic activations, Figure 23, confirming that the participants' contractions were not in phase with the cycling activity and hence probably not caused by a cooperation to the movement. Thus, we supposed that, given the muscle hypertonia of the two subjects, the observed cyclic contractions were not functional to the movement but were rather caused by the stretch reflex during hip extension. The spinal stimulation did not seem to affect such activations in terms of temporal characteristics but only in terms of amplitude.

Compared to *Case Study 1*, the force values show significant oscillations around the passive mean force cycle, suggesting moments of greater cooperation with the movement alternated with phases of resistance. In particular, greater oscillations were observed in subject 03 when the stimulation was combined with voluntary intent of movement, while during tSCS alone, oscillations were similar to those of subject 02, Figures 20(B) and 21(B). Cooperation during the final pulling phase is present for all frequencies, aligning these results with those of *Case Study 01*. On the other hand, in the trials with the volitional intent addition, the subject also cooperates at around 50° during the pushing phase, with a distinct increase in the active force. This underlines spinal stimulation's potential of amplifying residual volitional signals and lays out promising perspectives.

A similar behaviour was observed in subject 04, where the stimulation remarkably increased the force on the right pedal compared to the passive setting. In particular, subject 04 cooperates well at the end of the pushing phase of the cycling revolution, between 100° and 200°. The passive trials combined with the voluntary intent (black in Figure 22(B)) before and after the stimulation caused an opposing active mean force, suggesting that the addition of voluntary intent in the absence of stimulation caused resistance to the pedalling. However, the post-tSCS trial scored better than the initial one while still slightly negative, suggesting some tSCS-related improvements. Forces on the right pedal during stimulation cycling blocks increased significantly

over the passive reference for all frequencies, with no consistent difference between the tSCS-only sessions and those with tSCS combined with the voluntary intent. While this observation is not consistent among subjects, results from subject 04 suggest that the reduction of the cyclic activation, here identified as a stretch reflex, has a beneficial effect on the motor outcome. Indeed, EMG data shows higher activation during passive and passive+voluntary trials, whose respective active forces are lower compared to those during the stimulation.

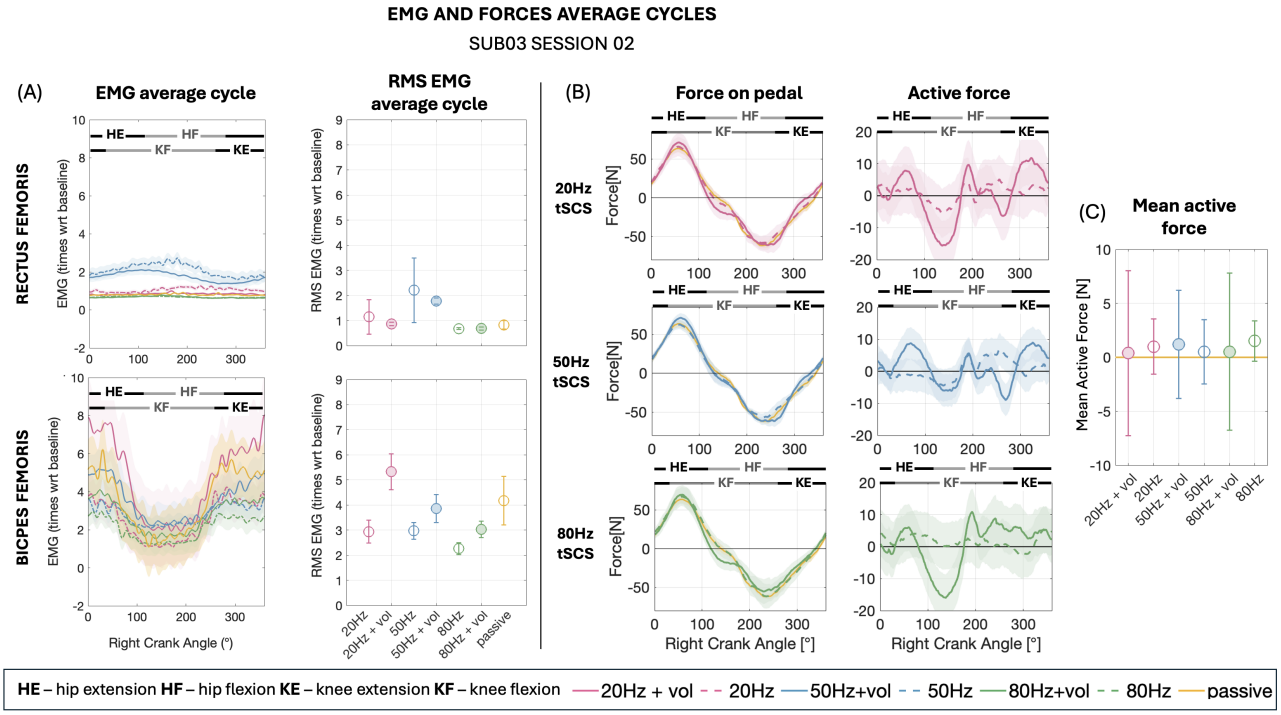

Figure 21: EMG and Forces results for Subject 03 in the second session

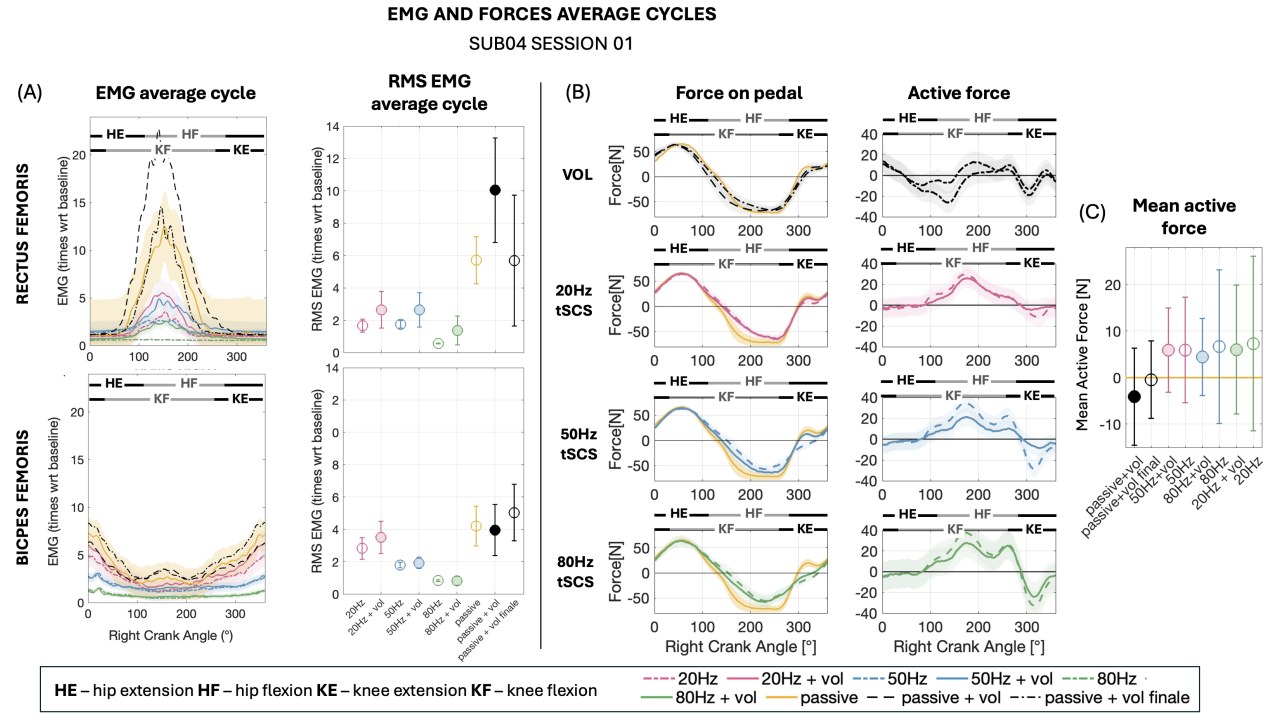

Figure 22: EMG and Forces results for Subject 04 for his only session

On the other hand, the increase of active force with the addition of voluntary intent in the pushing phase was followed by a resistance (negative active force) at the end of the pushing phase (100-200°) for both subjects 03 and 04. As for the positive phase, the oscillation was augmented significantly by the voluntary intent addition, compared to the stimulation alone, for all stimulation frequencies, suggesting that the residual volitional signals may not be cooperative to the movement during the entire cycling revolution, at least not during these preliminary trials.
These results suggest a tSCS-related amplification of the residual motor ability of the subject, as well as the benefits on hypertonia decrease, in the reduced EMG amplitude during tSCS cycling, which was likely causing resistance to movement in the passive setting.

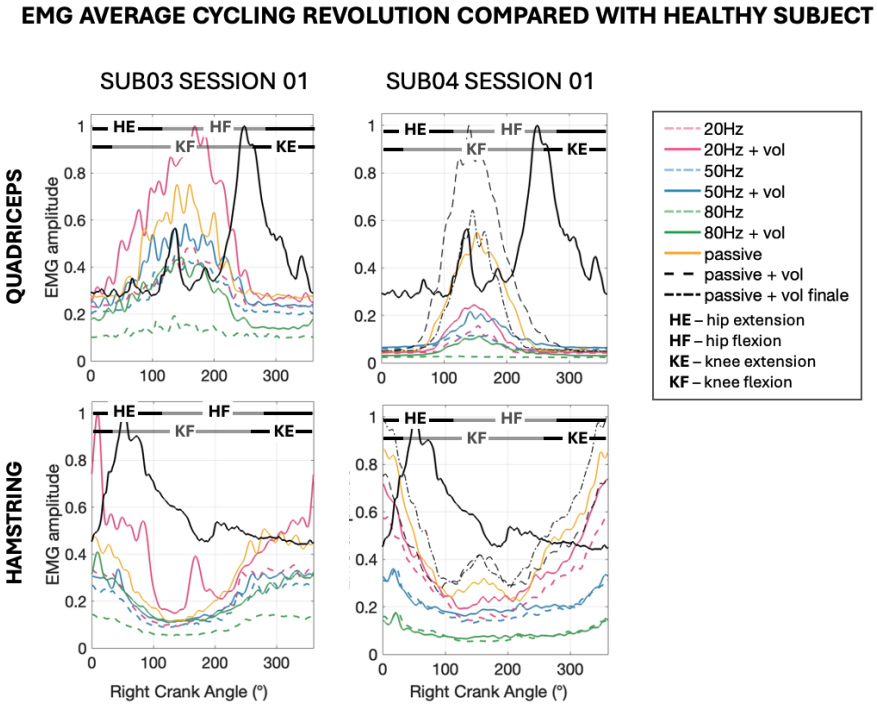

Figure 23: EMG temporal trend comparison between subjects 03 and 04 with a healthy subject activation (black). EMG values are normalized for each subject and muscle to the maximum value during the average cycle. Hence, the amplitude comparison between the physiological control and the study's participants is not valid.

4.5. Secondary effects of tSCS

Participants were asked for feedback 24/48 hours after the stimulation session. No one reported any discomfort or negative feelings following the stimulation. On the other hand, lower limb rigidity and bladder- and bowel-related benefits were reported. While not strictly related to the motor facilitation aim of the study, these non-motor effects are worth mentioning.
All subjects reported feeling their legs heavy and tired after the stimulation session, a feeling similar to that caused by FES-cycling. Subject 04, who has not used FES-cycling, communicated that this feeling is not common after his swimming exercise. Subject 01 reported intestinal benefits, with a significantly reduced bowel evacuation time the day after the stimulation. Similarly, subject 02 regained bladder sensibility for 5-7 days after the stimulation. He reported that the feeling of a full bladder was accurate as it effectively corresponded to significant urine evacuations. He also communicated bowel sensibility after the second stimulation session.
Subjects 02, 03 and 04 reported reduced lower limb muscle rigidity for 48 hours after the spinal stimulation session. Subjects 02 and 03 communicated not having to stretch their legs in the morning, as usual. Subject 03 reported feeling the legs heavy and tired the hours immediately after tSCS cycling and reduced spasticity and clonuses for the next couple of days. As the literature analysis highlights, tSCS for spasticity reduction has been investigated, and its benefits have been proven in the past years [14, 16]. Hofstoetter et al. [15] reported improved spasticity metrics 2h after a 30-minute tSCS session and a carry-over effect up to 7 days after the stimulation.
The reported non-motor effects of SCS offer new perspectives for further research. In particular, the bladder and bowel benefits are promising as they could significantly impact the daily activities of subjects with SCI.

5. Conclusions

Spinal Cord Injury (SCI) can lead to the loss of movement control in the upper and lower limbs, significantly reducing the independence of the affected subjects. Spinal Cord Stimulation (SCS) has emerged in the past decades as a SCI motor-rehabilitation technique, showing reinstatement of volitional motor control in previously completely paralyzed subjects in its epidural, invasive version. Transcutaneous Spinal Cord Stimulation (tSCS) is a non-invasive, accessible, cost-effective alternative to the epidural approach. Despite significantly lacking selectivity, tSCS has shown promising results and high efficacy in SCI neurorehabilitation. While most of the SCI motor-rehabilitation research is focused on walking-based protocols, passive cycling removes the weight-bearing- and falling-related risks of walking and has shown beneficial changes across cardiovascular, musculoskeletal, and neurological systems in individuals with SCI.

We delivered an integrated tSCS and trike-based cycling protocol to four complete and incomplete SCI participants to evaluate the stimulation's motor-facilitating effects during pedalling. We also evaluated a combination of tSCS and volitional effort to determine the potential contribution of volitional signals to the movement.

Our trials demonstrated the feasibility of the proposed protocol and setup. The subjects tolerated the stimulation well and did not experience any discomfort during trike cycling. While our results are preliminary and do not reflect the significant motor improvements reported in the literature, they have to be contextualized to the low number of trials performed. Indeed, studies showing improved motor abilities during and after the stimulation in complete and incomplete SCI subjects reported motor benefits after weeks of SCS sessions.

Although preliminary, our results show that tSCS modulates muscle activation during movement, both amplifying and reducing it, depending on muscle groups and subjects. In addition, force data shows no direct correlation between higher muscle activation and improved forces during cycling. In one subject, stimulation combined with volitional effort improved force during pedalling compared to stimulation alone, highlighting SCS's potential amplification of residual volitional signals. EMG data showed a stretch reflex during cycling in participants with hypertonia, which was often reduced in amplitude by the stimulation, improving the motor outcome with increased force on pedals and underlining the spasticity-related benefits of SCS.

In the days following the stimulation, participants communicated reduced lower-limb rigidity and spasticity, reduced bowel-evacuation time, and regained bladder sensitivity, revealing interesting side benefits to the motor-oriented protocol.

The study has some limitations, mainly caused by the small number of participants recruited and trials conducted and the absence of long-term evaluations. Overall, the results discussed showed that tSCS combined with cycling is a feasible approach for SCI motor rehabilitation and carries multiple interesting side benefits. Future work should explore cycling-based tSCS motor rehabilitation and evaluate the motor-facilitating effects of longer protocols during and after stimulation.

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			Category 1: SCS hardware			
Study	**DOI**	**Year**	**Device name, manufacturer, model and software**	**Electrode manufacturer, product number and size**	**Material and size of handmade electrodes**	**Application**
Murray et al.	10.1371/journal.pone.0213696	2019	constant current stimulator (DS7A, Digitimer, UK) triggered by Spike 2 scripts (Cambridge Electronics Design Ltd., UK)	self adhesive electrodes, all: 10.2 × 5.1 cm2 (Uni-PatchTM EP84169, MA, USA)	/	SCI motor
Moon et al.	10.3390/brainsci11030289	2021	custom-built constant current stimulator (BioStim-5, Cosyma, Moscow, Russia)	cathode: 3.2cm ø (ValuTrode, Axelgaard Ltd., Fallbrook, CA, USA), anode: 7.5 × 13 cm,(UltraSim, Axelgaard Ltd., Fallbbrook, CA, USA)	/	Post-stroke PRM study
Pinter et al.	10.1038/sj.sc.3101040	2000	implanted, programmable pulse generator (Itrel 3, Medtronic)	quadripolar electrode (3487A, Medtronic) to allow both bipolar and monopolar stimulation	/	SCI spasticity
Atkinson et al.	10.1152/jn.00456.2021	2023	constant current stimulator (DS8R; Digitimer Ltd., Welwyn Garden)	cathodes: 5cm ø, anode cervical: 5x9cm, anode lumbar: oval 7.5x13cm, all electrodes: PALS; Axelgaard Manufacturing,	/	tSCS study
Fleming et al.	10.3390/biomedicines11020332	2023	constant current stimulator (DS8R; Digitimer Ltd., Welwyn Garden)	3x3 cathode matrix (ø 3.2 cm2; Axelgaard, Fallbrook, CA), anode: 5 × 10 cm; Axelgaard, Fallbrook, CA)	/	tSCS study
Dalrymple et al.	10.1088/1741-2552/acabe8	2023	/	adhesive electrode for tSCS - cathode: 3.2 cm Ø, anode: 7.5 × 13 cm (ValuTrode, Axelgaard Manufacturing Co. Ltd, USA)	/	tSCS study
Bryson et al.	10.1088/1741-2552/ace552	2023	constant current stimulator (DS8R, Digitimer Ltd., UK)	cathode conventional : 5x9 rectangular, cathode multielectrode: six 3.2 Ø, anode: 7.5x10cm	/ /	tSCS study
Danner et al.	10.1371/journal.pone.0147479	2016	current-controlled stimulator (Stimulette r2x+, Dr.Schuhfried Medizintechnik GmbH, Vienna, Austria)	cathode: 3 interconnected silver-silver chloride electrodes (1 cm Ø, T-60, Leonhard Lang GmbH, Innsbruck, Austria), anode: 8x13 cm, STIMEX, schwa-medico, Ehringshausen, Germany	/	tSCS study
Inanici et al.	10.1109/TNSRE.2021.3049133	2021	experimental device developed by NeuroRecovery Technologies Inc. (now ONWARD Medical BV, Eindhoven, Netherlands).	cathodes: 2.5 cm Ø, anodes: two 5x10 cm rectangular (Axelgaard Manufacturing Co., Ltd., USA)	/	SCI motor
Inanici et al.	10.1109/TNSRE.2018.2834339	2018	NeuroRecovery Technologies Inc. (now ONWARD Medical BV, Eindhoven, Netherlands).	cathodes: 2.5 cm Ø, anodes: two 5x10 cm rectangular (Axelgaard Manufacturing Co., Ltd., USA)	/	SCI motor
Barss et al.	10.3390/jcm11030639	2022	constant current stimulator (NEOSTIM-5, Cosyma Ltd., Moscow, Russia)	cathodes: two 2.5 cm Ø round (Axelgaard); anodes: two 5x10cm rectangular (Axelgaard)	/	study tSCS nueromodulation
Hoover et al.	10.1089/NEU.2022.0322	2023	implanted, not specified, see ESTAND trials infor	/	implanted, not specified, see ESTAND trials infor	SCI
Angeli et al.	10.1016/j.pneurobio.2017.10.004	2014	epidural spinal cord stimulation unit (Medtronics, RestoreADVANCED)		16-electrode array implanted	
Hofstoetter et al.	10.1371/journal.pone.0192013	2018	Stimulette r2x+, Dr. Schuhfried Medizintechnik GmbH, Moedling, Austria	anode: Ø 5cm, cathode: 8x13cm both by (Schwa-medico GmbH, Eringshausen, Germany)	/	PRM reflex study
Hofstoetter et al.	10.1371/journal.pone.0227057	2019	Stimulette r2x+, Dr. Schuhfried Medizintechnik GmbH, Moedling, Austria	self adhesive, anode: 5x9cm, cathode: wo 8x13cm interconnected	/	PRM reflex study

Parhizi et al.	10.3389/fnins.2021.615103.	2021	constant current stimulator (NEOSTIM-5, Cosyma Ltd., Moscow, Russia)	cathodes: two 2.5 cm Ø (Axelgaard); anodes: two 5x10cm rectangular (Axelgaard)	/	Combined cervical and lumbar tSCS
Zheng et al.	10.1088/1741-2552/ab8f6f	2020	multichannel stimulator (Multichannel System, Reutlingen, Germany) controlled with custom MATLAB GUI		12 gel based electrodes, each 1x2 cm rectangle. 9 used as anode in 3x3 matrix	tSCS cervical investigation
Powell et al.	doi: 10.1038/s41591-022-02202-6	2023	/	/	two linear electrodes implanted mediolaterally spanning dorsal roots (C4-T1)	Post-Stroke motor
Minassian et al.	10.1177/1545968315591706	2016	stimulator DS7AH, Digitimer Ltd, Hertfordshire, England and pulse generator (DG2A, Digitimer Ltd)	anode: Ø 5cm diameter, cathode: 8x13cm both by (Schwa-medico GmbH, Eringshausen, Germany)	/	SCI motor
Minassian et al.	10.1002/mus.20700	2007	/	anode: Ø 5 cm (TENS), cathode: 8x13cm both by (Schwa-medico GmbH, Eringshausen, Germany)	/	/
Phillips et al.	10.1089/neu.2017.5082	2018	/	self adhesive, anode: Ø 30 mm (Value Trode), cathode: 5x9cm (Value Trode)	/	SCI CV normalization
Hofstoetter et al.	10.1179/2045772313Y.0000000149	2014	constant voltage stimulator, not specified which	self adhesive electrodes two Ø 5cm and two 8x13cm (Schwa-medico GmbH, Eringshausen, Germany). Both pairs connected together to function as larger electrodes	/	SCI spasticity
Chandrasekaran et al.	10.3389/fnins.2023.1210328	2023	microcontroller (Texas Instruments class-D amplifier TAS5825P in voltage mode) + 12:1 step-up transformer (Xicon 42TM003-RC). Controlled with MATLAB based GUI	anode: 5x10cm self adhesive hyfrogel electrodes (Axelgaard Manufaturing Co., Ltd, USA)	cathode: Flexible PCB electrode array - electroless nickel immersion gold (ENIG) or immersionsilver plated square contacts (10x10mm) in a 8x5 pattern with 11 mm center-to-center electrode separation	SCI motor
Gerasimenko et al.	10.1016/j.rehab.2015.05.003	2015	/	cathodes: Ø 2.5(Leak-Lok, Sandpoint, US), anodes: 5x10.2cm (Ambu, Ballerup, Germany)	/	SCI motor
Pena Pino et al.	10.3389/fnsys.2020.00035	2020	subcutaneous placement of a primary cell internal pulse generator (IPG) (Tripole and Proclaim Elite, Abbott, Plano, TX, United States), and self developed software given to patients to control the stimulator	/	multilectrode array, 16-contact paddle	SCI motor
Hofstoetter et al.	10.1111/aor.12615	2015	constant-voltage stimulator	self-adhesive stimulating electrodes - anode: Ø = 5 cm - cathode 8x13 cm (Schwa-medico GmbH, Ehringshausen, Germany)	/	SCI motor
McHugh et al.	10.1038/s41394-020-00359-1	2020	Vectra Neo (Chattanooga; Hixson, TN)	cathode 5x5cm oval, anodes 7.5x13 rectancular	/	SCI motor
Meyer et al.	10.3390/jcm9113541	2020	RehaMove 3.0, Hasomed GmbH	cathode 5 × 9 cm, anode 7.5 × 13 cm; RehaTrode, Hasomed GmbH, Magdeburg, Germany		SCI motor
Wagner et al.	10.1038/s41586-018-0649-2	2018	implantable pulse generator - Medtronic IPG Activa RC and self-delveloped mobile app for control during activity	/	multielectrode array, 16 electrodes paddle with 10 mm	SCI motor
Monterosso thesis		2023	RehaMove Pro, Hasomed GmbH	self adhesive electrodes 5x5cm^2 (PALS, Axelgaard Manufacturing Co., Ltd, Fallbrook, CA, USA)	/	Post-stroke motor

			Category 2: SCS characteristics										
Study	**DOI**	**Year**	**Frequency**	**Cathode Placement**	**Anode Placement**	**Intensity**	**Waveform**	**PW**	**Intensity Threshold**	**Carrier Waveform**	**Temporal Characterisics**	**Charge-balance**	**Phase-duration & inter-pulse**
Murray et al.	10.1371/journal.pone.0213696	2019	0.2Hz	one, covered from T10 to L1-L2 vertebral levels (L1 and S2 spinal segments)	two, bilaterally over iliac crests	alternated suprathreshold stimulation (15-min for SCI group) that evoked	monophasic rectangular	1ms	stimulation that evoked bilateral leg extension	/	continuous	unbalanced (monophasic)	/
Moon et al.	10.3390/brainsci11030289	2021		one medially between the L1 and L2 spinous processes (L5–S5 spinal segments)	symmetrically over the anterior superior iliac spines	5 mA increments, increasing from 5 mA to threshold	rectangualr monophasic	1ms	minimum between 250 mA and the subject's maximum tolerance	/	single pulses delivereed 3 times at 5s intervals for each current	unbalanced (monophasic)	/
Pinter et al.	10.1038/sj.sc.3101040	2000	50-100Hz	quadripolar electrode implanted T11-L1 vertebral levels, final position determined by evoking muscle twitches during surgicla procedure. four contacts were used in pairs (cathode, anode)		1-10V	biphasic and monophasic	/	/	/	/	balanced when biphasic	/
Atkinson et al.	10.1152/jn.00456.2021	2023	/	midline (cervical) betwen C5-C6 + (lumbar) between T11-T12	(cervical) anterior aspect of the neck + (lumbar) symmetrically to the lumbar cathodewith respect to the saggital plane over the abdomen	from 30mA to observed muscle response	square	1ms	muscle response	/	double pulse (two 1ms pw) every 6 s, continuous	not specified but seems monophasic	50ms between pulses in the double pulse
Fleming et al.	10.3390/biomedicines11020332	2023	0.25 Hz	3x3 cathode matrix, centrally over c5-c6, c6-c7 and c7-t1 intervertebral spaces and ~3.2 cm laterally on either side	on neck at the same height as the cathode	RMT and RMT+20%, with 5mA increases from 10mA to threshold	monophasic rectangular	1ms	minimum between 80mA and maximum tolerance	/	three paired pulses	unbalanced (monophasic)	50ms between three paired
Dalrymple et al.	10.1088/1741-2552/acabe8	2023	/	two paravertebrally left of the T12-L1 spinous processes	one on left anterior superior iliac spine	15 amplitudes between 5 mA below the PRM reflex threshold and 5–10 mA above the maximum amplitude,	convetional is monophasic, carrier is biphasic	1ms	minimum between 5-10 mA over PRM threshold and180mA	half the time: 10 kHz pulse, 50% DC	stimuli 10s apart and repeated each stimulation 4 times	balanced when carrier, unbalanced when no carrier	0.1ms when carrier
Bryson et al.	10.1088/1741-2552/ace552	2023	/	two on abdomen bilaterally interconnected	conventional: rectangular electrode over T11/T12 central multielectrode: six round electrodes 3cm lateral to the midline centered at T11-T12 interspinous ligament, 1 cm distance between them	from 5 mA below the motor threshold to the saturation amplitude, with 8 steps	biphasic	2ms	minimum between saturation (no longer saw an increase in response amplitude of the first recruited muscles) and the maximum amplitude	/	single pulses	balanced (biphasic)	1ms phase duration, 33.3ms interpulse
Danner et al.	10.1371/journal.pone.0147479	2016	/	Three interconnected between the T11 and T12 inter-spinous processes. central electrode was medially placed and the other two left and right (2 cm distance)	lower abdomen, two interconnected forming a medially positioned transversely oriented 16x13 cm reference electrode.	5-mA increments from 5 mA up to 125 mA or threshold	rectangular symmetric	1ms	maximal tolerable level by participants	/	single and paired pulses	balanced (biphasic)	30ms interpulse in the paired pulses
Inanici et al.	10.1109/TNSRE.2021.3049133	2021	30Hz	two, symmetrically over the anterior iliac crests	two on neck midline, one above and one below the injury level with the guidance of the occipital inion and spinous processes as landmarks	from 0 to 120mA, 5mA increments up to subthreshold level	biphasic or monophasic, rectangular	1ms	feedback from participant about which intensity made the task easiest (usually 40-90mA).	10kHz	continous	both biphasic and monophasic (compared)	from frequency, 32 ms
Inanici et al.	10.1109/TNSRE.2018.2834339	2018	30Hz	midline at C3-4 and C6-7 bony landmarks	two, symmetrically over the anterior iliac crests	increased in 10 mA intervals from 10 to 120 mA	biphasic or monophasic, rectangular	1ms		10kHz	continous	biphasic	/
Barss et al.	10.3390/jcm11030639	2022	30Hz	midline (cervical) C3-C4 and C6-C7 + (lumbar) T11 and L1	two bilaterally over iliac crests for cervical stimulation and two lumbar bilaterally for lumbar stimulation	threshold	biphasic square	1ms	tolerability	5kHz	continuous	balanced (biphasic)	/
Hoover et al.	10.1089/NEU.2022.0322	2023	/	lumbar implanted within the ESTAND trial, not specified		/	/	/	/	/	/	/	/
Angeli et al.	10.1016/j.pneurobio.2017.10.004	2014	25-30Hz	implanted at T11-T12 vertebral levels (spinal cord segments L1-S1)		set to optimal for subject	/	/	/	/	/	/	/
Hofstoetter et al.	10.1371/journal.pone.0192013	2018	/	two on abdomen bilaterally interconnected	paraspinally T11 and T12 spinous processes	threshold	biphasic rectangular symmetrical	1ms	'common threshold': responses with peak-to-peak amplitudes 100 µV in all muscle groups, or max tolerability	no	three paired pulses	balanced (biphasic)	interpulse 50ms

Hofstoetter et al.	10.1371/journal.pone.0227057	2019	/	two on abdomen bilaterally interconnected	one covering T11 and T12 spinous processes	threshold	biphasic rectangular symmetrical	1ms	PRM induction	no	series of double pulses	balanced (biphasic)	20, 40, 60, 80, 100, 120, 150, 200, 250, 300, 500, 1000, 2000,
Parhizi et al.	10.3389/fnins.2021.615103.	2021	30Hz	midline (cervical) C3-C4 and C6-C7 + (lumbar) T11 and L1	two bilaterally over iliac crests for cervical stimulation and two lumbar bilaterally for lumbar stimulation	1 to 5mA increments up to tolerability	biphasic square	1ms	tolerability	10kHz biphasic	continuous	balanced (biphasic)	/
Zheng et al.	10.1088/1741-2552/ab8f6f	2020	120, 30 Hz, in separate trials	area of midsaggital plane from C5 to T1	1x3 array placed above the clavicle about 6 cm from the midsaggital plane	5.32 +- 1.70 mA (for 120Hz) and 6.13 +-1.90 mA (for 30 Hz)	rectangualr monophasic	600 µs	set so that moderate or strong joint movements can be elicited	/	15x3s stimulation trains delivered in each trial, 2s resting between trains	unbalanced (monophasic)	/
Powell et al.	doi: 10.1038/s41591-022-02202-6	2023	60 Hz (sub. 1); 50-100 Hz (sub.2)	C3-C7 implanted lateral, near dorsal root entry zone		2.4-6.2 mA (sub.1); 4.2-5.9 mA (sub.2)	square symmetrical	200 µs (sub. 1); 400 µs (sub. 2)	/	/	continuous	balanced (biphasic)	/
Minassian et al.	10.1177/1545968315591706	2016	single pulse or 30Hz	lower abdomen	paraspinally 1cm apart on T11-T12 interspinous space	5mA increments	rectangular monophasic	1ms	up to highest PRM threshold among muscles	/	bursts length limited since unbalances	unbalanced (monophasic)	/
Minassian et al.	10.1002/mus.20700	2007		two on anterior abdomen, symmetrically to umbilicus	paraspinally 1cm apart on T11-T12 and L4-L5 interspinous space	0 to 50V, 1V increase for interval	rectangular symmetric	2ms		no	3 individual stimuli at 5s intervals	balanced (biphasic)	50ms interstimulus interval
Phillips et al.	10.1089/neu.2017.5082	2018	30Hz	two, symmetrically over the anterior iliac crests	between T7 and T8 spinal spinous processes (~ T8 spinal segment)	10-70mA	rectangular monophasic	1ms	blood pressure normalized	no	continuous	unbalanced (monophasic)	/
Hofstoetter et al.	10.1179/2045772313Y.0000000149	2014	50Hz	two on anterior abdomen, symmetrically to umbilicus, then connected	two, paraspinally on T11 and T12 spinal processes, then connected	from 0 to threshold	rectangular biphasic	2ms	Inducing parasthesia	no	continuous	balanced (biphasic)	1ms phase duration
Chandrasekaran et al.	10.3389/fnins.2023.1210328	2023	50Hz	5x8 electrode array on cervical segments	two on lumbar spinal cord (return electrodes)	from 0 to threshold		0.5 ms	maximal tolerable level by participants (usually ~ 140-160mA)	10kHz biphasic sinusoidal	continuous	balanced (biphasic)	/
Gerasimenko et al.	10.1016/j.rehab.2015.05.003	2015	5-40Hz	C5, T11, L1 spinous processes	two symmetrically on iliac crests (return electrodes)	30-200 mA	biphasic rectangular	0.3-1ms	/	10kHz biphasic	/	balanced (biphasic)	/
Pena Pino et al.	10.3389/fnsys.2020.00035	2020	16-400 Hz	implanted T11–T12 spinal processes, multielectrode paddle (configured with cathodes inferiorly, anodes superiorly)		2-15mA	/	200-500 µs	maximal volitional movement while supine	no	/	/	/
Hofstoetter et al.	10.1111/aor.12615	2015	30Hz during treadmill stepping	two on lower abdomen (paraumbilically)	paraspinally on T11 and T12 spinal processes	not specified	rectangular symmetric	1ms	to produce paresthesias covering most of the lower limb dermatomes as perceived by the subjects, yet sub-threshold for leg muscle activation.	no	continous	balanced (biphasic)	/
McHugh et al.	10.1038/s41394-020-00359-1	2020	50Hz (preferential for spasticity)	two on lower abdomen	midline on T11-T12 spinal processes	20-80mA	rectangular symmetric	1ms	in each session set to individual tolerance or submotor threshold, whichever was less	no	continous	balanced (biphasic)	20ms
Meyer et al.	10.3390/jcm9113541	2020	15, 30, 50 Hz	two on lower abdomen	T11-T12 spinal processes, longitudinally over spine	/	rectangular symmetric	1ms	/	no	continous	biphasic	30, 50 , 120 ms
Wagner et al.	10.1038/s41586-018-0649-2	2018	20, 25, 30, 40, 60, 80, 100 Hz	L1-S2 multielectrode array		not specified (order of magnitude 1-10mA)	square	/	defined for each region ny analyzing EMG signal, to have ax selectivity	no	continuous during activation of selected area	1ms	/
Monterosso thesis		2023	50Hz	midline T11-T12	midline L2-L3	from 5mA to max tolerability in 5mA increments	biphasic rectangular	1ms	tolerability	/	5 minutes continuous stimulation	balanced (biphasic)	20ms

			Category 3: SCS intervention											
Study	**DOI**	**Year**	**Delivery method**	**Session Duration**	**Sessions per Week**	**Total Sessions**	**Adjunct therapy**	**Open or closed loop**	**Adverse events**	**Target function**	**Participant position**	**Edits to treat. plan**	**Environmental setting**	**Program adherence**
Murray et al.	10.1371/journal.pone.0213696	2019	Transcutaneous	60 ± 2 mins	5	16.6 ± 1	/	open	none	evaluate the effects of tSCS on motoneuron output of multiple segments of the spinal cord in SCI subjects	supine			
Moon et al.	10.3390/brainsci11030289	2021	Transcutaneous	/	/	/	/	open	/	evaluate PRM reflex evoked by lumbosacral tSCS in post-stroke chronic subjects	supine	/	Lab, supervised	/
Pinter et al.	10.1038/sj.sc.3101040	2000	Epidural	/	/	/	anti-spasticity medication prior and during treatment	open	/	evaluate SCS effect on spasticity reduction in SCI subjects	/	/	Lab, supervised	/
Atkinson et al.	10.1152/jn.00456.2021	2023	Transcutaneous	/	/	/	/	Open	/	test effects of combined cervical and lumbar tSCS on motor facilitation vs nerve stimulation and no stimulation	/	/	Lab, supervised	/
Fleming et al.	10.3390/biomedicines11020332	2023	Transcutaneous	/	/	/	/	Open	low back pain in one subject, probably unrelated	Investigate controlateral selectivity of upper-limb motor pools with cervical tSCS	sitting	/	Lab, supervised	/
Dalrymple et al.	10.1088/1741-2552/acabe8	2023	Transcutaneous	/	/	/	/	Open	/	determine the efficacy of a high frequency carrier in tSCS, concludes that it's not reccomended	sitting	/	Lab, supervised	/
Bryson et al.	10.1088/1741-2552/ace552	2023	Transcutaneous	/	/	/	/	Open	/	investigate the selectivity of conventional single electrode and multi-eletrode arrays approaches	supine	/	Lab, supervised	/
Danner et al.	10.1371/journal.pone.0147479	2016	Transcutaneous	/	/	/	/	open	/	study the influence of body position on the tSCS elicited PRM reflex, on healthy subjects	supine, standing and prone	/	Lab, supervised	/
Inanici et al.	10.1109/TNSRE.2021.3049133	2021	Transcutaneous	up to 120 mins	not specified	4 weeks by two times (8 in total)	Intensive functional task training both before and during stimulation	Open	only mild allergic rash on patient with dermatitis history	upper limbs rehabilitation in SCI subjects, with combined cervical tSCS and intensive training	sitting	/	Lab, supervised	Participant 1 was unavailable during the third month of follow-up
Inanici et al.	10.1109/TNSRE.2018.2834339	2018	Transcutaneous	60 ± 20 minutes	4-5	1451 min over 5 weeks	standard stretching, active assistive range of motion exercises, and intensive gross and fine motor skill training	Open	none reported	upper limbs rehabilitation in SCI subjects, with combined cervical tSCS and intensive training and study of tSCS-induced neuroplasticity	sitting	/	Lab, supervised	
Barss et al.	10.3390/jcm11030639	2022	Transcutaneous	/	/	/	leg and arm cycling	open	/	investigate the neuromodulation of cervical and lumbar combined tSCS during cyclic movements	sitting on cycloergometer	/	Lab, supervised	/
Hoover et al.	10.1089/NEU.2022.0322	2023	Epidural	8 minutes	1 per month	/	cycling on active/passive cycloergometer	open	none reported	combined eSCS and cycling activity for lower limbs motor rehabilitation in complete SCI	sitting on wheelchair	/	Lab, supervised	/
Angeli et al.	10.1016/j.pneurobio.2017.10.004	2014	Epidural	/	/	long protocol with pre and post implantation	training with BWS for 80 sessions before SCS	open	/	neuromodulate the spinal cord with eSCS in complete SCI subjects to facilitate movement	various depending on activity	/	Lab and home	/
Hofstoetter et al.	10.1371/journal.pone.0192013	2018	Transcutaneous	/	/	/	/	Open	/	study of PRM eliciting from lumbar posterior roots tSCS	supine	/	Lab, supervised	/
Hofstoetter et al.	10.1371/journal.pone.0227057	2019	Transcutaneous	/	/	/	/	Open	/	Study the recovery cycles of PRM reflex elicited by lumbar tSCS	supine	/	Lab, supervised	/

Parhizi et al.	10.3389/fnins.2021.615103.	2021	Transcutaneous	/	/	/	Leg cycling and one arm cycling during tSCS	Open	/	determine the effect of cervical, lumbar, or combined tSCS on spinal reflex and corticospinal excitability during a static or cycling cervico-lumbar coupling task.	sitting on cycloergometer	/	Lab, supervised	/
Zheng et al.	10.1088/1741-2552/ab8f6f	2020	Transcutaneous	/	/	/	subjects asked to naturally flex the wrist and elbow joints before sstimulation started	Open	/	Elicit arm and hand motion by cervical tSCS in healthy subjects	sitting	/	Lab, supervised	/
Powell et al.	doi: 10.1038/s41591-022-02202-6	2023	Epidural	4 hours	5	29	task oriented therapy	Closed (EMG based)	None	eSCS to facilitate arm and hand motor control in post-stroke hemiparesis	Seated and supine	/	Lab, supervised	All sessions attended
Minassian et al.	10.1177/1545968315591706	2016	Transcutaneous	/	/	/	treadmill stepping with 60% BWS robotic aid (LokomatPro)	open	/	tSCS for spinal rhythm generation by step-induced feedback in incomplete SCI	supine first, then standing with BWS	/	Lab, supervised	/
Minassian et al.	10.1002/mus.20700	2007	Transcutaneous	/	/	/	/	open	/	PRM reflex eliciting by tSCS on healthy subjects	supine	/	Lab, supervised	/
Phillips et al.	10.1089/neu.2017.5082	2018	Transcutaneous	1 to 10 mins	/	/	/	open	/	tSCS for CV normalization in complete cervical SCI subjects	supine	/	Lab, supervised	
Hofstoetter et al.	10.1179/2045772313Y.0000000149	2014	Transcutaneous	30 mins	/	/	after the stimulation walking based protocol (10 m test)	open	/	tSCS to reduce spasticity in lower limbs in adults with spastic muscle hypertonia	lying supine	/	Lab, supervised	/
Chandrasekaran et al.	10.3389/fnins.2023.1210328	2023	Transcutaneous	45-60 mins	/	16 weeks of tSCS + exercise, then 3 weeks exercise only	Activity based training	open	/	cervical tSCS to improve arm function in SCI subjects	sitting	/	Lab, supervised	/
Gerasimenko et al.	10.1016/j.rehab.2015.05.003	2015	Transcutaneous	/	/	/	/	Open	/	tSCS to facilitate stepping performance after SCI	/	/	Lab, supervised	/
Pena Pino et al.	10.3389/fnsys.2020.00035	2020	Epidural	/	/	/	task oriented therapy	open	none reported	Long-Term SCS After Chronic Complete SCI Injury Enables Volitional Movement in the Absence of Stimulation	/	/	/	/
Hofstoetter et al.	10.1111/aor.12615	2015	Transcutaneous	/	/	/	Stepping on treadmill	open	none reported	tSCS effects on stepping ability in incomplete SCI subjects	Standing and walking	/	Lab, supervised	/
McHugh et al.	10.1038/s41394-020-00359-1	2020	Transcutaneous	30 mins of tSCS+gait, then 90 mins just gait	3	23	walking based protocol, some with weight bearing support	Open	none reported	tSCS combined with walking-based therapy for gait rehabilitation in people with motor incomplete SCI	Standing and walking	/	Lab, supervised	/
Meyer et al.	10.3390/jcm9113541	2020	Transcutaneous	up to 15 mins	/	/	/	open	none	estanblish lumbar tSCS motor immediate effects in incomplete SCI (ankle control)	/	/	Lab, supervised	/
Wagner et al.	10.1038/s41586-018-0649-2	2018	Epidural	up to 60 min	4 to 5	20 to 25	overground locomotor training with a gravity-assist device	Closed, IMUs control signal	None	Restore walking in complete SCI subjects	Standing and walking	/	Lab, supervised	All sessions attended
Monterosso thesis		2023	Transcutaneous	5 minutes sessions	/	/	/	Open	some subjects fainted when anode on the abdomen	definition of a protocol of lumbar tSCS for lower limbs rehabilitation in post-stroke, on healthy subjects	supine in calibration, then standing	/	Lab, supervised	/

Abstract in lingua italiana

La lesione del midollo spinale (SCI) può portare alla perdita del controllo del movimento negli arti superiori e inferior, riducendo in modo critico l'indipendenza dei soggetti affetti. La stimolazione elettrica spinale (SCS) invasiva si è affermata negli ultimi decenni come tecnica di riabilitazione motoria nell'ambito della mielolesione, portando al ripristino del controllo motorio volontario in soggetti precedentemente completamente paralizzati. La stimolazione spinale transcutanea (tSCS) è un'alternativa non invasiva, accessibile ed economica all'approccio epidurale. Nonostante la mancanza di selettività, la tSCS ha mostrato risultati promettenti e un'elevata efficacia nella neuro-riabilitazione post mielolesione. È stato dimostrato che combinare la stimolazione spinale con l'intento volontario e/o movimenti passivi è più efficace nella riabilitazione motoria, rispetto alla sola stimolazione. Sebbene la maggior parte della ricerca sulla riabilitazione motoria in soggetti mielolesi sia focalizzata su protocolli basati sulla deambulazione, la pedalata passiva elimina i rischi legati al sostegno di carichi e alle cadute. Nell'ambito della presente tesi si propone un protocollo integrato di tSCS e pedalata per la riabilitazione motoria in individui con lesione spinale.

Metodi Per valutare la fattibilità e la potenziale facilitazione motoria della tSCS e della tSCS combinata con lo sforzo volontario durante la pedalata è stato condotto uno studio con quattro soggetti con SCI. I partecipanti hanno svolto sessioni di stimolazione spinale su un trike con un motore per pedalata assistita della durata di 30 minuti. Gli elettrodi di stimolazione sono stati posizionati sui segmenti spinali T11-T12 e L1-L2 e la stimolazione è stata applicata a 20, 50 e 80 Hz durante intervalli di pedalata consecutivi. I dati dell'elettromiografia (EMG) degli arti inferiori e le forze sui pedali del triciclo sono stati analizzati per valutare l'attivazione muscolare in presenza di stimolazione e i possibili effetti sul movimento.

Risultati I risultati raccolti hanno dimostrato la validità dell'approccio proposto e hanno dimostrato che la tSCS a livello lombare modula l'attivazione dell'EMG negli arti inferiori durante la pedalata. I dati di forza dei pedali non hanno rilevato una proporzionalità diretta tra attivazione muscolare e forze durante. In un soggetto, la stimolazione combinata con lo sforzo volontario ha incrementato la forza durante sul pedale rispetto alla sola stimolazione, evidenziando il potenziale effetto amplitificatore dei segnali volontari residue della SCS. I dati dell'EMG hanno mostrato un riflesso di stiramento durante la pedalata nei partecipanti con ipertonia, spesso ridotto in ampiezza dalla stimolazione. Tutti i partecipanti non hanno riportato alcuna sensazione negativa durante e dopo la stimolazione e hanno comunicato di aver sperimentato una riduzione della rigidità muscolare e un miglioramento della sensibilità intestinale e vescicale nei giorni successivi alla sessione di stimolazione.

Conclusioni Lo studio ha dimostrato che la tSCS combinata con il ciclismo è un approccio praticabile e promettente per la riabilitazione motoria SCI e legato a diversi benefici non motori.

Parole chiave: stimolazione spinale transcutanea, lesione spinale, riabilitazione motoria