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Executive Summary of the Thesis

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

Laurea Magistrale in Biomedical Engineering - Ingegneria Engineering

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1. Introduction

Transcutaneous Spinal Cord Stimulation is a non-invasive spinal stimulation technique that engages spinal circuits [1]. Spinal Cord Stimulation (SCS) was traditionally employed as an epidural invasive strategy for pain management; it then developed into a motor rehabilitation technique at the end of the 20th century, eventually landing into its non-invasive transcutaneous alternative (tSCS). In the past decades, the motor reflexes elicited by tSCS have been fully characterized [2], and the approach has shown promising results and demonstrated high efficacy in neurorehabilitation [1, 3]. It improved arm and hand function [4], stepping [5] and walking [5, 6] performances and effectively reduced spasticity [7] in neurologically impaired subjects. Technological advancements and complications related to the epidural approach allowed tSCS to become a competitive alternative to the invasive solution and contributed to increasing the attention towards it.

PRM reflex and motor facilitation

The motor effects of Spinal Cord Stimulation rely on the engagement of neural spinal circuits reached by an electrical stimulation current. The primary motor response observed depends upon 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 [8]. The sensory fibres elicit an action potential in the efferent motor fibres by inter-synaptic excitation within the spinal cord (Figure 1(A), and the activation of motor fibres induces short latency artificial muscular contractions. The observed motor response to single pulses of current is named Posterior Root Muscle (PRM) reflex, and it is the distinctive element of spinal stimulation. PRM reflexes have been comprehensively studied in the past decades, leading to a clear picture of the physiological phenomena defining the reflex. While the reflexes represent the motor response to the spinal cord excitation, these reflexes induced with single pulses of stimulation do not produce movements and are thus not well-suited for a rehabilitative setting. Also, continuous tSCS patterns are not intended to induce motor output by itself but rather to increase the excitability state of spinal circuits. Indeed, these FES-induced activations are integrated with residual supraspinal information reaching the spinal cord and strengthening them, making them capable of inducing an Action Potential (AP). Usually, continuous tSCS is delivered at a threshold level (i.e., the level inducing the PRM reflex) as it has been observed to allow SCI subjects with no residual motor ability to regain control of the targeted structures and immediately produce movement during the stimulation [9]. The neurological mechanisms that facilitate movement and

the recruitment patterns during SCS are very complex and not entirely clear yet. The underlying idea is that a threshold-level 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 strong enough to induce APs on motor neurons. This stands on the hypothesis that there are either some residual descending fibres [9] or that the other spinal circuits can be recruited to elicit motor neurons.
The engagement and modulation of spinal circuits with electrical stimulation have shown multiple effects on neural structures in healthy and neurologically impaired subjects. The spatiotemporal contingency between supraspinal commands and SCS-induced spinal activation has shown spike-time-dependent plasticity [10], suggesting that there is room for plasticity benefits when targeting the spinal cord in neurologically impaired subjects. In particular, SCS rehabilitation can potentially strengthen the residual spinal pathways and aid in recovering independent volitional motor control [10]. This technique would be particularly relevant for the large number of complete SCI subjects proven to preserve neural connections across the lesion, referred to as "discomplete" [11]. Based on the latter notion, multiple studies reported the recovery of volitional motor control after months of SCS [12] and the months-long persistence of the motor benefits even in the absence of stimulation [13]. In this scenario, combining electrical stimulation with residual descending motor commands is essential to beneficial neuroplastic change [14]. These significant improvements in motor outcomes for complete SCI subjects were experimentally reported both in the short [13] and in the long term [4].

tSCS for SCI lower-limb motor recovery

Despite significantly lacking selectivity compared to the epidural approach, tSCS has shown promising results and demonstrated high efficacy in SCI neurorehabilitation [1, 3], both for motor functions and spasticity reduction. In the SCI scenario, 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 [14]. The combination of voluntary drive and stimulation has shown improved results in multiple cases [13, 14].
In particular, when focusing on the lower limb, SCS targets spinal circuits at the lumbar level. Such stimulation often goes hand in hand with the interneuronal modulation of spinal circuits dedicated to rhythmic movements, named Central Pattern Generator (CPG). Both walking and cycling are cyclic movements relying on CPG interactions, which often remain unaffected by the injury, resulting in viable targets for the stimulation. Indeed, SCS was proven able to induce rhythmic motor patterns in complete SCI subjects [13, 15], hence improving the motor outcome during cyclic movements. While both walking and cycling employ the CPGs, cycling is well suited to the neurorehabilitation scenario since it eliminates the risk of falling and the weight-bearing issues that intrinsically characterize the early stages of walking-based therapy [13, 14].
The present thesis aimed to investigate the effects of lumbosacral tSCS on motor facilitation during cycling in individuals with spinal cord injury. Specifically, we applied tSCS during motor-assisted trike cycling and collected data about muscle activation and force produced at pedals to assess the stimulation effects on lower limb motor outcomes. We also evaluated a combination of tSCS and volitional effort to determine the potential contribution of residual volitional signals during cycling, as suggested by the literature [13].

2. Materials and Methods

The following experimental protocol, protocol number 50/2023, was approved by Politecnico di Milano's ethical committee on December 12th, 2023. It conforms to the Helsinki Declaration of 1975, as revised in 2000.

Subjects

We recruited four individuals with chronic motor- and sensory-complete or incomplete SCI, classified as American Spinal Injury Association Impairment Scale (AIS) "A" or "B" using the International Standards for Neurological Classification of SCI. The participants were otherwise healthy adults, and medication was not changed for the study. Participants' data is summed up in Table 1. Franco Molteni, MD, the study's clinical supervisor, reviewed and approved the participants' medical records for tSCS. Participants were also asked to fill out an anamnestic form before each stimulation session. Subjects 03 and 04 had lower limb muscle rigidity and hypertonia and presented some involuntary contractions and clonuses.

tSCS cycling setup

The cycling assessment required the participant to sit on a motor-assisted trike (model 700, Catrike, US), Fig. 1(C). The trike's motor was controlled via a custom-developed Android-based app, and orthoses were used to keep the legs in place on the sensorized pedals (X-Power, SRM GmbH, Germany). The trike setup provided the instantaneous force on the pedals during cycling and the motor's power.
tSCS was delivered with self-adhesive electrodes

	Lesion type	Lesion level	Time since lesion	Metal implants	BMI	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	≈ 12 months	none	25.18	ossibutinine, urivesch

Table 1: Included subjects' characteristics

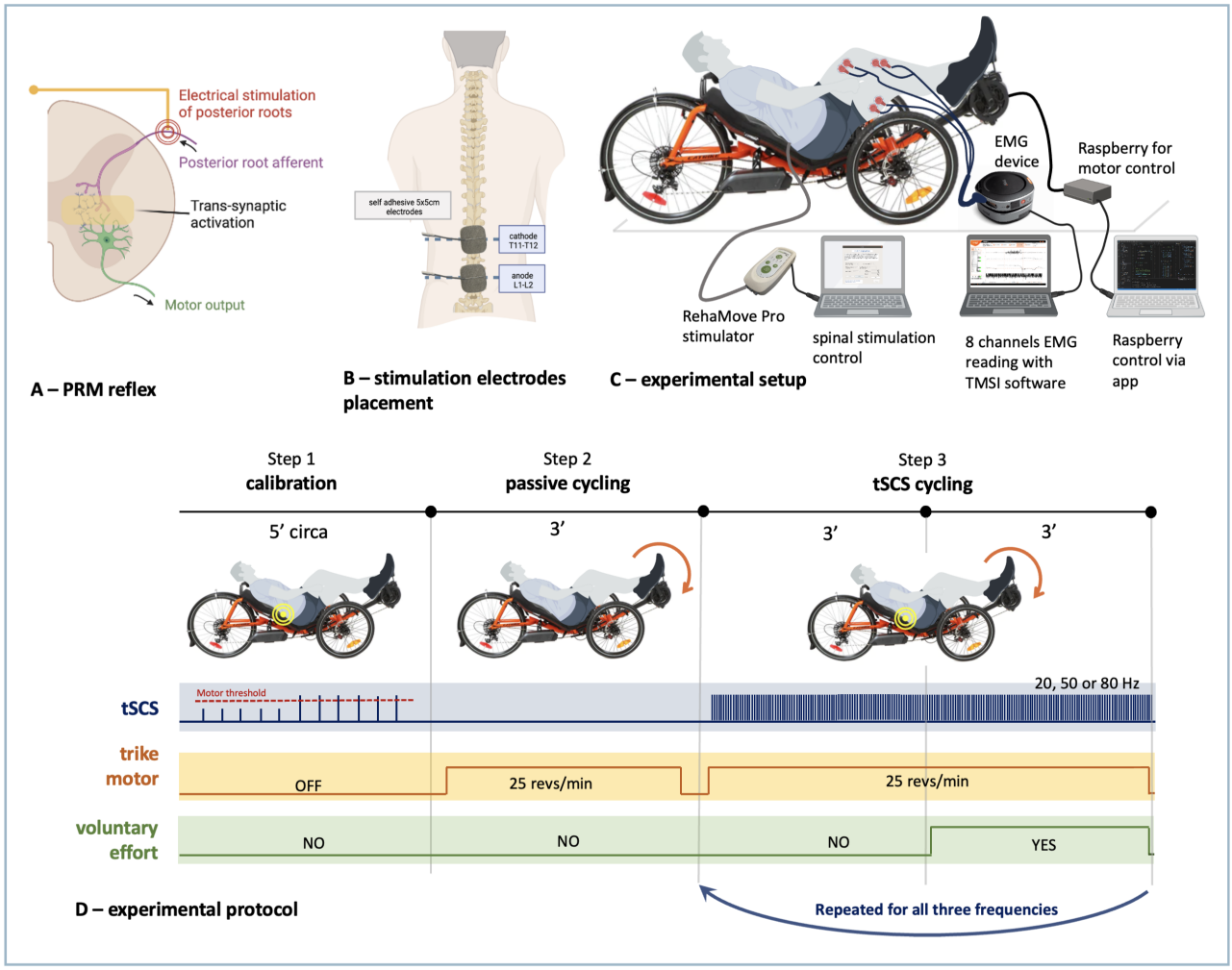

Figure 1: Experimental setup and protocol. (A) PRM reflex. (B) Placement of transcutaneous stimulation electrodes along the spine at L1-L2 and T11-T12 levels for anode and cathode, respectively. (C) Experimental setup with the subject sitting on the trike and laptops to control the stimulation via RehaMove Pro, the EMG acquisition and the motor, respectively. (D) Stimulation protocol has three phases: calibration, passive cycling and tSCS cycling and the combinations of stimulation, motor and voluntary effort during the steps.

(PALS Neurostimulation Electrodes, 5x5cm, Axelgaard Manufacturing Co. Ltd., Fallbrook, USA), placed centrally along the spine, the anode over L1-L2 spinous processes and the cathode over T11-T12 spinous processes, as shown in Fig. 1(B). A RehaMove Pro (Hasomed GmbH, Germany) stimulator delivered charge-balanced, biphasic square pulses, starting with the anodic front, with 2ms pulse width (1ms per phase) and amplitude and frequency depending on the protocol's phase. The stimulation was controlled via a custom-developed C++-based GUI.

Electromyographic (EMG) data was acquired with a TMSI SAGA 32+/64+ REV 2 (Twente Medical Systems International B.V., Netherlands) and its proprietary software SAGA. An 8-channel configuration was used to record EMG data from four muscles for each leg: rectus femoris, biceps femoris, tibialis an-

terior and gastrocnemius.

tSCS cycling protocol

The proposed cycling protocol, Fig. 1(D) is divided into three phases and lasts around 70 minutes. Before the stimulation session, the participant was asked to fill out the anamnestic form and basal data (heart rate, arterial pressure and oxygen blood saturation) was acquired. In the preliminary *Calibration* phase, single tSCS pulses with 5s inter-pulse distance were delivered to the subject sitting in the trike, with the motor off and the legs in a standard position, with the right pedal in a vertical position. The current amplitude started from 10 mA and was increased by 5 mA every five pulses until the PRM reflex appeared, determining the *motor threshold* amplitude. The PRM reflex was visually identified by looking at the real-time EMG signal on the SAGA software. The *passive cycling phase* followed, consisting of three minutes during which the motor was on at the constant cadence of 25 cycles/min, with the stimulation off. Then the *tSCS cycling* started, where the two 3-minute blocks were repeated for three stimulation frequencies (20Hz, 50Hz, 80Hz). During the first block, the motor was on at a constant cadence, and the tSCS was delivered at the set frequency and with the minimum amplitude between the participant's *motor threshold* and the maximum tolerated value. The second block, for each stimulation frequency, also added the intent of movement to tSCS and motor assistance. tSCS was switched off after each 6-minute block to change the stimulation frequency. The sequence of all stimulation frequencies was randomized between different sessions and subjects to remove any order bias.

Data Analysis

EMG and force data acquired were analyzed in MATLAB (v. Rb2023). EMG data was filtered with 10-500Hz bandpass and 50Hz notch filters, offset cleared, rectified, and its envelope computed with a 5th order 10Hz low-pass Butterworth filter. Cycling revolutions were then segmented 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 in passive conditions. Similarly, force data were segmented and averaged in order to achieve an average force cycle for the right and left pedals for each phase of the protocol. In addition, the active force was computed, subtracting the average force cycle of the passive phase from each *tSCS cycling* average force cycle. The active force is meant to evaluate if and in which phases of the cycling revolution the stimulation and/or the stimulation plus the volitional intent of the subject changed the force produced at the pedals.
Furthermore, participants were asked to fill out a questionnaire rating their feelings of pain, burning, cramping, tingling and pressure on a scale from 0 to 10 for each stimulation frequency. 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. Results

We performed two trials with subjects 01, 02, and 03 and a single one with subject 04. Given the participants' unique clinical histories and the low number of trials performed, the EMG and forces data were analyzed for each participant individually rather than as a population. Hence, the figures in this summary are samples of the obtained results. The EMG data showed stimulation-related modulations of muscle activation, varying from amplification to reduction of EMG amplitude depending on muscle groups and participants.
Contrary to expectations, EMG during passive cycling was not null nor inactive in various 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 stimulation frequencies often showed values over the passive range and sometimes slightly below, with the 50Hz 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 protocolsa.
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.
Subjects 01 and 02 showed similar behaviours for both EMG activation and forces on pedals, which are discussed in the *Case Study 01*. Similarly, subjects 03 and 04 had similar trends and are analyzed as *Case Study 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.

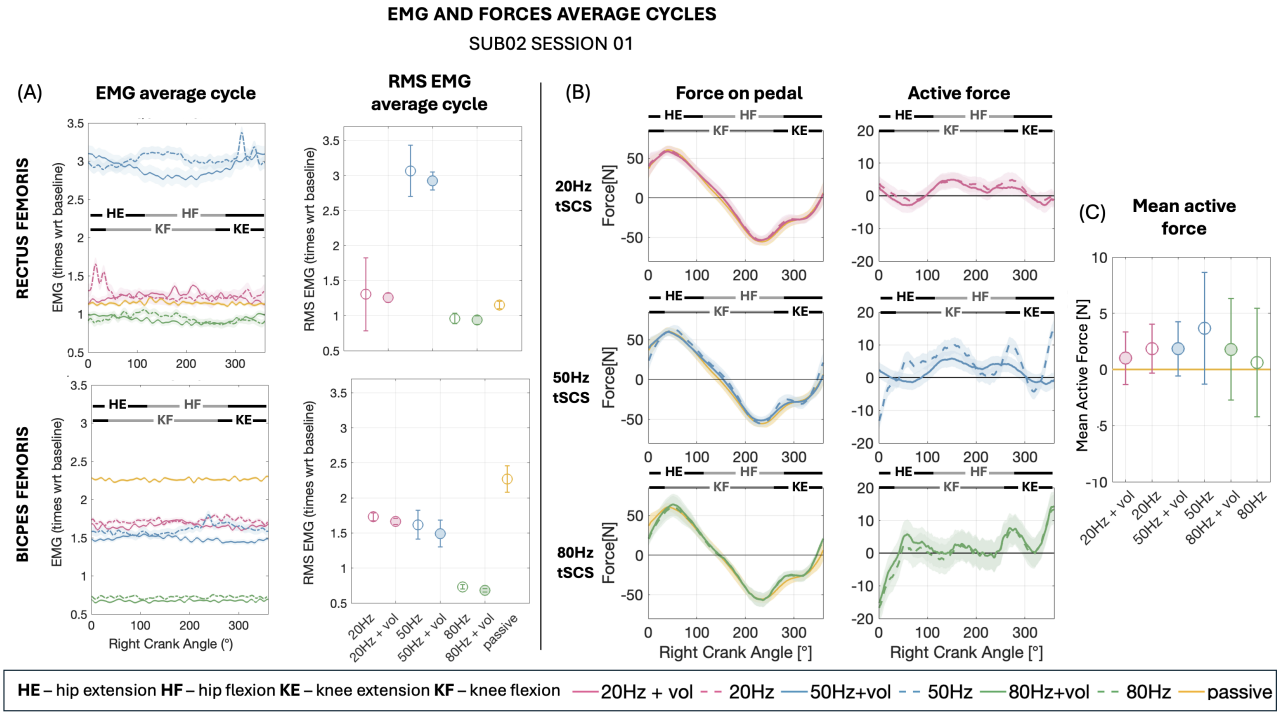

Figure 2: Data from first trial of subject 02, representing the *Case Study 01*. (A) Right rectus and biceps femoris EMG during an average cycling revolution, reported as mean ± SD (Standard Deviation), and mean RMS values of the EMG amplitudes. Data are normalized with respect to the subject's baseline (EMG activation when in the standard position in the trike, not moving). The right crank angle is null when the right pedal is at 90° upright. Knee and hip flexion and extension intervals are indicated with the black (extension) and grey (flexion) bars superimposed on the EMG average cycle graphs. (B) Average cycles of absolute force on the right pedal 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 during the passive trial (right). Each row is relative to a different tested frequency. (C) Mean and SD of the active force for all tSCS cycling conditions.

Case Study 01

EMG and force results for the right leg during the first session of Subject 02 are summed up in Fig. 2. Panel A reports on the left side the EMG data for the right rectus femoris and bicep femoris normalized to the subject's baseline. On the right side, the Root Mean Squared (RMS) mean values and Standard Deviations (SD) of EMG amplitudes of the same trials are displayed. Hip and knee flexion and extension ranges were measured in the experimental setup and are 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 results for the left side are not reported here since they show an analogue behaviour.

In 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 Hz and 80Hz stimulation frequency, respectively. The 50Hz stimulation amplifies the activation to three times the baseline. On the bicep femoris, the passive activation is the highest, approximately 2.2 times the baseline, with all stimulations reducing its amplitude. In addition, the 50Hz stimulation introduces a cyclic trend on both muscles, 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 the 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 for subject 02 in Fig.2(B). A minimum of cycling cooperation during *tSCS cycling* with respect to the passive condition can be observed around 280-300° 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. The overall mean active force, Fig.2(C), shows an increase for all tSCS

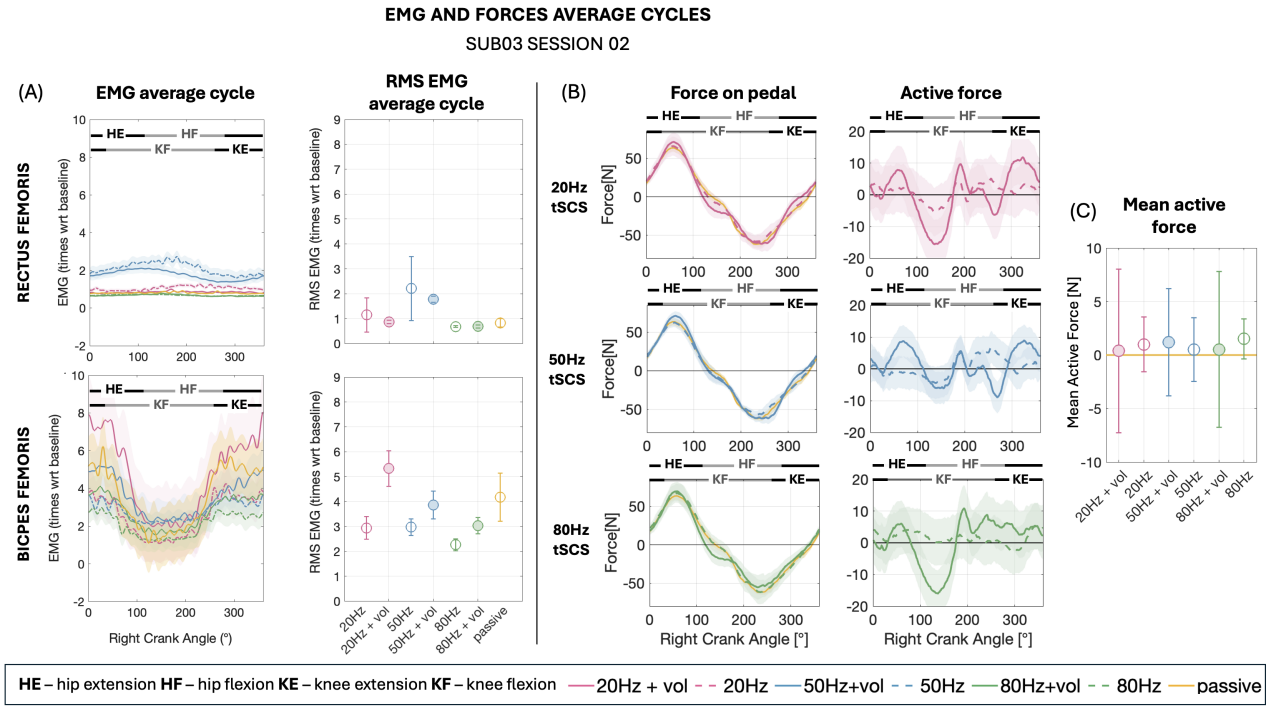

Figure 3: Data from second trial of subject 03, representing the *Case Study 02*. (A) Right rectus femoris and bicep femoris EMG during an average cycling revolution, reported as mean $\pm SD$ (Standard Deviation), and mean RMS values of the EMG amplitudes. Data are normalized with respect to the subject's baseline (EMG activation when in the standard position in the trike, not moving). The right crank angle is null when the right pedal is exactly upright. Knee and hip flexion and extension intervals are indicated with the black(extension) and grey (flexion) bars superimposed on the EMG average cycle graphs. (B) Average cycles of absolute force on the right pedal 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 during the passive trial (right). Each row is relative to a different tested frequency. (C) Mean and SD of the active force for all tSCS cycling conditions.

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.
While EMG data for subjects 01 and 02 do not suggest noticeable motor facilitation during the stimulation, mean force data show a promising preliminary result.

Case Study 02

Results for the second stimulation session of subject 03 are reported in Fig.3 and considered in the discussion of the second *Case Study*'s results. Panels in the figure are organized as for the *Case Study 01*.
In the rectus femoris, the EMG activation shows passive activation around the baseline, with the 80 and 20 Hz stimulations slightly reducing and amplifying it, respectively. The 50Hz stimulation, on the other hand, amplifies the signal to about twice the baseline, with a clear cyclic component. While this behaviour is similar to the first *Case Study*, that on the bicep femoris reveals the critical difference between the two groups. The EMG on the right bicep femoris shows a significant cyclic activation with amplitude up to 8 times the baseline, both during the passive- and the stimulation-cycling conditions, with the stimulation not affecting the cyclic pattern and sometimes reducing and sometimes amplifying its amplitude. Similar activations were observed on the left leg and in subject 04. Subject 04 showed increased cyclic activations in the right leg, which is more affected by hypertonia. A comparison of these cyclic activations of the knee and hip extension and flexion ranges revealed that they were not in phase with a physiological cycling contraction. 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.
Force trends on the right pedal during an average cycling revolution for the second trial of subject 03 are shown in Fig.3(B). 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 are observed when the stimulation is com-

bined with voluntary intent of movement, while during tSCS alone, oscillations are similar to those of subject 02, Fig. 2(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, right column of Fig. 3(B). This underlines spinal stimulation's potential of amplifying residual volitional signals and lays out promising perspectives. However, the increase of active force with the addition of voluntary intent in the pushing phase is followed by a resistance (negative active force) at the end of the pushing phase (100-200°). As for the positive phase, the oscillation is 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.
A similar behaviour was observed in subject 04, where the stimulation remarkably increased the force on the right pedal compared to the passive setting. The participant has a minimum motor residual ability on the right leg. In his case, passive trials with the addition of the voluntary effort were performed twice, before and after the *tSCS cycling* blocks. Force results showed that both trials caused a negative active mean force. Hence, the addition of voluntary intent 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. 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.

tSCS induced sensations

Participants were asked to rate feelings of pain, burning, cramping, tingling and pressure on a scale from 0 to 10 for each stimulation frequency. No clear consensus was found among subjects regarding the stimulation type perceived as the most uncomfortable. Subject 01 scored 0 in all categories, indicating no stimulation perception. The other participants reported feeling the stimulation, with intense tingling both in the lower back and proximal legs, a heating sensation and pain in some cases. Their scores were proportionate to the lesions' levels, with subject 03 communicating the most discomfort (lesion D12). Subject 03 also reported a pain increase when adding the volitional control to the 20Hz stimulation. The single pulse in the calibration phase was described as a "push" on the lower back, while continuous tSCS caused more discomfort. However, this decreased over the three-minute session, indicating an adaptation phenomenon. Supporting the latter hypothesis, subjects 02 and 03 scored lower in all categories in the second session compared to the first one.

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. Specifically, subjects communicated reduced bowel evacuation time, regained bladder sensibility, reduced muscle rigidity, and reduced spasticity and clonuses. These secondary effects suggest that spinal cord stimulation could significantly impact the daily activities of individuals with spinal cord injury and warrant further investigation.

4. Conclusions

Transcutaneous Spinal Cord Stimulation (tSCS) is a promising non-invasive technique for motor rehabilitation in individuals with Spinal Cord Injury (SCI). We delivered a cycling-based protocol to four SCI individuals to evaluate the stimulation's motor-facilitating effects during cycling. 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 while cycling with tSCS. 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, 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, which showed interesting side benefits of a 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. 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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