Quantifying the effect of trans-spinal magnetic stimulation on spinal excitability

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***Abstract*— During the last decades, spinal cord stimulation (SCS) has attracted much attention due to its capability to modulate the motor and sensory networks. The potential of this technique has been proved, and several investigations have focused on applying it for restoring lower limb function. The majority of SCS approaches are based on electrical stimulation, and few studies have explored magnetic fields for non-invasive SCS. This paper presents a trans-spinal magnetic stimulation (ts-MS) protocol and studies its effects on spinal circuits with seven healthy subjects, considering central and peripheral nervous systems. Motor evoked potentials (MEP) and trans-spinal motor evoked potentials (ts-MEP) were assessed before and after the ts-MS intervention to characterize excitatory responses. After the intervention, we found an increase of almost 30% (not statistically significant) in MEP amplitude, but no changes in ts-MEP amplitude. Further research is required to confirm, in a larger population of subjects, the potential of this technology, which could be used to improve rehabilitation therapies for patients with motor disabilities.**

I. INTRODUCTION

Much research in last decades has focused on the neuromodulation of the excitability of spinal cord neural circuits for rehabilitation of patients with motor disabilities, such as spinal cord injury (SCI) [1], [2]. Spinal cord stimulation (SCS) has appeared as a powerful technology to induce changes in the spinal circuits [3], [4] which could result in motor recovery of patients with motor impairments [5], [6]. Therefore, there is a considerable increasing interest in understanding how the stimulation interacts not only with spinal networks, but also with cortico-muscular circuits, in order to design optimal SCS interventions for rehabilitation after paralysis.

Numerous investigations based on electrical stimulation, both invasive (i.e., epidural) [5], [6] and non-invasive (i.e., transcutaneous) [2], [7], [8], have evidenced the capability of SCS to neuromodulate the spinal networks. Magnetic stimulation has also been presented as a non-invasive approach to stimulate the spinal circuits [9] and an adequate protocol design of repetitive trans-spinal magnetic stimulation (ts-MS) demonstrated facilitation of locomotion [10], [11].

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However, little is still known about how the ts-MS affects spinal circuits and interacts with the central and peripheral nervous system. So far, few studies have addressed this question, and they mostly investigated the effects of stimulation on peripheral reflexes [12], [13]. Filling this gap of knowledge is of great relevance since it would help us to understand the effects of electromagnetic stimulation on sensorimotor neural networks and lead us to design better rehabilitation therapies based on ts-MS for lower limb impairment.

In the present study, we aim at evaluating the effect of ts-MS on the excitability of spinal neural networks and its influence in cortico-spino-muscular tracts. For this purpose, we recruited 7 healthy subjects who underwent one session of ts-MS. In order to characterize the neurophysiological effects of the stimulation on central and peripheral nervous system, motor evoked potentials (MEPs) and trans-spinal motor evoked potentials (ts-MEPs) were recorded before and after the intervention (0 min and 30 min after finishing the stimulation).

II. METHODS

A. Subjects

Seven healthy subjects with no neurological disorders and full leg mobility were involved in one experimental session. The study was conducted at the University of Tübingen (Germany), and ethical approval for the experimental procedure was provided by the ethics committee of the Faculty of Medicine of the University of Tübingen. All subjects gave written informed consent before participating in the study.

B. Experimental design and procedure

The subjects were asked to sit comfortably on a chair with their back straight, and their knee and ankle joint angles at 120° and 90°, respectively. Maintaining the body posture during all the session, especially during the measurements, is essential for the robustness of the measurements, and the subjects were requested to keep it.

The subjects underwent an intervention of trans-spinal magnetic stimulation (ts-MS), and electrophysiological assessments were conducted before and after to measure the effects of the stimulation on the excitability of the motor networks. The intervention consisted of 20 trials, which started with 7 seconds without stimulation followed by 5 seconds with stimulation. In total, the intervention lasted 4 minutes, from which 1 min 40 sec corresponded to stimulation (2000 pulses delivered in total). The subjects were instructed to be relaxed during the whole intervention, without performing any motor command. For the electro-physiological assessments, motor evoked potentials (MEP) and trans-spinal motor evoked potentials (ts-MEP) were recorded. These assessments were conducted three times, one before the intervention (Pre), one right after concluding the intervention (Post0) and one 30 min afterwards (Post30).

C. Trans-spinal magnetic stimulation (ts-MS)

Given the unnatural (and sometimes unpleasant) feeling that ts-MS can induce, and to ensure that all the subjects could bear the stimulation, all of them performed a familiarization session of ts-MS one day before the experiment. The stimulation setup consisted of a circular coil (90 mm diameter) powered by a Rapid2 magnetic stimulator (MagStim, UK). Before starting the session, the experimenter localized and marked the vertebrae from T12 to L5 following anatomical landmarks. The coil was centrally placed over the midline of T12 and moved downwards in steps of one vertebra. Single pulses above the motor threshold were applied in each location, and the spot eliciting largest evoked potentials in the right soleus muscle was selected and marked as hot-spot for the experiment. The motor threshold (Mth) for each participant was defined as the minimum stimulator output intensity required for inducing at least 5 evoked potentials of at least 50 μV out of 10 consecutive stimuli on the selected stimulation spot. During the intervention, continuous magnetic stimulation was delivered at 20 Hz (following [11]) on the hot-spot at the motor threshold intensity.

D. Data acquisition

Electromyographic (EMG) activity of both legs was registered using Ag/AgCl bipolar electrodes (Myotronics-Noromed, Tukwila, WA, USA) with 2 cm inter-electrode space. The EMG of four muscles (*vastus medialis*, *tibialis anterior*, *soleus* and *gastrocnemius medialis*) was acquired at a sampling rate of 5 kHz using an MR-compatible bipolar amplifier (BrainProducts GmbH, Germany). Ground electrode was placed on the right *peroneal malleolus*.

E. Assessments of excitability

1) Motor evoked potentials (MEP): The strength of the descending volleys from the cortex to the target muscle along the cortico-muscular pathway can be assessed through MEPs. The Rapid2 magnetic stimulator with a double cone coil (110mm diameter) was employed to stimulate the area projecting to the right soleus muscle on the left primary motor cortex. The scalp of each subject was registered and used in a neuronavigation system (Localite, GmbH, Germany) in order to plan and control the stimulation spot during the entire session. The standardized procedure described in [14] was followed to determine the cortical motor threshold (CMth) as the minimum stimulation intensity needed to elicit 5 evoked potentials of at least 50 μV out 10 stimuli. In pre- and post-intervention assessments, 10 MEP repetitions at 120% of CMth were applied at a rate of one pulse every 5 to 5.5 seconds.

2) Trans-spinal motor evoked potentials (ts-MEP): The assessment of peripheral neural networks was conducted eliciting volleys from the spinal cord to the target muscle using the Rapid2 magnetic stimulator and the 90 mm-circular coil. The determination of the stimulation spot at the lumbar level and the calculation of the Mth were realized as explained in Section *II-C*. A permanent marker was used to draw reference lines on the skin to reduce variability during coil positioning. Ten trials of ts-MEPs were delivered at 120% of the spinal Mth in pre- and post-intervention assessments every 5 to 5.5 seconds.

F. Data analysis

The EMG activity of the soleus muscle was band-pass filtered between 10 and 1000 Hz with a 2nd order Butterworth filter. MEP and ts-MEP trials from pre- and post-assessments were separately averaged for each subject. We measured the efficacy of cortico-spino-muscular tracts by analyzing the amplitude of the MEPs, as the peak-to-peak difference from the most negative to the most positive deflection, and the latency of the MEPs applying the cumulative sum technique on the rectified signal [15]. Similarly, we assessed the efficacy of spino-muscular tracts by analyzing the amplitude and latency of the ts-MEPs. In addition, subtracting the onset of ts-MEPs from the onset of MEPs, we obtained the central motor conduction time (CMCT), which reflects the processing time of the cortico-spinal segment [14].

We conducted statistical analyses (Friedman's test for related samples) to assess the effects before (Pre) and after the intervention (Post0 and Post30) for the five outcome measurements: peak-to-peak amplitude and latency of MEPs and ts-MEPs, and the CMCT.

III. Results

The optimal stimulation spot was found in L4-L5 intervertebral spaces for all the subjects, resulting in spinal-roots stimulation as presented in [9].

A. Influence of ts-MS in cortico-spino-muscular tracts

Figure 1a shows the mean$\pm$std of the MEPs in the soleus muscle from an illustrative subject before and after the intervention. The mean peak-to-peak amplitude of the MEPs across all participants increased 29.42% for Post0 and 28.97% for Post30 with respect to the baseline (pre-intervention). The boxplots in Figure 2a display the distribution of the MEP amplitudes for all the subjects in the three performed assessments. The changes in amplitude between the three assessments were not statistically significant ($\chi^2(2) = 2.0$; $p = 0.37$). The latencies of the MEPs remained more stable after the intervention (0.17% decrease for Post0 and 1.26% decrease for Post30, see Figure 2b). These latencies were not significantly different between the three assessments ($\chi^2(2) = 3.12$; $p = 0.21$).

B. Influence of ts-MS in spino-muscular tracts

The mean$\pm$std of the ts-MEPs in the soleus muscle before and after intervention from an illustrative subject is presented

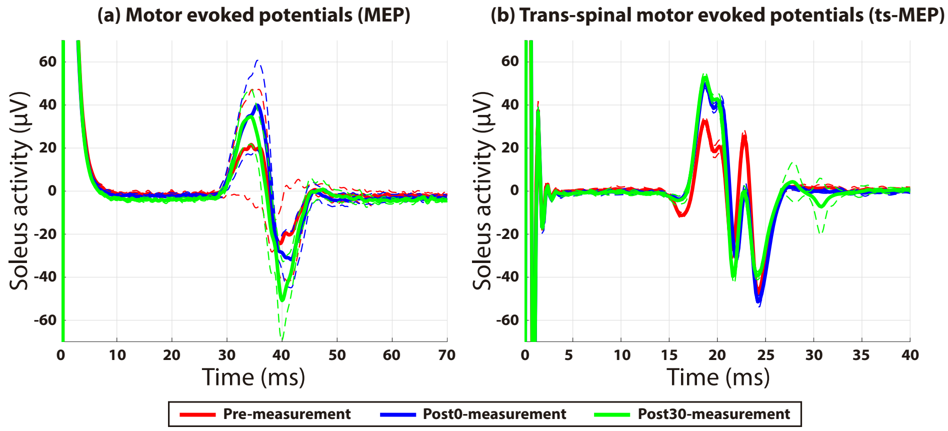

Fig. 1. Mean *(solid line)* ± std *(dashed line)* of the *(a)* MEPs and of the *(b)* ts-MEPs from an illustrative subject in the right soleus muscle. Pre-, Post0- and Post30-assessments are represented in red, blue and green, respectively. Note the stimulation artifact at 0 ms.

in Figure 1b. The changes in ts-MEP amplitude across all participants were lower than for the MEPs. In Post0, there was an increase of 3.20% in ts-MEP amplitude, while in Post30 it increased to 10.71% with respect to Pre (see Figure 2c). The amplitudes of the ts-MEPs were not significantly different between the three assessments ($\chi^2(2) = 1.14;\ p = 0.56$). The latencies of the ts-MEP were also stable after the intervention (0.69% increase for Post0 and 3.65% increase for Post30, see Figure 2d). The ts-MEPs latencies were not significantly different between the three assessments ($\chi^2(2) = 2.27;\ p = 0.32$).

C. Influence of ts-MS in cortico-spinal tracts

For the assessment of cortico-spinal tracts, we determined the conduction time. The CMCT, as the other latency assessments, remained stable with respect to before the intervention: 0.97% decrease in Post0 and 5.77% decrease in Post30 (see Figure 2e). The CMCT was not significantly different between the three assessments ($\chi^2(2) = 3.43;\ p = 0.18$).

IV. Discussion and Conclusions

The objective of the present study was to investigate whether cortico-spino-muscular neural networks can be modulated by trans-spinal magnetic stimulation (ts-MS) in healthy subjects. With this aim, we proposed a ts-MS intervention and evaluated its effects on synaptic efficacy in healthy subjects.

There is not much evidence in the literature about detailed quantification of electrophysiological effects induced by magnetic spinal cord stimulation. In general, studies propose setups that are specific to certain applications, which hinders results comparison. A study by Nielsen and Sinkjær proposed thoracic (T8) stimulation with a train of 16 stimuli at 25Hz with an intensity of 60% of maximum stimulator output [12]. They measured the effects on MEP amplitude at different intervals (10 to 25000 ms) following the intervention in three healthy subjects, and only one out of the three subjects showed an increase in soleus MEP amplitude. Further, they proposed another stimulation protocol, in which repetitive magnetic stimulation was delivered for 5 min at 25 Hz in sequences of 5 seconds of stimulation and 5 seconds of rest. They did not use MEPs, but H-reflexes to characterize the effect of the magnetic stimulation, observing an initial amplitude increase, followed by an amplitude decrease 8 min after the intervention that remained even 30 min later [12]. A more recent study by Knikou recorded single pulses of ts-MS over thoracic (T10) and assessed the neurophysiological changes by amplitude of soleus H-reflex in intervals of milliseconds before and after the stimulation [13]. Their results are in line with the ones of Nielsen and Sinkjær, confirming that ts-MS can decrease amplitude or inhibit spinal reflexes. These studies could be complementary to our results as long as the differences in ts-MS protocols and neurophysiological assessments (i.e., reflexive responses instead of motor pathways) are considered.

We observed that MEP peak-to-peak amplitudes increased almost 30% after the intervention, while the changes in the other metrics were less pronounced. However, none of these changes was statistically significant. Therefore, this study does not provide conclusive evidence about the potential of ts-MS to enhance the excitability of the motor networks. It should be further disclosed with new experiments whether the lack of statistical significance in our results is due to a real absence of an effect after the ts-MS, or to the lack of statistical power due to the low number of recruited subjects. Nevertheless, the potential of spinal cord stimulation is undeniable, with increasing evidence showing that it can be used to restore movement after complete paralysis [1], [5]. The integration of this technology in closed-loop systems has already been successfully applied in animal [16] and human models [17]. Developments for improving the integration of spinal stimulation with non-invasive brain-controlled systems [18] is also an attractive field of research that may serve to improve future motor rehabilitation therapies [19].

Future research continuing this work should focus on investigating in a larger number of subjects the effects of ts-MS on excitatory and inhibitory mechanisms. A more detailed assessment, including reflexes and sensory processing could also provide a better characterization of the whole sensorimotor network [20] in response to ts-MS. Finally, the influence of the protocol parameters such as the duration,

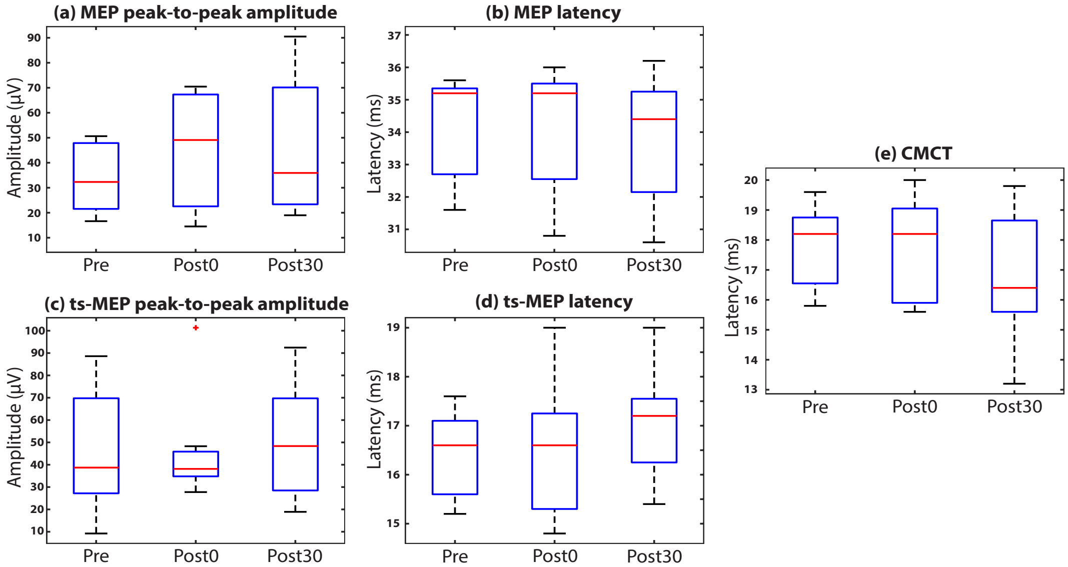

Fig. 2. Changes in *(a)* MEP amplitude, *(b)* MEP latency, *(c)* ts-MEP amplitude, *(d)* ts-MEP latency and *(e)* CMCT for right soleus across all participants displayed in boxplots. The red lines represent the median of the distribution, and the blue boxes represent the 25th and 75th-percentiles, respectively.

intensity and frequency of stimulation or the number of pulses administered need to be investigated in order to have a clear understanding of the effects of spinal cord stimulation and expedite their application to rehabilitation.

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