Transcutaneous Spinal Cord Stimulation Induces Temporary Attenuation of Spasticity in Individuals with Spinal Cord Injury

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Title: Transcutaneous spinal cord stimulation induces temporary attenuation of spasticity in individuals with spinal cord injury

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Abstract

Epidural spinal cord stimulation (SCS) is currently regarded as a breakthrough procedure for enabling movement after spinal cord injury (SCI), yet one of its original applications was for spinal spasticity. An emergent method that activates similar target neural structures noninvasively is transcutaneous SCS. Its clinical value for spasticity control would depend on inducing carry-over effects, because the surface-electrode-based approach cannot be applied chronically. We evaluated single-session effects of transcutaneous lumbar SCS in twelve individuals with SCI by a test-battery approach, before, immediately post- and two hours post-intervention. Stimulation was applied for 30 minutes at 50 Hz with an intensity sub-threshold for eliciting reflexes in lower extremity muscles. The tests included evaluations of stretch-induced spasticity (Modified Ashworth Scale (MAS) sum score, pendulum test, electromyography-based evaluation of tonic stretch reflexes), clonus, cutaneous-input-evoked spasms, and the timed 10-meter walk test. Across participants, the MAS sum score, clonus, and spasms were significantly reduced immediately after SCS, and all spasticity measures were improved two hours post-intervention, with large effect sizes and including clinically meaningful improvements. The effect on walking speed varied across individuals. We further conducted a single-case multi-session study over six weeks to explore the applicability of transcutaneous SCS as a home-based therapy. Self-application of the intervention was successful; weekly evaluations suggested progressively improving therapeutic effects during the active period and carry-over effects for seven days. Our results suggest that transcutaneous SCS can be a viable non-pharmacological option for managing spasticity, likely working through enhancing pre- and postsynaptic spinal inhibitory mechanisms, and may additionally serve to identify responders to treatments with epidural SCS.

Key Words

human, noninvasive, spasticity, spinal cord injury, spinal cord stimulation, transcutaneous

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Introduction

Spasticity is an emergent feature of disordered sensorimotor control resulting from lesions of the central motor system and expressed as involuntary activation of muscles.[1,2] Following a spinal cord injury (SCI), spasticity develops gradually over several months, affects about 70% of the individuals in the chronic stage,[3–5] and can manifest as velocity-dependent, abnormal activation of muscles to an externally imposed stretch,[6] as clonus, spasms, continuous muscle activation even in a state of rest, and uncoordinated movement patterns.[7] Spasticity may debilitate residual motor function, contribute to the development of contractures and pain conditions, restrict activities of daily living, disturb sleep, and hamper rehabilitative efforts.[4,5,8,9]

Spasticity is caused by lesions of descending brainstem pathways[10,11] and results from the loss of monoaminergic modulation of spinal interneurons and motoneurons[12–14] as well as from plastic changes at the cellular level to compensate for the lack of these neuromodulators below the lesion.[15–17] Consequences are a reduced depression of neurotransmitter release from Ia muscle spindle afferents upon their repeated activation,[12,18–20] hyper-excitability of interneurons that mediate polysynaptic excitation,[17,21] a decrease of the inhibitory capacity of postsynaptic inhibitory circuits,[22,23] and an increase of motoneuronal excitability.[24–26] Morphological changes in skeletal muscle and connective tissue secondary to spastic conditions may further accentuate resistance to passive stretch.[27–30]

In spite of the clinical and social need, effective management of spasticity has remained a challenge because of its various presentations, the multitude of underlying mechanisms, and the variability of these factors across individuals.[7,9] Current options for the clinical management of spasticity involve, in the first instance, physiotherapy and oral administration of anti-spasticity drugs, and further, chemical neurolysis, intramuscular injections of botulinum toxin, and more invasive approaches like intrathecal drug pumps or rhizotomy.[7,31,32] These treatments either reduce the afferent transmission to the motoneurons or the efferent drive to muscles.[16,31] Notably, orally administered anti-spasticity agents, the most common treatment, do not act locally within the spinal cord but produce a generalized depression of the central nervous system, often resulting in

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weakness and dizziness. Furthermore, the modulation of spinal circuits that normally regulate motoneuronal output is generally not the target of current therapies.[16,31] Hence, alternative treatment options are continuously being sought.

The use of epidural spinal cord stimulation (SCS) in recent high profile studies reporting unprecedented improvements of motor function following severe SCI has triggered a resurge of interest in the therapeutic potential of this intervention.[33–35] Remarkably, epidural SCS was originally considered a promising therapy for spasticity in this subject population.[36–38] Indeed, computational modelling,[39,40] human physiological studies,[38,41,42] as well as microdialysis techniques in animal experiments[43,44] collectively suggest that SCS can recruit local inhibitory spinal circuits transsynaptically through the stimulation of afferent fibers and enhance the release of inhibitory neurotransmitters.

In parallel to our early studies to identify the neural structures electrically activated by epidural lumbar SCS,[45–47] we developed the method of transcutaneous SCS to target the same neural input structures to the spinal cord noninvasively,[48] i.e., predominantly medium-to-large diameter afferent fibers within posterior rootlets/roots.[49,50] In three individuals with incomplete SCI, we previously presented that some manifestations of spasticity were reduced immediately after a single 30-minute session of transcutaneous SCS.[51] Others recently reported a decline of stretch-induced quadriceps spasticity 45 minutes after a single 30-minute session of transcutaneous SCS.[52] In fact, transiently persisting therapeutic effects beyond the period of the active intervention are of particular clinical relevance, because as a surface-electrode based method, transcutaneous SCS cannot be applied chronically, and the stimulation conditions are considerably influenced by changes in body position.[53]

The objective of the present study was to gain a comprehensive understanding of the carry-over effects of transcutaneous SCS on various presentations of spinal spasticity. Using multiple assessment measures, we investigated the effects of a 30-minute session of transcutaneous SCS on stretch-induced spasticity, clonus, cutaneous-input-evoked spasms, and walking speed immediately as well as two hours after the intervention in twelve individuals with chronic SCI. Further, we tested for the first time the applicability of transcutaneous SCS as a home-based therapy over a period of six weeks and whether

multiple stimulation sessions would lead to cumulative and longer-term therapeutic effects in one of the participants.

Materials and Methods

Participants

Twelve otherwise healthy adults (41.3 ± 19.1 years, mean ± SD) with traumatic, chronic SCI (≥ 1 year post-injury) were studied (Table 1). Participants 1, 3, 7, 8 and 10 were on oral anti-spasticity medication (*cf.* Table 1) and took the last dose 12–15 hours before the experiments. Among the exclusion criteria were active and passive implants at vertebral level T9 or caudally, such as osteosynthesis material. The study was approved by the Ethics Committee of the City of Vienna, Austria, and conducted in accordance with the Declaration of Helsinki. All participants signed written informed consent prior to their participation.

Study protocols

Carry-over effects of a 30-minute session of 50 Hz transcutaneous SCS on spasticity were investigated using comprehensive assessments conducted before (A0), immediately after (A1), and two hours after (A2) the cessation of the stimulation (Fig. 1A). The assessments at the different time points were identical and comprised, in this sequence, the clinical evaluation of lower-extremity muscle tone using the Modified Ashworth Scale (MAS);[54] the 10-m walk test (if possible) with walking aids as required (same in all three assessments); the Wartenberg pendulum test;[55] and an electromyography (EMG) based evaluation of lower-extremity muscle activation during a set of manual testings.[56,57] In the clinical evaluation, the resistance of a relaxed single joint to movement throughout its full range of motion imposed by an examiner was rated from 0 to 4 according to the MAS. Movements tested were flexion, extension, abduction, adduction, as well as internal and external rotation of the hip; flexion and extension of the knee with the hip in an extended position; and ankle dorsiflexion with the hip and knee in a flexed position as well as dorsiflexion, plantar flexion, and pronation of the ankle with the hip and knee in an extended position (12 separate tests per side). For the pendulum test, participants were in a supported sitting position with the trunk reclined by approximately 30 degrees, while the

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examiner lifted one leg to a horizontal position, released it, and let it oscillate passively until it stopped. The EMG-based evaluation was conducted with the participants lying supine and included passive unilateral hip and knee flexion-extension movements performed by the examiner (3 s each for flexion, holding hip and knee flexed at 90°, and extension), the attempt to elicit an Achilles clonus by a brisk manual ankle dorsiflexion, and cutaneous-input-evoked spasms by stroking the foot sole with a blunt rod. The pendulum test as well as the tests of the EMG-based evaluation were repeated three times each on both sides, separated by 10 s phases of relaxation without detectable EMG activity. The assessments were thus selected to evaluate abnormal muscle tone (MAS, pendulum test, and passive-movement segment of the EMG-based evaluation), clonus, spasms, as well as residual walking function. Between the two post-SCS assessments A1 and A2, the participants rested in their wheelchairs.

Additionally, in participant 3, the applicability of transcutaneous SCS as a home-based therapy as well as the potential to induce cumulative and longer lasting therapeutic effects by multiple stimulation sessions over a period of six weeks were tested (Fig. 1B), six months after his participation in the single-session protocol. Specifically, after an initial baseline evaluation of spasticity, 50 Hz transcutaneous SCS was applied from Mondays to Thursdays for 30 minutes per day. On Fridays, 24 hours after the preceding stimulation session, the participant underwent a re-evaluation of spasticity, followed by another 30-minute application of transcutaneous SCS. Stimulation was paused on Saturdays and Sundays. After six weeks, transcutaneous SCS was withdrawn and two follow-up evaluations were conducted after 7 and 17 days. The baseline and weekly evaluations as well as the follow-ups included the same tests as the single-session protocol. Additionally, the participant completed a daily questionnaire on the average perceived spasticity using the visual analogue scale,[58] the frequency and intensity of spasms according to the Penn spasm frequency scale,[59] and on bladder and bowel function.

Stimulation

Transcutaneous SCS was applied through a pair of self-adhesive hydrogel surface electrodes (each 5 cm in diameter; Schwamedico GmbH, Ehringshausen, Germany) positioned between the T11/T12 spinous processes, left and right to the spine, and a pair

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of indifferent electrodes (8 x 13 cm each) placed para-umbilically over the lower abdomen.[48,51,60] The electrodes of each pair were interconnected and used as single, larger electrodes. A current-controlled stimulator (Stimulette r2x+, Dr. Schuhfried Medizintechnik GmbH, Moedling, Austria) delivered charge-balanced, symmetric, biphasic rectangular pulses of 1 ms width per phase. With reference to the abdominal electrodes, the paraspinal electrodes were the anode for the first and the cathode for the second pulse phase. The second phase of the biphasic rectangular pulses was the effective stimulating phase.[50]

Electrode placement over the lumbar spinal cord was verified by applying single stimuli to elicit posterior root-muscle (PRM) reflexes[48] in the L2–S2 innervated rectus femoris, biceps femoris, tibialis anterior, and triceps surae muscle group bilaterally with the participants relaxed in the supine position (Fig. 2A). Across participants, the mean threshold (± SD) for the elicitation of PRM reflexes was 49.6 ± 25.1 mA (per phase of the biphasic stimulation pulse), ranging from 16 mA to 100 mA. Stimulation of afferent fibers was tested by applying double stimuli at intervals of 30 ms, 50 ms, and 100 ms and confirmed by the depression and gradual recovery[61,62] of the responses evoked by the second pulse of each pair of stimuli.[48,63,64]

Subsequently, the stimulator was set to continuous mode to deliver stimulation at a frequency of 50 Hz, in accordance with previous experience with epidural SCS for spasticity control.[38] With the participants lying supine, the stimulation amplitude was slowly increased from 0 mA to an amplitude that generated distant paraesthesias (tingling sensations) in bilateral L2–S2 lower extremity dermatomes but was subliminal to the PRM-reflex threshold (Fig. 2B). The generation of paraesthesias was previously used in epidural SCS to guide the effective stimulation amplitude for spasticity control.[37] In participants 10–12 with complete absence of sensory perception below the level of SCI, the stimulation amplitude was set at 90% of the lowest PRM-reflex threshold across muscles. For the 30-minute intervention, the stimulation amplitude across participants was 40.8 ± 24.1 mA, ranging from 15 mA to 90 mA.

In participant 3, in whom transcutaneous SCS was repetitively applied for six weeks as a home-based therapy, the placement of the paraspinal stimulating electrodes was

identified in the baseline evaluation and re-verified in the weekly assessments. For the identification of the correct placement at home, moles and anatomical landmarks on the back were used by the participant's partner. 50 Hz stimulation applied from such site and with an appropriate amplitude induced paraesthesias in the lower extremity dermatomes with characteristic, reproducible distribution, which served the participant as feedback for correct stimulation application. During the six weeks of repetitive sessions of 50 Hz transcutaneous SCS, the participant applied an average stimulation amplitude of 24.0 ± 4.8 mA.

Data Acquisition

EMG was acquired from rectus femoris, biceps femoris, tibialis anterior, and triceps surae muscle group of both legs with pairs of silver-silver chloride surface electrodes (Intec Medizintechnik GmbH, Klagenfurt, Austria), placed in longitudinal alignment and an inter-electrode distance of 3 cm [56]. Common ground electrodes were placed over the fibular heads bilaterally. Abrasive paste (Nuprep, Weaver and Company, Aurora, CO) was used for skin preparation to minimize signal noise. EMG signals were recorded via instrumentation amplifier (INA 118, Texas Instruments Inc., Dallas, TX), amplified with a gain of 600, filtered to a bandwidth of 10–500 Hz within the analogue front end and digitized at 2048 samples per second and channel with a USB-NI 6261 data acquisition card (National Instruments Inc., Austin, TX) and recorded using DasyLab 11.0 (Measurement Computing Corporation, Norton, MA). In participants 5, 10, 11, the Phoenix multichannel EMG system (EMS-Handels GmbH, Korneuburg, Austria) was used, set to a gain of 502 over a bandwidth of 10–1000 Hz and digitized at 2048 samples per second and channel. All EMG signals were additionally bandpass-filtered offline between 10 and 500 Hz using a 2nd order Butterworth filter. For the Wartenberg pendulum test, electro-goniometers (SG150, Penny & Giles Biometrics, Ltd., Gwent, UK) were used to monitor knee joint angles. The goniometer output signals were low-pass filtered to 15 Hz, and digitized at 2048 samples per second.

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Data Analysis and Statistics

Data were analyzed offline using Matlab R2017b (The MathWorks, Inc., Natick, MA) and IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, New York, NY).

Resistance to passive leg movements was clinically graded according to the MAS.[54] A single score, the MAS sum score, was obtained per assessment (A0, A1, A2) by summing the individual scores of the twelve different movements tested per leg (with a value of 1.5 for the 1+ scoring category), resulting in a value ranging from 0–96 (0, no increase in muscle tone).

The spasticity index was calculated based on the knee angle of the initial horizontal leg position of the Wartenberg pendulum test[65] (*Start*), the angle at which the leg reversed for the first time from flexion to extension (*Flex*), and the final knee resting angle (*Rest*):

$$spasticity\ index = \frac{Flex - Start}{1.6 * (Rest - Start)}$$

Values ≥ 1 denote non-spastic conditions, and 0 extreme spasticity. For each assessment (A0, A1, A2), a single index was obtained by averaging the six values (three pendulum tests, two legs).

The time required to walk 10 m was measured and used to calculate the walking speed (m/s) for each assessment (A0, A1, A2).

The EMG during passive multi-joint movements was evaluated by calculating the total activity of ipsilateral leg muscles as the sum of the root mean square (RMS) values of the EMG of each muscle group from the onset to the offset of the movement (9 seconds). Analogously, the EMG of ipsilateral leg muscles in response to the attempt to elicit ankle clonus and cutaneous-input-evoked spasms were evaluated during 3-second time windows following the onset of each test. For each test (passive movement, clonus, spasms), mean RMS values per assessment (A0, A1, A2) were obtained by averaging the three repetitions on both sides.

To test the hypothesis that a single 30-minute session of 50 Hz transcutaneous SCS would ameliorate spasticity from before (A0) to immediately after the application (A1) and that these effects would persist for two hours (A2), the measures obtained in A1 and A2

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were separately compared to those of A0 using the non-parametric Wilcoxon signed-rank test ($\alpha = 0.05$). To assess potential cumulative effects of repetitive sessions of transcutaneous SCS over a period of six weeks in participant 3, the results of each measure taken were ranked from best (rank 1) to worst (rank 9) over the nine evaluations conducted (baseline, six weekly evaluations, two follow-ups), and a mean rank across measures was then calculated for each evaluation. Spearman's rank correlation ($\alpha = 0.05$) was calculated to evaluate the relationship between rankings and evaluations (thus potentially providing information on the "training effect" of repetitive stimulation sessions).

Results

Carry-over effects of a single 30-minute session of transcutaneous SCS

Thirty-minute sessions of transcutaneous SCS at 50 Hz and with the targeted amplitude could be successfully applied in all participants. The stimulation continuously produced mild tingling sensations in the leg dermatomes of the participants with partially preserved sensory function (see Fig. 2B). Local sensory and neuromuscular stimulation beneath the stimulating electrodes was well tolerated by all participants.

The stimulation resulted in several significant improvements of the measures of spasticity that persisted for the duration of data acquisition in the post-SCS assessments (Figs. 3, 4). Immediately after the intervention (assessment A1 compared to A0), the MAS sum score, clonus and cutaneous-input-evoked spasms were significantly improved. Two hours post-stimulation (A2 compared to A0), all spasticity measures evaluated were significantly improved. All significant changes met the criteria of large effects sizes.

Specifically, the MAS sum score was significantly reduced from A0, median 31.75 (interquartile range (IQR): 18.63–37.38) to 23.50 (14.63–32.25) in A1 ($z = -2.944$, $p = .003$, $r = .850$), and to 24.75 (13.25–30.88) in A2 ($z = -2.590$, $p = .010$, $r = .748$) (Fig. 3A*(i)*), with a clinically relevant decrease of abnormal muscle tone (i.e., single MAS scores reduced by values of ≥ 1)[66,67] occurring in each of the participants (Fig. 3A*(ii)*).

The median spasticity index was 0.765 (IQR: 0.668–0.890) in A0 and 0.900 (0.630–0.953) in A1, showing no statistical difference ($z = -1.452$, $p = .146$, $r = .419$), and was

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significantly improved to 0.870 (0.778–0.943) in A2 (z = -2.787, p = .005, r = .805) (Fig. 3B*(i)*), reflecting changes of the swinging movement of the lower leg (Fig. 3B*(ii)*). Individually, in A1, the angle at which the leg reversed for the first time from flexion to extension showed an increase by ≥ 12° in six participants, which was previously suggested to be a clinically meaningful difference following an anti-spasticity treatment;[52,68] in one participant, the change was moderate (increases of 6°–11°), and mild in two participants (1°–5°). In A2, three participants showed a clinically meaningful increase, five a moderate increase, and three a mild increase.

In the EMG-based evaluation, the median RMS of the EMG activity produced during passive unilateral hip and knee flexion and extension was 26.2 μV (IQR: 17.8–39.8 μV) in A0 and 22.9 μV (15.9–42.7 μV) in A1, showing no statistical difference (z = -.784, p = .433, r = .226), and was significantly reduced to 25.2 μV (14.8–36.3 μV) in A2 (z = -2.824, p = .005, r = .815) (Fig. 4A*(i)*). The EMG traces in Fig. 4A(*ii)* show abnormal tonic stretch reflexes and reflex spread induced by the imposed movement and their attenuation following the stimulation. The median EMG RMS values of the activity associated with clonus were significantly reduced in both post-stimulation assessments, from 46.9 μV (IQR: 20.2–94.8 μV) in A0 to 42.2 μV (16.7–76.1 μV) in A1 (z = -2.589, p = .010, r = .747) and to 39.1 μV (22.1–66.0 μV) in A2 (z = -2.589, p = .010, r = .747) (Fig. 4B*(i)*). Figure 4B*(ii)* illustrates an example of sustained clonus evoked by the examiner after rapidly flexing the ankle in A0, while an equivalent stretch (see initial deflections in the goniometric traces) applied in A1 induced a shorter-lasting clonus, and only a few beats in A2. The median RMS values of the EMG produced in response to plantar stimulation were significantly reduced from 45.7 μV (IQR: 19.4–103.8 μV) in A0 to 34.0 μV (19.0–76.1 μV) in A1 (z = -2.040, p = .041, r = .589) and to 41.6 μV (17.0–61.5 μV) in A2 (z = -2.275, p = .023, r = .657) (Fig. 4C*(i)*). The attenuated cutaneous-input-induced spasms were also seen as reduced withdrawal movements from the mechanical stimulation (Fig. 4C*(ii)*).

Eight of the twelve participants were able to complete the 10-m walk test. Across these individuals, there were no changes in the median walking speed from 0.26 m/s (IQR: 0.12–0.72 m/s) in A0 to 0.24 m/s (0.12–0.66 m/s) in A1 (z = -.634, p = .526, r = .224) and to 0.25 m/s (0.15–0.73 m/s) in A2 (z = -.985, p = .325, r = .348) (Fig. 3C*(i)*). The individual

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results showed some noticeable variability, both between participants as well as the time points of post-SCS evaluation (Fig. 3C*(ii)*). The largest relative changes in walking speed were seen in participants 1 and 8. Participant 1 improved by 19% in A1 and by 43% in A2. Participant 8 (with knee and ankle extensor motor scores of 1) critically depended on the considerable tone of his extensor muscles to cover the distance of 10 m in A0, with a walking speed of 0.12 m/s. In A1, hypertonia was visibly reduced and leg extension during stance clearly compromised, resulting in a reduced walking speed of 0.08 m/s. In A2, his ability to perform steps improved and the walking speed increased to 0.19 m/s, likely related to the re-appearance of some critical level of lower-extremity muscle tone. Participant 7 (AIS C) was unable to complete the test in any assessment, and participants 10–12 had a complete SCI (AIS A), being unable to stand or step.

Applicability of transcutaneous SCS as a repetitively applied home-based therapy

Transcutaneous SCS was repetitively self-administered in a home-based setting for six weeks by participant 3 without any complications or intervention-related adverse events. In weeks 2–3 of the stimulation period, the participant was affected by an acute urinary tract infection.

The generation of tingling sensations in the lower extremities, both in terms of the sequence in different leg areas when stimulation amplitude was gradually increased, as well as the final paraesthesia coverage, served the participant as reliable guidance for the correct usage of the stimulation. The participant applied an average stimulation amplitude of 24.0 ± 4.8 mA at home, and the mean PRM reflex threshold identified in the weekly evaluations was 23.9 ± 8.0 mA.

The MAS sum scores of the participant's lower-extremity muscle hypertonia tested clinically in the weekly evaluations showed a strictly monotonous decrease during the stimulation period, a maintained improvement one week after withdrawal of the stimulation followed by an increase another ten days later (Fig. 5A). The evolution of the other outcome measures was less obvious, including some intermittent worsening in weeks 2 and 3 (Fig. 5B–D). Yet, four out of the six outcome measures attained their respective best values in the two last evaluations during the stimulation period (W5, W6) as well as the first follow-up (F1) and showed deterioration thereafter. Considering all

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outcome measures, there was a negative correlation between rankings and evaluation time points (ρ = -.411, p = .002; Fig. 5E), indicating that spasticity improved over the stimulation period. It should be repeated at this point that each evaluation during the stimulation period was conducted 24 hours after the preceding stimulation session.

The participant rated his average perceived spasticity as 65 on the visual analogue scale in the baseline evaluation, and as 50 after the first week of stimulation until ten days after the final stimulation session. Thereafter, the participant assigned scores between 60 and 63, and raised his daily dose of baclofen from 20 mg to 30 mg. There were no effects on frequency and intensity of spasms, with scores of 1, respectively, on the Penn spasm frequency scale throughout the evaluation period. Bladder function (managed by a suprapubic catheter with continuous drainage) and bowel movement remained unchanged.

Subjectively, the participant reported several beneficial effects during the stimulation period, including increased trunk stability, facilitation of upright standing, improved endurance during activities of daily life, and enhanced sensory perception in the foot soles. Further, he described effects in his upper extremities, including reduced muscle tone (Supplementary Fig. 1A), the absence of spasms otherwise induced by touching hot surfaces, increased range of movement of fingers and wrists, improved fist closure, and augmented dexterity, including improved handwriting (Supplementary Fig. 1B).

Discussion

Thirty minutes of 50 Hz transcutaneous SCS improved several measures of lower-extremity spasticity for two hours post-intervention across twelve individuals with chronic SCI. Since exaggerated stretch reflexes are regarded as the core feature of spasticity,[6,11] three complementary assessment methods were used to evaluate abnormal muscle tone during passive movement. The clinical evaluation using the MAS[54] and testing different joints was applied to obtain a single, comprehensive measure for the overall lower-extremity hypertonia, the MAS sum score (*cf.* [68]). The pendulum test, which correlates with the MAS in persons with SCI,[68,69] was used as a biomechanical method, using gravity to provoke passive stretch for examining the tone of muscles spanning the knee joint.[52,65] The EMG-based evaluation of tonic stretch reflexes tested abnormal tone independently of

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soft-tissue properties of the muscles.[2,56] These measures were complemented by the assessments of other presentations of spasticity, i.e., clonus and muscle spasms, the latter being pathophysiologically distinct from exaggerated stretch reflexes.[17] This thorough set of assessments of the severity of spasticity demonstrated treatment efficacy across participants:[70] the MAS sum score, clonus, and spasms were significantly improved immediately after the intervention, and all spasticity measures were significantly improved two hours post-intervention. The 10-m walk test was chosen to assess whether alterations in spasticity would impact walking function. Walking speed did not change significantly across participants. Additionally, a single case study showed that transcutaneous SCS could be adequately self-administered without complications over a period of six weeks and suggested carry-over effects on spasticity and cumulative improvements over the stimulation period that endured for at least one week after withdrawal of the stimulation.

In the following, we will propose that the anti-spasticity effects of transcutaneous SCS based on the generation of multi-segmental afferent synaptic inputs, which engaged pre- and postsynaptic mechanisms. With the relatively low stimulation amplitudes and high stimulation frequency used, inhibition of spinal reflex circuits outweighed the excitatory actions on motoneuronal activity. We will further briefly reflect on how the stimulation could have provoked the transiently enduring effects. Finally, we will address some methodological considerations.

Neural structures electrically stimulated by transcutaneous SCS

The key characteristics of transcutaneous SCS are the generation of a current flow across the spine at the thoracolumbar junction[48,49,71,72] and the activation of afferent fibers with origins in *distant* dermatomes and myotomes.[47,50,51,73,74] A fraction of the generated current flows through the vertebral canal[49] mainly via the ligaments and intervertebral discs. Of all intrathecal neural structures, large-to-medium diameter afferent fibers[75,76] within the posterior rootlets have the lowest excitation thresholds upon entering the spinal cord, because of changes in their spatial fiber orientation with respect to the electric field and the voltage drop at the electrical conductivity boundary between the cerebrospinal fluid and the spinal cord.[45,49,71,77,78] Transcutaneous SCS hence activates similar neural target structures as epidural lumbar SCS.[35,49,50,79]

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For the intervention, stimulation was applied at 50 Hz with an amplitude below PRM-reflex elicitation, yet generating tingling sensations in multiple lower extremity dermatomes, which reflect the electrical stimulation of A-beta/group II afferents from skin mechanoreceptors.[41,80] As group I afferents have larger diameters than those of group II and thus lower thresholds for external electrical stimulation,[75–77] Ia muscle spindle afferents must have been recruited as well, yet only producing volleys subliminal to evoke measurable reflex activation of motoneuron pools.[62,81] This is supported by the detection of antidromic potentials in mixed peripheral nerves during epidural stimulation applied over the low-thoracic dorsal columns[41] and lumbar posterior roots[79] with intensities eliciting paraesthesias in the legs without producing visible muscle contractions. Furthermore, the recruitment of group Ia muscle spindle afferents by sensory-level epidural stimulation was demonstrated by monosynaptic facilitation of motoneurons during slight voluntary activity.[41] It can be thus concluded that tonic transcutaneous SCS as applied here generated afferent volleys in group I and II fibers to lumbar and upper sacral spinal cord segments. In turn, these repetitive afferent inputs likely enhanced intrinsic inhibitory mechanisms in the spinal cord. Indeed, the stimulation parameters were in accordance to previous studies employing epidural SCS to reduce spasticity that had emphasized the importance of applying stimulation amplitudes generating paraesthesias in the affected extremities without muscle activation, at frequencies of 50-100 Hz.[37,38]

Potential neural mechanisms recruited by transcutaneous SCS underlying the anti-spasticity effects

Presynaptic inhibition from homonymous and heteronymous nerves is reduced following SCI in humans,[12,82] as is post-activation depression[18,20] of repetitively activated Ia afferents.[17,83] Dysfunction in these presynaptic regulatory mechanisms following SCI thus results in an increased excitatory neurotransmitter release from Ia afferents and likely contributes to the exaggerated stretch reflexes and hypertonia associated with spasticity.[17,19,31] The continuous generation of Ia activity in multiple roots by transcutaneous SCS, especially in those containing afferents from flexor nerves, would increase the level of presynaptic inhibition distributed to Ia terminals associated with ipsilateral leg muscles.[41,62,84,85] Further, the repetitive activation of Ia afferents at 50 Hz

would profoundly decrease the neurotransmitter release from the activated afferent terminals to motoneurons and thus the transmission within the stretch reflex arc.[17,41,83]

Postsynaptically acting Ia inhibitory interneurons[86] are effectively activated by Ia muscle spindle afferents.[87] In epidural SCS, the recruitment of reciprocal Ia inhibitory circuits has been suggested by computational modelling[39,40] and by reciprocally organized EMG activities in human physiological studies.[42,88] Tonically increasing the activity of Ia inhibitory interneurons by the stimulation-induced synaptic inputs would reduce the overall excitability of the lumbosacral motoneuron pools.[89] An increase of postsynaptic inhibition would be of further relevance for attenuating spasticity;[90] enhanced activation of persistent inward currents in SCI has been suggested to play a major role in the generation of long-lasting exaggerated reflexes and muscle spasms in response to brief or weak afferent volleys[17,25] in animal[26,91] and human studies.[24,92–94] Hyperpolarization of the motoneuronal membrane potential through postsynaptic inhibition can deactivate persistent inward currents and hence terminate plateau potentials and self-sustained firing of the motoneurons.[95–97]

The role of the stimulation of afferents from skin mechanoreceptors is less evident, because of their complex connectivity to excitatory and inhibitory interneurons within the lumbar spinal cord.[87] Other electrical stimulation approaches have attributed the reduction of spasticity to the stimulation of cutaneous afferents,[31] yet the exact mechanisms by which these structures exert their effects have not been identified.[98] Various hypotheses were put forward, including the enhancement of reciprocal inhibition[99] and presynaptic inhibition,[100] and depression of the propriospinal system.[101]

Carry-over effects of transcutaneous spinal cord stimulation

The above discussed pre- and postsynaptic mechanisms triggered by the stimulation-induced afferent activity typically last only for a few milliseconds[71,76] to a few seconds.[62,102] The observed carry-over effects would require temporary alterations of the transmission along the spinal circuits following their repetitive stimulation, but at this stage, we can only speculate about the mechanisms.

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Previous studies applying electrical stimulation to peripheral nerves have shown carry-over effects on impaired motor function and spasticity, both with single as well as repetitive sessions,[99–101,103–107] but the underlying mechanisms remained unclear. One explanation could be long-term potentiation,[101] an increase in synaptic efficacy resulting from repetitive activation of the synapse that outlasts a conditioning high-frequency stimulation of afferent pathways by at least 30 minutes.[108] Long-term potentiation was demonstrated between dorsal root afferents and neurons in the spinal cord of rats,[109] but studies have focused on nociceptive pathways.[110] The induction of long-term potentiation requires the depolarization of the postsynaptic membrane, the activation of NMDA receptors by synaptically released glutamate, and a temporal coincidence between the post- and presynaptic activities.[109]

The depolarization of the very proximal portions of lower-extremity afferents by transcutaneous SCS would produce highly synchronized afferent inputs to multiple lumbar and upper sacral spinal circuits, and thus result in a sharp temporal relationship between the postsynaptic activity and the excitatory synaptic inputs, likely mediated through glutamate.[111,112] With the prolonged stimulation at 50 Hz, long-term potentiation could presumably be induced and increase the transmission in local inhibitory pathways, e.g., by strengthening the glutamatergic Ia afferent effect upon the Ia inhibitory interneurons or on the first-order excitatory primary afferent depolarization interneurons. Concurrently, the Ia inhibitory synapse on the motoneuron could be potentiated.[113] Furthermore, the repetitive and highly synchronous neurotransmitter release from the Ia terminals to motoneurons at 50 Hz could result in a prolonged decrease of neurotransmitter release probability from the activated afferents and hence reduce excitatory postsynaptic potentials in target motoneurons,[109] increasing post-activation depression in the spastic individuals.

Finally, repetitively applied sessions of transcutaneous SCS may change further cellular properties by partially reversing longstanding receptor up or downregulation, enhancing the potassium-chloride cotransporter KCC2 activity and reducing the facilitation of persistent inward currents.[16,23]

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Ascending effects on cervical spinal cord segments

Striking effects on upper extremity function were reported in early studies employing epidural stimulation of the mid-thoracic spinal cord in multiple sclerosis patients,[114,115] including a near-identical observation of improved handwriting as reported here.[116] In humans, evidence for intraspinal transmission of afferent signals from lower extremity nerves to the cervical spinal cord was provided by the elicitation of ascending interlimb reflexes in upper extremity muscles in individuals with (motor) complete cervical SCI.[117–119] These studies proposed long propriospinal pathways that couple the lumbar spinal cord with the cervical enlargement, or sprouting of disrupted sensory fiber branches ascending from the lumbar spinal cord.

Methodological considerations and limitations

The study is neither blinded nor placebo controlled. As with epidural SCS, a patient-blinded study is not realizable with transcutaneous SCS because of the inherent stimulation-induced paraesthesias. As for many other non-pharmacological treatments, a sham-intervention without any potential active effect may not exist.[52,120] Importantly, information about the non-intervention related effects in the present work can be directly inferred from a recent study in which the sham intervention consisted of a brief ramp-up and ramp-down electrical stimulation after which the SCI participants remained reclined with their lower extremities extended for 30 minutes without any further stimulation.[52] This sham-intervention significantly increased stretch-induced quadriceps spasticity, indicating that immobility in this position even for short durations increases spasticity in SCI individuals.

Stimulation parameters were not optimized individually. In applications of epidural SCS in spinal spasticity, the stimulation parameters are individually adapted, often within a trial phase, which can last up to two weeks to optimize the attainable therapeutic outcomes. Effective stimulation frequencies vary individually between 50-100 Hz.[37,38] In the present study, we had chosen to test the same stimulation frequency of 50 Hz across all participants. It can be assumed that in clinical applications, individually tailored parameter settings could further enhance the effects of transcutaneous SCS. The use of two interconnected horizontally placed paraspinal electrodes in the present study was

owing to the original electrode set-up for transcutaneous SCS.[48] The idea was to later utilize this set-up for field steering, but asymmetrical stimulation then never appeared to be a critical issue. We would hence suggest a single stimulating electrode placed midline over the spine for future studies.

Use of anti-spasticity medication. It is not trivial to suspend anti-spasticity medication for a longer period of time in study participants, considering the direct impact on their quality of life. Five of the twelve participants were under oral anti-spasticity medication and took the last dose 12-15 hours prior to the experiments. With the exception of tetrazepam (used by a single subject), the half-lives of the medications taken are relatively short (approximately 2-4 hours), hence drug effects on the study assessments must have been negligible. Any residual effects would have affected the baseline assessments (A0) the most, because the elimination is a logarithmic function in time, thus rather resulting in an underestimation of the transcutaneous SCS effects.

Variability in functional outcome. We had chosen the 10-m walk test to explore the effect of the modification of spasticity on function.[70] Influences upon functional tasks following an intervention aimed at reducing spasticity are complex, and modification in spasticity can have positive or negative effects in individuals with different injury severity and profiles. For individuals with low lower extremity motor scores, hypertonia in extensors can assist with weight-bearing, while resistance in joint movement or restricted active range of motion would be detrimental for those with some capacity to ambulate.[32,70,121] This complexity was reflected in our data. Our personal experience was also that participants with chronically adopted walking strategies had difficulties to adapt to the acute changes in spasticity, including changes in their overall posture. An improvement in the effects of transcutaneous SCS on ambulation could be realized by individual optimization of the stimulation parameters[60,122] or by multiple applications of the intervention.[120,123] Alternatively, single applications of transcutaneous SCS could be used just before dedicated locomotor rehabilitation sessions to adjust the individual spasticity level.

Limitation of the single case multi-session study. The single case study exploring the applicability of transcutaneous SCS as a repetitively applied home-based therapy had no

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long-term baseline nor control data. Yet, several measures of lower extremity spasticity clearly worsened after withdrawal of the stimulation, following their improvements during the active stimulation period, suggesting a causal relation of the changes in spasticity with the intervention. Furthermore, improvements in upper extremity function happened with no expectation bias neither by the rater nor the subject. Therefore, we believe that sharing our early experience with this protocol would be useful for planning future studies that will focus on multi-session effects of transcutaneous SCS.

Conclusions

By using a comprehensive test-battery approach, we have shown that transcutaneous lumbar SCS can decrease various presentations of spinal spasticity for at least two hours beyond a single application. A single case study further suggested that administration of the stimulation over a longer period of time is feasible and safe in a home-based setting. The anti-spasticity effect of transcutaneous SCS with relatively low stimulation amplitude and high stimulation frequency based on the generation of multi-segmental afferent synaptic inputs, which likely enhanced the intrinsic inhibitory mechanisms in the spinal cord. Activation of the spinal cord circuits to normalize reduced inhibition appears as a more natural method to alleviate spasticity than anti-spasticity medication and would be free from sedation and dizziness. Compared to other non-pharmacological interventions, the equipment is affordable and accessible, the time required for a therapist to apply the intervention would be short, and advantages could be in the treatment of diffuse types of spasticity[31] as well as in a longer duration of the induced carry-over effects.[52] Finally, transcutaneous SCS could be used to identify responders for the treatment of spasticity with epidural stimulation to justify the invasiveness and higher costs of the implantable system.

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Author Disclosure Statement

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Table 1. Participants' data and neurological status according to the International Standards for Neurological Classification of Spinal Cord Injury

Part.nr.	Sex	Age (y)	Time post-SCI (y)	Neurol. level of SCI	WISCI II score	AIS	LEMS total (max. 50)	PP sensory subscore, L1–S2 (max. 28)	LT sensory subscore, L1–S2 (max. 28)	Anti-spasticity medication (daily dosage)
1	M	66	7	T4	16	D	42	14	14	10 mg baclofen
2	F	53	8	C7	16	D	40	14	14	NA
3	M	52	2	C7	16	D	39	18	18	20 mg baclofen
4	M	47	4	C4	19	D	38	14	14	NA
5	M	61	43	T4	16	D	28	0	0	NA
6	F	70	48	T6	16	D	27	28	28	NA
7	M	26	9	C4	1	C	21	14	14	50 mg baclofen, 24 mg tizanidine, 100 mg tetrazepam
8	M	21	2	C6	2	C	8	14	28	50 mg baclofen
9	M	20	5	T6	9	C	7	0	14	NA
10	M	26	1	C4	0	A	0	0	0	100 mg baclofen, 12 mg tizanidine

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11	M	35	15	C7	0	A	0	0	0	NA
12	F	18	1	T7	0	A	0	0	0	NA

AIS, American Spinal Injury Association Impairment Scale; LEMS, lower-extremity motor score; LT, light touch; Neurol., neurological; Part., participant; PP, pin prick; WISCI, Walking index for spinal cord injury

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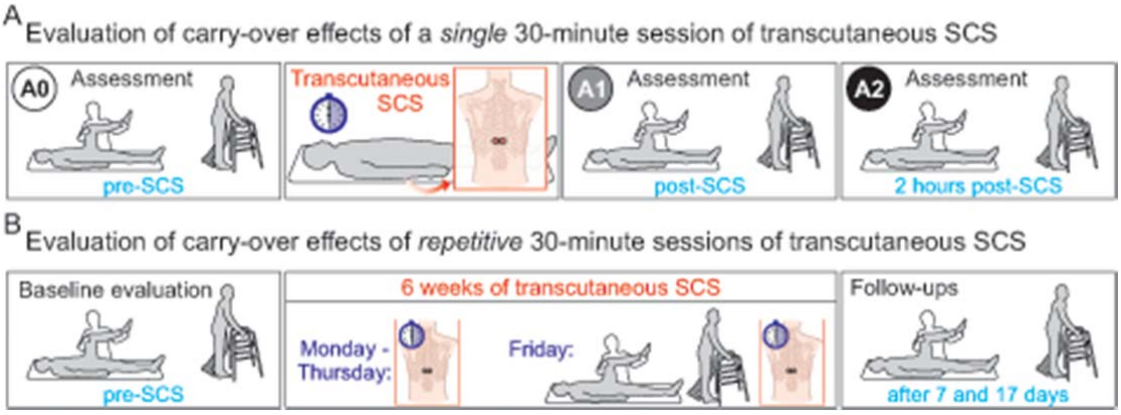

FIG. 1. Evaluation of carry-over effects of transcutaneous spinal cord stimulation (SCS) on spinal spasticity and walking speed. **(A)** The effects of a single 30-minute session of 50 Hz transcutaneous SCS were assessed at two different time points, immediately post-SCS (A1), and two hours post-SCS (A2), and compared to baseline (A0). The assessments at the different time points were identical and comprised the clinical evaluation of lower-extremity muscle tone, the 10-m walk test, the Wartenberg pendulum test, and an electromyography-based evaluation of various presentations of spasticity. **(B)** The effects of repetitive 30-minute sessions of 50 Hz transcutaneous SCS conducted as a home-based therapy were tested in one participant (# 3). A baseline evaluation was conducted prior to the first stimulation application, which was then applied for 30 minutes five times a week for six weeks. Weekly evaluations were conducted 24 hours after the preceding stimulation sessions. Follow-up assessments were performed 7 and 17 days after the final SCS session.

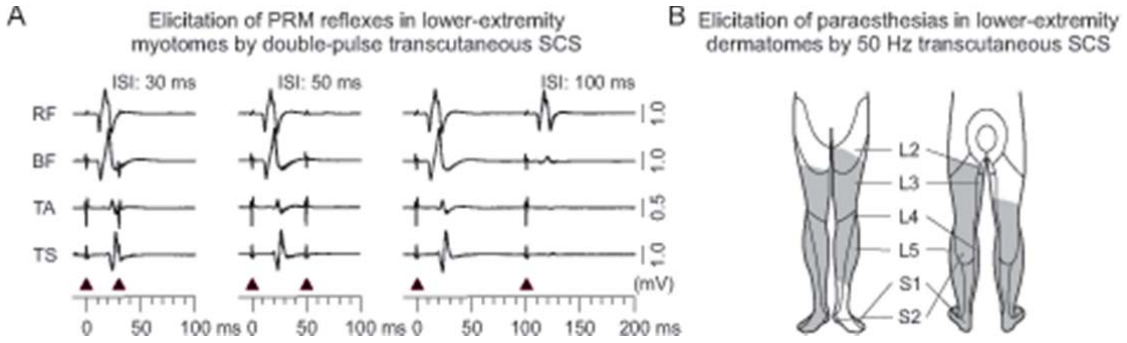

FIG. 2. Verification of bilateral L2–S2 afferent fiber stimulation. **(A)** The correct placement of the paraspinal electrodes was verified based on the elicitation of posterior root-muscle (PRM) reflexes in L2–S2 innervated leg muscles.[48] Afferent stimulation was confirmed by the depression and gradual recovery of the PRM reflexes using a paired-pulse paradigm (ISI, interstimulus intervals).[48,51] Exemplary responses of one leg electromyographically recorded from rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA), and triceps surae (TS); three repetitions superimposed; participant 2. Arrowheads mark stimulation artifacts. **(B)** Transcutaneous spinal cord stimulation (SCS) at 50 Hz and with an amplitude below the PRM-reflex threshold produced paraesthesias in L2–S2 dermatomes.[50,51] Exemplary distribution of paraesthesias (shaded areas) as perceived by participant 6 during the intervention.

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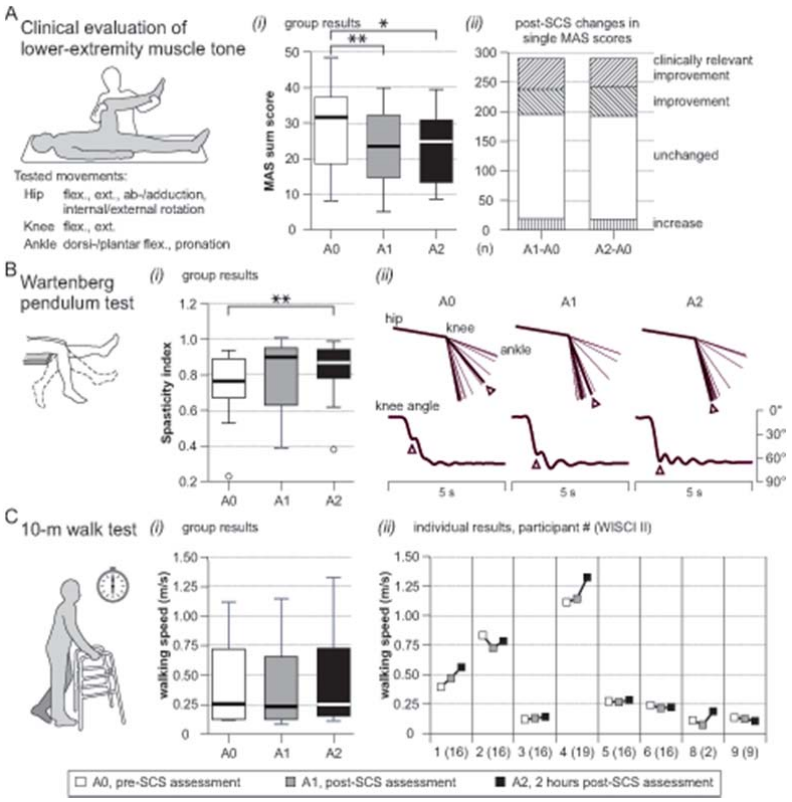

FIG. 3. Carry-over effects of a 30-minute session of 50 Hz transcutaneous spinal cord stimulation (SCS) on lower-extremity muscle hypertonia and walking speed. **(A)** Comprehensive clinical grading of the resistance to passive movement of muscles spanning the hip, knee, and ankle joints based on the Modified Ashworth Scale (MAS). *(i)* Group results of the MAS sum scores before and after the intervention, represented by box plots. *(ii)* Post-intervention changes in individual MAS values (one value for each of the twelve different movements tested per leg and participant). Stacked bar charts categorize the differences in MAS values as clinically relevant improvement (MAS differences of ≤ -1), improvement (-0.5), unchanged (0), and increase (> 0). **(B)** Hypertonia of muscle groups spanning the knee tested by the Wartenberg pendulum test. *(i)* Group results of the spasticity index at the different time points of evaluation. *(ii)* Lower-leg movements recorded during the Wartenberg pendulum test of participant 2, right leg; first repetitions of the test conducted before and after the intervention, respectively. Bottom: Goniometric data recorded from the knee joint; arrowheads point to the maximum flexion angle at the end of the first swing, i.e., the angle at which a spastic reflex contraction is elicited by the quadriceps stretch. Top: Stick figures illustrating the swinging movement of the lower leg

following its release from an extended position, constructed from the goniometric data (4 samples per s). Leg position at the end of the first swing indicated by bold line and arrowhead; final resting position indicated by bold line. **(C)** Walking speed over a distance of 10 meters. *(i)* Group results and *(ii)* individual results of the 8 participants who were able to complete the walk test (with walking ability as classified by the WISCI II in parentheses). Box plots represent medians, i.e., central tendencies of data, by bold horizontal lines within boxes that span the interquartile range (IQR), i.e., the corresponding measure of statistical dispersion. The IQR represents the middle 50% of data, splitting off the lowest and highest 25%, respectively. Whiskers extend to the smallest and largest values that are not outliers. Outliers, i.e., here values between 1.5-3 IQR of the lower quartile, are shown as separately plotted points. Asterisks denote significant changes in the group results between the respective post-SCS assessments and A0 (*, $p < .05$; **, $p < .01$). ext., extension; flex., flexion; WISCI, Walking index for spinal cord injury.

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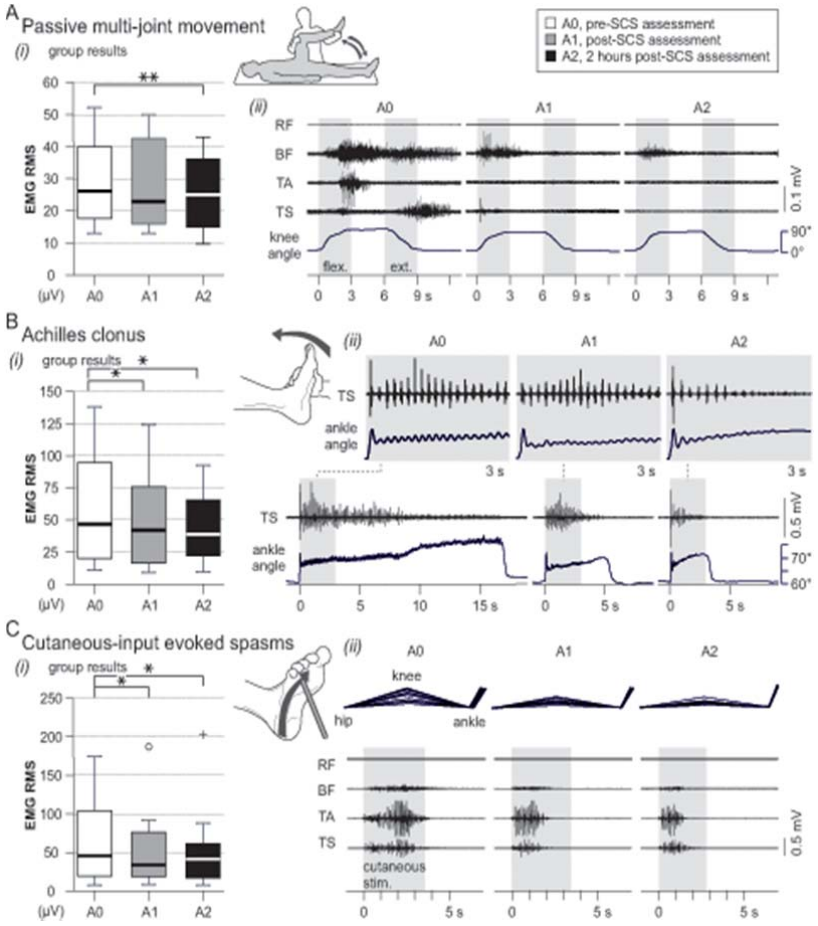

FIG. 4. Carry-over effects of a 30-minute session of 50 Hz transcutaneous spinal cord stimulation (SCS) on various presentations of spasticity tested by an EMG-based evaluation. **(A)** Abnormal muscle activation through tonic stretch reflexes during passive unilateral leg flexion (flex.) and extension (ext.) movements. *(i)* Group results of the root mean square (RMS) values of the EMG recorded during the pre- and post-SCS evaluations represented by box plots and *(ii)* exemplary EMG recordings of rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA), and triceps surae (TS) along with knee goniometric data. **(B)** Evaluation of Achilles clonus. *(i)* Group results of the RMS values of the EMG produced following a brisk manual ankle dorsiflexion and *(ii)* exemplary EMG activity of TS together with ankle goniometric data. Magnified signals reveal the characteristic bursts of EMG activity associated with clonus as well as involuntary ankle oscillations at a typical clonus frequency of 6.5 Hz. **(C)** Evaluation of cutaneous-input-evoked lower extremity spasms. *(i)* Group results and *(ii)* exemplary EMG recordings, with the periods of mechanically stroking the foot sole indicated (cutaneous stim.). Top: Stick figures illustrate withdrawal-like

movements of the examined leg, constructed from goniometric data of knee and ankle joints (4 samples per s). Group results are derived from all studied participants. Box plots represent medians, i.e., central tendencies of data, by bold horizontal lines within boxes that span the interquartile range (IQR), i.e., the corresponding measure of statistical dispersion. The IQR represents the middle 50% of data, splitting off the lowest and highest 25%, respectively. Whiskers extend to the smallest and largest values that are not outliers. Outlier, i.e., here a value between 1.5-3 IQR of the upper quartile, shown as separately plotted point, and extreme value, i.e., here a value > 3 IQR of the upper quartile, as a '+' on the box plot. Asterisks denote significant differences between A0 and the respective post-SCS assessments (*, $p < .05$; **, $p < .01$). Exemplary results show first repetitions of the respective tests conducted before and after the intervention; participant 8.

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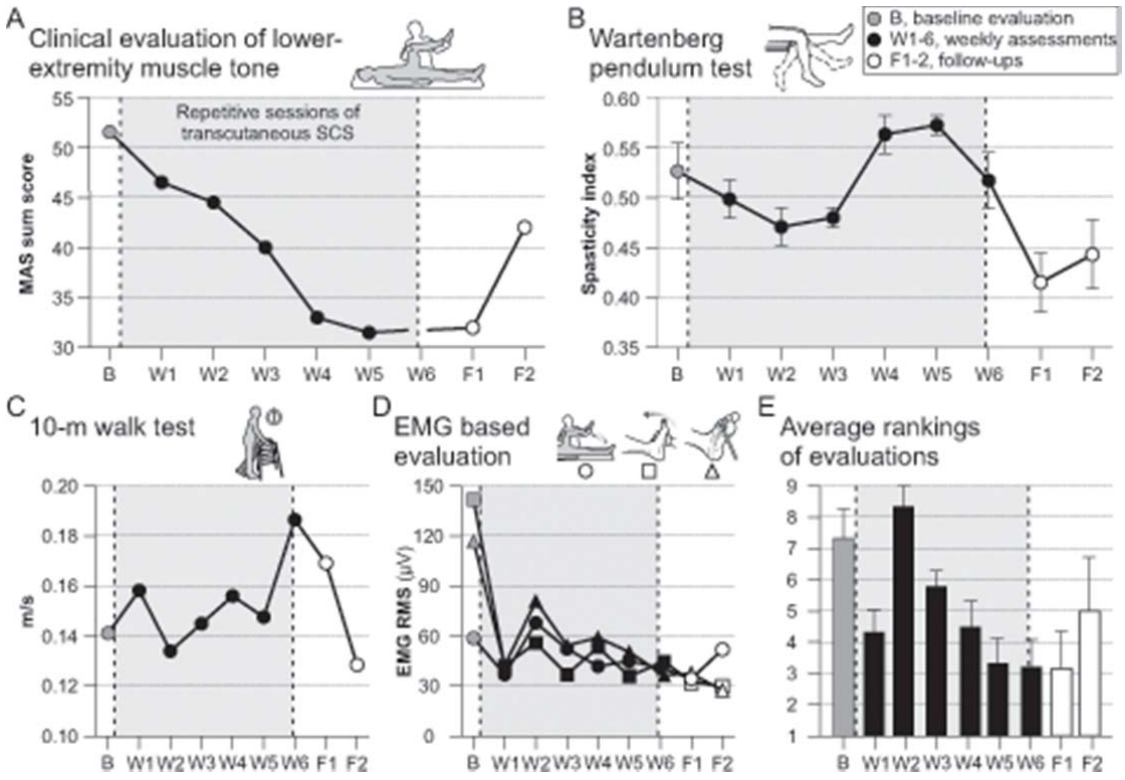

FIG. 5. Effects of repetitive 30-minute sessions of 50 Hz transcutaneous spinal cord stimulation (SCS) administered over a period of six weeks in a home-based setting; participant 3. Results of weekly evaluations of **(A)** the clinically graded resistance of lower-extremity muscles to passive movements expressed as the Modified Ashworth Scale (MAS) sum score, **(B)** the spasticity index (± SD) calculated from the Wartenberg pendulum test, **(C)** the walking speed derived from the 10-m walk test, and **(D)** the root mean square (RMS) values of the EMG derived from the evaluation of tonic stretch reflexes (circles), clonus (squares), and cutaneous-input-evoked spasms (triangles). **(E)** Average rankings (± SD) of the results and the time points of evaluation were negatively correlated. Shaded areas mark the 6-week period of stimulation. B, baseline evaluation; W1–6, weekly evaluations, each conducted at a 24-hour interval after the preceding stimulation session; F1 and F2, follow-ups conducted 7 and 17 days after the final stimulation session. MAS sum score at W6 is a missing data. In W2–3, the participant had an acute urinary tract infection. Ten days after the final stimulation session, the participant increased his daily baclofen dose from 20 mg to 30 mg.

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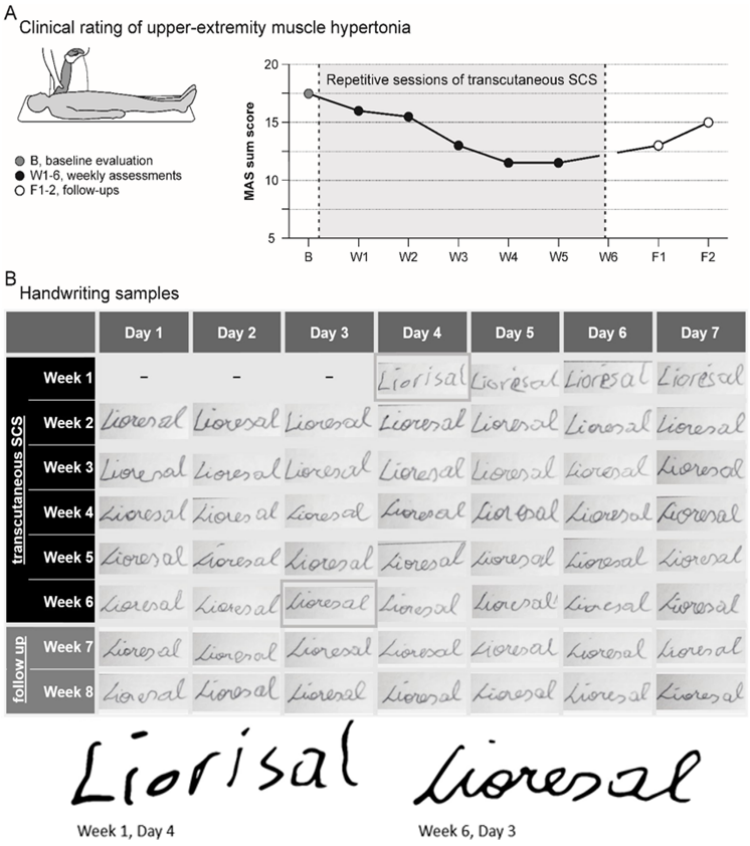

Supplementary FIG. 1. Effects of transcutaneous lumbar spinal cord stimulation administered for six weeks on upper extremities; participant 3. **(A)** Upper-extremity muscle hypertonia was clinically classified based on the Modified Ashworth Scale (MAS) using a comprehensive movement protocol, comprising scapular depression, protraction, and external rotation; flexion, abduction, adduction, and external rotation of the shoulder; flexion/supination of the elbow with the shoulder joint at 0° and 90°, respectively, as well as extension/supination and extension/pronation of the elbow; dorsiflexion of the wrist with the shoulder joint at 0° and 90°, respectively; palmar flexion; flexion and extension of the fingers; and extension and reposition of the thumb (18 separate tests per side; W6 missing data). **(B)** Retrospective examination of the participant's handwriting based on the word "Lioresal" from daily questionnaires (first 3 days missing data). B, baseline evaluation; W1–6, weekly evaluations, each conducted at a 24-hour interval after the preceding stimulation session; F1 and F2, follow-ups conducted 7 and 17 days after the final stimulation session.