Consecutive Transcutaneous and Epidural Spinal Cord Neuromodulation to Restore Complete Paralysis

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Abstract

In this study the effect of transcutaneous (tSCS) and epidural electrical spinal cord stimulation (EES) to facilitate volitional movements, balance, and non-motor functions was consecutively tested in two subjects with motor complete spinal cord injury (SCI). We hypothesized that tSCS and EES have different but complimentary effects on restoration after SCI. In both subjects tSCS demonstrated minimal improvement in volitional movements critical to initiate tSCS-enabled rehabilitation. Compared to tSCS, following EES demonstrated immediate restoration of volitional movements, while tSCS was more effective in improving balance. Continuous improvement in non-motor functions was found during tSCS-enabled and then EES-enabled rehabilitation. These results show significant difference in effect of tSCS and EES on recovery of neurologic functions and demonstrate advantages of consecutive tSCS and EES therapy of SCI. Proposed approach will help to select responsive to neuromodulation subjects and early initiate therapy, particularly for motor complete SCI with minimal effect from conventional rehabilitation.

Introduction

Spinal cord injury (SCI) impairs communication between brain and sub-lesional circuitry, leading to motor, sensory, and autonomic dysfunctions[1]. Patients with complete motor and sensory (AIS-A) or complete motor (AIS-B) injury consist of 50-60% all SCI cases[2,3]. Within this population, if no changes observed within the first year, patients have extremely low chances for improvement[4], even with the most advanced rehabilitation and neuromodulation programs[5–9]. Epidural electrical spinal cord stimulation (EES) was successfully implemented to restore motor function in multiple animal models[10–19]. Combination of EES and rehabilitation therapy in subjects with motor complete SCI led to unexpected restoration of volitional control over paralyzed limbs[20], recently successfully replicated by several groups[8,9,21,22]. These findings support the hypothesis that combination of spinal cord neuromodulation and motor rehabilitation provides necessary for recovery sensorimotor integration via spared across injury fibers[5,23], although, some recent works demonstrated significant level of EES-enabled recovery without intensive rehabilitation[22,24]. Another approach with noninvasive transcutaneous electrical stimulation (tSCS) demonstrated great potential as a therapy for chronic SCI with significant impact on multiple systems[25–28]. Recent reports on radically increased effect of spinal cord stimulation[8,9,20,21,22,29,30] led to the race for the best improvement, often presented without well-comparable between different studies metrics and with little clarity on underlying mechanisms. Facing the large variability across patients' population, pros and cons of using spinal cord neuromodulation, and unknown effect of consecutive tSCS and EES application on recovery of the different functions after SCI, we found it urgent to demonstrate effect of non-invasive and invasive neuromodulation in the same study. We evaluated two subjects, one with significant improvement achieved with spinal cord stimulation and in another one who minimally responded to the same neuromodulation therapy, comparing the effect of consecutively applied tSCS and EES on enabling volitional motor control, balance, and restoration of non-motor functions after complete paralysis. We test hypothesis *thattSCS and EES have different but complimentary effects on functional restoration after motor complete SCI*. Our initial observation that tSCS facilitates some level of volitional

motor control over paralyzed limbs was essential for initiating tSCS-enabled rehabilitation. Following implantation and stimulation with EES system led to EES-enabled motor training and opportunity to assess the effect of consecutively applied tSCS- and EES-enabled rehabilitation, demonstrating clear difference between both therapies in two subjects and potential advantages of consecutive application of tSCS and EES after SCI.

Results

Study design and timeline: After initial examination, both subjects (S1 and S2) signed an informed consent and comprehensive electrophysiological assessment was performed (Fig. 1). The following initial trial of tSCS (tSCS1) demonstrated minimal restoration of volitional movements in both subjects. Then, tSCS-enabled rehabilitation was performed for 8 weeks (see methods for details) with the following testing with tSCS (tSCS2) and clinical examination. EES system was implanted with intraoperative electrophysiological assessment. EES performed on the 2^{nd} postoperative day (EES1) demonstrated EES-enabled volitional motor control and robust movements. After the following 4 weeks of rest, subjects received 8 weeks of EES-enabled motor rehabilitation with the following testing with EES (EES2) and final clinical examination, demonstrating large variations between both subjects in effect of neuromodulation with tSCS and EES (Fig. 1).

Figure 1 about here

Primary clinical assessment: During the initial neuro exam S1 was classified as an AIS-A and S2 as an AIS-B and both subjects were assessed throughout the multiple clinical scales (Supplementary Table. 1).

Initial electrophysiological assessment*:* To assess functional connectivity across the lesion, Somatosensory Evoked Potentials (SSEPs), H- and M- responses, and Spinally Evoked Motor Potentials (SEMPs) were tested alone and in combination with Jendrassik maneuver (JM) (Fig. 2). In addition, Transcranial Magnetic Stimulation (TMS), and Electromyographic (EMG) activity were evaluated during attempts of volitional motor control (Fig. 3 and Fig. 4 correspondingly).

Somatosensory evoked potentials (SSEPs) during stimulation of the tibial nerve in S1 were found below Th12-L1 level and in S2 below Th8-9 level bilaterally, indicating no ascending connectivity above the injury (Fig. 2A).

Figure 2 about here

M-response and H-reflex: The recruitment curves of M-response and H-reflex recorded from the soleus muscle (SOL) on both legs presented on Figure 2B. For S1 H/M ratio was lower on the left leg (44.05% – left leg vs. 79.39% – right leg) and for S2 was lower on the right leg (59.19% – left leg vs. 45.42% – right leg). H-reflex was assessed with and without JM (Fig. 2C). In S1 JM facilitated H-reflex to 104.3±1.09% of the control values on the right side (2.66±0.028 mV vs. 2.54±0.045 mV, p=0.045) with some inhibition of H-reflex on the left side to 90.99±0.27% (2.40±0.024mV vs. 2.49±0.023mV, p=0.02). In S2 JM inhibited H-reflex on the right side to 93.60±1.54% (4.25±0.70mV vs. 4.54±0.15mV, p=0.037) with no significant effect on H-reflex on the left side (Fig. 2D).

Spinally evoked motor potentials (SEMP) were tested with tSCS (T12-L1) applied as a single or paired pulse with 50ms intervals[31,32]. During paired stimulation, the amplitude of SEMP was affected by the post-activation depression in all tested muscles in both subjects. (Fig. 2E and F). In S1 the difference in RF was 0.42±0.03mV (p=0.002), in BF 1.63±0.12mV (p=0.018), in TA 0.43±0.07mV (p=0.007), and in SOL 1.67±0.1mV (p=0.005). In S2 the difference in RF was 0.89±0.09mV (p=0.005), in BF 0.98±0.28mV (p=0,001), in TA 0.10±0.01mV (p=0.001), and in SOL 0.13±0.02mV (p=0.017). The examples of the SEMPs to tSCS (Th11-12) in RF and SOL without (black line) and with JM (red line) presented on Figure 2G. In S1 the amplitude of SEMP in RF wasn't significantly changed, although, in SOL SEMPs were facilitated on both legs during JM. In S2 SEMP amplitude during JM was increased in left RF and in SOL on both sides (Fig. 3G). The effect of JM on SEMP amplitude across all tested muscles presented on Figure 2H. In S1 JM facilitated SEMP in left and right SOL (167.90±15.55% and 238.66±11.42%, p=0.001). In S2 JM facilitated SEMP in left RF (230.39±18.93%, p=0.006), in right TA (142.01±30.91%, p=0.045), and in right SOL (228.76±84.15%, p=0.009) (Fig. 2H).

Transcranial magnetic stimulation (TMS) demonstrated no responses to TMS in tested muscles on both sides in both subjects. Also, no significant changes were observed in SEMP evoked by tSCS (Th11-12) during conditioning with TMS (Fig. 3).

Figure 3 about here

Volitional EMG activity: Attempts to perform general flexion on both legs demonstrated no changes in EMG when applied without JM (Fig. 4A), while some increase in EMG amplitude was found during attempts of flexion with JM in S2 (Fig. 4B).

Figure 4 about here

In summary, electrophysiological assessment alone demonstrated no functional connectivity across ascending or descending pathways, while in combination with JM, H-reflex and SEMPs demonstrated modulation in both subjects, indicating on discomplete character of their injuries.

Volitional motor control with tSCS and EES: Volitionally initiated rhythmic activity in legs with tSCS was observed in both subjects (Fig. 5 and Supplementary videos 1 and 2). tSCS was applied at two sites simultaneously (Th11-Th12 and Th12-L1) that was shown to be more effective compared to tSCS applied at either location alone[33,34] (Fig. 5A). Both subjects demonstrated a good tolerance to tSCS with no discomfort during trial period and following training sessions. After implantation of chronic EES system (Specify 5-6-5 and RestoreSensor, Sure-Scan MRI, Medtronic), EES was applied within a range of previously tested settings[8,9] with the initial evaluation demonstrating optimal motor performance with interleaving program (20Hz, PW=250usec, intensity range 4-10V) (Fig. 5B). The intensity of stimulation was gradually increased, while subjects attempted initiating a stepping-like activity, imagining themselves biking or running. The amplitude of movements was evaluated during 15sec intervals right before stimulation (tSCS or EES), during stimulation, and right after stimulation was stopped. Variations in main joint angles were calculated and compared (Fig. 5C). tSCS facilitated only minimal volitional movements from the motor threshold and up to the maximal intensity (120mA). EES at motor threshold (5-6V for S1 and 3-5V for S2) caused minimal legs' motion, while at the optimal intensities (7-8V for S1 and 5-6V for S2) EES facilitated robust movements with ability volitionally initiate-terminate and increase-decrease the amplitude and frequency of movements. Further increase in EES intensity caused spasticity in muscles on both legs. Without EES both subjects were unable to initiate any movements. Comparison of tSCS- and EES-enabled motor performance demonstrated increase in kinematics and EMG activity throughout the study in both subjects (Fig. 5D,E,F).

Figure 5 about here

S1 during the 1st assessment with tSCS (tSCS1), demonstrated increased movements in left knee and right knees during tSCS (15.47±0.90°and 10.11±0.50°) compared to before (6.22±1.11° and 2.87±0.34°) and after tSCS (7.82±0.32°and 3.14±0.35°, correspondingly) (p=0.001) (Fig. 5E). Movements in left ankle were increased during (7.05±1.10°) compared to before (3.68±0.81°) and after tSCS (2.95±0.50°) (p=0.003), although, in right ankle they were not different between during, before, and after tSCS1 (Fig. 6A). *During the 2nd assessment with tSCS (tSCS2) after 8 weeks of tSCS-enabled motor training*, S1 demonstrated increased movements in left knee during (16.01±1.82°) compared to before (10.50±1.30°) (p=0.015) and after tSCS (6.65±1.00°) (p=0.001) and in right knee during (7.13±1.10°), compared to before (0.40±0.05°) and after tSCS2 (3.14±0.34°) (p=0.05) (Fig. 5E). Movements in left ankle weren't different between during tSCS (7.49±1.14°) and before (6.47±0.87) tSCS2, although were higher after tSCS (16.78±1.08°) (p=0.05). Movements in right ankle were higher after (2.79±0.40°) compared to before (0.61±0.07°) and during tSCS2 (1.19±0.20°) (p=0.05) (Fig. 6A). *Thus, 8 weeks of tSCS-enabled training in S1* led to improvement in left leg movements, both in knee (6.22±1.1° before vs. 10.49±1.30 after training) and in ankle (3.67±0.7° before vs. 6.47±0.87° after training). At the same time, on the right leg S1 demonstrated no improvement in knee and in ankle when tested without stimulation.

S1 during the 1st assessment with EES (EES1) demonstrated no difference in left knee movement during EES1 compared to before and after EES1. In right knee movements significantly increased during EES1 (22.86±1.44°) compared to before (4.68±0.55°) and after EES1 (5.32±0.59°) (p=0.001) (Fig. 5E). Movements in left and right ankle with EES1 were not different from the movements before and after EES1 (Fig. 6A). *During the 2nd assessment with EES (EES2), after 8 weeks of EES-enabled motor training*, S1 demonstrated increased movements in left knee during (57.29±1.03°) and after EES2 (64.91±1.91°) compared to before EES2 (23.97±3.73°) (p=0.001) and in right knee during (32.01±1.97°) and after (41.26±2.91°) compared to before EES2 (6.89±0.57°) (p=0.001) (Fig. 5E). Movements in left ankle during EES2 were not different from movements before or after EES and in right ankle movements during (2.2±0.34°) were higher compared to before EES2 (1.06±0.16°) (p=0.003), but not different from after EES2 (Fig. 6A). *Thus, 8 weeks of EES-enabled training in S1* led to improvement in volitional movements in left knee (15.42±1.00° before vs. 23.96±3.70 after training) and right knee (4.68±0.50 before vs. 6.88±0.60° after training), but not in ankle. At the same time S1 demonstrated significant improvement in performance with EES.

S2 during the 1st assessment with tSCS (tSCS1), demonstrated increased movements in left and right knees during (26.85±1.02° and 4.14±0.6°) compared to before (17.79±0.56° and 1.23±0.14°) and after tSCS1 (4.76±0.79° and 2.66±0.26°) correspondingly (p=0.001) (Fig. 5F). Movements in left ankle during (24.25±1.54°) and before (22.79±2.64) were higher compared to after tSCS1 (4.01±0.48°) (p=0.001). Right ankle movements were higher during (15.89±2.53°) compared to before (5.01±1.11°) and after tSCS1 (2.62±0.56) (p=0.001) (Fig. 6B). *During the 2nd assessment with tSCS (tSCS2), after 8 weeks of*

tSCS-enabled training, S2 demonstrated increase in the left knee movement during (10.44±1.18°) and after tSCS2 (13.48±0.66°) compared to before tSCS2 (5.38±0.47°) (p=0.05). Movements in right knee were increased with tSCS2 (7.41±0.97°) compared to before (1.92±0.29°) and after tSCS2 (2.5±0.44°) (p=0.05) (Fig. 5F). Movements in left ankle were higher with tSCS2 (23.52±2.82°) compared to before (9.73±1.43°) and after tSCS2 (1.59±0.20°) (p=0.05), while movements in the right ankle during tSCS2 (2.14±0.36°) were lower compared to movements before (8.79±0.93°) and after tSCS2 (5.48±0.52°) (p=0.05) (Fig. 6B). *Thus, 8 weeks of tSCS-enabled training in S2* led to decrease in volitional movements in left knee (17.79±0.60° before vs. 5.38±0.50° after) and minimal improvement in right knee movements (1.23±0.10° before vs. 1.9±0.20° after training). Left ankle movements also decreased (22.79±2.64° before vs. 9.7±1.40° after training) with some improvement observed in right ankle (5.01±1.11° before vs. 8.79±0.90° after).

S2 during the 1st assessment with EES (EES1), demonstrated increased movements in left knee (58.04±1.55°) compared to before (28.01±0.62°) and after EES1 (37.88±5.15°) (p=0.001). and in right knee during (26.55±4.31°) compared to before (12.15±2.81°) and after EES1 (12.19±1.86°) (p=0.05). Movements in left and right ankle were higher during (9.97±1.11° and 17.76±3.43°) compared to before (0.46±0.06° and 8.07±1.31°) and after EES1 (0.5±0.07° and 8.33±0.98°) (p=0.008 and p=0.001) correspondingly (Fig. 6B). *During the 2nd assessment with EES (EES2), after 8 weeks of EES-enabled motor training*, S2 demonstrated increased movements in left knee during (51.91±1.95°) compared to before (8.66±0.51°) and after EES2 (5.16±0.57°) (p=0.001). Movements in right knee where higher with EES2 (45.77±1.11°) compared to before (6.80±0.86°) and after ESS2 (6.04±0.48°) (p=0.001). Left ankle movements were higher during (20.20±2.07°) compared to before (0.50±0.08°) and after EES2 (0.63±0.16°) (p=0.001). Movements in right ankle during EES2 (8.89±1.56°) were higher compared to the movements before (0.92±0.15°) and after EES2 (1.05±0.08°) (p=0.001) (Fig. 6B and Supplementary Table 2). *Thus, 8 weeks of EES-enabled training in S2* led to decrease in volitional movements in left knee (28.01±0.62 before vs. 8.66±0.51° after training), in right knee (12.15±2.81° before vs. 6.8±0.86° after training), and in right ankle (8.07±1.31 before vs. 0.91±0.14° after training), and no change in left ankle (0.46±0.06° before vs. 0.5±0.07° after training). At the same time S2 demonstrated significant improvement in performance with EES.

Figure 6 about here

Balance control with tSCS and EES: Balance control was evaluated while subjects were sitting with arms 'forward', 'sideward', and 'upright' based on metrics of head, arms, and trunk position during tSCS and then, during EES. With tSCS S1 demonstrated improvement of trunk, hands, and head control in 'hands forward' position, although, with 'hands sideward' and 'hands upward' only some parameters were

improved with tSCS. With EES S1 demonstrated decline in balance in all three positions compared to before stimulation. With tSCS S2 demonstrated improvement in trunk, hands, and head control in 'hands forward' and 'hands sideward' positions and improvement of trunk control in 'hands upright' position. With EES S2 demonstrated less trunk control with minimal improvement in arms and head control in all three positions (Fig. 7 and Supplementary Table 3).

S1 sitting with both hands forward, with tSCS demonstrated *improvement in all metrics of trunk, head, and arms control* (Supplementary Table 3). *In regards of the trunk control* tSCS led to decrease of abdominal curvature (Sa) in -5.0±3.4% (p=0.019), decrease of spinal curvature (St) in -11.1±4.7% (p=0.031), decreased low back inclination from the vertical line (At) in -15.34±6.1% (p=0.002), decreased the distance between tragus and scapular spine (TSc) up to -14.69±7.2 (p=0.005), and no changes in the line connecting ear (tragus) and main horizontal line at H1 (TH1) and horizontal line connecting umbilicus and main horizontal line at V3 (UV3), compared to assessment before stimulation. With EES both Sa and St were increased in 38.4±5.9% and 46.5±6.4% respectively (p<0.001), TSc increased in 18.8±3.6% (p=0.002), TH1 increased in 11.56 %±0.31 (p<0.001), and UV3 increased in 22.723±0.476% (p=0.001), overall indicating disturbance in trunk control. *Head position control* was improved with tSCS with the line connecting nose and vertical line at V1 (NV1) decreased in -4.2±1.8% (p=0.008) and no changes in distance between nasal apex and main horizontal line at H2 (NH2). With EES NH2 increased in 14.53±1.94% (p=0.001), while NV1 increased in 16.9±3.6% (p=0.004), indicating disturbance in head control. S1 demonstrated *improvement in arms control* during tSCS with increase the distance between wrist and horizontal line at H3 (WH3) in 67.7±20.8% (p=0.001), increase the distance between wrist and vertical line at V2 (WV2) in 32.7±8.65% (p=0.001), and angle indicating elbows position (Ae) in 60.66±13.10% (p=0.001). With ESS WV2 increased only in 15.4±1.9% (p=0.001), while WH3 and Ae didn't change (Fig. 7, S1 A-F; Supplementary Table 3).

S2 sitting with both hands forward, with tSCS demonstrated *improvement in trunk and head control* with decreased Sa in -19.47±1.62% (p=0.001), St in -29.13±2.10%, At in -27.25±3.60% (p=0.03), TSc in -10.34±1.99 (p=0.004), UV3 in -11.55±0.94 (p=0.001), and no changes in TH1. EES also demonstrated improvement with Sa and St decreased in -13.96±1.69% (p=0.001) and -3.73±0.91% (p=0.012), TH1 increased in 2.64%±0.55 (p=0.004), and no changes in At, TSc, and UV3*. Head position control* improved during tSCS with NV1 decreased in -14.15±0.9% (p=0.031) and during EES with NH2 increased in 3.04±0.6% (p=0.004). *S2 demonstrated decline in arms control* during tSCS with WH3 decreased in -9.42±1.54% (p=0.002) and WV2 decreased in -5.34±0.68% (p<0.001), while Ae increased in 2.91±0.67% (p=0.007) compared to no stimulation. During ESS WH3 increased in 3.64±1.29% (p=0.049) and WV2 didn't change. (Fig. 7, S2 A-F; Supplementary Table 3).

Figure 7 about here

S1 sitting with both hands sideward, with tSCS demonstrated *variable changes in trunk control* with Sa decreased in -20.48±1.81% (p=0.001), St increased in 8.31±1.83% (p=0.006), At increased in 11.35±1.05 (p=0.001), UV3 decreased in -4.49±1.26% (p=0.018), and no changes in TSc and TH1. With EES S1 demonstrated overall decline *in trunk control* with Sa and St increased in 40.22±4.29% and 28.23±1.80%, respectively (p=0.001), At decreased in -14.29±1.13% (p=0.001), TSc increased in 25.31±2.71% (p=0.001), TH1 increased in 18.97 %±0.61 (p=0.001), and UV3 increased in 19.04±0.72% (p=0.001). *Head position control* declined during tSCS with the distance between nasal apex and main horizontal line at H3 (NH3) decreased in -4.91±1.97 (p=0.031), NV1 increased in 2.69±0.94% (p=0.036), while it was variable wduring EES with NH3 increased in 27.67±1.95% (p=0.001) and NV1 increased in 14.42±0.47% (p=0.031). *Arms control* was improved during tSCS with the distance between wrist and horizontal line at H2 (WH2) increased in 19.66±3.97% (p=0.005). Positive changes in arms control were also found during ESS with WV2 decreased in -28.92±3.52% (p=0.001) (Fig. 7, S1 A-F; Supplementary Table 3).

S2 sitting with both hands sideward, with tSCS demonstrated *improvement in trunk control* with Sa decreased in -22.51±1.99% (p=0.001) and St in -16.17±1.18%, At decreased in -15.68±2.4% (p=0.002), TSc increased in 5.96±1.04 (p=0.002), TH1 increased in 1.87%±0.55 (p=0.02), and UV3 decreased in -12.66±0.63 (p=0.001). With EES Sa, St, and At didn't change compared to before stimulation, while TSc increased in 9.65±1.90% (p=0.003), TH1 in 9.75%±0.67 (p=0.001), and UV3 in 6.56±0.58% (p=0.001), reflecting negative changes in trunk control compared to tSCS. *Head position control* was improved during tSCS with NV1 decreased in -5.08±0.47% (p=0.001) and was variable with EES with NH3 increased in 14.27±0.68% (p=0.001) and NV1 increased in 4.13±0.55% (p=0.001). *S2 demonstrated improvement in arms control* during tSCS with WV2 decreased in -47.33±4.30% (p=0.001) and during EES with WV2 decreased in -35.28±3.75% (p=0.001) (Fig. 7, S2 A-F; Supplementary Table 3).

S1 sitting with both hands upward, with tSCS demonstrated *some improvement in trunk control*, with Sa decreased in -10.98±1.08% (p=0.001) and no changes in other metrics, compared to before stimulation. With EES S1 demonstrated *decline in trunk control* with Sa and St increased in 45.55±0.83% and 29.09±3.54% respectively (p=0.001), the horizontal line connecting umbilicus and main vertical line at V4 (UV4) increased in 22.11±1.47% (p=0.001). *Head position control* didn't change during tSCS, while improved during EES with ChH2 increased in 19.67±0.89% (p=0.001). *Arms control* was variable during tSCS with the distance between wrist and horizontal line at H4 (WH4) increased in 26.72±1.09% (p=0.001), the distance between wrist and vertical line V1 (WV1) increased in 105.25±4.67(p=0.001), the line connecting elbow with main horizontal line at H3 (EH3) increased during tSCS in 18.33±1.10% (p=0.001), the line connecting elbow with main vertical line at V2 (EV2) increased in 63.9±17.27 (p=0.031), and Ae increased in 24.83±6.68 (p=0.009). *Arms control improved* during EES with WH4 increased in 16.87±3.24% (p=0.001) and EH3 in 19.04±2.61% (p=0.001) (Fig. 7, S1 A-F; Supplementary Table 3).

S2 sitting with both hands upward, with tSCS demonstrated *improvement in trunk control*, with Sa decrease in -11.54±2.49% (p=0.05), St in -23.03±3.64% (p=0.005), At in -14.21±4.65% (p=0.034), UV4 in -7.64±0.92% (p=0.001), and ScH1 increased in 11.37±3.20% (p=0.013). During EES trunk control was variable with St increased in 4.29±1.21% (p=0.014) and ScH1 in 6.955±0.39% (p=0.001), and no changes in other metrics. *Head position control improved* during tSCS with ChH2 increased in 7.84±2.31% (p=0.017) and during ESS with ChH2 increased in 8.87±0.60% (p=0.001). *S2 demonstrated no changes in arms control* during tSCS and *improvement* during EES with WH4 increased in 22.89±2.12% (p=0.001) and EH3 in 19.63±2.87% (p=0.001) (Fig. 7, S2 A-F; Supplementary Table 3).

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tSCS and EES effect on non-motor symptoms: Clinical evaluation before and after 8 weeks of tSCS-enabled training demonstrated improvement in non-motor functions. S1 reported 'feeling of abdominal wall' and 'fulness of the bladder' after 5-6wks of tSCS-enabled training and throughout the EES-enabled rehabilitation program. With EES S1 further reported improvement in bladder control and regained capacity to induce urination with maneuvers. The Neurogenic Bladder Symptom Score (NBSS) in S1 decreased from 46 points to 41 points and quality of life score increased from 4 to 5. S1 initially demonstrated low muscle tone, which was gradually increased with tSCS-enabled training from 0 to 1+ on Modified Ashworth Scale (MAS). The frequency of spasms increased from 0 to 1 during tSCS and to 2 during ESS. S1 also reported increase in neuropathic pain in both legs from 3/10 to 6/10 on right leg and from 6/10 to 8/10 on left leg on VAS (information from self-control diary) that was well controlled with Pregabalin (75 mg). S2 prior to enrollment described hyperhidrosis below the level of injury on the left side and reported improvement after about 6 weeks of tSCS-enabled training. Furthermore, during tSCS S2 observed some sensation below the level of injury, mostly on the left-side of his flank and hip and in the right leg. During EES-enabled motor training S2 continued to report same sensation and later it became consistent without EES. With EES S2 demonstrated increase of muscle tone from 1 to 2 points on MAS. Although increased muscles tone during EES-enabled motor training was reported by both subjects, it did not affect the motor performance. Both subjects demonstrated some variation in blood pressure during initial period of tSCS and EES with episodic increase of BP up to 160-180 mmHg in S1 and up to 140-160 in S2 with their normal BP 120-130mmHg. BP was normalized after 20 min of rest. After 2-3 days of training both subjects demonstrated normal range of BP.

Discussion

Recent reports on subjects with clinically complete SCI regaining volitional movements with EES combined with motor training generated a new hope for restoration after complete paralysis[6-9,20-22]. EES along with later introduced noninvasive tSCS demonstrated multiple positive outcomes in subjects with chronic SCI[25–30]. This study for the first time compares the effect of consecutively applied tSCS and EES on restoration of neurologic functions after motor complete SCI, demonstrating predominant effect of EES on restoration of volitional motor control and tSCS on improvement in balance. tSCS, similar to previous reports[26], facilitated only minimal improvement in volitional movements, still efficient to initiate

tSCS-enabled motor training with visual feedback, while EES facilitated high-amplitude volitional movements. These findings support our hypothesis that tSCS and EES have different effect on neurologic recovery. Both subjects in this study were diagnosed with motor complete SCI and electrophysiological assessment demonstrated evidence of translesional connectivity when combined with JM. This type of SCI, i.e. clinically complete injury associated with the evidence of translesional connectivity is known as 'discomplete[35–38]. Although, most of the subjects with clinically complete SCI have residual anatomical connectivity[39], instrumental assessment alone is not sensitive in identifying the functional role of these fibers. Functional connectivity demonstrated with facilitation of H-reflex and SEMP with JM, and increase in EMG activity during attempts to flex legs with JM, are similar to the previous report where electrophysiological assessment in combination with JM facilitated sub-functional connectivity in AIS-A subject[40]. Combination of initial electrophysiological assessment and following trial of tSCS further confirmed a discomplete injury in both subjects. EES facilitated high amplitude volitional movements already during the first test on the second day after implantation of EES system, suggesting that, although tSCS can facilitate some level of volitional control, the stronger effect of EES is likely related to more selective activation of the spinal structures and facilitation of the relevant to volitional motor control circuitry. This also suggests that all critical neural elements required for volitional movements are available even after several years of motor complete injury and can be engaged in motor tasks with optimal neuromodulation and rehabilitation protocols. At the same time, the effect of tSCS- and EES-enabled training in this study was not consistent with recently reported significant restoration of volitional control without stimulation[29,30]. Comparison of motor performance without stimulation before and after 8 weeks of tSCS- and EES-enabled training demonstrated only some improvement, primary in knee angle. This difference could be due to shorter compared to other studies stimulation-enabled training and/or individual differences between tested subjects. The effect of tSCS to improve balance was demonstrated in previous studies, although without direct comparison to EES[28,41]. Our results show that tSCS has stronger effect on balance improvement compared to EES, suggesting that tSCS can modulate spinal circuitry activating multi-segmental projections, necessary to engage the balance control. This effect could be attributed to the wider current field with tSCS and facilitation of the afferent systems not activated with EES[41]. tSCS effect on balance can be also related to direct neuro-muscular activation, thus, previous studies demonstrated that low-intensity FES can increase trunk displacement and improve balance through increased trunk stiffness[42]. Similar, wider current distribution during EES with more lateral electrodes placement could mediate FES-type effect via direct motor axons activation[30].

Observed difference between tSCS and EES raises several key questions. The optimal duration of tSCS-enabled rehabilitation to improve balance and maintain achieved with tSCS improvement, particularly, when it follows with EES, still needs to be determined. The effect of EES is likely to be mediated through the circuitry in the lumbosacral segments[43–45]. Our previous findings indicate that the same spinal pathways could mediate the effect of EES to facilitate locomotion and posture in SCI animals[16]. tSCS and EES can facilitate the common neuronal structures[46], although, widespread electrical field during tSCS[47] may activate additional sensory afferents in peripheral nerves, DRGs, dorsal and ventral roots

across several segments. It is important to note, that the effect of EES in this study was evident already during the first attempt after implantation, with both subjects being able to generate robust stepping-like movements. At this moment, however, any attempt volitionally adjusts motion by subject caused decrease in amplitude or termination of the rhythmic activity. Moreover, both subjects found it difficult to control movements in single joints, while activation of stepping-like pattern was easily triggered by imaging themselves running or cycling. Variations in facilitated with tSCS or EES control over motor performance must be evaluated with a great level of detail, considering variability between the subjects with SCI. Following SCI, reduced number of fibers responsible for precise coordination of the multiple muscles cannot provide the same level of accuracy, although, capacity to activate, terminate, and modulate rhythmic activity with EES remains even with limited connectivity in discomplete subjects. The key question is if the limited fibers across the injury could provide efficient accuracy and precision of movements and if this improvement can be achieved at all after motor complete SCI? The questions on individual variations and specific mechanisms of the effect of neuromodulation are critical for further development of effective therapeutic strategies. To address these questions further, comparison between 'good' and 'bad' responders to neuromodulation must be performed with comparable approaches. One possibility is that with consecutive tSCS- and EES-enabled rehabilitation, the sublesional circuitry will be tuned to respond to supralesional commands, leading to more accurate control. This hypothesis is supported by our previous observation that paraplegic subject with EES regained volitional movement in single joints at lower range of motion compared to the high-amplitude rhythmic legs movements[8]. After intensive EES-enabled rehabilitation, he was able to walk with minimal assistance, although, with smaller amplitude and slower movements[8,9]. Another possibility for improvement in motor control after SCI may come from integration of sub- and supralesional components of spinal network. Recent findings indicate on importance of the ascending signaling across SCI[23,48] and demonstrate benefits of translesional stimulation[49,50]. By activating supralesional circuitry and facilitating sublesional network, neuromodulation may further optimize motor and sensory control, compensating limited connectivity across the injury[23]. Another opportunity may come from recent spinal cord neuroanatomy studies and proposed segment-specific stimulation precisely tuned to the main stimulation targets[51,52]. Supporting this concept, recent report demonstrated that individually adjusted electrodes configuration leads to fast functional restoration[30]. The critical following step should elaborate advanced assessment of activated fibers[40] and segment-specific stimulation[52] for optimal activation of the spinal circuitry leading to functional restoration. Both subjects in this study demonstrated improvement in non-motor functions started during trial of tSCS and continued throughout the duration of this study. Non-motor effects of spinal neuromodulation and related mechanisms still need to be explored and connected with specific neural subtract[53,54].

In conclusion, the restoration of voluntary movements and neurologic functions in paralyzed patients with spinal cord stimulation is impressive outcome of the recent studies. This work demonstrates that this effect can be attributed to both tSCS and EES applied even years after SCI. New findings show that dormant spinal circuitry can be re-engaged by consecutive combination of noninvasive (tSCS) and

invasive (EES) neuromodulation, providing different functional outcome on volitional movements and balance. The extent of improvement in motor performance achieved with external or implantable stimulating devices and further optimization of neuromodulation and rehabilitation therapy will determine the key directions for the future studies, translating new findings in effective therapy.

Methods

Ethics statement: All procedures described herein were performed with the approval of the Kazan Federal University Institutional Review Board (Review board decision December 4th, 2017, protocol №7 and June 10th, 2019, protocol №16) and Internal Ethics Committee in accordance with the World Medical Association Declaration of Helsinki. The participants signed a written informed consent before enrolling in the study and informed consent for open access publication (print and digital) of their images. This investigation was carried out as a feasibility study.

Inclusion/exclusion criteria: The *inclusion criteria* for this study were consistent with evidence of complete paraplegia following traumatic spinal cord injury (AIS A or B) at Th1-Th12 level, with presence of spinal reflexes and the absence of other acute or chronic comorbidities in adult human participants (18–80 years) with a history of chronic (12 months post-injury) traumatic SCI. *Exclusion criteria* were consistent with the lower motoneuronal injury, high level of spasticity (>2 on Ashworth scale), active UTI, osteoporosis (T-score greater than −4), SCI <12 months post-injury, skin problems, pregnancy, tumor, history of other neurologic, psychiatric, cognitive or orthopedic conditions.

Subjects' information and medical history: Two subjects with traumatic spinal cord injury were enrolled.

Subject 1 (S1), a 48-year-old woman injured during motor accident two years before enrollment, with burst fracture at Th7 and spinal cord injury followed by paraplegia, sensory loss, loss of bladder and bowel control, and brain contusion. S1 underwent the posterior spinal fusion of the 5th to 9th thoracic vertebrae, laminectomy at the level Th7, and body fusion (vector lumbar interbody fusion (VLIF) 18-35) at the level Th6-Th8 (Fig. 8). S1 participated in-patient physical rehabilitation for 3 months to improve independence during activities of daily living. Over this time before enrolment, deep tendon reflexes of the bilateral knees and ankle joints were decreased up to 1 point according to NINDS scale, and muscle tone of bilateral lower extremities was 0 point by MAS. Neurological level of injury was determined as T5, AIS-A, according to the ISNCSCI protocol. Muscle strength evaluation showed grade 0 bilaterally below the injury.

Subject 2 (S2), a 28-year-old man, injured during fall from about 20 meters height five years before enrolment, with Th3 dislocation, T4 burst fracture, and spinal cord injury followed by paraplegia, sensory loss, loss of bladder and bowel control. He underwent decompression spine surgery at Th3-Th5, Th4

resection, and fusion with circular plate (Fig. 8). S2 participated in several rehabilitation programs (2-4 weeks each). His deep tendon reflexes on knees and ankles were decreased, although, muscle tone was consistently high 1+ points according to MAS with Babinski reflexes induced on both feet. Neurological level of injury was determined as Th4, AIS B, according to the ISNCSCI assessment.

Figure 8 about here

Initial assessment: The following laboratory assessment and instrumental examination were performed: blood sample collection to assess electrolyte balance, coagulation, liver, and kidney function and electrocardiogram to ensure proper cardiac function. All values were found in the normal range. Scales and questionnaires to assess the quality of life, mental health, bowel, bladder, and sexual function presented in Table 1. (Table 1). The bone mineral densitometry (BMD) for S1 was -0.636 g/cm with Z-score -2.2 and for S2 -1,27 g/cm with Z-score +1.4. Complete neurological examination was performed according to the International Standards for Neurological Classification of SCI (ISNCSCI). Both subjects were assessed throughout the following scales: Autonomic Standard Assessment Form (ASAF) to evaluate autonomic neuros system function; Spinal Cord Independence Measure (SCIM) to assess functionality; Neurogenic Bowel Dysfunction Score (NBDS) and Neurogenic Bladder Symptom Score (NBSS) to evaluate bowel and bladder functions; Patients Health Questionary-9 (PHQ9) for emotional and behavioral status; The Short Form-36 (SF-36) for quality of life; Modified Ashworth Scale (MAS) for spasticity; Berg Balance Scale (BBS) to evaluate the balance in sitting and standing position (Supplementary Table. 1). Clinical and neurophysiologic evaluations were performed during the first week after enrollment with the following 8-weeks tSCS-enabled motor training (2 sessions per week, 3 hours per session) and training in sitting position (1 session per week, 2 hours per session) (for details see *Training sessions*).

Electrophysiologic assessment of translesional neural connectivity across the injury was performed before tSCS-enabled motor training (Fig. 2) and included:

(a) Spinal cord somatosensory evoked potentials (SSEP): Electrical pulses were delivered to the tibial nerve bilaterally at the ankle area, while in a supine position with freely hanging feet. Stimulation intensities corresponded to the visual threshold of the motor response of the muscles (flexion of the toes). Stimuli consisted of monophasic rectangular electrical pulses of 0.3 ms duration at 3 Hz and 1.5x of threshold of visual motor response (visible contraction). SSEPs were recorded at five locations (popliteal region, L2-3, Th12-L1, Th8-9, and C5-6). Average response was calculated from 800 consecutive stimulus pulses (Fig. 2A).

(b) M response and H-reflex: M response and H-reflex were assessed by stimulation of the right and left posterior tibial nerve in the popliteal region using a stainless-steel bipolar electrode. Responses were recorded from the soleus muscle bilaterally using bipolar EMG surface electrode. The stimulation frequency was 0.1 Hz with the pulse duration 1 ms and with stimulation intensity gradually increased by step of 1 mA until the M-wave amplitude was no longer increased. The stimulation intensity required to evoke the maximum amplitude of the H-reflex was determined on each side (Fig. 2B).

(c) Jendrassik maneuver: To assess the influence of supraspinal signaling on the H-reflex and SEMPs, the testing with reinforcement maneuver (Jendrassik maneuver) was implemented as we described previously[40]. The subjects were asked on the command 'pull' to exert an effort with the fingers of both hands in a "lock" in front of the chest and sustain it for a few seconds[55]. Subjects were instructed to remain relaxed in all muscles other than those participating in the maneuver. To minimize muscle fatigue, 3–4 minutes resting period was maintained between the trials (Fig. 2C, D, G).

(d) Spinally evoked motor potentials (SEMP): SEMP were recorded using surface EMG electrodes placed over the rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA), and soleus (SOL) muscles bilaterally. To evoke SEMPs, active gel adhesive electrodes (diameter of 22 mm) were placed at the midline, in between the Th11-Th12, spinous processes and two reference electrodes (4x2 cm) were placed over the lower abdominal area. Electrical stimulation was performed with monophasic rectangular pulses with pulse duration of 1 ms every 10 seconds. Stimulation intensity was increased from 30 to 100 mA or to the maximum tolerable intensity. Ten stimuli were delivered at each stimulation intensity. SEMPs were recorded during stimulation at midline electrodes positions without and with Jendrassik maneuver. (Fig. 2G, H). At maximum stimulation amplitude, paired pulses, each at an interstimulus interval of 50 ms, were applied. The relative attenuation of the responses elicited by the respective second stimulation pulses was assessed to test the presence of post-activation depression and verify the reflex nature of the evoked responses[48] (Fig. 2E, F).

(e) Transcranial magnetic stimulation (TMS): TMS was used to assess the functional integrity of the cortico-spinal tracts[34,38,56]. Stimulation with circular coil 150mm in diameter (Neurosoft, Russia) centered over Fz point (10-20 system) at the projection of lower extremities was used. Stimulation frequency was 0.5Hz and intensity was gradually increased from 40 to 100% of the maximal intensity (2.2T). Motor evoked potentials were registered over TA and SOL muscles. As the areas of cortical stimulation were determined, the subthreshold TMS followed by the tSCS was applied. Intervals between the conditioning stimulus and testing stimulus (C-T) were ranged from 0 to 180 ms with 20 ms increasing increment[57]. The TMS intensity was set at the rate of 100% as MEP was not detected in both subjects. The amplitude characteristics of the MEP recorded from the TA and SOL muscles were analyzed without and with tSCS combined with TMS, and 5 samples were averaged at each time point (Fig. 3).

(f) EMG evaluation during attempts of volitional movements: Each subject underwent evaluation with electromyographic activity (EMG) after enrollment. EMG registration was performed during voluntary general flexion of the hips and knees of both legs without and then in combination with JM. Surface EMG

was recorded from the distal (tibialis anterior (TA), medial gastrocnemius (MG), extensor digitorum brevis (EDB), and flexor digitorum brevis (FDB) and proximal (rectus femoris (RF), vastus lateralis (VL), medial hamstring (MH) muscles and abdominal muscles (RA) bilaterally, while lying supine with enough head elevation for observing legs movements (Fig. 4). The registration settings were set before the beginning of the assessment and remained unchanged throughout the test. A three-minute relaxation was performed to differentiate involuntary (spasticity) and volitional movements.

tSCS stimulation: For tSCS a BioStim-5 (Kosima, Russia) was used. Electrodes with an adhesive conductive layer were fixed to the skin. Stimulating electrodes (cathode) with a diameter of 3.2 cm (PG479, Fiab, UK) was placed along the midline of the spine between the spinous processes at 2 levels Th11-12 and Th12-L1. With two level tSCS both subjects demonstrated better tolerance to discomfort caused by tSCS compared to one site stimulation. Anodes were placed symmetrically over the iliac crests. Stimulation was performed with monopolar rectangular pulses of 1 ms duration, filled with a 10 kHz carrier frequency. The intensity of tSCS was selected individually, so it was not painful and at the same time caused muscle contraction in the lower extremities. The amplitude range for tSCS was 30–110 mA. tSCS frequency was tested in range 20-60 Hz. tSCS was performed simultaneously with motor training, while subject was lying on a side or in a sitting position.

Training sessions: Each motor training session included initial stretching exercises up to 15 minutes to warm up, then functional training (passive lower extremities exercise and attempts to perform voluntary movements (flexion\extension) of each separate joint of legs) both in supine and side positions (30 min in total). Then, 2h side-position locomotor training with trainer assistance at the legs and pelvis was performed. Training for balance and task-specific strengthening exercises was performed for 1h 30m, while sitting[28]. During selected sessions, subjects were asked to modulate EMG activity with visual feedback provided by real-time streaming surface electromyography.

tSCS-enabled motor training*:* Following initial evaluation, and prior to surgery, each participant underwent 16 sessions of tSCS-enabled training on a side position, using a leg suspension system in a gravity-neutral position to entrain involuntary movements (2 session per week, 4 hours each session)[8,19]. The components of the leg suspension system included two loops fixed on the height of 1.5 meters supporting the top leg, while in a side-lying position (Fig. 3G). Training in sitting position was consisted with following tests: (a) sitting with hands forward, sideward, and upward, (b) anterior-posterior and lateral reaching, and (c) reaching of ipsilateral toe.

Implantation of EES system: After initial evaluation and tSCS-enabled training, both subjects received implantation of spinal cord stimulation system (RestoreSensor, Sure-Scan MRI, Medtronic) [8,58,59]. Stimulator was surgically implanted and connected to a 16-contact electrode array (Specify 5-6-5, Medtronic) positioned on the dorsal epidural surface of the lumbosacral spinal cord, confirmed with intraoperative fluoroscopy (Fig. 8B). Epidurally evoked motor responses were recorded to confirm the electrode position over the lumbosacral enlargement of the spinal cord[8,17,60] (Fig. 8D, E). Once electrode array was inserted, EMG recordings of EES-evoked motor responses were collected bilaterally from the rectus femoris (RF), vastus lateralis (VL), biceps femoris (BF), tibialis anterior (TA), medial gastrocnemius (MG), and soleus (SOL). Additionally, EMG recordings were captured from the paraspinal muscles to record a stimulation artifact, in order to sweep trigger. The position of the electrode array was evaluated with the recruitment of distal and proximal lower limb muscles and bilateral symmetry of evoked responses. Based on recording of EES-evoked motor responses, the best position with symmetrical muscles involvement was identified and the surgical lead was implanted in final position. In final position most of the electrodes on 5-6-5 array were located at the T12 vertebra level in both subjects (Fig. 8B).

Assessment of EES-enabled volitional motor control: After recovery from the surgery, volitional activation of the leg muscles was attempted without and with EES, while subject was positioned supine, side-lying, or sitting. Tasks included attempts to control flexion/extension of lower extremity, maintain posture in the sitting position, and performing motor tasks with trainer assistance provided as needed. Motor tasks were performed with the goal to identify the optimal EES electrode configurations and stimulation settings to enable optimal volitional control with EES. Electrode configurations and EES parameters were tested based on outcome of our previous studies[8, 9,60]. The intensity of EES was gradually increased until volitional control over leg muscle was observed.

EES-enabled motor training: During following 8 weeks, electrode configurations and intensity of EES were adjusted to allow optimal volitional control of the muscles. A systematic approach was used to determine the best parameter settings, as described in previous reports[8,9]. Overall, frequency was set at 20 Hz for volitional motor control and side-line stepping and 15 Hz for sitting, pulse duration was 250 msec, and intensity of EES was adjusted to the optimal outcome. The electrode configurations during training with EES were further adjusted based on algorithm we previously reported, starting with wide-field with the most distal electrodes on array vs. local-field with the pairs of closest electrodes, vs. combination of pairs of electrodes on right and left side of electrode array[9]. For each configuration the intensity was incrementally increased from 0 to 6V. During muscles spasm or any discomfort, the intensity of EES was reduced to a comfortable level or turned off. Once volitional control was achieved, EES settings were held constant for further repetitions of the tested task.

Balance training: Balance training sessions were performed while sitting in unsupported position with hips and knees flexed in 90° and feet hanged loose. No support (back, pelvic, arms or legs) was provided and with the therapist ready to assist behind the subject. The electrode configurations and parameters were selected and adjusted as described above. During each balance training session subjects were asked to hold both hands up, forward, and sideward within 1 minute in each position. Video recording was performed during the motor tasks while sitting and during training and analyzed with Kinovea software.

Data Processing and Analysis:

EMG activity was recorded and processed using LabChart software and Bioamp, PowerLab system (ADInstruments). The EMG data were filtered using a 60-Hz notch filter and a bandpass filter of 20 to 1000 Hz. Data were sampled at 4 kHz, exported and analyzed using MATLAB software (The Math-Works Inc). Peak-to-peak SEMP amplitudes and latencies were measured in a window of 5–30 ms stimulation artefact using MATLAB script. EMG data recorded during intraoperative monitoring sets were analyzed separately for each electrode configuration on the midline (Fig. 8). EMG data with reinforcement maneuver (JM) were analyzed as follows: five responses were averaged for each stimulation trial and the control amplitude values (1.5 of thresholds) were expressed as 100% for each muscle. Then, the rest of the amplitudes collected during JM were expressed as % (±SEM) of the control value.

Kinematics: Kinematic data were recorded at 30 fps using HD web-camera with 1280x960 resolution (C310 Logitech, Lausanne). Seven reflective markers were placed on lower limb laterally, while subject was in a side position (Fig. 3) at the 8th rib, iliac crest, thigh, knee, tibia, ankle, and 5^{th} toe. Camera was set at a height 1.5m. The recording was obtained simultaneously from each side during each trial. To assess volitional movements subjects were asked to perform stepping-like rhythmic movements at a self-selected speed. Three trials were collected during each session: before stimulation, during stimulation, and right after stimulation. The knee and ankle angles were analyzed using Kinovea software. The joint motion data included: maximum flexion and extension value of lower limb joint angles throughout the gait cycle in 1 plane to extract range of each angle motion. Both groups of variables were compared between three time points, i.e. before, during, and after spinal cord stimulation. To exclude possible inaccuracy caused by variation in markers position and patients position we evaluated the difference between the maximum flexion and extension to extract the maximum range of motion for each angle (Fig 3). Parameters were calculated as the average of the values obtained in 15 complete gait-cycles considered.

Balance assessment was performed during motor tasks, while sitting with camera placed on the right side at 2m distance from the subject and 1.5m from the ground. From 60 sec video 6 frames (every 10 sec) were collected and analyzed. Video analysis of balance was consistent of 11 metrics (2 angles, 2 squares, and 7 segments) used to calculate trunk and abdominal curvatures, as well as arms and head position (Fig 4). *Auxiliary lines:* Main horizontal line (red dash line) goes across the point of contact between pelvis and support surface and main vertical line (black dash line) goes through the most prominent point of spine curve. *Metrics of trunk position:* Sa (abdominal curvature) represents square of the abdominal area formed by V3, M, K and L points shows abdominal wall straightening during balance task; St (spinal curvature) represents square of the trunk area formed by segments connecting T-Sc, Sc-V3, V3-H1, T-H1 and shows spine erection during motor task. At (low back inclination from the vertical line) represents an angle formed by the line connecting V3 and H1 and line connecting tragus (T) and H1 shows trunk leaning forward; TSc (distance between tragus (T) and scapular spine (Sc)) represents trunk and neck stretching, demonstrating capacity to maintain upright posture during sitting; TH1 (line connecting ear (tragus) (T) and main horizontal line (H1)) shows spine reclination; UV3 (horizontal line connecting umbilicus (U) and main vertical line (V3)) points at abdominal wall straightening, demonstrating abdominal wall muscles engagement. *Metrics of head position (with hands forward):* NH2 (distance between nasal apex (N) and main horizontal line (H2)), demonstrating neck\head erection. NV1 (line connecting nasal apex (N) and vertical line (V1)), demonstrating head translation/displacement in sagittal plane. Slump sitting compared to upright sitting demonstrates greater head/neck flexion. *Metrics of arms position (with hands forward):* WH3 (distance between wrist (W) and horizontal line (H3)) shows ability to raise hands during unsupported sitting position; WV2 (distance between wrist (W) and vertical line (V2)) demonstrating an ability to stretch out in unsupported sitting position; Ae (angle of elbows position) represents an angle formed by line C-E that connects caput humerus (C) and elbow (E) and line E-W that connects elbow (E) and wrist (W) also shows hands-independent trunk control.

Additional metrics: Head position (with hands sideward): NH3 (distance between nasal apex and main horizontal line) represents line that connects nasal apex (N) and main horizontal line at H3.

Arms position (with hands sideward): WH2 (distance between wrist and horizontal line) represents line that connects wrist (W) with the main horizontal line at H2. *Trunk position (with hands upward):* ScH1 represents distance between scapular line and main horizontal line in sitting hands up position. UV4 (horizontal line connecting umbilicus and main vertical line) represents line that connects umbilicus (U) and the main vertical line at V4 in sitting hands up position. *Head position (with hands upward):* ChH2 (line connecting chin apex and horizontal line) represents line that connects chin apex (Ch) and main horizontal line at H2. ChV3 (line connecting chin apex and vertical line) represents line that connects chin apex (Ch) and main vertical line at V3. *Arms position (with hands upward):* WH4 (distance between wrist and horizontal line) represents line that connects wrist (W) with the main horizontal line at H4. WV1 (distance between wrist and vertical line) represents line that connects wrist (W) with main vertical line at V1. EH4 (distance between elbow and horizontal line) represents line that connects elbow (E) with the main horizontal line at H3. EV2 (distance between elbow and vertical line) represents line that connects

elbow (E) with the main vertical line at V2. Ae (angle of elbows position) represents an angle formed by line C-E that connects scapula (Sc) and elbow (E) and line that connects elbow (E) and wrist (W).

Statistical analyses: The normal distribution and the variation within each group of data was verified by using SigmaPlot 11.0 software. Statistical comparisons were made using paired t-test, and one-way repeated measures ANOVA (Student–Newman–Keuls) for comparison of the amplitudes of responses. All data were presented as the mean ± SEM. In all cases, $p < 0.05$ was considered statistically significant. To analyze gait kinematics one-way repeated measures ANOVA (Tukey test) for comparison range of movement before, during and after stimulation. To assess balance before and during stimulation Mann-Whitney U Test, and Student t-test were used. All results are presented as means ± standard error of the mean. $p<0.05$ considered as significant.

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Declarations

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Author contributions

Elvira Mukhametova and Alena Militskova: conceptualized study design, executed experimental stimulation protocol, executed motor performance and trunk control assessments, directed data analysis and interpretation, prepared the paper. Artur Biktimirov: performed neurosurgical procedures for epidural stimulation system implantation, contributed to study design conceptualization, revised paper. Kharin Nikita: led data acquisition, contributed to biomechanical data analysis. Elena Semenova: facilitated data acquisition and analysis. Oskar Sachenkov: contributed to study design and executed statistical data analysis. Tatiana Baltina: contributed to study design conceptualization, revised paper. Igor Lavrov: conceptualized study design, oversaw study execution, prepared, and revised paper.

Competing interests

All authors declare no competing interests

Figures

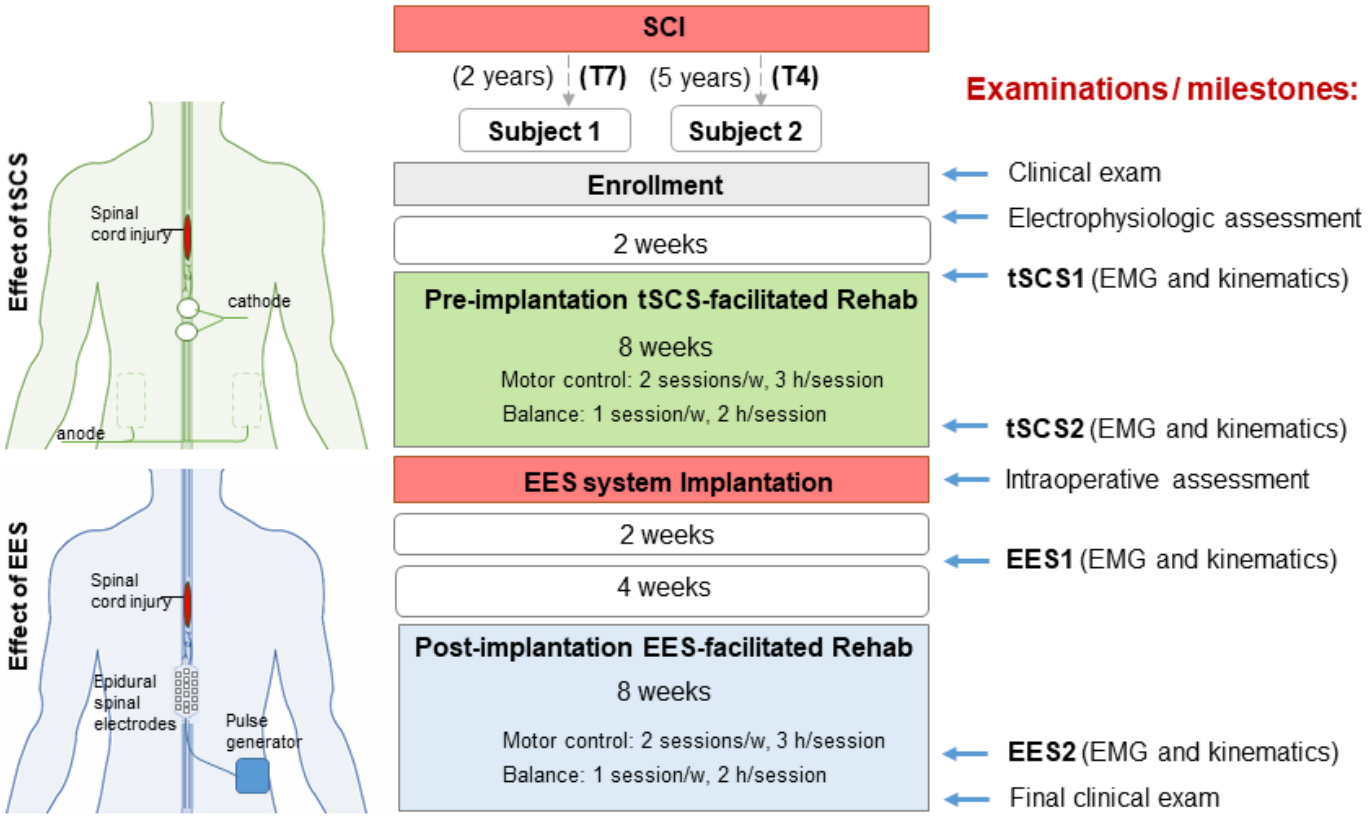

Figure 1

Timeline of the study. Two subjects (S1, AIS-A at T7 and S2, AIS-B at T4) with 2 and 5 years after SCI, correspondingly, were enrolled in this study. After initial clinical exam, electrophysiological assessment was performed and both subjects were tested with a 2-week trial of tSCS (tSCS1). The same stimulation protocol was used for the following 8 weeks of tSCS-enabled motor training with the following assessment (tSCS2). Both subjects were implanted with EES system with intraoperative electrophysiological assessment and were tested on the 2nd day after surgery, demonstrating ability to control legs' movements with EES (EES1). Then, both subjects received EES-enabled motor training for 8 weeks with the following evaluation (EES2). Schematic position of the electrodes during tSCS and EES presented on the left side and the main milestones and examinations presented on the right side of the figure.

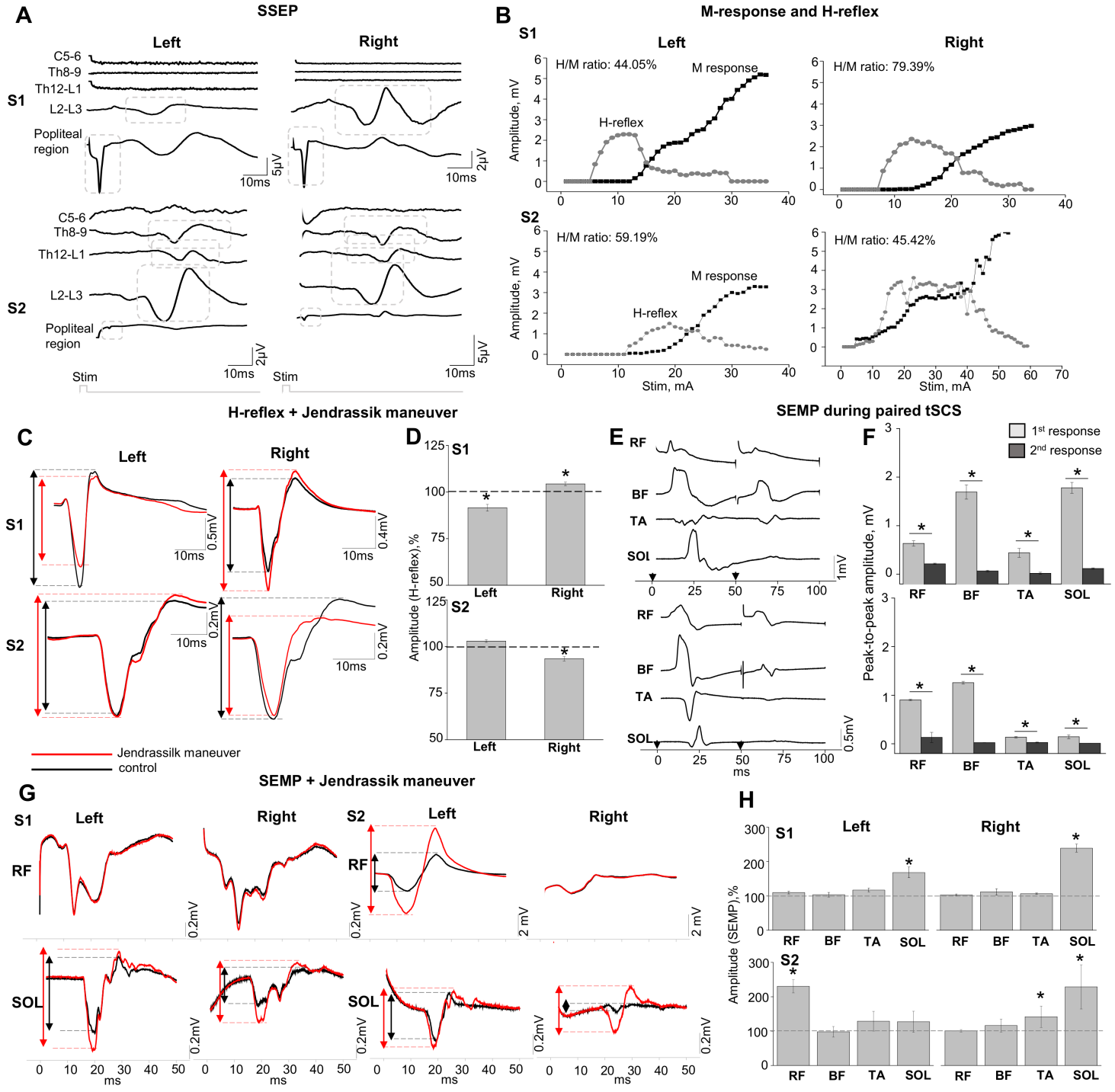

Figure 2

Assessment of transleisional connectivity. (A) Examples of SSEPs from the five locations (popliteal region, L2-3, Th12-L1, Th8-9, and C5-6) during bilateral stimulation of the tibial nerve (each line represents average from 800 responses). (B) Examples of recruitment curves of the M wave (black lines) and the H-reflex (light grey lines) for subjects 1 and 2. (C) Examples of M wave and H-reflex recorded from right and left Soleus muscles without (black lines) and with Jendrassik maneuver (JM) (red lines). (D) The amplitudes of the H-reflex recorded from right and left Soleus muscle during JM presented as % from H-reflex without JM (dashed line) (n=5). (E) Examples of SEMPs during paired tSCS at Th11-12 with a 50-

ms interstimulus interval (onset of each stimulus presented with black arrow). (F) Responses to the 1st and 2nd stimuli demonstrate that responses to the 2nd stimulus (dark grey bars) are lower compared to responses evoked by the first stimulus (light grey bars) for both subjects (n=6, p<0.05). (G) Examples of the SEMPs recorded from RF and SOL during stimulation at Th11-12 without (black lines) and with JM (red lines). (H) The amplitudes of the SEMPs recorded from left and right proximal (RF and BF) and distal (TA and SOL) muscles during tSCS at Th11-12 with JM, presented as % from SEMP recorded without JM (dashed line) (n=5).

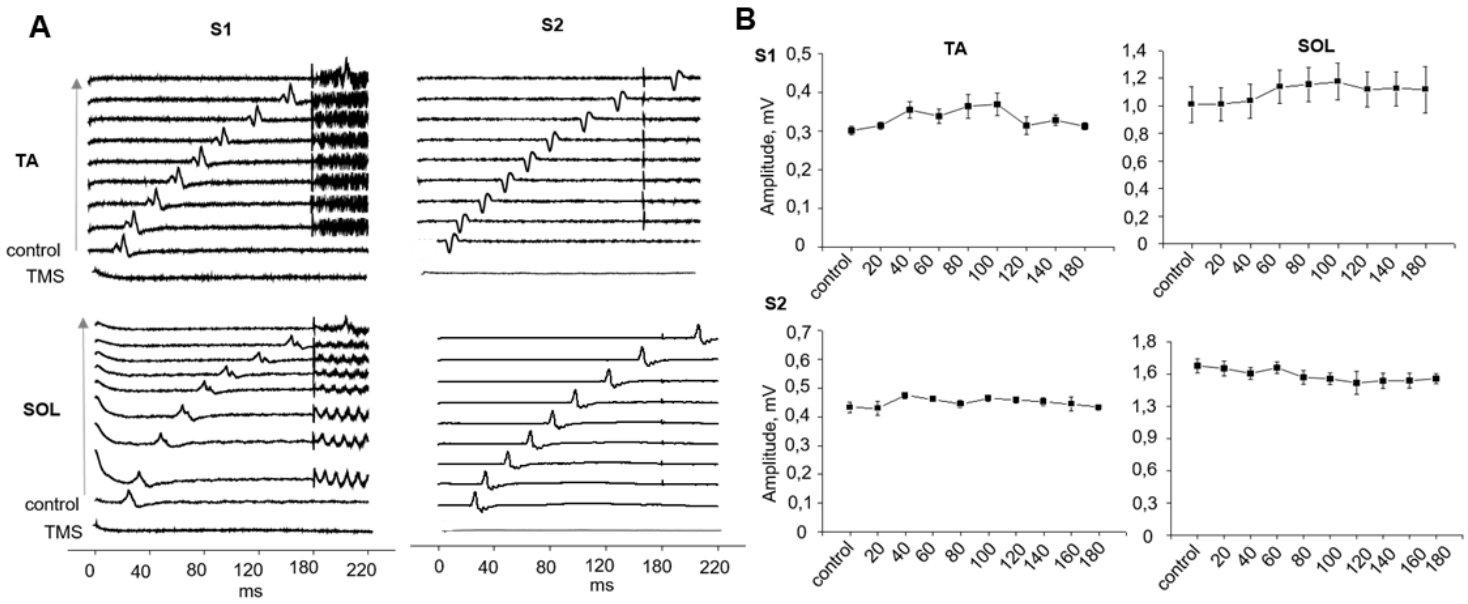

Figure 3

(A) Examples of the conditioning stimulation with TMS applied with tSCS at Th11-12 level. Transcranial magnetic stimulation (TMS) was applied with 20-180ms time intervals prior to tSCS and EMG activity recorded from TA and SOL. (B) Average amplitude of SEMPs recorded from TA and SOL demonstrate no conditioning effect of TMS delivered at different intervals (SEM, n=5).

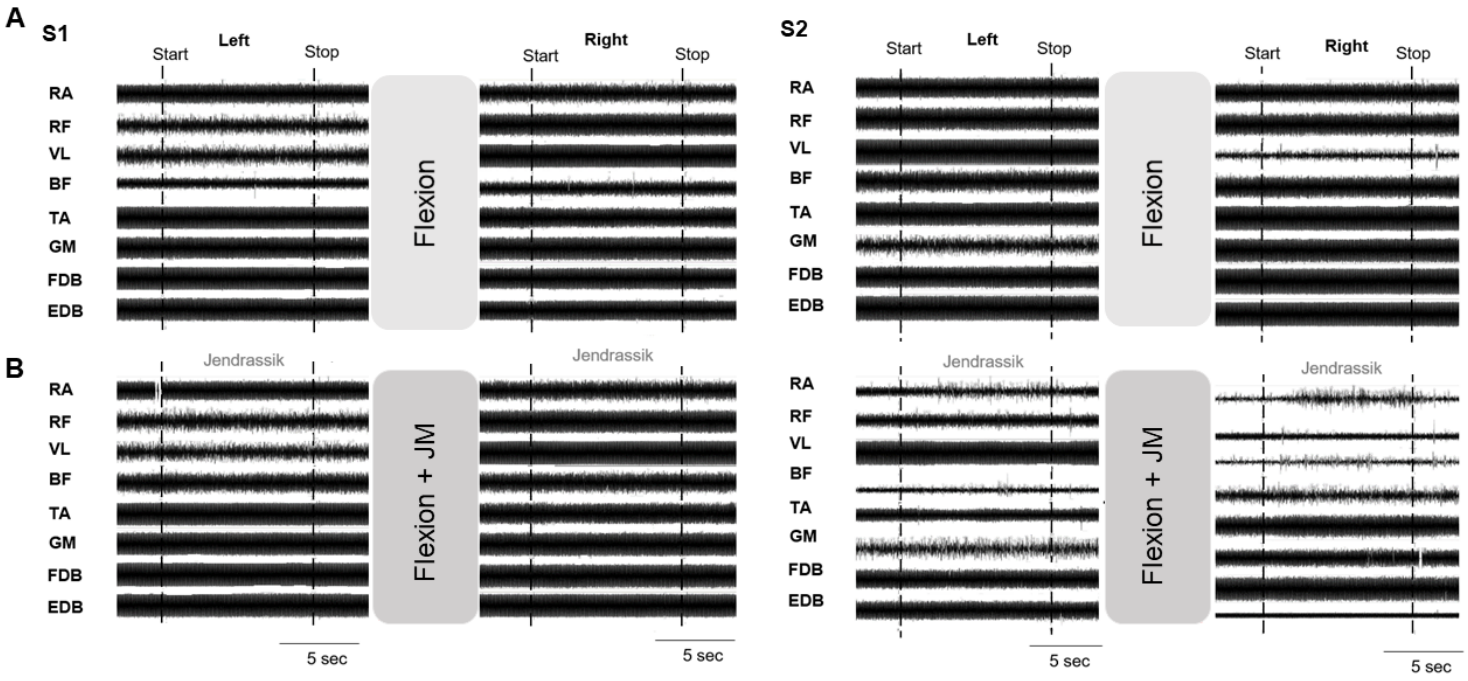

Figure 4

Examples of EMG recorded in subjects S1 and S2 during volitional attempts of simultaneous flexion of both legs without (A) and with JM (B). EMG was collected bilaterally in rectus abdominis (RA), rectus femoris (RF), vastus lateralis (VL), medial hamstring (MH), tibialis anterior (TA), medial gastrocnemius (MG), extensor digitorum brevis (EDB), and flexor digitorum brevis (FDB).

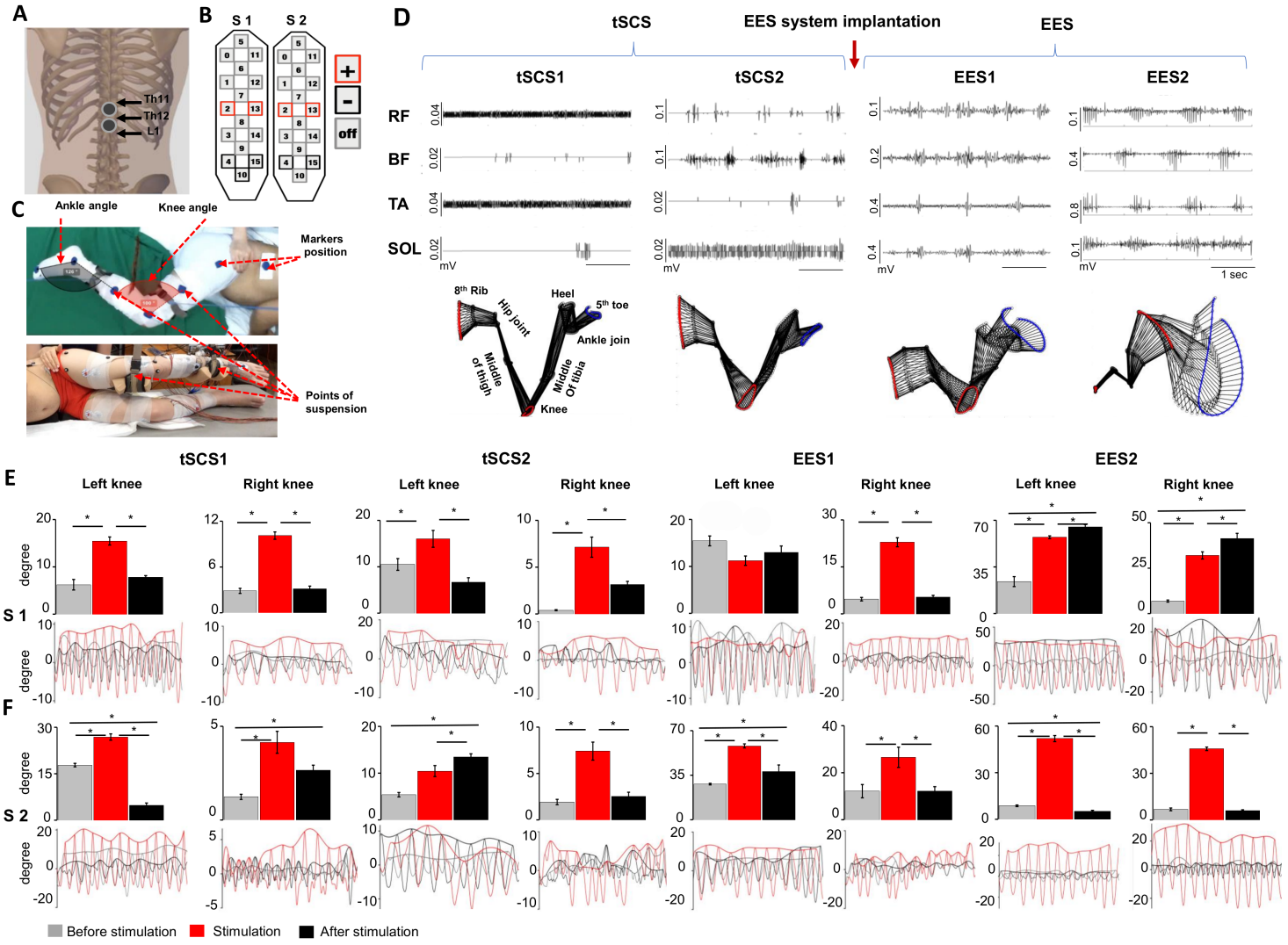

Figure 5

The restoration of voluntary legs movements tested in a side-line position. (A) Schematic localization of transcutaneous electrodes (cathodes) used for tSCS in relation to the vertebra levels. (B) Schematic diagrams of active electrodes on epidural electrode array (Medtronic, 5-6-5) used for evaluation of the volitional control with EES. (C) An example of reflective markers location for kinematic data collection and joint angle evaluation during legs' movements. (D) Examples of EMG activities generated in left legs' muscles – rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA), and soleus (SOL), during side position training with tSCS and EES across the study in S2. Examples of legs' kinematics collected with video capture system (Vicon) from the left leg in S2 during tSCS and EES corresponding to EMG samples. (E) Mean range of movements in knee joint in S1, collected from 15 complete gait cycles during tSCS1 with examples of knee flexion-extension before, during, and after tSCS1, tSCS2, EES1, and EES2 with a kinematic graphical representation of knee flexion-extension before (grey), during (red), and after stimulation (black), presented below as color lines (15sec duration). Y-axis reflects degree of max to min joint angle movements. (F) Mean range of movements in knee joint in S2, collected from 15 complete gait cycles during tSCS1 with examples of knee flexion-extension before, during, and after tSCS1, tSCS2,

EES1, and EES2 with the kinematic graphical representation of knee flexion-extension before, during, and after stimulation. Abbreviations are siilar to E. Asterisks indicate significant effects of stimulation (*, $p<0.05$). The error bars represent standard error of the mean (SEM).

Figure 6

The restoration of voluntary motor control with tSCS and EES tested in side-line position. (A) Mean range of movement in ankle joint obtained from 15 complete gait cycles during tSCS1 with examples of ankle flexion-extension before (grey), during (red), and after (black) tSCS and EES with the kinematic graphical representation of ankle flexion-extension before, during, and after stimulation in S1 presented below as color lines (15sec duration). Y-axis reflects the units in degree (max to min joint angle during movement). (B) Mean range of movement in ankle joint obtained from 15 complete gait cycles during tSCS1 with examples of ankle flexion-extension before, during, and after tSCS and EES with the kinematic graphical representation of ankle flexion-extension before, during, and after stimulation in S2. Asterisks indicate significant effects of stimulation (*, $p<0.05$). The error bars indicate standard error of the mean (SEM).

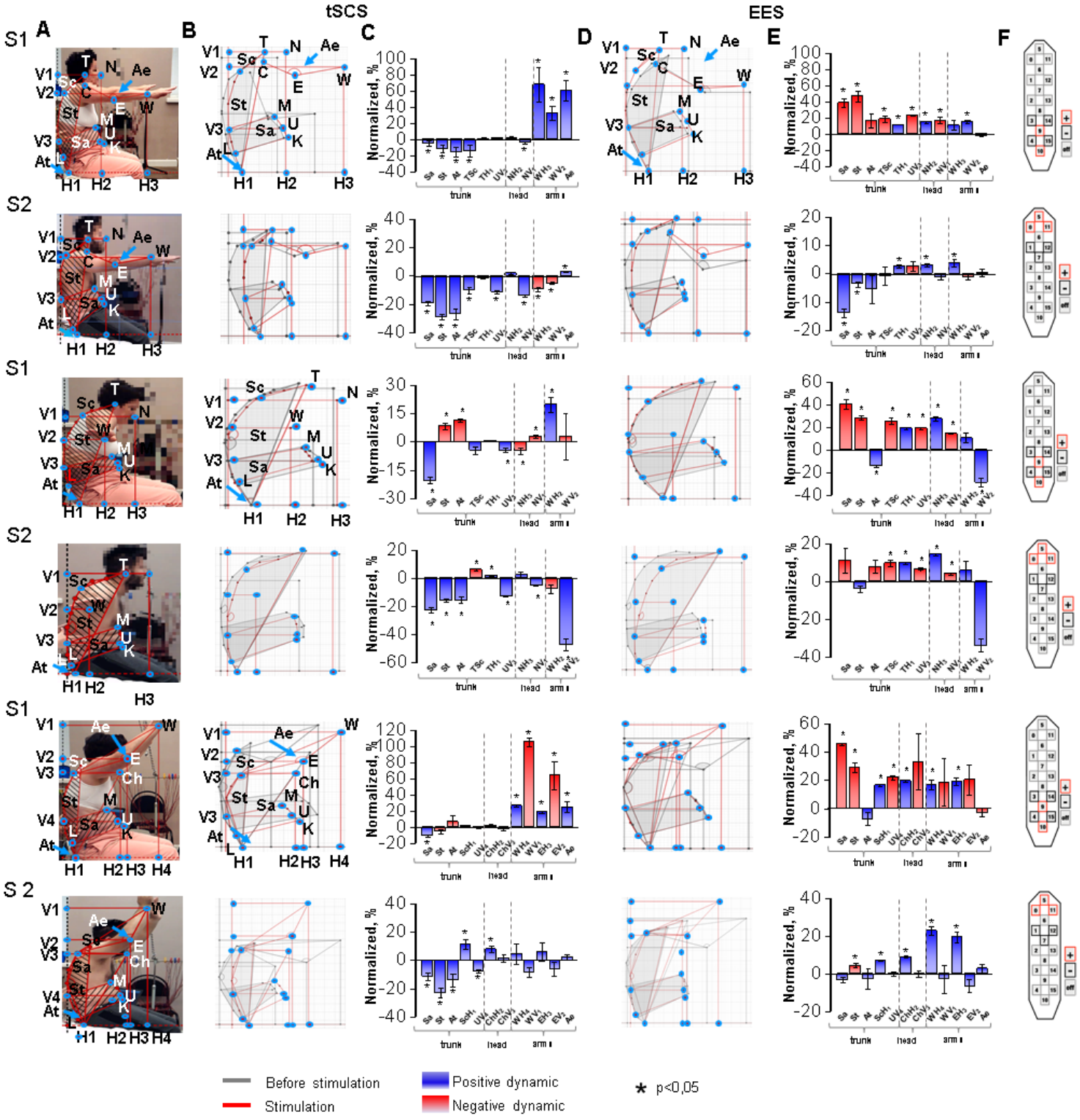

Figure 7

Balance control while sitting with hands forward, sideward, and upward. A. The perturbations in arm position relative to the main horizontal and vertical lines were assessed based on specific anatomic landmarks. In ‘arms up’ position with hands were covering nose, chin apex was used instead of nose apex. 11 metrics (2 angles, 2 squares, and 7 segments) were calculated to assess the balance control without and with stimulation (tSCS and EES) in S1 and S2. Main lines and metrics to evaluate trunk,

head, and arms position with hands forward, sideward, and upward described in detail in *Balance assessment (see methods).* B. Representative reconstruction of head, arms, and trunk position during testing with and without tSCS. C. Normalized values out of six frames recorded every 10 sec in 60 sec period (SE, p<0.05). Zero represents 100% of values recorded without tSCS. D. Representative reconstruction of head, arms, and trunk position during testing with and without EES. E. Normalized values from six frames recorded every 10 sec in 60 sec period (SE p<0.05). Zero represents 100% of values recorded without EES. F. Schematic diagrams with the optimal electrode configurations on epidural electrode array (Medtronic, 5-6-5) during balance testing in S1 and S2.

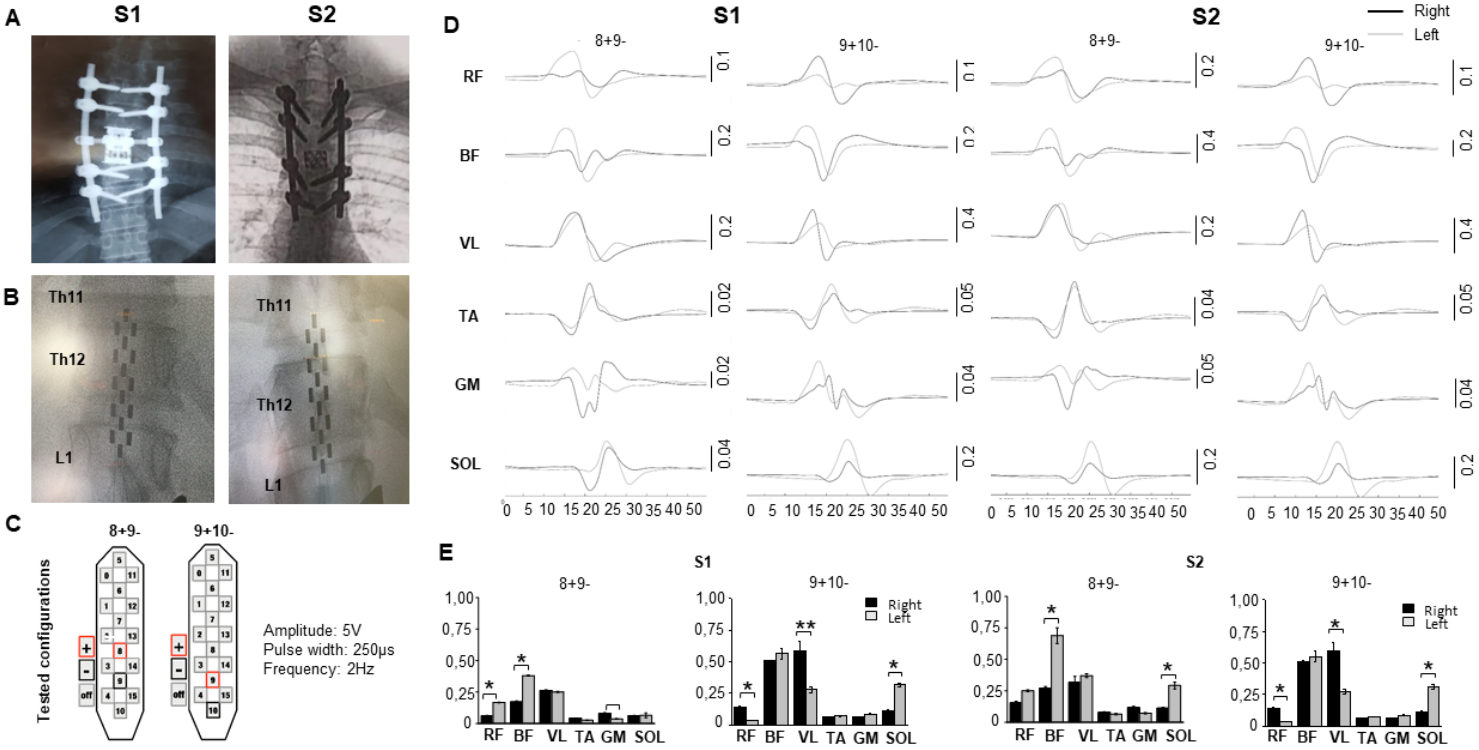

Figure 8

Visualization of the spine at the spinal cord injury site and EES electrodes implantation. (A) Image of the spine fixation structure for S1 and S2. (B) Intraoperative fluoroscopy of EES array (Medtronic, 5-6-5) location at the T11–L1 vertebral levels, captured in a prone position. (C) Examples of stimulation configurations used for intraoperative assessment (black '–' cathode, red '+' anode). Frequency was set as 2 Hz, pulse width as 250 us, and current amplitude as 5V. (D) Examples of the SEMPs during intraoperative assessment at 8+9- and 9+10- electrode configurations. Black lines represent SEMP in RF, BF, VL, TA, GM, and SOL during stimulation at 5V on the right side. Grey lines represent SEMP in RF, BF, VL, TA, GM, and SOL during stimulation at 5V on the left side. (E) The amplitude of SEMPs recorded during stimulation with midline electrode configurations demonstrate activation of both proximal muscle (RF, BF, and VL) and distal muscle (MG, TA, and SOL). Asterisks denote statistical significance: *p < 0.05, **p < 0.001

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