TARGETED NEUROTECHNOLOGY RESTORES WALKING IN HUMANS WITH SPINAL CORD INJURY

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ABSTRACT

Spinal cord injury (SCI) leads to severe locomotor deficits or even complete leg paralysis. Here, we introduce targeted spinal cord stimulation neurotechnologies that enabled voluntary control of walking in individuals who had sustained a SCI more than four years ago and presented with permanent motor deficits or complete paralysis despite extensive rehabilitation. Using an implanted pulse generator with real–time triggering capabilities, we delivered spatially–selective stimulation trains to the lumbosacral spinal cord with a timing that coincided with the intended movement. Within one week, this spatiotemporal stimulation reestablished adaptive control of paralyzed muscles during overground walking. Locomotor performance improved during rehabilitation. After a few months, participants regained voluntary control over previously paralyzed muscles without stimulation and could walk or bike in ecological settings during spatiotemporal stimulation. These results establish a technological framework to improve neurological recovery and support activities of daily living after SCI.

INTRODUCTION

Spinal cord injury (SCI) disrupts the communication within the nervous system, leading to the loss of essential neurological functions.

Activity–based therapies are the only medical practices for enhancing recovery[1-3]. The volitional production of active movements during training promotes a reorganization of neuronal pathways that augments recovery[4,5]. However, the most affected patients, who fail to produce active movements voluntarily, experience minimal benefits from these therapies[1].

This framework prompted the development of multifaceted neurotechnologies[6] such as lower limb exoskeletons, bodyweight support systems, functional electrical stimulation of muscles, and spinal cord neuromodulation therapies that all share the same goal: enable patients to sustain active movements during training to enhance the reorganization of neuronal pathways[4]. Three decades of clinical research employing these neurotechnologies suggest that epidural electrical stimulation (EES) of the spinal cord may be pivotal to achieve this goal[7-10]. EES not only enables the brain to exploit spared yet functionally–silent descending pathways to produce movements of paralyzed limbs[11,12], but also improves the ability of the spinal cord to translate task–specific sensory information into muscle activity underlying standing and walking[9,10,12-16].

To harness the therapeutic potential of EES, we studied the underlying mechanisms. We found that EES activates motoneurons through the recruitment of proprioceptive circuits within the posterior roots[17-20]. This understanding translated into EES protocols targeting individual posterior roots to access the motoneuron pools located in the segment innervated by each root[21]. To engage motoneurons at the appropriate time, spatially-selective EES trains are delivered with a timing that coincides with the intended movement. Compared to empirical stimulation protocols, spatiotemporal EES enhances the potency of leg movements, which enabled weight-

bearing locomotion in animal models of leg paralysis[21-23]. When combined with overground locomotor training enabled by a gravity–assist[24], this stimulation promotes an extensive reorganization of residual neural pathways that improves locomotion with and even without stimulation[21,25,26].

Here, we developed targeted neurotechnologies for delivering spatiotemporal EES during overground locomotor training with a gravity–assist in humans[27]. We hypothesized that spatiotemporal EES would immediately enable voluntary locomotion despite chronic paralysis. We postulated that the ability to sustain active movements during training would promote meaningful functional improvements with and even without stimulation.

RESULTS

Targeted neurotechnologies and surgery

We developed a wireless environment allowing real–time control over independently–adjusted EES trains to the spinal cord during overground walking (**Fig. 1a** and **Supplementary Video 1**). A gravity–assist applied multidirectional forces to the trunk to provide personalized bodyweight support in a safe workspace[27]. A recording platform allowed real-time processing of whole–body kinematics, ground reaction forces and electromyographic (EMG) activity of leg muscles. To deliver stimulation, we upgraded an implantable pulse generator commonly used for deep brain stimulation with wireless communication modules[23] that enabled real–time control over EES parameters (**Extended Data Fig. 1**). EES sequences could be pre–programmed in open-loop or adjusted in closed-loop based on external signals[21,22]. The lumbosacral posterior roots were targeted using a 16-electrode paddle array designed for pain therapies.

We enrolled three males with a chronic cervical SCI (**Fig. 1b**) who displayed severe lower limb deficits or complete paralysis that prevented them from ambulating overground (**Extended Data Table 1**).

To target the posterior roots projecting to motoneuron pools innervating leg muscles (**Fig. 2a**), we developed a surgical protocol including pre–operative imaging combined with intraoperative electrophysiology and radiology that guided the precise placement of the paddle array (**Extended Data Fig. 1b**).

EES enables control of paralyzed muscles

We aim to identify electrode configurations that target the posterior roots projecting to the spinal cord regions embedding motoneurons involved in mobilizing the hip, knee and ankle joints.

We compiled an atlas of motoneuron activation maps underlying flexion or extension of each joint in healthy individuals. We projected the EMG activity from leg muscles onto the expected anatomical location of the associated motoneuron pools[28,29]. We obtained consistent motoneuron activation maps. For example, hip flexions involved the activation of upper lumbar segments, while ankle extensions activated motoneuron pools restricted to upper sacral segments (**Fig. 2b**).

To identify electrodes that could target the posterior roots projecting to spinal cord regions underlying these motoneuron activation maps, we performed simulations using hybrid computational models of EES[18]. Each model was personalized using MRI and CT–scans. Simulations estimated the relative recruitment of each posterior root with each electrode (**Fig. 2c**).

These simulations guided the identification of optimal electrode configurations. While participants laid supine, we delivered monopolar pulses of EES at increasing intensities through the electrodes presenting the highest probabilities to activate the targeted posterior roots (**Extended Data Fig. 2**). Projection of muscle response amplitudes into circular plots described the spatial selectivity of each electrode, which we quantified with an algorithm (**Fig. 2d**). If the selectivity was insufficient, we steered the electrical fields with multipolar electrode configurations (**Extended Data Fig. 2**).

For all participants, computer simulations and electrophysiological experiments confirmed high correlations between the identified electrode configurations and the recruitment of the posterior roots projecting to each of the targeted spinal cord regions involved in mobilizing hip, knee and ankle joints (**Extended Data Fig. 3**).

We next tested whether spatially-selective EES could facilitate force production from the targeted muscles. While seated, participants were asked to produce an isometric force restricted to a single joint. P1 failed to produce hip flexion and ankle extension torques with his paralyzed leg (**Fig. 2e-f**). EES immediately enabled voluntary activation of the targeted muscles to produce the desired torque. These observations were obtained for all targeted joints and participants (**Extended Data Fig. 4**).

Without voluntary contribution, EES induced minimal muscle contraction (**Extended Data Fig. 4**). With these amplitudes, EES augmented the excitability of the targeted motoneurons, which enabled residual yet functionally–silent descending inputs to activate muscles.

EES modulates cortical activity

These results opened the possibility that the recruitment of proprioceptive pathways with EES modulates cortical excitability, which may facilitate movement[30].

To study this hypothesis, we recorded electroencephalographic (EEG) activity when participants attempted to produce knee extension torques without and with EES (**Extended Data Fig. 5a**). EES triggered a robust response in the sensorimotor cortex (latency: 90-140 ms, **Extended Data Fig. 5b**), likely resulting from the recruitment of proprioceptive afferents.

Attempts to activate knee extensor muscles triggered an event–related desynchronization (ERD) of the contralateral sensorimotor cortex in β–band frequencies, both without and with EES. This cortical activity has been linked to movement execution, and is followed by an event–related resynchronization (ERS) after movement termination[31]. Previous studies showed that the amplitude of ERS decreases proportionally to SCI severity[31]. Voluntary activation of paralyzed muscles during EES led to an increase in ERS amplitude (**Extended Data Fig. 5c-d**).

These results suggest that EES enhances cortical excitability, promoting more natural dynamics during movement execution[30].

Spatiotemporal EES enables walking

Walking involves reproducible sequences of muscle activation (**Fig. 3a**). The underlying motoneuron activation maps involve a succession of hotspots whose migration reflects body mechanics[28], ensuring weight-acceptance, propulsion and swing (**Fig. 3b**).

Targeted EES effectively activated the regions embedding these hotspots (**Fig. 3c**). To configure EES sequences (**Fig. 3d-e**), we fine-tuned the timing of each spatially–selective stimulation train using a closed–loop controller that triggered EES based on foot trajectory[21,22,32]. We adjusted the onset and duration of each train to approach motoneuron activation maps of healthy individuals (**Extended Data Fig. 6**). Relatively small changes in the timing of each train altered performance. Once optimized, EES could be delivered in open-loop: participants regulated the timing of their movements to pre-programmed EES sequences, which improved gait consistency.

To tune muscle activity, we adjusted EES amplitudes and frequencies (**Extended Data Fig. 6**). As observed in animal models[21,22], we found a monotonic relationship between EES frequency and flexor muscle activity (**Fig. 3f**), such that increasing frequency enhanced flexion proportionally (**Extended Data Fig. 6**). Unexpectedly, extensor motoneuron pools responded inversely. Proprioceptive afferents elicit strong monosynaptic responses in extensor motoneurons, whereas these afferents primarily engage flexor motoneurons through polysynaptic circuits[33]. In humans, monosynaptic projections are highly sensitive to low-frequency depression[34], which may explain the decrease in extensor motoneuron activation when increasing frequency.

Within 5 days, this procedure led to EES sequences (**Fig. 3e-d**) that enabled robust EMG activity in otherwise quiescent muscles during stepping on a treadmill (**Extended Data Fig. 7**).

Participants were then asked to walk overground with the gravity-assist and spatiotemporal EES. The stimulation enabled all participants to walk voluntarily until the stimulation was stopped. They could resume locomotion as soon as the stimulation was reintroduced (**Fig. 4a**, **Extended Data Fig. 8a** and **Supplementary Video 2**).

We next investigated their ability to adjust leg movements. First, we asked them to produce exaggerated step elevations without changing EES parameters. All participants were able to enhance their step elevation three-to-fivefold compared to regular steps (**Fig. 4b** and **Extended Data Fig. 8b**). Second, we asked them to adjust their stride to varying speeds. Not only were the participants able to adjust their stride length, but they also could stop locomotor movements despite the treadmill belt motion and ongoing stimulation (**Extended Data Fig. 8b,e**).

Finally, we asked participants to walk on a treadmill for one hour. All participants sustained more than 1200 steps, covering distances as long as 1.2 km without showing muscle exhaustion or gait impairments **(Fig. 4c, Extended Data Fig. 8c**).

These results show that spatiotemporal EES not only enabled completely or partially paralyzed individuals to walk overground, but also allowed them to adjust leg movements to stand and walk over a range of speeds for durations as long as one hour.

Continuous EES is poorly effective

Recent studies showed that continuous EES enabled overground walking after nearly one year of intense training[9,10]. Since spatiotemporal EES enabled locomotion within one week, we evaluated whether continuous EES could achieve similar efficacy.

We delivered widespread stimulation targeting the posterior roots associated with flexor motoneuron pools, as previously recommended[10]. However, we did not further optimize the stimulation. Continuous EES enhanced muscle activity, but was poorly effective to facilitate locomotion overground. All participants reported a loss of limb position awareness combined with co-activation across muscles (**Extended Data Fig. 9** and **Supplementary Video 3**). These detrimental outcomes are due to the cancellation of proprioceptive information during continuous EES[35].

Rehabilitation improves walking with EES

Participants followed a rehabilitation program four-to-five times per week for five months focused on walking on a treadmill and overground; complemented with muscle strengthening and standing—each enabled by task–specific EES (**Extended Data Fig. 10**).

With spatiotemporal EES, all participants improved their walking capacities following a reproducible chronology: non–ambulatory participants initially required crutches and the gravity-assist to walk overground. After one to three months, they could walk hands–free when provided with hip support in the gravity-assist. Eventually, P1 and P2 regained independent walking while 35% of their bodyweight was supported against gravity. P3 needed a walker to progress overground with EES (**Supplementary Video 4**).

Neurological recovery without EES

Improvements were not limited to walking with EES. Rehabilitation promoted a neurological recovery that translated into improvements without EES.

P1 and P2 could transit from sitting to standing and walking independently with crutches (**Fig. 5a**). P1 could even walk without assistive device for several steps (**Supplementary Video 5**). Consequently, P1 and P2 increased their WISCI score from 13 to 16 and 6 to 13, respectively. They displayed substantial improvements in clinical evaluations such as ten–meter and six–minute walk tests without EES (**Fig. 5b**). Several months after completing the rehabilitation program, both participants, who continued practicing once or twice per week with EES, maintained or further improved their performance.

Participants also recovered voluntary leg movements without EES. For example, P1 and P3 could sustain a full extension of their previously paralyzed legs against gravity (P3, lying only; **Fig.**

5c and **Supplementary Video 5**). Quantified measurements revealed that P1 and P2 improved their ability to produce a torque at each joint of both legs (**Fig. 5c**). This recovery translated into an increase of 16 and 11 points in lower extremity motor scores, respectively (**Fig. 5d**). Both participants had previously followed extensive conventional rehabilitation without showing neurological recovery. Lower extremity motor score increased by 4 points in participant P3, but without EES this recovery was insufficient to produce measurable forces when seated. However, force production improved during EES (**Fig. 5c**). He showed a considerable increase in mass and quality of thigh and trunk muscles (**Extended Data Fig. 11**). P1, P2 and P3 also ameliorated upper limb motor scores by 1, 2, and 2 points, respectively.

Support of activities in the community

Recovery of functional leg movements during spatiotemporal EES suggested that practical stimulation technologies could support activities of daily living. For this purpose, we engineered a solution based on a tablet enabling the selection of EES sequences that are switched on/off with a voice–controlled watch (**Fig. 6a**). To enable standing, walking or biking, EES sequences must be synchronized to the intended movements. We conceived algorithms that trigger and adjust the timing of EES trains in closed–loop based on real-time acquisition of signals from wearable inertial measurement units.

Robust event–triggered detections allowed participants to transit from sitting to standing and walking freely in ecological settings (**Fig. 6b** and **Extended Data Fig. 12**). A stimulation program specific for cycling permitted rides with an adapted trike powered with the arms and legs (**Supplementary Video 6**).

DISCUSSION

We developed targeted EES neurotechnologies that immediately restored voluntary control of walking in individuals with severe or complete paralysis. The electrode configurations targeted proprioceptive circuits through the recruitment of selected posterior roots[17-19,36]. This strategy was pivotal to enable the immediate control of walking despite chronic paralysis. This framework guided the rapid personalization of spatiotemporal EES sequences that continuously coincided with intended movements. Consequently, EES augmented the excitability of motoneuron pools that were concomitantly engaged by the natural flow of sensory information and residual supraspinal commands. This spatiotemporal convergence enabled a robust and more natural control of leg movements compared to empirical stimulation paradigms such as continuous EES[9,10].

We hypothesize that this spatiotemporal convergence is responsible for the neurological recovery observed in all participants without EES. We showed that mice lacking proprioceptive circuits exhibit defective rearrangement of descending pathways after SCI, which abolishes recovery[37]. Conversely, we propose that the spatiotemporal contingence between residual supraspinal commands and proprioceptive circuit activations with EES may increase the strength and number of terminals from spared descending projections through bidirectional spike–timing–

dependent plasticity[38,39]. Electrophysiological studies documented such plasticity in humans with SCI[40,41]. This interpretation is consistent with the pronounced reorganization of cortico–reticulo–spinal circuits observed in rodents when EES enables gait training despite paralysis[25,26]. As we observed in humans, rodents regained cortical control of leg movements that persisted without EES[25] when rehabilitation commenced early after SCI. We therefore anticipate that this therapy will be even more efficacious early after SCI in humans, when the potential for plasticity is elevated and the neuromuscular system has not yet undergone the atrophy that follows chronic paralysis[42]. Furthermore, improvement in muscle mass and other physiological functions[43,44] suggest that EES may contribute to counteracting these deteriorations.

Clinical trials starting early after SCI will require a stratification of participants who may benefit from the therapy, combined with statistical models that predict their potential for recovery[45]. Here, we validated our neurotechnologies in a few individuals. This proof–of–concept stresses the urgency to develop neurotechnologies that not only harness targeted EES to enable movement, but also provide the usability features to support rehabilitation in clinical settings and use in the community.

DATA AND CODE AVAILABILITY

Data that support the findings and software routines developed for the data analysis will be made available upon reasonable request to the corresponding author at gregoire.courtine@epfl.ch.

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Figure 1 | Technology study design. (a) Multidirectional assistance of trunk movements during overground locomotion while 3D kinematics, ground reaction forces and EMG activity are recorded wirelessly. Implantable pulse generator connected to a 16-electrode paddle array to target the posterior roots projecting to specific motoneuron pools, illustrated for hip flexors and ankle extensors, respectively. Real-time processing of residual kinematics ensures targeted EES coincides with movement intent. **(b)** Study timeline.

Figure 2 | Configuration of targeted EES. (a) Distribution of motoneuron pools within the spinal cord[46]. **(b)** Motoneuron activation map underlying isometric torque production in healthy subject (consistent across 3 repetitions and subjects). **(c)** Personalized computational model of EES. Simulated motoneuron activation map following EES targeting L1 and S2 posterior roots. **(d)** EMG responses when delivering single-pulse EES at increasing amplitudes (grey traces). Motoneuron activation maps correspond to optimal amplitudes (black traces). Circular plots report EMG amplitude (greyscale) at increasing amplitudes (radial axis). White circles highlight optimal amplitudes while polygons quantify selectivity at this amplitude. **(e)** Instrumented chair measuring single-joint torques. **(f)** Isometric torque and EMG activity while delivering targeted EES, including quantification (n = 3 repetitions, P1).

Figure 3 | Configuration of spatiotemporal EES for walking. (a) EMG activity during walking in healthy individuals. Spatiotemporal map of motoneuron activation highlights hotspots (mean, n = 12 gait cycles, representative subject). Equipotential lines: 45-75% activation. **(b)** Function of each hotspot. **(c)** Motoneuron activation map following 500 ms bursts of targeted EES during standing. Bar plots show Pearson's correlations for each hotspot (mean, n = 12 bursts, error bars: standard error; ***, $p < 0.001$. 1-way ANOVA, post-hoc HSD Tukey). (**d)** EMG activity and motoneuron activation map during stepping on a treadmill with support and assistance (P3). EES timing is indicated along foot trajectories (n = 73 steps) and below motoneuron activation maps. **(e)** Spatiotemporal EES sequence in (d). **(f)** Mean modulation of EMG amplitude in flexor and extensor muscles during walking when increasing EES frequencies (error bars: standard error; n = 20, 15, 16, 17, 15, 16, 15 gait cycles for 20, 25, 30, 40, 60, 80, 100 Hz respectively; P3).

Figure 4 | Voluntary control of adaptive and sustained locomotion. (a) Chronophotography, TA EMG activity and foot vertical position during overground walking with gravity–assist and sticks while EES is switched ON/OFF/ON. **(b)** Overground walking while requesting participants to perform steps with normal heights and then exaggerated step elevations. **(c)** Consecutive values of step height and EMG activity over 60-min of walking with EES (P1: 1.2 km; P2, P3: 1 km). Experiments (a) and (b) were repeated at least 5 times. Experiment (c) was performed once, but participants routinely walked for one hour during training.

Figure 5 | Rehabilitation mediates neurological recovery. (a) Chronophotography showing P1 and P2 transiting from sitting to walking with crutches without EES; P3 progresses overground

with a walker and EES; repeated at least 3 times on different days. **(b)** Plots reporting changes in 6-minute and 10-meter walk tests for P1 and P2. Tests were performed without gravity–assist, following clinical guidance. P3, plots report changes in walking distance during rehabilitation and walking speed with EES. **(c)** Evaluations of isometric torque production for each joint, quantified before surgery and after rehabilitation without EES for P1 and P2, and with EES for P3. **(d)** Schemes report changes in lower limb motor scores after rehabilitation. Changes in motor and sensory scores for all levels below injury are summarized (details in **Extended Table 1)**.

Figure 6 | Spatiotemporal EES in ecological settings. (a) Tablet featuring a mobile App allowing participants to select EES sequences, delivered in open–loop or closed–loop based on inertial measurement units (IMUs) located on both feet or attached onto the cranks and frame of a trike. A personalized voice–controlled watch allows switching EES ON/OFF. **(b)** Walking and cycling activities in ecological settings.

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Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare competing financial interests: G.C., J.B., Ma.C., V.D. hold various patents in relation with the present work. T.D., R.B. and N.B are Medtronic employees, and V.D., H.L., J.vZ., A.W., Mi.C. and E.Pa. are GTXmedical employees. In review of the manuscript they contributed to technical accuracy but did not influence the results or the content of the manuscript. G.C., J.B., V.D., and H.L. are founders and shareholders of GTXmedical, a company in direct relationships with the presented intervention.

Extended Data Fig. 1 | Surgical procedure and Technological Framework (a) Surgery. Step 1: High-resolution MRI for pre-surgical planning. The entry point into the epidural space is based on the position of the conus. **Step 2:** Placement of subdermal and intramuscular needle EMG electrodes for key leg muscles (abbreviations, see **Fig. 2a**) and paraspinal (PS) muscles. A subdermal needle is inserted over the sacrum and used as a return electrode for stimulation. Schematic of the 16-electrode paddle array. **Step 3:** Surgical openings based on pre-surgical planning, typically between the L1 and L2 vertebrae, which are identified through intraoperative X–ray. The mediolateral positions of the paddle array is evaluated with X–ray and recordings of EMG responses following single pulses of EES delivered to the most rostral or most caudal midline electrodes. **Step 4:** The rostrocaudal position of the paddle array is optimized based on EMG responses to single-pulse EES delivered to the electrodes located at each corner of paddle array. The aim is to obtain strong ipsilateral responses in hip flexors with the most rostral electrodes and strong ipsilateral responses in ankle extensors with the most caudal electrodes. **Step 5:** IPG placed within the abdomen. Once connected to the paddle array, the impedance of the electrodes is evaluated to verify that all the components were properly connected. **Step 6:** Post-surgical CT scan showing the location of the paddle array with respect to the vertebrae in each participant. **(b) Technological framework and surgical procedure Step 1:** The participants wear reflective markers that are monitored with infrared cameras. An algorithm assigns the markers to the joints in real-time. **Step 2:** The spatiotemporal trajectory of the foot around a calculated center of rotation (centroid, updated every 3 s) is converted into angular coordinates that trigger and terminate EES protocols when crossing a user-defined threshold. **Step 3:** EES commands are transmitted to the implantable pulse generator (IPG) via Bluetooth (1) to a module that converts them into infrared signals (2), which are then transferred to the stimulation programmer device (2'). **Step 4:** The stimulation programmer transmits EES commands into the IPG (4) via induction telemetry, using an antenna (3) taped to the skin and aligned to the IPG. EES is delivered through the paddle array (5).

Extended Data Fig. 2 | Identification of electrode configurations targeting selected posterior roots. Step 1: Single-pulse EES and EMG recording setup. **Step 2**: Motoneuron pools are located in specific segments, which informs on the relative recruitment of each posterior root with EES. For example, electrodes targeting the L3/L4 posterior roots will elicit the strongest EMG responses in the knee extensors. A personalized computational model of EES allows for performing simulations that evaluate the relative activation of a given posterior root with a given electrode over the entire amplitude range. Each curve corresponds to an electrode. The highlighted curve corresponds to the electrode selected after Steps 3-5. **Step 3:** Single pulses of EES are delivered through the subset of electrodes identified with simulations. The EMG responses are recorded over a broad range of EES amplitudes. **Step 4:** The EMG responses are concatenated, averaged across n = 4 repetitions for each EMG amplitude, and the peak-to-peak amplitude of the average responses calculated to elaborate a recruitment curve for each recorded leg muscle (black traces: targeted muscles). **Step 5:** The circular plots display the normalized EMG responses (greyscale) when delivering single-pulse EES at increasing amplitudes (radial axis), where the white circle highlights the optimal EES amplitude and the polygon quantifies the relative muscular selectivity at this amplitude (median response taken over n = 4 EES pulses). The motoneuron activation maps are shown for the optimal amplitudes. **Step 6:** Decision tree to validate or optimize electrode configurations. The selected electrode is tested during standing since the position of the spinal cord with respect to the paddle array can change between supine and standing. In this example, the selectivity improves during standing. When the selectivity is deemed insufficient, the current is steered toward the targeted posterior roots using multipolar configurations. The example shows the increased selectivity of a multipolar configuration with two cathodes

surrounded by three anodes, compared to the two corresponding monopolar configurations. These results are verified experimentally and with computer simulations.

Extended Data Fig. 3 | Spatial selectivity of targeted electrode configurations. Monopolar configurations (shown on paddle array schematics) experimentally selected to target the left and right posterior roots associated with hip flexion (L1), knee extension (L3), ankle flexion (L4) and ankle extension (S1) for the three participants. The circular plots and motoneuron activation maps use the same conventions as in **Fig. 2** and **Extended Data Fig. 2** (median taken over n = 4 pulses). The normalized selectivity index is reported above each motoneuron activation map. This index represents the percentage of posterior root selectivity for the electrode configuration selected experimentally, with respect to the maximum posterior root selectivity that can be achieved among all monopolar configurations (all selectivity indices obtained from computational simulations). Note that in participant P2, the electrode selected experimentally to target the right S1 root was located on the midline and resulted in bilateral activation within computational simulations, which resulted in a normalized selectivity index of zero.

Extended Data Fig. 4 | Single-joint movements enabled by targeted EES. Step 1: Participants are placed in standardized positions allowing the assessment of voluntary torque production at a single joint (isometric contractions) without and with targeted EES. **Step 2:** EES protocols elaborated from single-pulse experiments (**Extended Data Fig.2-3**) are optimized for each task: multipolar configurations and adjustments of EES amplitude and frequency. **Step 3:** Sequence of each trial: participants were asked to produce a maximal voluntary contribution, but failed in the vast majority of cases, as evidenced by the absence of EMG activity during this period. While they continued trying to activate the targeted muscle, EES was switched ON. After a few seconds, participants were instructed to stop their voluntary contribution. After a short delay, EES was switched OFF. For each sequence, the produced torque and EMG activity of the key agonist and antagonist muscles acting at the targeted joint are calculated over the four indicated phases of the trial. Plots reporting the measured torques and EMG activity during the various phase of the trial for the left leg of all participants for the four tested joints (cyan: flexor, magenta: extensor), together with EES parameters and electrode configurations. All measurements were performed before rehabilitation, except for hip extension in participants P1 and P2 (not tested before), and ankle extension in participant P3 (no capacity before rehabilitation), which were carried out after rehabilitation. Targeted EES enabled or augmented the specific recruitment of the targeted muscle, which resulted in the production of the desired torque at the targeted joint, except for ankle extension of participant P2. Plots show quantification of the EMG activity and torque for n = 3 trials per condition. Note that hip flexion can be enabled or augmented with EES targeting L1 and/or L4 posterior roots (heteronymous facilitation of flexor motoneuron pools).

Extended Data Fig. 5 | Modulation of EEG activity during volitional contraction of leg muscles without and with EES. (a) Recordings of EEG activity while asking participants to produce an isometric torque at the knee joint without and with continuous EES targeting motoneuron pools innervating knee extensors, as shown in (b). **(b)** Superimposed EEG responses (n = 40 repetitions) and temporal changes in the topography of average activity over the cortical surface after the onset of EES, as indicated above each map. The onset was calculated from the onset of EMG responses in the targeted vastus lateralis (VLat) muscle, as shown in the insets. The stimulation elicited a robust event-related response over the left sensorimotor cortex with a latency of 90 ± 40 ms for P1 and P3, and of 170 ± 40 ms for P2 (full range of the peaks and middle of this range indicated). **(c)** Average normalized time–frequency plots (n = 40 trials) showing event-related

desynchronization (ERD) and event-related resynchronization (ERS) over the Cz electrode (central top electrode) for each individual during the voluntary activation of knee extensor muscles without and with EES. The schematic drawings on the left indicate the motor scores of the tested legs, including the targeted muscles (*), at the time of enrollment in the study. Both legs were tested in participant P1 due to his asymmetric deficits**. (d)** Bar plots reporting normalized average power of the β–band over the Cz electrode during ERS from 0 to 500 ms following contraction termination without and with continuous EES (bars: mean power, error bars: standard error of the mean, n = 40 repetitions for each condition, individual data points shown except for outliers more than 3 median absolute deviations away from the median). ***, $p < 0.001$ (permutation tests, see also "statistics" section of the Methods)."

Extended Data Fig. 6 | Configuration of spatiotemporal EES to enable walking. (a) Spatial configuration. Step 1: Select electrode configurations from single-pulse experiments to target the three hotspots underlying the production of walking in healthy individuals (weight acceptance: L3; propulsion: S1; swing: L1 / L4). **Step 2:** Optimize EES amplitude and frequency while delivering EES during standing. Multipolar configurations can be used to refine selectivity of EES protocols. Example shows continuous EES targeting the right L3 posterior root to facilitate right knee extension during standing, and trains (500 ms) of EES targeting the right L1 posterior root stimulation to facilitate hip flexion. Two EES frequencies are shown (participant P3). **(b) Temporal configuration. Step 3:** Decision tree to select the best strategy to configure the temporal structure of EES protocols. If the participant is able to initiate leg movements consistently, use closed-loop EES based on real-time processing of foot trajectory. If the participant is not able to initiate consistent leg movements but can feel when EES is applied, use open-loop EES. If the participant is not able to generate movement and cannot feel EES, use closed-loop EES combined with physiotherapist assistance to move the legs. **Step 4:** Real-time monitoring of the spatiotemporal trajectory of the feet. The trajectory is modelled as a foot rotating in space around the centroid of the movement (updated every 3 s). Angular thresholds determine the onset and end of EES protocols. **Step 5:** Example showing the effect of three different angular thresholds on the onset of EES and resulting kinematics and EMG activity, including the quantification of kinematics for each step and condition that enables selecting the optimal onset of EES trains (participant P1). The same approach is used to optimize the duration of each train. **(c)** Comparisons between closed-loop and open-loop. Plots showing the vertical displacements of the left and right feet and successive step heights during walking with spatiotemporal EES delivered in closed-loop versus open-loop, showing the reduced variability of step height during pre-programmed EES sequences (participant P1). **(d)** Resulting EMG patterns. **Step 6:** Example of the progressive addition of EES protocols targeting specific hotspots. Plots show the quantification of EMG activity for the displayed muscles (n = 7 gait cycles for no EES and n = 9 gait cycles for each stimulation condition, participant P2). **Step 7:** EES amplitudes and frequencies are adjusted to avoid detrimental interactions between the different EES protocols and thus obtain the desired kinematic and EMG activity. Plots report the modulation of EMG activity and kinematic with increases in EES amplitude and frequency (amplitude data: n = 10, 12, 12, 30, 19, 12, 11, 10 gait cycles for amplitudes in increasing order, participant P2; frequency data: n = 20, 15, 16, 17, 15, 16, 15 gait cycles for frequencies in increasing order, participant P3, center measure: mean, error bars: standard error of the mean).

Extended Data Fig. 7 | Targeted modulation of muscle activity during walking. Each panel reports the same representative data and quantification for one participant. Left: EMG activity of leg muscles during walking on a treadmill without EES (EES OFF) and with spatiotemporal EES (EES ON) while applying 50%,

45% and 70% body weight support for participant P1, P2 and P3, respectively. Stance and swing phases indicated by grey and white backgrounds, respectively. The personalized spatiotemporal EES sequence (open-loop) is schematized on the top right corner. The colors of each EES protocol refer to the targeted hotspots: weight acceptance (salmon), propulsion (magenta) and swing (cyan). These colors are used in the EMG traces to indicate the temporal window over which each targeted EES protocol is active. The bar plots report the amplitude of muscle activity without EES and with spatiotemporal EES, for which the quantification was performed over the entire burst of EMG activity and during each temporal window with targeted EES. The temporal windows are labelled with a number that refers to the spatiotemporal EES sequence. These results show the pronounced increase in the EMG activity of the targeted muscles (participant P1, no EES: n = 7 gait cycles, EES: n = 11 gait cycles; participant P2, no EES: n = 9 gait cycles, EES: n = 9 gait cycles; participant P3, no EES: n = 10 gait cycles, EES: n = 57 gait cycles). The average spatiotemporal trajectories of both feet with respect to the hip in the sagittal plane are shown for walking without EES and with spatiotemporal EES. The presence of targeted EES is indicated with the same color code. The plots at the right bottom reports the relationships between EES frequency and the modulation of the EMG activity of flexor (blue) and extensor (magenta or salmon) muscles and maximum amplitude of hip movements during walking (participant P1: n = 14, 17, 15, 19 gait cycles for increasing frequencies, participant P2: n = 13, 16, 10, 17, 12 gait cycles for increasing frequencies, participant P3: n = 20, 15, 16, 17, 15, 16, 15 gait cycles for increasing frequencies, center measure: mean, error bars: standard error of the mean). ***, $p < 0.001$. Student's t-test.

Extended Data Fig. 8 | Volitional adaptations of walking during otherwise unchanged spatiotemporal EES. (a-c) Plots report quantifications of experiments shown in **Fig. 4a-c** for each participant. **(a)** Step height and TA EMG activity with and without EES during overground walking (participant P1, EES ON: n = 7 gait cycles; participant P2, EES ON: n = 16 gait cycles; participant P3, EES ON, n = 7 gait cycles). **(b)** Step height and TA EMG activity during normal steps and when participants were requested to perform exaggerated step elevations during overground walking (participant P1, n = 15 normal gait cycles, n = 11 exaggerated gait cycles; participant P2, n = 31 normal gait cycles, n = 23 exaggerated gait cycles; participant P3, n = 14 normal gait cycles, n = 10 exaggerated gait cycles). **(c)** Step height and TA EMG activity during the first and last 30 steps extracted from a sequence of one hour of locomotion on a treadmill (n = 30 gait cycles for all conditions). ***, $p < 0.001$. n.s., non-significant. Student's t-test. **(d)** EMG activity of representative leg muscles, vertical displacements of the foot and antero-posterior oscillations of the leg (virtual limb joining the hip to the foot) while participant P2 was walking continuously on the treadmill with spatiotemporal EES (open-loop). Participant was asked to suppress the effects of EES and stand during one cycle of open-loop spatiotemporal EES sequence, as highlighted in brown (SKIP) whereas he actively contributed to the production of movement the rest of the time. Plots report the quantification of the step height and TA EMG activity during walking and when skipping steps for each participant (participant P1, n = 13 normal gait cycles, n = 1 skipped cycles; participant P2, n = 36 normal gait cycles, n = 3 skipped gait cycles; participant P3, n = 11 normal gait cycles, n = 2 skipped cycles). **(e)** EMG activity of two representative muscles, vertical displacements of the foot and antero-posterior oscillations of the leg while participant P1 was walking on the treadmill and the speed of the belt increased progressively from 0.8 to 2 km/h. Plots repot the relationships between the treadmill speed and the mean values of the stride length and TA EMG activity in all participants (participant P1: n = 9, 9, 9, 9, 10, 18, 15, 9, 9 gait cycles for increasing speeds, participant P2: n = 13, 10, 7, 8, 10, 9 gait cycles for increasing speeds, participant P3: n = 8, 8, 10, 9, 9, 8 gait cycles for

increasing speeds , error bars: standard error of the mean). The range of tested speeds was adapted to the walking ability of each participant.

Extended Data Fig. 9 | Comparison between continuous and spatiotemporal EES during overground walking. Each panel represents one participant who is attempting to walk overground with gravity-assist without EES (left), with continuous EES (middle) and with spatiotemporal EES (right). EMG activity of representative leg muscles, vertical position of the foot and distance covered by the foot in the forward direction are displayed for each experimental condition. Continuous EES is applied throughout the trial (red). For participant P2 and P3, we optimized EES protocols that targeted the posterior roots on both sides, whereas EES was applied over the most rostral and most caudal midline electrodes for P1, as sketched next to each plot. Spatiotemporal EES is represented using the same color scheme as in **Fig. 3** and **Extended Data Fig. 7**. The plots report the quantification of EMG activity, step height and mean speed (based on distance covered) for the three experimental conditions (participant P1, n = 6, 7, 8 gait cycles for no EES, continuous EES and spatiotemporal EES; participant P2, n = 17, 7, 9 gait cycles for no EES, continuous EES and spatiotemporal EES; participant P3, n = 6, 10, 9 gait cycles for no EES, continuous EES and spatiotemporal EES). ***, $p < 0.001$; **, $p < 0.01$. n.s. non-significant. 1-way ANOVA, post-hoc HSD Tukey. These recordings were repeated at least on 3 different days for each participant.

Extended Data Fig. 10 | Rehabilitation program and evolution of walking capacities. (a) Rehabilitation programs were continuously personalized based on the current motor performance of participants. Walking capacities evolved in phases, shown in (b). For this reason, the relative percentage of training in the various tasks has been divided into clusters, which correspond to the evolution of walking capacities. To facilitate the sustained production of reproducible locomotor movements (**Extended Data Fig. 6c**), EES was delivered in open-loop mode during gait rehabilitation. **(b)** Walking capacities evolved through stereotypical phases that are illustrated in the snapshots. **(c)** Plots showing the progression of the three participants along the phases of recovery during the rehabilitation program, and during the subsequent 6 months for participant P1 and P2. P3 had just completed the rehabilitation program at the time of submission of this study. See also **Supplementary Video 4**.

Extended Data Fig. 11 | Changes in muscle mass and quality, and recovery of voluntary movements with and without EES in participant P3. (a) Skeletal muscle mass and quality were assessed at the pre- and post-rehabilitation timepoints using the X-ray attenuation from computed tomography (CT) images obtained at the abdominal (L3 vertebra) and mid-thigh (25 cm above femorotibial joint space) levels. Muscle mass was determined by measuring the cross-sectional areas (CSAs) of muscle tissues, while muscle quality was reflected by the CT attenuation numbers (in Hounsfield units, HU) within the CSAs. Muscle segmentations were performed semi-automatically using ImageJ and muscle-specific HU thresholds (-29 to 150 HU). Plots report the substantial changes in muscle mass at mid-thigh, for both flexor and extensor muscles, and of trunk muscles. Muscle quality was also improved at both levels: total mid-thigh, left: 52.9 to 56.1 HU, right: 51.9 to 56.7 HU; total L3, 45.9 to 48.3 HU. This increase in CT attenuation numbers between the baseline CT scan and the follow-up imaging reflected the decrease in muscle fiber lipid content mid-thigh and abdominal levels. These evaluations were part of a protocol amendment obtained when enrolling P3. **(b)** Assessment of voluntary torque production at the ankle (extension) with targeted EES before and after rehabilitation. Conventions are the same as in **Extended Data Fig. 4**. **(c)** Snapshots showing a voluntary **extension of the left leg** against the direction of gravity together with the concomitant sequence

of EMG activity in the **extensor and** flexor muscles of this leg. The zoomed window shows the relationship between the movement and the EMG activity, indicated with the numbers. This participant presented flaccid paralysis, and had thus no control over leg muscles before the surgery. This movement was observed repeatedly at the end of the rehabilitation period (at least 2 days per week for several weeks).

Extended Data Fig. 12 | Performance of closed-loop spatiotemporal EES to enable walking and cycling outside the laboratory. (a) Participants P1 and P2 were asked to walk freely overground with a walker (no body weight support) during six minutes. The concomitant vertical displacements of the foot show the consistency of EES-triggering events despite variable foot kinematics and voluntary breaks. The trajectory of the center of mass is shown from a top view to illustrate the ability to steer locomotion along any desired path. EES protocols took into account the deficits of each participant (cyan: EES targeting hip flexion, magenta: EES targeting knee and ankle extension). Histograms indicate the number of detected foot off events for the represented leg as a function of the latency with respect to real foot off events. The confusion matrix associated with these detections is represented below, as a percentage of the real events that were correctly or incorrectly classified. Detections were considered valid if they occurred between 400 ms before and 100 ms after real foot off events, as highlighted in green window in histograms (participant P1: n = 49 gait cycles, participant P2: n = 79 gait cycles). **(b)** Closed-loop spatiotemporal EES was delivered in participant P3 using an electric trike powered by hand and foot pedals. Traces show EMG activities of the targeted hip flexor and knee extensor muscles on one leg together with the tangential acceleration of the pedal and power generated at the foot pedal. Plots report the quantification of flexor and extensor EMG activities, peak tangential accelerations and generated power without and with EES. The successive ankle trajectories during cycling are shown together with the timing of EES protocols targeting hip flexor and knee extensor muscles. The histograms and confusion matrices report the performance of the controller following the same conventions as in (a), except that the correct detection window was restricted to 50 ms before and 100 ms after the desired crank position (participant P3: n = 73 pedaling cycles). ***, $p < 0.001$. Student's t-test.

Extended Data Table. 1 | Neurological status of the three participants. Subjects' neurological status according to the International Standards for Neurological Classification of Spinal Cord Injury at study entry and after completion of the 5-months training program. *Reason for AIS C classification in spite of motor scores of 0 throughout all lower extremity key muscles is the presence of voluntary anal contraction.

LEGENDS OF SUPPLEMENTARY VIDEOS

Supplementary Video 1 | Technological framework and surgical procedure. Description of the gait rehabilitation environment, together with the methods to construct the spatiotemporal maps of motoneuron activation underlying walking. An animation shows the surgical placement of the electrode paddle array, and the methods underlying the delivery of spatially-selective stimulation trains through real-time movement feedback during walking assisted with a multidirectional body weight support system.

Supplementary Video 2 | Spatiotemporal EES enables voluntary walking. (1) Overground walking without and with spatiotemporal EES for all participants, where EES sequences are displayed in real-time and EMG traces are colored during stimulation targeting this muscle. (2) voluntary modulation of leg movements, including exaggerated foot elevation, stepping across speeds, and walk/stand/walk transition. Spatiotemporal EES is delivered in open-loop, without any change in EES parameters. All recordings were repeated at least on 5 different days for each participant. (3) Beginning and end of a one hour bout of walking (1.2 km). This recording was performed only once in each participant, but participants routinely walked longer distance during training.

Supplementary Video 3 | Comparison between continuous and spatiotemporal stimulation. Example of overground locomotion without EES, with continuous EES, and with spatiotemporal EES. Conventions are the same as in Supplementary Video 2. These recordings were repeated at least on 3 different days for each participant.

Supplementary Video 4 | Improvements with rehabilitation. Evolution of walking capacities with EES over the course of the rehabilitation program for the three participants. Conventions are the same as in Supplementary Video 2. Similar observations were made on at least 5 different days for each participant and condition.

Supplementary Video 5 | Improvements with rehabilitation. Evolution of voluntary leg movements and walking capacities without EES over the course of the rehabilitation program for participants P1 and P2. Performance of participant P3 is shown during overground walking with an assistive device and EES, but without body weight support. Examples of voluntary hip flexion and sustained knee extension without EES are also shown. Conventions are the same as Supplementary Video 2. Similar observations were made on at least 3 different days for each participant and condition.

Supplementary Video 6 | Integrated solution to use spatiotemporal EES in ecological setting. Wearable, voice-controlled technology that supports closed-loop spatiotemporal EES to walk outside the laboratory environment and to ride a trike powered with the arms and legs.