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Targeted neurotechnology restores walking in humans with spinal cord injury

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Spinal cord injury 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 spinal cord injury 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 trains of spatially selective stimulation to the lumbosacral spinal cord with timing that coincided with the intended movement. Within one week, this spatiotemporal stimulation had re-established adaptive control of paralysed muscles during overground walking. Locomotor performance improved during rehabilitation. After a few months, participants regained voluntary control over previously paralysed muscles without stimulation and could walk or cycle in ecological settings during spatiotemporal stimulation. These results establish a technological framework for improving neurological recovery and supporting the activities of daily living after spinal cord injury.

Spinal cord injury (SCI) disrupts communication within the nervous system, leading to the loss of essential neurological functions. At present, activity-based therapies are the only medical practices that can be used to enhance recovery[1–3]. The volitional production of active movements during training promotes reorganization of neuronal pathways and thereby augments recovery[4,5]. However, the most affected patients, who fail to produce active movements voluntarily, experience minimal benefits from these therapies[1].

This situation has 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, all of which share the same goal: to enable patients to sustain active movements during training to enhance the reorganization of neuronal pathways[4]. Three decades of clinical research using these neurotechnologies suggested 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 but functionally silent descending pathways in order to produce movements of paralysed limbs[11,12], but also improves the ability of the spinal cord to translate task-specific sensory information into the muscle activity that underlies standing and walking[9,10,12–16].

To harness the therapeutic potential of EES, we studied its underlying mechanisms. We found that EES activates motor neurons by recruiting proprioceptive circuits within the posterior roots of the spinal cord[17–20]. This understanding translated into EES protocols that target individual posterior roots to access the motor neuron pools located in the spinal cord segment innervated by each root[21]. To engage motor neurons at the appropriate time, spatially selective EES trains are delivered with 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 device[24], this stimulation promotes extensive reorganization of residual neural pathways that improves locomotion with and even without stimulation[21,25,26].

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

Targeted neurotechnologies and surgery

We developed a wireless environment that allows real-time control over independently adjusted EES trains to the spinal cord during overground

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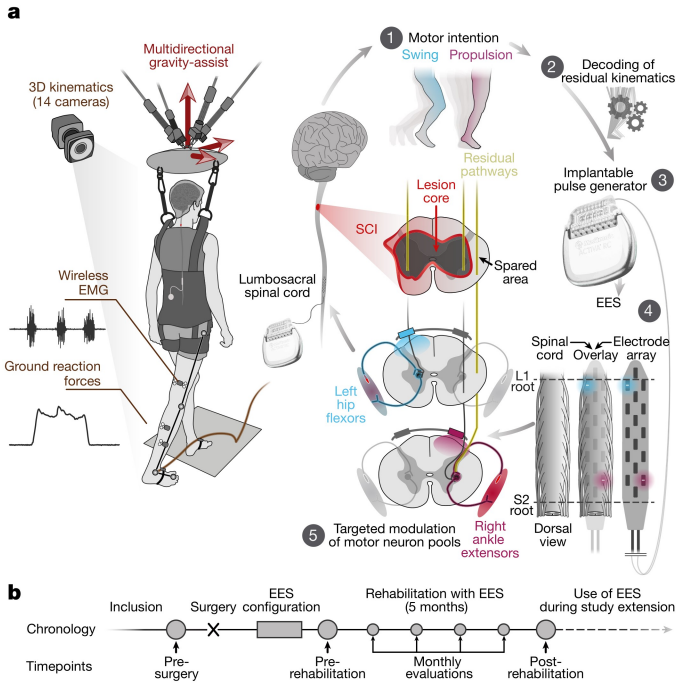

Fig. 1 | Technology and study design. a, Targeted neurotechnologies enable walking after SCI. Multidirectional assistance of trunk movements during overground locomotion while 3D kinematics, ground reaction forces and EMG activity are recorded wirelessly. An implantable pulse generator connected to a 16-electrode paddle array was used to target the posterior roots projecting to specific motor neuron pools, illustrated for hip flexors and ankle extensors. Real-time processing of residual kinematics ensures that targeted EES coincides with movement intent. **b**, Study timeline.

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 an open loop or triggered in a closed loop on the basis of external signals[21,22]. The lumbosacral posterior roots were targeted using a 16-electrode paddle array designed for pain therapy.

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

To target the posterior roots that project to motor neuron pools that innervate leg muscles (Fig. 2a), we developed a surgical protocol consisting of 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 paralysed muscles

We aimed to identify electrode configurations that target the posterior roots that project to spinal cord regions, containing motor neurons involved in mobilizing the hip, knee and ankle joints.

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

To identify electrodes that could target the posterior roots that project to the spinal cord regions associated with these motor neuron activation maps, we performed simulations using hybrid computational models of EES[18]. Each model was personalized using magnetic resonance imaging (MRI) and computerized tomography (CT) scans. Simulations estimated the relative recruitment of each posterior root by each electrode of the array (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 that had the highest probabilities of activating 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 field 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 that project 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. Participant 1 (P1) failed to produce hip flexion and ankle extension torques with his paralysed leg (Fig. 2e, f). EES immediately enabled voluntary activation of the targeted muscles to produce the desired torque. These observations were repeated for all targeted joints and participants (Extended Data Fig. 4).

Without any voluntary contribution, EES induced minimal muscle contraction (Extended Data Fig. 4). At the amplitudes used, EES augmented the excitability of the targeted motor neurons, which enabled residual but 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), probably resulting from the recruitment of proprioceptive afferents.

Attempts to activate knee extensor muscles triggered 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 event-related resynchronization (ERS) after movement termination[31]. Previous studies showed that the amplitude of ERS decreases in proportion to severity of SCI[31]. Voluntary activation of paralysed 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 motor neuron activation maps involve a succession of hotspots for which the 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 on the basis of foot trajectory[21,22,32]. We adjusted the onset and duration of each train to approach the motor neuron activation maps of healthy individuals (Extended Data Fig. 6). Relatively small changes in the timing of each train altered performance (Extended Data Fig. 6b). Once optimized, EES could be delivered in an open loop: participants regulated the timing of their movements

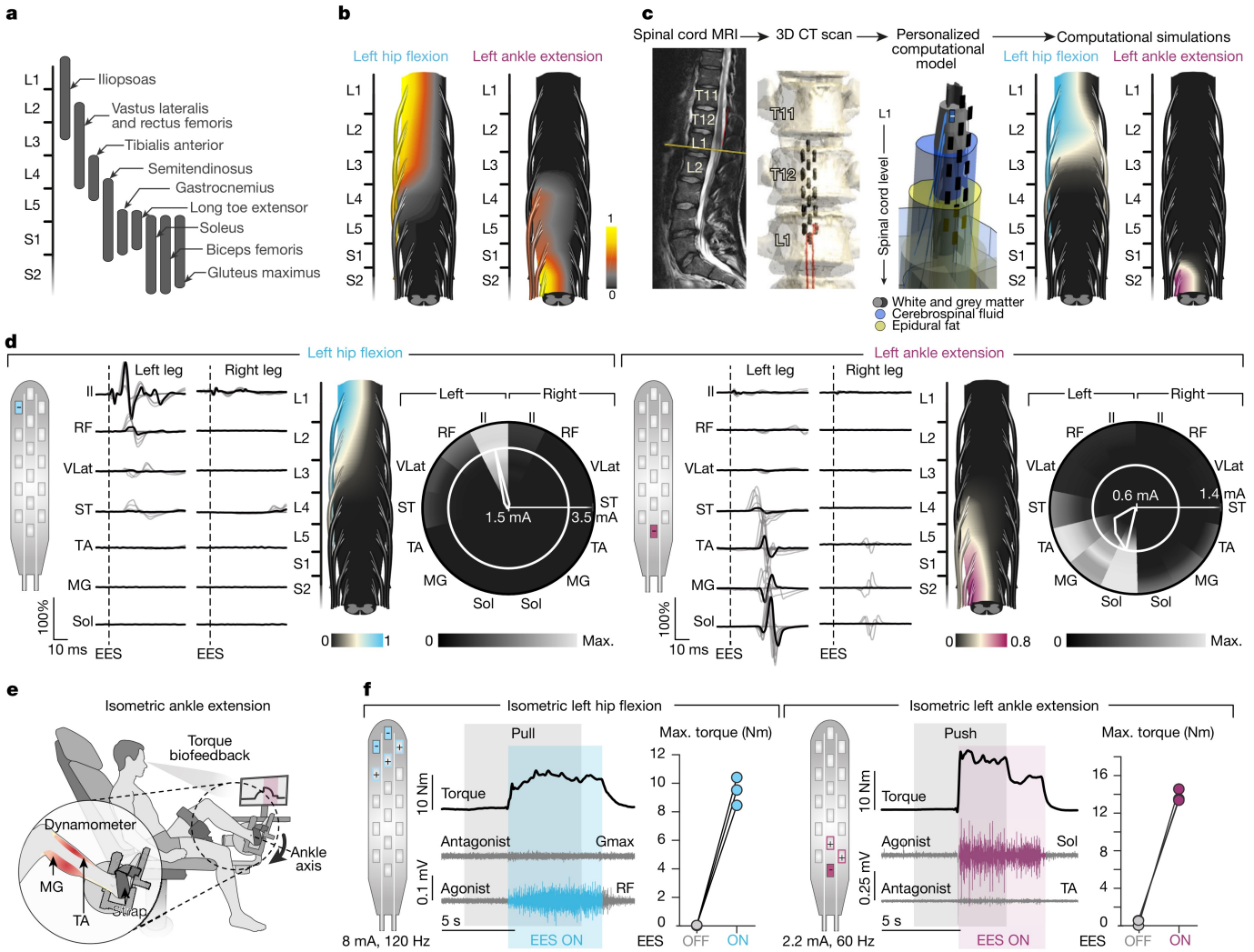

Fig. 2 | Configuration of targeted EES. a, Distribution of motor neuron pools within the spinal cord[46]. **b**, Map of motor neuron activation underlying isometric torque production in a healthy subject (consistent across three repetitions and subjects). **c**, Personalized computational model of EES. Simulated map of motor neuron activation following EES targeting the L1 and S2 posterior roots. **d**, Electrophysiological experiments were used to determine optimal electrodes and amplitudes for targeting specific spinal cord regions. EMG responses when delivering single-pulse EES at increasing amplitudes are shown (grey traces). Motor neuron activation maps correspond to optimal amplitudes (black traces). Circular plots report EMG amplitude (in grey scale) at increasing amplitudes (radial axis). White circles show optimal amplitudes; polygons quantify selectivity at this amplitude. **e**, Instrumented chair used to measure single-joint torques. **f**, Targeted EES enables voluntary force production by paralysed muscles. Isometric torque and EMG activity while delivering targeted EES, including quantification ($n = 3$ repetitions, P1). Gmax, gluteus maximus; Il, iliopsoas; MG, medial gastrocnemius; RF, rectus femoris; Sol, soleus; ST, semitendinosus; TA, tibialis anterior; VLat, vastus lateralis.

to pre-programmed EES sequences, which improved gait consistency (Extended Data Fig. 6c).

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 proportionally enhanced flexion (Extended Data Fig. 6d). Unexpectedly, extensor motor neuron pools responded inversely. Proprioceptive afferents elicit strong monosynaptic responses in extensor motor neurons, whereas these afferents primarily engage flexor motor neurons through polysynaptic circuits[33]. In humans, monosynaptic projections are highly sensitive to low-frequency depression[34], which may explain the decrease in extensor motor neuron activation with increasing frequency.

Within five days, this procedure led to EES sequences (Fig. 3d, e) 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 using 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 participants' 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 1,200 steps, covering distances as long as 1.0 km without showing muscle exhaustion or gait impairments (Fig. 4c and Extended Data Fig. 8c).

These results show that spatiotemporal EES not only enabled completely or partially paralysed 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.

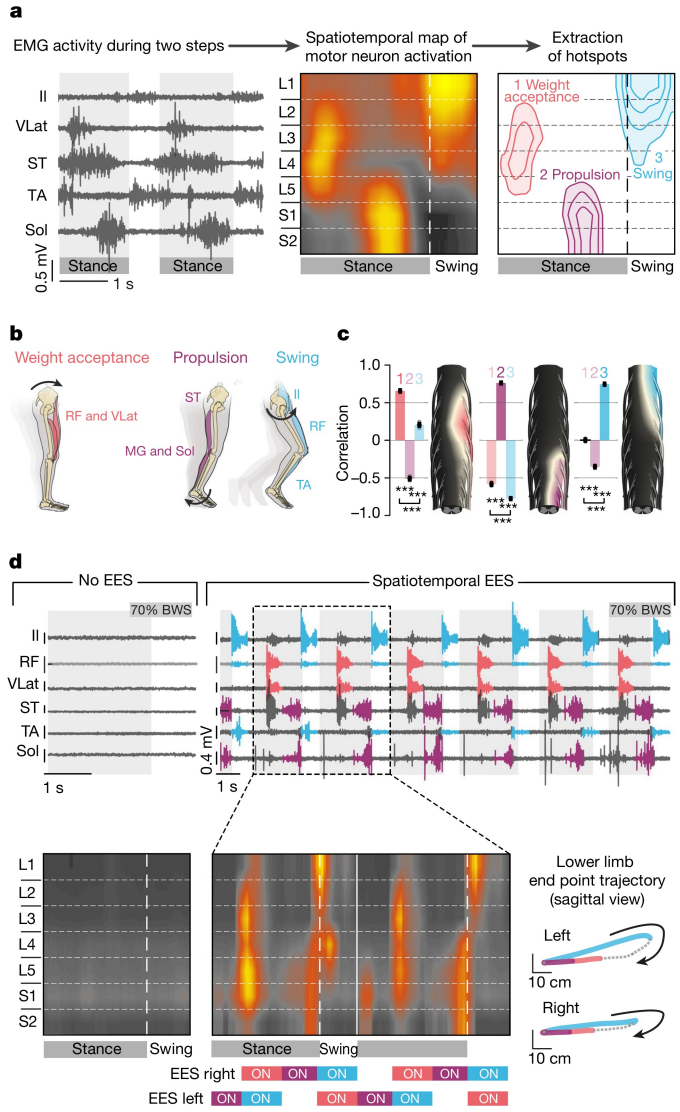

Fig. 3 | Configuration of spatiotemporal EES for walking. a, EMG activity during walking in healthy individuals. Spatiotemporal map of motor neuron activation highlights hotspots (mean, $n = 12$ gait cycles, representative subject). Equipotential lines represent 45–75% activation. **b**, Functional target of each hotspot. **c**, Map of motor neuron activation following 500-ms bursts of targeted EES during standing. Bar plots show Pearson's correlations for each hotspot (mean ± s.e.m., $n = 12$ bursts, $^{***}P < 0.001$; one-way ANOVA, post hoc Tukey's honest significant difference (HSD) test). **d**, EMG activity and map of motor neuron activation during EES or without EES after a motor complete SCI while stepping on a treadmill with support and assistance (P3). EES timing is indicated along foot trajectories (bottom right; $n = 73$ steps) and below motor neuron activation maps. **e**, Spatiotemporal EES sequence for data shown in **d**. **f**, Mean (± s.e.m.) modulation of EMG amplitude in flexor and extensor muscles during walking with increasing EES frequencies ($n = 20, 15, 16, 17, 15, 16, 15$ gait cycles for 20, 25, 30, 40, 60, 80, 100 Hz, respectively; P3).

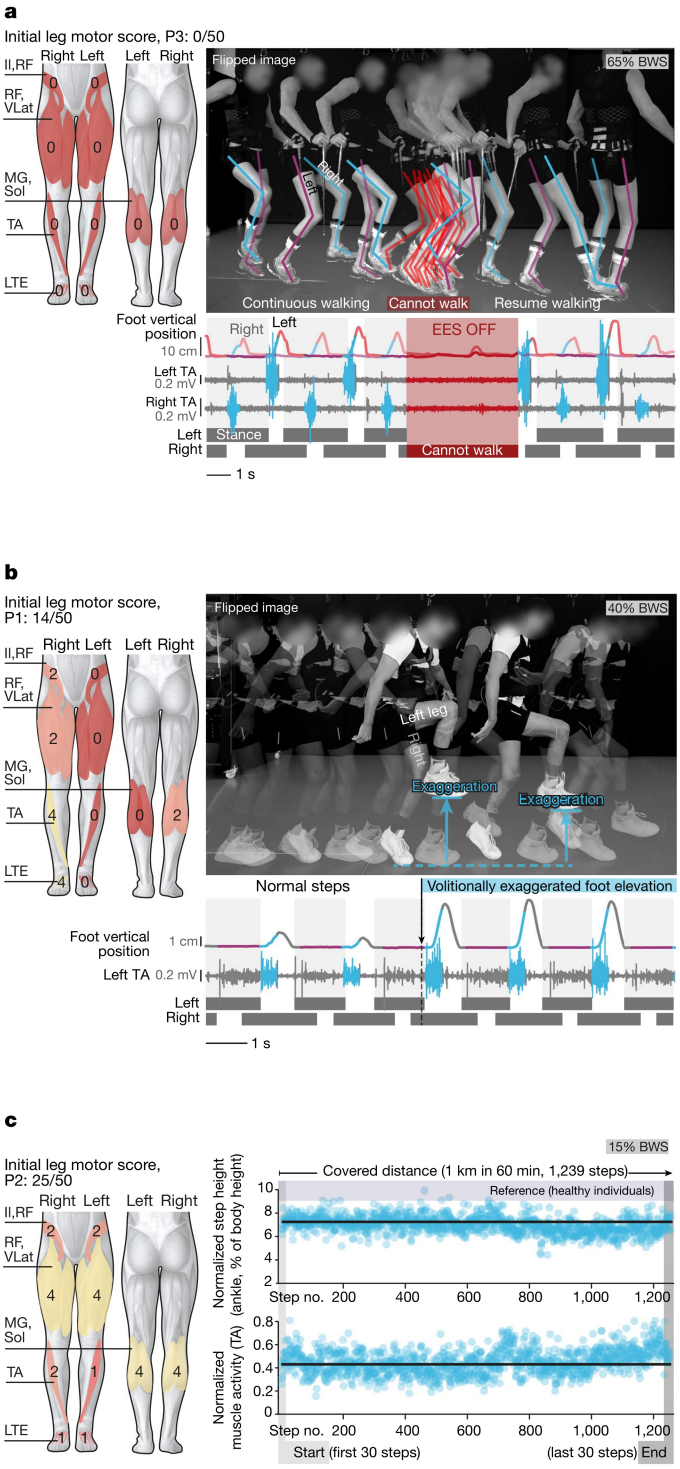

Fig. 4 | Voluntary control of adaptive and sustained locomotion. **a**, Spatiotemporal EES enables voluntary control of overground walking. Chronophotography, tibialis anterior (TA) EMG activity and foot vertical position during overground walking with gravity-assist and sticks while EES is switched on, then off, then on. Leg motor scores shown on muscles in diagrams: 0, total paralysis; 1, palpable or visible contraction; 2, active movement, gravity eliminated; 3, active movement against gravity; 4, active movement against some resistance; 5, active movement against full resistance. **b**, Spatiotemporal EES enables voluntary control of leg kinematics. Overground walking when participants were requested to perform steps with normal heights and then exaggerated step elevations. **c**, Spatiotemporal EES enables sustained walking. Consecutive values of step height and EMG activity over 60 min of walking with EES (P1: 1.2 km; P2, P3: 1 km). Experiments in **a**, **b** were repeated at least five times; the experiment in **c** was performed once, but participants routinely walked for 60 min during training. BWS, bodyweight support.

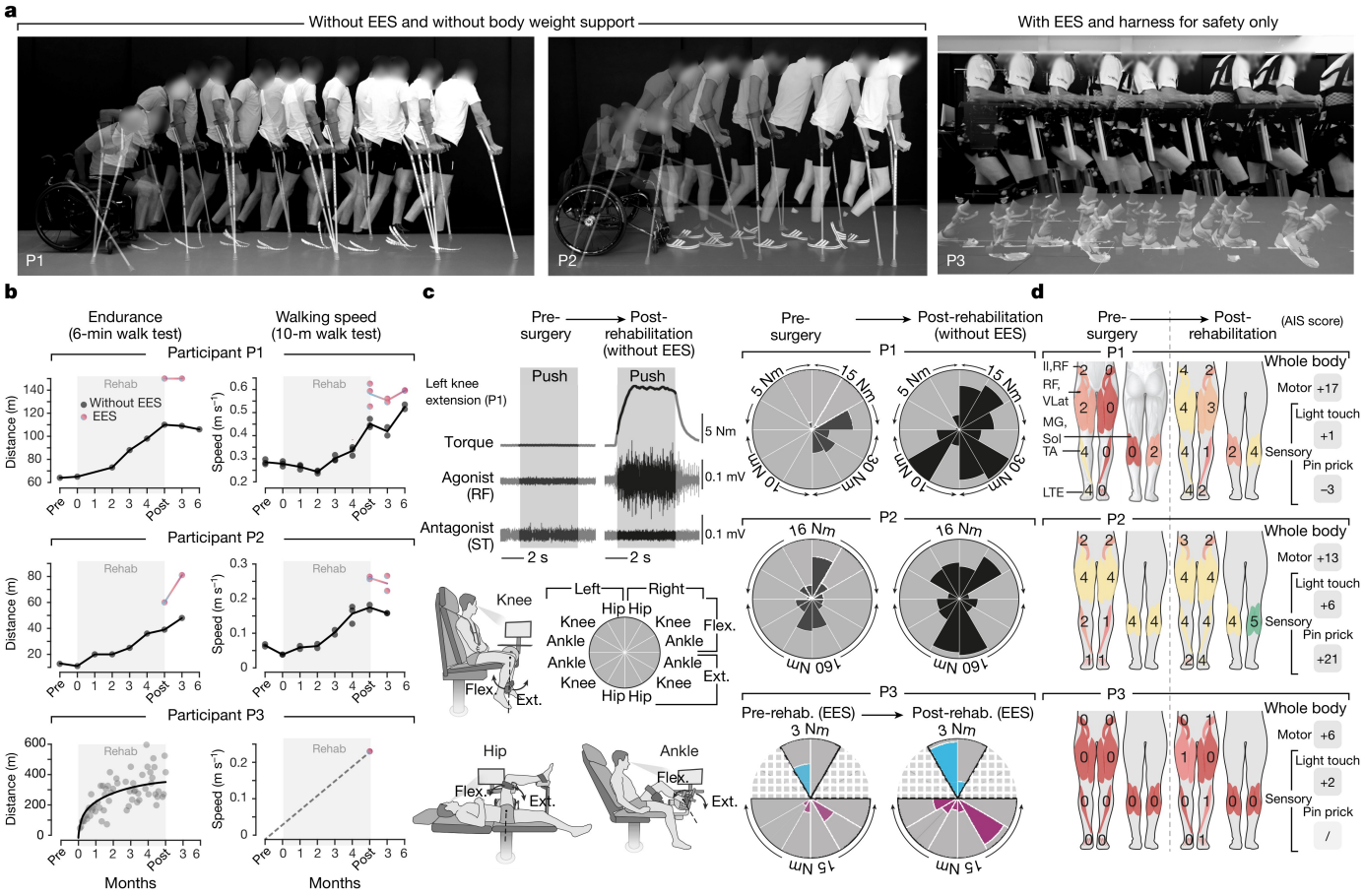

Fig. 5 | Rehabilitation mediates neurological recovery. a, Improved mobility after rehabilitation. Chronophotography shows P1 and P2 transiting from sitting to walking with crutches without EES; P3 progresses overground with a walker and EES; repeated at least three times on different days. **b**, Plots reporting changes in 6-min and 10-m walk tests for P1 and P2. Tests were performed without gravity-assist, following clinical guidance. For P3 plots report changes in walking distance during rehabilitation and walking speed with EES (with transparent body weight support). **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**, Changes in lower limb motor and sensory scores after rehabilitation. Changes in motor and sensory scores on abbreviated injury scale (AIS) for all levels below injury are summarized (see Extended Data Table 1).

Continuous EES is poorly effective

Recent studies have shown that continuous EES enabled overground walking after nearly one year of intense training[9,10]. As 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 motor neuron pools, as previously recommended[10]. However, we did not further optimize the stimulation. Continuous EES enhanced muscle activity, but was poorly effective in facilitating 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 (Fig. 1b), focused on walking on a treadmill and overground; this was complemented with muscle strengthening and standing, each of which was enabled by task-specific EES (Extended Data Fig. 10a).

With spatiotemporal EES, all participants improved their walking capacities following a reproducible chronology (Extended Data Fig. 10b): 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 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 an assistive device for several steps (Supplementary Video 5). Consequently, P1 and P2 increased their WISCI (walking index for spinal cord injury) scores from 13 to 16 and 6 to 13, respectively. They displayed substantial improvements in clinical evaluations such as ten-metre and six-minute walking 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 paralysed legs against gravity (P3, lying only; Extended Data Fig. 11c and Supplementary Video 5). Quantified measurements revealed that P1 and P2 improved their ability to produce a torque at each joint of

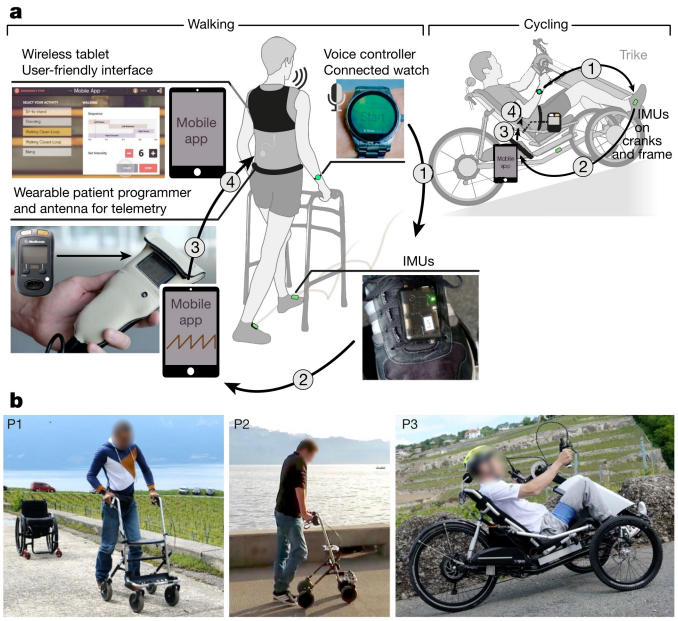

Fig. 6 | Spatiotemporal EES in ecological settings. a, System to support activities of daily living. Tablet featuring a mobile App allows participants to select EES sequences, delivered in open loop or closed loop based on inertial measurement units (IMUs) located on both feet or attached onto the cranks and frame of a trike. 1. A personalized voice-controlled watch allows the user to switch EES on or off. 2. IMUs detect foot or crank motion during walking or cycling. 3. Controller sends commands to the patient programmer. 4. Spatiotemporal EES is adjusted in a closed loop. **b**, Walking and cycling activities in ecological settings are enabled by spatiotemporal EES.

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. The 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 showed improvements in upper limb motor scores of 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 to enable the selection of EES sequences that are switched on or off with a voice-controlled watch (Fig. 6a). To enable standing, walking or cycling, EES sequences must be synchronized to the intended movements. We conceived algorithms that trigger and adjust the timing of EES trains in a closed loop based on real-time acquisition of signals from wearable inertial measurement units.

Robust event-triggered detection 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 participants to ride 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 motor neuron pools that were concomitantly engaged by the natural flow of sensory information and residual supraspinal commands. This spatiotemporal convergence enabled more robust and 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 have 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, improvements in muscle mass and other physiological functions[43,44] suggest that EES may help to counteract 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 of developing 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 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.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at https://doi.org/10.1038/s41586-018-0649-2.

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