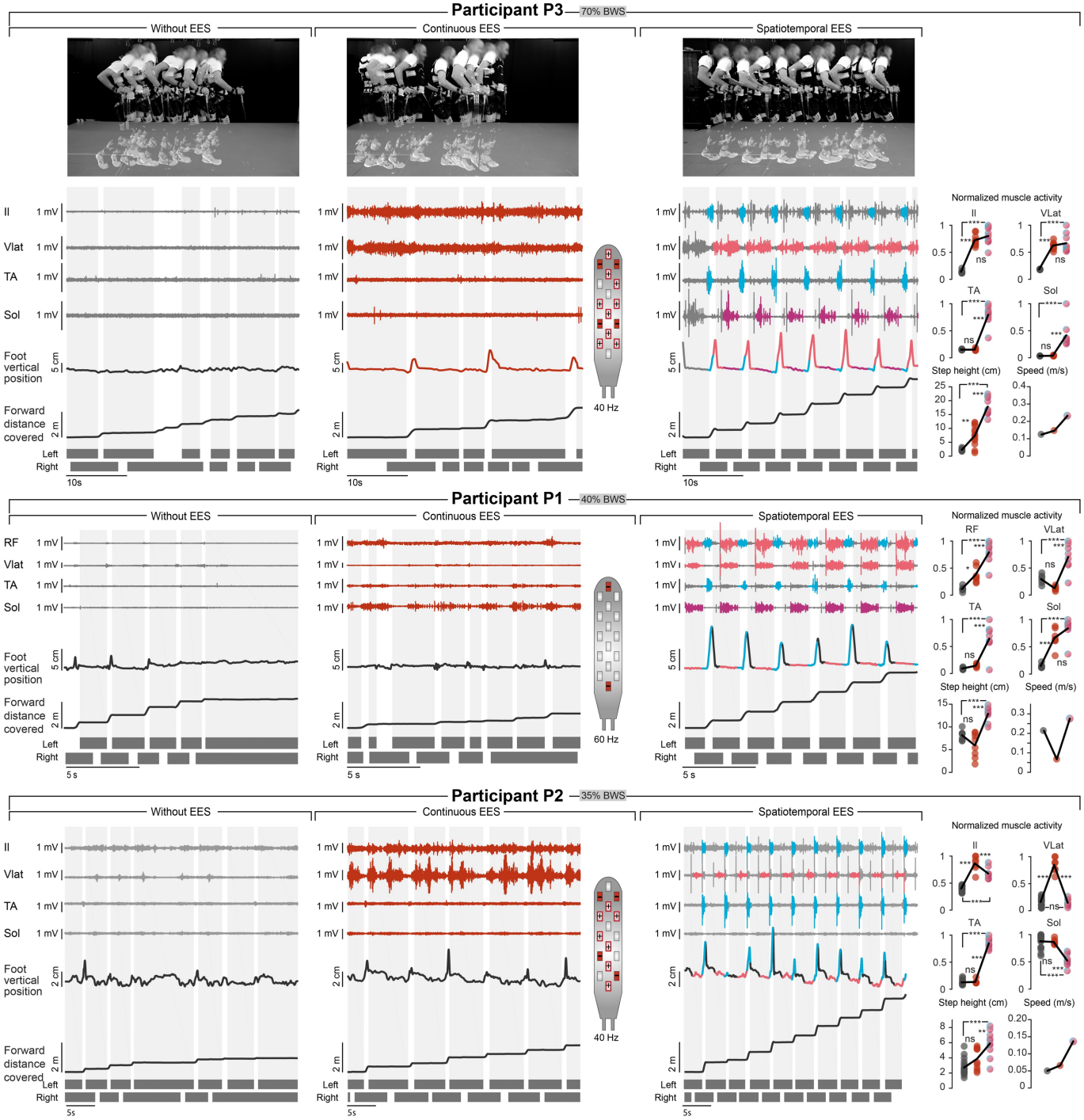
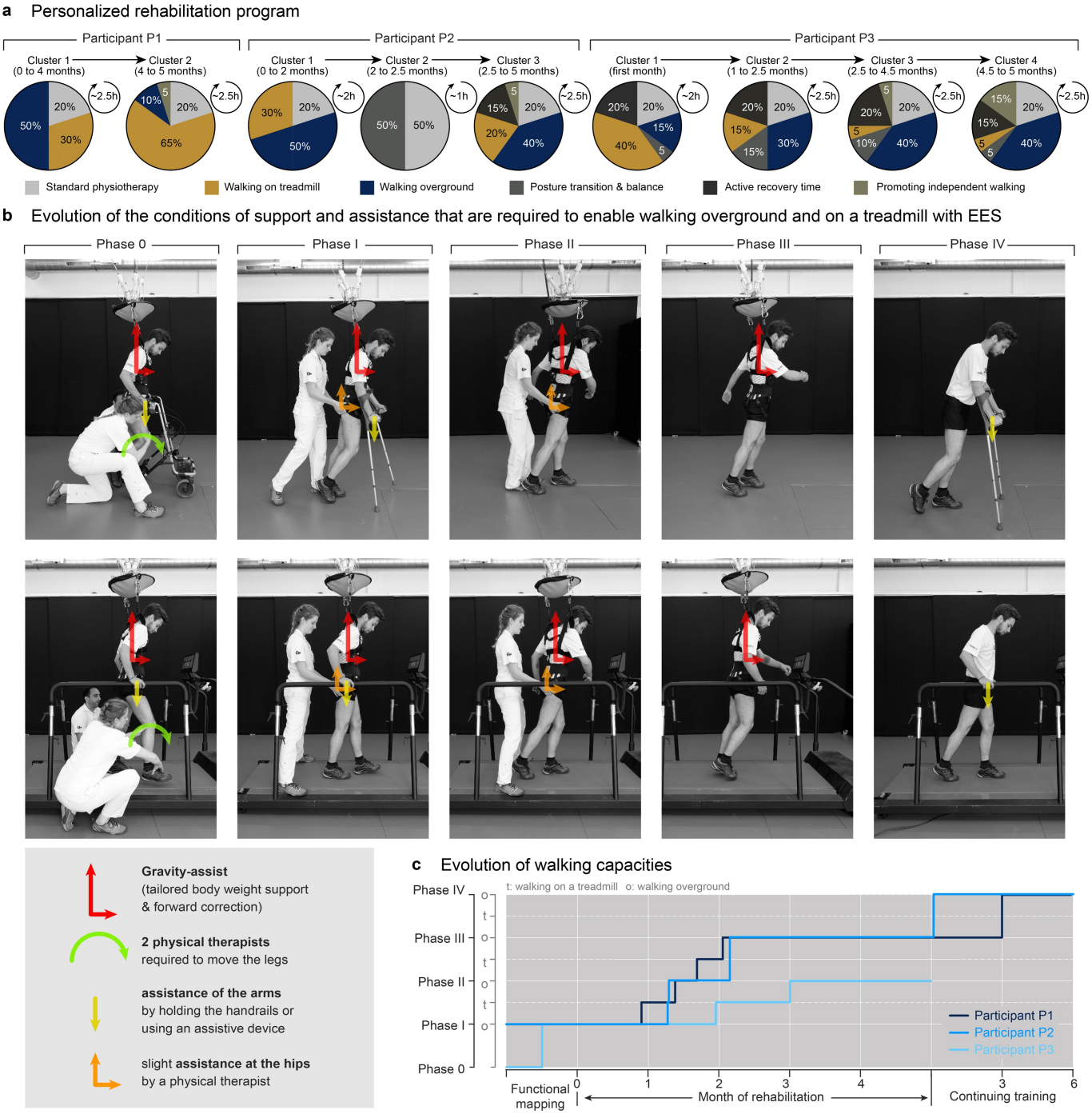
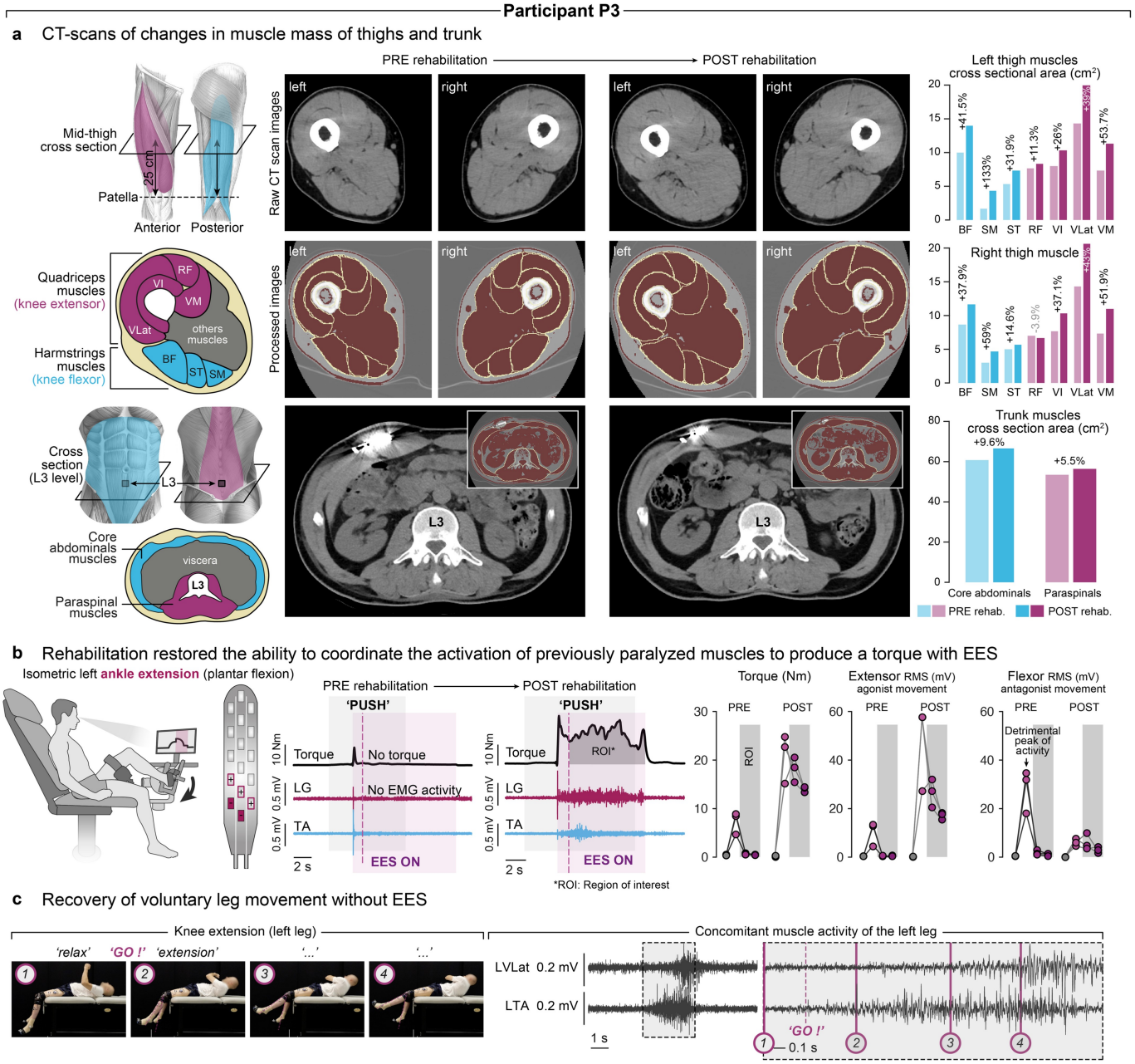


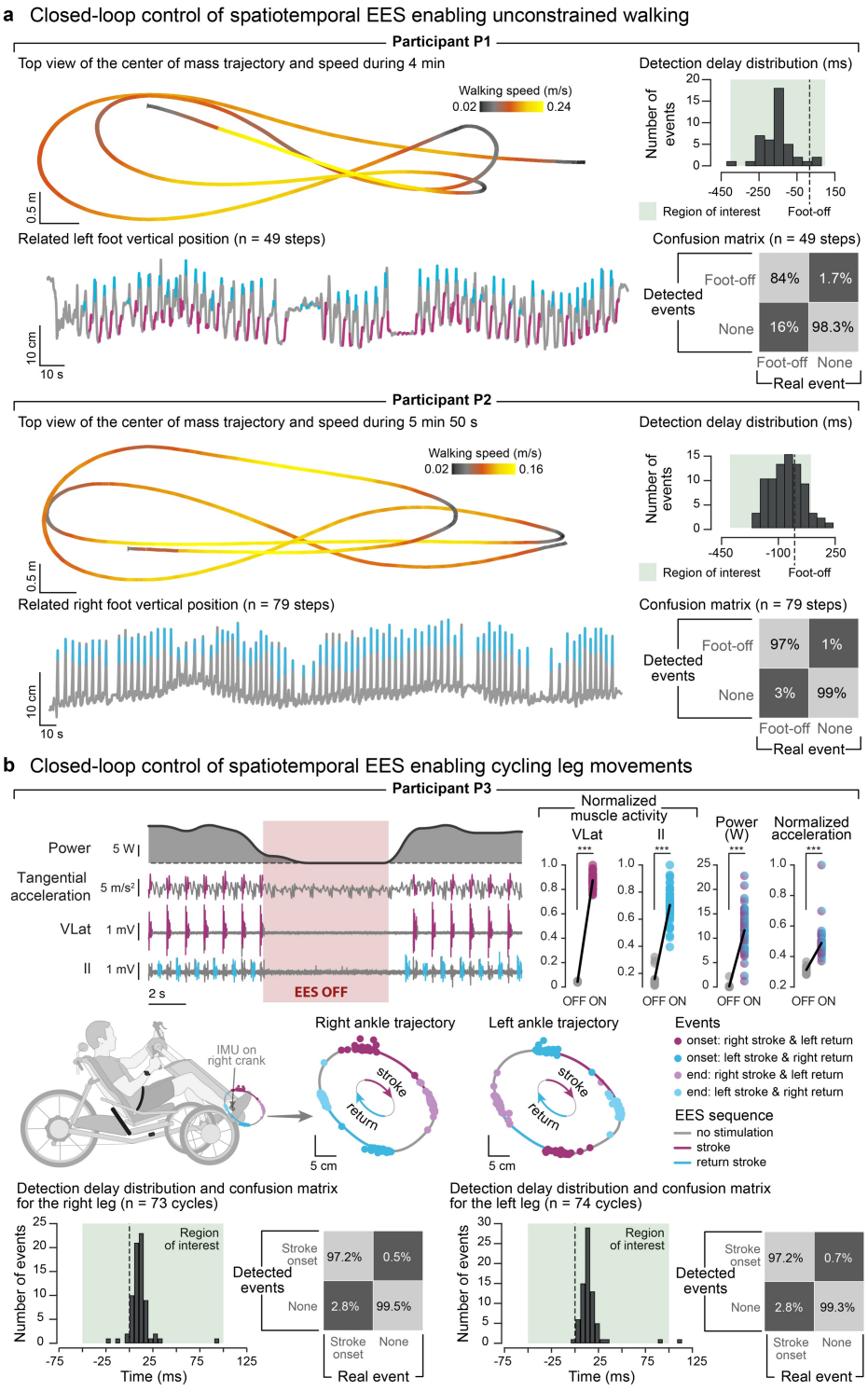
Extended Data Fig. 9 | Comparison between continuous and spatiotemporal EES during overground walking. Each panel represents one participant who is attempting to walk overground with gravity-assist without EES (left), with continuous EES (middle) and with spatiotemporal EES (right). EMG activity of representative 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 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 shown next to each plot. Spatiotemporal EES is represented using the same colour scheme as in Fig. 3 and Extended Data Fig. 7. The plots report quantification of EMG activity, step height and mean speed (based on distance covered) for the three experimental conditions (P1, $n = 6, 7, 8$ gait cycles for no EES, continuous EES and spatiotemporal EES; P2, $n = 17, 7, 9$ gait cycles for no EES, continuous EES and spatiotemporal EES; 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. One-way ANOVA, post hoc Tukey's HSD. These recordings were repeated on at least three different days for each participant.



Extended Data Fig. 10 | Rehabilitation program and evolution of walking capacity. a, Rehabilitation programs were continuously personalized on the basis of the current motor performance of participants. Walking capacities evolved in phases (**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 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 time points using X-ray attenuation from CT images obtained at the abdomen (L3 vertebra) and mid-thigh (25 cm above femorotibial joint space). Muscle mass was determined by measuring the cross-sectional areas (CSAs) of muscle tissues, while muscle quality was reflected by 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 fibre lipid content at the mid-thigh and abdomen. 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 as in Extended Data Fig. 4. **c**, Snapshots showing 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 two 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, P1 and P2 were asked to walk freely overground with a walker (no body weight support) for 6 min. 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 centre 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 on histograms (P1, $n = 49$ gait cycles; P2, $n = 79$ gait cycles). **b**, Closed-loop spatiotemporal EES was delivered in 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. Successive ankle trajectories during cycling are shown together with the timing of EES protocols targeting the 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 (P3: $n = 73$ pedalling cycles). $^{***}P < 0.001$. Student's t-test.

Extended Data Table 1 | Neurological statuses of participants

Participant		P1		P2		P3	
Gender		m		m		m	
Age (y)		28		35		47	
Years after SCI		6		6		4	
Assessments at study enrollment (Pre) and after rehabilitation period (Post)		Pre	Post	Pre	Post	Pre	Post
Walking index for spinal cord injury (WISCI II score; max. 20)		13	16	6	13	0	0
American Spinal Injury Association Impairment Scale (AIS)		C	D	D	D	C*	C
Neurological level of injury		C7	C8	C4	C4	C7	C7
Upper Extremity Motor Scores:							
C5, elbow flexors	(right | left)	5 | 5	5 | 5	5 | 5	5 | 5	5 | 5	5 | 5
C6, wrist extensors	(right | left)	5 | 5	5 | 5	5 | 4	4 | 4	5 | 5	5 | 5
C7, elbow extensors	(right | left)	5 | 5	5 | 5	4 | 4	4 | 4	5 | 4	5 | 5
C8, finger flexors	(right | left)	4 | 4	5 | 4	1 | 0	3 | 1	4 | 4	4 | 5
T1, finger abductors	(right | left)	4 | 4	4 | 4	3 | 0	3 | 0	4 | 4	4 | 4
(max. 5 per side)							
Total (max. 50)		46	47	31	33	45	47
Lower Extremity Motor Scores:							
L2, hip flexors	(right | left)	2 | 0	4 | 2	2 | 2	3 | 2	0 | 0	0 | 1
L3, knee extensors	(right | left)	2 | 0	4 | 3	4 | 4	4 | 4	0 | 0	1 | 0
L4, ankle dorsiflexors	(right | left)	4 | 0	4 | 1	2 | 1	4 | 4	0 | 0	0 | 1
L5, long toe extensors	(right | left)	4 | 0	4 | 2	1 | 1	2 | 4	0 | 0	0 | 1
S1, ankle plantar flexors	(right | left)	2 | 0	4 | 2	4 | 4	5 | 4	0 | 0	0 | 0
(max. 5 per side)							
Total (max. 50)		14	30	25	36	0	4
Light Touch Sensory Scores:							
L1-S2 dermatomes subscore	(right | left)	7 | 7	7 | 7	5 | 8	2 | 10	1 | 4	2 | 5
(max. 14 per side)							
Total (max. 112)		75	76	65	71	55	57
Pin Prick Sensory Scores:							
L1-S2 dermatomes subscore	(right | left)	0 | 0	0 | 0	4 | 8	1 | 13	0 | 0	0 | 0
(max. 14 per side)							
Total (max. 112)		33	30	65	86	28	28

Subjects' neurological status according to the International Standards for Neurological Classification of Spinal Cord Injury at study entry and after completion of the five-month 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.

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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	EMG system: Myon 320, Myon AG, Schwarzenberg, Switzerland Motion capture system: Vicon Nexus software v1.8.5, Vicon Motion Systems, Oxford, UK Data acquisition system: Twincat 3.1, Beckhoff Automation GmbH & Co. KG, Huelshorstweg 20 33415 Verl Germany Custom C++ code to control stimulation in real-time inside the laboratory environment Custom C# code to control stimulation in real-time outside the laboratory environment Microsoft Visual Studio Professional 2012 (for development in C++) Microsoft Visual Studio Community 2017 (for development in C#)
Data analysis	Custom code in MATLAB R2018a used for all data analysis Kinematic analysis performed using Vicon Nexus software v1.8.5, Vicon Motion Systems, Oxford, UK Sim4Life v3.4 ImageJ 1.52

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Data that supports 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.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We report proof-of-concept results in three patients who contributed to a First-in-Man study. No previous data existed to predetermine sample size. Previous studies employing spinal cord stimulation or novel implanted neurotechnologies (e.g. brain machine interface) in individuals with spinal cord injury reported their results in 1 to 4 participants.
Data exclusions	No data were excluded from the analyses.
Replication	Reproducibility of the experimental findings was verified across several steps, several recording sessions and between all 3 participants.
Randomization	Randomization was not sought in the present study. Each participant served as his own control (stimulation off vs. on conditions; evaluations at different points over time throughout the rehabilitation training period)
Blinding	Investigators were not blinded. Their expertize was required to optimize the intervention and to apply the intervention during evaluations. Furthermore, the effects of the intervention were obvious, acutely producing changes in the kinematics and muscle activities of the participants during walking.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	Three male individuals, aged 28-47 y, all with a traumatic cervical spinal cord injury participated in the study. All participants had completed standard of care rehabilitation following their injury and were in a chronic state, 4-6 y post-injury. All displayed low motor scores in the lower limbs or complete motor paralysis, which bound them to a wheelchair.
Recruitment	Participant recruitment was done via the clinicaltrial.gov website where the principal investigators' contact details were disclosed (NCT02936453). Patients and physicians contacted them directly to communicate their interest to participate or to

refer a patient to the STIMO study. The clinical study nurse communicated with the patients or the referring physician and reviewed the clinical status of the patient for compliance with the inclusion and exclusion criteria listed below. Patients meeting the inclusion criteria were given the study's flyer and the informed consent form to understand further their implications and involvement within this clinical study. The participants' selection was also based on their ability to live independently and their autonomy in their daily living activities.

Inclusion Criteria:

- Age 18-65 (women or men)
- Incomplete SCI graded as AIS C & D
- Level of lesion: T10 and above, based on AIS level determination by the PI, with preservation of conus function
- The intact distance between the cone and the lesion must be at least 60mm
- Focal spinal cord disorder caused by either trauma or epidural, subdural or intramedullary bleeding
- Minimum 12 months post-injury
- Completed in-patient rehabilitation program
- Able to stand with walker or 2 crutches
- Stable medical and physical condition as considered by Investigators
- Adequate care-giver support and access to appropriate medical care in patient's home community
- Agree to comply in good faith with all conditions of the study and to attend all required study training and visits
- Must participate in two training sessions before enrolment
- Must provide and sign Informed Consent prior to any study related procedures

Exclusion Criteria:

- Limitation of walking function based on accompanying (CNS) disorders (systemic malignant disorders, cardiovascular disorders restricting physical training, peripheral nerve disorders)
- History of significant autonomic dysreflexia
- Cognitive/brain damage
- Epilepsy
- Patient who uses an intrathecal Baclofen pump.
- Patient who has any active implanted cardiac device such as pacemaker or defibrillator.
- Patient who has any indication that would require diathermy.
- Patient who has any indication that would require MRI.
- Patient that have an increased risk for defibrillation
- Severe joint contractures disabling or restricting lower limb movements.
- Haematological disorders with increased risk for surgical interventions (increased risk of haemorrhagic events).
- Participation in another locomotor training study.
- Congenital or acquired lower limb abnormalities (affection of joints and bone).
- Women who are pregnant (pregnancy test obligatory for woman of childbearing potential) or breast feeding or not willing to take contraception.
- Known or suspected non-compliance, drug or alcohol abuse.
- Spinal cord lesion due to either a neurodegenerative disease or a tumour.
- Patient has other anatomic or co-morbid conditions that, in the investigator's opinion, could limit the patient's ability to participate in the study or to comply with follow-up requirements, or impact the scientific soundness of the study results.
- Patient is unlikely to survive the protocol follow-up period of 12 months.

Magnetic resonance imaging

Experimental design

Design type	clinical structural MRI
Design specifications	N/A
Behavioral performance measures	N/A

Acquisition

Imaging type(s)	structural
Field strength	3 Tesla
Sequence & imaging parameters	Scanning sequence: TSE (Turbo Spin Echo) SPACE (Sampling Perfection with Application optimized Contrasts using different flip angle Evolution), imaging type: Cartesian, field of view: 200 mm x 200 mm, matrix size: 320 pixels x 320 pixels, slice thickness: 1 mm, orientation: axial, TE: 133 ms, TR: 1500 ms, flip angle: 125 degrees
Area of acquisition	spine

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	N/A

Normalization: N/A

Normalization template: N/A

Noise and artifact removal: N/A

Volume censoring: N/A

Statistical modeling & inference

Model type and settings: N/A

Effect(s) tested: N/A

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016): N/A

Correction: N/A

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis