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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see <u>Authors & Referees</u> and the <u>Editorial Policy Checklist</u>.

Statistical parameters

| | en statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main t, 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 <u>central tendency</u> (e.g. means) or other basic estimates (e.g. regression coefficient) AND <u>variation</u> (e.g. standard deviation) or associated <u>estimates of uncertainty</u> (e.g. confidence intervals) |
| | For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i> |
| X | For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| \times | 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 <i>d</i> , Pearson's <i>r</i>), indicating how they were calculated |

Our web collection on <u>statistics for biologists</u> may be useful.

Software and code

Policy information about availability of computer code

State explicitly what error bars represent (e.g. SD, SE, CI)

Clearly defined error bars

Data collection

Data collection was performed with the following commercial and custom code:

- NIM Eclipse system software (Medtronic plc, Fridley, Minnesota, USA), to record the neural activity induced by epidural electrical stimulation (EES) in humans.
- Custom code developed using the TwinCat software system (Beckhoff Automation GmbH & Co. KG, Verl, Germany), to record joint kinematic and surface EMG signals during the assessment of proprioceptive functions, and during the assessment of EES-induced responses during passive joint movements performed in humans.
- The Vicon motion capture system software (Vicon Motion Systems, Oxford, UK), to record kinematic and EMG signals during treadmill locomotion in rats and humans, and to record the ankle kinematic during the assessment of EES-induced responses during passive joint movements performed in rats
- Custom code developed in RPvdsEx to control an RZ2 BioAmp Processor (Tucker-Davis Technologies, Alachua, US), to record EMG signals in rats.

Data analysis

Computer simulations were performed in python 2.7 using the NEURON simulation environment to run the spiking neural network models and OpenSim for the biomechanical model of rats and humans. The code to perform and analyze the neural simulations is available as supplementary information and at https://github.com/FormentoEmanuele/MuscleSpindleCircuitsModel.git. Custom python 2.7 code was developed for data analyses, using the SciPy and StatsModels modules for statistical tests.

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.

| Policy information | about | availability | of | data |
|--------------------|-------|--------------|----|------|

Data

All manuscripts must include a <u>data availability statement</u>. 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

Acquired data are available from the corresponding author upon reasonable request.

Field-specific reporting

| Please select the best fit for | your research. If you are not sure, re | ead the appropriate sections before making your selection. | | |
|--|--|--|--|--|
| X Life sciences | Behavioural & social sciences | Ecological, evolutionary & environmental sciences | | |
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For a reference copy of the document with all sections, see <u>nature.com/authors/policies/ReportingSummary-flat.pdf</u>

Life sciences study design

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

Sample size No statistical methods were used to pre-determine sample sizes but our sample sizes are similar to those reported in previous publications using similar experimental procedures.

Data exclusions No data were excluded from the analyses.

Replication All experimental findings were replicated different times. For example, experiments in humans and rats during walking were collected

multiple times on different days with the same outcomes

Randomization -The assessment of proprioceptive functions during epidural electrical stimulation, performed in humans, was performed randomizing both the sequence of the tested stimulation parameters and the sequence of imposed passive movements.

-The assessments of EES-induced responses during passive joint movements, performed in humans and rats, were performed by randomizing the sequence of the tested stimulation parameters.

-The experiments on continuous EES during treadmill locomotion, performed in humans and rats, were performed by randomizing the sequence of the tested stimulation parameters.

Blinding The investigators were not blinded to tested conditions.

Reporting for specific materials, systems and methods

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| n/a | Involved in the study |
|-----|-----------------------------|
| X | Unique biological materials |
| X | Antibodies |
| X | Eukaryotic cell lines |
| X | Palaeontology |

| | 97 |
|-------------|-----------------------------|
| \boxtimes | Animals and other organisms |
| X | Human research participants |

| ı/a | Involved in the study |
|----------|-----------------------|
| \times | ChIP-seq |
| \times | Flow cytometry |

MRI-based neuroimaging

Animals and other organisms

| Policy | / information about | studies involving | animals: Al | RRIVE guidelines | recommended for | r reporting animal | researc |
|--------|---------------------|-------------------|-------------|------------------|-----------------|--------------------|---------|
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Laboratory animals

Experiments in animals were conducted in:

- Female Lewis rats, 11 weeks old.
- Female Long-Evans rats, 11 weeks old.

Wild animals

The study did not involve wild animals.

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

The study did not involve samples collected from the field.

- 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.