

Restoration of sensory feedback from the foot and reduction of phantom limb pain via closed-loop spinal cord stimulation

Received: 15 September 2022

Accepted: 27 October 2023

Published online: 14 December 2023

 Check for updates

Ameya C. Nanivadekar  ^{1,2,3,11}, Rohit Bose  ^{1,2,3,11}, Bailey A. Petersen ^{1,2,3,11}, Elizaveta V. Okorokova  ⁴, Devapratim Sarma ^{1,5}, Tyler J. Madonna ^{1,6}, Beatrice Barra ^{1,7}, Juhi Farooqui ^{1,3}, Ashley N. Dalrymple  ^{1,5,8,9}, Isaiah Levy ⁶, Eric R. Helm ⁶, Vincent J. Miele ¹⁰, Michael L. Boninger  ^{1,2,3,6}, Marco Capogrosso  ^{1,2,3,10}, Sliman J. Bensmaia  ^{4,12}, Douglas J. Weber ^{1,5} & Lee E. Fisher  ^{1,2,3,6} 

Restoring somatosensory feedback in individuals with lower-limb amputations would reduce the risk of falls and alleviate phantom limb pain. Here we show, in three individuals with transtibial amputation (one traumatic and two owing to diabetic peripheral neuropathy), that sensations from the missing foot, with control over their location and intensity, can be evoked via lateral lumbosacral spinal cord stimulation with commercially available electrodes and by modulating the intensity of stimulation in real time on the basis of signals from a wireless pressure-sensitive shoe insole. The restored somatosensation via closed-loop stimulation improved balance control (with a 19-point improvement in the composite score of the Sensory Organization Test in one individual) and gait stability (with a 5-point improvement in the Functional Gait Assessment in one individual). And over the implantation period of the stimulation leads, the three individuals experienced a clinically meaningful decrease in phantom limb pain (with an average reduction of nearly 70% on a visual analogue scale). Our findings support the further clinical assessment of lower-limb neuroprostheses providing somatosensory feedback.

Every year, approximately 150,000 people in the United States undergo amputation of a lower limb¹. Loss of a lower limb leads to chronic challenges including major mobility impairments and emergence of chronic pain that appears to emanate from the missing limb (that is, phantom limb pain, PLP). Current clinical practice involves

prescribing a prosthetic limb to improve functional mobility, along with neuroleptic and opiate pharmaceuticals to treat PLP. Even with these interventions, people with lower-limb amputation exhibit a high rate of falls, a lack of confidence during gait, abnormal gait patterns and persistent PLP. All these problems have been associated with the

¹Rehab Neural Engineering Labs, University of Pittsburgh, Pittsburgh, PA, USA. ²Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, USA. ³Center for the Neural Basis of Cognition, Pittsburgh, PA, USA. ⁴Department of Organismal Biology and Anatomy, University of Chicago, Chicago, IL, USA. ⁵Department of Mechanical Engineering, Carnegie Mellon University, Pittsburgh, PA, USA. ⁶Department of Physical Medicine and Rehabilitation, University of Pittsburgh, Pittsburgh, PA, USA. ⁷Department of Neuroscience and Movement Science, University of Fribourg, Fribourg, Switzerland.

⁸Department of Biomedical Engineering, University of Utah, Salt Lake City, UT, USA. ⁹Department of Physical Medicine and Rehabilitation, University of Utah, Salt Lake City, UT, USA. ¹⁰Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA, USA. ¹¹These authors contributed equally: Ameya C. Nanivadekar, Rohit Bose, Bailey A. Petersen. ¹²Deceased: Sliman J. Bensmaia.  e-mail: lef44@pitt.edu

Table 1 | Study participant demographics and amputation data

Participant	Age (years)	Gender	Ambulation level	Years since amputation	Side of amputation	Nature of amputation	Time with prosthesis (months)	Prosthesis wear time (h per day)	Implant duration (days)
1	56	M	Limited community	3.5	Left	Diabetic	42	8	28
2	56	M	Active	7	Left	Traumatic	84	8	28
3	65	W	Limited community	5	Left	Diabetic	52	20	84

disruption of somatosensory feedback from the missing limb. Tactile feedback from the sole of the foot is critical for maintaining balance and postural stability², and the loss of somatosensory feedback after an amputation causes a sensorimotor mismatch between attempted movements and expected sensory feedback. This mismatch and the persistent absence of somatosensory input to the brain have been implicated in the development and maintenance of PLP^{3,4}. One potential way to address the sequelae of lower-limb amputation is to restore somatosensation in the missing limb, thereby improving functional outcomes and reducing PLP.

Previous studies have demonstrated that electrical stimulation of peripheral nerves in the residual limb can evoke sensations in the missing hand or foot^{5–7}. Tactile feedback via peripheral nerve stimulation has been shown to enhance control of the prosthesis and improve balance and gait^{8–12}. In addition, anecdotal evidence suggests that chronic peripheral nerve stimulation reduces PLP^{8,13–15}. To date, most studies to restore somatosensory feedback from the missing limb have relied on complex surgical techniques to implant devices inside or around peripheral nerves or to reroute those nerves to other regions of the body^{7,8,10,12,16,17}. While these approaches clearly showed the promise of electrical stimulation, their surgical complexity remains a barrier to widespread clinical adoption. Evoking sensations via peripheral nerve stimulation may also be challenging in individuals with severe peripheral neuropathy, a common co-morbidity for people with amputations related to vascular disease and diabetes, which account for up to 82% of lower-limb amputations¹⁸. To our knowledge, no study to date has demonstrated restored somatosensation in the amputated foot for people with diabetic amputation.

In this Article, we aimed to address these challenges by leveraging spinal cord stimulation (SCS) as an alternative to peripheral nerve stimulation, to restore somatosensory feedback from the missing lower limb. SCS is an existing clinical technology that is implanted in as many as 50,000 people each year to treat chronic pain¹⁹. The surgical procedures involved in the implantation of these devices and the associated risks are well understood, and most major medical centres throughout developed countries have physicians that routinely perform SCS implants²⁰. Recently, we have shown that cervical SCS can be used to restore somatosensation from the missing hand in people with upper-limb amputation²¹. Our goal in this study was to demonstrate that lumbosacral SCS could evoke sensations in the missing foot and that the restored somatosensory feedback could improve functional use of the prosthesis and reduce PLP. Importantly, we aimed to demonstrate that we could achieve these effects regardless of whether the amputation was traumatic or secondary to diabetic peripheral neuropathy, which substantially increases the pool of people that might benefit from these devices. To that end, we included participants both with and without sensory neuropathies in the residual and contralateral limb (Extended Data Fig. 1 and Supplementary Table 1).

In three people with below-knee amputation (Table 1), we implanted commercially available SCS leads in the thoracolumbar epidural space to stimulate the lateral lumbosacral spinal cord. Participants attended multiple testing sessions each week for the duration of the implantation period. Testing sessions typically lasted 4–6 h. During those sessions, we identified electrode contacts that evoked sensation experienced on the missing foot and performed psychophysical



Fig. 1 | Schematic of the closed-loop SCS system used in this study. Electrical stimulation was delivered to the spinal cord via two or three 8- or 16-contact leads implanted percutaneously near the lateral lumbosacral spinal cord. The leads were tunneled through the skin and connected to an external stimulation system. A sensorized insole was inserted into the shoe to measure pressure under the prosthetic foot, the signals from this insole were used to modulate stimulation amplitude for SCS electrodes implanted in the lateral thoracolumbar epidural space, and the stimulation evoked sensations that appeared to emanate from the missing limb. The purple region of the leg and foot shows the location of evoked sensation in one participant, and the red dotted line represents the end of the residual limb for this participant with left trans-tibial amputation.

assessments to characterize those sensations. We developed a closed-loop system (Fig. 1 and Supplementary Video 1) where SCS was modulated by pressure signals wirelessly recorded from an insole in the shoe under the prosthetic limb. Using this system to deliver real-time somatosensory feedback, we assessed balance and gait, as well as changes in PLP over the duration of the multi-week implantation period. Our results indicate that lumbosacral SCS is a promising intervention to restore sensations, improve function and reduce PLP in lower-limb amputees.

Results

SCS evokes sensations in the missing foot

The first goal of this study was to characterize the location and perceptual qualities of sensations evoked by lumbosacral SCS. To map the location of evoked sensations, we delivered 1-s-long stimulation trains and asked the participants to draw the location of the perceived sensations on a graphic representation of the foot and legs. For all three participants, SCS evoked sensations in the missing limb,

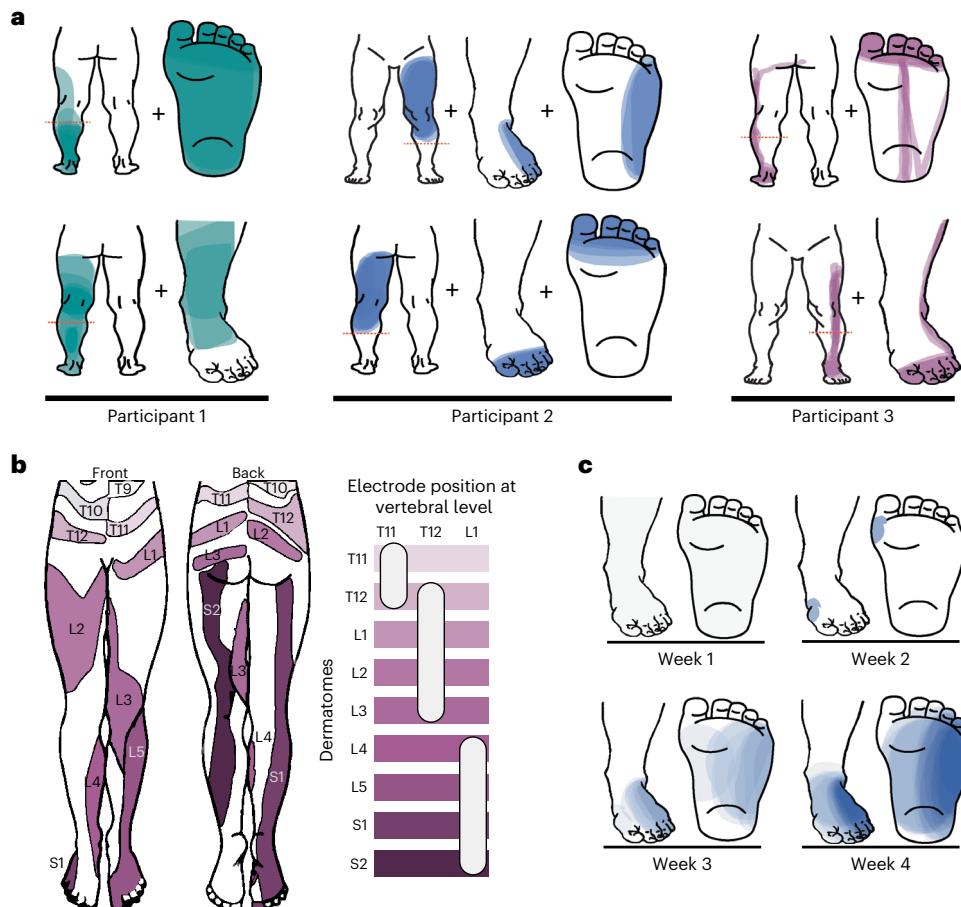


Fig. 2 | SCS evokes percepts in the missing limb. **a**, Examples of percepts evoked in the missing and residual limbs from one session for each participant. Two different sensations (corresponding to stimulation through two different electrodes) are shown for each participant (top and bottom). The red dashed line indicates the level of the amputation. The coloured area represents the location of the perceived sensation, with darker colours representing more frequent reports of sensation at that location across trials, normalized within each participant. **b**, Dermatome activation by electrodes located at different

vertebral levels for participant 3. Left: expected dermatomal innervation in the leg, adapted from ref. 22. Right: horizontal bars indicate different dermatomes, and the white ovals indicate the approximate electrode position that evoked sensations in those dermatomes, with respect to vertebral level. **c**, Rate of occurrence of sensations in the missing limb across weeks from one electrode in participant 2. Darker shades indicate more frequent reports of evoked sensations in the foot.

including the toes and heel (Fig. 2a). The sensations were absent during the first 1–2 weeks of the study and gradually stabilized in the missing foot over the following weeks (Fig. 2c and Extended Data Fig. 2). During experiments to characterize the location of evoked sensations, the choice of stimulation electrodes and parameters was randomized, and participants were blinded to those choices. The sensations in the missing limb were always accompanied by sensations in the residual limb, and higher stimulation amplitudes were required to evoke sensations in the missing limb than in the residual limb alone (Extended Data Fig. 3). The rostral–caudal arrangement of the electrodes across different levels of the spinal cord elicited sensations that corresponded to the dermatomal distribution²² (Fig. 2b and Extended Data Fig. 4).

The participants also reported the perceived quality of the sensations using a list of descriptors compiled from previous literature²³. For analytical purposes, we grouped these descriptors as sensations that participants might experience commonly in their daily life (naturalistic) or rare, less familiar sensations (paresthetic). All participants reported a combination of naturalistic and paresthetic descriptors in different proportions (Extended Data Fig. 5). We explored the effect of stimulation frequency on perceived sensations but did not find a consistent relationship between frequency and properties such as intensity or quality of the evoked sensations across participants.

Sensory magnitude can be systematically manipulated by varying stimulation amplitude

A key step in designing a sensory prosthesis is to assess the dependence of the sensation on stimulation parameters. With this in mind, we first established the stimulation intensity required to evoke a conscious percept. To this end, we had the participants perform a detection task in a two-alternative forced choice paradigm. In brief, a 1 s stimulation train at 1 of 5 to 10 amplitudes, determined in preliminary experiments to be peri-liminal, was presented in 1 of 2 visually cued stimulus intervals, and the participant's task was to report which interval contained the stimulus. Each stimulus was presented at least four times, and we tallied the proportion of times the participant correctly identified the interval containing the stimulus for each amplitude (Fig. 3a). The detection threshold was the amplitude (estimated from the fitted logistic psychometric function) at which the participant would correctly identify the stimulus interval 75% of the time. Detection thresholds varied across electrodes and participants from 0.6 to 4 mA, but there were no large and systematic differences across participants (Fig. 3b). We also measured detection thresholds for a small set of multipolar configurations of cathodes and anodes to determine whether there were any differences compared to monopolar stimulation. The detection thresholds for multipolar stimulation were slightly higher than for monopolar stimulation

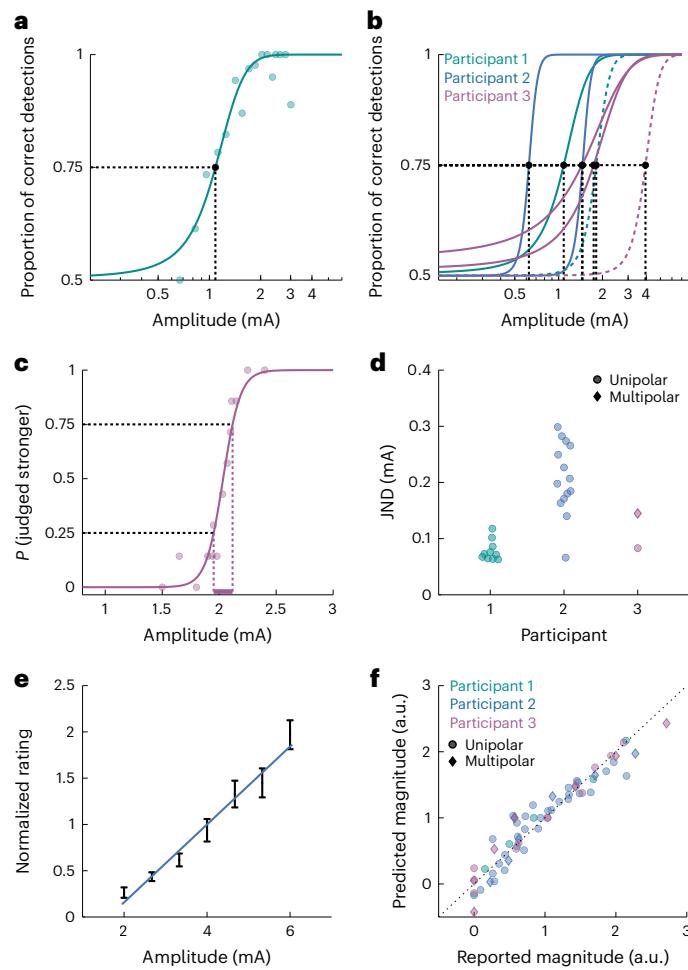


Fig. 3 | Psychophysical assessment of evoked sensations. **a**, Performance of participant 1 on the detection task for one electrode, showing the proportion of times the stimulus interval was correctly selected as a function of stimulus amplitude. The bold line shows a cumulative-normal curve fit to the data. **b**, Psychometric functions for the subset of electrodes ($N = 7$ across all participants) in which psychophysical assessment of detection threshold was assessed, colour-coded by participant. Solid lines correspond to monopolar electrode configurations, and dashed lines correspond to multipolar configurations. The vertical black dashed lines indicate the detection threshold for each electrode. **c**, Performance of participant 3 on the amplitude discrimination task with a standard amplitude of 2 mA for one electrode. The bold line shows the fitted psychometric function, and the dashed lines indicate the range used to compute the JND (in this case 0.08 mA), given by half the distance between the dotted lines. **d**, Distribution of JNDs across the three participants on a subset of electrodes ($N = 10$ sessions from 1 electrode for participant 1, $N = 14$ sessions from 3 electrodes for participant 2 and $N = 2$ sessions from 2 electrodes for participant 3). Filled circles correspond to monopolar electrode configurations, and filled diamonds correspond to multipolar configurations. **e**, Average normalized magnitude ratings as a function of stimulus amplitude for one electrode for participant 2 with 6 repetitions of each stimulus amplitude. The bold line indicates the linear fit to the data. The error bar denotes the mean \pm standard deviation across repeated presentations of the same stimulus. **f**, Scatter plot showing predicted magnitude estimated by a linear model for each electrode ($N = 3$ sessions from 1 electrode for participant 1, $N = 11$ sessions from 4 electrodes for participant 2 and $N = 4$ sessions from 3 electrodes for participant 3) and participant versus the actual stimulation magnitude. Points show average magnitude for each presented amplitude for each electrode, colour-coded by participant. Filled circles correspond to monopolar electrode configurations, and filled diamonds correspond to multipolar configurations. The dashed line represents the unity line.

(mean monopolar detection threshold across all participants, 1.27 ± 0.43 mA; multipolar detection thresholds for participants 1 and 2, respectively, 1.81 and 3.95 mA).

Next, we measured the participants' sensitivity to changes in stimulation amplitude. To this end, we had them perform an amplitude discrimination task. On each trial, the participant was presented with two stimuli: (1) a standard, the amplitude of which was fixed within the block, and (2) a comparison, the value of which varied from trial to trial. After both presentations, the participant reported which of the two felt stronger (Fig. 3c). For each electrode and participant, we fitted a logistic psychometric function and computed the just-noticeable difference (JND), the change in amplitude required for the participant to correctly identify the more intense stimulus 75% of the time. JNDs varied from 0.05 to 0.3 mA across participants and electrodes (Fig. 3d and Extended Data Fig. 6). The range of JNDs overlapped across participants, although participant 2 tended to have higher JNDs than the other two participants. We also measured the JND for a single multipolar configuration in participant 3. The JND for multipolar stimulation was slightly higher than for monopolar stimulation, although this difference was within the interparticipant variability of JNDs (mean monopolar JND across all participants, 0.15 ± 0.08 mA; multipolar JND for Participant 3, 0.14 mA).

Finally, we wished to explicitly measure the relationship between stimulation amplitude and perceived magnitude. To this end, we delivered stimuli that spanned a range of intensities and had the participant report how intense the stimulus felt with the following instructions: (1) If they did not feel the stimulus, they ascribed to it a rating of 0; (2) if one stimulus felt twice as strong as another, it was to be ascribed a number that was twice as high (other examples were also provided); and (3) they could use any scale they wanted and were encouraged to use decimals, if necessary. Perceived magnitude increased nearly linearly with stimulation amplitude for all participants and electrodes (R^2 of the linear regression for participant 1 was 0.978, participant 2 was 0.854 and participant 3 was 0.952; Fig. 3e,f), as has been previously found with stimulation of the peripheral nerves^{9,24–26} and of the somatosensory cortex²⁷. We also measured this relationship for one multipolar configuration each in participants 2 and 3 and found the relationship to be similarly linear to that of monopolar stimulation. Because of this linear relationship between the perceived intensity and stimulation amplitude, we used linear modulation of stimulation amplitude in subsequent experiments assessing functional outcomes (see below).

SCS improves functional use of a prosthesis

The second goal of this study was to demonstrate that restored somatosensation can improve functional use of a prosthetic limb. To restore somatosensation during functional tasks, such as standing and walking, we placed a wireless pressure-sensing insole (Moticon Insole 3) under the prosthetic foot and used the output from that insole to control stimulation in real time. For participants 2 and 3, we selected an SCS electrode that reliably evoked sensation on the plantar surface of the missing foot and used the pressure signal from the same location under the prosthetic foot to control stimulation amplitude (Fig. 1a). Due to time constraints, we could not perform these experiments in participant 1. We used clinical measures of balance and gait to compare postural stability with and without restored somatosensory feedback.

To assess standing balance with and without sensory feedback, we used the Sensory Organization Test (SOT), a clinical outcome measure that quantifies reliance on visual, vestibular or somatosensory feedback to maintain balance control. The SOT requires the participant to maintain balance (Fig. 4a) despite erroneous visual information from a visual surround that can sway and/or erroneous somatosensory information from a support surface that can also sway. To characterize reliance on vision, vestibular sense and somatosensory feedback, the SOT comprises six different conditions, with each condition obscuring different combinations of the relevant sensory feedback. With somatosensory feedback restored via SCS, both participants 2 and 3 achieved improvements in SOT scores (Fig. 4c; participant 2, +4.6 points; participant 3, +19.0 points), with greater improvements in the

most challenging conditions (platform sway with eyes closed and platform sway with visual surround sway; Extended Data Fig. 7). Notably, both participants experienced at least one ‘fall’ without stimulation (that is, one fall for participant 2, three falls for participant 3), but neither participant fell with stimulation (Fig. 4c). A ‘fall’ denotes a failure to complete the trial due to taking a step, falling in the harness or grabbing the walls for support. Performance was slightly worse with stimulation during the least challenging conditions (that is, no visual or support surface sway) with eyes open and eyes closed (Extended Data Fig. 7), although this difference was negligible (that is, smaller than the minimum clinically important difference). In participant 2, we implemented a sham stimulation condition, in which stimulation evoked sensation only in the residual limb and not in the missing foot. In this case, we saw decreased performance from baseline for condition 2 (static platform with eyes closed, -5.3 points), condition 5 (platform sway with eyes closed, -8.0 points) and condition 6 (platform sway with visual surround sway, -10.9 points), and the decrease for condition 6 was larger than a minimum clinically important difference (that is, >8.0 points; Extended Data Fig. 7). Biomechanical analyses of centre of gravity traces (Fig. 4d) revealed that both participants exhibited decreases in sway area (indicating greater stability) with eyes closed condition and an unstable support surface during stimulation (mean sway area decreased for participant 2 by 13.72 cm^2 and decreased for participant 3 by 41.83 cm^2).

To assess stability during gait, participants performed the Functional Gait Assessment (FGA), a clinical measure of dynamic balance, commonly applied to detect reliance on visual and somatosensory systems for maintaining balance during walking^{28,29}. This task consists of ten items, including walking with eyes closed, walking with a narrow base of support and walking over obstacles. Restored somatosensation led to a clinically meaningful improvement (>4 points) in FGA score for participant 3 (5-point improvement) but not participant 2 (1-point improvement; Fig. 5b). Notably, participant 2 demonstrated baseline performance 3.9 points below age-matched able-bodied controls, whereas the baseline score for participant 3 was 13.5 points below age-matched normative data²⁸.

SCS reduces PLP

To assess the impact of stimulation on PLP, we examined participants’ reports of their current pain level on a visual analogue scale (VAS). Participants were instructed to report the pain level perceived specifically in the missing limb for this assessment. As the study progressed, we observed a clinically meaningful decrease in PLP score (defined as a 50% reduction from the baseline pain score) for participants 1 and 3 (Fig. 6). While the PLP score for participant 2 also decreased to 0.48 from 1.2 points, this improvement is considered sub-clinical because it is less than 1 point. For both participants 1 and 3, the first clinically meaningful decrease in PLP coincided with the emergence of electrically evoked sensations in the missing limb (that is, week 3 and week 2, respectively). For participant 3, experiments were suspended over a

1 week holiday (week 11), at which time pain scores increased sharply (3.65 times greater than week 10), consistent with the hypothesis that SCS relieves PLP.

We also conducted the McGill Pain Questionnaire³⁰ (MPQ) once per week to characterize the sensory and affective dimensions of the

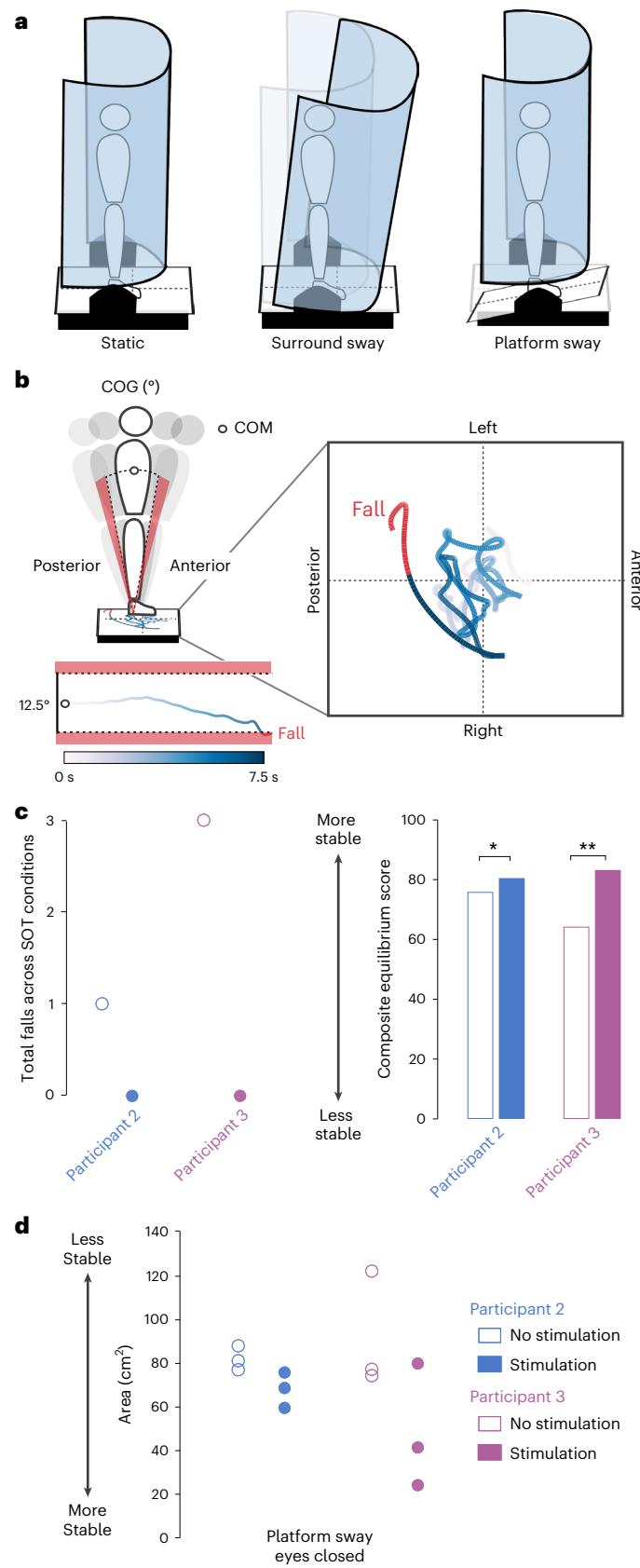


Fig. 4 | Closed-loop sensory feedback improves postural stability. **a**, The SOT comprises six conditions, defined by whether the visual surround (middle) and/or platform (right) are swaying while participants have their eyes open or closed. **b**, For analysis, the centre of gravity (COG) is a projection of the pressure trace onto the force plate to indicate their centre of mass (COM) movement throughout a trial. The equilibrium score is an indication of how well participants maintain their COM within a normative 12.5° limit of anteroposterior sway. Beyond these limits, a fall can occur (red). **c**, Falls occurred only during conditions without stimulation for both participants (left), and both participants exhibited an improvement in composite equilibrium score (right, $N=1$ per condition). This improvement was above the MDC for participant 2 (*MDC = 3.98) and above the threshold for a clinically meaningful difference in participant 3 (**clinically meaningful difference = 8.0). **d**, Both participants showed a decrease in sway area, indicating greater stability, with stimulation.

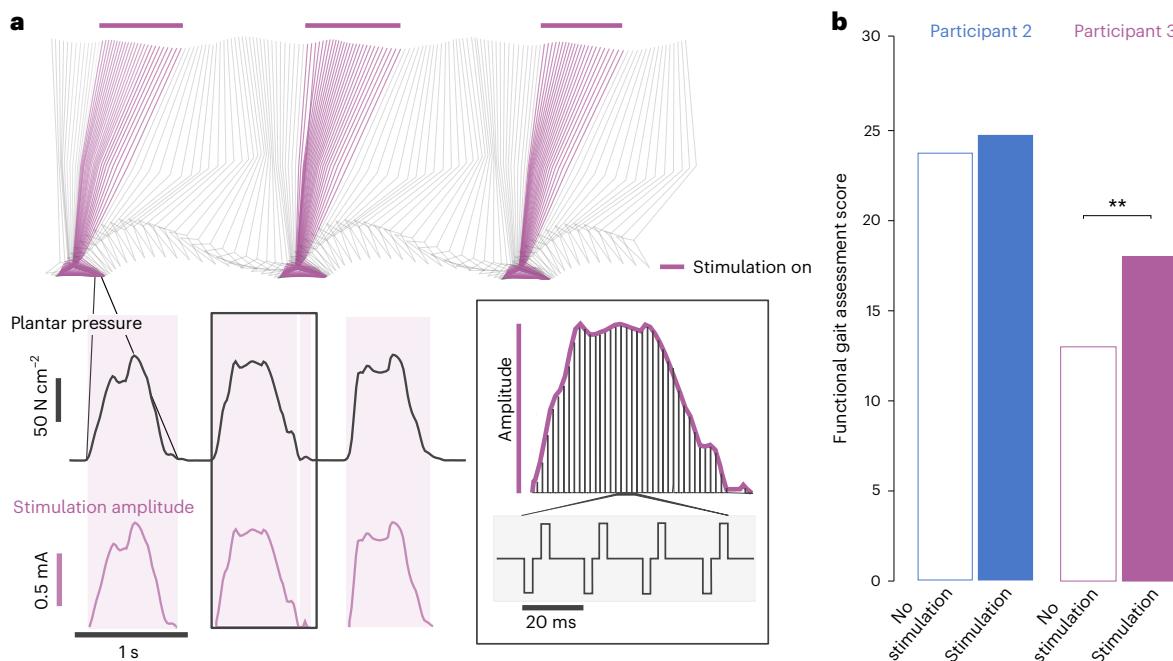


Fig. 5 | Closed-loop sensory feedback improves gait stability. **a**, Example of amplitude modulation with plantar pressure throughout the gait cycle. Stimulation was triggered above a threshold for the metatarsals (purple shading), and either it was maintained at a constant amplitude (for participant 2)

or amplitude was modulated linearly with pressure signals (for participant 3). **b**, The FGA score increased in both participants with stimulation and increased beyond the MDC (**MDC > 4 points) for participant 3, who had a lower baseline score. For bar plot, $N=1$ for each participant per condition.

participants' pain. This questionnaire provides a holistic measure of a patients' pain experience and can be used to infer overall patient well-being. All participants were instructed to rate their pain in the missing limb over the most recent week of the study (Extended Data Fig. 8). We observed a clinically meaningful decrease in the MPQ scores (defined as a >5-point decrease) for participant 1 (28 points) and participant 2 (10 points) across the 4 week implant phase. For participant 3, across the 12 week implant, there was a reduction in the pain scores until week 8 (15 points) followed by an increase from week 9 onwards, including a 24-point increase that coincided with the break in testing during week 11. However, participant 3 anecdotally reported a substantial reduction in PLP episodes.

Discussion

In this study, we provide preliminary evidence that lateral lumbosacral SCS can evoke sensations in the missing limb in people with transtibial amputation and that this restored somatosensation can improve balance control and gait stability and reduce PLP. Importantly, we showed these effects in a heterogeneous cohort of three participants, including persons with amputations that spanned 3–7 years before enrolment in the study, and with different levels of mobility. Among this cohort, we included one participant with traumatic amputation and two others with diabetic peripheral neuropathy and associated distal sensory impairments. Critically, the implantable electrodes used in this study were commercially available devices that are currently implanted in more than 50,000 people each year for the treatment of pain¹⁹. The devices were implanted via a percutaneous approach in an outpatient surgical procedure, and future development and translation of our approach can leverage the vast infrastructure of clinicians and surgical techniques that already exist for SCS. While we cannot demonstrate broad claims of safety of efficacy from a study with three participants with devices percutaneously implanted for fewer than 29 or 90 days, and translation will still require substantial technical and clinical development, this study shows the feasibility of using SCS to restore somatosensation from the missing foot with

the potential to improve quality of life for people with lower-limb amputation.

In all participants, we found that multiple SCS electrodes evoked sensations in the missing limb, and each participant reported more than one sensation in different locations on the missing limb. However, we also found that the sensations evoked in the missing limb always co-occurred with sensations in the residual limb. Participants 1 and 2 reported simultaneous sensations in distinct areas of the residual and missing limb, whereas participant 3 reported contiguous sensations spanning the residual and missing limb. This may reflect a difference in the electrodes used in participants 1 and 2 versus participant 3 (that is, devices manufactured by Boston Scientific versus Abbott Laboratories), although the differences in electrode geometry were small (for example, lead diameters of 1.3 mm and 1.4 mm, respectively; a ~7% difference in electrode size) and there were not clear differences in the size of the percepts evoked in the foot. In a previous study that focused on people with upper-limb amputation, we observed similar coincidence of SCS-evoked sensations in the residual and missing limbs in only two out of four participants, and the sensations on the residual limb tended to be more focal in the arm than in the leg²¹. This difference may reflect anatomical differences between the cervical and lumbosacral regions of the spinal cord. Indeed, sensory neurons enter the cervical spinal cord at a shallow angle, nearly perpendicular to the rostrocaudal axis, whereas they travel parallel to the rostrocaudal axis for several spinal segments before entering the lumbosacral cord³¹. Accordingly, afferents that innervate multiple regions of the legs are more densely packed in the lumbosacral region than in the cervical region. Delivering charge in the epidural space using the large commercially available SCS electrodes likely recruits more sensory afferents in the lumbosacral cord, increasing the likelihood of activating neurons projecting from both missing and residual limbs. While there were small differences in detection threshold and JNDs within a participant for monopolar versus multipolar stimulation, there was not a clear improvement in focality when using multipolar configurations of electrodes. Moving forward, designing SCS leads with smaller and

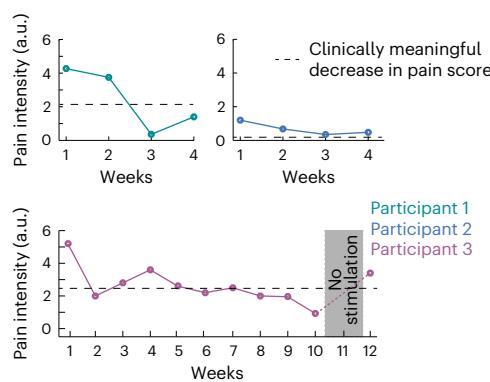


Fig. 6 | SCS reduces PLP. PLP intensity as reported weekly on a VAS for participants 1 and 2 (top row, implanted for 4 weeks) and participant 3 (bottom row, implanted for 12 weeks). The dashed line indicates a clinically meaningful decrease in the pain score. For participant 3, no experiments were conducted during week 11 (marked with a grey box).

more densely packed electrodes may allow us to achieve more selective stimulation and, consequently, more focal sensations in the missing limb. Future work should examine the relationship between the size of epidural SCS electrodes and the focality of stimulation to understand the trade-offs between electrode size, interelectrode spacing and the added complexity of tuning stimulation delivered by a device with higher channel count and a higher density of electrodes.

We also found that participants did not report sensations in the missing limb until the second or third week of the study. Throughout the study, participants attended testing sessions multiple times per week, and during the first 1–2 weeks, a majority of reported sensations were diffuse and limited to the residual limb. Following this period, participants consistently reported sensations in the missing limb. Other studies using peripheral nerve stimulation to evoke sensation in the missing foot have also reported that the incidence of sensations in the missing limb increases with time⁷. This delayed emergence of sensations in the missing foot stands in contrast to our previous study, in which participants frequently reported sensations in the missing upper limb during intraoperative testing of cervical SCS²¹. In future studies, functional imaging of the brain and spinal cord pre- and post-implantation could shed light on the possible reorganization of neural circuitry following amputation and sensory restoration^{32,33}. Understanding this reorganization may help guide future therapeutic development of systems to restore somatosensation.

We found that the magnitude of electrically evoked sensations can be systematically manipulated by modulating the stimulation amplitude, as has been previously reported across a variety of stimulation modalities and neural targets^{21,24}. JNDs ranged from around 0.05 to 0.3 mA across participants and leads (mean = 0.15 mA). The JNDs were independent of the reference amplitude (Extended Data Fig. 6), violating Weber's law, which states that the JND should be directly proportional to reference amplitude³⁴. This is similar to results reported for both peripheral nerve stimulation²⁴ and intracortical microstimulation³⁵. Together, these results suggest that approximately 20 discriminable steps can be achieved from threshold (typically less than 2 mA) to maximum amplitude (4–6 mA). The dynamic range of SCS-based tactile feedback is thus comparable to or wider than its counterparts in the peripheral nerve²⁴.

One of the goals of this study was to demonstrate that restored somatosensation could improve standing balance and gait stability. We found that SCS-evoked somatosensory feedback improved standing balance, particularly in the more challenging conditions (in which visual and somatosensory feedback were altered), consistent with previous results using peripheral nerve stimulation to restore sensation

in the foot¹¹. Furthermore, the stimulation-induced reduction of falls in the SOT constitutes a critical improvement in balance control. Note that these substantial and clinically meaningful improvements in balance were observed even though evoked sensations extended from the missing limb onto the residual limb. While evoking focal sensations in the missing limb is likely to further improve balance, our results suggest even non-focal sensations projecting from both the missing and the residual limbs may be sufficient to improve function.

During gait, we saw a clinically meaningful improvement in the FGA for participant 3. Notably, participant 3 had a lower baseline score than participant 2, allowing the possibility for greater improvements with stimulation. Because this clinical assessment serves as a relatively crude measure of dynamic balance control during ambulation, it may not be sensitive to changes with sensory feedback and, like many other clinical measures, is subject to ceiling effects. In addition, we have recently demonstrated that spatiotemporal analysis of level walking is insensitive to large differences in somatosensory ability across individuals with an amputation and is similarly unlikely to be able to reveal subtle improvements with restored sensation³⁶. These findings indicate that, while we see improvements with stimulation, we should identify more sensitive and more challenging outcome measures to detect improvements in function with restored somatosensory feedback. In addition, evaluating fall risk itself over a longer time period will be critical in future studies to demonstrate the clinical importance of restored somatosensation after amputation.

In addition to functional improvements, we also found evidence that stimulation reduced PLP. Participants 1 and 3 showed a clinically meaningful decrease in PLP during the week in which they first reported experiencing evoked sensations in the missing limb. This observation is similar to the gradual decrease in PLP reported in other studies with lower-limb amputees and suggests neuroplastic changes in the brain may follow evoked sensations in the missing limb⁹. Participant 3 also reported that PLP increased when testing was paused for a week. The recurrence of PLP aligns with anecdotal evidence from traditional SCS studies that report that the wash-in and wash-out period of SCS can be 3–7 days³⁷. Our observations build on growing evidence that somatosensory neuroprosthetic systems are associated with a decrease in PLP^{8,12–15}.

Several important limitations remain to be addressed in future studies. First, the participant pool in this study was small and heterogeneous, including two people with diabetic neuropathy and substantial mobility limitations and a third person with a traumatic amputation and a high degree of active mobility. Further, many of the experiments in the study were not blinded to either the participant or the investigators. It is possible that participants were motivated to better performance when they knew that we were delivering stimulation. However, the use of the sham stimulation in participant 2 suggests that providing sensory feedback in the residual limb was insufficient to improve balance, and instead sensation in the missing limb was important for improving postural stability. In addition, a blinded reviewer confirmed the improvements in FGA that occurred when SCS was used to provide sensory feedback. Still, future studies should use additional sham stimulation conditions (for example, tonic stimulation, sub-threshold stimulation, stimulation at incongruent time periods) and assessor blinding to further demonstrate efficacy of restored sensations for improving balance and gait. While we demonstrated initial feasibility of our approach, larger randomized controlled trials will be critical for demonstrating that SCS can improve function and reduce PLP after lower-limb amputation³⁸. Second, the intervention in this study involved a percutaneously implanted device tested over 29 or 90 days in a laboratory setting. Future studies should include a fully implanted system, including an implantable pulse generator wirelessly communicating with external sensors on the prosthesis, as well as long-term testing of performance in real-world settings. Third, the stimulation delivered during this study involved simple, constant frequency trains in which amplitude was modulated based on pressure

signals from an insole under the prosthetic foot. More complex trains of stimuli, such as biomimetic patterns that more closely match the naturalistic patterns of activity across the population of somatosensory afferents, may produce more naturalistic sensations, yielding greater functional gains and possibly stronger pain relief^{39–43}. While epidural SCS is unlikely to achieve the fibre-type selectivity that would likely be required to evoke fully naturalistic percepts, biomimetic patterns (for example, that include higher stimulation amplitude and/or frequency at the onset of ground contact with the foot) may produce more salient sensations that better convey differences in limb state than simple amplitude-modulated trains. Fourth, we administered the MPQ to measure PLP during laboratory sessions only. Several studies^{38,44–48} have shown that retrospective assessment of pain can yield significantly higher pain scores than diary assessment. Future studies should include a computerized diary or at-home questionnaire to assess changes in pain intensity, location, medications and activities that improved or intensified pain. In addition, we only report VAS PLP ratings for the time period during implantation and do not compare them to pre-implantation levels. Pre-implant MPQ scores were highly elevated for participants 1 and 3 (Extended Data Fig. 8), and we instructed participants to specifically report their PLP levels, but elevated pain in other regions of the body (for example, at the surgical incision site) could produce an associated elevation in perceived PLP during the first week after implantation and this could have affected our results. Future studies should include extensive pre-intervention assessment of PLP.

This study represents a step forward towards the clinical translation of somatosensory neuroprosthetics for people with lower-limb amputation. We demonstrated that SCS delivered via commercially available electrodes and implanted through a common clinical procedure could evoke sensations in the missing foot in people with transtibial amputation. Importantly, this includes two people with amputations related to diabetic peripheral neuropathy and associated distal somatosensory impairments. We also demonstrated in two participants that these sensations, when controlled by a wireless insole in the shoe, improved balance control and gait stability. Finally, we measured decreases in PLP in all three participants during their participation in the study. Building on these promising results, we believe that SCS may be a clinically viable approach to restore sensation and improve quality of life for people with transtibial amputation.

Methods

Participants

Three participants with transtibial amputation (Table 1) were recruited for this study. Two participants had diabetes and peripheral neuropathy associated with the amputations (Supplementary Table 1 and Extended Data Fig. 1), while one participant had a traumatic amputation. All participants were active users of a non-motorized prosthetic limb before beginning the study. The two participants with diabetes (participants 1 and 3) were limited-community ambulators, and the participant with traumatic amputation was an active ambulator (exceeding community ambulation skills, participant 2). All three participants reported normal or corrected-to-normal vision. The study was approved by the University of Pittsburgh Institutional Review Board, and the extended-duration implant in participant 3 was performed under an Investigational Device Exemption from the US Food and Drug Administration (FDA). Both studies (that is, 29 day and 90 day implant periods) are registered at ClinicalTrials.gov (NCT03027947 and NCT04547582). Participants provided informed consent before participation.

Inclusion/exclusion criteria

Participants 21–70 years old were included in the study if they had a unilateral transtibial amputation and were not excluded for partial amputation (for example, one or more toes) on the contralateral limb. Participants were at least 6 months post-amputation at the time of SCS lead implantation, with no serious co-morbidities that could increase

risk of participation. Women who were pregnant or breast feeding, people taking anticoagulant drugs and people with implanted metal not cleared for magnetic resonance imaging or implanted medical devices such as pacemakers, defibrillators and infusion pumps were excluded. Participants were also excluded from the 90 day implant study if they had a glycated haemoglobin level above 8.0 %, because of the increased infection risk associated with this condition.

Electrode implant

SCS leads were implanted percutaneously via a minimally invasive procedure, under local and/or twilight anaesthesia. Participants were in the prone position while leads were inserted into the dorsal epidural space using a 14-gauge 4-inch epidural Tuohy needle, and the leads were steered posterior laterally using a stylet under live fluoroscopic guidance. The connector from each lead was externalized so that we could connect it to an external stimulator. From the fluoroscopic images, we used the pedicles of each vertebra to mark the boundaries between spine levels²¹. These boundaries provided an anatomical marker to establish the rostrocaudal location of each electrode. In the thoracic and lumbosacral region of the spinal cord, the difference between the vertebral level and spinal cord level (that is, the level at which the nerve roots exit the spinal canal) is approximately three to four segments⁴⁹. As such, to target the L4–S1 spinal cord, the electrodes were typically placed near the T12–L2 spine. We performed intraoperative stimulation, and participants verbally reported the location of evoked sensations so we could iteratively adjust the placement of the leads to evoke sensations in the missing limb or as close to the end of the residual limb as possible.

In participant 1, two 16-contact leads (Infinion, Boston Scientific) were implanted near the T12–L2 vertebral levels, and a third 16-contact lead was inserted through the sacral hiatus to target the cauda equina. The third lead did not produce useful sensations in the missing limb, so this type of insertion was not repeated in subsequent participants. In participant 2, two 16-contact leads (Infinion, Boston Scientific) were inserted near the T12–L2 vertebral levels. Before enrolment of participant 3, we sought FDA approval of an investigational device exemption to allow for lead implantation for up to 90 days. For this portion of the study, we used leads manufactured by Abbott Laboratories. As such, in participant 3, three 8-contact leads (Octrode, Abbott Laboratories) were inserted near the T12–L2 levels. For participants 1 and 2, contacts were 1.3 mm in diameter and 3 mm long, with 1 mm inter-contact spacing. For participant 3, contacts were 1.4 mm in diameter and 3 mm long, with 3 mm inter-contact spacing. Lead migration was monitored by comparing intraoperative fluoroscopic images to weekly X-rays for the first 4 weeks and then bi-monthly X-rays for the following weeks for participant 3. In participant 1, leads were anchored with sutures to the superficial layers of skin at the exit sites, and all three leads showed substantial caudal migration across weeks during the implant. Therefore, to better stabilize the electrode placements, in participants 2 and 3 the leads were anchored to subcutaneous fascia via a small incision. With this anchoring procedure, we saw minimal lead migration across weeks. Participants attended testing sessions (typically 4–6 h per session) in our lab multiple days per week (average weekly testing days, 4 ± 0.8 , 4 ± 2.1 and 1.8 ± 1 , for participants 1, 2 and 3, respectively) for the duration of the implantation period, with the exception of a 1 week gap in testing for participant 3 at week 11. During these testing sessions, we mapped the location of percepts evoked by SCS; performed psychophysical experiments to characterize the threshold, JND, and intensity of evoked sensations; performed functional assessments of balance and gait; and measured PLP. At the end of the study, all leads were removed from the body using a procedure similar to implantation.

Stimulus pulse parameters and electrode configurations

Stimulation was delivered using a custom-built circuit board and three 32-channel stimulators (Nano 2+Stim; Ripple)²¹. Stimulus pulses were

always charge balanced, biphasic and rectangular with symmetric anodic and cathodic phases. Each phase was 200 µs in duration with a 60 µs interphase interval. Except where otherwise noted, all stimuli were monopolar with a transcutaneous patch electrode at the scapula used as the return. For participants 1 and 2, all monopolar stimuli were anodic-first. Due to a change in the software that controls our stimulator, which we identified after completing testing in participants 1 and 2, monopolar stimulation in participant 3 was cathodic-first. This change in polarity did not drive any obvious changes in the response to stimulation (for example, a change in threshold or the focality of evoked sensations), likely because of the biphasic symmetric shape of the stimulus waveforms.

For a subset of psychophysical experiments, we explored multipolar configurations of cathodes and anodes to determine whether there was any advantage in terms of the focality or psychophysical properties of evoked sensations. To select each of these multipolar configurations, we used a single primary electrode contact that evoked sensations in the missing limb or near the end of the residual limb and added one or more neighbouring contacts to serve as the return path. We tested multiple neighbouring return electrodes to find a combination that produced the most focal sensation in the missing limb. When more than one neighbouring return electrode was selected, current was evenly divided between them. The specific configurations of cathodes and anodes are described in relevant sections below.

Mapping evoked sensations

To map the location of evoked sensations, we delivered stimulation through each electrode contact using a 1-s-long pulse train. We stimulated with amplitudes from 0.5 to 6 mA and with frequencies from 1 to 1,000 Hz. After each stimulation train, the participant reported the location of the evoked sensation on the residual and/or missing portions of the limb as well as the quality of the sensation using our previously developed touchscreen interface⁵⁰. The quality of the sensation was described using a predefined list of descriptors developed specifically for characterizing sensations evoked by electrical stimulation²³, including mechanical, movement, tingle and temperature sensations. The presentation of stimulation trains through different electrodes and with different parameters was randomized, and the participant was blinded to these parameters. For analytical purposes, we grouped these descriptors as sensations that participants might experience commonly in their daily life (naturalistic) or rare, less familiar sensations (paresthetic). In total, 13 descriptors were used for naturalistic modalities (pulsing, pressure, touch, sharp, tap, urge to move, vibration, flutter, itch, tickle, prick, cool and warm), and 5 descriptors were used for paresthetic modalities (electric current, tingle, buzz, shock and numb).

Psychophysical analysis: detection threshold estimation

We used a two-alternative forced choice task in which the participants were presented with two visually cued 1-s-long blocks with a variable delay period: one with stimulation and one without stimulation, assigned randomly. The participants were instructed to select the block in which they felt a sensation. The stimulus amplitudes were centred around the rough detection threshold we observed from the mapping trials on that day. Overall, stimulus amplitudes ranged from 0.5 to 6 mA, and each amplitude was repeated 4–10 times. The stimulation frequency remained constant at 50 Hz for all trains. For each stimulus amplitude, we calculated the number of times the participant responded correctly (accuracy rate). For electrodes with densely sampled stimulation amplitudes (that differ by less than 0.1 mA), the values were re-binned with 0.1 mA steps, and the amplitudes that were in the same interval bin were replaced by their mean. A logistic curve constrained between 0.5 and 1 was fit to the accuracy rate for each participant and electrode, and the stimulus amplitude corresponding to 75% accuracy rate was selected as the detection threshold. Electrodes

with insufficient repetitions per condition (<5) or poor logistic fit (goodness of fit of the model is insignificant at 10%) were excluded from analysis. Overall, we tested two electrodes for participant 1, two electrodes for participant 2 and three electrodes for participant 3. One electrode each in participants 1 and 3 was used to deliver stimulation in a multipolar configuration. For the multipolar configuration in participant 1, the most rostral contact on one lead was the anode, and the third and fourth most rostral contacts on the same lead were the return path. In participant 3, the multipolar configuration included a single cathode with the neighbouring rostral contact on the same lead acting as the return path.

Psychophysical analysis: JNDs

We used a similar two-alternative forced choice task to determine the JND for the evoked sensations (that is, the minimum detectable change (MDC) in stimulation amplitude). On each trial, the participant was presented with two stimuli: (1) a standard, the amplitude of which was fixed within the set, and (2) a comparison, the value of which varied from trial to trial. The participant was asked to report which of the two stimuli felt more intense. Standard amplitudes across different sets ranged 1–3.5 mA for participant 1, 1.2–4.55 mA for participant 2 and 2–4.74 mA for participant 3. Comparison amplitudes ranged from 50% to 150% of the standard amplitude in that set. The frequency and pulse width of both standard and comparison stimuli remained constant (50 Hz, 0.2 ms). In each set, each stimulus pair was presented at least five times, and both the order of stimuli within the pair and the order of the pairs were varied pseudo randomly.

A logistic function was fit to the percentage of times the comparison interval was selected by the participant to obtain psychometric curves for each standard amplitude. Then, the JND was calculated as the change in amplitude that led to 75% accuracy according to the psychometric curve. We tested for 10 sessions from 1 electrode for participant 1, 14 sessions from 3 electrodes for participant 2 and 2 sessions from 2 electrodes for participant 3. One electrode in participant 3 was used to deliver stimulation in a multipolar configuration using the same configuration described above for the threshold detection experiment. Specifically, a single cathode was used with the neighbouring rostral contact on the same lead serving as the return path. Sets with poor psychometric fits (goodness of fit of the model is insignificant at 10%) were omitted from the analysis.

Psychophysical analysis: perceived stimulation intensity

To understand the relationship between the stimulus amplitude and the perceived intensity of the sensation, we conducted a magnitude estimation experiment. On each trial, a 1-s-long pulse train was delivered, and the participant was asked to state a number whose magnitude corresponded to the magnitude of the evoked sensation. Participants were instructed to use their own scale including decimals. If a stimulus was imperceptible, it was ascribed to the number 0. If one stimulus felt twice as intense as another, it was given a number that was twice as large. The tested amplitudes ranged from 0.5 to 6 mA and were restricted to amplitudes above detection threshold for each channel. The maximum amplitude delivered was below the pain/discomfort threshold for each participant. Each test amplitude was presented at least five times.

Ratings of sensation magnitude were normalized by the mean rating of their respective set, and linear regression was fit to the observed data for each channel separately. The residuals of regression models were tested for normality with Kolmogorov–Smirnov test to justify linear fit. We tested for 3 sessions from 1 electrode for participant 1, 11 sessions from 4 electrodes for participant 2, and 4 sessions from 3 electrodes for participant 3. One electrode each in participants 2 and 3 was used to deliver stimulation in a multipolar configuration. For the multipolar configuration in participant 2, the most caudal contact on one lead was the anode, and the neighbouring rostral contacts on the

same lead was the return path. In participant 3, the multipolar configuration included a single cathode with the neighbouring rostral contact on the same lead acting as the return path.

Closed-loop stimulation for functional tasks

To use these evoked sensations for real-time feedback in a functional task, such as gait or balance, data from wireless plantar pressure sensing insoles (Moticon Insole 3) was used to trigger stimulation of the spinal cord in real time. For participants 2 and 3, an electrode that evoked sensations in the missing limb (based on perceptual mapping experiments described above) was selected to provide real-time feedback of plantar pressure. We delivered biphasic, symmetric, charge-balanced monopolar pulses, with a transcutaneous patch electrode at the scapula as the stimulation return. In both participants, the evoked sensations were in the toes and metatarsals (Fig. 1). As participant 1 experienced substantial lead migration, we spent the majority of the implant duration mapping new locations of percepts and quantifying psychophysical parameters of those evoked percepts. Due to these time constraints, participant 1 did not participate in this portion of the study. For participants 2 and 3, plantar pressure above a minimum threshold triggered stimulation in the same region as the mapped sensation. Pressure was processed and encoded linearly using custom-built software in Python (v.2.7) and MATLAB (v.2019a). Participant 2 experienced sustained quadriceps contractions for stimuli above 2.5 mA. Because of the small range of stimulation amplitudes available between threshold and these contractions (2.25–2.5 mA), for participant 2 we utilized constant amplitude stimulation, in which stimulation turned on when insole pressure was above a threshold and turned off when below that threshold. For participant 3, plantar pressure linearly modulated stimulation amplitude; as she put more weight on her metatarsals, she felt a more intense sensation (Fig. 5a). Plantar pressure was normalized and scaled within the range of stimulation amplitudes (2–3 mA). Stimulation frequency (50 Hz for participant 2, 90 Hz for participant 3) and pulse width (200 µs for both participants) were kept constant, and stimulation amplitude was updated every 20 ms. Stimulation parameters were selected empirically for each participant based on perceptual mapping experiments with the goal of evoking comfortable and salient sensations in the missing limb.

Functional assessments

The SOT was used to determine changes in balance ability using the NeuroCom Equitest system (Fig. 4b). The SOT is a clinical measure of reliance on visual, vestibular and somatosensory systems for balance using six conditions in which either the surround or platform can sway. Three 20 s trials were completed per condition. The SOT was completed pre-implant without stimulation and repeated later with stimulation. Centre of pressure traces were recorded from the support surface at 100 Hz, filtered with a low-pass fourth-order Butterworth filter and analysed for biomechanical and clinical measures of posturography. Standard posturography measures were calculated, including excursion, sway velocity, 95% confidence interval ellipse of sway area, sample and approximate entropy⁵¹. The primary clinical outcome measure for each condition is the equilibrium score, a measure of the participant's ability to stay within a normative 12.5° of anteroposterior sway (Fig. 4b).

During walking, the FGA and kinematics of walking on a level surface were evaluated. The FGA is a ten-item test of dynamic balance, including challenging items such as walking with eyes closed, walking with a narrow base of support and walking backwards²⁸. Each item is scored by a trained physical therapist on a scale from 0 to 3 points, where 3 indicates no impairment and 0 indicates an inability to complete the task. Videos of the FGA for participant 3 were also assessed by an additional blinded expert reviewer (also a physical therapist) and showed excellent reliability. Gait kinematics were recorded with a 16-camera OptiTrack motion analysis system (Natural Point). Sixteen reflective markers were placed

on anatomical landmarks according to the OptiTrack 'Conventional Lower Body' model. Motion capture data were collected at 100 Hz and filtered using a fourth-order low-pass Butterworth filter at 12 Hz. Participants were instructed to walk at their self-selected speed across a 6 m walkway. For participant 2, 14 trials of walking without stimulation and with stimulation were analysed. For participant 3, 28 trials without stimulation and with stimulation were compared.

For clinical measures, published standards for clinically meaningful difference or MDC were used to compare baseline and stimulation trials^{52–54}. For biomechanical measures of gait, comparisons between outcomes were performed using permutation testing, a non-parametric method often used for smaller sample sizes⁵⁵. We completed 10,000 permutations of six 20 s plantar pressure traces for each condition at both baseline and with-stimulation groups to estimate the means of the underlying Gaussian distributions, and the difference in means of biomechanical data across trials was determined for each participant⁵⁶. The *P* value in permutation testing is the count of permutations in which the observed difference in means is above the actual difference in means. An α of 0.05 was used for all statistical analyses.

PLP

To quantify PLP, we asked the participants to report their current pain level on a VAS at the beginning of each testing day. The scale ranged from 0 to 10 where 0 indicated no pain and 10 indicated the worst pain imaginable. VAS scores were averaged over each week. Typically, a 50% decrease (and at least a 1-point decrease) in VAS score is considered clinically meaningful^{57,58}.

Participants also completed the MPQ once per week to describe their pain over the previous week. The MPQ is a multi-dimensional survey of the affective, evaluative and other experiences of pain and requires the participant to select from ranked lists of descriptor words (such as dull, sore, hurting, aching, heavy) about their pain. Participants also select a value ranging 0–5 to describe the intensity of their pain. The total score from this instrument is intended to reflect both the intensity and the disruptive nature of pain, and a 5-point decrease is considered clinically meaningful.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Source data for the figures in this study are available in the Data Archive for the Brain Initiative, with the identifier <https://doi.org/10.18120/8qby-hk82> (ref. 59). The raw and analysed datasets generated during the study are available for research purposes from the corresponding author on reasonable request.

Code availability

The custom code used to generate figures for this manuscript is available at https://github.com/pitt-rnel/NatureBME2023_SCSLowerLimb.

References

1. Sexton, A. T. & Fleming, L. L. Lower extremity amputations. In *Medical Management of the Surgical Patient: A Textbook of Perioperative Medicine* (eds Walker, H. K., Lubin, M. F., Spell, N. O., Smith, R. B. & Dodson, T. F.) 741–743 (Cambridge University Press, 2006).
2. Viseux, F. J. F. The sensory role of the sole of the foot: review and update on clinical perspectives. *Neurophysiol. Clin.* **50**, 55–68 (2020).
3. Petersen, B. A., Nanivadekar, A. C., Chandrasekaran, S. & Fisher, L. E. Phantom limb pain: peripheral neuromodulatory and neuroprosthetic approaches to treatment. *Muscle Nerve* **59**, 154–167 (2019).

4. Kuffler, D. P. Origins of phantom limb pain. *Mol. Neurobiol.* **55**, 60–69 (2018).
5. Valle, G. et al. Mechanisms of neuro-robotic prosthesis operation in leg amputees. *Sci. Adv.* **7**, eabd8354 (2021).
6. Petrini, F. M. et al. Enhancing functional abilities and cognitive integration of the lower limb prosthesis. *Sci. Transl. Med.* **11**, eaav8939 (2019).
7. Charkhkar, H. et al. High-density peripheral nerve cuffs restore natural sensation to individuals with lower-limb amputations. *J. Neural Eng.* **15**, 056002 (2018).
8. Petrini, F. M. et al. Sensory feedback restoration in leg amputees improves walking speed, metabolic cost and phantom pain. *Nat. Med.* **25**, 1356–1363 (2019).
9. Raspopovic, S. et al. Restoring natural sensory feedback in real-time bidirectional hand prostheses. *Sci. Transl. Med.* **6**, 222ra19–222ra19 (2014).
10. Dhillon, G. S. & Horch, K. W. Direct neural sensory feedback and control of a prosthetic arm. *IEEE Trans. Neural Syst. Rehabil. Eng.* **13**, 468–472 (2005).
11. Charkhkar, H., Christie, B. P. & Triolo, R. J. Sensory neuromodulation improves postural stability during Sensory Organization Test in lower-limb amputees. *Sci. Rep.* **10**, 1–13 (2020).
12. Ortiz-Catalan, M. et al. An osseointegrated human-machine gateway for long-term sensory feedback and motor control of artificial limbs. *Sci. Transl. Med.* **6**, 257re6–257re6 (2014).
13. Horch, K., Meek, S., Taylor, T. G. & Hutchinson, D. T. Object discrimination with an artificial hand using electrical stimulation of peripheral tactile and proprioceptive pathways with intrafascicular electrodes. *IEEE Trans. Neural Syst. Rehabil. Eng.* **19**, 483–489 (2011).
14. Tan, D. W. et al. A neural interface provides long-term stable natural touch perception. *Sci. Transl. Med.* **6**, 257ra138–257ra138 (2014).
15. Davis, T. S. et al. Restoring motor control and sensory feedback in people with upper extremity amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves. *J. Neural Eng.* **13**, 036001 (2016).
16. Marasco, P. D., Schultz, A. E. & Kuiken, T. A. Sensory capacity of reinnervated skin after redirection of amputated upper limb nerves to the chest. *Brain* **132**, 1441–1448 (2009).
17. Rossini, P. M. et al. Double nerve intraneuronal interface implant on a human amputee for robotic hand control. *Clin. Neurophysiol.* **121**, 777–783 (2010).
18. Dillingham, T. R., Pezzin, L. E. & MacKenzie, E. J. Limb amputation and limb deficiency: epidemiology and recent trends in the United States. *South. Med. J.* **95**, 875–883 (2002).
19. Kumar, K. & Rizvi, S. Historical and present state of neuromodulation in chronic pain. *Curr. Pain Headache Rep.* **18**, 387 (2014).
20. Fanciullo, G. J., Rose, R. J., Lunt, P. G., Whalen, P. K. & Ross, E. The state of implantable pain therapies in the United States: a nationwide survey of academic teaching programs. *Anesth. Analg.* **88**, 1311–1316 (1999).
21. Chandrasekaran, S. et al. Sensory restoration by epidural stimulation of the lateral spinal cord in upper-limb amputees. *Elife* **9**, 1–26 (2020).
22. Lee, M. W. L., McPhee, R. W. & Stringer, M. D. An evidence-based approach to human dermatomes. *Clin. Anat.* **21**, 363–373 (2008).
23. Kim, L. H., McLeod, R. S. & Kiss, Z. H. T. A new psychometric questionnaire for reporting of somatosensory percepts. *J. Neural Eng.* **15**, 13002 (2018).
24. Graczyk, E. L. et al. The neural basis of perceived intensity in natural and artificial touch (accepted). *Sci. Transl. Med.* **142**, 1–11 (2016).
25. Page, D. M. et al. Discriminability of multiple cutaneous and proprioceptive hand percepts evoked by intraneuronal stimulation with Utah slanted electrode arrays in human amputees. *J. Neuroeng. Rehabil.* **18**, 12 (2021).
26. Mastinu, E. et al. Grip control and motor coordination with implanted and surface electrodes while grasping with an osseointegrated prosthetic hand. *J. Neuroeng. Rehabil.* **16**, 49 (2019).
27. Fleshner, S. N. et al. Intracortical microstimulation of human somatosensory cortex. *Sci. Transl. Med.* **8**, 361ra141–361ra141 (2016).
28. Wrisley, D. M. & Kumar, N. A. Functional gait assessment: concurrent, discriminative, and predictive validity in community-dwelling older adults. *Phys. Ther.* **90**, 761–773 (2010).
29. Koehler-McNicholas, S. R., Danzl, L., Cataldo, A. Y. & Oddsson, L. I. E. Neuromodulation to improve gait and balance function using a sensory neuromodulation in people who report insensate feet—a randomized control cross-over study. *PLoS ONE* **14**, e0216212 (2019).
30. Melzack, R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* **1**, 277–299 (1975).
31. Cho, T. A. Spinal cord functional anatomy. *Contin. Lifelong Learn. Neurol.* **21**, 13–35 (2015).
32. Muret, D. & Makin, T. R. The homeostatic homunculus: rethinking deprivation-triggered reorganisation. *Curr. Opin. Neurobiol.* **67**, 115–122 (2021).
33. Selvarajah, D. et al. Structural and functional abnormalities of the primary somatosensory cortex in diabetic peripheral neuropathy: a multimodal MRI study. *Diabetes* **68**, 796–806 (2019).
34. Ekman, G. ös Weber's law and related functions. *J. Psychol.* **47**, 343–352 (1959).
35. Kim, S. et al. Behavioral assessment of sensitivity to intracortical microstimulation of primate somatosensory cortex. *Proc. Natl Acad. Sci. USA* **112**, 15202–15207 (2015).
36. Petersen, B., Sparto, P. J. & Fisher, L. E. Clinical measures of balance and gait cannot differentiate somatosensory impairments in people with lower-limb amputation. *Gait Posture* **99**, 104–110 (2023).
37. Jones, M. G. et al. Neuromodulation using ultra low frequency current waveform reversibly blocks axonal conduction and chronic pain. *Sci. Transl. Med.* **13**, eabg9890 (2021).
38. Lewandowski, A. S., Palermo, T. M., Kirchner, H. L. & Drotar, D. Comparing diary and retrospective reports of pain and activity restriction in children and adolescents with chronic pain conditions. *Clin. J. Pain* **25**, 299–306 (2009).
39. Saal, H. P. & Bensmaia, S. J. Biomimetic approaches to bionic touch through a peripheral nerve interface. *Neuropsychologia* **79**, 344–353 (2015).
40. Okorokova, E. V., He, Q. & Bensmaia, S. J. Biomimetic encoding model for restoring touch in bionic hands through a nerve interface. *J. Neural Eng.* **15**, 66033 (2018).
41. Valle, G. et al. Biomimetic intraneuronal sensory feedback enhances sensation naturalness, tactile sensitivity, and manual dexterity in a bidirectional prosthesis. *Neuron* **100**, 37–45.e7 (2018).
42. George, J. A. et al. Biomimetic sensory feedback through peripheral nerve stimulation improves dexterous use of a bionic hand. *Sci. Robot.* **4**, 1–12 (2019).
43. Sankar, S. et al. Texture discrimination with a soft biomimetic finger using a flexible neuromorphic tactile sensor array that provides sensory feedback. *Soft Robot.* **8**, 577–587 (2021).
44. Stone, A. A. & Broderick, J. E. Real-time data collection for pain: appraisal and current status. *Pain Med.* **8**, S85–S93 (2007).
45. Gwaltney, C. J., Shields, A. L. & Shiffman, S. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. *Value Health* **11**, 322–333 (2008).

46. Broderick, J. E. et al. The accuracy of pain and fatigue items across different reporting periods. *Pain* **139**, 146–157 (2008).
47. Garcia-Palacios, A. et al. Ecological momentary assessment for chronic pain in fibromyalgia using a smartphone: a randomized crossover study. *Eur. J. Pain* **18**, 862–872 (2014).
48. Teirlinck, C. H., Sonneveld, D. S., Bierma-Zeinstra, S. M. A. & Luijsterburg, P. A. J. Daily pain measurements and retrospective pain measurements in hip osteoarthritis patients with intermittent pain. *Arthritis Care Res.* **71**, 768–776 (2019).
49. Toossi, A. et al. Comparative neuroanatomy of the lumbosacral spinal cord of the rat, cat, pig, monkey, and human. *Sci. Rep.* **11**, 1955 (2021).
50. Nanivadekar, A., Chandrasekaran, S., Gaunt, R. & Fisher, L. RNEL PerceptMapper (2020). <https://doi.org/10.5281/ZENODO.3939658>
51. Prieto, T. E., Myklebust, J. B., Hoffmann, R. G., Lovett, E. G. & Myklebust, B. M. Measures of postural steadiness: differences between healthy young and elderly adults. *IEEE Trans. Biomed. Eng.* **43**, 956–966 (1996).
52. Cripps, A., Livingston, S. C. & DeSantis, B. M. The test-retest reliability and minimal detectable change of the Sensory Organization Test and Head-Shake Sensory Organization Test. *J. Sports Med. Allied Health Sci.* **2**, 2 (2016).
53. Wrisley, D. M., Marchetti, G. F., Kuharsky, D. K. & Whitney, S. L. Reliability, internal consistency, and validity of data obtained with the functional gait assessment. *Phys. Ther.* **84**, 906–918 (2004).
54. Beninato, M., Fernandes, A. & Plummer, L. S. Minimal clinically important difference of the functional gait assessment in older adults. *Phys. Ther.* **94**, 1594–1603 (2014).
55. Pesarin, F. & Salmaso, L. The permutation testing approach: a review. *Statistica* **70**, 481–509 (2010).
56. Powell, M. P. et al. Epidural stimulation of the cervical spinal cord for post-stroke upper-limb paresis. *Nat. Med.* **29**, 689–699 (2023).
57. Sdrulla, A. D., Guan, Y. & Raja, S. N. Spinal cord stimulation: clinical efficacy and potential mechanisms. *Pain Pract.* **18**, 1048–1067 (2018).
58. Forouzanfar, T., Weber, W. E. J., Kemler, M. & van Kleef, M. What is a meaningful pain reduction in patients with complex regional pain syndrome type 1? *Clin. J. Pain* **19**, 281–285 (2003).
59. Nanivadekar, A. C., et al. Dataset for 'Restoration of sensory feedback from the foot and reduction of phantom limb pain via closed-loop spinal cord stimulation.' Data Archive for the Brain Initiative (2023); <https://doi.org/10.18120/8qby-hk82>

Acknowledgements

We dedicate this work to our dear friend and colleague Sliman J. Bensmaia, without whose support, insight and passion for science and mentorship this project would not have been possible. We wish to thank P. Sparto for his assistance with the blinded review of functional outcome measures. All authors acknowledge support for the

research described in this study from the National Institutes of Health cooperative agreement UH3NS100541. B.A.P. acknowledges support for the research described in this study from National Institutes of Health training grant F30HD098794. B.B. acknowledges support for the research described in this study from Swiss National Science Foundation Doc.Mobility fellowship P1FRP3_188027.

Author contributions

L.E.F., D.J.W., S.J.B. and M.L.B. conceived the study and designed the research. A.C.N., R.B., B.A.P., D.S., T.J.M., B.B., J.F., A.N.D., I.L. and L.E.F. performed experiments. E.R.H. and V.J.M. performed implantation procedures. E.R.H., V.J.M., M.L.B. and I.L. managed medical care and oversight for the study. A.C.N., R.B., B.A.P. and E.V.O. performed data analysis. L.E.F., A.C.N., R.B., B.A.P., E.V.O., S.J.B. and M.C. wrote the manuscript with input from all authors. L.E.F. supervised the study.

Competing interests

The authors declare no competing interests.

Additional information

Extended data is available for this paper at <https://doi.org/10.1038/s41551-023-01153-8>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41551-023-01153-8>.

Correspondence and requests for materials should be addressed to Lee E. Fisher.

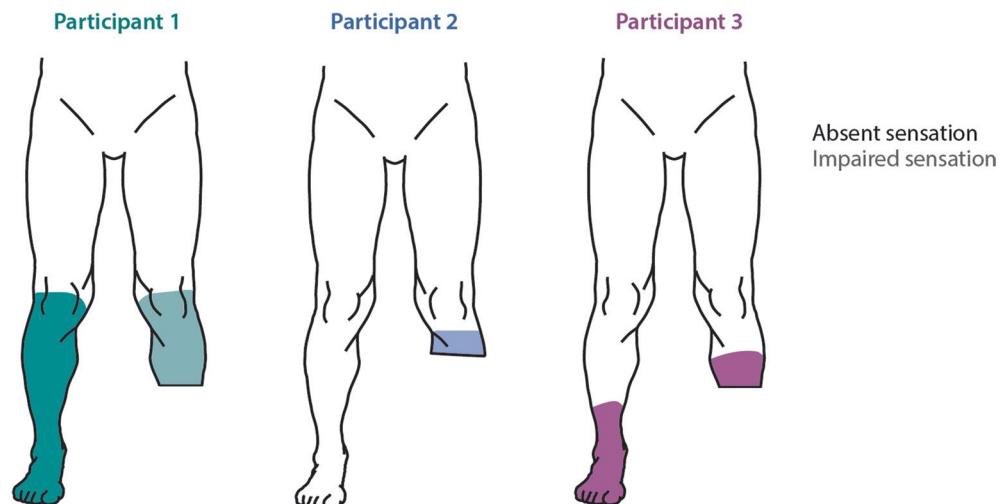
Peer review information *Nature Biomedical Engineering* thanks Rickard Bränemark, Troels S. Jensen, Winfried Mayr, Solomon Tesfaye and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

Reprints and permissions information is available at www.nature.com/reprints.

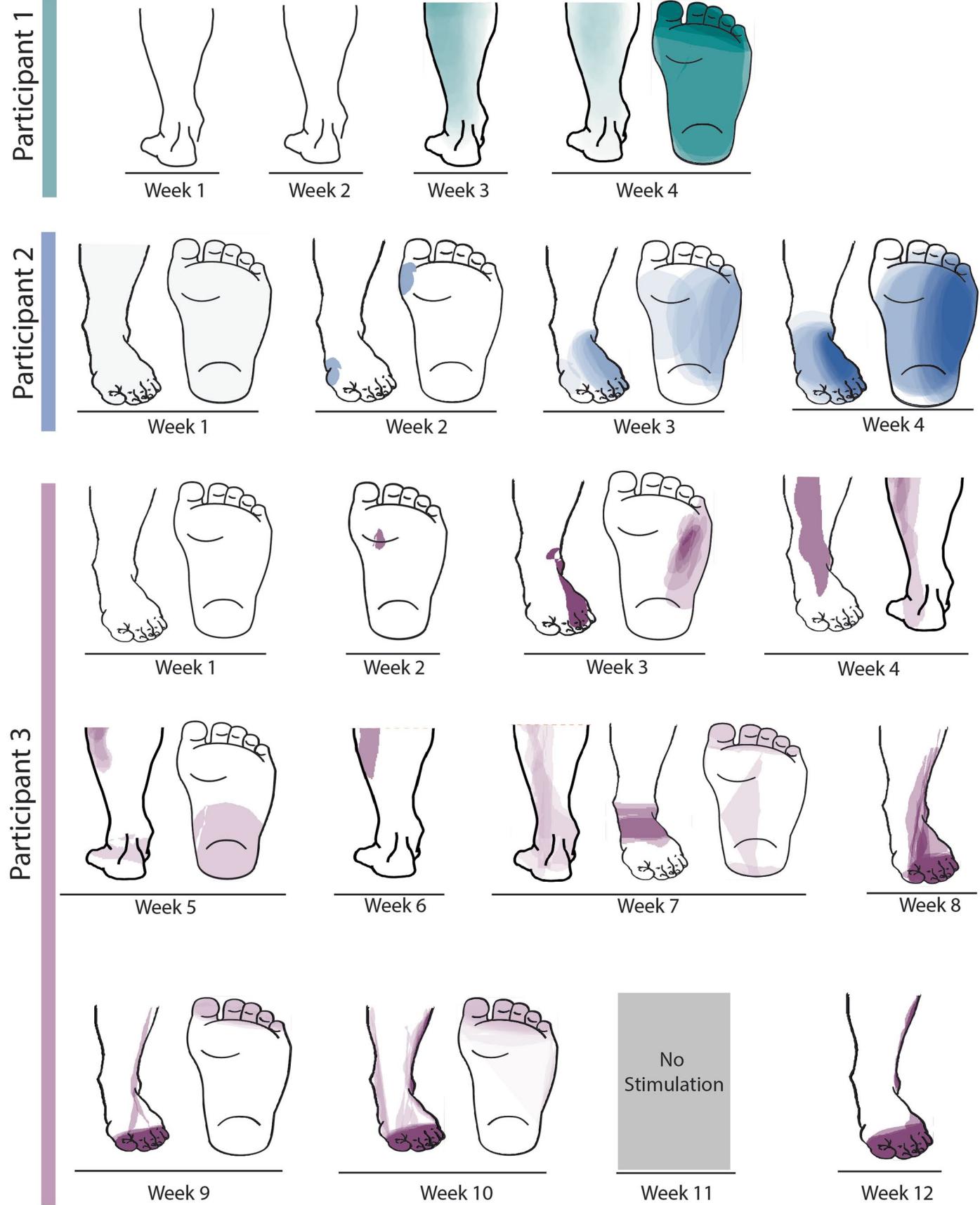
Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

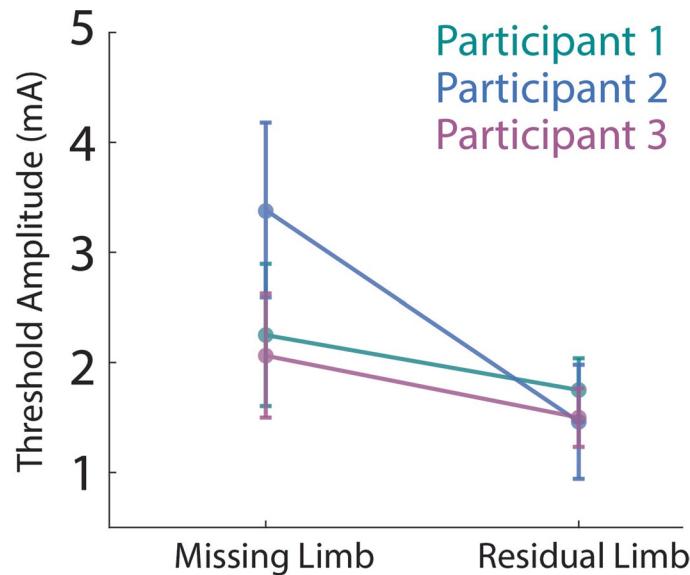
© The Author(s), under exclusive licence to Springer Nature Limited 2023, corrected publication 2023



Extended Data Fig. 1 | Sensory integrity and impairments for each participant. Shaded regions indicate areas with either impaired (light) or absent (dark) light touch sensation as determined by clinical neurological testing.

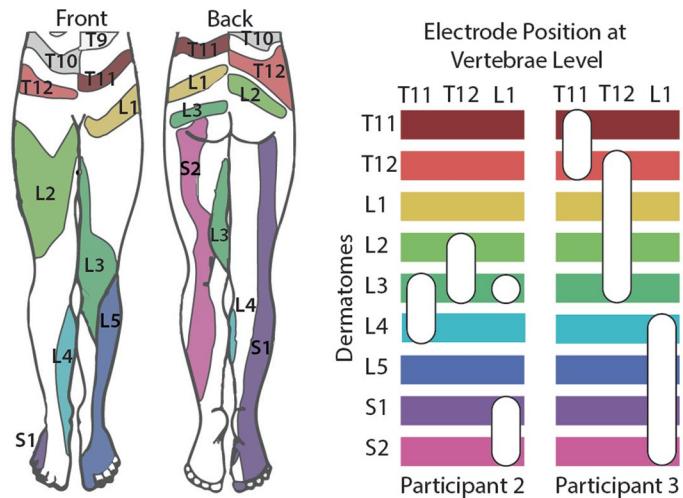


Extended Data Fig. 2 | Heatmaps showing the rate of occurrence of sensations in the missing limb across weeks. Darker shades indicate higher rate of occurrence of sensations in that location. No testing was done on week 11 for Participant 3.



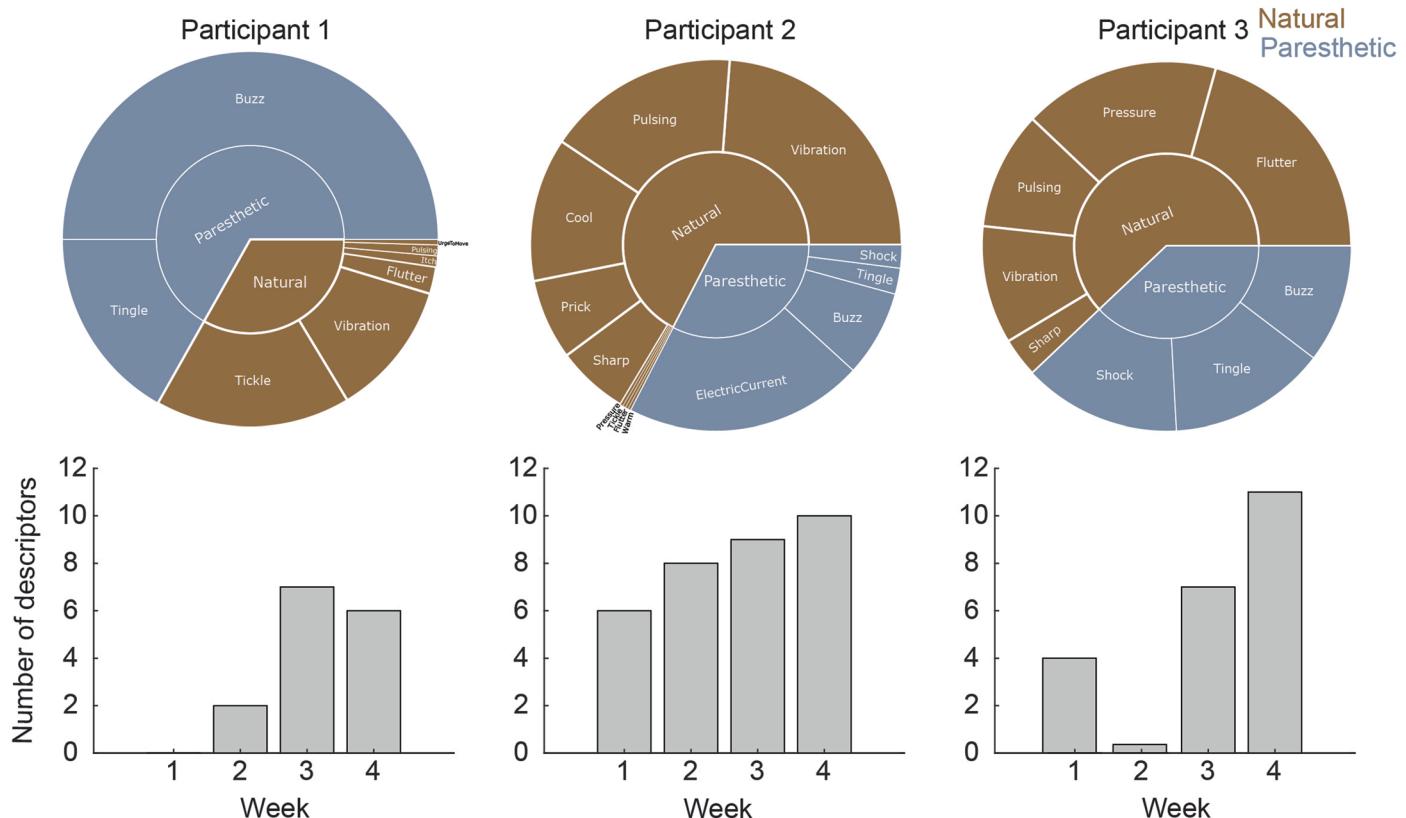
Extended Data Fig. 3 | Comparison of the threshold amplitude that evoked sensation in the missing limb (with co-activation in the residual limb) and the threshold amplitude that evoked sensation only in the residual limb. The threshold amplitude for each testing day was determined by increasing the

stimulation amplitude in 0.5 or 1 mA steps and asking the participants to report the location where they perceived the evoked sensation. Error bars show the mean \pm standard deviation across multiple days (N = 4 for Participant 1, N = 13 for Participant 2 and N = 8 for Participant 3).



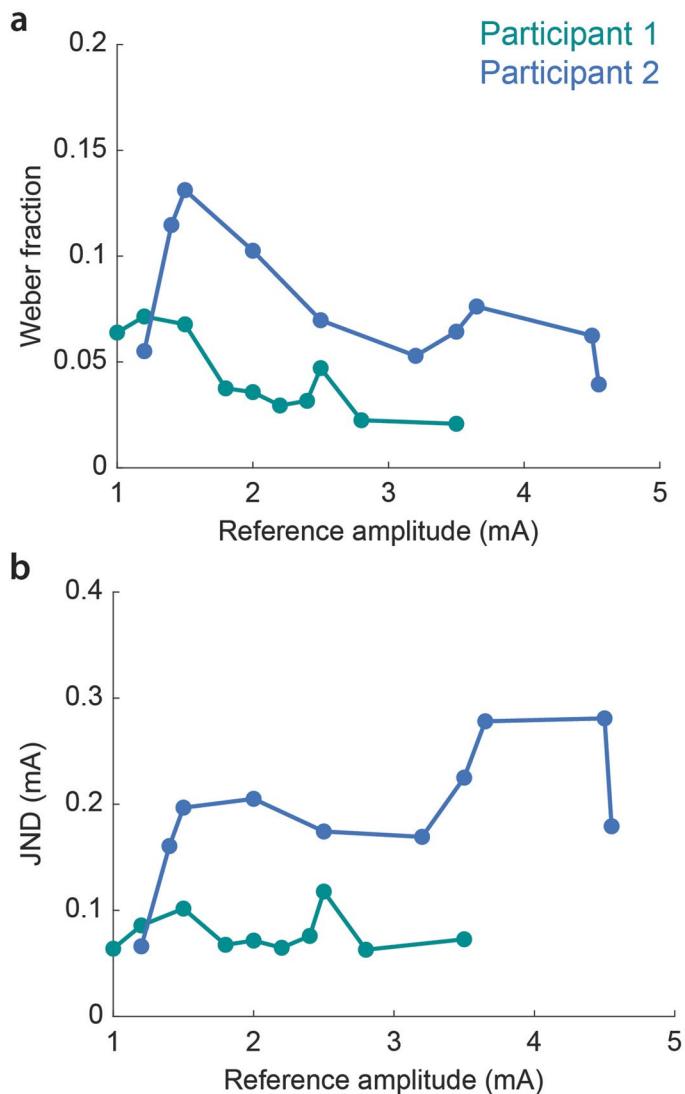
Extended Data Fig. 4 | Dermatomal activation by electrodes located at different vertebrae levels for Participant 2 and Participant 3. The left image shows the expected dermatomal innervation in the leg²². In the right, the horizontal bars indicate different dermatomes and the white ovals indicate the

approximate electrode position that evoked sensations in that dermatome with respect to the vertebrae level. Participant 1 had substantial lead migration across weeks, making it challenging to precisely define the location of the electrodes with respect to vertebrae levels, so we have not included those results.



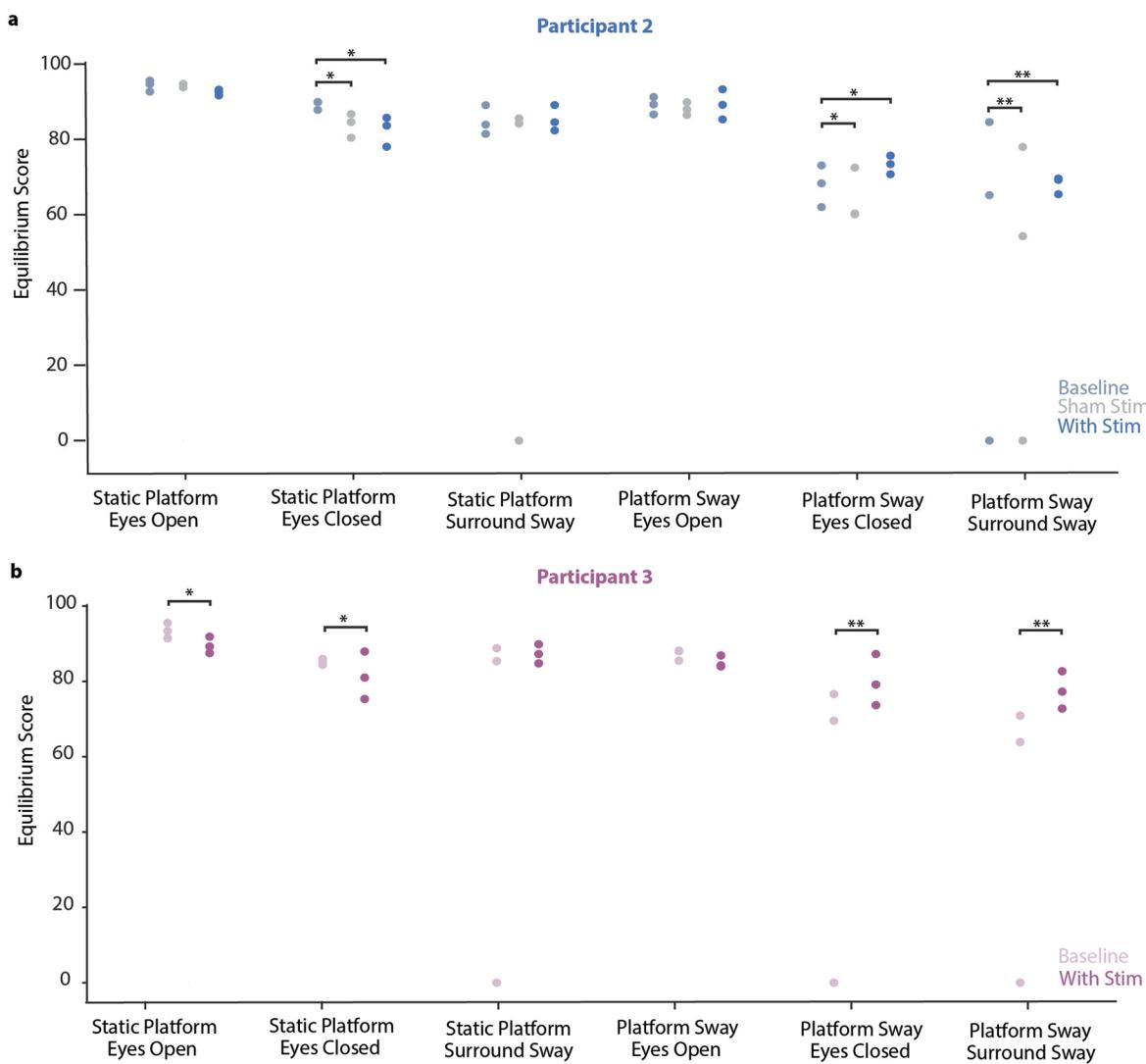
Extended Data Fig. 5 | Percept quality of evoked sensations in the missing limb. The participants were given a list of 13 natural descriptors and 5 paresthetic descriptors to describe the quality of the sensation. The top panel shows the frequency of each descriptor for the two evoked sensations for each participant

shown in Fig. 2a. For all reported sensations, we stimulated via each electrode with a 1-sec long pulse train. The bottom panel shows the total number of descriptors used to describe the sensations each week.



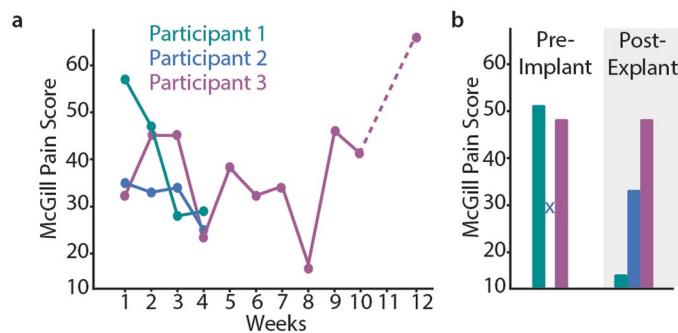
Extended Data Fig. 6 | Additional results from psychophysical discrimination assessment. **a**, Variation of Weber fraction for different electrodes in Participant 1 and 2 as a function of the reference amplitude in the discrimination task.

b, Variation of JND for the same electrodes in Participants 1 and 2 as a function of the reference amplitude. Participant 3 was discarded from these analyses due to insufficient data points.


Extended Data Fig. 7 | Full results of Sensory Organization Test (SOT).

a, Participant 2 performed the SOT without stimulation (light blue) with sham stimulation (that is, stimulation in the residual limb only, gray) and with stimulation (stimulation in the prosthetic foot, dark blue). Sham stimulation substantially decreased performance for three of six conditions (with greater than minimum detectable change [MDC, 3.98]), suggesting that stimulation on the residual limb alone was not sufficient to improve performance. **b**, Participant 3 performed the SOT without stimulation (light magenta) and with stimulation (dark magenta). Both Participant 2 and Participant 3 exhibited improved

performance on conditions with platform sway and eyes closed (+5.12 Participant 2, +9.60 Participant 3) and with visual surround sway (+4.04 Participant 2, +13.39 Participant 3). Both participants, however, exhibited decreased performance with stimulation during static standing with eyes closed (-6.25 Participant 2, -4.32 Participant 3). Additionally, Participant 3 had worse performance on static standing with eyes open with stimulation (-4.13). Change in median values reported. * represents a MDC, ** represents a clinically meaningful difference (>8.0).



Extended Data Fig. 8 | McGill Pain Questionnaire results. **a**, Weekly McGill Pain Questionnaire results. **b**, McGill Pain Questionnaire score before the implant and 1-month post-explant. The pre-implant score for Participant 2 was not recorded and we did not perform testing on week 11 for Participant 3 (indicated by the dashed line).

Reporting Summary

Nature Portfolio 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 Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the 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
- A statement on 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 statistical parameters 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

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection Custom computer code was written in Matlab 2019a and Python 2.7 and 3.5 to control the Ripple stimulator and to record data.

Data analysis Analyses were performed in Python 2.7 and 3.8. The analysis code for generating all figures in the manuscript is available at https://github.com/pitt-rnel/NatureBME2023_SCSLowerLimb

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Source data for the figures in this study are available in the Data Archive for the Brain Initiative, with the identifier <https://doi.org/10.18120/8qby-hk82> (ref. 59). The raw and analysed datasets generated during the study are available for research purposes from the corresponding author on reasonable request.

Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

Reporting on sex and gender	Gender data are reported in Table 1, although gender-based analyses were not performed because of the exploratory nature of this study.
Population characteristics	Age and diagnosis data are reported in Table 1 and Supplementary Table 1.
Recruitment	Participants were recruited via advertisements (for example, on buses), research registries, and direct outreach at clinics that treat people with amputation. Some aspects of this process may introduce selection bias because we primarily reached people that attend clinics for treatment or who would be inclined to participating in research activities. Additionally, because the study involves implantation of a medical device and participation in experiments multiple days each week, there may be a selection bias towards people more comfortable with surgical procedures or those that with fewer day-to-day commitments.
Ethics oversight	The study was approved by the University of Pittsburgh Institutional Review Board, and some procedures of the study were approved by the FDA. All participants provided informed consent before participating in any study procedures.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is 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/documents/nr-reporting-summary-flat.pdf

Life sciences study design

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

Sample size	This is a prospective open-label study in which the goal was to establish feasibility of improving function and reducing pain by restoring sensory feedback via spinal cord stimulation in people with transtibial amputation. As such, a sample size of 3 subjects was selected to establish feasibility. This sample size was chosen because not all study procedures were performed in all subjects, but a sample size of 3 ensures that all procedures (e.g., balance and gait testing) were performed in at least two subjects, demonstrating preliminary repeatability.
Data exclusions	No data were excluded from this study.
Replication	Experiments were repeated across multiple subjects. All three subjects participated in experiments to quantify the location, modality, and psychophysical properties of evoked sensations. Both Subjects 2 and 3 participated in experiments to quantify the effects of restored somatosensation on balance and gait. All three subjects participated in experiments to quantify changes in phantom limb pain over the duration of the study. All attempts at replication were successful. Because the study focuses on restoring sensation, it is not possible to blind subjects, but whenever possible, subjects were blinded to the type of stimulation and parameters that were used, and the order of testing of parameters was randomized. Also, for quantifying the effects of restored sensation on balance control, a sham condition (which only evoked a sensation in the residual limb) was tested in Subject 2.
Randomization	Randomization of samples was not relevant here because all subjects underwent the experimental intervention. Wherever possible, trial order was randomized to avoid order effects.
Blinding	Group allocation was not applied in this study, so for most experiments, investigators were not blinded. For evaluation of functional gait assessment in Subject 3, a blinded reviewer used videos of the task to confirm the reliability of results from an unblinded reviewer.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
<input checked="" type="checkbox"/>	Antibodies
<input checked="" type="checkbox"/>	Eukaryotic cell lines
<input checked="" type="checkbox"/>	Palaeontology and archaeology
<input checked="" type="checkbox"/>	Animals and other organisms
<input type="checkbox"/>	Clinical data
<input checked="" type="checkbox"/>	Dual use research of concern

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	ChIP-seq
<input checked="" type="checkbox"/>	Flow cytometry
<input checked="" type="checkbox"/>	MRI-based neuroimaging

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration NCT03027947 and NCT04547582

Study protocol The study protocols are described at clinicaltrials.gov (<https://clinicaltrials.gov/study/NCT03027947>; <https://clinicaltrials.gov/study/NCT04547582>).

Data collection All data were collected at the Rehab Neural Engineering Labs at the University of Pittsburgh between 2018 and 2021. Experiments were performed in a lab environment. Perceptual experiments (such as psychophysics) were typically performed in a small quiet room, whereas behavioural experiments (such as balance and gait testing) were performed in a larger gait laboratory with motion-capture equipment.

Outcomes The primary outcome measure for this study was pre-defined to focus on the location of evoked sensations, and on perceptual and neurophysiological thresholds. Primary outcomes were assessed via self-reporting (such as drawing on a picture of the leg) and through psychophysical assessments (for example, via two-alternative forced-choice tasks). Secondary outcome measures included effects on phantom limb pain and effects on prosthetic control with sensory feedback. Secondary outcome measures were assessed with validated clinical measures including a visual analog scale and a McGill Pain Questionnaire for pain and the Sensory Organization Test and Functional Gait Assessment for balance and gait.