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Lightening the perceived prosthesis weight with neural embodiment promoted by sensory feedback

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Summary

One of the main reasons why amputees report poor satisfaction with prostheses is their excessive weight perceived¹, despite the fact that it typically weighs less than half of the natural limb². Weight perception can be a subjective percept that is influenced by cognitive processes³⁻⁵. Even though recent developments in prosthetics have shown that sensory feedback restoration positively influences cognitive aspects (as embodiment of the device and cognitive load^{6,7}), the potential benefits on prostheses heaviness perception have never been investigated. In this study, we explored this matter using intraneural sensory feedback in a transfemoral (above-knee) amputee. We hypothesized that providing neural feedback would affect the integration of the prosthesis in the amputee's body schema, hence influencing the prosthesis weight perception. The results indicate that, after performing an over-ground walking task, the sensory feedback allowed a 23% decrease in prosthesis heaviness perception compared to the no feedback condition. Our hypothesis was confirmed by a significant increase in the embodiment of the prosthesis (by 60.5%) and confidence (by 36%) while walking with the sensory feedback. A subsequent dual-task (i.e. walking while spelling backwards) showed that the sensory feedback abolished the reduction of walking speed and accuracy observed during the no-feedback condition and normally seen with increased mental workload, suggesting a cognitive integration of the system. These results show the importance of providing a close-to-natural sensations from the missing limb, to allow a good integration of the prosthesis and increase the satisfaction of their users.

Keywords: Weight perception, Embodiment, Sensory Feedback, Intraneural, Prosthesis

Results

Undergoing a leg amputation has severe physical and psychological consequences⁸⁻¹⁰. Developing technological strategies is important for amputees to accept the new changed body and to adapt to the use of an artificial limb¹¹. Even if great strides have been made towards the optimization of prostheses functionality¹², one of the main complaints from

amputees remains its perceived weight ^{1,11}. Indeed, almost 70% of amputees perceive their prosthesis as uncomfortably heavy ¹, despite being about half-weight of a natural limb². In particular, transfemoral -compared to transtibial- amputees are significantly less satisfied with the weight of the artificial leg ¹¹.

Nevertheless, weight perception can be influenced by many factors ³, resulting in a combination of top-down (e.g., previous experience, expectations) and bottom-up processes (e.g., muscle contraction, feedback from peripheral receptors) ^{4,13} and it might be connected to the body schema of the subject ¹⁴⁻¹⁶.

On the relationship between peripheral and cognitive factors, from previous studies we know that weight perception is a complex phenomenon that arises from the combination of several factors: feedback from cutaneous mechanoreceptors ¹⁷, proprioceptive signals from muscular or tendinous mechanoreceptors or joint receptors¹⁸, sense of effort ¹⁹, vision ²⁰ and prior expectations³. Fleury et al. ²⁰ studied weight discrimination ability in a deafferented subject, finding that compensatory mechanisms (e.g., visual cues) can allow the subject to obtain results similar to healthy controls. Also, Gandevia and colleagues found that anesthetizing the thumb makes an object lifted by it feel heavier ²¹, highlighting peripheral factors role in heaviness perception. The subjective nature of weight perception, and the influence of higher cognitive processes on it ²², can be explained considering the size-weight illusion (SWI), where a small object is perceived heavier than an equally heavy bigger object ²³.

On the other side, plastic changes into an individual's body schema can drive changes in weight perception (e.g., incorporating a larger - vs smaller - hand results in objects feeling heavier) ¹⁴⁻¹⁶. This plasticity that allows us to incorporate tools into our body representation is a well-established mechanism ²⁴, important for prosthetic users. To this purpose, progress has been made towards the restoration of sensory feedback (SF), which has demonstrated to enhance the embodiment (i.e., ownership) of the prosthetic device ^{6,25}.

However, it is not clear yet whether providing a SF to amputees results in a lighter perception of the device. Indeed, the majority of the studies exploring weight perception focus on how heavy an external lifted object feels, rather than on how heavy feels a tool incorporated into the body schema (e.g., the prosthesis).

In this study, we explored the impact of intraneural SF restoration (Figure 1) on the perceived prosthesis heaviness in a transfemoral amputee (Table S1) and how this might be linked to the incorporation of the device into the body schema. We hypothesized that a higher level of integration and embodiment of a prosthesis would reduce the perceived heaviness of the artificial leg towards that of the healthy counterpart. The most distal portion of the residual tibial nerve was stimulated through implanted transversal intrafascicular multichannel electrodes (TIMes ⁷). The subject performed a motor task (over-ground walking at self-selected speed for 10 minutes) with and without the SF and then judged the heaviness of the prosthesis. After each motor task, we asked the subject to answer to an embodiment questionnaire ^{6,26,27} and to rate on a VAS scale his self-confidence⁷. During this Weight Perception (WP) task, we found that only after walking with SF the subject perceived the prosthesis as significantly lighter (Kruskal-Wallis test with Tukey-Kramer post-hoc test $p=0.003$), yielding a 23% reduction in weight perception compared to the no feedback condition. Interestingly and according to our hypothesis, both the embodiment (by 60.5%) and confidence (by 36%) of the subject were significantly higher after performing the motor task with SF.

To confirm that this finding was a result of a cognitive integration of the prosthesis, thus both functional and cognitive ²⁸, and to provide an objective measurement apart from the questionnaires, we designed a dual cognitive-motor task, the Mental Workload task (MW). During this task, the subject had to walk for five meters while spelling backwards several words. The dual nature of the task was chosen on purpose to differentiate how SF impacted on the cognitive integration. Changes in the motor performance (i.e. walking speed) or cognitive performance (i.e. spelling backward) of the amputee could provide insights on the level of integration of the SF. Indeed, according to the central capacity sharing model ²⁹, this type of task requires the ability to redistribute the cognitive and attentional resources between tasks performed simultaneously. Since walking with a prosthesis requires great attentional resources because of the lack of information from the foot-ground interaction, amputees have an additional cognitive burden during gait ³⁰. Artificial SF can provide some of the missing information. Therefore, a positive outcome in the secondary task could suggest a lower need of cognitive vigilance and attentional resources ³¹, thus indicating a cognitive integration of the system. We found that the subject significantly improved both his walking speed (NF Speed_{MW-ON}=1.17 ± 0.07 m/s; SF Speed_{MW-ON}=1.28 ± 0.07 m/s; Wilcoxon rank sum test, $p=0.005$) and his accuracy (Acc_{NF}=58%; Acc_{SF}=82%; Fisher's Exact Test $p=0.001$) while performing the dual task with the SF on compared to the no feedback condition.

Increments of electrical stimulation can be discriminated.

The sensation extent (i.e. the area where the stimulation was perceived) varied between minimum and maximum intensity reported, for every channel (Figure 2A), accordingly to the amount of charge injected. Furthermore, the sensation elicited from one channel never spatially overlapped with the ones evoked from the other channels. The electrode active sites selected for the sensory feedback elicited pressure-like and touch-like percepts in three locations referred on the phantom foot. The evoked percepts were close to the location of the pressure sensors (Figure 2A and 2B). Systematic changes in stimulation parameters yielded systematic changes in the perceived intensity of the elicited percepts, as shown by smooth psychometric functions (Figure 2C)^{32,33}. The JNDs (defined as the change in a stimulation parameter that yields 75% correct discrimination^{34,35}) are reported in Figure 2C.

To better compare discriminability across different stimulation conditions, we computed the Weber fraction³⁵. Smaller Weber fractions indicate a higher sensitivity of the subject (i.e. a higher sensitivity indicates that to perceive an increase of intensity, a smaller injected charge is needed). The Weber fractions were 0.055, 0.057 and 0.038 for the three stimulation channels.

Increasing stimulation input monotonically increases sensation intensity perception.

Achieving natural somatosensory feedback would require that the artificial sensation perceptions span a wide range of sensory intensities³⁶. To test the range of evoked sensations, the subject was asked to provide estimates of perceived intensity across the range of safe and comfortable stimulation parameters in a free magnitude scaling paradigm³⁵. All the stimulation channels showed a significant linear relationship with the stimulation parameter (the coefficient of correlation (R) was always >0.92 and p always <0.0001) (Figure 2D).

Intraneural sensory feedback reduces the perceived weight of a prosthesis.

We investigated with the WP task, whether the perception of the leg prosthesis would be altered after performing a motor task while providing or not a real-time SF. The motor task consisted of 10 minutes of over-ground walking, where the subject had to walk in a room with no obstacles in his preferred direction at a self-selected speed. Then, we added ankle weights to the healthy leg while the subject was sitting on a table with the below-knee part of the leg hanging down (Figure 3A). To judge the heaviness, the subject chose to lift first one limb and then the other one and rate which limb was perceived as heavier or if they were perceived as equal. The experimenter did not place any constraints upon the style, height, or time course of the lift: the subject was instructed to adopt the preferred strategy in a natural fashion as he would have done outside the laboratory³. Then, each answer was assigned to a number (1=healthy leg heavier, 2=equally heavy or 3=prosthesis heavier). We collected these data while the subject was sitting both before (PRE condition) and after 10 minutes of walking task without SF (POST-NF condition) and with SF (POST-SF condition) (Figure 3A).

First, we compared with a Kruskal Wallis test with Tukey-Kramer post-hoc test the participant answers in the different conditions (Figure 3B). The SF condition was statistically different both from the baseline measurement ($p=0.0005$) and from the NF condition ($p=0.0025$). Baseline and NF conditions were not statistically different ($p=0.89$).

Subsequently, we used the answers of the subject to calculate the mean for each of the three conditions at each of the six added weights. We used a psychometric function (logit) to fit the data with a linear method (fitting values in Table S2).

We did not find significant differences (for all comparisons $p > 0.4$) between PRE and POST-NF conditions (Figure 3C). Therefore, walking without SF did not provide any benefit on the heaviness perception of the prosthesis, since it yielded the same answers as for the baseline trials (PRE). Only for the POST-SF condition, three different weights showed a significant difference in their perception with respect to the PRE and POST-NF conditions: 1 kg ($p = 0.0159$, statistical power³⁷ 61%), 1.5 kg ($p < 0.0001$, statistical power 82%) and 2 kg ($p < 0.0001$, statistical power 72%). For these weights, the subject rated the prosthesis as being significantly lighter compared to the answers he gave during the PRE and POST-NF trials, suggesting a positive impact of SF on the weight perception. Indeed, the PSE for the POST-SF condition had a 0.48 Kg shift compared to the POST-NF (23% weight perception reduction). Furthermore, we found that the mean scores were significantly higher both for the embodiment ($Emb_{NF} = -1.2 \pm 0.39$, $Emb_{SF} = 2.43 \pm 0.54$; Friedman test $p=0.01$) (Figure 3G) and the confidence ($Conf_{NF} = -3.4 \pm 0.51$, $Conf_{SF} = 7 \pm 0.47$; Friedman test $p=0.01$) questionnaires (Figure 3H). This result strongly supports our initial hypothesis of a cognitive integration of the prosthesis in the subject's body schema.

Intraneural sensory feedback allows a cognitive integration of the prosthesis.

We performed a mental workload (MW) task to objectively investigate the integration of SF on the sensorimotor and cognitive levels. We first collected the walking speed without mental load (MW-OFF), without (NF) and with sensory feedback (SF). Subsequently, we collected the same parameter during the dual task (MW-ON), which consisted in walking and spelling backwards five-letter words (in the native language) asked by the experimenter, while both the accuracy (Acc) (i.e. the # correct / # wrong letters) and the gait speed (Speed) were recorded (Figure 3D).

To analyse outcomes, we performed an ANOVA on ranks with two factors (feedback and mental workload). This analysis showed a significant interaction ($F[1,1]=3.8$, $p=0.05$), while the main effect was significant only for the feedback ($F[1,1]=10.1$; $p=0.002$) and not for the mental workload ($F[1,1]=1.78$; $p=0.18$). Then, we proceeded with Wilcoxon rank-sum post-hoc comparisons between the different conditions.

In the NF condition, there was a significant decrease in speed ($p=0.03$, statistical power =86%) when the mental load was added ($\text{Speed}_{\text{MW-OFF}}=1.25 \pm 0.05$ m/s, $\text{Speed}_{\text{MW-ON}}=1.17 \pm 0.07$ m/s) (Figure 3E). This finding could indicate that the subject is spending some of his cognitive resources in walking and since he has no feedback his performance slightly decreases because of the addition of a cognitive burden. This decrement was absent ($p=0.85$) while performing the same task with SF ($\text{Speed}_{\text{MW-OFF}}=1.29 \pm 0.1$ m/s, $\text{Speed}_{\text{MW-ON}}=1.28 \pm 0.07$ m/s) (Figure 3E). Therefore, this result could indicate that even though the subject was cognitively more occupied with the mental task, SF may have allowed him to keep his speed constant. Furthermore, during the MW-ON condition, the subject had a significantly higher Speed ($p=0.005$, statistical power= 96%) with the SF ($\text{Speed}_{\text{MW-ON}}=1.28 \pm 0.07$ m/s) compared to NF ($\text{Speed}_{\text{MW-ON}}=1.17 \pm 0.07$ m/s). The comparison between SF ($\text{Speed}_{\text{MW-OFF}}=1.29 \pm 0.1$ m/s) and NF ($\text{Speed}_{\text{MW-OFF}}=1.25 \pm 0.05$ m/s) without mental workload did not show a statistical significance (Wilcoxon ranks sum test, $p=0.5$), which could be related to the fact that the motor task alone was not challenging enough to see a positive impact of the SF. Eventually, the results could have been related just to a different strategy adopted by the subject: higher speed at the expense of accuracy. Instead, he showed also a higher Acc score with SF, reaching 82% for SF versus 58% accuracy for NF (Fisher's Exact Test, $p=0.001$, statistical power 90%) (Figure 3E and 3F).

Discussion

In this study, we explored in a transfemoral amputee if using a prosthesis with intraneural sensory feedback could allow to perceive the heaviness of the prosthetic leg as more similar to the healthy counterpart and assessed if this could be connected to the cognitive integration of the artificial limb.

To achieve this, we first characterized the sensations elicited by our sensory feedback system. The subject perceived natural sensations (i.e. pressure and touch) on the phantom foot while walking. The characterization procedure (intensity estimation and JND) showed that subject was able to discriminate different levels of intensity delivered. This means that he was able to correctly differentiate between higher and lower forces exerted on the prosthetic foot, a primary feature in sensory-feedback neuroprosthesis³⁶.

After a detailed sensation characterization procedure, we conducted the first experiment, the weight perception task (WP). We hypothesized that the cognitive embodiment of a prosthesis with an artificial SF could allow to perceive the prosthesis as lighter. Our scientific hypothesis was driven by the fact that artificial SF has already shown to be useful for both motor and cognitive issues concerning prosthesis use^{6,7,31}. For instance, Petrini et al. showed that providing an intraneural SF decreased the number of falls and increased the walking speed⁶. From a cognitive point of view, SF allowed a lower mental load in a dual-task paradigm and enhanced confidence in the prosthesis⁷. Importantly, artificial SF showed to have benefits also on the prosthesis users subjective experience of the device. Indeed, evidence has suggested that cutaneous touch is strictly related to the sense of body self-identification^{26,38,39}. Similarly, several studies have reported an increased embodiment of the prosthetic device thanks to the addition of a neural SF^{6,40}.

In this study, we found that adding an intraneural SF allowed the perception of the prosthesis weight to become more similar to the healthy leg. Specifically, the subject reported a 23% reduction in the weight perception after performing tasks with the sensory feedback on. This decrease was absent in the no feedback condition. This substantial lightening of almost ¼ of the perceived heaviness is extremely noteworthy and strongly supports the implementation of SF in prosthetic

devices. A lighter perception of the prosthesis may lead to a higher acceptance and an increased use of the device. This is particularly important because previous studies have found that higher level of satisfaction and lower levels of body disturbance are positively correlated to higher levels of hourly use of the device ⁴¹. The reasons of our finding may be explained considering the results from the embodiment and confidence questionnaires. Indeed, the ratings of the subject confirmed that the intraneural sensory feedback allowed a higher confidence while performing a motor task and increased the embodiment of the artificial device. This suggests that sensory feedback impacted on the subjective experience of the prosthesis, allowing it to be perceived more as a natural limb, which could have been a consequence of the cognitive integration of the device ²⁸.

The second experiment, Mental Workload task (MW), allowed us to obtain an objective measure of the cognitive integration of the prosthesis. The amputee improved both his walking speed and his accuracy in this task. Also, the gait speed while adding the cognitive task, decreased only in the no feedback condition, while it remained constant for the SF condition. These findings can be interpreted as a good integration of the sensory feedback, which could be the reason of the findings in the WP task.

However, we have to consider that this was a single case study. Although the number of repetitions showed statistical reliability of our results, further studies recruiting a bigger pool of amputees in a randomized clinical trial are necessary to confirm our findings. Additionally, future studies should explore more in detail whether changing the type of stimulation, its intensity or the number of channels may lead to dose effects.

Taken collectively, the results of this study suggest the importance of an appropriate artificial neural sensory feedback to be added to a prosthesis to increase the satisfaction of its user. This should provide benefits both functionally and cognitively, and therefore induce the perception of the artificial limb heaviness to decrease. Importantly, since embodiment is a complex phenomenon and hard to be objectively quantified, we suggest considering the perceived weight as a global evidence of the human-machine integration. In conclusion, a full prosthesis integration in the amputees' body schema thanks to a natural sensory feedback, greatly supports the possibility of taking the experience of the artificial device closer to that of a natural limb.

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Author contributions

G.P. analyzed the data, performed statistical analyses, made the figures and wrote the paper; G.V performed the sensation characterization and the experiments, developed the software and the overall system integration, edited the figures and reviewed the paper; F.M.P. discussed results and reviewed the paper; S.R. designed the study, performed and supervised the experiments, managed the regulatory path and reviewed the paper. All authors had access to the relevant data. All the authors authorized submission of the manuscript, while the final submission decision was taken by the corresponding author.

Declaration of interest

S.R. and F.P. hold shares of "Sensars Neuroprosthetics Sarl", a start-up company dealing with commercialization of neurocontrolled artificial limbs. The other authors do not have anything to disclose. The authors declare no competing interest.

Figures

Figure 1. Intraneural sensory feedback system. Intraneural sensory feedback based on intraneural stimulation delivered by means of implantable electrodes. The system is composed by the following steps: (Step 1- Force sensing) the wearable sensors capture in real-time the force exerted by the subject under the prosthetic foot; (Step 2- Sensory encoding) then, the sensory encoding embedded in a microprocessor converts the acquired data in values to be sent to the electrical stimulator; finally, (Step 3) the train pulses are delivered through intraneural electrodes, evoking somatosensory perception (Step 4) on the phantom foot.

A INTRANEURAL MAPPING

B

Location	Sensation type
Central met	touch
Lateral met	pressure
Heel	pressure

C Just Noticeable Difference - JND

D Perceived intensity

Figure 2. Intraneurally-evoked sensations characterization. (A) Results of the sensory mapping procedure: locations of the evoked sensations as perceived and reported by the subject. Sensations are perceived on the phantom foot, and the location spread varies depending on the minimum and maximum intensity of the stimulation, as represented by a different color shading. (B) Types of evoked sensations for different stimulation channels. The sensation perceived is homologous (touch & pressure). (C) Results of the discriminatory procedure: probability to judge a stimulus higher than a reference, as a function of the intensity of the stimulation, separately for each channel. The point of subjective equality (PSE) is obtained as the stimulation intensity associated with a 50% performance. The just noticeable difference (JND) is obtained as the difference between the PSE and the intensity at a 75% performance. Data is presented as mean answer. (D) Results for the intensity estimation task: variations of the perceived level of the evoked sensations, depending on the stimulation intensity. In all cases there is a linear relationship ($p < 0.0001$) between the provided intensity and the perceived level. Data is presented as mean answer and SEM.

Figure 3. Weight perception (WP) and Mental Workload (MW) tasks. (A) WP experimental protocol: subject was sitting blindfolded on a table with the below-knee part of the leg hanging down without touching the floor. Ankle weights were added before (Weight measurement -PRE- i) and after (Weight measurement -POST- iii) the motor task (Motor task -10 min- ii). (B) Occurrence of the answers: prosthesis lighter (P<HL) in no opacity grey, healthy leg lighter (P>HL) in light opacity grey or equal (P=HL) in medium opacity grey (Kruskal Wallis test with Tukey Kramer post-hoc comparisons). (C) Plot shows the fitted curves for WP task of the mean weight perception ratings (Y-axis) for each added weight (X-axis). PRE mean answers for each weight are shown in medium opacity, POST-NF are shown in light opacity and POST-SF are shown without opacity. The gray horizontal line represents the point where the subject rated the prosthesis and the healthy limb as equally heavy. Vertical dashed lines report the point of subjective equality (PSE) for each condition. P=prosthesis; HL=healthy leg. See Table S2 for curve fitting values. (D) MW experimental protocol: the subject walked for 5 meters with SF or with NF, while not performing any mental task (MW-OFF) (upper row) or spelling backwards (lower row). (E) Velocity results. Bar plots of the mean speed in m/s (Y-axis) and standard deviations (SD) during NF (shaded blue) and SF (filled blue). Grey bars are the MW-OFF condition, and the coloured bars are the MW-ON condition. (F) Accuracy results. Bar plots of the percentage (%) of correct answers (y) and relative standard error of mean (SEM) for the MW-ON condition for NF (shaded blue) and SF (filled blue). (G) Embodiment results. Bar plots show mean answer and the standard deviations. (H) Confidence results. Bar plots show the mean answer and the standard deviations.

STAR METHODS

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to the Lead Contact, Stanisa Raspopovic (stanisa.raspopovic@hest.ethz.ch).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Subjects

One transfemoral amputee participated to this study (Table S1). The Subject was participating in an ongoing 90 days study of intraneural TIME implants (registered in ClinicalTrials.gov with the number NCT03350061). The Subject is a 35-years old male with a traumatic (car accident) amputation of the distal two-thirds of the right leg occurred in 2007. The subject was a proficient user of a prosthesis, classified in the K4 category following the 5-level functional classification system (MFCL) defined by the US Health Care Financing Administration's (HCFA) Common Procedure Coding System. The ethical commission of the Clinical Center of Serbia (num. 836) gave approval, and the Medicines and Medical Devices Agency of Serbia (ALIMS) gave legal permission. The subject read and signed the informed consent.

Surgery

The tibial branch of the sciatic nerve of the subject was implanted with 4 Transversal Intrafascicular Multichannel Electrode (TIMEs⁷). The tibial nerve conveys the majority of somatosensory innervation of the foot along with sensory-motor innervation of the leg. The implant of the intraneural electrodes was performed in an operating room under general anesthesia. The participant was implanted with five TIME-4H electrodes in the sciatic nerve. A small window was performed in the epineurium, where the surgeon inserted the electrode in order for it to transversally cross the nerve and allow direct contact of the active sites with the fascicles. Then, it was sutured thanks to its fixation tabs and a patch fascia was cut to raise a flap that was wrapped around the electrode cables. These cables were tunneled out up to the iliac crest, where they were transcutaneously connected with an external neurostimulator. To control that the impedance of the active site was <100kOhm, a contact check was performed at the end of the surgery. The surgical procedure lasted approximately 4 hours.

METHOD DETAILS

Inclusion and exclusion criteria

The patient fulfilled the inclusion and exclusion criteria for the study. Specifically, the inclusion criteria were: uni-lateral transfemoral amputation above the knee level; the stump of the subject should have healed; the subject should otherwise be healthy and able to carry out the experiment; presence of phantom limb pain (chronic and stable, other treatments for pain tried with poor results, pain level >6 on a VAS scale). The exclusion criteria were: cognitive impairment; pregnancy; prior or current psychological diseases such as borderline, schizophrenia, depression or maniodepression; acquired brain injury with residual impairment; prior neurological or musculoskeletal diseases; history of or active substance abuse disorder; excessive sensitivity to electrical stimulation; fear for electrical stimulation.

Sensorized insole and force-acquisition system

The sensors used in the insole were the FlexiForce A301 (Tekscan Inc., United States), with a resolution of approximately 0.005Kg for each sensor; this range was chosen to obtain a good dynamic range for a pressure exerted over a 1 cm² area (the active size of a sensor) for subjects weighting a maximum of 100 Kg. The space configuration of the sensors followed

a distribution of force pressures during gait and is the same already used in ⁶ and ⁷. The ADC used had a 12-bit data resolution.

Prosthesis leg with intraneural sensory feedback

The prosthesis was composed of commercially available components provided by Össur hf: a custom made transfemoral flexible brim socket fitted to an Iceross Seal-In X5 TF silicon liner, Pro-Flex XC prosthetic foot component and a RHEO KNEE XC. The weight of the prosthesis amounts to 2.28 kg (1.61 kg for the knee and 0.670 kg for the foot). A sensorized insole, purposely developed for this neuroprosthesis, was placed under the prosthetic foot. An external controller (implemented on Raspberry pi 3, Raspberry Pi Foundation, UK) was wired through SPI to the external stimulator and communicated via Bluetooth with both the sensorized insole and the RHEO KNEE XC. This portable processor managed the acquisition and recording of sensor readouts and the encoding algorithm transducing it into stimulation parameters needed for driving the neural stimulator (STIMEP, Axonic, and University of Montpellier). The execution of the code for acquisition, recording and encoding lasted less than 50 ms. Sensors and active sites were coupled (Figure 1) following the results of the sensation characterization procedure (Figure 2). The readouts of three insole sensors were used to drive the intraneural stimulation of three active sites on the intraneural electrodes. The electrode active sites selected for the neuroprosthetic insole elicited a sensation of touch or pressure in a position of the phantom foot that minimized the distance with the position where the insole sensors were placed (Figure 2A): one sensor placed in the central metatarsus area related to a sensation in the central metatarsus, one to the lateral metatarsus and one to the heel area. Due to the redundancy of active sites of TIME electrodes, the stimulation channels with the lowest minimum charge (required to evoke a perception), were selected.

The amplitude of the train of pulses was modulated following the linear relationship described below:

$$\begin{aligned} I &= (I_{max} - I_{min}) * (s - s_0) / (s_{max} - s_0) + I_{min}, & \text{when } s_0 \leq s \leq s_{max}; & (1) \\ I &= 0, & \text{when } s < s_0; & (2) \\ I &= I_{max}, & \text{when } s > s_{max}; & (3) \end{aligned}$$

where: I is the amplitude of the pulses of current, s is the readout of sensors; s_0 and s_{max} represent for the insole sensors the minimum and maximum load recorded when the subject was walking on a flat rigid surface; I_{min} and I_{max} are the current pulse amplitudes that evoked, respectively, the minimum and below pain threshold sensations that were determined during the sensation characterization procedure. The frequency of the stimulation was 50 Hz as in previous literature^{6,7,34}.

Sensation characterization procedure

For each channel the following characterization procedures were performed: *sensory mapping*, *intensity discrimination* and *intensity estimation*, as previously done for upper-limb sensory feedback³⁵.

The stimulation was composed by trains of biphasic balanced pulses at a fixed frequency (50Hz)⁶ and current pulse-width previously found during the initial calibration: 60 μ s for the frontal electrodes, 60 μ s for the laterals and 80 μ s for the back ones. The following tasks were automatized using a custom-made graphical software developed in Matlab 2016b to control the neural stimulator and to record the subject's answers.

Sensory mapping

Trains lasting one second and separated by one second were generated. The subject was blinded to the intensity values and was instructed to report whenever he felt a perception. The single pulse amplitude was varied between 10 μ A and 980 μ A (steps of 10 μ A), while duration was set between 10 μ s and 120 μ s (according to the active site), and pulse frequency to 50 Hz. In particular, we first set the pulse width at minimal value (e.g. 10 μ s) and increased the stimulation amplitude in order to find the perceptual thresholds (from 10 μ A to 980 μ A). If the perceptual threshold was not found, we repeated the procedure with a higher pulse width.

Once a sensation was reported, we repeated the amplitude ramp with the same pulse-width for five times. The perceptual threshold was the average of the charges at which the minimum sensation was reported by the subject. Once perceptual threshold was reached, the stimulation was paused, and the subject was asked to report the location, extent and intensity of the evoked sensation. After the description, the stimulation was started again and increased using the same steps and timings as before. The subject was instructed to report at which point he felt the maximum intensity (below uncomfortable level); the subject was then asked to report location, extent and intensity of the evoked sensation again. Location and extent were indicated on a picture of a foot, shown by the graphical user interface of our software. The type of the sensation was described by the subject and recorded through the software.

At the end of the sensation characterization procedure, we found all the charges necessary to reach the perceptual thresholds and the maximum values for each active site.

Intensity discrimination

During the task, couples of stimuli were provided (constant stimuli method³²): one was always the same (reference) and the other could be either of the same intensity, lower, or higher. For each couple, the subject had to indicate which one of the two stimuli was perceived as more intense. The two stimuli were separated by one second and lasted one second, and the reference was chosen as the midpoint between the minimum and maximum pulse-width or amplitude previously found during the sensory mapping. The reference points were: 780 μ A for the hindfoot, 780 μ A for the midfoot, and 680 μ A for

the forefoot channel. From these reference values, the range of stimulation was calculated as their 125% *for the maximum value* and 75% *for the minimum value* (adapted from ^{35,42}). In this range, the value compared to the reference was either equal or picked between 10 equally spaced values (five lower and five higher with respect to the midpoint). Both the intra-couple stimuli order and the couples' order was pseudorandomized, and the subject was blinded to the intensities. Each of the 11 generated couples was presented five times, for a total of 55 repetitions for each channel.

The resulting points were used to fit the psychometric curve with a general linear model. For each channel, using the obtained psychometric curve, we calculated the point of subjective equality (PSE) corresponding to the stimulus intensity associated with a performance of 50%; the just-noticeable difference (JND) was calculated as the distance between the intensity that resulted in a performance of 75% and the PSE ^{35,42}.

Intensity estimation task

During the intensity estimation task, a series of 21 incremental stimuli were presented. Every stimulus lasted 1.5 seconds, and between each train there was a pause of 1 second. The pulse-width or amplitude of the stimulation was incremented of a fixed step each time, calculated to have equally spaced values between the previously obtained average minimum and maximum. The subject was instructed to report, first as soon as he perceived something in order to define the starting point of the amplitude ramp (perceptual threshold), and then each time he felt an increase in the intensity. In this case, the subject had to report a number between 1 and 10 whose magnitude corresponded to the magnitude of the evoked sensation. If an increment was imperceptible, the same numerical value of the previous one was registered. The subject was encouraged to be precise and to use decimals as needed. This task was repeated five times for each channel, for a total of 105 stimulations for each channel. It's worth noting that the exploited method adopted a monotonical increase of the electrical stimuli. Other magnitude estimation experiments could consider a randomized order presentation of the stimuli.

Experiment 1: Weight perception task

The weight perception task (WP) was performed over the same week in which the subject performed the mental workload (WM) task. The subject was asked to sit on an elevated surface with his thigh almost completely leaning on it and the below-knee part of the leg hanging down, without touching the floor with the feet (Figure 3A). During the experiment, he was blindfolded in order to remove any visual bias. While he was sitting, an ankle weight (York Fitness, UK) was placed on his healthy leg, and he was asked to rate which limb was perceived as heavier. These weights were decided based on the subjective perception of the prosthesis weight before the beginning of the experiment: we evaluated what was the point of subjective equality (PSE), hence the weight necessary to be added to the healthy leg in order for him to perceive the legs as equally heavy. The resulting PSE was 2 Kg. After assessing this, we evaluated the weight perception during the experiment adding 6 different weights (equally spaced by 0.5 Kg) on the healthy leg that ranged from -1 kg to +2.5 kg from the PSE. Therefore, during the experiment the subject was asked to rate which leg he felt as heavier after adding a weight to the healthy limb that ranged from 1 Kg to 3.5 Kg. The answers of the subject were collected at baseline (PRE) and after a 10 minutes over-ground walking task performed with (POST-SF) or without (POST-NF) sensory feedback (performed in a random order). After each motor task, the subject was asked to answer to an embodiment questionnaire^{26,27} (the same one used in ⁶ without the vividness and prevalence questions) and to a 10 cm VAS scale measuring his confidence during the motor task. The weight data was acquired in 3 sessions. During each session, the subject performed the trials in a random order between SF and NF. The trials consisted in measuring the weight perception at baseline condition (PRE), then performing the motor task and finally measuring the weight perception after the task with (POST-SF) or without (POST-NF) sensory feedback. Between each trial the subject rested for 15 minutes, in order for him not to be fatigued, stressed or still influenced by the previous trial. In total, in each session and for every condition, we performed 180 weight measurements (each of the 6 ankle weights was added 10 times per session for each of the 3 conditions). Hence, since we performed 3 sessions, we obtained in total 540 measurements.

Experiment 2: Mental Workload task

The mental workload task (MW) was performed over a period of one week. First, the subject was walking forward for 5 meters (MW-OFF) while timing him for 20 times (in total 10 times with feedback (SF) and 10 times without feedback (NF) performed in a random order). Subsequently, he was asked to walk for the same distance while performing a dual task (MW-ON). He had to spell backwards in his mother-tongue language a five-letter word, which had not been previously presented (Figure 3C). Also this task was performed 20 times (in total 10 times with feedback (SF) and 10 times without feedback (NF) performed in a random order). While the subject was performing the MW condition, both the walking speed and the accuracy of the spelling (%) were recorded.

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistics

The data was collected and analyzed using Matlab (R2016b, The Mathworks, Natick, MA, USA) and R software version 3.5.1. In Figure 2B, we calculated the proportion of trials in which the subject evaluated the comparison stimulus to be stronger than the standard for each stimulation channel, thus varied as a function of the physical difference between standard and comparison stimuli. This probability distribution of discrimination responses is modeled mathematically as

a function of the physical difference between standard and comparison stimuli, the so-called psychometric function. The parameters that define the shape of the psychometric function characterize perceptual performance, i.e., the difference in stimulation charge necessary for the subject to reliably discriminate two stimulation intensities. Perceptual discrimination performance is modeled by fitting a cumulative Gaussian function with two free parameters (midpoint m and standard deviation s) to the responses of the 2AFC *intensity discrimination task*. A cumulative Gaussian function describing an ‘S’-shape (Figure 2C) results from summing up (integrating) the values of a bell-shaped Gaussian function. The s parameter of the psychometric function corresponds to the distance x between the points of the psychometric function at which 0.5 (PSE) and 0.75 (JND) correct responses are reached. N ($=55$) refers to the number of repetitions for each channel (each of the 11 couples of stimuli was presented 5 times).

In Figure 2D, N ($=105$) refers to the total number of times the subject was presented with a stimulus (21 stimuli repeated for 5 times) and the data is presented as mean answer and SEM.

For the Mental Workload task, we recorded the time for each walking trial and then we calculated the velocities. We also kept track of how many correct/wrong letters the subject said. We calculated and reported the standard deviation (SD) of our distributions using bar plots (Figure 3E). The accuracy data is expressed in mean percentages and the standard error of the mean (SEM) in bar plots (Figure 3F).

Statistical analyses were also performed in Matlab R2016 (Mathworks) using the built-in functions and R software version 3.5.1. To test whether the collected data were normally distributed a one-sample Kolmogorov-Smirnov test was used. Since none of the datasets passed the test, we continued the statistical analyses using non-parametric tests. We performed the following statistical tests:

- Experiment 1: for the interaction between feedback and mental workload we performed an ANOVA on ranks (Figure 3B). N ($=180$) refers to the total measurements performed for each of the three conditions (PRE, POST-NF, POST-SF).
- Experiment 1: for the weight perception task, we compared the answers for the PRE, POST-NF and POST-SF conditions at each added weight point (i.e., one p-value resulted from the comparison of the answers for PRE, POST-NF and POST-SF for the 1 kg condition) using a Kruskal-Wallis (Figure 3C). N ($=180$) refers to the total measurements performed for each of the three conditions (PRE, POST-NF, POST-SF).
- Experiment 1: after performing the multiple groups comparison with the Kruskal-Wallis we applied a multi group Tukey-Kramer correction to specify which pair of groups were statistically different (with $\alpha=0.05$) (Figure 3C).
- Experiment 2: for the gait velocity between WM-ON and WM-OFF in NF and SF a Wilcoxon rank sum was used (Figure 3E). N ($=40$) refers to the total measurements performed for each of the SF and NF conditions.
- Experiment 2: for the answers’ accuracy in the dual task between NF and SF, we used a Fisher’s exact test (Figure 3F). N ($=20$) refers to the total measurements performed for each of the SF and NF conditions.
- Experiment 2: for the embodiment and confidence answers between NF and SF, we used a Friedman test (Figure 3G and 3H). N ($=20$) refers to the total measurements performed for each of the SF and NF conditions.

Levels that were found to have a statistical difference with $\alpha = 0.05$ and $p < 0.05$ were marked with an asterisk reported on the plots. For all the $p < 0.05$ we also performed post-hoc statistical power analysis using G*Power³⁷. We kept α err prob = 0.05, calculated the effect size through the built-in function of the tool (inserting means, standard deviations and correlation of our samples) and used the two-tail option. Subsequently, we performed in G*Power the corresponding statistical test used for the calculation of the p-value.

ADDITIONAL RESOURCES

The study was conducted as part of the clinical trial NCT03350061 (www.clinicaltrials.gov).

Supplemental Information

	Gender	Age	Amputation level and side	Amputation cause	Year of amputation	Prosthesis
Subject 1	M	35	Distal two-thirds of the right leg (transfemoral)	Trauma	2007	Össur RHEO KNEE XC and Össur PRO-FLEX XC foot

Table S1. Participant demographics. Related to STAR Methods.

Condition	SSE	r^2	RMSE
PRE	0.05	0.92	0.11
POST-NF	0.008	0.98	0.04
POST-SE	0.05	0.91	0.11

Table S2. Curve fitting values related to weight perception task answers. Related to Figure 3C.

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