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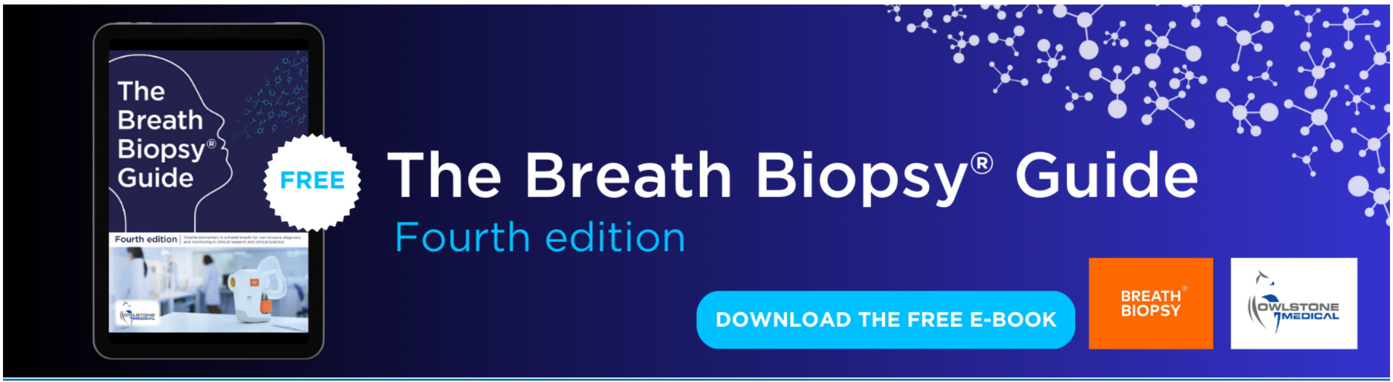

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High-density peripheral nerve cuffs restore natural sensation to individuals with lower-limb amputations

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Abstract

Objective. Sensory input in lower-limb amputees is critically important to maintaining balance, preventing falls, negotiating uneven terrain, responding to unexpected perturbations, and developing the confidence required for societal participation and public interactions in unfamiliar environments. Despite noteworthy advances in robotic prostheses for lower-limb amputees, such as microprocessor knees and powered ankles, natural somatosensory feedback from the lost limb has not yet been incorporated in current prosthetic technologies. *Approach.* In this work, we report eliciting somatic sensation with neural stimulation delivered by chronically-implanted, non-penetrating nerve cuff electrodes in two transtibial amputees. High-density, flexible, 16-contact nerve cuff electrodes were surgically implanted for the selective activation of sensory fascicles in the nerves of the posterior thigh above the knee. Electrical pulses at safe levels were delivered to the nerves by an external stimulator via percutaneous leads attached to the cuff electrodes. *Main results.* The neural stimulation was perceived by participants as sensation originating from the missing limb. We quantitatively and qualitatively ascertained the intensity, modality as well as the location and stability of the perceived sensations. Stimulation through individual contacts within the nerve cuffs evoked repeatable sensations of various modalities and at discrete locations projected to the missing toes, foot and ankle, as well as in the residual limb. In addition, we observed a high overlap in reported locations between distal versus proximal cuffs suggesting that the same sensory responses could be elicited from more proximal points on the nerve. *Significance.* Based on these findings, the high-density cuff technology is suitable for restoring natural sensation to lower-limb amputees and could be utilized in developing a neuroprosthesis with natural sensory feedback. The overlap in reported locations between proximal and distal cuffs

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indicates that our approach might be applicable to transfemoral amputees where distal muscles and branches of sciatic nerve are not available.

Keywords: neuroprosthesis, sensory feedback, peripheral nerve stimulation, transtibial amputees, high-density cuff electrodes

S Supplementary material for this article is available online

(Some figures may appear in colour only in the online journal)

1. Introduction

Individuals with lower-limb amputations use assistive technologies, such as prostheses, to overcome mobility limitations [1] and improve their functional capabilities in activities of daily living [2]. Design iterations of prostheses have focused on improving confidence in walking [3], reducing reliance on the intact limb [4, 5], and lowering metabolic energy expenditure during level-ground walking [6, 7] mainly by taking advantage of integrated robotic systems [8] and employing versatile control strategies [9]. However, human locomotion is a dynamic integration of motor and sensory systems where sensory signals generated in the lower limbs influence motor output [10]. Such natural sensory feedback is absent in current prosthetic devices.

Tactile sensation in the foot and proprioception play important roles in maintaining balance and stabilizing gait. In neurologically intact individuals, foot sole tactile afferents contribute to body posture awareness [11], erect stance maintenance [12], and sensing the direction of ankle movement [13]. It has been suggested that lack of sensory feedback in amputees contributes to asymmetric gait [14], poor balance [15], reliance on vision [16], slower cadence [17], and increased falling rates [18]. Amputees rely heavily on feedback from residuum-socket interactions to compensate for the loss of sensation of foot-floor contact or ankle loading [19]. Such limited feedback is often insufficient to allow amputees to navigate uneven terrain or traverse areas with compromised lighting. Moreover, the sensitivity of the residuum can change based on skin condition, shape of the residuum, or the level of amputation.

Various approaches have been utilized to provide more reliable somatosensory feedback to lower-limb amputees [17, 19–21]. Sensory substitution, such as audio and visual feedback, can positively impact gait symmetry in transtibial amputees [22, 23]. Fan *et al* [21] demonstrated that pneumatic balloon actuators placed on the upper leg in able-bodied individuals could provide accurate perception of directional forces on the foot during stance. Similarly, vibrating elements on the amputees' thighs can provide time-discrete feedback for control of gait [19]. In a different study [17], transcutaneous electrical stimulation applied to the residual limb based on the foot loading conditions during walking led to a significant improvement in stance time symmetry and step length in transfemoral amputees. Although findings from prior studies highlight the importance of sensory information for improving balance and gait, the feedback mechanisms are limited to a single feedback modality (e.g., magnitude or direction of the force acting on the prosthetic foot [17, 21]) or feedback about specific aspects of gait (e.g., symmetry [22, 23] or gait-phase transitions [19]). In addition, users of these systems must learn to associate feedback at different locations and disparate sensory modalities to information about their missing limb (e.g., electro-cutaneous sensation on the thigh substituting for load applied to the prosthetic foot). This can be non-intuitive and add to the cognitive load associated with such approaches [24, 25]. These limitations can inhibit widespread adoption of sensory feedback by prosthesis users. As such, there is a need for alternative approaches with low cognitive burden that provide meaningful and natural sensation that is instantly perceived as arising from the missing limb.

Directly interfacing with nerves remaining in the residual limb can be effective in eliciting useful sensations in people with different levels of amputation [20, 26–28]. Clippinger *et al* [20] delivered electrical stimulation to the sciatic nerves in the residual limbs of transfemoral amputees. Platinum–iridium electrodes were sutured to the nerve and the stimulation frequency was modulated based on readings from strain gauge sensors in the prosthesis. Although Clippinger *et al* reported that stimulation increased confidence in walking and improved function in poorly lit areas, no quantitative analysis was presented on psychophysical properties or effect of sensory feedback on balance or gait measures. Furthermore, it is unclear whether elicited sensations were perceived as natural, arising from the missing limbs, or consistent in their locations and modalities over time. With the advances in neural interface technology over the last decade, there is evidence that non-penetrating nerve cuff electrodes can restore motor and sensory function in people with disabilities [26, 29–31]. These devices do not breach the epineurium, can be fabricated to conform to the shape of the target nerves while exerting minimal pressure and maintaining blood flow, and preserve structural, physiological and clinical indications of nerve health during chronic applications [29].

In this work, we demonstrate the feasibility of restoring sensation in two individuals with transtibial amputation using high-density composite flat interface nerve electrodes (C-FINEs). Our approach allows selective stimulation of the sensory fibers of the peripheral nerves in the distal thigh above the knee and residuum. Elicited sensations are perceived immediately and interpreted by the participants as originating from the missing limb. Reported modalities include tactile as well as proprioceptive sensations and each could be modulated by changing stimulation parameters. In addition, we show that proximally implanted C-FINEs can reliably elicit similar sensations related to the foot and ankle as distally implanted cuff electrodes (i.e., on the sciatic nerve compared to the tibial or common peroneal nerves). This finding implies the suitability of our technology for restoring sensation in people with higher-level amputations.

2. Methods

Two human participants with unilateral transtibial amputation due to trauma enrolled in the study. The first participant (LE01), a 67-year-old male who lost his left leg below the knee in a blast injury, was 47 years post-amputation at the time of enrollment. He wears an energy-storage-and-return foot (Vari-Flex®; Össur, Reykjavik, Iceland) with a pin/lock suspension system. The second participant (LE02), a 54-year-old male who underwent transtibial amputation of the right leg after a motor vehicle accident, was 9 years post-amputation at the time of enrollment. He wears a powered ankle prosthesis (emPOWER Ankle; BionX Medical Technologies, Inc., Bedford, MA) with a vacuum suspension system. Both participants use their prostheses regularly and did not have any medical conditions that would exclude them from undergoing an elective surgery. All study procedures were approved by the Louis Stokes Cleveland Veterans Affairs Medical Center (LSCVAMC) Institutional Review Board and Department of the Navy Human Research Protection Program. The study was conducted under an investigational device exemption obtained from the US Food and Drug Administration.

2.1. Surgery and post-operative care

During an outpatient procedure, each participant received three high-density 16-contact C-FINEs (Ardiem Medical, Inc., Indiana, PA), with 0.5 mm^2 surface area per contact. The implanted system, its components, and the location of installed C-FINEs is depicted in figure 1. C-FINEs are designed to allow gentle reshaping of the nerve with minimal exertion of pressure along the length of the nerve [29]. Surgical planning included dissection of the sciatic nerve in human cadavers to estimate appropriate sizes for the C-FINEs and determine the optimal surgical access route to the target nerves. Ultrasound imaging of the popliteal area on the participant's posterior distal thigh was performed prior to surgery to locate the bifurcation of the sciatic nerve into tibial and common peroneal branches. In LE01, the C-FINEs were installed on the pre-branch sciatic and post-branch tibial and common peroneal nerves above the popliteal fossa. The C-FINE placed on the sciatic nerve was 15 mm × 1.5 mm (length × height), and the C-FINEs placed on the tibial and common peroneal nerves were 10 mm × 1.5 mm and 10 mm × 1 mm, respectively (figure 1(b)). In LE02, we installed the C-FINEs on the proximal sciatic (about 3 cm above the bifurcation point), distal sciatic (immediately pre-branch), and post-branch tibial nerves (figure 1(b)). The proximal sciatic, distal sciatic, and tibial C-FINEs were 15 mm × 3 mm, 15 mm × 2 mm, and 15 mm × 1.5 mm, respectively.

After implanting the C-FINEs, three superficial incisions were made along the iliotibial band and superior to the initial incision point. The C-FINEs' leads were routed medially and proximally to the new incision points, where they were connected to percutaneous leads via inline connectors (Medtronic, Minneapolis, MN) and tunneled out of the skin on the anterior upper thigh. The final skin exit site was arranged in a 6 × 4 grid of tandem-wound leads to provide access to every contact in all three cuffs. To avoid discomfort we positioned the connector sites and lead exit sites above the area of the leg covered by the prosthesis liner. A sterile pad (Covidien, Mansfield, MA) and waterproof adhesive dressing (Tegaderm™; 3M, St. Paul, MN) were used to cover the leads and the lead exit site. We confirmed proper installation of the implanted components with a set of post-operative x-ray images taken within 1 d of the surgery. The participants were provided with instructions to regularly change dressings and maintain skin hygiene.

We instructed both participants not to use their prostheses for at least 1 week post-surgery to avoid excess strain on the incision sites, all of which were above the prosthetic socket. Three weeks after surgery, the participants returned to the LSCVAMC for the surgeon to inspect incisions and assess wound healing. Pins were crimped to the ends of the percutaneous leads and placed in CENTI-LOC strip connectors (ITT Cannon, Irvine, CA) to create a reliable interface for the external stimulator.

2.2. Stimulation delivery and data collection

With the incisions completely healed and no signs of swelling or discomfort, we began electrical stimulation through the implanted C-FINEs 4 weeks post-surgery. The participants continued to visit the laboratory for testing on a weekly basis.

We used a custom-designed, 24-channel, microprocessor-controlled stimulator to deliver stimulation in the form of biphasic, charge-balanced, current-controlled, asymmetric, cathodic-first waveforms with a 2 in × 2 in surface electrode on the anterior superior iliac spine serving as a common exterior anode [26, 29]. Stimulus pulse amplitude (PA) could be set independently on each output channel from 0 to 2 mA in 0.1 mA steps and from 2.2 to 5.6 mA in 0.2 mA steps, with continuously variable pulse width (PW) from 1 to 255 μs and inter-pulse frequency from 0 to 1000 Hz. The stimulator was controlled in real time through a custom model in Simulink (MathWorks Inc., Natick, MA) running in an xPC Target environment. The compliance voltage of the stimulator was 50 V. For safety, line powered components were optically isolated and stimulating currents were restricted so that charge densities per phase remained within suggested levels for electrical nerve stimulation given by

$$\log(QD) = k - \log(Q),$$

where QD is the charge density per phase (μC cm^{-2}) and Q is charge per phase (μC) [32]. Based on prior work, $k < 1.5$–1.7 is considered safe for pulse trains with inter-pulse frequency of 50 Hz and up to 7 h continuous stimulation [33, 34]. We limited stimulus parameters so that k was less than 1.4 for

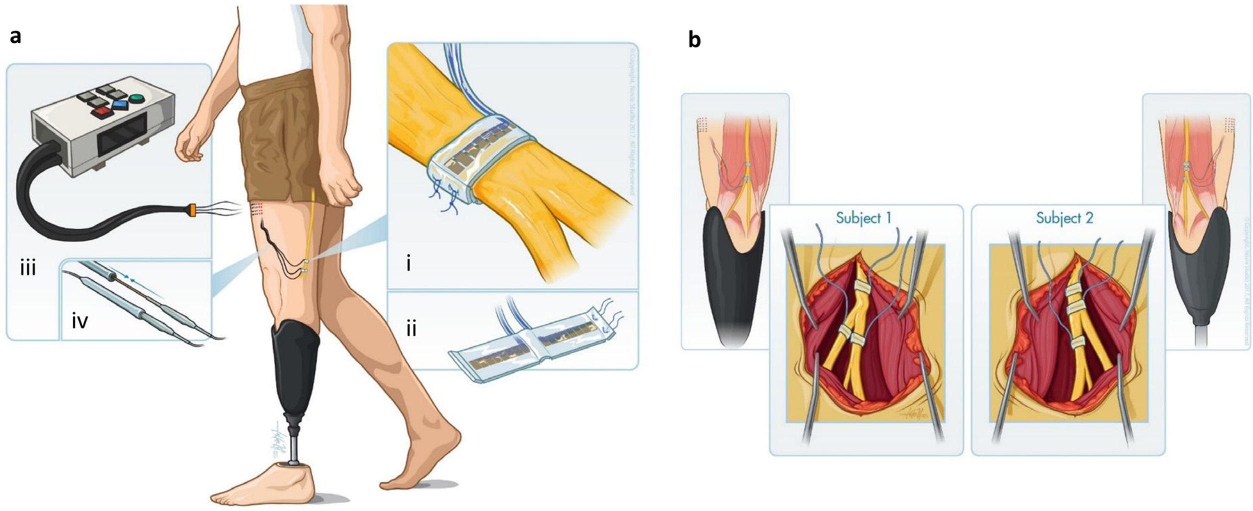

Figure 1. (a) Illustration of implanted system and its components. The C-FINEs each had 16 contacts and wrapped around the nerve ((a)(i) and (ii)). Access to the C-FINEs was through percutaneous leads routed to the upper thigh where they exited the body. The connection between the C-FINEs and the percutaneous leads was through inline connectors (a)(iv). An external stimulator was utilized to deliver electrical stimulation to the nerves (a)(iii). (b) The location of implanted C-FINEs for each subject. The C-FINEs were implanted to allow access to proximal and distal points of the nerves in the popliteal fossa.

all injected charges. Stimulation duration was typically 4–5 s with 50 ms inter-pulse intervals (IPI).

2.3. Determining threshold levels and location maps

During experimental procedures, participants were seated with their prosthesis removed and their residual limb resting on a padded stool with their knee comfortably extended. Following every stimulation trial, participants verbally described the modality of perceived sensations and drew the location on a diagram of the foot and leg. LE01 drew on paper for the first few sessions and later, to facilitate data processing and storage, on a digital touchscreen display (Cintiq 27QHD Touch; Wacom Co., Japan) controlled by a custom routine in MATLAB (MathWorks Inc., Natick, MA). LE02 also used the digital touchscreen display. Participants were blind to stimulation strength for all trials.

An auditory cue announced the start of every trial. However, we randomly intermixed trials with no stimulation to control for effects of anticipation. Stimulation parameter thresholds for eliciting sensation were determined by increasing PA in steps of 0.1 mA while the PW was kept at 255 μs. Once we established the minimum PA, we found the concomitant threshold for PW by using an adaptive staircase method [26] with a 5–10 μs resolution.

We created location maps for the sensations elicited by each contact using the intersection of reported areas at threshold levels from weeks 3 through 12 after the start of testing. Data from the first 2 to 3 weeks of experiments were excluded from location maps as participants were adjusting to the elicited sensations and discovering consistent language to describe percepts. To eliminate the impact of outliers, we discarded reported areas with less than 30% overlap with other areas reported for that contact. The final map for every contact was composed from at least three reported areas.

To determine the overlap between reported locations from contacts in two different C-FINEs, we calculated the intersection between the areas reported for the two contacts and compared it to the overall area reported for each contact. If the ratio of the intersection area to the area reported from one of the contacts was greater than or equal to 70%, we considered the reported locations to overlap. All the calculations for overlap between reported areas were performed using MATLAB Image Processing Toolbox Ver. 10.

2.4. Intensity discrimination and modality modulation

We examined the effect of change in PW on perceived intensity in a subgroup of contacts using the psychophysical analysis previously established for upper-limb amputees [35]. We selected contacts that elicited sensations at functionally relevant locations in the missing foot (e.g., toes, first metatarsal head, or heel). Participants were presented with two consecutive 2 s pulse trains separated from each other by 2 s. They then reported which of the two stimuli was perceived as stronger. We asked participants to only focus on intensity and did not probe for changes in location or modality of the sensation during this test. For the selected contacts, the stimulation parameter thresholds were determined first. Then, while keeping PA constant at the threshold level, the operational range for PW was determined by increasing PW in 10–20 μs steps until the participant reported discomfort or the safety limits (described in section 2.2) were reached. A reference PW was selected at the midpoint of the range and all other PW levels were compared against this reference. At the beginning of every test session, as part of the procedure to find the threshold and the reference PW, we asked participants to describe perceived locations and modalities in response to various PWs. The contacts selected for the intensity discrimination task did not show changes in modality or location for the range of PWs tested. Data were collected from a minimum of 20 repetitions of at least 10 different PW levels for the tested contacts in each participant.

Experimental blocks for each contact were limited to 80 trials to avoid confounding factors such as adaptation [35]. Although we did not probe effects of adaptation in this work, prolonged exposure to stimuli could lead to adaptation as reported in various approaches including nerve stimulation [36], electro-cutaneous stimulation [37], and vibrotactile sensory substitution [38]. Characterization of adaptation and other neurodynamic phenomena are beyond the scope of this study. The order of stimuli within a pair was randomized and participants were blind to stimulation conditions. A sigmoid function was fitted to the data showing the proportion of times a PW was judged stronger compared to the reference. The just noticeable difference (JND) was estimated as the change in the PW that yielded 75% correct identification of the stronger stimuli.

We also ascertained how changes in PW could affect perceived sensory modality using data from all responding contacts of the sciatic C-FINE in LE01 and the tibial C-FINE in LE02. The threshold for each contact was first determined and then PW levels were increased in steps of 20 μs until the charge density reached the safety limit or PW exceeded 255 μs. At every step, participants described the elicited sensation and we categorized each description as either the proprioceptive or the tactile modality.

2.5. Strength-duration curves

We measured strength-duration (SD) curves to probe for any peripheral nerve degeneration [39] due to the implanted C-FINEs. For a subgroup of contacts selected randomly, SD curves were calculated by determining the thresholds at multiple PA levels followed by fitting the data to Wiess's equation [30],

$$\mathrm{PA} = I_0\,(1 + \tau_{\mathrm{SD}}/\mathrm{PW}),$$

where I_0 is the base current—the minimum current required to excite the nerve when PW is very large—and τ_{SD} is the SD time constant indicating the minimum PW required to excite the nerve at $2I_0$. SD curves were collected at months 2 and 3 post-surgery to examine changes to the excitability of the nerves over time. In addition, we applied stimuli with two different IPIs, 50 ms and 10 ms, to evaluate how the responses varied with frequency.

2.6. Phantom limb perception

We assessed changes in phantom limb perception and sensation in the residual limb by administering a series of baseline questions at the beginning (before stimulation) and the end (after stimulation) of every test session. Questions covered the location of the perceived phantom limb in space (the distance from the end of the residuum to the farthest point perceived on the phantom), its orientation, unusual sensation in the residual limb, as well as changes in prosthesis fit. After the first 3 months of experiments, reported distances from the end of the residuum to the farthest point perceived on the phantom became more consistent, so we made measurements less frequently in subsequent months.

2.7. Chronic stability of the responses

We defined the yield for each C-FINE as the ratio of number of contacts through which stimulation produced sensation to the total number of contacts within the C-FINE (i.e., 16). In addition, the charge densities at threshold values were calculated on a monthly basis for the contacts that responded to stimulation. Impedance for every contact was measured using delivery of subthreshold 0.3 mA cathodic pulses with 50 μs PW. The yield, impedance, and charge densities at thresholds were monitored monthly for at least 7 months post-surgery.

The stability of location maps was probed between months 2 and 7 post-surgery. Only contacts that responded to stimulation for the whole period were considered in this analysis. At every time point that a contact was tested, we calculated the centroid of the reported location at threshold relative to a coordinate system with the origin at the upper left corner of the diagram image. The magnitude of the centroid vector and its angle in polar coordinates were compared to those from the second month, as the baseline, to detect spatial variation in reported locations over time.

2.8. Statistical analysis

One sample *t*-tests were used to compare the location stability over time. In this analysis, values were compared to the mean of values reported in the second month of the experiment. Repeated measures analysis of variance (ANOVA) with a between effect for nerve and a within effect for time was performed to determine significance of changes in charge densities over time within a C-FINE and to probe effects between C-FINEs. We evaluated differences in distance from the end of the residuum to the farthest point perceived on the phantom limb over the course of the experiment with a repeated measures ANOVA with a between effect for month and within effect for before/after stimulation. We quantified differences between months with post-hoc Tukey tests. For all the other comparisons, we used two tailed *t*-tests. In all tests, a significance level of $\alpha = 0.05$ was used. Statistical analyses were performed using MATLAB Statistics and Machine Learning Toolbox Ver. 11.1 or IBM SPSS Statistics Ver. 22 (IBM Corp., Armonk, NY).

3. Results

3.1. Elicited sensation: location and modality

We found that stimulation via C-FINEs elicited sensation with different modalities projected to discrete areas of the missing limb as well as the residual limb in both participants. During the first 2 weeks of experiments, LE01 reported that stimulation elicited sensations in his missing foot. However, the described locations for this period were diffuse areas of plantar and dorsal surfaces of the foot that he was not able to differentiate into specific areas such as the toes or heel. Often, the reported locations in the first 2 weeks were inconsistent for the same set of stimulation parameters from session to session. Beginning in week 3, the modality and location of the perceived sensations became more robust and repeatable.

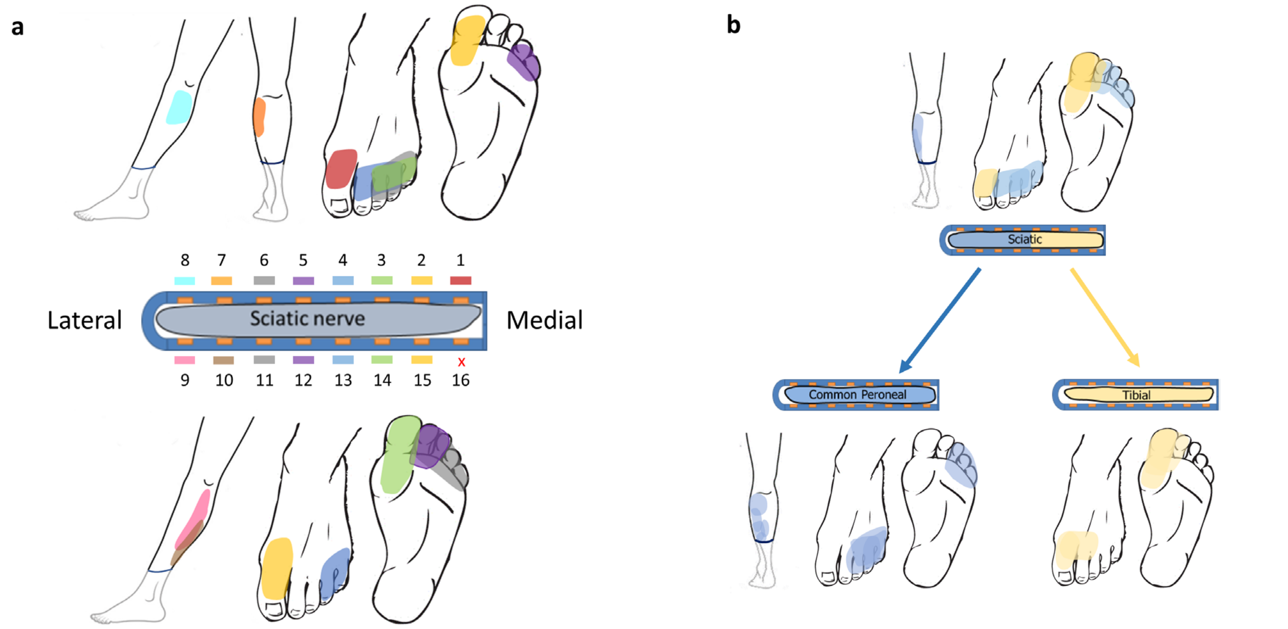

Figure 2. (a) Locations reported by LE01 when electrodes in the sciatic C-FINE were stimulated at threshold pulse width and pulse amplitude. Color indicates different contacts, numbered 1 through 16, where contacts 1 and 16 were on the medial side of the nerve while contacts 8 and 9 were on the lateral side of the nerve. (b) Overlap of locations reported by LE01 during stimulation of the electrodes on the sciatic nerve with locations reported during stimulation of electrodes on the common peroneal (blue) and tibial (yellow) nerves.

He was able to consistently report sensation arising from single toes in his missing foot in response to the same stimulus parameters delivered via specific electrode contacts. As such, location maps were made using data after week 4. For LE01, sensory location maps at threshold stimulation levels suggest selective activation of nerve fibers through different contacts within the C-FINE as the reported locations vary between areas of the foot and the residual limb (sciatic nerve, figure 2(a)). The location map for every contact was made based on six to nine measurements at threshold levels. For 44% of the contacts, there were no outliers in reported locations, as specified in the methods section. 37% and 19% of the contacts showed only one and two outliers in the reported locations, respectively. The maps for contacts on the lateral versus medial side of the cuff showed a distinct spatial separation, which suggests stimulation activated anatomically separate afferent fibers within the nerve. Contacts located on the medial side of the sciatic C-FINE evoked sensations in the big toe, which correspond to cutaneous innervation by the medial plantar nerve. In contrast, lateral contacts in the sciatic C-FINE evoked sensations on the lateral side of the residual limb and foot, which correspond to cutaneous innervation by the superficial peroneal nerve. LE01 generally reported similar locations for stimulation of contacts in the same relative position on the bottom and top of the C-FINE. Stimulation of the tibial nerve elicited sensations confined to the first and second toe (nine contacts, supplementary figure 1) (stacks.iop.org/JNE/15/056002/mmedia), while stimulation of the common peroneal nerve elicited sensations in the third through fifth toes (six contacts) and the lateral side of the residuum (six contacts) (supplementary figure 2). LE02 initially reported that stimulation elicited sensations limited to his residuum. In weeks 2 and 3, he gradually described the sensations as originating from his missing limb. The described sensations settled to discrete and repeatable locations afterward with minimal changes over time. Although LE01 reported sensations mostly in the toes and residuum, LE02 reported elicited sensations through greater portions of the foot sole, around the heel, and on the ankle in addition to the residuum. Stimulation of the tibial nerve generated the most variety in locations reported by LE02. The location maps (figure 3) were made using six to seven measurements at threshold levels for all contacts except for one contact in which stimulation did not evoke any sensations a month after beginning the experiments. For this contact, the map consisted of three measurements. For 67% of the contacts, we did not observe any outliers in the reported locations and 37% of the contacts showed only one outlier in the reported locations. Contacts positioned on the lateral side of the tibial C-FINE generated sensations primarily located on the lateral side of the foot, ankle, or residuum, which correspond to cutaneous innervation by the lateral plantar nerve (figure 3, see locations for contacts 1, 2, 3, 13, 15, and 16). In contrast, C-FINE contacts located medially on the nerve generated sensations that were reported on the medial side of the foot and ankle, which correspond to cutaneous innervation by the medial plantar nerve (figure 3, see locations for contacts 5, 6, 8, and 11). Contacts on both the top and bottom of the C-FINE elicited sensations in the heel, which correspond to areas innervated by the medial calcaneal branches of the tibial nerve.

Perceived modalities included tactile and proprioceptive sensations in both participants (table 1, supplementary video 1). We did not provide participants with keywords to avoid biasing their descriptions of perceived sensations. When stimulated at threshold level, none of the contacts caused pain or discomfort.

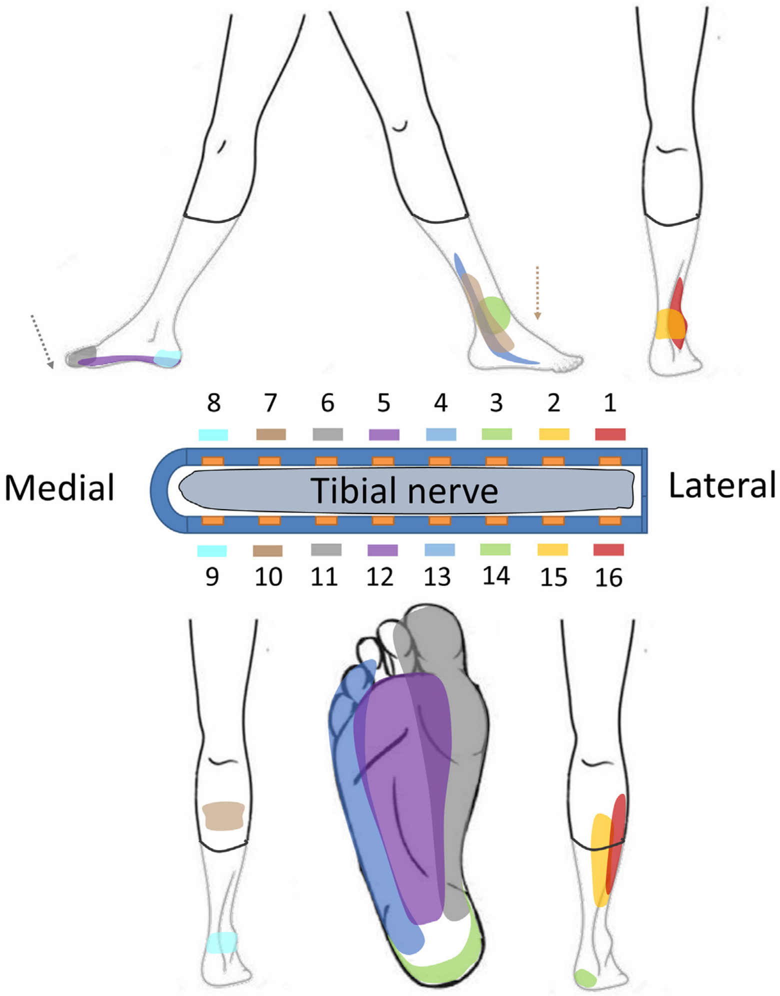

Figure 3. The locations reported by LE02 at threshold pulse width and pulse amplitude levels for the tibial C-FINE. Color indicates different contacts, numbered 1 through 16, where contacts 1 and 16 were on the lateral side of the nerve while contacts 8 and 9 were on the medial side of the nerve. The dotted arrows indicate a pre-movement sensation where the subject reported that his ankle was about to move down but that he did not feel any movement.

3.2. Overlap in responses among the C-FINEs

We observed overlap of reported locations of perceived sensations between the proximal and distal C-FINEs in both participants. In LE01, locations reported from stimulation of 69% and 75% of the contacts in the tibial and common peroneal C-FINEs, respectively, overlapped with those reported from sciatic C-FINE stimulation. Medial sciatic contacts elicited sensations that overlapped with those from the tibial nerve, while lateral sciatic contacts elicited sensations that overlapped with those from the common peroneal nerve (figure 2(b)). Similarly, in LE02 locations reported from stimulation of 81% of proximal sciatic nerve contacts and 75% of distal sciatic nerve contacts overlapped those reported from stimulation of contacts on the tibial nerve.

3.3. The effect of PW on perceived modality and intensity discrimination

Varying PW caused changes in the modality and intensity of perceived sensations (figures 4 and 5). Both participants typically described the sensations elicited by threshold stimulation levels as light pressure, tingling, awareness, or non-movement sensation projected to their missing limb. With an increase in charge density, sensations elicited by the majority of the contacts became movement-related perceptions projected to the same region as the tactile percepts, which we categorized as proprioception (figure 4(a)). The induced proprioception included bending/lifting of the toes as well as plantarflexion/dorsiflexion or inversion/eversion of the ankle. With further increase in PW, palpable residual muscle contractions accompanied proprioceptive sensations in some cases. Changes in modality with applied charge were most frequently observed from contacts in the sciatic and tibial C-FINEs in LE01 and LE02, respectively (figure 4(b)). A 50% increase in charge density led to a modality transition from tactile to proprioception for 44% of the contacts. Further increases in charge density caused an increase in percent of sensations reported as proprioceptive until no tactile sensations were reported when charge density reached three times higher than the threshold levels. As we modified PW to increase charge density, the number of contacts that could be utilized for stimulation decreased as the charge density reached the safety limit for stimulation.

Table 1. Modalities elicited by stimulation, as described by the two subjects. S, T, and P for LE01 indicate sciatic, tibial, and common peroneal nerve cuffs, respectively. For LE02, DS, PS, and T indicate distal sciatic, proximal sciatic, and tibial cuffs, respectively. The number after each letter indicates the contact number within the cuff.

Electrode	Elicited sensation described by the subject	Modality
LE01-P15	'My toes are pushing down against a surface'	Proprioceptive
LE01-T8	'My big toe wanted to move, but there was not enough to do it'	Tactile
LE01-T14	'Very light touch, on top of the big toe'	Tactile
LE01-S7	'Like a piece of hair, or piece of grass rubbed against my calf'	Tactile
LE02-DS6	'It was in the ankle, made my foot go down'	Proprioceptive
LE02-DS3	'Felt like a pressure in the heel'	Tactile
LE02-T3	'It was like pressure on one side of my ankle'	Tactile
LE02-PS4	'Bottom of my foot was waking up'	Tactile

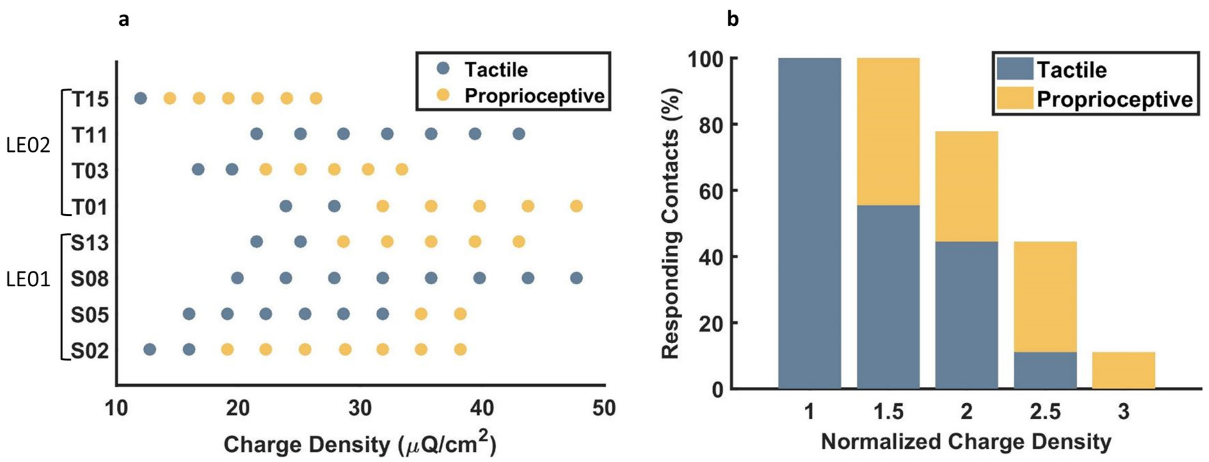

Figure 4. Changes in the perceived modality with increases in stimulation charge density. (a) Data shown from representative C-FINE contacts in both subjects. (b) The distribution of tactile versus proprioceptive sensations as a function of charge density normalized to the value at threshold for the all of the contacts that responded in LE01's sciatic C-FINE and LE02's tibial C-FINE.

As shown in figure 5, the intensity discrimination data for the tested contacts in both subjects followed psychometric curve profiles ($R^2 = 90 \pm 2.1$, mean $\pm$ SEM, $n = 4$). For the contacts examined in the sciatic nerve cuff, LE01 exhibited estimated JNDs of 39 μs and 27 μs for contacts 2 and 12, respectively. At the reference PWs, LE01 described evoked sensations as pressure at the bottom of the big toe for contact 2 and lifting in the second and third toes for contact 12. LE02 exhibited estimated JNDs of 24 μs and 27 μs for contacts 3 and 15, respectively, in the distal sciatic cuff. Stimulation of contact 3 elicited a sensation of pressure about the back of the heel while stimulation of contact 15 elicited sensation on the lateral side of the foot. No significant difference appeared to exist between the JNDs for the two participants, which suggests that they share a common relationship between applied charge and associated changes in perceived intensity.

3.4. Nerve health and SD curves

Over the entire study period, no incidents of painful, unpleasant, or unusual sensations unrelated to stimulation occurred, which indicates that participants were free of excessive pressure or impingement of the nerve by the electrodes. Participants began using their prostheses again 2 to 3 weeks post-surgery without mobility issues and qualitatively reported that the implanted system had minimal impact on their daily life activities.

The SD curves show the required PW at different PA levels to elicit sensation (figure 6). As expected, the PW required to elicit a detectable sensation (threshold) decreased as the PA level increased. SD curves at 2 and 3 months post-surgery (figures 6(a) and (b)) were indistinguishable from each other, with no statistical difference in their base current (I_0) and SD time constant (τ_{SD}) parameters, which suggests that the nerves were free of neural trauma or pathology. With a decrease in IPI from 50 to 10 ms, τ_{SD} decreased from 60.9 μs to 30.5 μs in contact 2 of the sciatic nerve cuff for LE01 ($p < 0.05$) and from 63.4 μs to 40.1 μs in contact 3 of the tibial nerve cuff for LE02 ($p < 0.05$) whereas the changes in I_0 remained insignificant (figures 6(c) and (d)). When the inter-pulse intervals decreased, lower pulse widths excited sensory fibers; this behavior and characteristic shape of the SD curves indicated normal, healthy nerve function.

3.5. Changes in the phantom limb

Prior to initial electrical stimulation, LE01 perceived the big toe of the phantom limb as being 6 cm below the end of his residuum (figure 7). After stimulation, he indicated that the phantom limb big toe was 14 cm below the end of his

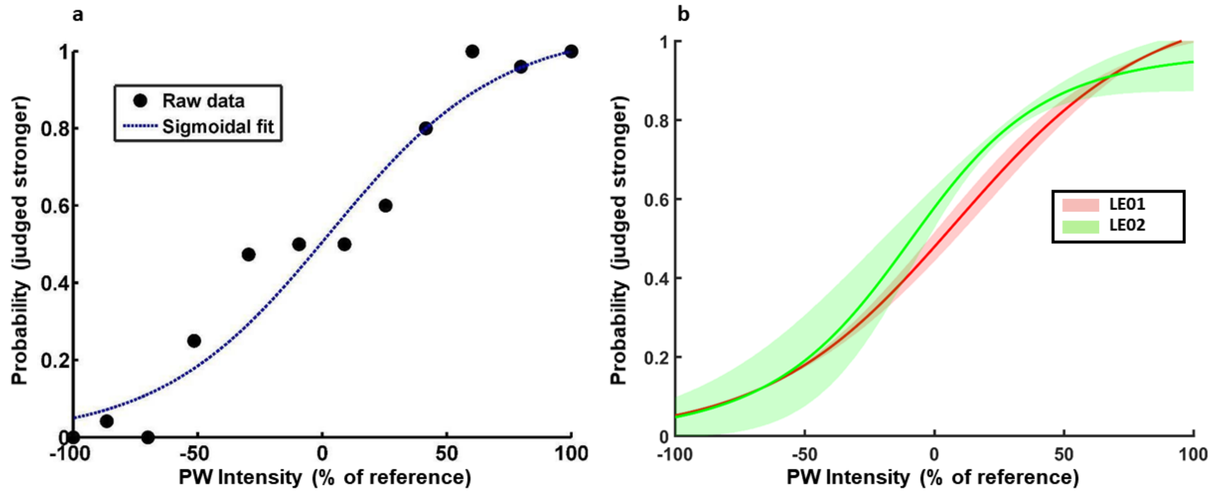

Figure 5. Intensity discrimination as a function of PW. (a) The intensity discrimination data (black dots) and the fitted curve (dashed line) for contact S12 in LE01. The data points indicate the probability of presented stimuli to be judged correctly, i.e., stronger or weaker than the reference PW. (b) Combined discrimination curves for both subjects ($n = 2$ contacts per subject, solid line is the mean and the shaded area denotes the standard error of the mean).

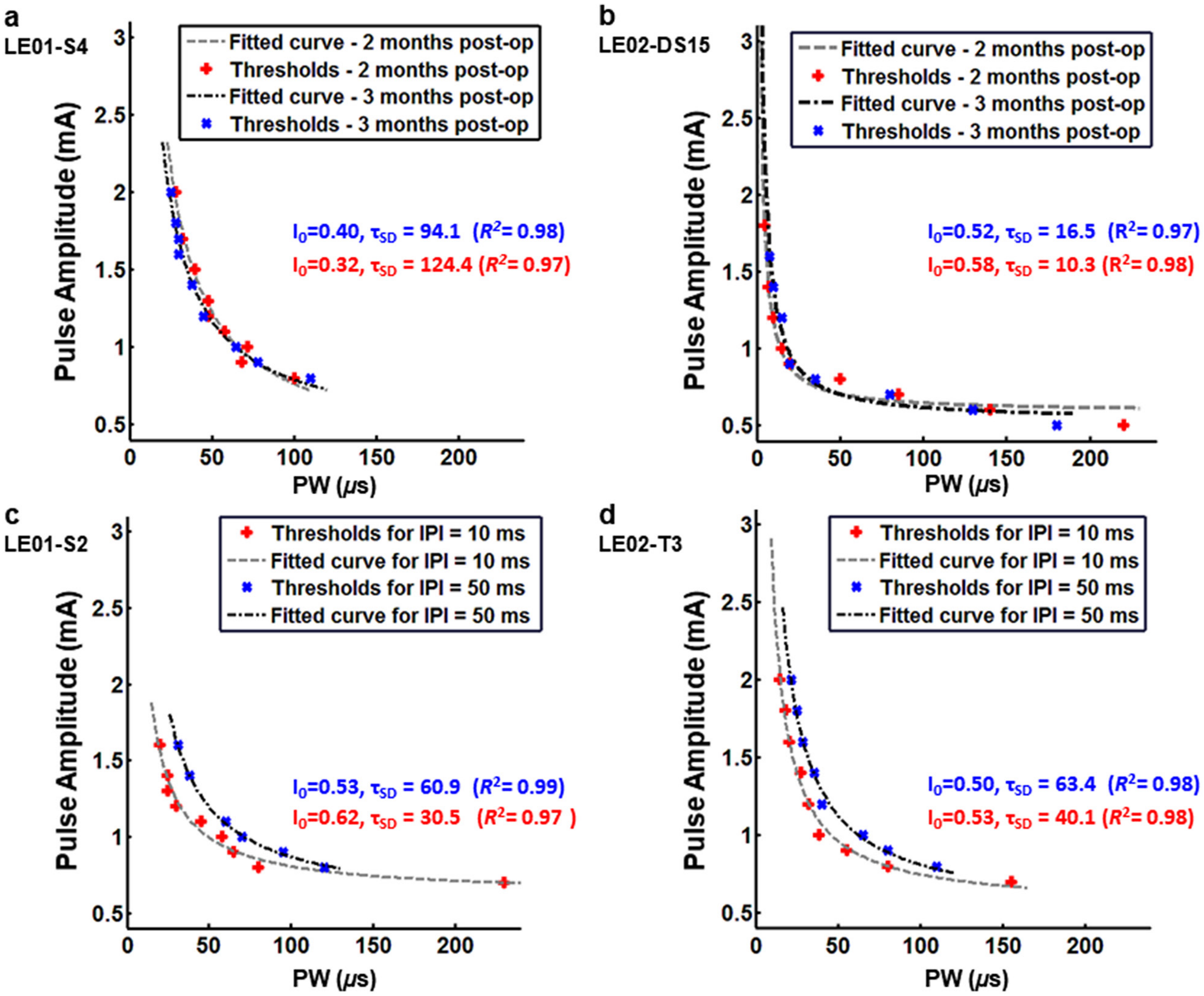

Figure 6. Strength-duration curves measured 2 and 3 months post-surgery for LE01 (a) and LE02 (b) with default 50 ms inter-pulse intervals (IPIs). We also compared SD curves at 10 ms versus 50 ms IPIs for LE01 (c) and LE02 (d) to examine changes in SD time constant (τ_{SD}) and base current (I_0).

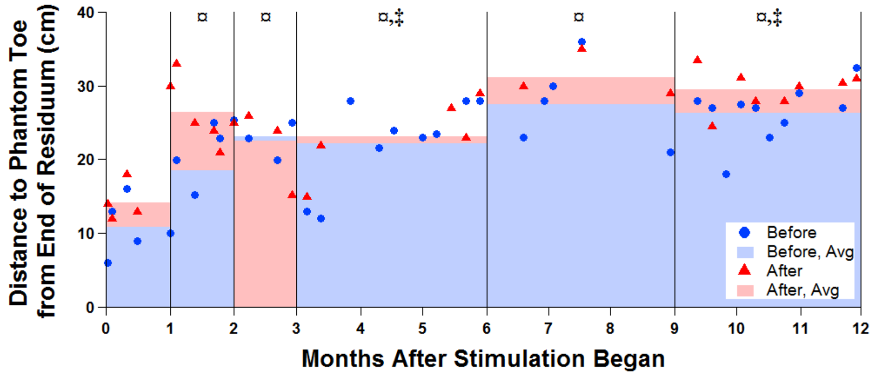

Figure 7. The distance to the phantom big toe from the end of the residuum over time reported by LE01. Distances reported before (blue) and after (red) stimulation was applied in a given day are shown as points for measurements from individual days while the average across a month are shown as bars. The phantom toe moved farther away from the end of the residuum during month 1 and the beginning of month 2, then remained closer to the floor in subsequent months compared to month 1. ¤ indicates a significant difference compared to month 1 (post-hoc Tukey test ($p < 0.05$) across measurements before and after stimulation). ‡ indicates a significant difference between months 4–6 and months 10–12 (post-hoc Tukey test ($p < 0.05$) across measurements before and after stimulation). There is also a significant difference between measurements before and after stimulation (main effect, $p = 0.011$).

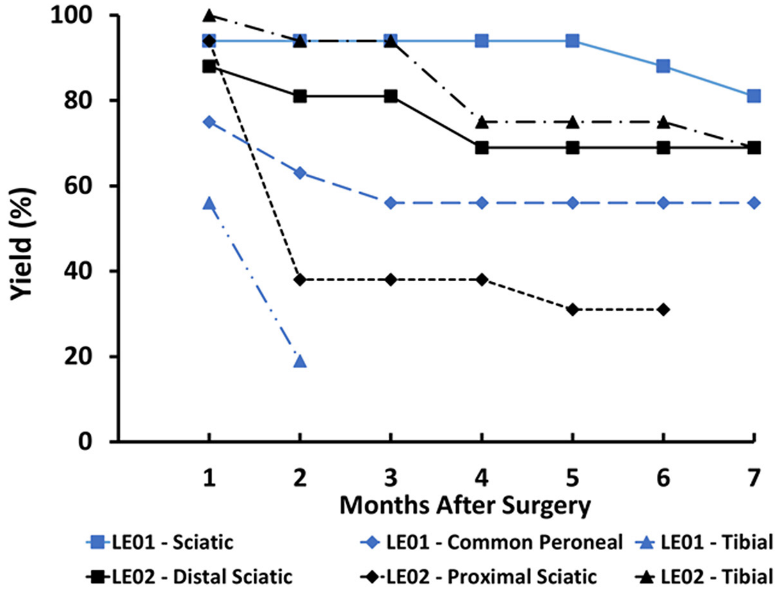

Figure 8. The yield for each of the C-FINEs (indicated by line style and marker type) over time after surgery across two subjects, LE01 (blue) and LE02 (black).

residuum. This partial extension of the telescoped phantom limb persisted between sessions and increased with additional sessions. During the first month of testing, LE01 perceived his phantom big toe an average of 11 cm and 14 cm below the end of his residuum before and after stimulation, respectively. His perceived phantom limb locations became closer to the floor in months 2 and 3 compared to month 1 (main effect $p < 0.001$, Tukey post-hoc tests $p < 0.01$). In the second month of testing, his phantom limb reached a new equilibrium location with the big toe 19 ± 3 cm and 27 ± 2 cm (average $\pm$ standard error of the mean) beyond the residuum before and after stimulation, respectively. LE01 reported similar locations in the third month of testing (23 ± 1 cm and 23 ± 3 cm before and after stimulation). Over the course of a year of testing, LE01 continued to perceive the toes of his phantom limb farther from the end of his residuum compared to their original location at the beginning of the experiments (Tukey post-hoc tests $p < 0.05$) (figure 7). Across all months tested, the distance from the phantom toe to the end of the residuum was shorter before stimulation than after stimulation on a given day (main effect $p = 0.011$). LE02 initially perceived his phantom limb as a ‘solid mass’ located under his residuum without any resemblance to an intact foot. After three visits where he received stimulation, the initial amorphous phantom limb this participant perceived transformed into a more anatomical representation of the missing foot, with distinguishable toes, heel, and ankle. After nine visits, he could also perceive the arch of his phantom foot.

3.6. Chronic stability in response

During the first 1 to 3 weeks of stimulation tests, the reported locations of sensation covered large areas of the foot in LE01 and were mainly limited to areas on the residual limb in LE02.

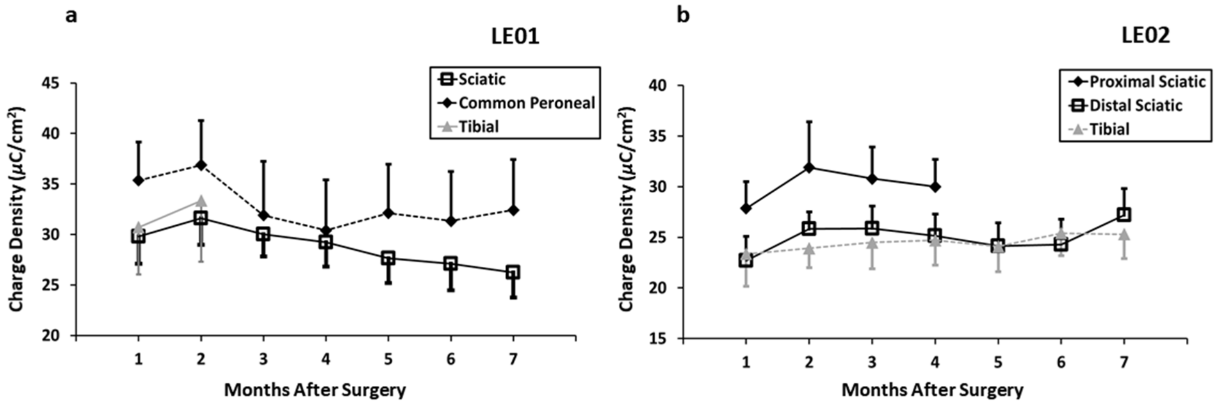

Figure 9. The charge density thresholds to elicit sensation in LE01 (a) and LE02 (b) over time for each of the C-FINEs (indicated by line style and marker type). Markers indicate the mean for a given month post-surgery and error bars represent standard error of the mean. For the sake of clarity, only the top or bottom half of the error bars are shown.

During this period, small changes in stimulation parameters in both participants caused noticeable variations in reported sensation location. However, in following sessions, stimulation that LE01 originally perceived as located in the foot shifted toward the toes and LE02 started reporting locations projected to the missing limb. Between months 2 and 7 post-surgery, the centroids of the reported locations remained unchanged in 78% and 65% of contacts for which stimulation elicited sensation in LE01 and LE02, respectively.

In LE01, the yields of responding contacts from the sciatic and common peroneal C-FINEs remained as high as 81% and 56%, respectively (figure 8). In LE02, the yields of contacts responding from the tibial and distal sciatic C-FINEs persisted above 69% over 7 months post-surgery. However, 2 months post-surgery, we noticed a decline in responses from tibial and proximal sciatic C-FINEs in LE01 and LE02, respectively. The impedance measurements suggested electrical disconnection of the contacts without response. Radiographic imaging of the implanted components showed breaks in the leads between the low-yield C-FINEs and the inline connectors. However, imaging did not reveal signs of dislocation or damage to the cuffs themselves.

The charge density thresholds to elicit sensation in both participants remained stable with no significant changes over time (figure 9). In LE01, the charge densities for sciatic and common peroneal C-FINEs remained unchanged, and no significant difference emerged between the threshold values for the two C-FINEs (figure 9(a)). In LE02, the thresholds during the same post-surgery period remained unchanged in both distal sciatic and tibial C-FINEs, and we did not find any difference in threshold values between the C-FINEs (figure 9(b)). The electrical impedance of electrodes for which stimulation elicited responses varied between 2 and 5 kΩ, consistent with previously reported values for cuff electrodes [26].

4. Discussion

We demonstrated that non-penetrating nerve cuff electrodes located above the knee could elicit sensations described by participants as natural and perceived as originating from the missing leg and foot. The spatial distribution of reported perceptions indicates that high-density C-FINEs installed on nerves in the thigh proximal to the knee could provide selective access to sensory nerve fibers. Locations and modalities of sensations elicited by stimulation of pre- and post-branch C-FINEs were similar, indicating that stimulation more proximally on the sciatic nerve selectively activated afferent fibers innervating the missing foot as effectively as stimulation of the tibial or common peroneal nerves. Previous work with 8-contact nerve cuff electrodes implanted in individuals with transradial amputations showed that multi-contact nerve cuff electrodes could elicit selective sensory responses from small nerves (medial, ulnar, and radial) [26]. Our observations using 16-contact C-FINEs in this study confirm that high spatial resolution is also possible when accessing sensory fibers in larger nerves, such as the sciatic nerve. Since responses to stimulation at proximal and distal locations overlap, and selective activation of sensory axons in large nerves is possible, this high-density electrode technology appears to have potential for restoring tactile sensation in transfemoral amputees where the tibial and common peroneal nerves have been removed. People with transfemoral amputation would benefit from sensory restoration as their fall risk [40, 41], reliance on vision [16], and concentration on gait [41] is higher compared to transtibial amputees, partly because of poor ground contact sensory feedback through the residuum and lack of proprioception about the knee joint [42, 43].

We observed that increasing stimulus PW could change the perceived modality from tactile perception to proprioception. This indicates that our sensory restoration approach allows the tuning of modality. However, the underlying neural pathway for the reported proprioception is not clear yet. It is possible that the electrical stimulation directly excites afferent fibers from muscle or joint sensory receptors. Alternatively, the stimulus could recruit motor fibers that activate downstream muscles in the residuum, causing muscle contraction and concomitant muscle sensory receptor activation. This sequence of recruited motor fibers causing muscle contraction that activates muscle sensory receptors might be more likely for stimuli that generated palpable muscle contraction in the residuum. However, such observable muscle contractions were not observed for all reports of proprioceptive responses, leaving open the possibility for direct activation of afferent fibers. Regardless of the neural pathway, our approach can elicit tactile and proprioceptive sensations, both of which provide important contributions to postural control [44, 45]. Future work will explore how these sensations affect balance and gait.

Compared to proprioception, tactile sensations were elicited at lower charge densities. Such an observation might at first seem counterintuitive because proprioceptive fibers Ia and Ib are considered larger than group II tactile fibers and, as such, it is expected that proprioceptive fibers be recruited first by electrical stimulation. Although group I fibers consist of large spindle (Ia) and tendon organ (Ib) afferent fibers, not all proprioceptive fibers belong to group I. It has been shown that certain group II fibers are responsible for proprioceptive sensation as well [46]. In fact, Mitchel and Schmidt report that afferent fibers from the lateral gastrocnemius and soleus muscles are 30%, 15%, and 32% Ia, Ib, and II fibers, respectively [47], suggesting marked contribution of group II fibers to proprioception in these skeletal muscles. Furthermore, prior work indicates information from cutaneous receptors contribute to the perception of joint movement or joint position [48]. For example, Ruffini corpuscles, a group of subcutaneous mechanoreceptors, respond to skin stretch and play an important role in sensation related to joint movement [49]. As such, in addition to activation of group I fibers, information from smaller diameter fibers seem necessary for proprioception. Another explanation for tactile sensation at lower charge densities could be the topography of the cutaneous fibers within the peripheral nerves. The cross-sectional microscopic anatomy of the sciatic nerve and its main branches suggest that cutaneous nerve branches are located close to the outer perimeter of the nerve [50], which put such cutaneous fibers in close proximity of the electrode contacts and make them more likely to be activated at lower stimulation currents.

Both participants reported changes in their perception of the phantom limb during the first month of sensory restoration experiments which persisted between sessions. In LE01, the phantom foot moved from its location close to the end of the residuum prior to stimulation to a distal location closer to the level of the intact foot. In LE02, the phantom foot remained in relatively the same location close to the end of the residuum, but transformed from an irregularly shaped mass to a more anatomical foot. These changes in the mental image of the limb align with previous work suggesting that conscious body image arises from several sources of input, including tactile afferents (for review, see [51]). Although a controlled study with more amputees is required to generalize how sensory stimulation affects perception of the phantom limb, our observations with two participants indicate that it may be highly subject-dependent.

Our results from intensity discrimination experiments corroborate previously reported observations in sensory restoration in the upper limb [35, 52]. However, to discriminate between sensations, our participants needed differences in stimulus PWs about five times longer than those reported for people with upper limb amputation [35]. This finding suggests poorer resolution in response to changes in stimulus intensity for the lower limb compared to the upper limb, which may be partly explained by inherent differences in somatosensation in the foot and hand [53–55]. Compared to the glabrous skin of the hand, the skin of the foot sole has a lower proportion of slowly adapting (SA) receptors, which respond to continuous stimuli like those used in the JND test [53]. In addition, receptive field areas for mechanoreceptors in the foot are three times larger than those found in the hand [53, 54], leading to poorer location discrimination [55]. As the physiologic foot has poorer resolution than the hand, it is unsurprising that restored sensation in the foot also has poorer resolution than restored sensation in the hand. Nerve fibers available to transmit sensations are limited compared to the hand and the portion of the somatosensory cortex allocated to processing afferent information from the foot is also smaller [55].

The chronic stability of percept locations and threshold values indicate the consistency in nerve fiber recruitment as well as minimal change in excitability of the nerve over time. Because of the overlap in sensations evoked by stimulation of different C-FINEs, the loss of response in one out of three C-FINEs in each participant did not negatively impact our ability to elicit sensations in functionally relevant areas, including the toes, heel, and ankle. Radiographic imaging of the implanted components and overlapping responses from other cuffs indicated that the loss of response was due to lead failure rather than defects in the C-FINEs or compromise of nerve function. Similar technology has been implanted for over four years in people with upper limb amputation without failure in response [26, 56]. It appears that over time the leads were exposed to repetitive radial deformation and axial tension, which may have contributed to the failure. The larger stiffness and diameter of the connectors relative to the highly flexible leads may have also have been a factor in the discontinuities. Our observations highlight the more rigorous physical environment and relative movement that implanted neural interfaces encounter in the lower limb compared to the upper limb. The impact of large musculature, wide ranges of motions, and higher loading conditions in the lower limb should be considered in designing new implantable neural interfaces intended for this area and use case.

Our approach enables direct activation of peripheral sensory nerves, which likely leverages existing biological circuits and cognitive processes. Communicating directly through the sensory pathways that previously connected the missing limb to the central nervous system holds the promise of accelerating retraining while eliminating distracting substitute sensations. An implanted system for feedback would also help minimize the inconvenience of donning/doffing external body-worn devices for feedback. Direct access to sensory-neural pathways also provides a unique model to investigate the sensory system and to isolate the contribution of tactile sensation to balance and locomotion in ways that have not been previously possible.

5. Conclusion

We successfully evoked tactile and proprioceptive sensations in two individuals with long-term (47 and 9 years) transtibial limb loss via high-density, non-penetrating C-FINE nerve cuffs located above the knee on the sciatic, tibial, or common peroneal nerves. These evoked sensations were localized to specific regions projected to the foot, ankle, and lower leg and perceived as arising from the missing limb. Perceptions, modality, and stimulus thresholds were stable for the 7 months tested post-implantation, with no discernable changes to nerve health and function. These findings support the suitability of non-penetrating nerve cuff electrode technology for sensory restoration in individuals with lower-limb loss. We also demonstrated the overlap in the evoked sensory responses from distal post-branch and proximal pre-branch locations in the thigh. This suggests that the same technology may also be applicable to restoring tactile sensation in transfemoral amputees. Future work will explore how elicited sensations influence balance control and locomotion in both transtibial and transfemoral amputees.

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