RESEARCH ARTICLE

Six-Month Assessment of a Hand Prosthesis with Intraneural Tactile Feedback

Francesco M. Petrini, PhD,[1]* Giacomo Valle, MS,[1,2]* Ivo Strauss, MS,[1,2]* Giuseppe Granata, MD, PhD,[3,4]* Riccardo Di Iorio, MD, PhD,[3,4] Edoardo D'Anna, PhD,[1] Paul Čvančara, MS,[5] Matthias Mueller, PhD,[5] Jacopo Carpaneto, PhD,[2] Francesco Clemente, PhD,[2] Marco Controzzi, PhD, Prof,[2] Lorenzo Bisoni, PhD,[6] Caterina Carboni, PhD,[6] Massimo Barbaro, PhD, Prof,[6] Francesco Iodice, MD,[3,4] David Andreu, PhD, Prof,[7] Arthur Hiairrassary, MS,[7] Jean-Louis Divoux, MS,[8] Christian Cipriani, PhD, Prof,[2] David Guiraud, PhD, Prof,[7] Luigi Raffo, PhD, Prof,[6] Eduardo Fernandez, MD, Prof,[3,4] Thomas Stieglitz, PhD, Prof,[5] Stanisa Raspopovic, PhD, Prof,[9†] Paolo M. Rossini, MD, Prof,[3,4†] and Silvestro Micera, PhD, Prof[1,2†]

Objective: Hand amputation is a highly disabling event, which significantly affects quality of life. An effective hand replacement can be achieved if the user, in addition to motor functions, is provided with the sensations that are naturally perceived while grasping and moving. Intraneural peripheral electrodes have shown promising results toward the restoration of the sense of touch. However, the long-term usability and clinical relevance of intraneural sensory feedback have not yet been clearly demonstrated.

Methods: To this aim, we performed a 6-month clinical study with 3 transradial amputees who received implants of transverse intrafascicular multichannel electrodes (TIMEs) in their median and ulnar nerves. After calibration, electrical stimulation was delivered through the TIMEs connected to artificial sensors in the digits of a prosthesis to generate sensory feedback, which was then used by the subjects while performing different grasping tasks.

Results: All subjects, notwithstanding their important clinical differences, reported stimulation-induced sensations from the phantom hand for the whole duration of the trial. They also successfully integrated the sensory feedback into their motor control strategies while performing experimental tests simulating tasks of real life (with and without the support of vision). Finally, they reported a decrement of their phantom limb pain and a general improvement in mood state.

Interpretation: The promising results achieved with all subjects show the feasibility of the use of intraneural stimulation in clinical settings.

ANN NEUROL 2018;00:1–18

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25384

Received May 26, 2018, and in revised form Nov 15, 2018. Accepted for publication Nov 15, 2018.

Address correspondence to Dr Micera, Bertarelli Foundation Chair in Translational Neuroengineering, Center for Neuroprosthetics and Institute of Bioengineering, School of Engineering, Federal Institute of Technology in Lausanne, Lausanne, Switzerland, E-mail: silvestro.micera@epfl.ch, silvestro.micera@santannapisa.it or Dr Rossini, Institute of Neurology, Catholic University, Rome, Italy, E-mail: paolomaria.rossini@policlinicogemelli.it

From the [1]Bertarelli Foundation Chair in Translational Neuroengineering, Center for Neuroprosthetics and Institute of Bioengineering, School of Engineering, Swiss Federal Institute of Technology of Lausanne (EPFL), Lausanne, Switzerland; [2]Biorobotics Institute, Sant'Anna School of Advanced Studies (SSSA), Pisa, Italy; [3]Institute of Neurology, Catholic University, Rome, Italy; [4]Department of Geriatrics, Neuroscience, and Orthopedics, Policlinic A. Gemelli Foundation–IRCCS, Rome, Italy; [5]Laboratory for Biomedical Microtechnology, Department of Microsystems Engineering–IMTEK, Bernstein Center Freiburg and BrainLinks-BrainTools Center, University of Freiburg, Freiburg, Germany; [6]Department of Electrical and Electronic Engineering, University of Cagliari, Cagliari, Italy; [7]INRIA, CAMIN Team, University of Montpellier, Montpellier, France; [8]Axonic, Vallauris, France; and [9]Laboratory for Neuroengineering, Department of Health Sciences and Technology, Institute for Robotics and Intelligent Systems, ETH Zürich, Zürich, Switzerland

*F.M.P., G.V., I.S., and G.G. contributed equally as junior authors.
†S.R., P.M.R., and S.M. contributed equally as senior authors.
Additional supporting information can be found in the online version of this article.

The loss of a hand affects a person's quality of life.[1] From the first manufactured prostheses,[2] more effective clinical solutions have been provided; commercially available hands have been developed,[3] enabling users to control the movement of up to six degrees of freedom. In parallel, a major effort has been conducted in research to provide more dexterous artificial devices,[3] along with decoding methods allowing their control,[4,5] and, as requested by the final users,[6,7] to re-establish the sensory flow of information between the hand prosthesis and the central nervous system, through noninvasive and invasive approaches.[8–21]

Efforts have been dedicated to the use of implantable peripheral interfaces to elicit sensations.[14–20] After the pioneering studies with longitudinal intrafascicular electrodes (LIFE)[14], 3 interfaces have been used with human subjects: epineural (cuff[15–17] and flat interface nerve electrode (FINE)[15,16]), penetrating (Utah array[18,19]), and intraneural (transverse intrafascicular multichannel electrode [TIME][20] and LIFE[21]) electrodes.

Tyler's group showed that FINEs could be implanted for >48 months[15,16] in 2 upper-limb amputees allowing them to pull the stem from a cherry.[15] Notwithstanding preliminary encouraging results,[22] there is still no evidence that FINE-induced stimulation can be used to modulate some levels of the prosthesis grasping force, a priority for amputees, and one of the reasons such devices are abandoned.[6,7,23] Moreover, the quality of the elicited sensations was little differentiated (mostly paresthesia was reported[15]).

Utah arrays[18,19] have been shown to evoke percepts of more varied quality (tingle, vibration, pressure) in upper-limb amputees but with poor reproducibility in time. About 80% of the sensations evoked in 2 subjects changed location or type over a period of 5 weeks.

Finally, TIMEs[24] were transversally implanted into the residual nerves of an amputee for a period limited to 30 days by EU medical device regulations. During this experiment, TIMEs have been used to restore several features of the sense of touch including sophisticated ones such as the ability to control grasping force and to discriminate different textures, along with object compliance and shape.[20,25]

To date, TIMEs may represent an interesting tradeoff between the other 2 solutions, reducing their specific limitations in terms of sensation quality (FINEs) and stability (Utah arrays), and allowing the restoration of features such as prosthesis grasping force control. However, the sole study investigating it in humans was conducted on a single subject for only a month and with no detailed characterization of all the evoked sensations. Moreover, it is not yet clear[26] to what extent sensory feedback elicited by all these interfaces (not only TIMEs) can improve motor control performance in simulated ecological conditions[27] (eg, handling fragile objects when users can exploit both visual and tactile feedback). Finally, although it has been anecdotally reported that direct nerve stimulation induces phantom limb pain relief,[15,21] a more systematic characterization of the phenomenon has never been conducted.

To address these 3 issues, we conducted a 6-month clinical study with 3 transradial amputees implanted with 4 TIMEs in the residual median and ulnar nerves. We intentionally recruited subjects with different clinical conditions (long or short time since the amputation, affected or not by phantom pain) to investigate the exploitability of our approach for a variegated population of transradial amputees.

After characterizing the subjects' response to the intraneural stimulation, we investigated the effects of sensory feedback on the performance of the subjects during different reaching and grasping tasks accomplished with the support of vision (in ecological conditions) and without it. Finally, we assessed the effect of intraneural stimulation on phantom limb pain as well as on mood states during the period of study.

Patients and Methods

Patient Recruitment

Three left transradial amputees were included in the study (Table 1). The first subject (FNG) was a 37-year-old male, left-handed, who had a traumatic transradial amputation of the distal two-thirds of the left forearm 2 years before the enrollment in the trial. At the time of the trial he was affected by strong phantom limb pain and very frequent nonpainful phantom sensations. Other than the amputation and the consequent phantom limb syndrome, the clinical condition of the patient was unremarkable.

The second subject (ALM) was a 48-year-old female, right-handed, with a traumatic transradial amputation of the distal one-third of the left forearm, which occurred 23 years before the study. She was free of phantom pain and experienced very mild and infrequent spontaneous nonpainful phantom sensations.

The third subject (LRP) was a right-handed, 53-year-old female transradial (distal two-thirds of the left forearm) amputee. The amputation occurred in December 2015, following a traumatic accident at work. She was affected by phantom pain.

Ethical approval was obtained from the institutional ethics committees of Policlinic A. Gemelli-Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) at the Catholic University, Rome, Italy, where the surgery was performed. The protocol was also approved by the Italian Ministry of Health, Division for Experimental Devices.

TABLE 1. Patient Demographics

Patient	Amputation Cause	Amputation Level and Side	Age, yr	Time Since Amputation, yr	Phantom Limb Pain	Gender	Own Prosthesis	Frequency of Use	Handedness	Myoelectric Control Experience
FNG	Trauma	Distal two-thirds of left forearm (medium residual limb)	37	2	Strong	M	Cosmetic	Daily	Left-handed	None
ALM	Trauma	Distal third of left forearm (long residual limb)	48	23	None	F	None	None	Right-handed	None
LRP	Trauma	Distal two-thirds of left forearm (short residual limb)	53	1.5	Medium/ strong	F	Cosmetic	Daily	Right-handed	None

Clinical features of the volunteers enrolled in the trial are reported, including age, sex, cause of the amputation, used prosthesis, and frequency of its exploitation.
F = female; M = male.

All subjects signed the informed consent. During the entire duration of our study, all experiments were conducted in accordance with EU guidelines and regulations.

Surgical Procedures

Four TIMEs (14 active sites each) were implanted in the median and ulnar nerves of FNG on November 14, 2015; of ALM on June 24, 2016; and of LRP on June 24, 2017 (Fig 1A and Supplementary Video 1). The explant of the electrodes was executed on June 11, 2016, on December 17, 2016, and on December 16, 2017, for FNG, ALM, and LRP, respectively.

The surgical approach used to implant TIMEs has been extensively reported elsewhere.[20] Briefly, during general anesthesia, through a 15 cm-long skin incision on the left arm, the median and ulnar nerves were exposed to implant a proximal and a distal TIME in each nerve (see Fig 1A). The microelectrodes and a segment of their cables were drawn through 4 small skin incisions into proximity with the exposed nerve, 2 laterally and 2 medially to the center of the main surgical cut. The cable segments were located in subcutaneous pockets, externalized (and secured with sutures and subcutaneous strain release loops) to be available for the transcutaneous connection with a neural stimulator. Then, using an operating microscope (Pentero; Carl Zeiss, Oberkochen, Germany), the single microelectrode was implanted transversally within the nerve fascicles. Appropriate microsutures secured the nerve implant. This implantation procedure lasted 11 hours for FNG, 8 hours for ALM, and 11 hours for LRP. The impedance of the electrode active sites was monitored intraoperatively, to verify the integrity and functionality of the implant. After 180 days, the microelectrodes were removed under an operating microscope in accordance with the protocol and the obtained permissions.

A clinical and electrophysiological follow-up was executed at 4 months for ALM, 10 months for FNG, and 3 months for LRP.

Perceived Sensations Characterization

Regarding the subjects' response to the intraneural stimulation (sensation characterization or mapping procedure), the prosthesis was not worn, and the patient was connected only to the neurostimulator using the transcutaneous cables of the implanted TIMEs. The stimulation was triggered by the experimenter using custom-made software (MATLAB, R2016b; MathWorks, Natick, MA). The patient was blind to the stimulation configuration delivered. We injected trains of biphasic charge-balanced cathodic-first current-controlled pulses of increasing amplitude from 10 μA to 980 μA (steps of 10 μA), and fixed pulse width (chosen in the range of 10–120 microseconds depending on the active site) and

frequency (50 Hz as in our previous study[20]). Pulse trains of 2-second duration were delivered with an interval between trains of 2 seconds. The same set of stimulation parameters was delivered 3 times per active site. Hence, for example, per each active site the sensory threshold was determined as the average of the 3 minimum values of charge (1 per repetition, ie, 2-second train of current pulses) at which the subject reported a percept.

In each of these trains of increasing amplitude, patients had to press a button to stop the stimulation ramp when and if they perceived a sensation. Then, they had to report using a custom-made graphical user interface (MATLAB, R2016b) the sensation properties (location, type, quality, and intensity). The patients could select a word from a list (similar to the one prepared by Kim and colleagues[28]) to describe the evoked sensation, but they could also add a new word if needed.

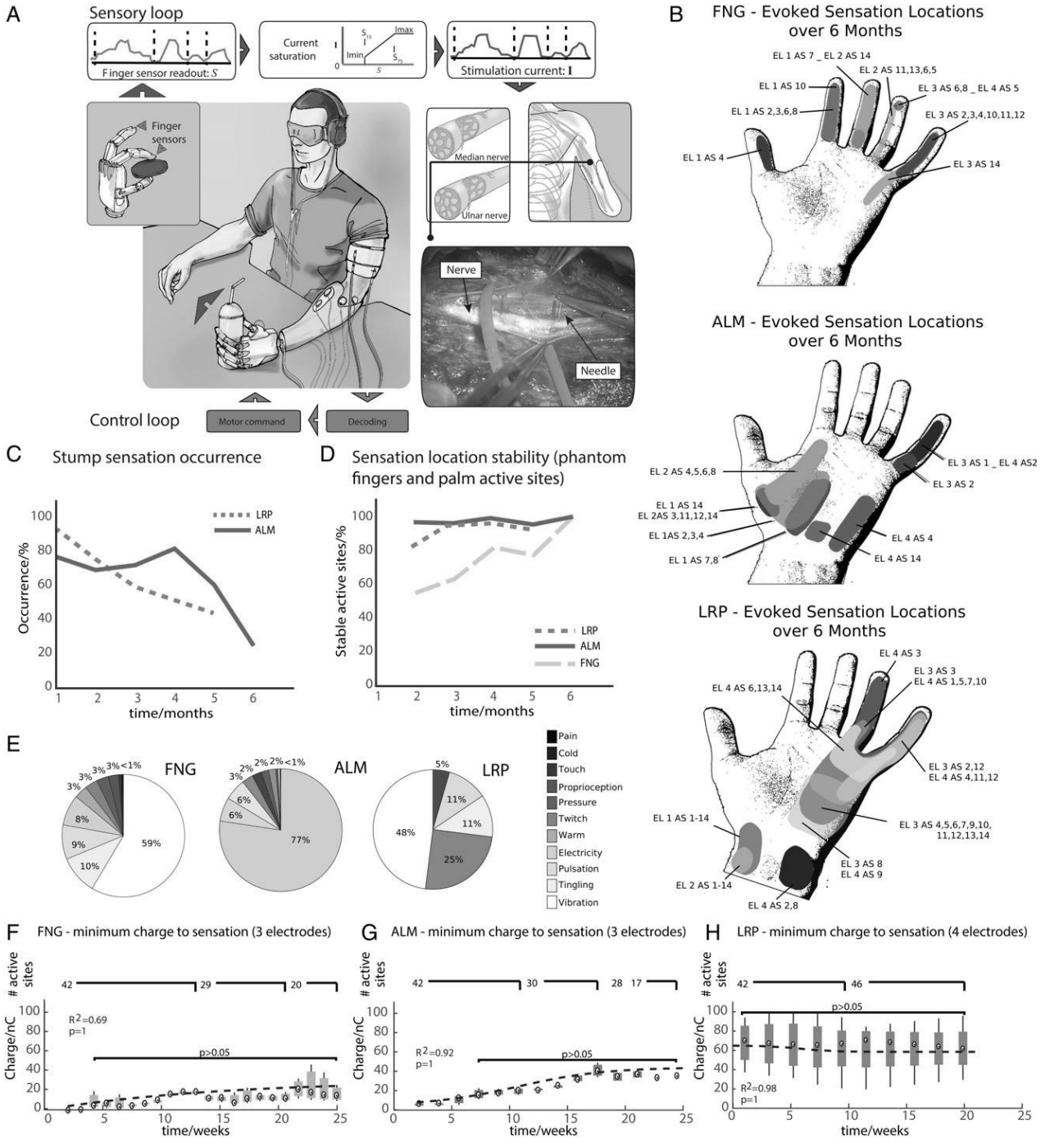

FIGURE 1: (legend on next page)

At the end of this procedure, a map of the sensation type, location, extent, and intensity (including the sensory threshold) referring to the correspondent active sites was obtained and used for the calibration of the sensory feedback restoration system.

The sensation characterization was performed once per week or every 2 weeks, according to the availability of the subjects (depending on whether they were spending the whole week at the clinical site for performing the tests or only part of it). Specifically, FNG and ALM did it weekly, whereas LRP did it every 2 weeks.

Finally, we assessed the stability of the elicited sensations on the phantom hand over time as change of location. Specifically, we considered 9 location clusters on the phantom hand (5 fingers and 4 palm areas). A sensation was considered stable when, from one week to another, an elicited sensation was perceived in the same cluster. We did not consider stump percepts in this analysis, because their stability was not of interest for the study. Conversely, we studied the occurrence of stump sensations over time.

Electrode Characterization

For the characterization of the electrode–nerve impedance we delivered trains of cathodic-first, biphasic, symmetric square-shaped, current-controlled stimulation pulses of variable intensity, duration, and frequency through dedicated software controlling the external electrical neural stimulator. The impedance was computed as the ratio of the potential difference between the selected active site and the ground of the electrode (both grounds of the electrodes were tested) at the end of the cathodic pulse phase. The potential resulted from the average of 5 pulses with an amplitude of 20 μA and a width of 300 microseconds, repeated at a frequency of 1 Hz. Electrodes were considered still working if their impedance was <100kΩ.

Prosthesis Movement Control

The subjects controlled a research hand prosthesis (IH2 Azzurra; Prensilia, Pontedera, Italy) using the muscle activity of their forearm residuum. In total, 2 pairs of disposable surface electrodes (Ag/AgCl, 24 mm diameter, 20 mm interelectrode distance) were placed on the digit flexor and the extensor extrinsic muscles. The signals were sampled at 2 kHz and digitally filtered using a 4th order pass-band (15–375 Hz) Butterworth IIR filter and a notch filter to remove the 50 Hz power line interference (through a Grapevine system; Ripple Neuro, Salt Lake City, UT). A robust 3-state (open = −1, close = 1, rest = 0) k-Nearest Neighbor (kNN, k = 3) classifier with a decision-based velocity ramp[29] was used to control the hand. The classifier was fed with the waveform length (WL) of each electromyographic (EMG) channel, computed over a window of 100 milliseconds, and allowed a gated-ramp control[30] of the speed of the robotic hand movements, as in the following relation:

$$V_{hand} \leftarrow V_{hand} + A \times Class_{output}; \quad \text{when } Class_{output} = -1, 1; \tag{1}$$

$$V_{hand} \leftarrow 0; \quad \text{when } Class_{output} = 0; \tag{2}$$

where A is a proportional factor that can be controlled by the experimenter, $Class_{output}$ is the output of the classifier, and V_{hand} is a number in the range between 0 and 511, which controls the velocity of the motors of the robotic hand. When V_{hand} = 1, the angular velocity of the robotic hand is 0.297°/s; when V_{hand} = 511, the angular velocity of the robotic hand is 511 × 0.297°/s = 151.76°/s.

FIGURE 1: Intraneural stimulation stabilized over time. (A) The subjects, after the implantation of 4 transverse intrafascicular multichannel electrodes in the median and ulnar nerves, periodically received sessions of stimulation in combination with or without the prosthesis. For the bidirectional control, sensor readout was used to drive intraneural stimulation. The relationship between these parameters was linear. The robotic hand was controlled through the electromyographic signal from the forearm residual muscles. The stimulation, when delivered without the prosthesis, was driven by custom-made software, through which the parameters of current were set, and the subjects' reports were recorded. (B) The results of the characterization shown in A as 75th percentile of the phantom sensation locations evoked during the 6-month clinical trial. AS = active site; EL1 = electrode #1 implanted in the proximal part of the median nerve; EL2 = electrode #2 implanted in the distal part of the median nerve; EL3 = electrode #3 implanted in the proximal part of the ulnar nerve; EL4 = electrode #4 implanted in the distal part of the ulnar nerve. (C, D) The number of sensations reported by subjects ALM and LRP on the stump (the same value from subject FNG is negligible) over time is plotted (C), along with the stability of the sensations elicited from the phantom hand (and not the stump) of FNG, ALM, and LRP (D). The stability was evaluated in terms of the location of the percept. The characterization results were used to calibrate the sensory feedback restoration system of the bidirectional prosthesis, whose motion was instead controlled by means of the electrical activity of the residual muscles of the amputated limb. (E) The types of sensation reported during the whole trial. (F–H) The minimum charge needed to evoke a sensation in FNG, ALM, and LRP. The boxplots are computed from the sensory thresholds of 3, 3, and 4 electrodes, respectively, for FNG, ALM, and LRP. The averages are obtained from the sensory thresholds of the active sites, which were < 120nC. Per each active site the threshold was determined as the average of 3 repetitions. The fitting performance (R^2 and p) of the saturating exponential function *(dashed lines)* is reported. The function is defined as $-D + C / (B + \exp[-x/A])$. B, C and D determine the saturation value (C/B - D), while A is the characteristic charge for the saturation process. Two-tailed Friedman test with Tukey–Kramer correction for multiple groups of data was performed. [Color figure can be viewed at wileyonlinelibrary.com]

The classifier required a training session every time the surface EMG electrodes were newly placed. During the training the user was asked to relax (one time for 2 seconds), then open (one time for 2 seconds), and finally close (one time for 2 seconds) the phantom hand. The resulting EMG activity was recorded and manually separated into 3 classes basing on the WL.

Prosthesis Sensory Feedback

Two force sensors embedded in the little and index fingers of the prosthesis were used as control inputs for the intraneural stimulation of 2 active sites in the sensory innervation territories of the median and ulnar nerves. Specifically, the amplitude of biphasic, symmetric, cathodic-first, and rectangular charge-balanced pulses was modulated according to the following linear relationship:

$$c = (c_{max} - c_{min}) \times (s - s_{15})/(s_{75} - s_{15}) + c_{min}, \quad \text{when } s_{15} \le s \le s_{75}; \tag{3}$$

$$c = 0, \quad \text{when } s < s_{15}; \tag{4}$$

$$c = c_{max}, \quad \text{when } s > s_{75}; \tag{5}$$

where c is the amplitude of stimulation current, s is the sensor readout, and s_{15} and s_{75} represent 15% and 75%, respectively, of the maximum range of the sensor readout, which characterize, respectively, the contact threshold of the robotic hand and a value tuned to exploit the full range of sensations for all objects. c_{min} and c_{max} are the stimulation current amplitudes that elicited, respectively, the minimum and maximum (ie, below pain threshold) touch sensations as reported by the subject according to the last sensation characterization procedure. The frequency of the stimulation is 50 Hz.[20] The overall control scheme is provided in Fig 1A.

We used 2 active sites for the development of the bidirectional prosthesis, one in the sensory innervation territories of the median nerve and one in those of the ulnar nerve, eliciting sensations respectively in an area of the phantom hand that was the closest to the prosthesis index finger and in an area closest to the little finger. This was chosen to maximize the somatotopy of the phantom sensations during prosthesis exploitation.

Neurostimulators

Three neural stimulators were used to inject currents into the nerves of the 3 subjects by means of TIME electrodes: STIMEP, EARNEST, and the Grapevine Neural Interface System.

STIMEP (University of Montpellier, Montpellier, France and Axonic, Vallauris, France) is a wearable neural stimulator based on a generic neural stimulation architecture.[31,32] It allows the control of 64 poles of implanted electrodes, divided into 4 ports of 16 poles each. Therefore, up to 4 TIME electrodes can be driven in real time (pulse width, intensity, frequency). Each port addressing each TIME electrode includes 14 capacitively coupled active outputs (channels) and 2 noncapacitively coupled references. STIMEP further embeds safety procedures (charge limit) and impedance measurements. This stimulator was used for all the tests on FNG.

EARNEST (University of Cagliari, Cagliari, Italy) is a prototypical, wearable, complete embedded platform for neural prosthetic applications.[33] It allows simultaneously control and use of up to 4 implantable multisite (16 channels) electrodes, placed on the same subject, for a total of 64 stimulation/recording channels. The device allows recording of neural signals and, at the same time, provides electrical stimulation fully programmable in terms of amplitude, duration, shape, and frequency. It embeds also a recording module for EMG signals from 4 differential surface electrodes. This stimulator was used on ALM for Sensation Characterization, Force Control Test (FCT), and Blindfolded Sensory Blocks Test (BSBT).

The Grapevine Neural Interface System (Ripple Neuro) is a commercial device that can be used for the recording of neurophysiological data and for delivering current-controlled stimulation through up to 32 high-impedance microelectrodes. This system was used on ALM for the Sensation Characterization, FCT, and Virtual Eggs Test (VET), and for the whole trial with LRP.

Validation Tasks

To verify whether sensory feedback could allow subjects to improve performance in the prosthesis movement control, 3 functional tasks were used: VET,[34] BSBT,[12] and FCT.[20]

First, to assess whether intraneural stimulation in addition to vision could improve motor control, we asked the subjects to perform a test resembling the realistic task of transferring fragile objects (such as eggs), namely the VET. The VET is a recently proposed test for sensorimotor assessment.[34] In brief, it is a modification of the well-known box and blocks test[35] except that fragile/breakable blocks (resembling virtual eggs) are used instead of the standard wooden ones. During the VET, the subjects, wearing the prosthesis, are instructed to transfer the fragile blocks presented in front of them from one side to the other over a 15 cm-tall wall as fast as possible and without breaking them. The performance is measured as the percentage of the number of transferred blocks out of the total number of blocks (transferred plus broken) during 1-minute trials, similar to the standard box and blocks test. In this work, the virtual eggs ($40 \times 40 \times 40$ mm^3

blocks, ~80 g) exploited a magnetic fuse mechanism, which would collapse/break when grasped with a grip force larger than a specified threshold. The latter was calibrated at a force value that was roughly 50% larger than the grip force required by the artificial hand to lift it (1.23 ± 0.02 N). This value was validated during the tests with FNG (4 trials feedback-on and 4 trials feedback-off). The test is schematized in Fig 2A and shown in Supplementary Video 2. The VET was performed by FNG at month 4 after the surgery, by ALM at months 2 and 3, and by LRP at months 2 and 3.

Once we assessed the benefit of intraneural sensory feedback in addition to vision during tasks requiring sensibility, we further tested the efficacy of our approach during 2 additional experiments, in which the volunteers were blindfolded and acoustically isolated: the BSBT and the FCT.

In the BSBT, subjects wearing the prosthesis transferred wooden and unbreakable blocks, during 240-second sessions, from one side of a table to the other (see Fig 2D and Supplementary Video 2). In particular, an operator presented or did not present objects to the prosthesis, and the subjects had to decide whether he/she had successfully grasped them, and then had to transfer them to the other side of the table. If the participant felt that no object was gripped, he/she was instructed to reopen the hand for the next repetition. The performance was rated through a score; 1 point was attributed for every successfully transferred block or when the subjects correctly identified that there was not an object in their robotic hand; in any other condition, no points were assigned, and errors were counted. Because the same score was given to the recognition of a grasped object and of a missing object, the number of transfers (hence, the overall score) depended on the time the subjects spent to make a decision about a grasp. The number of object presentation events was balanced with the case in which no object was placed in the prosthesis. This design was put in place to avoid performance discrepancies between trials due to object seeking. The BSBT was performed by FNG at months 2 and 3 after the surgery, by ALM at month 2, and by LRP at month 2.

In the FCT (Fig 3A), as in Raspopovic et al.,[20] the subjects were acoustically shielded and blindfolded and asked to apply 3 levels of grasping force (low, medium, and high) on a dynamometer, using (but not wearing) the robotic hand. The prosthesis and the dynamometer were constrained by 2 presses at a constant position, to guarantee the repeatability of the grasps. The participants were instructed to rely on the sensory information to judge how much force they were applying and to stop when they considered they had reached the desired level (low, medium, or high). They had to decide the amount of force required to apply its minimum, medium, and maximum level. The patients performed a short familiarization session (~5 minutes), during which they could squeeze the dynamometer with the bidirectional prosthesis exploring the sensory feedback. Then, the experiment was performed. The experimenter requested the various force levels by touching the patients' shoulder once (low), twice (medium), or 3 times (high). Patients reproduced the desired force level, maintaining the level for 2 seconds, and then they returned to the initial hand position (fully open hand), ready for the next level. The velocity of the hand movement execution was randomly modified (3 velocities, by setting A = 1, A = 2, A = 3 as in Equation 1) without informing the participants, to prevent them from relying on learned closing times to execute the task. The FCT was performed by FNG at months 2 and 5 after the surgery, by ALM at months 2 and 5, and by LRP at months 2 and 5.

Phantom Limb Pain and Mood States Assessment

FNG and LRP were asked to fill out Neuropathic Pain Symptom Inventory (NPSI),[36] visual analogue scale (VAS),[37,38] and Profile of Mood States[39] questionnaires during the 6 weeks before the implant and each day they received the intraneural stimulation (ie, every week). ALM, not having any phantom limb syndrome, did not fill out the questionnaires.

Statistical Analysis

All data were extracted and processed in MATLAB (R2016b). The normality of the data was first checked (1-sample Kolmogorov–Smirnov test). Because none of the data was normally distributed, for the analyses in the paper a 2-tailed Friedman test was used to analyze data and, when needed, a Tukey–Kramer correction for multigroup comparison was applied. For performance comparisons over time only, that is, first and last session of VET (see Fig 2), BSBT (see Fig 2), and FCT (see Fig 3), a Fisher exact test was computed. For the comparison of different levels of intensity of sensations, a Kruskal–Wallis test was executed.

Additionally, for the analysis of the force levels (see Fig 3), for each trial, the duration was normalized, and an average force value was computed over a fixed interval (interval from 60% to 90% of trial completion). To compute the "performance" score (given as a percentage of correct trials), we first obtained the average force value for each force level, using the method outlined above. Then, we assigned each repetition to the nearest force level. Finally, we computed the performance score as the percentage of repetitions correctly assigned to the right force level.

The number of repetitions per session and the number of sessions per test are reported in the figure captions.

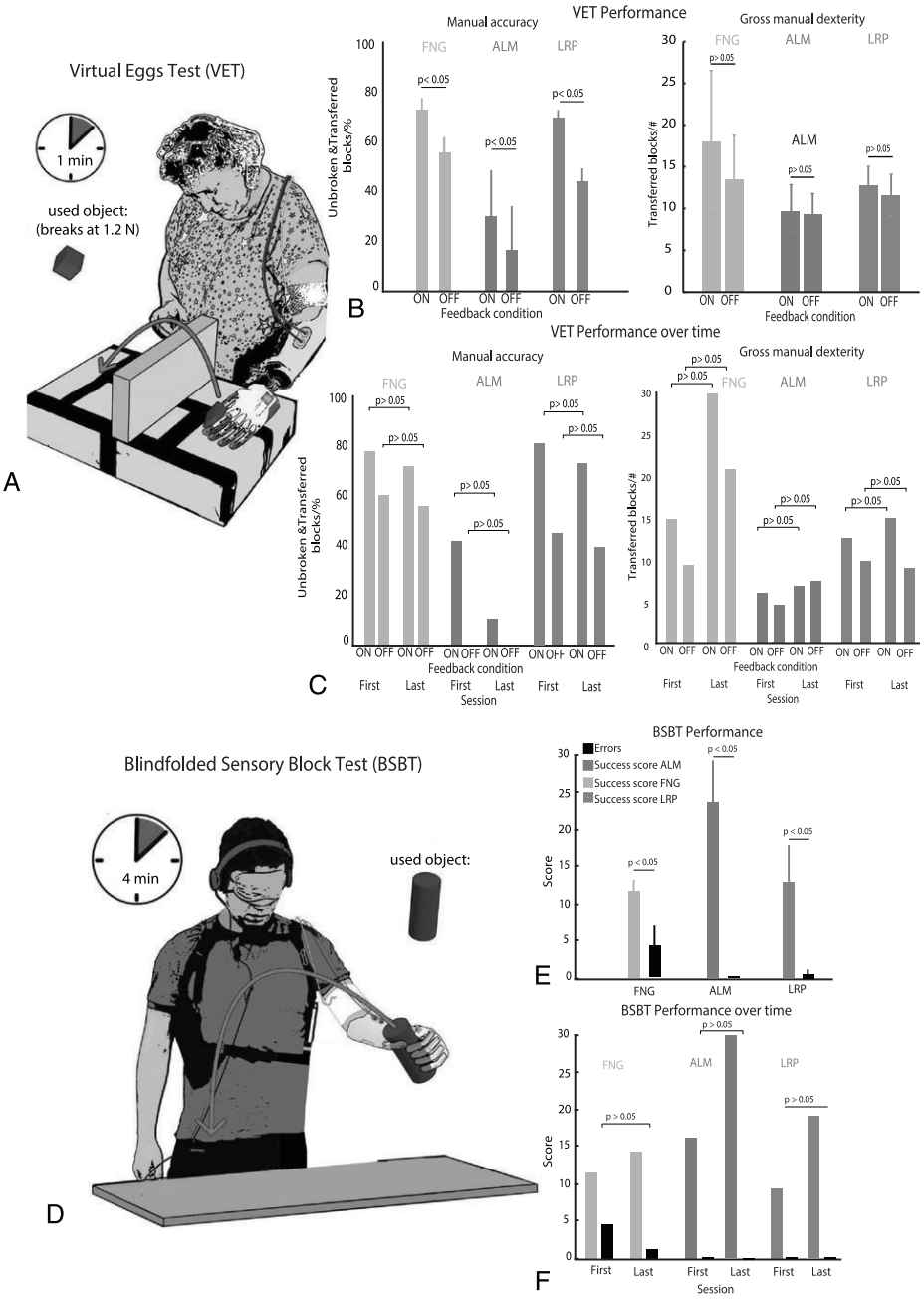

FIGURE 2: The Virtual Egg Test (VET) and Blindfolded Sensory Blocks Test (BSBT). (A) During the VET, the subjects are instructed to transfer the fragile blocks presented in front of them from one side to the other over a 15 cm-tall wall as fast as possible without breaking them. (B) Performance for subjects FNG (n = 4 × 2 repetitions), ALM (n = 27 × 2 repetitions), and LRP (n = 5 × 2 repetitions). The percentage of transferred blocks out of the total number of blocks (transferred plus broken) with and without sensory feedback is indicated on the left. On the right, the total number of transferred blocks is displayed. Data are shown as mean values ± standard deviation (SD). Statistical evaluations results in B were obtained using the Friedman test. (C) Performance and total number of transferred blocks over time. The data related to the first and the last sessions, with and without sensory feedback for both subjects, are reported. Statistical evaluation results were obtained using Fisher exact test. (D) Schematic of the BSBT experiments. (E) The performance on the BSBT for FNG (n = 9), ALM (n = 3), and LRP (n = 3) is shown. The score and errors are indicated, and the data are reported as mean values ± SD. Statistical evaluations results in E were obtained using the 2-tailed Friedman test. (F) BSBT performance over time is shown. The data related to the first and the last sessions for both subjects are shown. Statistical evaluation results were obtained using Fisher exact test. [Color figure can be viewed at wileyonlinelibrary.com]

Results

Surgical Results

No side effect related to the surgical procedures was observed. Complications related to the median and ulnar nerves secondary to surgical injury, infection, bleeding, or relocation of the electrodes were not observed in FNG and LRP during the trial. ALM had an infection from 3 of the implants (*Staphylococcus aureus*, confirmed by

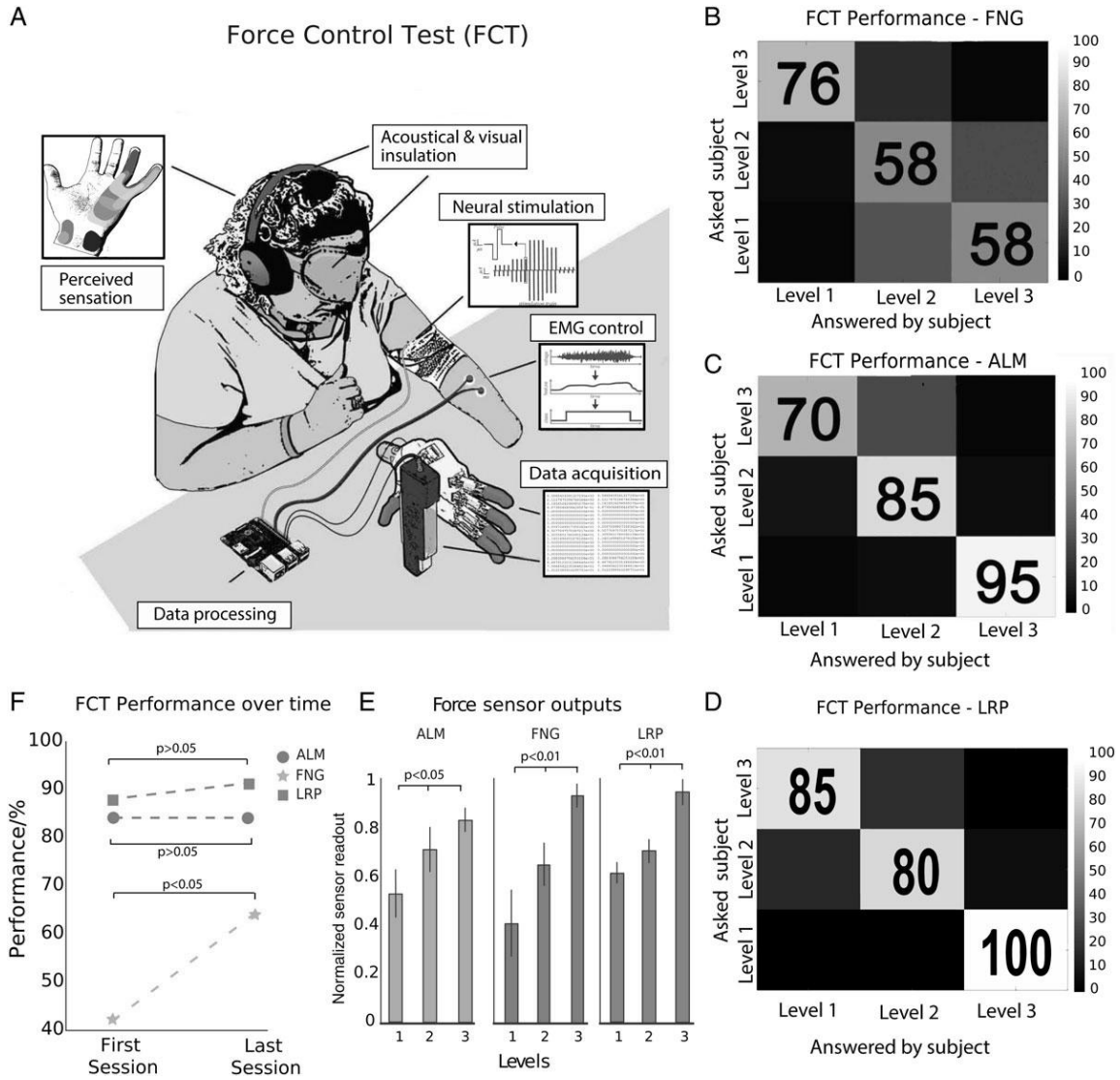

FIGURE 3: Force Control Test (FCT). (A) Schematic of the FCT experiments. EMG = electromyographic. (B) The performance in the last executed FCT for subjects FNG (n = 90), (C) ALM (n = 90), and (D) LRP (n = 90) are shown. The confusion matrices for all subjects are indicated. (E) For FNG, ALM, and LRP, the sensor readings in the 3 force levels are reported as mean values ± standard deviation. Statistical evaluations (results in the figure) were performed using the 2-tailed Friedman test. (F) FCT performance over time for all subjects (n = 180 for FNG, n = 180 for ALM, n = 180 for LRP) is shown. Statistical evaluation results in E were obtained using Fisher exact test. [Color figure can be viewed at wileyonlinelibrary.com]

wound swab culture) 2 weeks after the surgery. During this period, 1 electrode fell out (after 7 weeks) while the patient was sleeping. The infection was treated and eradicated with 6 weeks of combined antibiotic therapy. Nevertheless, also in the case of ALM, there were no complications related to the median and ulnar nerve injury at the end of the trial. The follow-up excluded long-term complications or loss of function compared to presurgery conditions. The results presented in the rest of the article take into consideration 3 electrodes for FNG and ALM, and 4 for LRP. As mentioned, ALM lost an electrode after 7 weeks, and for FNG the external connector of one implant completely broke at week 20.

Perceived Sensation

Throughout the whole trial, all subjects reported sensations elicited by intraneural stimulation on the phantom hand (see Fig 1). In terms of location, FNG reported sensations in all his phantom digits, whereas ALM felt phantom sensations more on the palm and LRP more on the ulnar territories of innervation of the hand. Interestingly, at the beginning of the trial, ALM and LRP reported sensations mainly localized at the residuum, whereas over time most of these perceptions progressively moved to the phantom hand.

Along with the trial, the perceptions became very stable; almost 100% of the active sites for ALM, FNG,

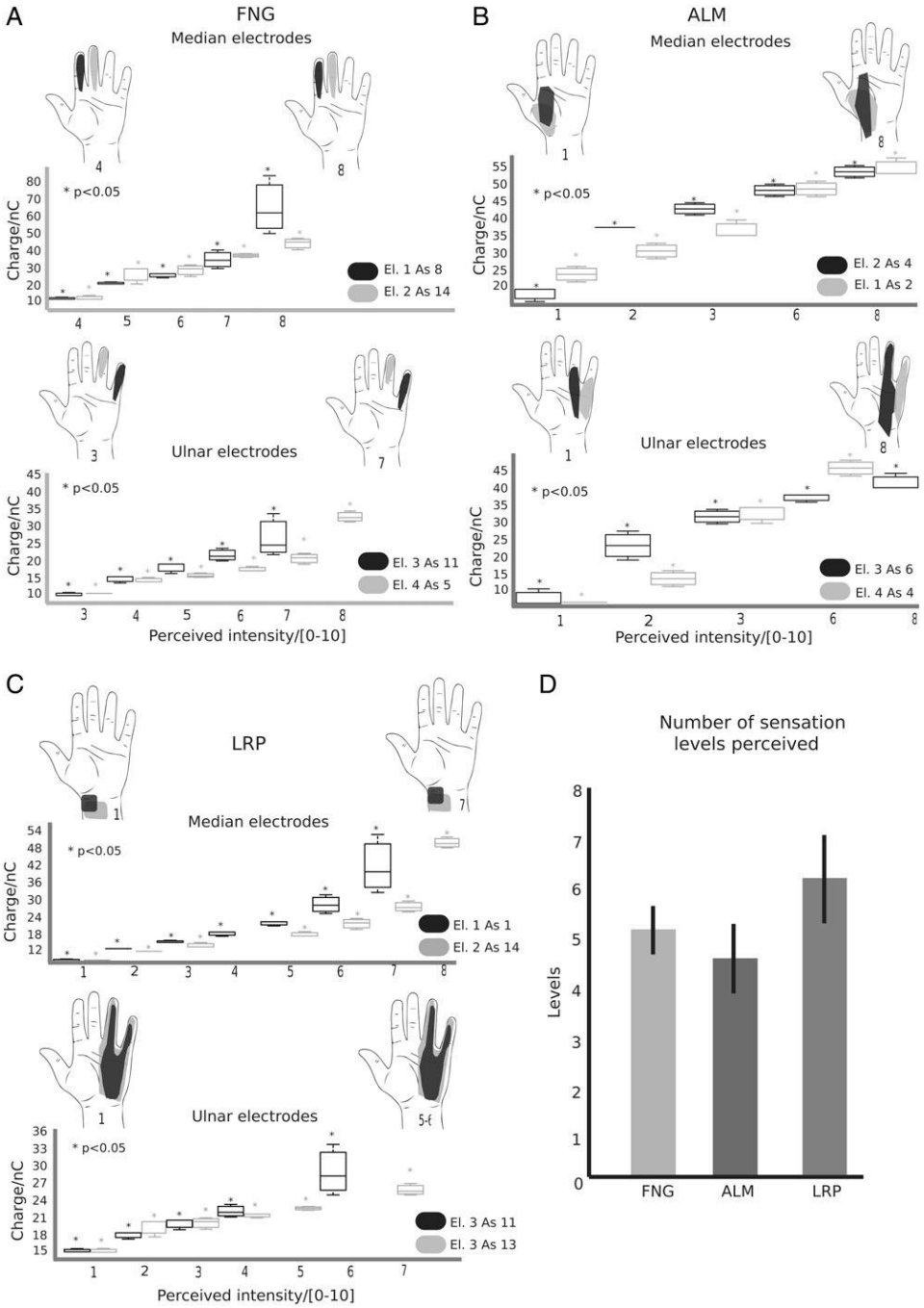

FIGURE 4: Perceived sensation levels and locations. (A–C) The ranges of injected charge for each pressure level perceived by subjects FNG (A), ALM (B), and LRP (C) related to 4 active sites per subject used for the implementation of the bidirectional prosthesis are reported. Data in the figure are represented as median and 25th–75th percentiles. Two-tailed Kruskal–Wallis test with Tukey–Kramer correction for multiple groups of data was performed. *$p < 0.05$. Sensation locations for maximum and minimum intensities reported by each patient during the modulation of charge of the stimulation train are reported (top). In the maps of hand sensations, each shaded area indicates the 75th percentile of the phantom sensation evoked at 4 active sites for each patient (2 on the median and 2 on the ulnar nerve). As = active site; El. = electrode. (D) The number of statistically different pressure levels perceived by the subjects, shown as mean ± standard deviation. [Color figure can be viewed at wileyonlinelibrary.com]

and LRP elicited a sensation that maintained the exact same phantom hand location (see Fig 1D). ALM and LRP very soon reached this level of stability, whereas FNG, who reached about 80% stability at the 4th month, needed the entire study period.

A wide range of sensation types (11 different ones) was elicited by the intraneural stimulation (see Fig 1E); as a note, FNG and LRP experienced a feeling of electricity in the phantom hand less than about 10% of the times, whereas in ALM such a percept was reported in 3 of 4 cases.

Analogously to the location of the elicited sensations, also the minimum charge (threshold) required to elicit a percept reached a plateau at around 20nC for FNG, 40nC for ALM, and 60nC for LRP (see Fig 1). It is interesting that whereas for the first 2 subjects, the plateau was reached after a period of adaptation (4 and 7 weeks for FNG and ALM, respectively, $p < 0.05$), for LRP the threshold recorded during the first week of experiments remained the same until the explant. All these thresholds were far below the tolerated maximum safe charge injection capacity of the TIMEs, determined to be 120nC.[24]

Finally, all subjects reported a direct proportional correlation between the charge of the current injected in the electrode active sites and the intensity of the evoked sensations (Fig 4). Conversely, raising the injected charge, even if producing a very limited increase of the extent of the area of the elicited sensations, did not affect their location cluster (intended as defined before).

Electrode Characterization

The impedance of the active sites was stable for FNG and LRP at 80kΩ and 70kΩ, respectively, since the beginning of the study, whereas for ALM it changed after the implant in the residual nerves, to stabilize after 3 weeks around a plateau of 40kΩ ($p > 0.05$; Fig 5). Equally important, we noticed a reduction of around 45% of usable channels (impedance >100kΩ) from the 3 studied electrodes toward the end of the study for FNG and ALM. Further investigation, however, of the explanted electrodes allowed us to relate this event exclusively to a loss of electrical continuity between the extracorporeal connectors and the transcutaneous cables due to repeated mechanical stress during connection and disconnection of the TIMEs from the stimulator. Neither the active sites nor the 2 segmented counter electrodes per TIME showed signs of corrosion due to electrical stimulation or delamination from the substrate and the insulation. No alterations of the assembling structures of the ceramic carrier with the thin-film structure, the precision mechanics cables, or the cables themselves were observed during optical inspection. Wire breakage at the connector site was the only failure mode that occurred.

To avoid this breakdown, the portion of the electrode cables for LRP that was affected by the continuous connection and disconnection with the external stimulator was reinforced with an additional layer of silicon. Thanks to this expedient, the 4 electrodes for LRP had about 90% of active sites functioning until the end of the study (see Fig 5C, bottom).

Validation Tasks

In the VET, all subjects transferred a significantly larger number of unbroken virtual eggs when the intraneural feedback was provided compared to the no-feedback condition (57% vs 72% for FNG, 18% vs 28% for ALM, 45% vs 70% for LRP, $p < 0.05$; see Fig 2B). Interestingly, all the patients increased the percentage of unbroken and transferred blocks (manual accuracy) when using the sensory feedback condition, maintaining the number of transferred blocks in total (gross manual dexterity).

No significant improvement over time in the number of transferred virtual eggs (overall number or successfully displaced items) was observed (see Fig 2C).

The BSBT was successfully executed by FNG, ALM, and LRP. The objects displacement score for all of them was higher than the error count (12 vs 4, 24 vs 0, and 13 vs 1 for FNG, ALM, and LRP, respectively, $p < 0.05$; see Fig 2E). For ALM, remarkably, we did not observe any mistaken trial. As in the VET, even if a positive trend in score was observed over the course of the study, this was not statistically significant (see Fig 2F).

Finally, during the FCT, the subjects were able to modulate their grip force at the 3 different levels at the end of the study ($p < 0.05$ for FNG and $p < 0.01$ for ALM and LRP; see Fig 3). ALM and LRP managed from the beginning to complete the task with a performance of about 83% and 88%, respectively, which was maintained until the last session of tests (22nd week for ALM and 13th week for LRP, $p > 0.05$). FNG instead began with a score just above chance level (41%) but improved by >50%, achieving a score of about 65% in the last trial (23rd week for FNG, $p < 0.05$).

Phantom Limb Pain and Mood States Assessment

Remarkably, during the whole period of provision of the intraneural stimulation, both FNG and LRP experienced a reduction of pain, according to all the rating scales that were provided to them. FNG reported a significant decrease of 36% on the NPSI and 57% on the VAS ($p < 0.01$; Fig 6). Similarly, the NPSI for LRP decreased from 18 to 5 ($p < 0.05$), and her VAS from 6 to 3.2 ($p < 0.01$). Finally, we observed that the mood states of the subjects benefited from the use of the bidirectional prosthesis (eg, the subjects felt less nervous or miserable at the end of the study).

Discussion

Long-Term Usability of Intraneural Electrodes

We have proved for the first time that intraneural interfaces are stable (in terms of elicited sensations and from a materials science viewpoint) and functional during chronic implantation in humans to deliver tactile sensory feedback. After the clinical trial, the location and the minimum charge needed to elicit a sensation were stable as well as the impedance of the working active sites,

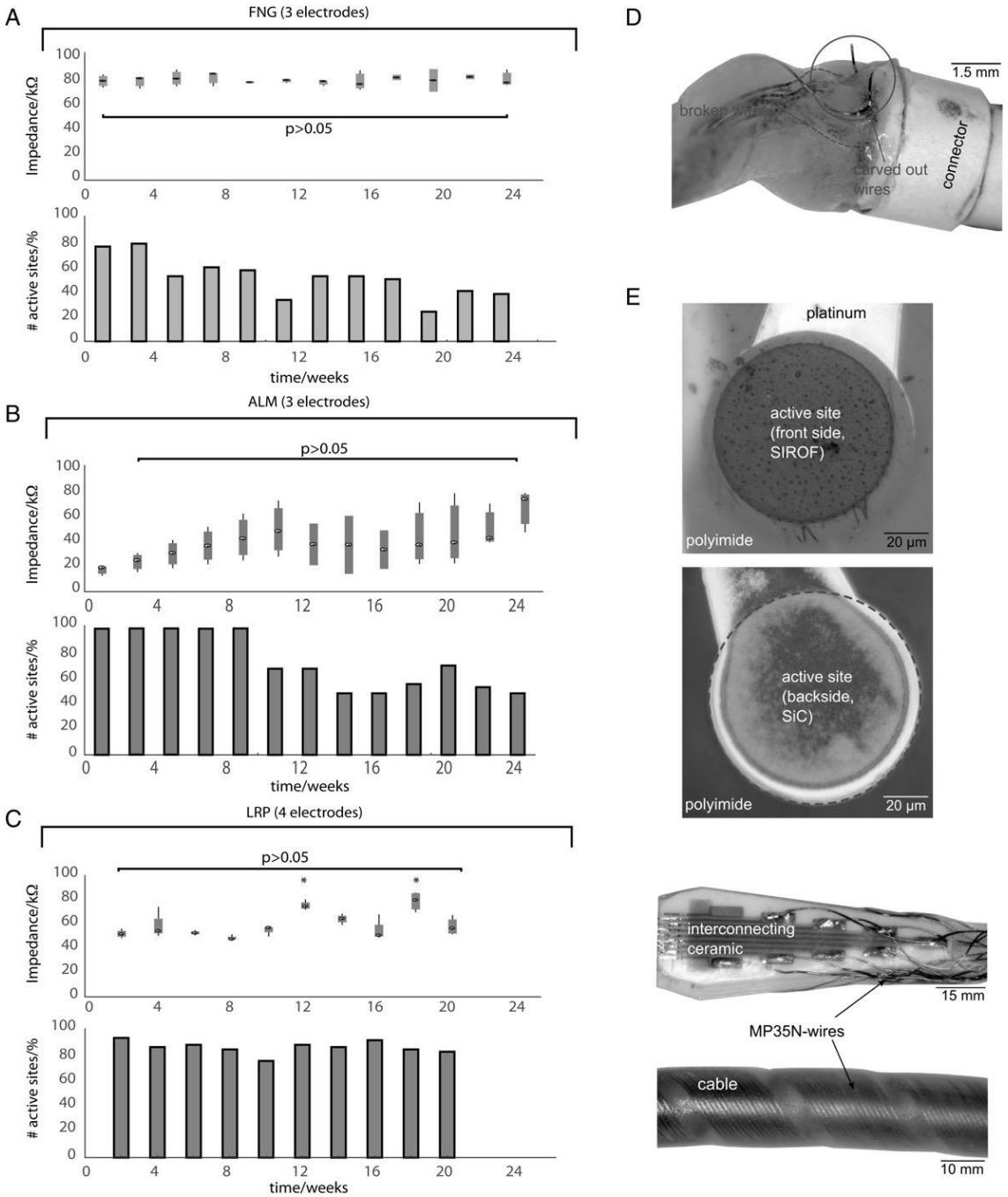

FIGURE 5: Intraneural electrodes are stable over time. (A, B) The impedance of the electrode active sites after an initial increase reached a plateau for both subject FNG and subject ALM (respectively, A, B, top). (C) For subject LRP, the impedances were stable from the first week. The number of active sites with impedance <100 kΩ, used to compute the average impedance, is displayed for FNG, ALM, and LRP (respectively, A–C, bottom). Per each active site, a single measure of impedance was executed. Two-tailed Friedman test with Tukey–Kramer correction for multiple groups of data was performed. *$p < 0.05$. The loss of active sites (impedance >100 kΩ) is due to the mechanical stress related to the connection and disconnection of the electrode cables with the external stimulator. (D, E) Microscopic inspection indicates damage only at the extracorporeal transition between cables and plugs and not at the implanted transition between cables, ceramic portion, and polymer thin-film structure. The deposited thin-film electrodes adhered well on the polymer substrate and showed no signs of corrosion or deterioration. SiC = silicon carbide; SIROF = sputtered iridium oxide film. [Color figure can be viewed at wileyonlinelibrary.com]

confirming our previous results with animal models.[40] During the whole study period, all subjects reported sensations from the phantom hand when intraneural stimulation was provided. These (above all the stability of the location of the sensations) are the most important requirements to guarantee the clinical exploitation of the

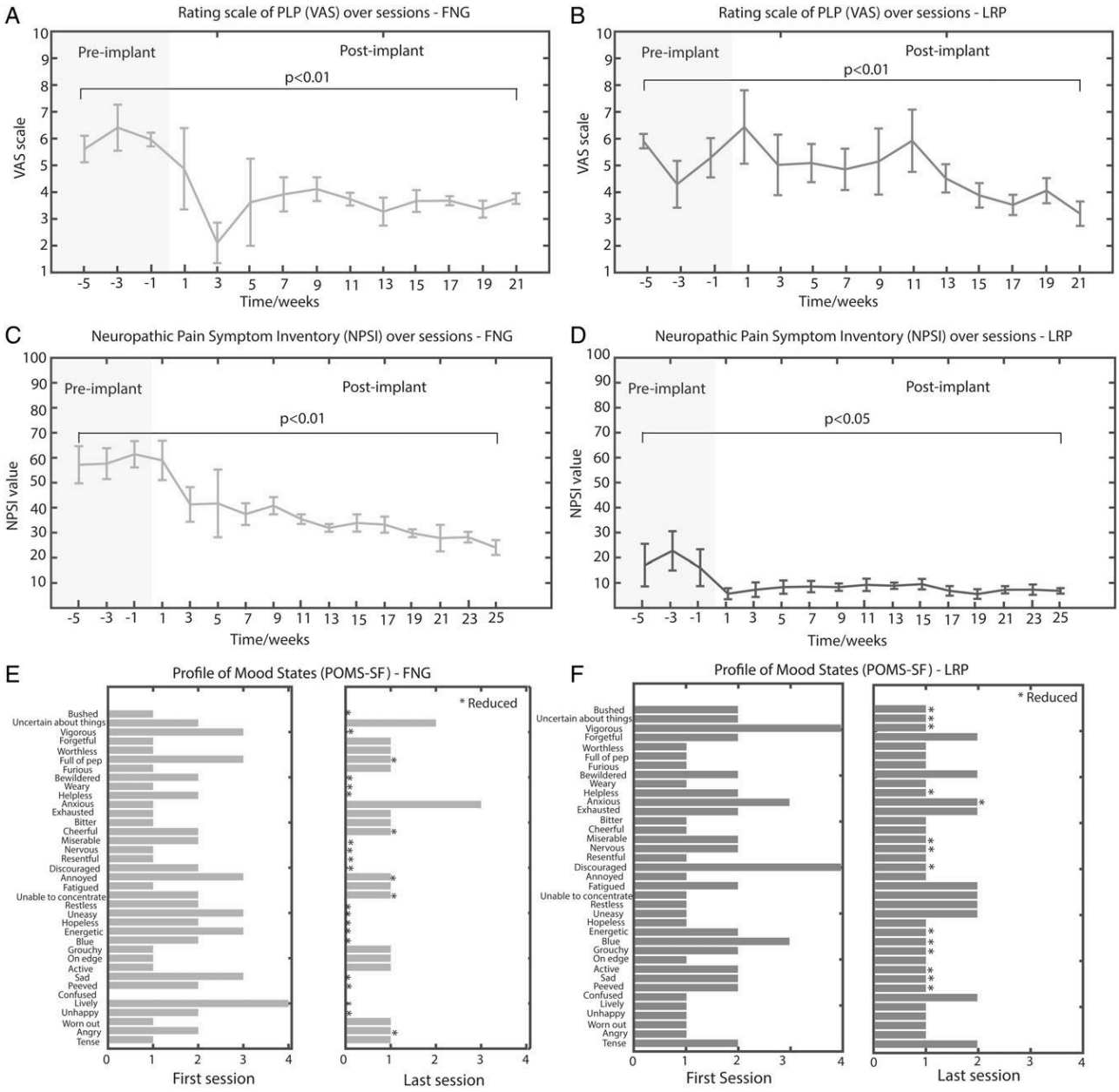

FIGURE 6: Phantom limb pain (PLP) evaluation. The Neuropathic Pain Symptom Inventory (NPSI), visual analogue scale (VAS), and short form of the Profile of Mood States (POMS-SF) were recorded before the implant and during each session of neural stimulation before the explant. (A, B) The VAS scores evolution throughout the weeks is displayed for subjects FNG (A) and LRP (B). (C, D) The NPSI scores are displayed for FNG (C) and LRP (D). The data are reported as mean values ± standard deviation. Statistical evaluations were performed between first and last session using the 2-tailed Friedman test. (E, F) The POMS-SF results related to the first (left) and the last (right) session are shown for FNG (E) and LRP (F). * Reduction from the first to the last session. [Color figure can be viewed at wileyonlinelibrary.com]

intraneural sensory feedback restoration device. A slight oscillation in the number of active sites with impedance <100kΩ was observed from week to week in FNG, ALM, and LRP, probably due to the impedance measuring setup. Also, for subject LRP we observed an increase in the number of active sites with a sensation threshold <120nC. This was possibly due to a minor increase over time of the sensitivity of the subject to stimulation.

A great variety of sensation qualities have been elicited both within and between subjects. Many of these sensations (~60%, ~15%, ~50% for FNG, ALM, LRP, respectively; see Fig 1E) can be associated with those that can be perceived with the healthy limb when interacting with objects (eg, pressure or vibration, which we consider "natural" in this article, ie, similar to those that are perceived with the intact limb). It is worth mentioning that in FNG and LRP we also

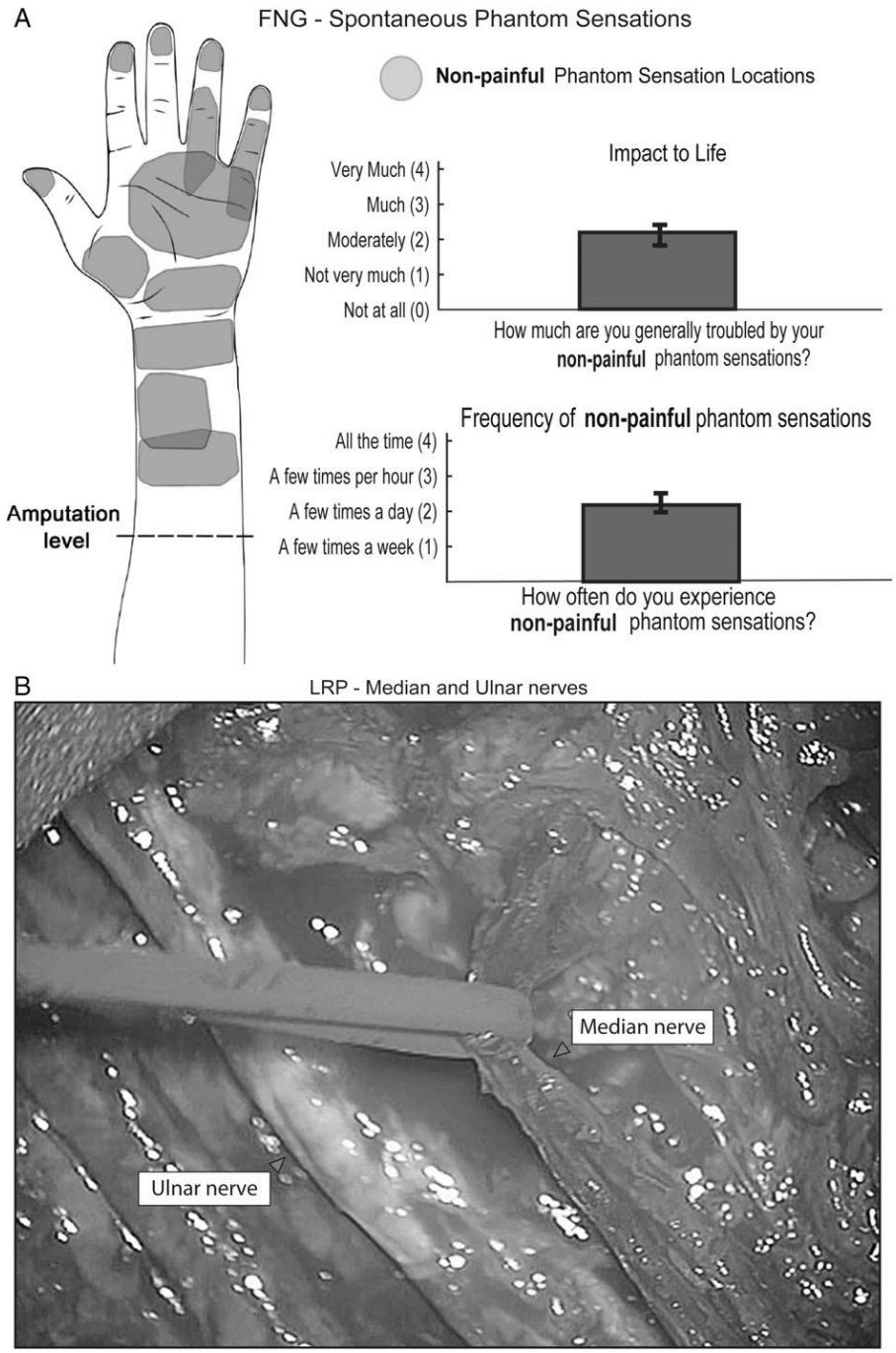

FIGURE 7: Subject FNG spontaneous phantom sensations and subject LRP median and ulnar nerves. (A) On the left, the localization of FNG's nonpainful spontaneous phantom sensations is depicted. On the right, respectively from top to bottom, are responses on impact to life and frequency of occurrence evaluation questionnaires of phantom sensations filled out by FNG. (B) The picture, taken from the intraoperative microscope, shows the small size and the altered aspect of the median nerve (in comparison with the adjacent ulnar nerve) in LRP. [Color figure can be viewed at wileyonlinelibrary.com]

demonstrated that the intraneural stimuli were able to elicit brain responses in the sensory areas (somatosensory evoked potentials) with a shape similar to those evoked when stimulating sensory fibers in intact nerves.[41] Similar sensation qualities were reported in studies on amputees implanted with penetrating electrodes; however, the stability of the percepts obtained with them were low compared to our results.[18,19] Mostly unnatural percepts (paresthesia) were instead reported with epineural electrodes.[15] This observation leads us to hypothesize that the quality of elicited sensations is primarily coded by the types of nerve fibers recruited through neural stimulation. This suggests that electrodes able to target a circumscribed population of fibers (likely of similar type[42,43]) may be more suitable to elicit natural sensations; the

simultaneous activation of fibers of different types is not physiologic, as they have their own specific firing rates.[44]

We also need to note that some of the sensations reported by the 3 subjects were unnatural (eg, electricity). We believe that new encoding strategies must be identified in the future to elicit more natural sensory feedback. We think that, since sensory feedback is one of the requirements of amputees for future prostheses and one of the reasons for abandonment of presently available ones,[7] the quality of the restored sensations will play an important role in device acceptance.[45,46] Neural stimulation should elicit sensory feedback that is at the same time efficient (ie, usable to increase motor control performance) and highly natural, as the naturalness of the feedback plays a pivotal role in prostheses acceptance.[22] More investigations are necessary to test whether more natural sensory feedback could improve not only acceptance but other factors such as prosthesis control, dexterity, and embodiment in amputees.

An interesting phenomenon was reported by subjects ALM and LRP during the study. In their case, many sensations moved from the residuum to the phantom hand throughout the weeks. We hypothesize that both subjects had a deeply reorganized connectivity between the central nervous system and the peripheral nerves of the stump, compared to FNG. In LRP, the nerve ultrasound, performed before the electrodes were implanted, showed a reduced cross-sectional area (between 4 and 5mm^2) of the median nerve in the tract between the elbow and the proximal third of the arm compared to the physiological values for median[47] and ulnar nerves.[48] The surgery confirmed the reduced size of the median nerve compared to the ulnar one (Fig 7B). In ALM, the long interval between the amputation and enrollment in the study (>20 years) may have induced great and stabilized plastic changes in the paths between the brain and the peripheral nerves.[49] It is known[49] that in such conditions the deafferented areas of the brain can be "invaded" by the adjacent ones (the forearm and the face, in the case of hand amputees), and that the passive electrical activation of fibers originally directed to the lost body part can generate a sensory perception in these areas and not in the phantom.[49] The 6-month stimulation of these fibers, combined with the use of a prosthetic hand, may have induced a partial regression of the abovementioned plastic changes. Another possibility (not excluding the previous one) is that the continuous stimulation of peripheral nerves (generating a peculiar pattern of sensation) combined with the intensive use of the prosthetic hand may have promoted a process of embodiment of the device (taking advantage of brain plasticity), with a progressive association of the peculiar pattern of sensations with the prosthetic hand itself.[50]

Because the clinical features of ALM and LRP were very different, we hypothesize that this phenomenon could affect a larger population of amputees, with no restriction. Further studies on this matter are needed.

Also, this phenomenon could be exploited in the future to develop novel therapies of neurorehabilitation, which could involve the combination of neurostimulation with other techniques such as virtual reality.[37,51]

As a side but important note, the results from FNG and ALM clearly confirm that the use of a transcutaneous device makes the overall approach more fragile and prone to stress-induced mechanical failures while connecting and disconnecting electrodes and stimulators. These sites of the connectors have undergone redesign on LRP to increase strength and deliver higher strain relief during everyday handling. This solution provided a great step toward immunity to active site failure until the end of the study. For future clinical practices, however, the solution may be represented by a fully implantable system, which will avoid any daily connection and disconnection between the electrodes cables and the neural stimulator.

Intraneural Stimulation Improves Prosthesis Control Performance and Mood States, and Reduces Phantom Limb Pain

Results from the BSBT strengthen the evidence regarding the benefit of using sensory feedback to complete functional tasks, without any visual or acoustic clue, that was previously shown in trials with 2 subjects implanted with FINE electrodes.[52,53] In the very same trials, the outcome of the clinical tests executed by the 2 amputees seemed to indicate that very low or no improvement is obtained when sensory feedback is provided when vision is also available.

In this work, notably, with the VET, we demonstrated that the control of the prosthesis in ecological conditions is improved by the sensory feedback. Finally, with the FCT, we reinforced previous findings[20] of the capability, given by intraneural stimulation, to modulate the grasping force exerted through the prosthesis, which is one of the main users' requirements. The ability of the subjects to modulate the prosthesis grasping force comes probably from the combination of (1) the proportional relation between the charge of the intraneural stimulation and the intensity of the elicited sensation and (2) the independency of the cluster location of the evoked perception on the charge of the intraneural stimulation. These properties come probably from the unique selectivity of intrafascicular electrodes, which allow fiber recruitment in a confined area of a fascicle.[25] To date, the capability of controlling several different levels of prosthesis force through the sensory feedback induced by intraneural

stimulation has not been shown with other implantable electrodes. As expected, after the results of the sensation characterization proving the stability of intraneural stimulation over time, the subjects were able to execute the different functional tasks throughout the whole study.

Also, we demonstrated that combining sensory feedback to the control of a myoelectric prosthesis results in significant decrease of phantom limb pain and amelioration of the user's mood. This is a great advantage for users, because it would allow them to avoid undergoing additional therapies for pain treatment.

Intraneural Stimulation Is Usable with Patients with Different Clinical Conditions

The participants involved in the study presented very different clinical conditions. In more detail, FNG had a phantom limb syndrome, which moderately affected his daily activities. He had painful and painless phantom sensations (see Figs 6A, C, E and 7A).

Only painful phantom sensations were reported by LRP, but these did not affect her activities of daily living. Both LRP and FNG underwent amputation <3 years before enrollment in the study. ALM did not report any phantom pain and lost the hand >20 years before the start of the pilot trial.

The clinical differences between FNG, ALM, and LRP could justify some discrepancies in terms of elicited sensations and task performance. FNG reported difficulty in clearly identifying percepts evoked by intraneural stimulation because of the continuous presence of spontaneous sensations from the phantom hand. This could explain the reduced performance of FNG compared to ALM and LRP on the FCT.

Conversely, intraneural stimulation evoked in FNG and LRP sensations that could be associated with those perceived by the healthy hand, mostly located over the fingers, whereas in ALM they evoked mostly perceptions of electricity, which rarely extended to the digits. In this case, the long interval from the amputation and the consequent plastic changes in the central nervous system pathways and relays connected to the stump nerves could have been the reason for the less natural quality of the sensations and their location perceived by ALM. In the case of LRP, even at the end of the study, the stimulation of the median nerve evoked no sensations on the hand. We hypothesize that the Wallerian degeneration of a consistent contingent of fibers innervating the hand (see Fig 7B) after the amputation was to a point that did not allow eliciting sensations from corresponding areas of the phantom limb (ie, the phantom fingers).

Encouragingly, independently of the peculiarities of each subject, FNG, ALM, and LRP felt sensations on the phantom hand induced by intraneural stimulation for the whole duration of the trial and exploited these sensations to improve the control of the prosthesis. This suggests that bidirectional prostheses can be used by subjects of very different clinical conditions, which would allow medical doctors to adopt loose inclusion criteria for the selection of users.

Conclusions

We believe that our findings support the hypothesis that intraneural stimulation represents a valuable clinical solution to provide sensory feedback to transradial amputees and that this approach is ready to be tested with a larger cohort of patients during long-term clinical trials outside the controlled hospital environment, after a transcutaneous solution is replaced by a fully implantable one. We showed that intraneural stimulation represents a solution that meets amputees' requirements for future prostheses, such as control of grip force; improves control of myoelectric prostheses for the completion of tasks executed with or without the assistance of vision; reduces phantom limb pain; and ameliorates patients' mood state.

Acknowledgment

This work was supported by EU grant CP-FP-INFSO 224012 (TIME project), the project NEMESIS (Neurocontrolled Mechatronic Hand Prosthesis) funded by the Italian Ministry of Health, EU grant FP7-611687 (NEBIAS; NEurocontrolled BIdirectional Artificial upper limb and hand prosthesiS), EU grant FP7-HEALTH-1602547 (EPIONE; Natural Sensory Feedback for Phantom Limb Pain Modulation and Therapy), the Swiss National Science Foundation through the National Center of Competence in Research Robotics, and the Bertarelli Foundation.

We thank the participants who committed 6 months of their lives to the experimentation.

Author Contributions

F.M.P., G.G., M.C., C.Ci., E.F., T.S., D.G., J.-L.D., M.B., L.R., S.R., P.M.R., and S.M. contributed to the conception and design of the study. F.M.P., S.R., I.S., G.V., E.D., J.C., G.G., R.D.I., F.I., F.C., P.C., M.M., D.A., A.H., L.B., and C.Ca. contributed to the acquisition and analysis of data. S.M., F.M.P., G.V., G.G., and I.S. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

S.R., F.M.P., and S.M. hold shares in Sensars Neuroprosthetics Sarl, a startup company dealing with

commercialization of neurocontrolled artificial limbs. C. Ci., M.C., and F.C. hold shares in Prensilia, a startup company commercializing robotic hands and assessment tools. D.G. is author of the patent WO2006027473 A1. The other authors have nothing to report.

References

1. Meyer TM. Psychological aspects of mutilating hand injuries. Hand Clin 2003;19:41–49.
2. Tropea P, Mazzoni A, Micera S, Corbo M. Giuliano Vanghetti and the innovation of "cineplastic operations". Neurology 2017;89:1627–1632.
3. Belter JT, Segil JL, Dollar AM, Weir RF. Mechanical design and performance specifications of anthropomorphic prosthetic hands: a review. J Rehabil Res Dev 2013;50:599–618.
4. Farina D, Vujaklija I, Sartori M, et al. Man/machine interface based on the discharge timings of spinal motor neurons after targeted muscle reinnervation. Nat Biomed Eng 2017;1:0025.
5. Micera S, Carpaneto J, Raspopovic S. Control of hand prostheses using peripheral information. IEEE Rev Biomed Eng 2010;3:48–68.
6. Biddiss EA, Chau TT. Upper limb prosthesis use and abandonment: a survey of the last 25 years. Prosthet Orthot Int 2007;31:236–257.
7. Wijk U, Carlsson I. Forearm amputees' views of prosthesis use and sensory feedback. J Hand Ther 2015;28:269–278.
8. Kaczmarek KA, Webster JG, Bach-y-Rita P, Tompkins WJ. Electrotactile and vibrotactile displays for sensory substitution systems. IEEE Trans Biomed Eng 1991;38:1–16.
9. Zhang D, Xu H, Shull PB, et al. Somatotopical feedback versus non-somatotopical feedback for phantom digit sensation on amputees using electrotactile stimulation. J Neuroeng Rehabil 2015;12:44.
10. Antfolk C, D'Alonzo M, Controzzi M, et al. Artificial redirection of sensation from prosthetic fingers to the phantom hand map on transradial amputees: vibrotactile versus mechanotactile sensory feedback. IEEE Trans Neural Syst Rehabil Eng 2013;21:112–120.
11. Chai G, Sui X, Li S, et al. Characterization of evoked tactile sensation in forearm amputees with transcutaneous electrical nerve stimulation. J Neural Eng 2015;12:066002.
12. D'Anna E, Petrini FM, Artoni F, et al. A somatotopic bidirectional hand prosthesis with transcutaneous electrical nerve stimulation based sensory feedback. Sci Rep 2017;7:10930.
13. Marasco PD, Kim K, Colgate JE, et al. Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees. Brain 2011;134:747–758.
14. Horch K, Meek S, Taylor TG, Hutchinson DT. Object discrimination with an artificial hand using electrical stimulation of peripheral tactile and proprioceptive pathways with intrafascicular electrodes. IEEE Trans Neural Syst Rehabil Eng 2011;19:483–489.
15. Tan DW, Schiefer MA, Keith MW, et al. A neural interface provides long-term stable natural touch perception. Sci Transl Med 2014;6:257ra138.
16. Tan DW, Schiefer MA, Keith MW, et al. Stability and selectivity of a chronic, multi-contact cuff electrode for sensory stimulation in human amputees. J Neural Eng 2015;12:026002.
17. Ortiz-Catalan M, Håkansson B, Brånemark R. An osseointegrated human-machine gateway for long-term sensory feedback and motor control of artificial limbs. Sci Transl Med 2014;6:257re6.
18. Davis TS, Wark HAC, Hutchinson DT, et al. Restoring motor control and sensory feedback in people with upper extremity amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves. J Neural Eng 2016;13:036001.
19. Wendelken S, Page DM, Davis T, et al. Restoration of motor control and proprioceptive and cutaneous sensation in humans with prior upper-limb amputation via multiple Utah Slanted Electrode Arrays (USEAs) implanted in residual peripheral arm nerves. J Neuroeng Rehabil 2017;14:121.
20. Raspopovic S, Capogrosso M, Petrini FM, et al. Restoring natural sensory feedback in real-time bidirectional hand prostheses. Sci Transl Med 2014;6:222ra19.
21. Rossini PM, Micera S, Benvenuto A, et al. Double nerve intraneural interface implant on a human amputee for robotic hand control. Clin Neurophysiol 2010;121:777–783.
22. Graczyk EL, Schiefer MA, Saal HP, et al. The neural basis of perceived intensity in natural and artificial touch. Sci Transl Med 2016;8:362ra142.
23. Atkins DJ, Heard DC, Donovan WH. Epidemiologic overview of individuals with upper-limb loss and their reported research priorities. J Prosthet Orthot 1996;8:2–11.
24. Boretius T, Badia J, Pascual-Font A, et al. A transverse intrafascicular multichannel electrode (TIME) to interface with the peripheral nerve. Biosens Bioelectron 2010;26:62–69.
25. Oddo CM, Raspopovic S, Artoni F, et al. Intraneural stimulation elicits discrimination of textural features by artificial fingertip in intact and amputee humans. Elife 2016;5:e09148.
26. Farina D, Aszmann O. Bionic limbs: clinical reality and academic promises. Sci Transl Med 2014;6:257ps12.
27. Courtine G, Bloch J. Defining ecological strategies in neuroprosthetics. Neuron 2015;86:29–33.
28. Kim LH, McLeod RS, Kiss ZHT. A new psychometric questionnaire for reporting of somatosensory percepts. J Neural Eng 2018;15:013002.
29. Simon AM, Hargrove LJ, Lock BA, Kuiken TA. A decision-based velocity ramp for minimizing the effect of misclassifications during real-time pattern recognition control. IEEE Trans Biomed Eng 2011;58:2360–2368.
30. Humbert SD, Snyder SA, Grill WM. Evaluation of command algorithms for control of upper-extremity neural prostheses. IEEE Trans Neural Syst Rehabil Eng 2002;10:94–101.
31. Andreu D, Guiraud D, Souquet G. A distributed architecture for activating the peripheral nervous system. J Neural Eng 2009;6:026001.
32. Guiho T, Andreu D, López-Alvarez VM, et al. Advanced 56 channels stimulation system to drive intrafascicular electrodes. In: *Converging clinical and engineering research on neurorehabilitation II*. Cham, Switzerland: Springer, 2017:743–747.
33. Bisoni L, Carboni C, Raffo L, et al. An HV-CMOS integrated circuit for neural stimulation in prosthetic applications. IEEE Trans Circuits Syst II Express Briefs 2015;62:184–188.
34. Clemente F, D'Alonzo M, Controzzi M, et al. Non-invasive, temporally discrete feedback of object contact and release improves grasp control of closed-loop myoelectric transradial prostheses. IEEE Trans Neural Syst Rehabil Eng 2016;24:1314–1322.
35. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the box and block test of manual dexterity. Am J Occup Ther 1985;39:386–391.
36. Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 2004;108:248–257.
37. Ortiz-Catalan M, Guðmundsdóttir RA, Kristoffersen MB, et al. Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: a single group, clinical trial in patients with chronic intractable phantom limb pain. Lancet 2016;388:2885–2894.
38. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain 1983;16:87–101.

39. Nyenhuis DL, Yamamoto C, Luchetta T, et al. Adult and geriatric normative data and validation of the profile of mood states. J Clin Psychol 1999;55:79–86.

40. Wurth S, Capogrosso M, Raspopovic S, et al. Long-term usability and bio-integration of polyimide-based intra-neural stimulating electrodes. Biomaterials 2017;122:114–129.

41. Granata G, Iorio RD, Romanello R, et al. Phantom somatosensory evoked potentials following selective intraneural electrical stimulation in two amputees. Clin Neurophysiol 2018;129:1117–1120.

42. Jabaley ME, Wallace WH, Heckler FR. Internal topography of major nerves of the forearm and hand: a current view. J Hand Surg 1980;5:1–18.

43. Raspopovic S, Petrini FM, Zelechowski M, Valle G. Framework for the development of neuroprostheses: from basic understanding by sciatic and median nerves models to bionic legs and hands. Proc IEEE 2017;105:34–49.

44. Johansson RS, Flanagan JR. Coding and use of tactile signals from the fingertips in object manipulation tasks. Nat Rev Neurosci 2009;10:345–359.

45. Valle G, Mazzoni A, Iberite F, et al. Biomimetic intraneural sensory feedback enhances sensation naturalness, tactile sensitivity, and manual dexterity in a bidirectional prosthesis. Neuron 2018;100:37–45.e7.

46. Valle G, Petrini FM, Strauss I, et al. Comparison of linear frequency and amplitude modulation for intraneural sensory feedback in bidirectional hand prostheses. Sci Rep 2018;8:16666.

47. Delgado-Martínez I, Badia J, Pascual-Font A, et al. Fascicular topography of the human median nerve for neuroprosthetic surgery. Front Neurosci 2016;10:286.

48. Cartwright MS, Shin HW, Passmore LV, Walker FO. Ultrasonographic findings of the normal ulnar nerve in adults. Arch Phys Med Rehabil 2007;88:394–396.

49. Flor H. Phantom-limb pain: characteristics, causes, and treatment. Lancet Neurol 2002;1:182–189.

50. Makin TR, Bensmaia SJ. Stability of sensory topographies in adult cortex. Trends Cogn Sci 2017;21:195–204.

51. Rognini G, Petrini FM, Raspopovic S, et al. Multisensory bionic limb to achieve prosthesis embodiment and reduce distorted phantom limb perceptions. J Neurol Neurosurg Psychiatry 2018; pii: jnnp-2018-318570.

52. Schiefer M, Tan D, Sidek SM, Tyler DJ. Sensory feedback by peripheral nerve stimulation improves task performance in individuals with upper limb loss using a myoelectric prosthesis. J Neural Eng 2016;13:016001.

53. Graczyk EL, Resnik L, Schiefer MA, et al. Home use of a neural-connected sensory prosthesis provides the functional and psychosocial experience of having a hand again. Sci Rep 2018;8:9866.