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A New Treatment for Phantom Limb Pain Based on Restoration of Somatosensory Feedback Through Intraneural Electrical Stimulation

Guiseppe Granata[1,2,*], Winnie Jensen[3], Jean-Louis Divoux[4], David Guiraud[5], Silvestro Micera[6,7], Xavier Navarro[8,9], Thomas Stieglitz[10,11,12], Ken Yoshida[13] and P. M. Rossini[1,2,*]

[1]Fondazione Policlinico Universitario A. Gemelli – IRCCS, Italy
[2]Università Cattolica del Sacro Cuore, Italy
[3]Department of Health Science and Technology, Aalborg University, Denmark
[4]Axonic, MXM, France
[5]LIRMM, University of Montpellier – INRIA, CNRS, Montpellier, France
[6]Bertarelli Foundation Chair in Translational Neuroengineering, Centre for Neuroprosthetics and Institute of Bioengineering, School of Engineering, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
[7]The BioRobotics Institute, Scuola Superiore Sant'Anna, Pisa, Italy
[8]Institute of Neurosciences, Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona, Bellaterra, Spain
[9]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Bellaterra, Spain
[10]Laboratory for Biomedical Microsystems, Department of Microsystems Engineering-IMTEK, Albert-Ludwig-University of Freiburg, Freiburg, Germany
[11]BrainLinks-BrainTools, Albert-Ludwig-University of Freiburg, Freiburg, Germany
[12]Bernstein Center Freiburg, Albert-Ludwig-University of Freiburg, Freiburg, Germany

[13]Department of Biomedical Engineering, Indiana University – Purdue University Indianapolis
E-mail: granata.gius@gmail.com
*Corresponding Authors

9.1 Introduction

Phantom limb pain (PLP) is a frequent consequence of amputation and can be defined as pain in a body part that is no longer present. Although phantom limb pain occurs in up to 85% of patients after amputation (Sherman and Sherman, 1983), the characteristics of this pain vary drastically. Throbbing, piercing and needle sensations are among the most commonly used descriptors of PLP. The heterogeneity of phantom limb pain is widely acknowledged, and it is recognized that the disorder likely arises from multiple mechanisms (Flor et al., 2006). PLP is commonly considered as neuropathic and the general view now is that many changes along the neuraxis, both peripheral and central, contribute to the experience of PLP. A gold standard for PLP treatment is still lacking since several studies, including large surveys of patients with amputations, have shown that most treatments are ineffective (Griffin and Tsao, 2014). Available therapies include acupuncture, deep brain stimulation (Flor, 2002), mirror/virtual reality therapies (Chan et al., 2007; Mercier and Sirigu, 2009), mental imagery (MacIver et al., 2008), transcutaneous nerve stimulation (Katz and Melzack, 1991), deep brain, motor cortex, spinal cord, dorsal root ganglion and peripheral nerve stimulation (Krainick et al., 1980; Bittar et al., 2005; Ahmed et al., 2011), drugs such as carbamazepine, opioids (Wu et al., 2008), gabapentin (Bone et al., 2002), amitriptyline (Robinson et al., 2004), calcitonin (Jaeger and Maier, 1992), ketamine (Eichenberger et al., 2008) and memantine (Nikolajsen et al., 2000), local anaesthesia, sympathectomy, dorsal root entry-zone lesions, cordotomy and rhizotomy (see Sherman et al., 1980; Sherman, 1997).

Following limb amputation and, consequently, truncation of nerves at the stump level, a part of the nerve fibers originally directed to the lost part of the body degenerates (because of retrograde Wallerian degeneration); however, a significant part of them survives in the residual portion of the nerve. Thanks to the rapid development of neural interfaces for the peripheral nervous system, e.g. intraneural multichannel electrodes (Navarro et al., 2005), it was recently demonstrated that it is possible to induct meaningful sensations (Dhillon et al., 2005) in the phantom hand of amputees by stimulating the surviving fibers through these interfaces.

Peripheral nerve stimulation was the first clinical application of the gate control theory proposed by Melzack and Wall (1965). This technique requires the implantation of electrodes near, across or along a nerve trunk (see Rasskazoff and Slavin, 2012) to provide stimulation-induced paresthesia. Anecdotical reports showed efficacy of peripheral nerve stimulation in PLP treatment.

Some studies have demonstrated a positive effect of providing sensory feedback from the lost part of the body to alleviate PLP, e.g. through mirror/virtual reality therapies, myoelectric prosthesis or daily discrimination training of surface stimuli, electrical or mechanical, applied to the stump (Antfolk et al., 2010; Antfolk et al., 2012; Börjman et al., 2012).

In the frame of a European founded project (called TIME), we implemented a system able to perform a peripheral nerve stimulation, providing, at the same time, meaningful somatosensory feedback from the lost hand in amputees (Raspopovic et al., 2014). This is a pilot study aiming to test the feasibility, the safety of this system and its efficacy in treating PLP.

9.2 Methods

All procedures were approved by the local Ethics Committee and, being an experimental trial using non-CE marked medical devices, also by the Italian Ministry of Health. An informed consent was signed by the patient before beginning the trial.

The system that we implemented was composed of two different medical devices:

(1) intra-fascicular multichannel electrodes (TIMEs)
(2) multichannel stimulator system (Stim'ND)

The system was tested in a 34-year-old male with a traumatic transradial (proximal third of the forearm) amputation of the left arm in January 2004. About a week after the amputation, the patient began to present a painful phantom limb syndrome, which at the time of the trial was reported as a constant sensation of "very intense painful clenched fist" of the amputated phantom hand, almost constant, worsening with the cold. On a scale from 0 (no pain) to 10 (maximum pain imaginable), the patient reported a constant pain intensity of 9. Apart from the amputation and consequent PLP, the clinical condition of the patient was unremarkable.

The TIMEs consist of a $10\ \mu\mathrm{m}$ thick polyimide-based substrate with seven active electrode sites on each side of a loop-like structure and two

reference electrodes, connected through a ceramic adaptor with a 18 mm long polyimide ribbon ending with a 16 pole circular connector (NPC-16, Omnetics Inc., Minneapolis, USA). Four electrodes (Boretius et al., 2010) were surgically implanted into the median and ulnar nerves of the amputee at the arm level. In both nerves, the two TIMEs were implanted, one distally (closer to the elbow) and the other proximally (closer to the axilla).

To implant the TIMEs, in the operating room, a 15 cm long incision was made in the left arm of the patient (along the internal bicipital groove) in order to expose the nerves. The surgical intervention was performed in general anesthesia. The median and ulnar nerves were dissected from the surrounding tissue along all the length of the opening. In order to implant the TIMEs, the same following procedure was performed for each electrode. A short incision was made in the epineurium of selected nerves to have visual feedback on the location of individual fascicles. Then, using a guiding needle (Ethicon needle diameter $125\ \mu\mathrm{m}$ attached to a 10-0 Prolene suture), each polyimide loop was implanted transversally (with respect to the longitudinal direction of the nerve) to place the active sites inside the nerve, inside or between fascicles. In order to check the positioning of the electrodes, inside the operating room, each TIMEs was connected with the Stim'ND stimulator to assess the electrode–tissue impedance and verify that the active sites had been properly placed inside the nerve. After the check, in the case of proper positioning, the electrode was anchored to the epineurium (with 8-0 non-absorbable Silk suture) and surrounding tissues (with 4-0 non-absorbable Silk suture) to avoid migration. A subcutaneous pocket was created to house the lead-out cables of the TIMEs and, after a small skin incision, the electrode was externalized to make it available for percutaneous connection with the stimulator. Finally, the muscle and tissue were repositioned in their original location and the wound was closed with 3-0 non-absorbable Ethilon suture. Each cable was fixed at the exit point (3-0 non-absorbable Silk sutures).

The surgical operation lasted 7 hours. The participant was discharged from the hospital 48 hours later with no post-surgical complications.

The Stim'ND is a multichannel electrical stimulator that, connected with the TIMEs, was able to deliver electrical stimulation to the nerve through the active sites of TIMEs, individually or simultaneously, with an amplitude range of $20\ \mu\mathrm{A}$–5.1 mA (step size of $20\ \mu\mathrm{A}$ between current levels) and a pulse width range of 1–511 $\mu\mathrm{s}$ (minimum step size of $1\ \mu\mathrm{s}$).

As previously stated in the introduction, it is possible to elicit sensations in the phantom hand by stimulating the nerve fascicles (with intraneural

multichannel electrodes) originally directed to the hand before the amputation. However, it is impossible to know in advance which type of feedback and where it is possible to evoke these sensations. The only possibility to discover the potential of the system is to perform a mapping of each electrode and corresponding contacts (a process called sensation characterization) in order to know the following:

- the location, type and strength of the generated sensation with respect to the active stimulation sites used to generate them;
- the lower (thresholds) and upper (saturation) limits of the current to be delivered in order to induce meaningful sensations (defined, respectively, as the lowest stimulus pulse charge at which the subject reliably feels a sensation and the pulse charge at which the sensation becomes close to uncomfortable or painful);
- which electrode channels are useful and able to induce reliable sensory feelings in the patient's phantom hand (the sensation is considered reliable if, when using the same characteristics of current, the generated sensation is the same considering the strength, the location and the type in at least two out of three repeated trials of stimulation; the charge delivered for the three repeated trials is between the lower thresholds and upper limits).

For this purpose, each channel of each electrode was connected with the electrical stimulator in order to deliver short trains of current of variable intensity and duration. More precisely, monopolar, charge-balanced, biphasic and rectangular stimulation pulses were applied; the single pulse duration varied between 25 and 300 μs (steps of 25 μs) and the pulse amplitude between 40 and 300 μA (steps of 20 μA), and the pulses were delivered with a frequency of 50 Hz over a 500 ms time window. The stimulator – and consequently the parameters of the current to be injected into the nerves – was managed by the operators, thanks to a specific software. The procedure was performed as follows. First, train of current of increasing amplitude from 40 to 300 μA (steps of 20 μA) with a fixed pulse duration (the lowest, i.e. 25 μs) were delivered. After each stimulus, the patient was asked to provide his feedback on the type, strength and location of the sensation (if any) through a computer interface properly designed for the study. If no sensation was reported, a second train of stimuli with the same range of amplitude but with a higher step duration of 25 μs was delivered. The same procedure was repeated progressively increasing the duration of the current (never exceeding the maximum chemical safe charge injection limit per electrode site, i.e. 120

nC) until the patient felt a mild sensation in the phantom hand for the first time. In this case, the last train of stimuli was repeated twice with the same characteristics and, if the same sensation was reported at least once, the pattern of electrical parameters able to generate this sensation was identified as the lowest threshold and coupled with the type, the localization and the intensity of the sensation reported by the patient. The active sites not able to elicit any sensation using the maximum charge possible, i.e. 120 nC, were discarded from further use.

In order to determine the upper limit of sensation, we continued to deliver trains of increasing current until the generated sensation became uncomfortable. Also, in this case, the procedure was repeated twice with the same characteristics and, if the same sensation was reported at least once, the pattern of electrical parameters able to generate the uncomfortable sensation was identified as the upper limit. Since minor changes of the electrode–tissue interface can be expected during the weeks following surgery (i.e. formation of fibrosis around the TIME device and possible micro-motion of the polyimide loop placed inside the nerve), this procedure was repeated once a week to ensure that the stimulation levels were appropriate.

When the lower threshold and upper limits were identified, a level of current (in the range previously defined between the lower threshold and the upper limit) able to evoke sensation perceived as medium-strength (according to a scale from 0 to 10: 0 corresponding to no sensation and 10 to pain) was delivered and the corresponding location, quality and kind of evoked sensation were characterized.

Finally, strategies of simultaneous synchronous multichannel electrical stimulation (i.e. stimulation of median and ulnar nerves with two or more channels in parallel and simultaneously) were explored. As the number of combinations of electrode channels was extremely large and time-consuming, we first proceeded combining two channels of electrodes implanted in the two different nerves (i.e. one in the median and one in the ulnar nerves) choosing channels able to generate stable and reliable sensations with a minimum amount of charge injected (among those with the same kind of sensory feeling generated, i.e. the channel with the lower "lower threshold"). In order to try to cover a wider area with the evoked sensation of the phantom hand, we proceeded adding one or more channels in different combinations with the aim of reaching the widest surface possible according to the feedback of the patient. Since minor changes to the electrode–tissue interface can be expected, this procedure was also repeated once a week.

The TIMEs were explanted 30 days after the implantation for reasons related to ethical and legal authorization.

9.2.1 Therapy

The most efficacious train of multichannel stimulation was used for pain treatment. More precisely, the stimulation pattern delivered to the patient as therapy was represented by sequences of 15 biphasic pulse trains lasting 0.5 seconds. The time interval between two consecutive trains was 1 second, while that between two consecutive sequences was 10 seconds. The therapy consisted of three sessions of 30 minutes (9 minutes stimulation, 1 minute rest) each separated by 5 minutes. Every session lasted 100 minutes. The daily session of treatment was repeated with the selected set of stimulation parameters and active sites that produced reliable, distinct and the most comfortable and pain-releasing sensations while injecting the minimum amount of charge. The stimulation sessions were performed for 10 days.

Pain assessment

To assess the effect of treatment, we used three different questionnaires: the abbreviated version of the McGill Pain Questionnaire (sfMcGill), the present pain intensity scale (PPI) and the pain visual analogue scale (VAS). In addition, the participant's own qualitative descriptions of his pain perception were recorded in an open-ended session. The questionnaires were used the first time before the surgical implantation of TIMEs, second time after implant of the TIME devices (but before starting the treatment) and daily where we applied repeated stimulation sessions (either after the session only or both before and after the session), and on day 30 (the day of the removal of the TIMEs).

9.2.2 Assessment of Cortical Organization

Cortical reorganization was recorded with two different methods: electroencephalography (EEG) and somatosensory evoked potentials (SEP). Both the examinations were performed before and after the therapy.

9.2.2.1 EEG

EEG signals were recorded using a cap with 31 recording electrodes placed according to the positions of the 10–20 international system (excluding Fpz and Oz). The reference was at Fz and the ground at Fpz. An automatic artifact

rejection algorithm excluded from the average all runs containing transient exceeding +65 mV at any recording channel. Data were processed in Matlab R2011b (MathWorks, Natick, MA) using scripts based on EEGLAB 11.0.5.4b toolbox (Swartz Center for Computational Neurosciences, La Jolla, CA). EEG signals were bandpass filtered from 0.1 to 47 Hz using a finite impulse response (FIR) filter. Imported data were divided in 2 second duration epochs and visible artifacts in the EEG recordings (i.e. eye movements, cardiac activity and scalp muscle contraction) were removed using an independent component analysis (ICA) procedure (Formaggio et al., 2013; Hoffmann et al., 2008; Jung et al., 2000) performed using the Infomax ICA algorithm (Bell et al., 1995) as implemented in the EEGLAB. Artifact-free EEG signals were used for the further analyses.

The recordings were performed in resting state, with the patient seated in an arm chair for 5 minutes with eyes open and 5 minutes with eyes closed.

EEG power spectral density

We selected artifact-free EEG epochs and calculated the spectral density (EEG signal bandwidth from 0.5 to 45 Hz with a resolution of 0.5 Hz, frequency bands at delta: 2–4 Hz, theta: 4–8 Hz, alpha 1: 8–10.5 Hz, alpha 2: 10.5–13 Hz, beta 1: 13–20 Hz, beta 2: 20–30 Hz and gamma: 30–45 Hz).

EEG cortical source analysis

We estimated the three-dimensional distribution of the EEG activity by the use of the standardized Low Resolution Electromagnetic Tomography Algorithm (sLORETA). The output of the algorithm integrates information on localization of signal sources with the brain tomography. Selected artifact-free EEG segments were used for calculating the sLORETA intracranial spectral density, with a resolution of 0.5 Hz, from 0.5 to 45 Hz. All EEG data epochs were normalized and re-computed into cortical current density time series at 6239 cortical voxels7. The voxels were collapsed at four regions of interest (ROI) in each hemisphere, central (Brodmann areas: 8–11 and 44–47), frontal (Brodmann areas: 1–4 and 6), parietal (Brodmann areas: 5–7, 30, 39–40 and 43) and occipital (Brodmann areas: 17–19) coded according to the Talairach space. The signal at each cortical ROI consisted of the averaged electric neuronal activities of all voxels belonging to that ROI. The sLORETA has shown to provide improved results over other methodologies, such as the LORETA algorithm. The exact, zero-error localization property of the method has been demonstrated, and no localization bias is introduced even in the presence of measurement or biological noise (Pascual-Marqui et al., 2002;

Pascual-Marqui et al., 2011). Also, localization agreement has been shown with functional magnetic resonance imaging (fMRI), structural MRI, positron emission tomography (PET) and intracranial recordings in humans.

Functional connectivity analysis

Brain connectivity was computed by sLORETA/eLORETA software on 84 ROIs defined according to the 42 Brodmann areas (BAs: 1–11, 13, 17–25, 27–47) for each hemisphere. Among the eLORETA current density time series of the 84 ROIs, intracortical lagged linear coherence, extracted by "all nearest voxels" method, was computed between all possible pairs of the 84 ROIs for each of the seven EEG frequency bands (delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz) and gamma (30–45 Hz). The values of connectivity computing between all pairs of ROIs for each frequency band were used as measure of weight of the graph in the follow graph analyses. The lagged linear coherence method was originally developed as a measure of physiological connectivity that was not affected by volume conduction and low spatial resolution. It has been shown to provide an improved connectivity measure8 in comparison to the imaginary coherence method (Nolte et al., 2004).

Graph analysis

A network is a mathematical representation of a real-world complex system and is defined by a collection of nodes (vertices) and links (edges) between pairs of nodes. Nodes in large-scale brain networks usually represent brain regions, while links represent anatomical, functional or effective connections (Friston et al., 1994), depending on the dataset. Anatomical connections typically correspond to white matter tracts between pairs of grey matter (cortical areas or subcortical relays) brain regions.

Functional connections correspond to magnitudes of temporal correlations in activity and may occur between pairs of anatomically unconnected regions. The nature of nodes and links in brain networks is determined by combining brain mapping methods, anatomical parcellation schemes and measures of connectivity. Nodes should ideally represent brain regions with coherent patterns of extrinsic anatomical or functional connections (Rubinov et al., 2006; Sporns et al., 2006). Two core measures of graph theory were computed: characteristic path length (L) and weighted clustering coefficient, representative of global connectedness and local interconnectedness, respectively (Watts et al., 1998). The length of a path is indicated by the number of connections it contains. The characteristic path length L (averaged shortest

path length between all node pairs) is an emergent property of the graph, which indicates how well its elements are integrated/interconnected. The mean clustering coefficient is computed for all nodes of the graph and then averaged. It is a measure for the tendency of network elements to form local clusters 14. The respective distributions of global (L-random) and local (C-random) connectedness values were calculated and averaged to obtain a mean value for each core measure. The scale-free value, Gamma (γ) was evaluated from the normalized C (C/C-random) and Lambda (λ) from the normalized L (L/L-random). "Small-worldness" (Sigma σ) is the γ:λ ratio and is used to describe the balance between the local connectedness and the global integration of a network. When this ratio is larger than 1, a network is said to have small-world properties.

9.2.2.2 SEP

To assess the cortical topography and responsiveness to sensory stimulation, we analyzed somatosensory evoked maps. To obtain SEP, we stimulated the median nerve at the elbow. The SEP amplitudes were measured in relation to baseline recordings. SEP cortical components were identified on the basis of their latency and polarity, and we created cortical maps based on the N20 component. The N20 component corresponds to arrival of the peripheral nerve stimulation at the primary somatosensory area.

Somatosensory evoked potentials were performed by using a Micromed System Plus Evolution, Mogliano Veneto, Italy. The somatosensory evoked potentials were recorded using a cuff with 31 recording electrodes placed according to the positions of the 10–20 international system 31 electrodes, Fp1, Fp2, AF3, AF4, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T3, C3, C7, C4, T4, CP5, CP1, CP2, CP6, T5, P3, P7, P4, T6, PO3, PO4, O1 and O2. The common reference was placed at the vertex and the ground at the forehead.

The signal was amplified and filtered (bandpass 0.3–70 Hz). An automatic artifact rejection algorithm was used in order to exclude all runs containing transient exceeding +65 mV at any recording channel from the average. Peripheral nerve stimulation was performed with a surface bipolar electrode stimulating the median nerve at the elbow, medially to the distal tendon of biceps brachii. The electrical stimulation was performed with the stimulator integrated in the Micromed System, and a pulse intensity able to generate a clear motor twitch of flexors carpi and/or finger muscles was used. The frequency of the stimulation was 1 Hz. Two separate averages – each composed by 500 stimuli – were performed. If needed, according to the operator's judgment on the quality of the somatosensory evoked potentials recorded,

one or more averages were added. The whole procedure was repeated on the amputee side before and after the therapy and on the spared side only before the therapy.

9.3 Results

The surgical implantation and removal of TIME electrodes on an amputee was smooth and efficient after its careful planning. No complications related to the surgical procedure and daily stimulation were observed. In particular, no complications related to nerve injury, infection, bleeding and relocation of the electrodes were observed.

The four implanted electrodes functioned during all the trials. It was possible to stimulate the four implanted nerves using all channels except seven contacts. The intraneural stimulation was able to evoke different sensations referred by the patients as "touch", "pressure", "vibration", "a touching wave" and "warm". The more common reported sensations were "touch" and "vibration". The sensations were primarily located on the palm, thumb, index and little finger of the phantom hand. The anatomical distribution of this sensation was always congruent with the electrode used: electrodes inserted on median nerve generated sensation in the median nerve innervated part of the phantom hand and electrodes implanted on ulnar nerve evoked sensation on the ulnar innervated portion of the phantom hand. Some channels, when stimulated, produced an evident muscular twitch of the stump. The combined stimulation of two or more different channels usually had two common effects:

(1) The area of the phantom hand where the patient felt the sensation was not simply the sum of the two portions of hand stimulated by using only one of the channels.
(2) The current threshold needed to evoke a sensation was usually lower than the threshold of the same electrode when used alone.

The charge required to elicit a specific sensation increased over time; however, the quality and strength of the sensation generated remained stable over time.

Many combinations of channels were tried and a combination of five different active sites was selected for the treatment. This combination of channels produced a reliable, distinct, pain releasing and comfortable sensation perceived by the patient as "a touching wave" covering the majority of the palmar side of his phantom hand (Figure 9.1).

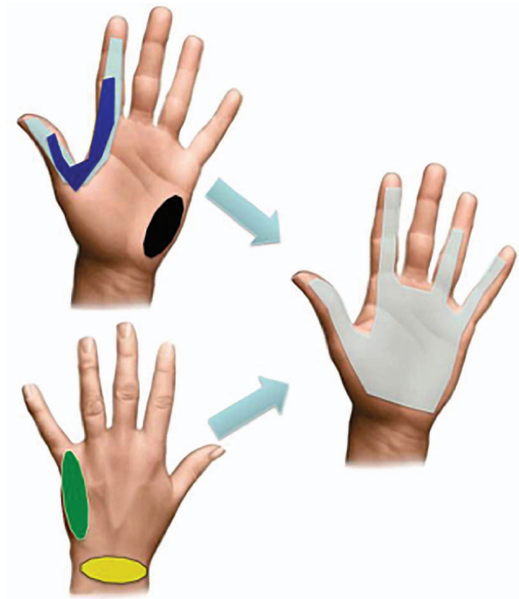

Figure 9.1 Schematic representation of the areas of the patient's phantom hand involved by the sensation during intraneural stimulation. On the left side of the picture, the areas of the phantom hand where the patient felt the sensation stimulating with five channels individually can be seen. On the right side of the picture, the area of phantom hand where the patient felt the sensation by stimulating simultaneously with the same five channels can be seen.

During the 10 days of treatment, the patient described a significant and progressive decrease of his phantom limb pain (Figure 9.2) that was referred as less "stabbing", "sickening", "sharp", "fearful", "gnawing", "cramping", "hot", "aching" and "heavy". The patient experienced a maximum decrease of pain intensity from 9 to 4/5 according to the VAS. A sensation of partial opening of the phantom "clenched fist" was also referred by the patient together with the pain decrease. However, the effect of treatment was of short duration lasting only some hours after therapy; during the first three days of therapy (lowest VAS score between 6 and 7, PPI score 4 and McGill score between 12 and 20), the pain came back to normal before the patient went to sleep, whereas during the last days of therapy, the relief from pain lasted until the patient went to sleep and pain came back to normal when the patient woke up (lowest VAS score between 4 and 5, PPI score 3 and McGill scores between 6 and 9).

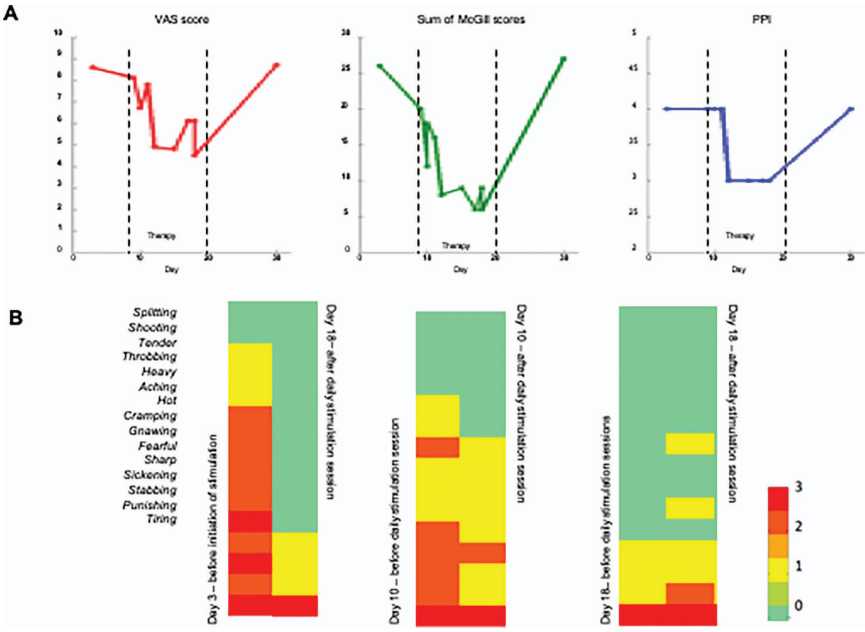

Figure 9.2 Results of questionnaires for PLP evaluation. (A) A clear reduction of PLP is evident in all three questionnaires: VAS, McGill and PPI. (B) Results of McGill more in detail: a clear reduction of different qualities of pain during the treatment is evident.

The TIMEs were removed 30 days after the implantation without any side effects.

From a neurophysiological point of view, the somatosensory evoked potentials mapping showed a modification of the cortical topography in the central–parietal areas contralateral to the amputation site, i.e. evaluated while stimulating the left median nerve (Figure 9.3A). For comparison, we included a map on the evoked potentials while stimulating the right median nerve. The EEG source analysis (Figure 9.3B–C) showed a widespread reduction of delta activity and a significant increase of alpha activity in the central–parietal areas in both hemispheres following the repeated stimulation sessions, indicating a shift of the EEG activity towards normal states.

Finally, the analysis of the cortical connectivity showed a less random architecture of cerebral networks following the repeated stimulation sessions, evident as a reduction on delta band and an increase on alpha band frequencies (Figure 9.3D).

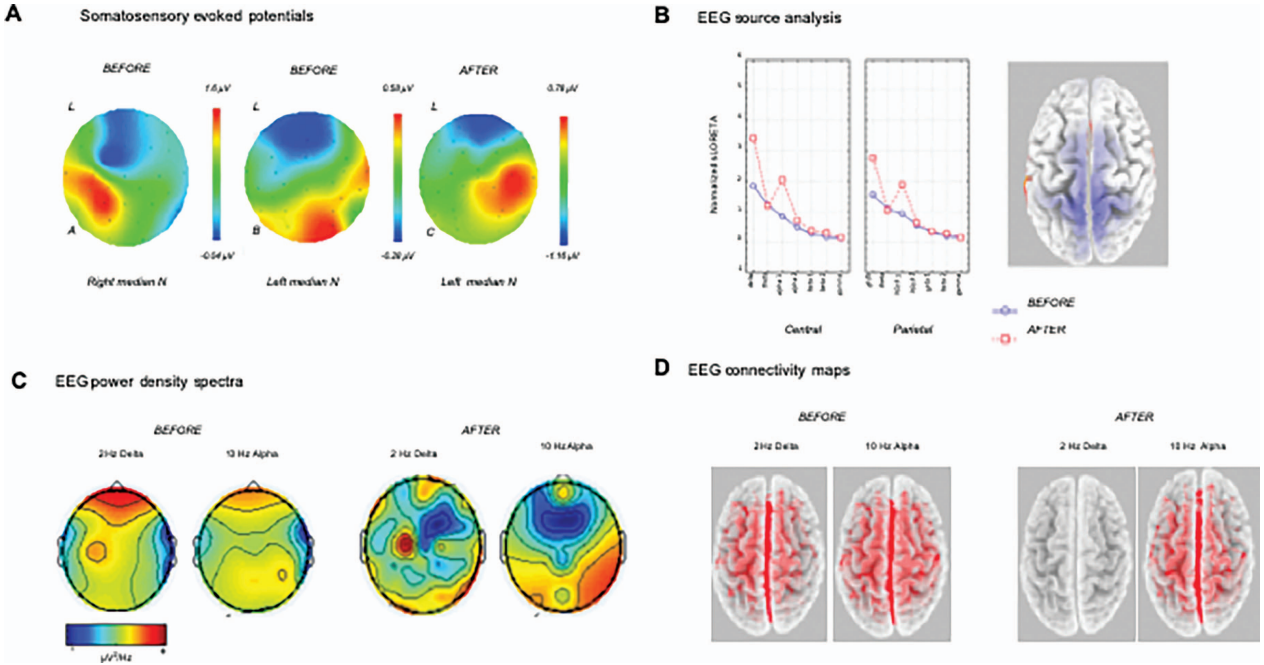

Figure 9.3 Assessment of cortical organization and reorganization before and after repeated stimulation sessions. (A) Somatosensory evoked cortical potentials evaluated before and after the repeated stimulation sessions. For comparison, we included a map on the evoked potentials while stimulating the right median nerve. (B) EEG current sources determined before and after the repeated stimulation sessions. The analyses in A and B show a modification of the cortical topography in the central–parietal areas contralateral to the amputation. (C) Analysis of the EEG power and (D) cortical connectivity before and after the repeated stimulation sessions. The EEG analysis in C and D demonstrated a scattered reduction of delta activity and increase of alpha activity, indicating a shift of the EEG activity towards normal states and towards less random architecture.

9.4 Discussion

To the best of our knowledge, in this study, we present for the first time the results of a new approach, based on peripheral nerve stimulation, for PLP treatment. Our system combines the characteristics of peripheral nerve stimulation with the new kind of intraneural interface that makes it possible to evoke somatosensory sensation on the phantom hand of amputees. The philosophy at the base of this new system was the possibility to combine two kinds of treatment that individually already demonstrated, although in a very small number of cases, efficacy in dealing with intractable (or poorly responsive) PLP. Paresthesias are assumed essential for pain relief when using conventional spinal cord, dorsal root ganglion or peripheral nerve stimulation systems (Kumar et al., 1998; North et al., 2006). The other assumption of these kinds of systems is the possibility to cover the areas of the body involved by pain with paresthesia generated by electrical stimulation. In the design of the protocol, along the lines of already existing and previously cited kinds of stimulations, we decided to choose a pattern of stimulation able to cover, as much as possible, the phantom hand surface, i.e. the painful area in our amputee patient. In this perspective, median and ulnar nerves were chosen for the implantation of TIMEs because their innervation territory covers almost entirely the palmar and the finger sensory fields. In addition to the previous anatomical consideration, a practical aspect was also taken into account in choosing nerves to be implanted; given the level of amputation with a single incision at the medial aspect of the arm, it was possible to expose both median and ulnar nerves. To implant the radial nerve would have meant a second incision and an even greater duration of surgery.

Paresthesias can be uncomfortable for some patients and sometimes can limit the acceptable amplitude of stimulation during conventional spinal cord, dorsal root ganglion or peripheral nerve stimulation systems (Kuechmann et al., 2009). One of the advantages of our system is that we are able to avoid this unpleasant sensation by substituting it with a natural, meaningful and pleasant sensation in the missing part of the body. Moreover, the selective stimulation of sensory fibers bypass the difficulty to stimulate mixed sensory and motor nerve, avoiding recruitment of motor fibers. The latter is one of the reasons why the electrical stimulation of the end “fields” of peripheral nerves technique was developed and, also if in its infancy, is growing as an effective option for local generation of paresthesia. However, in amputees, this is not an option due to the absence of the area involved from pain. All conventional electrical stimulation treatments (spinal cord, peripheral and

dorsal root ganglion) require implantation of a dedicated device with the only purpose of pain treatment. The future of prosthetics is going toward the use of new generation prosthesis that can be controlled bidirectionally by the users. This kind of prosthesis is based on the possibility to provide a somatosensory feedback to the amputees, and that possibility is based on the implant of the same (or similar) electrode used in our system (Raspopovic et al., 2014; Tan et al., 2014). So, in the future perspectives, the great advantage of our approach is that the same system will be used both for PLP treatment and for the functioning of this new generation prosthesis.

During the 10 days of treatment, the patient experienced a decrease in his phantom pain intensity together with a change in the qualitative perception of his pain. However, this was only a transient effect (only for few hours following the treatment). It is outside the purpose and possibilities of this work to understand the mechanism of pain decrease and at what level of the nervous system the stimulation might have acted, but some considerations can be made. Peripheral nerve stimulation represented the first clinical application of the gate control theory proposed by Melzack and Wall (1965). According to this theory, the A-beta fibers interact within the substantia gelatinosa of the posterior horn in the spinal cord with inhibitory interneurons able to influence the wide dynamic range neuron, where both the large and small pain fibers synapse, closing the gate and inhibiting the conduction of pain (Treede, 2016). Although some recent evidence has questioned this theory, the concept of early large fiber recruitment inhibiting small fiber conduction remains the basis of the theory of electrical stimulation for pain treatment, and recent studies demonstrated that peripheral nerve stimulation is able to suppress subjective complaints of pain associated with noxious laser-induced nociception (Ellrich and Lamp, 2005). The kind of sensation mainly evoked with intraneural stimulation in our study was touch and vibration, and for this reason, it is possible to hypothesize that with our system, large diameter sensory fibers, like A-beta fibers, were the most likely recruited (probably because of their lower excitability threshold). According to this assumption, it is possible to speculate that one of the possible effects of our system was mediated by the activation of these fibers with a mechanism similar to what usually happens with peripheral nerve or other kinds of electrical stimulations (e.g. spinal cord or dorsal root ganglion stimulations). The transient duration of pain relief seems in accordance with this mechanism. However, other mechanisms and levels of stimulus-induced plastic changes, both peripheral and central, cannot be excluded. In particular, our results showed plastic changes in the primary somatosensory area and a general increase of alpha

band power density and connectivity following the trial that could have contributed to the pain relief.

Our study confirmed the possibility, also after years from the amputation, to deliver intraneural electrical stimulation and to generate meaningful and comfortable sensations perceived from the phantom hand by amputees.

The majority of the channels of TIMEs remained functional during the whole trial and the system was safe. No side effects related to the implant/explant of TIMEs and repeated intraneural stimulation were observed within a three-year follow-up.

Since the implant of the TIMEs cannot be fully controlled to target specific sensory nerve fibers, we had to perform a mapping procedure in order to match the different channels of the four electrodes with the corresponding potentially evoked sensations. This is a highly time-consuming procedure but, without a conceptual redesign of described procedures, should be considered a necessary pre-condition for the proposed treatment.

The charge of electrical stimulation increased over time, likely due to the ongoing healing process of the tissue and formation of fibrosis. For this reason, a quick check of threshold at the beginning of each week was needed. This is an issue that should be taken into account for future clinical applications. The chronic application of this kind of treatment remains a big unsolved issue and longer studies should be performed in order to test the stability of the system over time.

Other limitations of the study are the following. (1) Data were obtained only from one patient and thus generalization to a population should be cautioned. However, this was a pilot study, and it is important to underline the strong effort, in terms of time and money, performed in order to obtain this proof of concept. (2) Intensity and dosage of treatment were fixed, and it was not possible, also for ethical reasons, to blind the intervention neither for the participant nor for the experimenters. Moreover, it was not possible to conduct a SHAM stimulation. However, regarding this point, it is important to underline that the simple procedure of intraneural stimulation did not provoke any modification to PLP in our patient.

This study provides the demonstration of feasibility, safety and efficacy of a newly developed system for PLP treatment. Other studies are needed in order to test this treatment in a larger number of patients. Using the same system, different paradigms of stimulation, in terms of frequency and duration of treatment, could also be tested. The ongoing process of development of new generation prosthesis, able to provide a somatosensory feedback, should be considered as an opportunity to test this new therapeutic approach.

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