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Double nerve intraneural interface implant on a human amputee for robotic hand control

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ABSTRACT

Objectives: The principle underlying this project is that, despite nervous reorganization following upper limb amputation, original pathways and CNS relays partially maintain their function and can be exploited for interfacing prostheses.
Aim of this study is to evaluate a novel peripheral intraneural multielectrode for multi-movement prosthesis control and for sensory feed-back, while assessing cortical reorganization following the re-acquired stream of data.
Methods: Four intrafascicular longitudinal flexible multielectrodes (tf-LIFE4) were implanted in the median and ulnar nerves of an amputee; they reliably recorded output signals for 4 weeks. Artificial intelligence classifiers were used off-line to analyse LIFE signals recorded during three distinct hand movements under voluntary order.
Results: Real-time control of motor output was achieved for the three actions. When applied off-line artificial intelligence reached >85% real-time correct classification of trials. Moreover, different types of current stimulation were determined to allow reproducible and localized hand/fingers sensations. Cortical organization was observed via TMS in parallel with partial resolution of symptoms due to the phantom-limb syndrome (PLS).
Conclusions: tf-LIFE4s recorded output signals in human nerves for 4 weeks, though the efficacy of sensory stimulation decayed after 10 days. Recording from a number of fibres permitted a high percentage of distinct actions to be classified correctly. Reversal of plastic changes and alleviation of PLS represent corollary findings of potential therapeutic benefit.
Significance: This study represents a breakthrough in robotic hand use in amputees.

1. Introduction

One of the most intriguing fields for translational medicine deals with the application of robotics technologies to human health. In particular, the ability to interface a robotic device with a human brain after a given damage opens up a number of exciting applications in replacing lost function. An important chapter in translational research within the field of bio-engineering and biomaterials aiming to restore lost abilities in humans, deals with the development of a robotic hand to replace the missing limb following amputation.

Upper limb amputees compensate for cosmetic and functional deficits using prostheses whose present performance is poor for dexterity, control features, anthropomorphism and interface effi-

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cacy (e.g., information transfer rate, rate of correct classification and quality/amount of feed-back) (Micera et al., 2006; Tonet et al., 2007). In fact, commercially available hand prostheses are little more than unidimensional pincers operating under electromyographic (EMG) and sight control, without natural or artificial sensory feed-back. Current research focuses on bionic anthropomorphic prostheses connected to the peripheral nervous system (PNS) via bidirectional neural interfaces, which can restore physiological conditions to some extent (Dhillon et al., 2004; Jia et al., 2007), or on nerve transposition for targeted reinnervation (Kuiken et al., 2007, 2009). Peripheral nerve interfaces aim to detect electrical activity of the nerve fibres and/or to excite them as selectively as possible (Navarro et al., 2005; Stieglitz et al., 2005; Tesfayesus and Durand, 2007; Micera et al., 2008). Recently, a novel thin film longitudinal intrafascicular flexible multielectrode (tf-LIFE4), assuring biocompatibility and flexibility for long-term use, has been developed for multiple-site recordings (Hoffmann and Kock, 2005; Citi et al., 2008) and tested in experimental models (Lago et al., 2007). In the present study, the first implant of tf-LIFE4s was carried out on a human volunteer with the following aims:

- o to test reliability and compatibility of tf-LIFE4s for the 4 week period allowed by the European Health Authorities;
- o to record electroneurographic (ENG) signals from motor fibres during rest and voluntary emitted commands for three distinct movements dispatched to the missing hand/fingers
- o to implement classifiers to correctly interpret commands and govern a robotic hand;
- o to deliver sensory feed-back as a surrogate of action-driven perception;
- o to correlate performance and training-related changes with topographical reorganization of sensorimotor brain areas and with clinical modifications.

2. Subject and methods

A 26-year-old right-handed male university graduate had suffered trans-radial amputation of left arm in a car accident in 2007. He had previously tried aesthetic and myoelectric prostheses. Forearm stump muscles were entirely atrophied and non-functional on EMG evaluation. Previous medical history was unremarkable. Full neurological and neurographic/electromyographic examinations were normal. Neuropsychological and neuropsychiatric tests (MMPI-2, WAIS) demonstrated normal comprehension and intellectual capacity, and excluded personality disorders.

Phantom awareness and phantom-limb syndrome (PLS) were evaluated pre-surgically and were followed up at the end of the training period and 3 months after implant removal, using an abbreviated version of the McGill Pain Questionnaire (sfMcGill), the present pain intensity scale (PPI), the pain visual analogue scale (VAS), and an open section for description of phantom awareness. The study was approved by the local Ethics Committee and by the assigned office of Italian Ministry of Health and an informed consent was signed by the patient in the presence of a witness from his family.

After general anaesthesia, the skin was incised along the medial edge of the biceps muscle for 10 cm to expose the ulnar and median nerves in the distal upper arm; following epineural microdissection, two tf-LIFE4s (Hoffmann and Kock, 2005) (Figs. 1 and 2), separated by 3 cm, were inserted into each nerve under surgical microscope (Opmi Vario/NC33, Zeiss) (Fig. 1A). A tungsten needle allowed electrode filament introduction into the nerve fascicle (Fig 1B). tf-LIFE4s were introduced 45° obliquely to assure stability and to increase the probability of intercepting nerve fibres. The distal handle of the electrode was anchored to the epineurium by an 8.0 nylon suture (Fig. 1C). Four separate holes lateral to the incision allowed transit of the tf-LIFE4 cables (Fig. 1D). Four weeks later, tf-LIFE4s were removed.

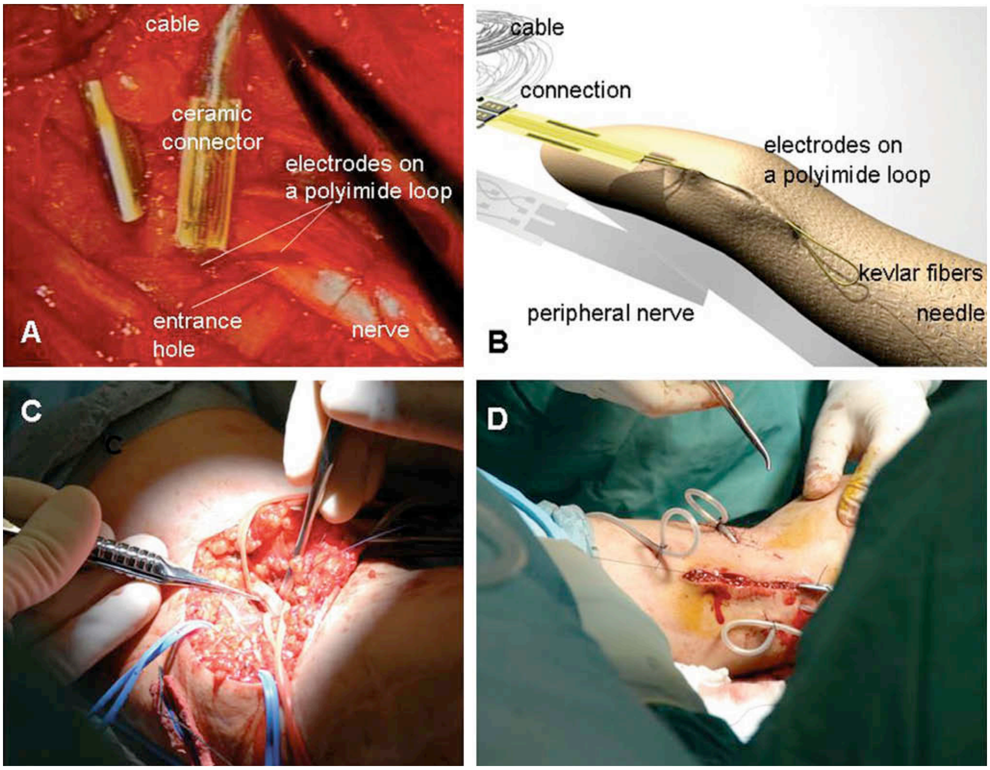

Fig. 1. Surgical implantation of tf-LIFE4 system – (A) intraoperative microphotographic view and (B) descriptive illustration of the insertion of tf-LIFE4 system with needle, polyimide fibre, electrode filament and ceramic connector in the median nerve. (C) General view of the exposed median nerve and tf-LIFE4 cable; (D) tf-LIFE4s skin transit cables.

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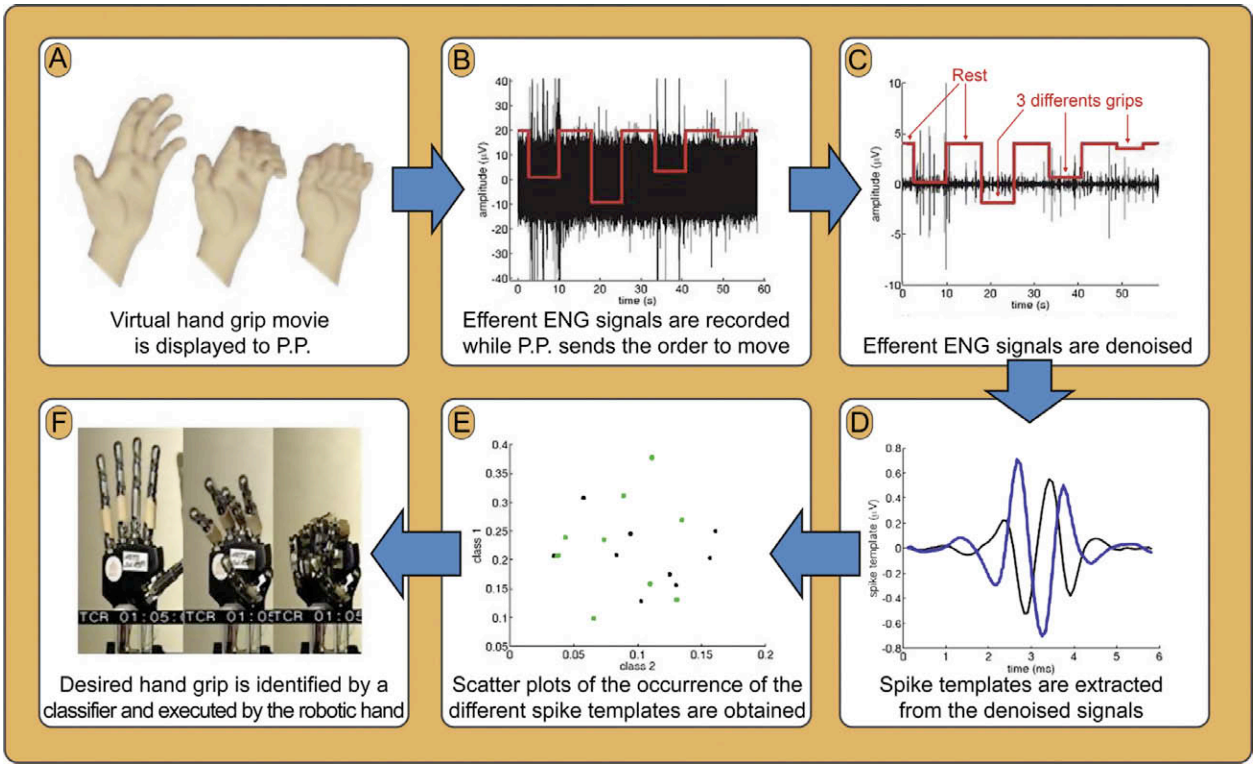

Fig. 2. Clockwise scheme of the implemented method for interpreting the motor command embedded in tf-LIFE4s efferent signals: (A) virtual hand grasping; (B) recording and preprocessing; (C) de-noising. In B and C black lines are the ENG recorded signals from which are extracted spike templates, while red lines represent the movements triggers presented in the movie as a function of time; (D) features extraction; (E) selection of the motor command using a classifier; (F) control of the prosthesis for the three distinct movements.

The subject worked on the project 4–6 h/day for 6 days/weekly and did not report any complication during a 9 months follow-up period.

The tf-LIFE4 micro structure consists of a Polyimide substrate with overall thickness and length of 10 µm and 5 cm respectively. tf-LIFE4s were arranged as a loop with eight Pt 300 nm-thick recording or stimulating sites (four on each side of the loop, i.e., L1, L2, L3, L4, R1, R2, R3, R4) and proximal sites (reference- and ground electrode on each side, i.e., L0, R0, GND, GND). On both ends of the structure, there are bond pads to contact the flexible part with an adaptor (Fig. 1B).

A stand-alone version of the CyberHand prototype, which approximates dimensions and grasping capabilities of the human hand with five fingers actuated by six motors (five for the independent flexion/extension of each of the underactuated fingers, one for the opposition of the thumb), was employed (Carrozza et al., 2006). It was endowed both with proprioceptive (i.e., 6 position sensors and 5 tensiometers able to measure tension of the cables controlling finger flexion, similar to Golgi tendon organs), and with exteroceptive sensors (i.e., tactile receptor). However, validation of real time artificial-sensor feed-back was not part of the present experiment; sensory stimulation and feed-back were delivered to be patient by the experimenters and not by the sensors embedded in the robotic hand which were only used to close the low-level servo loop.

Neural signals (ENG) and surface EMG (biceps/triceps) were simultaneously recorded via four blocks of 4-channel amplifiers (Grass QP511 Quad AC; ENG amplified: 10.000, filtered: 100 Hz–10 kHz; EMG amplified: 5.000, filtered 30 Hz–3 kHz; 16 bit, 1 Ms/s analogue-to-digital converter). A two-channel stimulator (Grass S88X Dual Output Square Pulse Stimulator) delivered trains of stimuli in accordance with tf-LIFE4s safety limits (maximum electrical charge: 100 µC/cm^2).

2.1. Motor output recordings

The protocol included the following phases: (1) pre-implant training with a virtual hand for standardizing the types of movements the subjects should voluntarily dispatch to the missing limb; (2) post-implant training to control output of tf-LIFE4s during the command to move the missing limb; (3) on-line prosthesis control designed to train the subject to control and standardise tf-LIFE4 output induced movement commands; (4) off-line development of a classifier-algorithm for optimal prosthesis control.

During phase (1), the subject practised sending three individual commands to the missing hand with the same speed/amplitude shown in dedicated videos by a virtual hand: (i) power grip; (ii) pinch grip; (iii) flexion of the little finger. These three actions were considered representative of the variety of movements controlled by the nerves under investigation: mostly median nerve fibres for the pinch, mostly ulnar nerve fibres for little finger flexion, and both for the power grip.

Following tf-LIFE4s implantation, phase (2) began, in which the same videos were used to trigger the subject's motor commands – without any activation of stump muscles – while recording neural signals. Videos showed alternating open-relaxed hand movements and were synchronised with the recording system. Signals from tf-LIFE4s and the EMG of, biceps and triceps were simultaneously recorded using a 48 kHz sampling rate, and were data-windowed in 1000 samples for mean rectified value calculation. Such recordings were acquired with the aim of eliminating eventual EMG contamination from tf-LIFE4 signals; contribution of EMG-derived control to the prosthesis was not an endpoint of the present study.

In phase (3), the ENG channels with the best signal-to-noise ratio were selected while analyzing the recordings from the previous phase. The online activities of the best channels, together with

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EMG activity, were shown to the subject, who was asked to modulate them while keeping the EMG silent in order to avoid EMG contamination of the tf-LIFE4 signals.

Once a stable level of training was achieved, LIFE signals were translated into robotic hand actions and the subject had direct visual feed-back on the correct/wrong execution of the intended movement. Each movement type was triggered by the signal level of a proper single channel. In order to exclude contamination by unwanted contractions from stump muscles or environmental noise, only rectified values greater than 3–8 μV in a time window ranging from 5 to 20 ms were used. Channels were chosen depending on their signal-to-noise ratio and anatomical-functional location (i.e., channels from the median nerve for power or pinch grip, channels from the ulnar for little finger flexion).

For phase (4), off-line examination of the original ENG signals and their processing was carried out to optimise the prosthesis control in order to avoid "false" positive (unwanted movement) and negative classifications (no movement performed despite dispatch of the command).

To achieve this goal (namely, to increase the sensitivity/specificity of signal processing), two main approaches were used: (1) extraction of selected features from the efferent signals as input to an artificial neural network for best identification of the motor command onset. (2) Wavelet de-noising of the efferent neural signals and spike-sorting using a template creation and matching approach (Citi et al., 2008). Support vector machines (SVM) were trained to use waveforms of the identified spikes so to infer the type of movement dispatched to the robotic hand.

Analysis was applied to a progressively higher number of electrodes/active sites in order to test whether correct classification of the tf-LIFE4 signals improved with processing or not. Whenever one type of action was classified, the robotic hand began and completed a movement after a time lag appropriate to a natural condition.

2.2. Sensory stimulation

To identify afferent fibres eliciting sensations, full mapping of all 32 contacts within the tested nerves was carried out. Rectangular cathodal pulses of duration 10–300 μs and current intensity 10–100 μA were employed. To avoid electrode damage, all stimulation trials were below 75% of the maximum charge (~4 nC), in the form of pulse trains at 10–500 Hz lasting 300–500 ms. The best active sites for sensation were characterised, beginning with short and low-current stimuli (10 μA, 10 μs) which were progressively increased in order to elicit different sensations; either the electrode's safety limits or subjective discomfort determined the maximal stimulus intensities. A psychometric staircase method ranging from the minimal perceived threshold (score = 1) to discomfort (score = 5), was used to quantify sensation.

Stimulation was also tested the 7th and the 8th day after implant as feed-back during a control motor task, in which was asked to the subject to produce a power grip every 5 s. In a set of trials, an operator triggered a stimulus train (0.3 s train of pulses, 10 μA, 10 μs at 70 Hz) after each burst of efferent activity recorded by tf-LIFE4s; success rates with or without sensory feed-back were then measured.

2.3. Transcranial magnetic stimulation

Cortical motor output was mapped via TMS (Magstim200; eight-shaped coil with an inner wing diameter of 70 mm; stimulus rate 0.1–0.2 c/s; intensity 10% above standardised excitability motor threshold (Rossini et al., 1994)) for each hemisphere before surgery and at the end of the training period. To check for interhemispheric differences, Motor Evoked Potentials (MEPs) were recorded from proximal muscles of both limbs (biceps and deltoid) during separate mapping of right and left hemispheres. Interhemispheric differences in the cortical representation of a given muscle have been demonstrated to remain stable in time in control populations, while they can be significantly modified by plastic reorganization following a monohemispheric lesion or a limb amputation (Flor et al., 1995; Rossini et al., 2003). Intensities reported in Fig 3 refer to the excitability threshold at rest.

The subject wore an elastic cap with a 99-square grid over the sensorimotor cortex. Square 1 corresponded to the point where the minimal intensity triggered MEPs of largest amplitude and shortest latency (*hot spot*); as in healthy subjects, this was coincident for biceps and deltoid on both hemispheres. A figure-of-eight coil was used with the virtual cathode centred on the site of the scalp to be stimulated and the holder oriented at 45° angle with respect to the approximate direction of the central sulcus, thereby making current in the brain flow in a postero-anterior direction.

3. Results

A progressive improvement of the tf-LIFE4s signal-to-noise ratio was observed in the post-surgery period, stabilising after 10 days. All the contacts of the 4 electrodes recorded properly during the entire 4-week experimental period. Three of the four electrodes elicited sensations with appropriate stimulation settings for 10 days. Before implantation, the patient experienced a moderate PLS, perceived as if, '*...the missing hand is still attached to the stump and tightly fastened and immobilized by a belt without any forearm*'. Pre-surgical training did not modify this perception. On the other hand, post-surgical training for robotic hand control and for sensory perception produced a selective reorganization of TMS motor cortical maps only on the hemisphere contralateral to the stump and resulted in clinical improvement of PLS, with a progressive return to perception of the full-length forearm and of the hand free of motion. Clinical improvement was no longer present at 3 months follow-up (Table 1).

Activity classes were identified before and after the trigger via de-noising and spike-sorting algorithms applied during a 500 ms refractory period after opening/closing command when the controller was unresponsive. From the de-noised signals, different templates of spikes were classified; these were used as inputs to the SVM classifier.

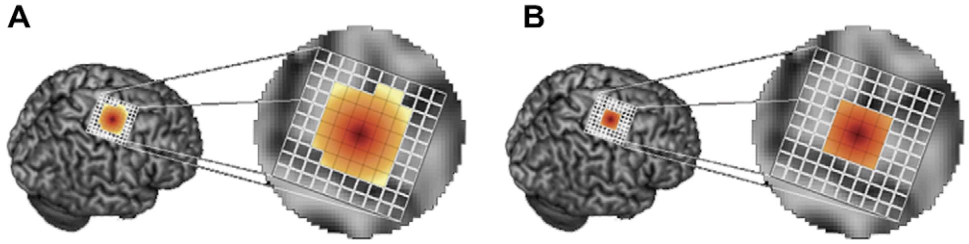

Fig. 3. TMS motor maps-Cortical motor maps to TMS from deltoid/biceps muscles before (A) and 4 weeks after (B) interface implant and training. Note the clear restriction of the excitable area in the hemisphere governing the missing limb (37 vs. 16 sites). The number of excitable sites in the left hemisphere remained stable in the two sessions.

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Table 1
Modification of phantom-limb syndrome during the experimental period and after 3 months.

	sfMcGill (0 → 45)	PPI (0 → 5)	VAS (0 → 100%)	Subjective description of PLS
Pre-implant	18	3	38	No forearm, blocked hand
1 week post-removal	11	2	23	Regain forearm, movable hand
3 months Follow-Up	17	3	36	No forearm, blocked hand

Evaluation of signals simultaneously recorded from several contacts of different electrodes from either nerve improved discrimination, with up to 85% of individual movements correctly classified when compared to information obtained from only one contact. Moreover, correct classifications improved with time (in particular from 75% on day 26 to >85% on day 28), indicating a learning effect. Dedicated control algorithms are a by-product of this research and are now available for the online control of a multi-degree-of-freedom hand prosthesis. The level of "shared control" between brain and the robotic controller can be modified according to the performance of the prosthesis (Cipriani et al., 2008) and to the preferences of the patient.

Pre-surgical TMS motor maps showed abnormal interhemispheric asymmetry of motor cortex excitability in the hemisphere governing the stump; this resulted in a larger area of representation of muscles adjacent to the stump than for the intact limb, while the other hemisphere showed dimensions as in the healthy controls. Following training, post-surgical maps, in parallel with decrement of PLS, showed a clear reduction of this asymmetry because of a restriction of the excitable area on the hemisphere contralateral to the stump, leading towards a more symmetrical muscle representation in the two hemispheres, as in control subjects (Fig. 3).

Discrete tactile sensations were elicited from different stimulating sites of three electrodes (i.e., from 4 sites of EL1 and EL 2 in the median nerve and from 5 sites of EL3 in the ulnar nerve) and referred in the fascicular projection territories of the corresponding nerves. As an example, touch and tingling sensations related to median nerve stimulation through L1 and L2 sites of EL1 electrode were referred to both the middle of the palm and near the base of the index and middle fingers, while those related to ulnar nerve stimulation through R1 site of EL3 electrode irradiated (black lines) towards 4th and 5th fingers (Fig. 4A and B). In agreement with the results of previous studies (Dhillon et al., 2004), stimulus frequency modulated the intensity of sensation on a log scale (see Fig 4B). When stimulation was added as sensory feed-back for the motor control task, the success rate increased significantly and rapidly (Fig 4C).

The electrical charge necessary to elicit sensations (minimal threshold) increased during the first ten days from 0.1 to 1 nC, until no sensation was elicited through any of the three electrodes despite stimulation with the maximum allowed charge (~4 nC). In

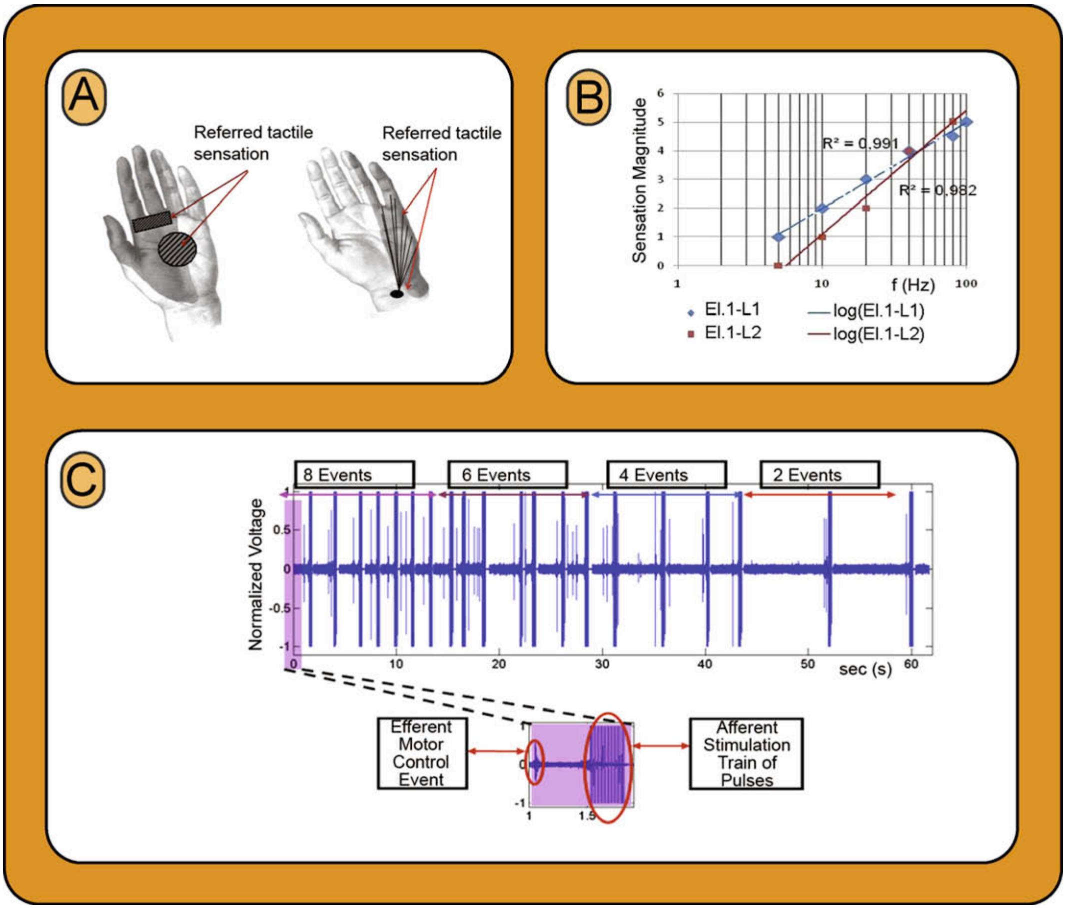

Fig. 4. Afferent stimulation – (A) Perceived localization of sensation after – median nerve tf-LIFE4 stimulation on left and after ulnar nerve tf-LIFE4 stimulation on right; (B) estimate of sensation magnitude (1 = threshold, 5 = discomfort) vs. frequency for two channels of the electrode 1 in the median nerve (trendline and R^2 are shown); (C) efferent/afferent signals during a one minute trial, while stimulation through tf-LIFE4s was used as feed-back. Each efferent movement control event was fed-back using a 0.3 s train of pulses at 70 Hz (intensity 10 μA, duration 10 μs). The subject improved his control after less than one minute of movement-related feed-back.

order to avoid irreversible electrochemical processes with the platinum electrode and thereby possible contamination of motor signal recordings, stimulation procedures were halted. Several, not mutually exclusive, explanations for this failure can be proposed: (a) progressive "habituation" of the patient, moving from an initial "hypersensitivity" due to long-lasting sensory deprivation (subjective sensory threshold below maximum of stimulation) which then progressively returned back and stabilised at a physiological level due to sensorimotor experiences with the tf-LIFE4 (subjective sensory threshold above maximum stimulation); (b) surface of the miniaturised contacts limiting the maximum applicable current charge, i.e., ~4 nC, well below parameters reported in previous reports (Dhillon et al., 2004); (c) fibrotic tissue reaction, suspected on visual inspection during LIFE removal but not confirmed histologically for ethical reasons.

4. Discussion

Limb amputation triggers anterograde/retrograde changes to and from the stump nerves extending to the contralateral cortex (Merzenich et al., 1984; Calford and Tweedale, 1988), as well as functional reorganization of the relevant CNS areas. In the de-efferented motor cortex, there is an increase in size and excitability of the representation of stump muscles, while the de-afferented S1 cortex progressively responds to inputs from skin and muscles adjacent to the stump (Cohen et al., 1991; Kaas, 1991; Flor et al., 1995; Knecht et al., 1998; Wu and Kaas, 1999). In spite of this, movement-related activity in M1 and S1 cortical areas controlling the hand and finger may still be found even years after amputation (Mercier et al., 2006; Reilly et al., 2006). Amputees maintain phantom limb awareness; however, the "orphan" CNS areas previously connected to the lost limb undergo "aberrant" reorganization, often provoking a disabling PLS (Hunter et al., 2003; Ephraim et al., 2005;). The fact that amputation does not eliminate the peripheral nerve connections or their CNS relay, makes them excellent candidates for re-establishing a nearly physiological control of an artificial prosthesis via a bidirectional intraneural electrode implant into the stump nerves (Di Pino et al., 2009).

Intraneural electrodes have higher selectivity and better signal-to-noise ratio than extraneural ones due to their intimate contact with afferent and efferent nerve fascicles (Yoshida and Horch, 1993; Lawrence et al., 2004). Given the same fibre-contact distance, the activity of large myelinated fibres is picked up more effectively than that of small myelinated and unmyelinated fibres. Therefore, tactile or position sensations can be selectively and focally elicited without concomitant pain, while motor signals to extrafusal fibres are recorded more easily than those to intrafusal and autonomic ones. On the basis of the current literature and of the present findings it is not possible to define which sensory fibres are stimulated within the nerve trunk; they might even come from the neuroma at the level of the stump. Nevertheless, it is clear from this and previous experience that once the site of stimulation and the pattern of impulses are precisely defined, sensory sensations are correctly, reliably and steadily localized by the subject within the missing hand/fingers. If recording sites within the nerve are sufficiently dense, the probability of recording signals from the fascicles originally innervating the missing limb and conveying the relevant information on the desired movement is therefore high (Navarro et al., 2005). Horch and colleagues pioneered stimulating nerve fascicles via thin insulated conducting wires implanted in nerves of amputees who, through training, succeeded in discriminating tactile and proprioceptive sensations (Dhillon et al., 2004, 2005), could rate force from a strain gauge on the thumb of a robotic hand and could match the elbow angle of the robotic arm with the intact arm (Dhillon and Horch, 2005). It is worth noting that the 4-week implant duration in the present study was dictated by the European Authorities as test period for an experimental medical device under scrutiny for biocompatibility. Moreover, the robotic hand was not worn by the subject, being too heavy in its present form. The hand operated on a table in front of the subject when connected to tf-LIFE4s. Despite such limitations, several new findings are worth mentioning: (1) tf-LIFE4s can be implanted and used in humans for several weeks with a high success rate in picking up signals with a good signal-to-noise ratio, remaining stable *in situ* even when carrying out everyday life activities (indeed, the patient lived at home except for the 3 days required for the surgical procedures); (2) multiple electrodes in different nerves with numerous contacts guaranteed a reliable flow of signals. In fact, simultaneous recordings from several sites on 3 electrodes from two nerves improved the rate of correct classification for movement control with higher sensitivity and specificity (i.e., less false positive/negative) compared to a single-contact classification, particularly when discriminating independent movements; (3) tactile sensations were elicited and modulated by afferent stimulation and it was shown that the quality and selectivity of efferent signals was augmented by concomitant sensory feed-back; (4) training improved the control of motor output to the prosthesis, combined with restriction of the cortical overrepresentation of muscles proximal to the stump and improvement of PLS.

In conclusion, combined use of tf-LIFE4s and advanced signal processing/stimulation techniques has allowed discrimination of signal patterns controlling independent types of hand grip and allowed delivery of sensory feed-back. Training and learning capabilities of human-interface interaction, a progressive reorganization of the input/output characteristics of the sensorimotor areas previously governing the lost limb, and parallel PLS modifications were also demonstrated. This study represents a nice model of a multidisciplinary, integrated approach for translating findings from bioengineering and bio-materials research in a clinical scenario.

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