Effects of Short-Term Training on Sensory and Motor Function in Severed Nerves of Long-Term Human Amputees

G. S. Dhillon, T. B. Krüger, J. S. Sandhu, and K. W. Horch

Department of Bioengineering, University of Utah, Salt Lake City, Utah; and Guru Nanak Dev University, Amritsar, Punjab, India

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Dhillon, G. S., T. B. Krüger, J. S. Sandhu, and K. W. Horch. Effects of short-term training on sensory and motor function in severed nerves of long-term human amputees. J Neurophysiol 93: 2625–2633, 2005; doi:10.1152/jn.00937.2004. Much has been studied and written about plastic changes in the CNS of humans triggered by events such as limb amputation. However, little is known about the extent to which the original pathways retain residual function after peripheral amputation. Our earlier, acute study on long-term amputees indicated that central pathways associated with amputated peripheral nerves retain at least some sensory and motor function. The purpose of the present study was to determine if these functional connections would be strengthened or improved with experience and training over several days time. To do this, electrodes were implanted within fascicles of severed nerves of long-term human amputees to evaluate the changes in electrically evoked sensations and volitional motor neuron activity associated with attempted phantom limb movements. Nerve stimulation consistently resulted in discrete, unitary, graded sensations of touch/pressure and joint-position sense. There was no significant change in the values of stimulation parameters required to produce these sensations over time. Similarly, while the amputees were able to improve volitional control of motor neuron activity, the rate and pattern of change was similar to that seen with practice in normal individuals on motor tasks. We conclude that the central plasticity seen after amputation is most likely primarily due to unmasking, rather than replacement, of existing synaptic connections. These results also have implications for neural control of prosthetic limbs.

INTRODUCTION

Peripheral nerve amputation has been shown to produce changes in cortical sensory and motor representation in various mammalian species, including humans (Chen et al. 2002; Cohen et al. 1991; Elbert et al. 1994; Hall et al. 1990; Jones et al. 2002; Merzenich and Jenkins 1993; Merzenich et al. 1984; Sanes et al. 1990). This central plasticity is thought to involve both immediate mechanisms, such as synaptic unmasking, and long-term effects, such as central neuronal sprouting (Calford 2002; Théoret et al. 2004; Wall et al. 2002). Moreover, chronic peripheral nerve transaction also produces atrophic changes in both sensory and motor neurons, including reduction of motor neuron dendritic arborizations (Carlson et al. 1979; Cragg and Thomas 1961; Hoffer et al. 1979; Horch 1978; Horch and Linshey 1981a,b; Kawamura and Dyck 1981; Kiraly and Krnjevic 1959; Mendell et al. 1974; Milner and Stein 1981; Sumner and Watson 1971; Sunderland 1978; Törnqvist and Aldskogius 1994). Although there is some evidence in animals that chronically amputated nerves retain at least some function (DeLuca and Gilmore 1976; DeLuca et al. 1982; Edell 1986), little is known about the extent to which nerve stumps in human amputees retain useful sensory or motor capabilities (Clippinger et al. 1974).

Work by different groups have shown that it is possible to interface microelectrodes to small clusters of motor and sensory neurons at a subfascicular level (Branner and Normann 2000; Branner et al. 2001; González and Rodríguez 1997; Goodall et al. 1991; Kovacs et al. 1992; 1994; Yoshida and Horch 1993, 1996). A recent study with long-term human amputees, involving implantation of intraneural electrodes in severed nerve stumps, demonstrated that it is possible through discrete stimulation of small micro-clusters of sensory neurons to provide feedback related to touch/pressure and joint position sense and to use these same electrodes to record motor neuron activity related to volitional attempts to move joints in a phantom limb (Dhillon et al. 2004). This indicates that central plastic changes notwithstanding, chronic section of peripheral nerves in humans does not eliminate all of their central sensory and motor pathway connections. What was not determined, however, is if repeated use of these pathways would result in a rapid and significant improvement in their functionality.

The present study was an attempt to explore the question of the effects of experience on function in residual neural pathways associated with peripheral nerve stumps. In addition to its importance in providing information about the limits of CNS plasticity in adult humans, this work has implications about the feasibility of interfacing with amputee nerve stumps to provide natural, closed-loop control of artificial limbs (Dhillon et al. 2004).

METHODS

Eight long-term (0.83–30 yr, average duration: ~7.3 yr) amputees voluntarily participated in the study. Institutional Review Board approval was obtained from both participating institutions, and the subjects were given adequate time to consider and provide informed consent. Although not selected on the basis of gender or handedness, all the subjects were right-hand dominant, adult males with an average age of 25.5 yr. All the amputations were of the right arm, above the elbow, and traumatic in nature. At the time of the study, the subjects were healthy and free from peripheral vascular disease or diabetes.

Fabrication procedures and performance characteristics of longitudi- dinal intrafascicular electrodes (LIFEs) are described elsewhere (Lawrence et al. 2003, 2004; Lefurge et al. 1991; Malagodi et al. 1989; Malmstrom et al. 1998; McNaughton and Horch 1996; Nannini and Horch 1991). The distal ends of the LIFEs were attached to the pins

Address for reprint requests and other correspondence: K. Horch, Dept. of Bioengineering, 50 S. Central Campus Dr., Rm. 2480, University of Utah, Salt Lake City, UT 84112 (E-mail: k.horch@mcc.utah.edu).

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of a miniature cable connector using conductive silver epoxy, which was thermally cured. A silicon rubber tube was used to provide strain relief for the fine LIFE wires. The connector assembly was embedded in glue and encased in a layer of silicone. A further layer of silicone was applied to the assembly to bond it to a circular silicon patch that was placed on the residual arm.

LIFEs were implanted within the healthy portion of the nerve proximal to any terminal neuroma to maximize recording signal-to-noise ratios and to ensure that recording and stimulation were performed in a part of the nerve that still maintained some degree of somatotopic organization. Partial epineurial dissection was performed at the site of implantation to allow visualization of the fascicle(s). The proximal ends of the electrodes were individually threaded through the skin using an 18-gauge needle as a trochar. Each electrode was then threaded through a 0.5- to 1.0-cm length of a fascicle with the aid of a 50-μm-diam tungsten needle attached to its leading end. Once the 1-mm recording/stimulating zone of the electrode was centered within the fascicle, the tungsten needle was removed. A reference LIFE electrode was sutured to the perineural surface of the nerve, level with the intraneuronal electrodes. More details on the implantation procedure are given in Dhillon et al. (2004).

After the amputees had fully recovered from the anesthetic, they underwent 2 wk of computer-aided motor and sensory studies to map the functionality of the implanted electrodes and the nerve fibers they interfaced with (Dhillon et al. 2004). The primary statistical analysis techniques used were regression analysis and ANOVA. After completion of the study, the electrodes were removed percutaneously by applying gentle longitudinal traction. This did not require application of an anesthetic.

Sensory input

An initial mapping of the electrodes was made to determine which of them could be used to elicit tactile or proprioceptive sensations. To do so, each electrode was stimulated, through a current-controlled stimulus isolation unit driven by a D/A converter interface to a laptop computer, with charge balanced pulses of 300 μs duration, in a current range between 1 and 200 μA. Starting at a low current level, stimuli were increased until either the upper limit was reached or the subject reported a distinct sensation. If the subject reported a discrete, distally referred sensation, a staircase method of limits was used to identify threshold and upper limit pulse amplitudes for the sensory unit (Gelfand 1998). Threshold was defined as the lowest average stimulus pulse amplitude at which the subject could reliably feel a sensation. The upper limit was defined as the current at which the nature or the location of the sensation changed or when the sensation became uncomfortable.

A psychometric scaling task was employed to evaluate the relationship between stimulus amplitude and sensation magnitude (Stevens 1986). A stimulus amplitude midway between threshold and upper limit was selected and 500-ms-duration pulse trains, with various pulse frequencies, were used to stimulate the nerve. Initially, the subject was presented with sample trains at each of the pulse rates so he had a feel for the range of sensations that would be experienced. For testing, the pulse train frequencies were logarithmically distributed, presented a fixed number of times (typically five each) in pseudorandom order, with a time period of 5 ± 5 s between successive trains. Subjects were asked to verbally assign an (open-ended) number to the magnitude of the elicited sensation for each stimulus presentation. Other than being instructed that a stronger sensation should result in a higher number, the subjects were not constrained in how they were to assign the numerical values. This procedure was used to avoid biasing them in the task (Stevens 1986). The subjects were not blindfolded or asked to close their eyes, but because the computer generated the stimuli automatically after a variable period following entry of the subject’s report, they had no external cue as to when a stimulus was to be delivered.

In addition to sensory psychophysical magnitude estimation as a function of stimulus frequency, the effects of changes in stimulus amplitude on perceived sensation magnitude and on the referred distributions of touch/pressure sensations were studied in some of the subjects. These changes were mapped by having the subject verbally report where on their phantom hand the sensations were perceived as coming from and having them assign perceived sensory magnitude values for the different areas of sensation that developed as the stimulus strength was increased. For some of the instances in which proprioceptive (finger flexion) sensations were reported, the subject was asked to indicate the perceived finger position with the contralateral finger. The angle of the matching joint was then measured with a goniometer.

Motor control

Candidate electrodes for evaluating motor control were identified by asking the amputee to attempt different movements in the amputated (phantom) part of the limb (e.g., the wrist or fingers) while recordings were made of neural activity from different implanted electrodes. Motor signals were recorded between the LIFE and the reference electrode with a differential amplifier (gain of ~20,000), band-pass filtered (0.3–4 kHz), sent to a loudspeaker with a noise clipper, and fed through a 16-bit A/D converter to a laptop computer (Dhillon et al. 2004). The subject was directed to select a phantom movement that resulted in maximum audible activity. Once the subject had learned to generate motor neuron activity, a simple computer game was used to evaluate his control over the rate of motor neuron action potential production.

Basically, the subject was asked to modulate recorded neural activity to control a cursor on the computer screen so that it would overlap and stay within a displayed target (Dhillon et al. 2004). At the start of a trial, the target would appear randomly in a screen area 480 pixels wide, and the cursor would appear at the left end of the screen. The subject’s task was to move the cursor and place it in the target for ≥500 ms (a “hit”). Simply placing the cursor in the target, no matter on how many occasions, counted as a failure unless the subject managed to hold the cursor in the target for the specified time. As preparation for the task, background noise was recorded and displayed on the computer with the subject relaxed (in the absence of volitional motor output, recordings from the nerve stumps gave no indication of neural activity). This allowed the experimenter to set a minimum threshold level for detecting neural activity. The subject was then asked to generate neural activity, and the recorded signals were used to set an upper threshold for detecting action potentials. To simulate the properties of physiological motor control, the efferent activity (in the form of a pulse train from a Schmidt trigger based on these 2 threshold levels) was passed through a leaky integrator to provide the control signal. Time constants between 400 and 600 ms for the integrator were tested during the first day of training. With shorter time constants, amputees were able to control the cursor more precisely but found it difficult to hit targets on the far side of the practice screen area. With longer time constants amputees were able to freely move the cursor to all regions of the screen but precision was much reduced. As a compromise between these conditions, 500 ms was chosen as the standard time constant.

Given the settings for the spike detector and firing rate integrator, minimum output corresponded to the subject making no attempt at the phantom movement and maximum output was determined by having the subject make a maximal effort at the phantom movement. Minimum activity placed the cursor at the left edge of the screen, maximum activity placed it at the right edge.

Each testing set consisted of 20 10-s-long trials, and a subject was limited to completing two sets per day. All subjects started off with a target width of 96 pixels. After the subject managed to successfully perform this task with a success rate >75%, the task was made more difficult by reducing the size of the target to 68 and then 48 pixels. For
one subject, who succeeded in hitting the smallest target >75% of the time, the dwell time requirement was increased to 750 ms for that target size.

RESULTS

Sensory input

All of the subjects reported either tactile or proprioceptive sensations from one or more electrodes. In half of the subjects, both types of sensations could be elicited (through different electrodes). On the first day of testing or when electrical stimuli were first delivered on subsequent days, subjects sometimes reported sensations of spiders crawling on the region of the referred sensation. After stimuli were delivered for 30–60 s or when the stimulus amplitude was increased, this would stabilize to a sensation of pressure/touch, joint position or movement. Usually electrical stimulation resulted in unimodal (i.e., touch, movement, or static joint position) sensations that showed stable topography. In ~10% of the cases, the location of the referred sensation tended to wander during the first 2 days. For tactile sensations, this movement was between the tips of different digits (middle and the index finger or thumb and the index finger). Over the duration of the study, these sensations eventually stabilized to one or more finger tips. In all cases, the sensations were in the fascicular projection territories of the implanted nerve, suggesting a stable electrode position, stimulating a small cluster of neurons. In ~20% of the cases, sensations were confused as to being either movement or pressure, vibration in a digit, and a mixture of tugging and movement localized to the palm or the fingers. The majority (~70%) of the cases resulted in stable sensations of touch/pressure or joint position/movement sense that were localized to the digits. In general, sensations were discrete, unimodal, repeatable, and could be painlessly elicited over the duration of the study. With increasing stimulus current, sensations of touch/pressure usually spread from distal (digit tip) to proximal locations (Fig. 1).

For proprioceptive sensations, amputees reported sensations related to finger flexion. If the sensation was that of a single joint movement, it was usually localized to the distal interphalangeal joint (DIP). With further increments in stimulus amplitude, the DIP flexion tended to increase and was followed by

FIG. 1. Distributions and magnitudes of pressure/touch sensations with time and stimulus amplitude in 3 different amputees for whom this was systematically mapped over a 2-wk period. Tactile sensations were evoked with 300-\(\mu s\) duration stimulus pulse trains. The legends to the right of each drawing indicate the stimulus amplitude (in \(\mu A\)) and frequency (in pulses/s). The bold number near each shaded region is the psychometric magnitude scale number assigned by the subject to the intensity of the sensation from that part of the phantom hand with the strongest stimulus strength listed. The 1st drawing in a row is the result from day 1 of testing, the 2nd is from day 7, and the 3rd is from day 14. Rows 2 and 3 are from 2 different electrodes in the same subject.
a sensation of PIP (proximal interphalangeal joint) flexion. Other amputees reported sensations of finger flexion involving the DIP, PIP, and MCP (metacarpal phalangeal) joints or just the flexion of the PIP.

During the course of the study, there was a small, but statistically significant (regression analysis, $P < 0.01$), increase in both the threshold and the upper limit for eliciting painless, unitary sensations of touch/pressure or joint movement, shown in Fig. 2 as values normalized to threshold for each subject on day 1. The mean value for threshold on day 1 was $7.0 \pm 2.5$ (SD) nC ($n = 12$).

By modulating stimulus frequency, the magnitude estimation, but not the modality or the topography, of referred sensations of touch/pressure or proprioception could be varied systematically: a logarithmic regression gave the best fit for the ratings of magnitude of sensation versus frequency of nerve stimulation (Fig. 3, $A$ and $B$). However, indicating perceived finger position by matching it with the contralateral finger produced a more linear relationship between both stimulus amplitude and frequency and reported phantom finger position (Fig. 3, $C$ and $D$). Visual inspection showed no systematic trend in the slopes of these regressions over the duration of the study, although they could change from one day to the next in some cases (Fig. 3B). This lack of a trend was confirmed by plotting slopes of the regression lines (normalized to the slope on day one) versus time. The data were best approximated by a linear regression with a slope not significantly different from 0 ($r = 0.04$, $P = 0.11$). Analysis of the variance of residuals around the regression lines for the magnitude scaling also showed no systematic trend over the course of the study, indicating no change in scatter of the data with time.

The resting position of a given phantom digit was consistently reported in full extension by the amputees. After stimulation with an impulse train of 500-ms duration, at different frequencies, subjects reported varying degrees of finger flexion (Fig. 3, $B$ and $D$). At the end of the impulse train, the digit would be perceived as having returned back into its original position (full extension). At the upper limit of stimulus frequency, the terminal aspect of the finger would appear to dig into the palm, explained by the amputees as a clenched fist but involving only one digit. For all subjects reporting sensations of joint position, there was a general decline in the upper limit frequency (at which the joint was perceived as maximally flexed), averaging $\approx 250$ Hz at 2 wk. Frequency of stimulation was also correlated with the perceived rate of digit flexion, but the dominant effect was the change in the sense of static joint position. Amputees could judge the rate of movement as fast or slow but were unable to quantify it on a numerical scale. In one amputee, 5 days after initial testing, perceived finger flexion could no longer be systematically controlled through modulation of stimulation parameters. Instead the subject reported

![Graph showing threshold and limit stimulus amplitudes](http://jn.physiology.org/)

**Fig. 2.** Threshold ($\bullet$) and upper limit ($\cdot$) stimulus amplitudes as a function of time. For each of the 12 electrodes included in the figure, amplitudes are normalized to the threshold stimulus amplitude on the 1st day of testing for that particular electrode. Not all electrodes were tested for the full 15 days due to limitations in subject availability.

![Graphs showing force and flexion ratings](http://jn.physiology.org/)

**Fig. 3.** Examples of psychometric sensory magnitude rating as a function of stimulation parameters. Each panel is based on data from a single subject, selected as a typical example of one or more specific points made in the text. $A$: magnitude estimates of pinch grip force as a function of stimulation frequency. $\bullet$ results from testing on day 1; $\cdot$ results from day 7 for subject 3245. The difference between slopes is not significant ($P = 0.62$). $B$: magnitude ratings of perceived finger flexion at the distal (DIP) and proximal (PIP) interphalangeal joints vs. stimulus frequency for subject 4532. The difference between slopes for day 1 ($\bullet$) and day 7 ($\cdot$) is significant ($P < 0.001$). $C$: reported phantom finger flexion as a function of stimulus amplitude for subject 8726 on day 5 ($\bullet$) and day 6 ($\cdot$). The difference between slopes is not significant ($P = 0.89$). The stimulus pulse width was 300 $\mu$s, and the stimulus frequency was 100 Hz. $D$: the effect of stimulus current on perceived finger flexion as a function of stimulus frequency for 32 $\mu$A ($\bullet$, $\cdot$) and 38 $\mu$A ($\circ$, $\cdot$). 300-$\mu$s-duration pulses in subject 4532. In this case, the stimuli were presented in incremental, rather than pseudorandom, order.
only two positions, full extension (no pulses applied) or full flexion (for any value of pulse amplitude or stimulation frequency between the threshold and upper limit). This behavior was not seen with any other electrode in this or other amputees. In all other cases, the duration of the study perceptions of digit flexion became smoother and less jerky.

Two amputees also reported a sensation of closing and opening of a pincer grip between the thumb, index, and middle fingers. For a stimulation frequency <10 Hz, the grip was felt as open. At ~30 Hz, the index and the middle fingers were perceived as coming into contact with the thumb. With further increments in frequency, pinch force became stronger (Fig. 3A).

When defining threshold and upper limit stimulation parameters, subjects reported increasing flexion of fingers with increments in injected charge. This was formally investigated by keeping the frequency of nerve stimulation constant and varying the stimulus amplitude, which demonstrated that the perception of joint flexion/extension could be systematically modulated by varying the stimulus amplitude (Fig. 3C). In addition, the stimulus frequency required to provide a sense of full flexion depended on stimulus magnitude. In one subject, for example, with pulse amplitudes of 24, 28, and 32 µA (pulse width = 300 µs), the maximum frequency required for perception of full flexion of a digit was 510, 100, and 60 Hz, respectively. This dependence of joint-position sense on the interaction of frequency and charge was quantitatively investigated in one amputee by varying the amplitude and examining the frequency dependence of perceived joint excursion (Fig. 3D). In general, the higher the stimulus amplitude the lower the frequency required to produce the sensation of flexion to a given position. Similar observations were made in other subjects, although psychophysical evaluation was not conducted.

**Motor output**

One or more electrodes recording controllable efferent activity were identified in six of the eight subjects. The success rates with which the subjects could strike and stay within (“hit”) the target increased with experience (Fig. 4). Once an amputee managed to score hits in >75% of the trials for a given target size, the target size was reduced. After a reduction in the target size, success rate initially declined and then eventually increased in subsequent sets of trials. Over a period of <70 min experience with the task, subjects demonstrated improved cursor control, progressing from successfully positioning it within a 96 pixel wide target to hitting a 48 pixel wide target (Fig. 4). One subject (not shown) even succeeded in hitting the smallest target 70% of the time with a 750-ms dwell time requirement.

Within a given set of trials, time to score a hit declined for the largest target (linear regression, \( r^2 = 0.43, n = 4 \)), but not for the middle or smallest target sizes. The was a small, but statistically significant, relationship between time to success and target size [96 pixel target = 4.8 ± 0.21 (SE) s, 68 pixel target = 4.3 ± 0.17 s, 48 pixel target = 5.0 ± 0.20 s; ANOVA, \( P = 0.02 \)].

Some, but not all, subjects showed an increase with time in the maximal neural output (as defined in METHODS) they could generate to drive the cursor (Fig. 5).

**DISCUSSION**

Distally referred sensations of touch and/or proprioception could be elicited in all of the subjects by electrical stimulation through one or more of the implanted LIFEs. This implies that sensory pathways retain at least some residual function even 30 yr after nerve amputation. Once established, the sensations evoked by such stimulation tended to remain stable in terms of modality (touch, joint movement, or joint position), referred location, and sensitivity (as measured by the slopes of the psychometric magnitude estimation curves). This implies that the extent of sensory experience provided by these experiments did not significantly alter the functionality of the residual sensory pathways. As discussed in the following text, it does...
not mean that continued or more extensive sensory practice would not do so.

We were unable to record volitionally induced neural activity in only two of the subjects. This does not mean that they did not have functional motor pathways, only that we were unable to identify them, perhaps due to the limited sampling provided by implanting only a few LIFEs in a given subject. Although motor performance did improve with time, given the generally limited increase in motor output seen with time, this improvement appears to be due more to practice with a novel task than to any significant change in central connectivity of the residual motor pathways. Given that the two longest (10 and 30 yr) amputees were among the subjects with good motor control, it appears that basic motor pathways are permanently established by early adulthood, even in the subsequent absence of effectors.

**Sensory input**

There was a small increase with time in the amount of charge per stimulus pulse needed to elicit a threshold sensation and somewhat larger increase in stimulus amplitude that could be delivered before the nature of the sensation changed. One might be tempted to interpret the former as being due to reactive changes around the active electrode stimulating sites, and the latter as being due to this plus, perhaps, a greater central tolerance for stimulation. However, note that all these measurements were made during the time when acute tissue responses to the surgery and implanted electrodes, such as edema, were active. One really needs to wait until these have resolved before making definitive statements about long-term effects and possible causes (Lefurge et al. 1991). One thing that did remain constant, though, was the relatively wide “safety zone” (the ratio of the upper limit to the threshold) for stimulation. Thus it was always easy to find a stimulus amplitude that reliably elicited a discrete, distally referred sensation without dropouts or spread, throughout the 2-wk period of the experiments.

In most cases, the elicited sensations could be systematically controlled through modulation of stimulus frequency and amplitude. Touch/pressure sensations were usually localized to the distal phalanx. With increasing stimulus amplitude, the sensation typically spread proximally. In the digits, the intensity gradient of referred phantom sensations was in the distal to proximal direction. This is consistent with the properties of the LIFEs as point stimulation electrodes, which stimulate progressively larger clusters of neurons with increasing charge injection (Meier et al. 1992; Nannini and Horch 1991), and the greater density of innervation as one moves distally along a digit (Vallbo and Johansson 1984).

Subjects showed a consistent ability to grade the intensity of elicited sensations over the duration of the study. However, there was no consistent pattern of improvement in this ability as evidenced by lack of definite trends in slopes of the regression lines or the variance of residuals around the regression lines. For the sensory studies, subjects were given random stimuli which elicited unitary, punctuate sensations for <10 min a day, and they graded the intensity of referred sensations without feedback as to what the stimulus level actually was. More experience, coupled with better feedback, may have improved their performance. Sensory reeducation has been shown to enhance sensory recovery after repair of nerve injuries (Dellon 1981; Mackin et al. 2002), but this recovery is not immediate: it occurs over many weeks. In the present study, sensory input was presented for only a short period of time (<75 min over the course of the study) and did not involve any formal training similar to that of sensory reeducation after nerve repair.

The location of elicited touch/pressure sensations either did not change or became better defined with time (e.g., row 2 of Fig. 1), the latter presumably because amputees could distinguish between intensity gradients, suggesting some beneficial effects of sensory stimulation in activating “silent” regions of the somatosensory cortex. The sensations elicited by the LIFEs tended to cover a larger area than those reported with microneurographic stimulation of intact sensory nerves (Schady and Torebjörk 1983; Schady et al. 1983). This may be related to the fact that our study was not designed to precisely map the sizes and the shapes of projected fields. Rather we were more interested in the stability of the elicited sensations and their spread with increasing charge injection. Therefore when the subjects indicated, for example, a sensation referred to the thumb tip, no extra time was spent on elucidating its precise topography, unless the subject volunteered the information. A more-detailed study needs to be undertaken to more precisely define the locations, sizes and shapes of evoked receptive fields. Still, with increasing stimulus strength there was a clear increase in the spread of tactile sensations.

For proprioceptive sensations, amputees reported either movement of a given finger joint or movement of the entire digit. Subjects could reliably distinguish different degrees of joint flexion, through either stimulus frequency or stimulus amplitude modulation. Two subjects consistently reported a referred sensation of phantom grip opening and closing. The perceived magnitude of this pincer grip between thumb, index, and the middle fingers could be reliably controlled through stimulus frequency or amplitude modulation. This finding suggests that the sensory fibers which mediate complex movement and touch sensations of pincer grip opening and closing are topographically grouped and segregated in peripheral nerves. The frequency at which the joint was perceived as maximally flexed (250 Hz on average at 2 wk) is comparable to the maximal frequency of firing of muscle spindle fibers (Clark and Horch 1986). In contrast, frequencies <510 Hz were correlated with stronger touch/pressure sensations (Fig. 3A). With time sensations related to finger flexion became smoother and less “jerky,” suggesting positive benefits of providing input to sensory cortex.

Although further studies are needed to more carefully investigate the relationship of stimulus pulse charge and frequency of stimulation to joint position sense, we did find that, in general, the lower the stimulus amplitude, the higher the frequency range needed to provide a sense of full joint excursion (Fig. 3D). This is consistent with encoding of joint position and movement information by the total afferent inflow from the pertinent sensory receptors.
Motor output

For motor control, in contrast to the sensory studies, the amputees were actively concentrating on improving their performance and were not simply passive subjects. The subjects were able to generate motor neuron activity related to phantom limb movements and demonstrated improvement in cursor control with practice. For example, the subjects managed to increase the precision of cursor control and score hits in 96 pixel targets on day 1, and by the end of the study, the majority of the subjects could proficiently control the position of the cursor in a 48 pixel wide target. For some, but not all, of the subjects there was gradual increase in the neural activity recorded by LIFEs associated with increased precision of cursor control. That is, through learning and practice, the subjects were able to improve motor control outflow to nerve fibers that had not been connected to muscle for periods of months or years. This is evidence of dynamic plasticity of CNS areas concerned with motor control even in the absence of proprioceptive feedback.

Implications for a neuroprosthetic arm

Upper limb amputees strongly desire a prosthetic control system that provides prehension feedback from the terminal device (Atkins et al. 1996). Referred sensations of pressure/touch resulting from intraneural stimulation were projected within the distribution of digital nerves and not scattered randomly throughout the hand. This is consistent with animal studies that have demonstrated that such stimulation is sufficiently localized that it is possible to elicit independent stimulation of microclusters within and between fascicles (Branner and Normann 2000; Branner et al. 2001; Yoshida and Horch 1993). Because the spread and topography of a pressure/touch sensation could be controlled through modulation of stimulation parameters, a given electrode could be used as a sensory channel for providing sensory feedback from a portion of the opposing ends of the gripper. With implants in separate fascicles, it is possible to get sensations in different digits. With implants of two or more electrodes in a given fascicle, different sensations could be distinguished within a given digit. Technologies under development may allow for stimulation of individual sensory neurons, increasing the number of sensory channels and resolution of sensory feedback (Dario et al. 1998; Donoghue 2002; González and Rodríguez 1997; Kovacs et al. 1992, 1994; Wallman et al. 2001).

For prehension feedback, sensors in the tip of the artificial hand/gripper would be adequate. Indeed, from a practical point of view the precise topography of elicited sensation does not need to be mapped for providing touch/pressure feedback from the gripper of the artificial arm. Rather it is only necessary that the modality of the elicited sensation be appropriate and that its referred location corresponds to the gripper. Because the intensity of the referred sensations can be reliably modulated, amputees would have appropriate information about contact and grip force.

Normal proprioception may not reflect a sense of joint angle (Scott and Loeb 1994; Soechting 1982), and recent work has demonstrated that extrinsic muscles of the hand signal fingertip position sense more precisely than individual joint angles (Biggs et al. 1999). Even though our subjects could distinguish flexion of different IP joints, information about the location of the terminal aspect of the artificial hand/gripper may be all that is required for prosthetic control. Furthermore, joint position sense from the digits is relatively poor as compared with that from more proximal joints (Clark et al. 1995). When appropriate nerves are implanted for control of artificial limbs, we would expect better results for more proximal joint position sense.

In short, our study implies that if a neuroprosthetic arm were to be interfaced to the residual nerve stumps, amputees might be able to improve control over its movements and incorporate it into their body image through the effects of training, learning and central plasticity.

Limitations of this study

The subjects received <10 min of sensory experience on a daily basis. Because they were not informed of what the actual stimulus amplitude or frequency was, they received essentially no graded feedback to use in “improving” their performance. This was necessary to guard against them picking up on some cue other than the strength of a sensation for the tactile ratings or perceived finger position for the proprioception ratings to use in producing their responses. Subjects were provided with a similarly limited amount of motor experience, although in this case feedback was provided on their performance. Clearly amputees receiving a wealth of sensory re-education and motor control training may show greater improvements in sensory perception and motor control than reported here. On the other hand, the fact that even a short period of training can lead to measurable improvement in phantom limb motor control implies that human amputees show dynamic plasticity that may be comparable to that demonstrated in normal subjects after practice of simple movements.

The second limitation to the study is that we really can’t say much about how the residual functions in the nerve stump central pathways compare with those in normal subjects. Ethical and regulatory constraints on human subject experimentation preclude implanting LIFEs in intact peripheral nerves, and similar data cannot be obtained via microneurographic studies that are not suitable for recording from and stimulating the same set of nerve fibers over periods of weeks.

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