Targeted reinnervation for enhanced prosthetic arm function in a woman with a proximal amputation: a case study

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Summary

Background The function of current artificial arms is limited by inadequate control methods. We developed a technique that used nerve transfers to muscle to develop new electromyogram control signals and nerve transfers to skin, to provide a pathway for cutaneous sensory feedback to the missing hand.

Methods We did targeted reinnervation surgery on a woman with a left arm amputation at the humeral neck. The ulnar, median, musculocutaneous, and distal radial nerves were transferred to separate segments of her pectoral and serratus muscles. Two sensory nerves were cut and the distal ends were anastomosed to the ulnar and median nerves. After full recovery the patient was fit with a new prosthesis using the additional targeted muscle reinnervation sites. Functional testing was done and sensation in the reinnervated skin was quantified.

Findings The patient described the control as intuitive; she thought about using her hand or elbow and the prosthesis responded appropriately. Functional testing showed substantial improvement: mean scores in the blocks and box test increased from 4·0 (SD 1·0) with the conventional prosthesis to 15·6 (1·5) with the new prosthesis. Assessment of Motor and Process Skills test scores increased from 0·30 to 1·98 for motor skills and from 0·90 to 1·98 for process skills. The denervated anterior chest skin was reinnervated by both the ulnar and median nerves; the patient felt that her hand was being touched when this chest skin was touched, with near-normal thresholds in all sensory modalities.

Interpretation Targeted reinnervation improved prosthetic function and ease of use in this patient. Targeted sensory reinnervation provides a potential pathway for meaningful sensory feedback.

Introduction

Improving the function of artificial arms remains a challenge, especially for amputations at the elbow or higher, where the disability is greatest. Motorised hooks, hands, wrists, and elbows are available, but existing methods of control are inadequate. Currently, most powered artificial limbs are controlled with the surface electromyogram (myoelectric signals) from a remaining pair of agonist-antagonist muscles in the amputated limb.[1] This method allows only a single motion to be controlled at a time; operation of the prosthetic elbow, wrist and hand, or hook must be done sequentially. Furthermore, current methods of myoelectric control do not have a natural feel because proximal muscle functions (eg, shoulder, bicep, or triceps muscles) are not normally used to direct wrist or hand movements. Thus, these methods are frustratingly slow and awkward. Furthermore, current prostheses have no intrinsic sense of touch and provide little sensory feedback to the user. They are instead operated only with visual feedback.

We developed a new biological neural machine interface for individuals with amputations, called targeted reinnervation. Targeted muscle reinnervation (TMR) uses the residual nerves from an amputated limb and transfers them onto alternative muscle groups that are not biomechanically functional since they are no longer attached to the missing arm. During the nerve transfer procedure, target muscles are denervated so that they can be reinnervated by the residual arm nerves that previously travelled to the arm before amputation. The reinnervated muscles then serve as biological amplifiers of the amputated nerve motor commands.[2,3] Subcutaneous tissue is removed so that surface myoelectric signals are optimised for power and focal recording. TMR thus provides physiologically appropriate electromyogram control signals that are related to previous functions of the lost arm. For example, transferring the median nerve to a segment of pectoralis muscle provides a hand-close myoelectric signal. The patient thinks about closing his or her hand and the median nerve reinnervated segment of the pectoralis muscle contracts. The myoelectric signal from this reinnervated muscle segment is then used to provide a control input to close the motorised hand. By transferring multiple nerves, TMR myoelectric signals allow intuitive, simultaneous control of multiple joints in an advanced prosthesis. TMR was first done in a man with bilateral shoulder disarticulation,[4,5] increasing his performance on standardised function tests by as much as 250%. Two men with long transhumeral amputations had successful targeted reinnervation surgery with similar functional results. Surgery was unsuccessful in a fourth man, because of nerve injuries discovered during the surgery.

Similarly, targeted sensory reinnervation (TSR) might potentially be used to provide the amputee a sense of touch in the missing limb. With this technique, a segment of skin near or overlying the TMR site is denervated and the regenerating afferent nerve fibres

Figure 1: Preoperative prep and drape

from the residual hand nerves are enabled to reinnervate this area of skin. As a result, when this skin is touched, the amputee feels as if their hand is being touched. We call this transfer sensation, and it is an exciting mechanism to potentially provide meaningful sensation to the amputee. For example, sensors in the prosthetic hand could quantify pressure, temperature, and texture of objects, and actuators over the reinnervated skin could apply proportional pressure, thermal, and shear stimuli back to the skin of the TSR site, so that the amputee seems to feel what he or she is touching. TSR developed unexpectedly in our first patient. By removing subcutaneous fat, his skin was denervated and afferent nerve fibres regenerated through his pectoral muscles to reinnervate his chest skin.

After the initial success with our first male patient we sought to improve our techniques in subsequent surgeries and address new challenges for female patients. Specifically, we would not be able to remove much subcutaneous tissue in female patients (ie, give them a mastectomy) to optimise surface myoelectric recordings as we did in the male patient. For this reason, surgical techniques were developed to work above and to the side of the breast. Additionally, a new technique was developed to purposefully apply targeted sensory reinnervation without subcutaneous tissue removal. We describe the application of targeted muscle and sensory reinnervation in a young woman with a very proximal transhumeral amputation.

Methods

Patient

The patient was a 24-year-old woman who had a traumatic transhumeral amputation in May, 2004, due to a motorcycle accident. She had severe phantom limb pain (9 out of 10 Likert scale) that abated with treatment over 6 months. Since only 3 cm of her humerus remained, the patient was fitted with a shoulder disarticulation level prosthesis. She received her first conventional myoelectric prosthesis in October, 2004, in a different city; the device

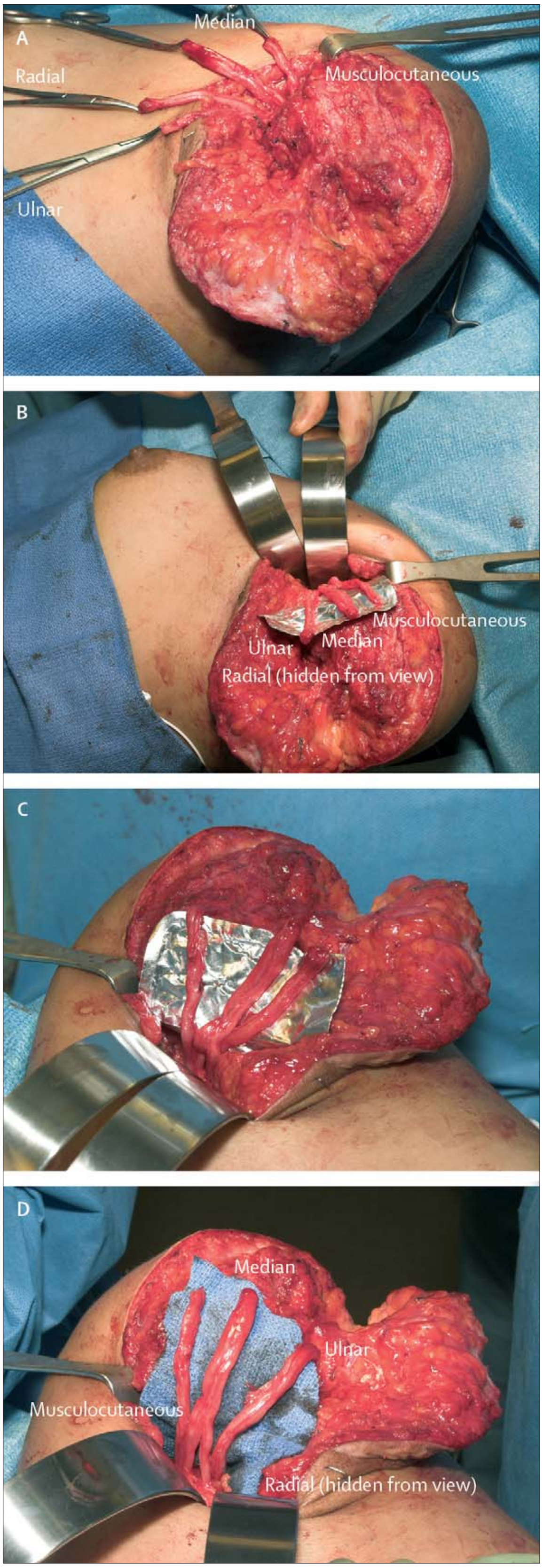


Figure 2: Exposure of four main motor nerves that used to travel down arm

consisted of a passive shoulder, a motorised elbow, a passive wrist rotator and a motorised hand. She used myoelectric signals from her pectoral and remnant triceps muscles to sequentially operate the prosthetic elbow and hand. She was trained to use the device in weekly occupation therapy sessions that lasted 3 months, starting in January, 2005.

Procedures

Targeted reinnervation surgery was done in August, 2005, with ethics committee approval and written informed consent from the patient. The risks of the procedure included permanent paralysis of the target muscles, recurrence of phantom limb pain, and development of painful neuromas, in addition to standard risks of elective surgery. Surgery was done under general anaesthesia and without muscle relaxation (figures 1–6). The patient's previous amputation incision was reopened. The musculocutaneous, median, ulnar, and radial nerves were all identified by their branching pattern and cut back to normal appearing fascicles. A branch of the radial nerve leading to a triceps remnant was identified using a nerve stimulator and carefully preserved. All fat and scar tissue over the remnant triceps muscle was excised to optimise the surface myoelectric signal of this muscle.

Inspection of the inferior aspect of the clavicular head of the pectoralis revealed two separate motor nerves entering this muscle segment. Two large (1·5 mm diameter) motor nerves were found innervating the sternal head of the pectoralis major, and the motor nerve to the pectoralis minor was also identified. These motor nerve branches were all divided a few mm from where the motor nerve

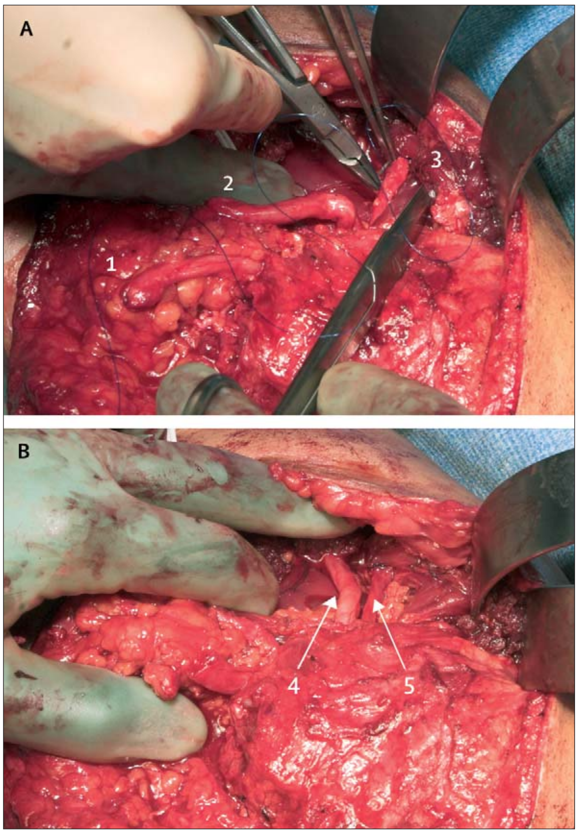


Figure 3: **Coaptation of nerves to pectoralis major**
(1) Ulnar nerve. (2) Median nerve. (3) Coaptation of musculocutaneous nerve to clavicular head of pectoralis major. (4) Coaptation of median nerve to sternal portion of pectoralis major. (5) Coaptation of musculocutaneous nerve to clavicular head of pectoralis major.

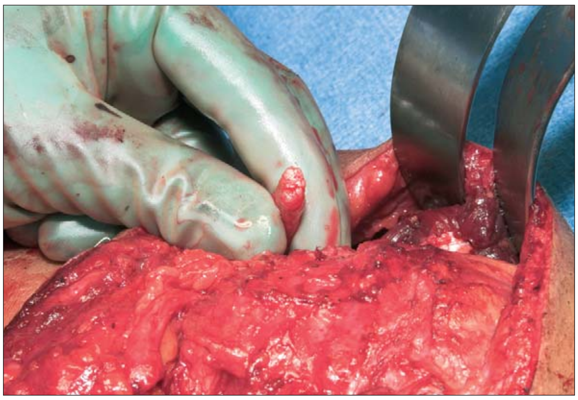


Figure 4: **Healthy fascicles of ulnar nerve**

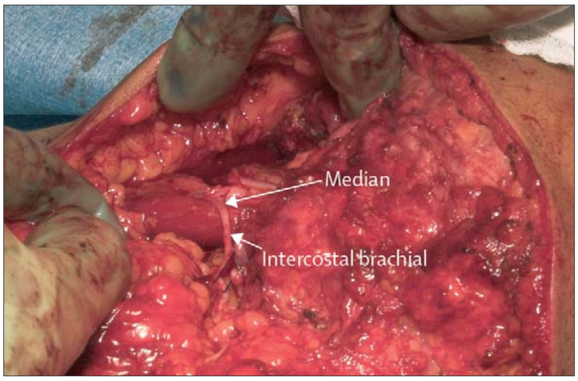


Figure 5: **End-to-side neurorraphy of intercostal brachial cutaneous nerve coapted to median nerve**

Figure 6: **Final appearance**
Lower incision marks area from which fat was removed from over serratus muscle.

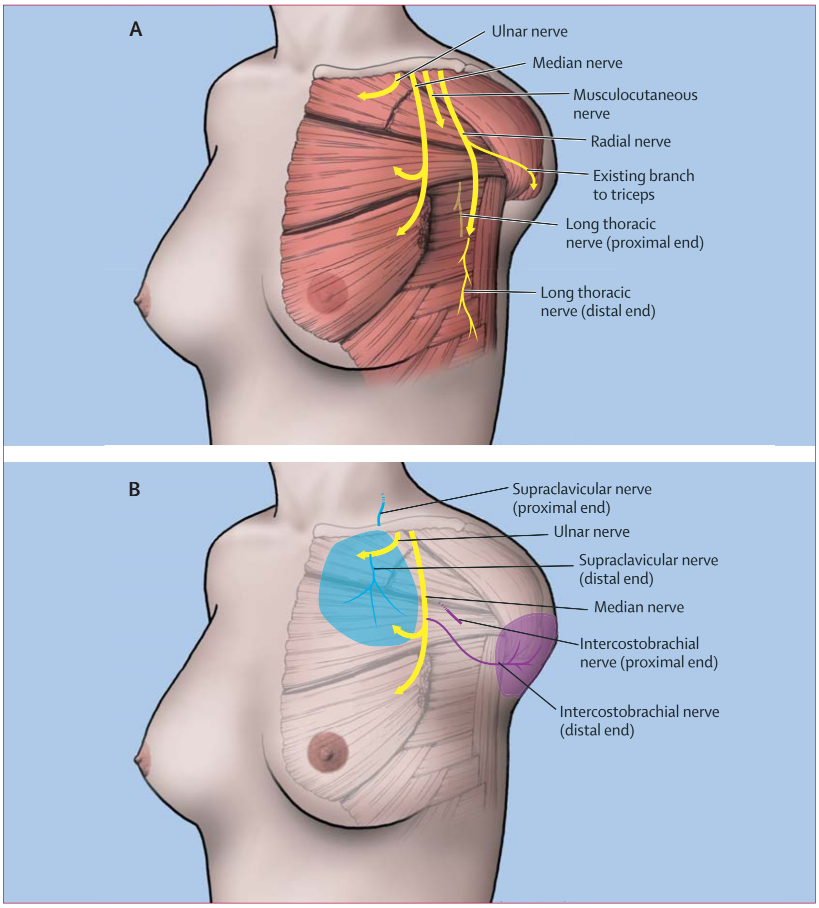


***Figure 7*: Diagram of targeted reinnervation surgery**
(A) Targeted muscle reinnervation. The musculocutaneous, ulnar, and median nerves were transferred to separate segments of the pectoralis major muscle. The long thoracic nerve innervating the inferior three slips of serratus anterior was divided and the distal segment was coapted to the radial nerve. (B) Targeted sensory reinnervation. The supraclavicular cutaneous nerve was cut and the distal segment was coapted to the side of the ulnar nerve. The intercostobrachial cutaneous nerve was cut and the distal end was coapted to the side of the median nerve.

entered the muscle segments. The proximal ends of these nerves were resected and mobilised away from the chest wall so that they could not reinnervate the target muscles.

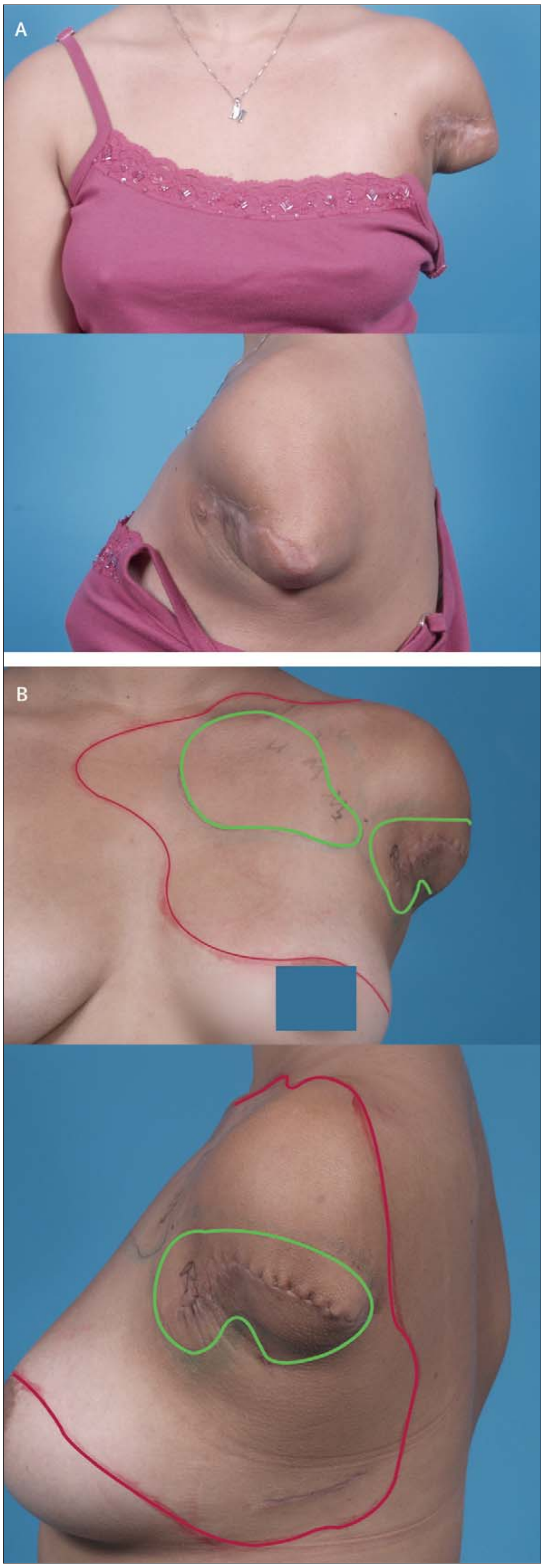
We then did four brachial plexus nerve transfers (figure 7A). The ulnar nerve was sewn to the motor nerve of the medial half of the clavicular head of the pectoralis major and the musculocutaneous nerve was sewn to the lateral motor nerve of the same muscle segment. The median nerve was divided in half lengthwise along its inner epineurium, and the split nerve endings were coapted to each of the two motor nerves of the sternal head of the pectoralis major. These large brachial plexus level nerves completely covered the areas where the small motor nerves entered the muscle segments. The radial nerve was sewn end-to-end to the long thoracic nerve for reinnervation of the distal slips of the serratus anterior muscle.

We did two sensory nerve transfers (figure 7B). The supraclavicular sensory nerve was located through a separate 3-cm transverse incision in the neck. This sensory nerve was divided and the proximal end was mobilised superiorly to prevent reinnervation of the chest skin. The distal end was passed through a subcutaneous tunnel into the chest dissection area and coapted end-to-side to the ulnar nerve. The intercostobrachial cutaneous nerve was identified and divided, and the distal segment was coapted in similar fashion to the median nerve.

The subcutaneous fat was thinned in a 4-cm diameter region over the clavicular head of the pectoralis muscle to enhance the surface electromyogram while not disfiguring the patient. Similarly, a 4-cm disk of fat over the serratus muscle was excised through a separate incision. A drain was placed, the surgical field was well irrigated, and the wounds were closed in layers. The drain was removed 2 days after the operation, and the patient returned to her home 4 days after the operation. She was monitored for wound problems, pain, and the initial development of reinnervation with telephone calls about once every 2 weeks.

When the patient was enrolled into our study in May, 2005, functional testing was done with her conventional myoelectric prosthesis control. At this time, she had had the prosthesis for 8 months, and had been regularly using it for 5 months. A box and blocks test[6] was done, in which the patient moves 2·5-cm square blocks from one box, over a 10-cm wall, and into another box. The test was modified slightly, allowing the patient 2 min, instead of 1 min, to move blocks. The patient was allowed to practise each test for several minutes until she felt comfortable with the task. She then did the task three times with rest breaks of several minutes in between. The Assessment of Motor and Process Skills (AMPS) test[7,8] was done by an occupational therapist certified in this validated, single-subject testing method. For testing with the patient's conventional prosthesis, the two tasks were: preparation of a peanut butter and jelly sandwich, including gathering items, preparing, cutting the sandwich in half, serving, cleaning up, and returning items to appropriate storage; and ironing a shirt, including setting up an ironing board, hanging the shirt on a hanger, safely storing the iron, and folding up the board. The patient was also asked to keep a diary of how much she used her prosthesis, recording changes in sensation, and documenting her impressions.

After the experimental surgery, the patient was instructed to try to use all aspects of her missing arm (elbow, wrist, hand, and fingers) daily in an attempt to activate pathways and strengthen muscle as soon as reinnervation occurred. In March, 2006, she was brought to our facility for 2 weeks to fit her with the new experimental prosthesis, train her in its use, and participate in studies. We did extensive surface electromyogram testing. A grid of 128 monopolar surface electrodes was placed over the muscles of interest in the patient's anterior chest, lateral chest, and shoulder. Monopolar myoelectric signals were recorded as the patient attempted to open her hand, close her hand, flex her elbow, and extend her elbow, following a video demonstration. Ten trials of each movement were recorded with a BioSemi Active II system (BioSemi, Amsterdam,



Netherlands) sampled at 2 kHz. The spatial electromyogram activity for each movement was characterised by contour plots where the average root mean square value of each channel's electromyogram was represented by different colours. Surface electrodes were mounted in the patient's prosthetic socket at the points corresponding to the maximum surface amplitude for each elbow and hand movement. During this 2-week period, the patient had training every day with the experimental prosthesis. On completion of this fitting and training period she went home and used her prosthesis for 5 weeks. She then returned to our facility for 1 week of testing and other experiments. The blocks and box test was repeated. The AMPs test was repeated with two different tasks: preparation of a grilled cheese sandwich, including preparation in a pan on the stove using butter, cutting the sandwich in half, and serving it with a beverage, opening and closing the container, returning items to the refrigerator, and cleaning of surfaces; and preparation and serving of a tossed salad with four ingredients, including peeling and slicing, getting out items and returning them to the refrigerator, pouring dressing, covering and storing leftovers, and cleaning up. The patient's subjective opinions of the new prosthesis were also obtained.

In the assessment of sensory reinnervation, the patient was asked to point to the areas of her chest where the transfer sensation for individual digits was most prominent. The positions of the points were recorded on a schematic diagram of her chest with a representative grid. The character of the sensory reinnervation was quantified for each type of sensory percept. Light touch thresholds were determined with Semmes-Weinstein monofilaments (North Coast Medical, Morgan Hill, CA, USA).[9] Sharp and dull sensibility was determined at 20 selected points distributed across the transfer site with a hand-held neurotip neurometer (Owen Mumford, Marietta, GA, USA). Ability to detect vibration was assessed by pressing a C128 tuning fork to various points on the chest. Temperature thresholds were assessed at two positions over the transfer site with a TSA II NeuroSensory Analyzer (Medoc, Ramat-Yishai, Israel).[10] The patient's normal contralateral chest and right thenar eminence served as control sites.

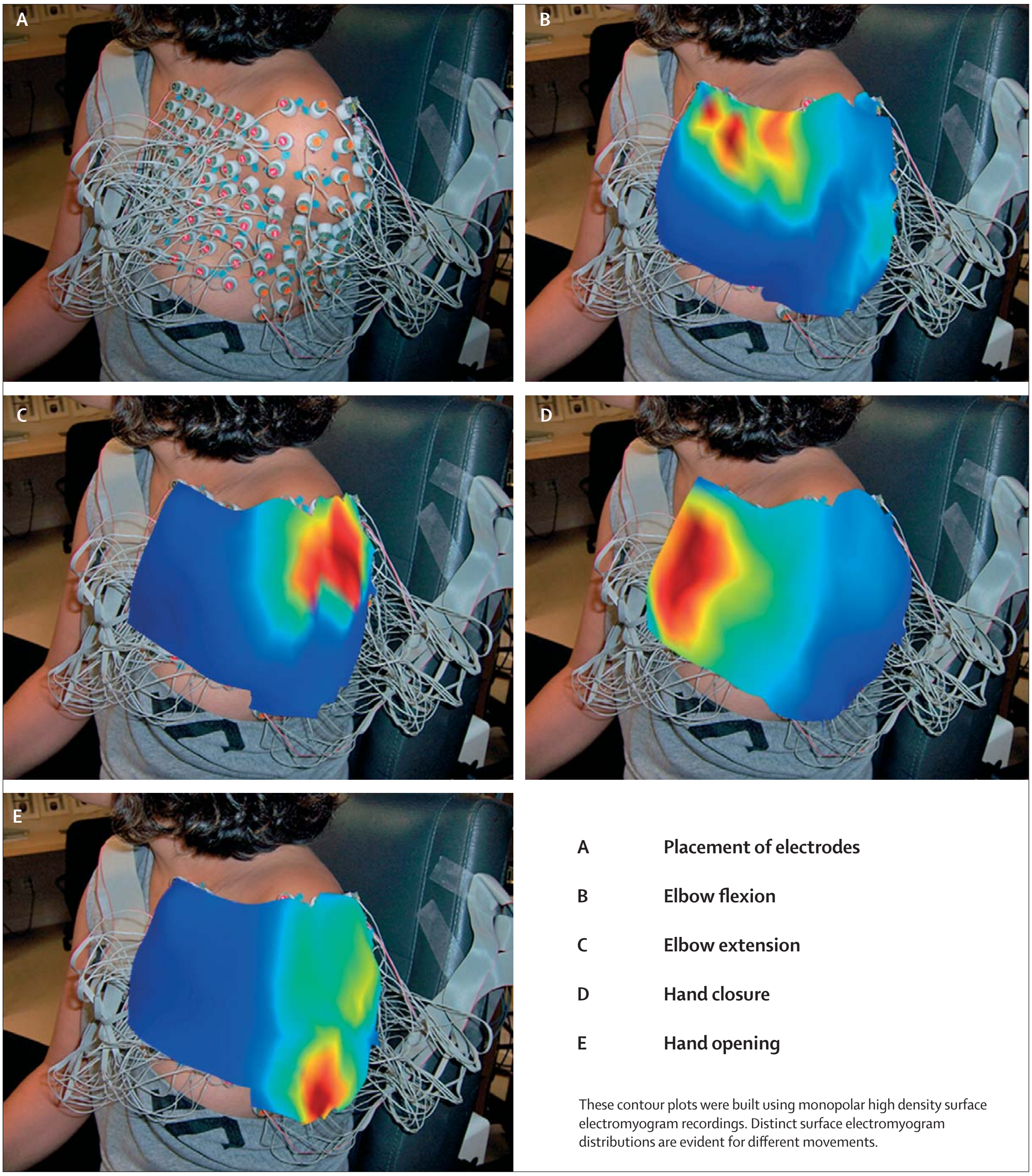
Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Postoperatively, the patient's phantom limb pain returned to a lesser degree (6 out of 10 Likert scale) but it resolved

Figure 8: **Surgical contours and skin denervation areas**
(A) Pre-surgical profiles. (B) Post-surgical profiles with outline of sensory impairment: green line indicates insensate area; red line indicates area in which patient reported that sensation was changed.



A	Placement of electrodes
B	Elbow flexion
C	Elbow extension
D	Hand closure
E	Hand opening

These contour plots were built using monopolar high density surface electromyogram recordings. Distinct surface electromyogram distributions are evident for different movements.

Figure 9: Map of surface electromyogram amplitude for four different movements

with treatment within 4 weeks. No other complications occurred. The surgery caused no disfigurement (figure 8). An area 11 cm wide by 9 cm high became insensate on the patient's anterior superior chest (figure 8). On her lateral chest wall, only a narrow band around her surgical wound site became numb.

The patient had the first indication of muscle reinnervation about 3 months after the surgery. She could feel the muscles of her chest twitching when she tried to close her hand or bend her elbow. By 5 months, strong muscle contractions could be seen and palpated. Extensive electromyogram testing was done 6 months after surgery following full muscle reinnervation; signals were recorded from all the nerve transfer sites (figure 9). A new experimental prosthesis was made (figure 10) consisting of a motorised elbow with a computerised arm controller (Liberating Technologies, Holliston, MA, USA), a motorised wrist rotator, and a motorised hand (Otto Bock, Minneapolis, MN, USA). The prosthesis had passive shoulder components. The computerised arm was programmed to use the myoelectric inputs from the TMR muscles to control the motorised hand and elbow. Two pressure-sensitive pads were mounted in the patient's socket that she used to control her motorised wrist, allowing independent, proportional, simultaneous control of all three joints (table 1).

With training, the patient became proficient in use of the prosthetic within a few days. She was able to operate the hand, wrist, and elbow simultaneously. She reported that operation of the hand and elbow was very intuitive: when she thought of opening the hand, closing the hand, bending the elbow, or straightening the elbow, the prosthesis responded accordingly. The patient was able to operate the wrist rotator with the pressure sensitive buttons at the same time as moving the hand and elbow; however, she rarely did so, because the cognitive burden of controlling all three joints simultaneously was high.

At the time of pre-operative testing the patient had been using her conventional prosthesis for 7 months. Testing with her conventional prosthesis showed poor function, as is typical with this level of amputation (table 2). Her functional outcomes were improved in all areas 7 weeks after beginning the fitting and training of the TMR-controlled experimental prosthesis. Webmovie 1 shows the patient undertaking the blocks and box test (left side is with conventional myoelectric control; right side is using TMR controlled prosthesis); she was almost four times as fast with TMR control, compared with the conventional prosthesis. AMPS testing showed substantial improvement in both motor and process scores. Webmovie 2 shows the patient undertaking daily living tasks with the experimental prosthesis.

	Control source	Nerve	Muscle
Elbow flexion	Electromyogram	Musculocutaneous	Lateral clavicular pectoralis major
Elbow extension	Electromyogram	Radial-triceps branch	Remnant triceps
Hand close	Electromyogram	Median	Sternal pectoralis major
Hand open	Electromyogram	Distal radial	Inferior serratus anterior
Wrist pronate	Anterior shoulder pressure button		
Wrist supinate	Posterior shoulder pressure button		

***Table 1:* Control pattern of targeted motor reinnervation prosthesis in this patient**

	Conventional prosthesis (5 months' use)	Experimental TMR prosthesis (7 weeks' use)
Blocks and box test, mean block number (SD)		
Three trials	4·0 (1·0)	15·6 (1·5)*
AMPS test, single score		
Motor	0·30	1·98
Process	0·90	1·98

Testing with conventional device occurred 14 months after amputation and 5 months after prosthetic training was started. Experimental prosthesis testing occurred 8 months after TMR surgery and 7 weeks after starting training.

***Table 2:* Functional outcome comparing conventional myoelectric prosthesis with experimental TMR-controlled prosthesis**

See **Online** for webmovies 1 and 2

***Figure 10*: Experimental prosthesis consisting of a motorised elbow, wrist, and hand, with passive shoulder components**

The patient was very satisfied with the cosmetic result of the surgery and enthusiastic about the improvement in her limb control. Although she initially tried to use her original conventional prosthesis on a regular basis, she said that it was very frustrating and difficult to operate. Her use of the conventional prosthesis decreased to only 1–2 times per month, when the device was worn mainly for cosmetic reasons. She reported that her experimental prosthesis was much easier and more natural to use than was the conventional prosthesis. She described operation of her hand and elbow as: "I just think about moving my hand and elbow and they move." Perhaps her most telling statement was: "My original prosthesis wasn't worth wearing—this one is." At time of writing the patient used her new TMR prosthesis for an average of 4–5 h a day (up to 16 h), 5–6 days per week for many functional tasks including cooking, putting on makeup, carrying things, eating, house cleaning and laundry, as well as for cosmetic purposes.

The patient had the first indication of sensory reinnervation at 3 months after the surgery. She reported a tingling sensation in her missing hand when her anterior

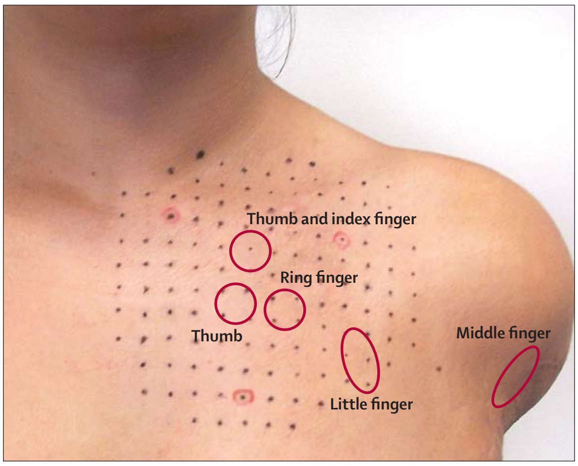


Figure 11: Map of areas that the patient perceived as distinctly different fingers in response to touch

chest was touched. By 5 months, any stimulus applied to the previously insensate anterior chest skin was perceived as being in her missing hand. After about 6 months, she developed a relatively faint percept of her middle finger on the lateral chest wall.

The supraclavicular cutaneous nerve was anastomosed end-to-side to the ulnar nerve and a percept of the fourth and fifth fingers was expected in the reinnervated anterior chest skin. However, the anterior chest skin was clearly reinnervated by both median and ulnar afferents. The perceptive fields of touch were quite complex; when the patient was touched at a single point she often perceived sensation in contiguous or disjoint areas of different digits and her palm. Figure 11 shows the spots that the patient identified as the primary points where she perceived sensation in just one digit.

All modalities of cutaneous sensation were present; however, the percept of tingling in response to touch of the target skin persisted (rather than a more normal pressure sensation). The lowest threshold at which light touch could be perceived in the reinnervated region was 0·4 g; the thresholds at most points in this area were under 4 g, compared with a threshold of 0·4 g at the same location on the right side and a light-touch threshold of 0·16 g on the right index finger. With increased pressure the patient felt an increased intensity of the tingling sensation—ie, she was able to feel graded pressure. She had appropriate thresholds for warm and cold sensation within her reinnervated region. The average threshold for perception of cold was 29·1°C in her reinnervation area, 29·9°C on the intact contralateral chest, and 31·3°C in her right palm, indicating that sensitivity to cold was slightly increased in the reinnervated skin. The average threshold for perception of warmth was 35·2°C in the reinnervated region, 34·7°C on the contralateral chest, and 33·2°C in the right hand, indicating that sensitivity to an increase in temperature was slightly reduced in the reinnervated skin. At 19 of the 20 selected points across the transfer site, the patient was able to correctly differentiate between sharp and dull sensation, and was also able to perceive vibration in the reinnervated skin. Stimulation of each of the aforementioned types of percept modalities within the reinnervation region was interpreted by the patient as occurring in her missing hand.

Discussion

Targeted reinnervation surgery was successful in this young woman. Four independent myoelectric sites were created that allowed improved control of a motorised artificial arm. Transfer sensation also developed; when the patient was touched on her reinnervated chest skin, she perceived the sensation to be in her missing hand.

A great need exists for neural-machine interfaces that can enable people with disabilities to interact with their environment. An effective interface should extract neural command signals to operate devices that overcome a person's motor impairment, provide sensory feedback to the person with a disability, or both. Research in brain-machine interfacing is developing new communication and control technology for people with severe motor disorders such as paralysis, stroke, cerebral palsy, and spinal cord injury.[11–19] The possibilities of extracting information from the peripheral nervous system with nerve-cuff electrodes, sieve electrodes, and penetrating arrays have also been examined.[20–23] To date, the cochlear implant is the most clinically successful neural-machine interface, and has improved the hearing of thousands of people by interfacing with the auditory neural system.[24]

Targeted reinnervation is a new neural-machine interface for individuals with amputations. TMR rewires peripheral nerves and uses available surface muscles as biological amplifiers to develop rich new sources of motor command signals. After TMR our patient found that her prosthesis was much easier and more natural to use, because she was using physiologically appropriate neural pathways to operate her artificial arm. The function of her prosthesis improved substantially, as shown by an increase in speed and efficiency of motion. This system has other distinct advantages: it is relatively simple to implement; no hardware is implanted in the body that could break, necessitating additional surgery; and the technique can be used with existing myoelectric prosthetic technology.

Our patient tried to use her conventional prosthesis for several months, but became frustrated with the device and then wore it rarely. This problem is typical of shoulder disarticulation amputees, since the prostheses have such limited function and are quite heavy (our patient's prostheses weighed just over 6 kg) and the harnessing is uncomfortable. The improved control led to improved satisfaction and wear time—the new device had similar weight and harnessing. The 4–5 h of use per day by the patient is judged to be heavy use for a unilateral proximal amputee. However, the prosthesis is still a tool that the patient uses when needed and takes off for comfort. Hopefully, improvements in arm prostheses will make them lighter and more comfortable, thus increasing the time for which they can be comfortably worn.

We faced a substantial challenge with this patient, in that her breast covered much of the primary target muscle—her pectoralis major muscle. It was helpful that a remnant of her humerus preserved the insertion of the pectoralis, holding the sternal head in its normal anatomical position, up and across the chest, allowing electromyogram detection over at least the upper portion of the muscle. With a complete shoulder disarticulation, the pectoralis retracts medially and inferiorly, thus less muscle would have remained above the breast. The long thoracic nerve and distal serratus anterior muscle were successfully used to develop an additional surface electromyogram control site not covered by the breast.

In this study, we used a commercially available prosthesis with simple algorithms based on the magnitude of the surface electromyogram to control only the elbow and a one degree-of-freedom hand. However, the residual nerves of the arm contain all the control commands for complex movement of the elbow, wrist, thumb, and fingers. Much of this information is transferred to the TMR muscle; thus the potential exists for further improvement in control, dexterity, and function of artificial arms. Advanced signal processing algorithms have been used to extract more information from the residual limbs in transradial amputees, showing improved, intuitive control of wrist rotation, wrist flexion, and hand movements.[25-27] Research is in progress to clinically implement these algorithms in advanced artificial arms that promise further improvement in control and function. Another developing technology that could benefit TMR is implantable myoelectric systems.[28] Telemetry of intramuscular myoelectric signals could increase access to muscles under subcutaneous fat, breast tissue, and deeper muscles. They might improve information content and stability, compared with surface myoelectric signals, and increase the robustness of this neural-machine interface.

In this study we showed that targeted sensory reinnervation can be purposefully implemented to provide a discrete region of transfer sensation—ie, a sensation of touch in the missing limb. The target skin is an excellent transducer for cutaneous sensory input into the nervous system. We hypothesise that the skin provided the environment for the amputated afferent axons to find appropriate end organs that yielded appropriate sensory perception. This patient's transfer sensation had high fidelity, in that all the cutaneous sensory modalities were present and the thresholds of perception were close to normal.

The clinical implications of TSR are exciting. The potential exists to provide meaningful light touch, graded pressure, texture, edge detection, and thermal feedback to amputees in an intuitive manner. For the patient, there is much to be gained with even a single point of pressure feedback. For example, the perception of simply touching an object can provide goal confirmation in grasping, and graded force feedback relates to how hard the user is squeezing an object; both have great functional value. This patient had a somatotopic organisation, in that different regions of the TSR skin felt like different fingers or her thumb. This occurrence might allow useful sensory feedback for multiple regions of the hand; sensors could be placed in each prosthetic digit and have the sensory feedback applied to the corresponding regions of reinnervated skin. Perhaps the most import aspect of TSR is psychological. Enabling patients a perception of feeling what they are touching could help them to incorporate their prosthesis into their self image in a more positive manner, and to better connect with their physical and social environments.

The sensory somatotopic organisation that developed differed from what we expected. In surgery, the distal segment of the intercostobrachial nerve was transferred to the median nerve and median sensation was anticipated on the lateral chest. Only a faint median percept developed, probably because the skin innervated by the intercostobrachial nerve was amputated with the arm leaving nothing for the median afferents to reinnervate. The distal segment of the supraclavicular nerve was transferred to the ulnar nerve, and ulnar sensation alone was expected on the anterior chest. However, a strong percept and large area of median nerve reinnervation were noted. The robustness of the median nerve sensory reinnervation was surprising. The median nerve afferents had to regenerate through the pectoralis major muscle and through a layer of subcutaneous tissue that was more than 1 cm thick while in competition with the regenerating ulnar afferents. Further study is clearly needed to better understand what guides, promotes, or impedes sensory axon regeneration. Research is also needed to assess the skin-receptor densities and receptor types and to characterise afferent-receptor interaction in this hyper-reinnervation model, in which a large excess of sensory afferents are competing to reinnervate a limited skin region.

The primary sensory cortex is able to undergo substantial change after amputation and nerve transfer.[29] Neural plasticity could be detrimental to the outcome of the TSR if the sensory cortex was to integrate the hand percepts into a chest body image. However, this problem has not happened in 4 years with our first patient or in 1 year with this second patient. Additionally, the motor pathways seem to be equally robust. In fact, targeted reinnervation shows the endurance of dormant central pathways. The time of complete non-use for these central pathways was at least 18 months in this patient (time from amputation to reinnervation), yet motor commands were readily elicited and complex transfer sensation developed. However, whether longer periods of dormancy might affect the viability of these pathways is unclear. Another interesting possibility associated with neural plasticity is that the sensory cortex might develop a more functional somatosensory representation of the TSR site with use and time. For example, repeatedly touching a spot of reinnervated skin that contains some thumb afferents in correlation to touching an object with the prosthetic thumb might cause the brain to interpret that skin spot more clearly as representing a thumb.

A key question for the application of targeted reinnervation is how long do amputated nerves remain viable? Voluntary signals can be recorded from motoneurons many years after amputation[30] and stimulating a nerve decades after amputation will produce a perception of sensation in the missing limb. Some axons are lost with time, but estimates of the time taken vary greatly.[31] Furthermore, targeted reinnervation uses hyper-reinnervation of the target muscle and skin. The proportion of viable axons that are needed is unknown, but a large excess of both motor and sensory axons are transferred. The procedure can probably be undertaken successfully many years after the initial amputation.

This patient and our other three patients represent early application of targeted reinnervation technique. Whether the improved function is enough to keep these patients wearing their devices in years to come, or whether they adapt to their new control even better and show greater functional gains, remains to be seen. Long-term follow-up is also needed to see how our patient's transfer sensation evolves. We need to ascertain whether the sensation persists unchanged or whether the character, localisation, and somatotopic organisation of the sensation are altered with time and use.

Contributors

T Kuiken participated in the all aspects of this article, including project management, surgery, data collection, and manuscript writing. L Miller, R Lipschutz, and B Lock participated in fitting of the prosthetic limb, data collection, and manuscript writing. K Stubblefield participated in the patient's training, data collection, and manuscript writing. P Marasco participated in data collection and manuscript writing. G Dumanian participated in the surgery, data collection, and manuscript writing. P Zhou participated in collection and analysis of electromyogram data. All authors saw and approved the final manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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References

1 Sears HH. Trends in upper-extremity prosthetics development. In: Atlas of Limb Prosthetics, St Louis: Mosby; 1992.

2 Hoffer JA, Loeb GE. Implantable electrical and mechanical interfaces with nerve and muscle. *Ann Biomed Eng* 1980; **8:** 351–60.

3 Kuiken TA, Childress DS, Rymer WZ. The hyper-reinnervation of rat skeletal muscle. *Brain Res* 1995; **676:** 13–123.

4 Kuiken TA, Dumanian GA, Lipschutz RD, Miller LA, Stubblefield KA. The use of targeted muscle reinnervation for improved myoelectric prosthesis control in a bilateral shoulder disarticulation amputee. *Prosthet Orthot Int* 2004; **28:** 245–53.

5 Hijjawi JB, Kuiken TA, Lipschutz RD, Miller LA, Stubblefield KA, Dumanian GA. Improved myoelectric prosthesis control accomplished using multiple nerve transfers. *Plast Reconstr Surg* 2006; **118:** 1573–78.

6 Mathiowetz V, Volland G, Kashman N, Wever K. Adult norms for the box and blocks test of manual dexterity. *Am J Occ Ther* 1985; **89:** 386–91.

7 Fisher AG. Assessment of motor and process skills. In: Development, standardization and administration manual. Colorado: Three Star Press, 2003.

8 Fisher AG. The assessment of IADL motor skills. An application of many faceted Rasch analysis. *Am J Occ Ther* 1993; 319–29.

9 Bell JA. Sensibility testing: current concepts. In: Rehabilitation of the hand. St Louis: Mosby-Year Book, 1995.

10 Dyck PJ, O'Brien PC, Johnson DM, Klein C, Dyck JB. Quantitative sensation testing. In: Peripheral neuropathy. Philadelphia: Elsevier Saunders; 2005.

11 Wolpay JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. Brain-computer interfaces for communication and control. *Clin Neurophysiol* 2002; **113:** 767–91.

12 Donoghue JP. Connecting cortex to machines: recent advances in brain interfaces. *Nat Neurosci* 2002; **5:** 1085–88.

13 Serruya MD, Hatsopoulos NG, Paninski L, Fellows MR, Donoghue JP. Instant neural control of a movement signal. *Nature* 2002; **416:** 141–42.

14 Taylor DM, Tillery SIH, Schwartz AB. Direct control of 3D neuroprosthetic devices. *Science* 2002*;* **296:** 1829–32.

15 Chapin JK. Using multi-neuron population recordings for neural prosthetics. *Nat Neurosci* 2004; **7:** 452–55.

16 Quian Quiroga R, Snyder LH, Batista AP, Cui H, Andersen RA. Movement intention is better predicted than attention in the posterior parietal cortex. *J Neurosci* 2006; **26:** 3615–20.

17 Hochberg LR, Serruya MD, Friehs GM, et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* 2006; **442:** 164–71.

18 Jdel R, Millan F, Renkens J, Mourino S, Gerstner W. Noninvasive brain-actuated control of a mobile robot by human EEG. *IEEE Trans Biomed Eng* 2004; **51:** 1026–33.

19 Deng J, Yao J, Dewald JPA. Classification of the intention to generate a shoulder versus elbow torque by means of a time-frequency synthesized spatial patterns BCI algorithm. *J Neural Eng* 2005; **2:** 131–38.

20 Branner A, Stein RB, Fernandez E, Aoyagi Y, Normann RA. Long-term stimulation and recording with a penetrating microelectrode array in cat sciatic nerve. *IEEE Trans Biomed Eng* 2004; **51:** 146–57.

21 Dhillon GS, Horch K. Direct neural sensory feedback and control of a prosthetic arm. *IEEE Trans Neural Systems Rehab Engr* 2005; **13:** 468–72.

22 Crampon MA, Brailovski V, Sawan M, Trochu F. Nerve cuff electrode with shape memory alloy armature: design and fabrication. *Biomed Mater Eng* 2002; **12:** 397–410.

23 Stieglitz T, Ruf HH, Gross M, Schuettler M, Meyer JU. A biohybrid system to interface peripheral nerves after traumatic lesions: design of a high channel sieve electrode. *Biosens Bioelectron* 2002; **17:** 685–96.

24 Middlebrooks JC, Bierer JA, Snyder RL. Cochlear implants: the view from the brain. *Curr Opin Neurobiol* 2005; **15:** 488–93.

25 Huang Y, Englehart K, Hudgins B, Chan AD. A Gaussian mixture model based classification scheme for myoelectric control of powered upper limb prostheses. *IEEE Trans Biomed Eng* 2005; **52:** 1801–11.

26 Barniv Y, Aguilar M, Hasanbelliu E. Using EMG to anticipate head motion for virtual-environment applications. *IEEE Trans Biomed Eng* 2005; **52:** 1078–93.

27 Chu JU, Moon I, Mun, MS. A real-time EMG pattern recognition system based on linear-nonlinear feature projection for a multifunction myoelectric hand. *IEEE Trans Biomed Eng* 2006; **53:** 2232–39.

28 Lowery MM, Weir RF, Kuiken TA. Simulation of intramuscular EMG signals detected using implantable myoelectric sensors (IMES). *IEEE Trans Biomed Eng* 2006; **53:** 1926–33.

29 Merzenich MM, Jenkins WM. Reorganization of cortical representation of the hand following alteration of skin inputs induced by nerve injury, skin island transfers, and experience. *J Hand Therapy* 1993; **6:** 89–104.

30 Dhillon GS, Horch K. Direct neural sensory feedback and control of a prosthetic arm. *IEEE Trans Neural Syst Rehab Eng* 2005; **13:** 468–72.

31 Sunderland S. Nerves and nerve injuries. New York: Churchill Livingstone, 1978.