A highly integrated bionic hand with neural control and feedback for use in daily life

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Abstract

Restoration of sensorimotor function after amputation has remained challenging due to the lack of human-machine interfaces that provide reliable control, feedback, and attachment. Here we present the clinical implementation of a transradial neuromusculoskeletal prosthesis – a bionic hand connected directly to the user's nervous and skeletal systems. In one person with unilateral below-elbow amputation, titanium implants were placed intramedullary in the radius and ulna bones, and electro-muscular constructs were created surgically by transferring the severed nerves to free muscle grafts. The native muscles, free muscle grafts, and ulnar nerve were implanted with electrodes. Percutaneous extensions from the titanium implants provided direct skeletal attachment and bidirectional communication between the implanted electrodes and a prosthetic hand. Operation of the bionic hand in daily life resulted in improved prosthetic function, reduced post-amputation, and increased quality of life. Sensations elicited via direct neural stimulation were consistently perceived on the phantom hand throughout the study. To date, the patient continues using the prosthesis in daily life. The functionality of conventional artificial limbs is hindered by discomfort and limited and unreliable control. Neuromusculoskeletal interfaces can overcome these hurdles and provide the means for the everyday use of a prosthesis with reliable neural control fixated into the skeleton.

One sentence summary

A neuromusculoskeletal hand prosthesis grants long term stable neural control, sensory feedback, and skeletal attachment.

Introduction

The ability to interact with everyday objects and perform mundane and complex tasks is greatly damaged after the amputation of a hand. Upper limb prosthetic devices aiming to restore function vary in their degree of anthropomorphism, from hooks and grippers, to hand-like robotic devices matching the patient's skin color. Prosthetic hardware aside, these assistive devices are only functionally useful provided that they can be controlled reliably. Moreover, prosthetic limbs are of limited use if patients cannot wear them comfortably and throughout the day, every day. Indeed, prosthetic attachment (mechanical interface) is a major source of problems for users (*1*, *2*). Likewise, reliable control of the prosthetic device ranks highly in priority for people with amputations (*3*, *4*), and in this case, the problem lies in the interface with the user's sensorimotor system (control interface). The overall human-prosthesis interface is therefore crucial for the restoration of function.

Osseointegration allows for direct skeletal attachment of limb prostheses overcoming the problems of socket suspension. Bone-anchored prostheses attached via osseointegration can be worn comfortably all day since there is no compression over the residual limb, while also providing better transfer of mechanical loads. Whereas osseointegration has proven beneficial at different levels of amputation, its benefits are limited to the mechanical interface. Control over the prosthesis, on the other hand, is commonly coupled to the electrical activity of muscles remnant in the residual limb, in other words, myoelectric signals). In its most widely spread form, myoelectric signals recorded by surface electrodes from an agonist-antagonist muscle pair are used to distinguish between two opposite movements (for example hand open and close) and to proportionally control one of them at the time (*5*). More complex approaches including pattern recognition classifiers (*6–9*) and parallel regressors (*10*, *11*) have demonstrated viable options to increase the number of simultaneously controllable movements .

Myoelectric signals recorded by surface electrodes are prone to disturbance and interference, thus rendering prosthetic control in daily life unreliable. Implanted electrodes have been found to provide

reliable control signals (*12–16*), but impose an additional communication requirement, namely that the signals must travel constantly from inside to outside of the body (*17*). The same challenge is present in the opposite direction to restore somatosensation. Numerous laboratory experiments have shown that electrodes implanted in or around nerves can be used to elicit sensations in the missing hand triggered by sensors embedded in the prosthesis (*18–22*). However, the communication between implanted electrodes and external prosthetic components has been a long-standing problem preventing the use of implanted electrodes in bionic limbs, ever since the first successful demonstrations of their utility for prosthetic control (*23–25*), and sensory feedback (*26*, *27*), over 60 years ago.

A neuromusculoskeletal interface employing an osseointegrated implant engineered to enable bidirectional communication between the prosthesis and implanted electrodes, in addition to skeletal attachment, can resolved the aforementioned problems (*28*, *29*). Here, we present the clinical implementation of this concept in a patient with below-elbow amputation, in whom surgical reconstruction of the residual limb was also performed to increase the number of myoelectric control sources and treat neuropathic pain (Figure 1 and Movie S1). As opposed to previously implanted neuroprosthetic systems used solely for research purposes, our implementation is self-contained, in other words, it requires no additional equipment such as large batteries or processing units to be worn by the patient, making it safe and reliable for unsupervised use in daily life. More importantly, the patient has used it successfully in activities of daily living over three years and continues using it at present.
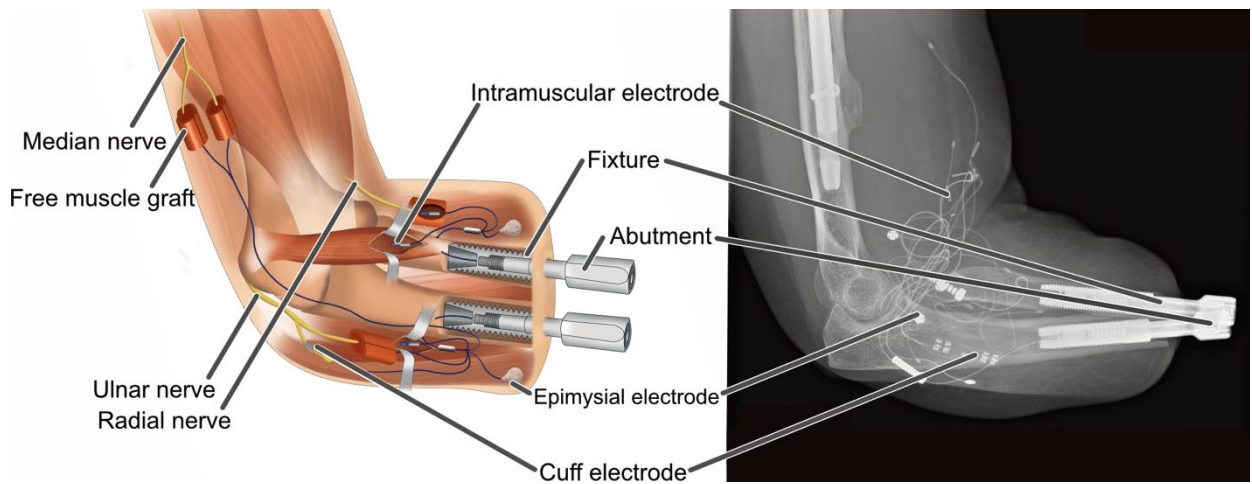
Figure 1 Schematic illustration and X-ray of a highly integrated human-machine interface in a patient with trans-radial amputation. *Four monopolar epymisial and four monopolar intramuscular electrodes were sutured on/in native residual muscles to provide myoelectric signals for prosthetic control. Furthermore, fascicles of the median, ulnar, radial nerve were transferred into non-vascularized muscle graft to create additional myoelectric sites. Each non-vascularized muscle graft was instrumented with a monopolar intramuscular electrode. Part of the ulnar nerve was wrapped with a cuff electrode for sensory feedback. A titanium fixture was implanted into both the radius and ulna bone and left to osseointegrate. Additionally, a percutaneous abutment was installed into each fixture, allowing for skeletal attachment of a prosthetic hand. Feed-through connectors allow for a wired electrical communication from the proximal end of the fixtures (inside the body) to the distal end of the two abutments (outside the body) – creating a bidirectional communication between the human and the prosthetic hand.*
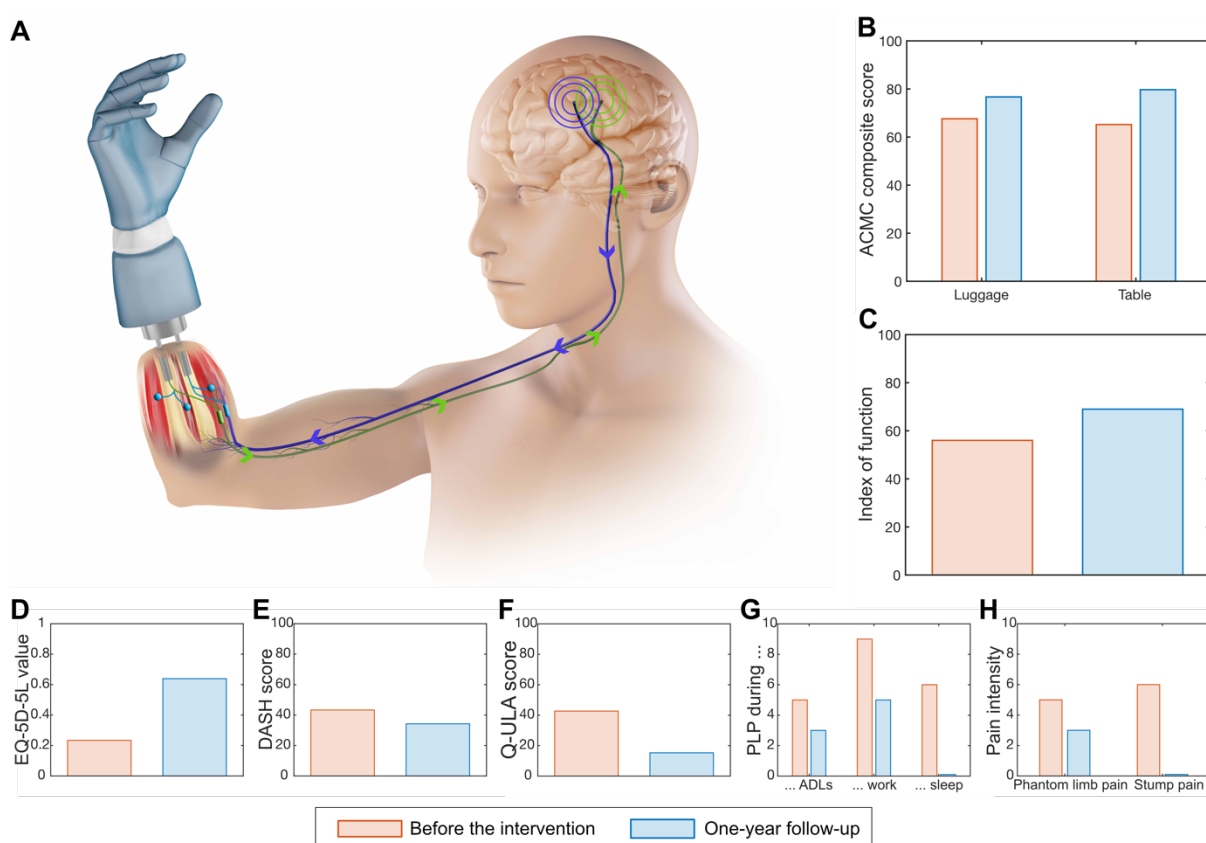
Results

Figure 2 Overview of outcomes comparing scores before the intervention to the scores one year after the intervention. *(A) Shown is an illustration of the intervention, a bidirectional neuromusculoskeletal interface for people with trans-radial amputation. (B) Shown are the individual scores of the two ACMC tasks. (C) Shown are the index of function outcomes from the SHAP. (D) Shown are the outcomes of the EQ-5D-5L questionnaire. (E) Shown are the outcomes of the DASH questionnaire. (F) Shown are the outcomes of the Q-ULA questionnaire. (G) Shown are the perceived interreference of phantom limb pain during activities of daily living, work, and sleep. (H) Shown are the reported perceived intensity of phantom limb pain and stump pain.*

Prosthesis functionality

Post-interventional testing using the highly integrated neuro-muscular interface (Figure 2A) showed that the patient's prosthesis functionality increased compared to pre-intervention (Table 1 and Figures 2B and 2C). Assessment of Capacity for Myoelectric Control (ACMC)outcome scores improved from 68 to 77, and from 65 to 80 for the luggage and table tasks, respectively; both improvements are above the minimum detectable change (30). Similarly, the Southampton Hand Assessment Procedure (SHAP) score improved by 23% from 56 to 69 after the intervention. Both evaluations demonstrate an improvement in prosthesis capability and functionality during the performance of activities of daily living. These tests were conducted using the same control scheme (two-site direct and proportional control), and therefore represent the difference between the conventional prosthetic interface

(socket and surface electrodes) and the neuromusculoskeletal interface (osseointegration and implanted electrode).

Table 1 Outcome scores of the functionality, quality of life, and pain assessments before the intervention compared to after the intervention. For the ACMC and SHAP higher scores represent better function, and for the EQ-5D-5, higher scores represent increased quality of life. For the DASH, Q-ULA, and Post-amputation pain, lower scores indicated improved function, a decrease of problems faced during prosthesis use, and a decrease pain and interference caused by pain, respectively. ACMC = Assessment of Capacity for Myoelectric Control. SHAP = Southampton Hand Assessment Procedure. DASH = Disability of the Arm Shoulder and Hand. Q-ULA = Questionnaire for Upper Limb Amputation. PLP = Phantom Limb Pain. ADL = Activities of Daily Life.

Functional Outcome	Before	After
ACMC		
Luggage	68	77
Table	65	80
SHAP	56	69
Experiential Outcome	**Before**	**After**
EQ-5D-5L	0.23	0.63
DASH	43.3	34.3
Q-ULA	42.7	15.5

Pain Outcome	Before	After
PLP Intensity	5	3
Stump Pain Intensity	6	0
PLP interference with ADLs	5	3
PLP interference with work	9	5
PLP interference with sleep	6	0

Questionnaire outcomes

Perceived disability, problems faced during prosthesis use, and pain, all decreased post-intervention whereas the quality of life increased (Table 1 and Figures 2D-2H). The EQ-5D-5L value improved by 0.4 (0.18 is the average minimal clinically important difference (MCID) for the EQ-5D-5L (*31*)) from 0.23 to 0.63. The Disabilities of the Arm Shoulder and Hand (DASH) score improved 9 points from 43.3 to 34.3 after the intervention (MCID is 10-15 points (*32*)) . The Questionnaire for Upper Limb Amputation (Q-ULA) score was 42.7 before the intervention and improved to 15.5 after the intervention. Phantom limb pain intensity decreased from 5 to 3, and stump pain vanished entirely compared to being at 6 out of 10 before the intervention. Interference with activities of daily living decreased by 2 scores, interference with work decreased from 9 to 5, out of 10, and interference with sleep decreased by 6 points to be absent after the intervention. Table 1 shows the summary of the study outcomes, and Figure 3A and 3B, and Movie S1 show prosthesis use during activities of daily living and an exploratory demonstration of the sensory feedback.
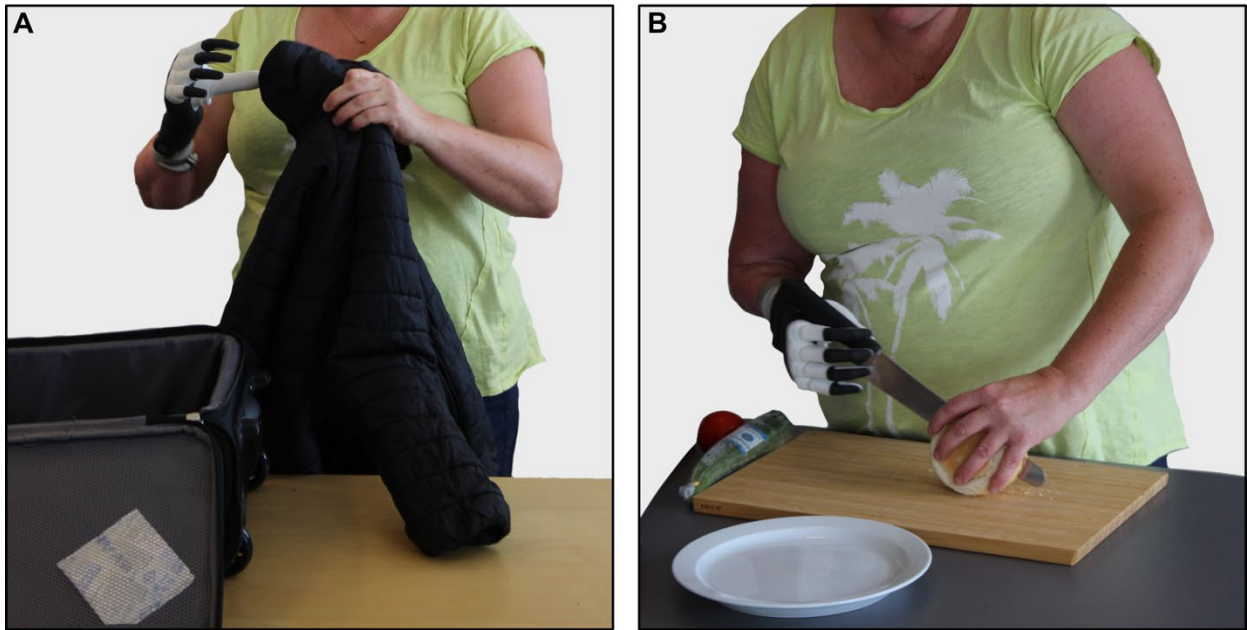
Figure 3 The patient performs tasks representative of daily life*. Following a short fitting session where control parameters were fine-tuned, the participant was able to use the neuromusculoskeletal prosthesis to perform daily tasks including packing a suitcase (A) and preparing food (B).*

Neuromusculoskeletal interface stability

The electrical impedance to each electrode contact was monitored over time to evaluate the stability of the interface with the patient's neuromuscular system (Figure S1). A very high or low impedance would indicate a broken or short-circuited connection, respectively, and both would represent a failure that prevents recording or stimulation. The implanted electrodes remained within working range (cuff: 8,325 ± 2,754 Ω; epimysial: 1,419 ± 775 Ω; intramuscular: 985 ± 733 Ω) with temporal exceptions attributed to external connections (Figure S1).

Neurostimulation and perception thresholds

The neural electrode allowed for stimulation of afferent nerve fibers that resulted in tactile sensations perceived consistently in the missing hand corresponding to the dermatome associated with the ulnar nerve, where the cuff electrode was implanted (Figure S2). The perception thresholds (minimum charge required to elicit sensations) remained within conservatively safe stimulation parameters with temporal exceptions (Figure S3). Overall, we were able to record myoelectric signals and elicit sensations via direct neural stimulation throughout the study.

Prosthesis control and signal quality

The signals from the native and newly created myoelectric sites allowed for the decoding of 6 phantom limb movements – equivalent to a 3 degrees-of-freedom (DoF) prosthesis – with a 100% completion rate in the Motion Test (Figure S4). In a separate Motion Test, the patient was able to control all five phantom fingers individually (5 DoF or 10 movements) with a completion rate of up to 95% (Figure S5). These findings illustrate the potential for further increasing prosthetic function using terminal devices with multiple DoF. The signal to nose ratio calculated based on data recorded for the Motion Test showed that after two years after the initial implantation, all epimysial electrodes (Figure S6), all except one intramuscular electrode in a native muscle (Figure S7), and all except one of the intramuscular electrodes in reinnervated free muscle grafts (Figure S8) feature a SNR higher than 10dB. The muscular electrodes allowed for higher grip precision as measured by the minimum force applicable to an object, which was improved on average by 3.8 times (5.7±4.7N using surface electrodes and 1.5±2.2N implanted electrodes, Figure S9).

Osseointegration failure and reimplantation

The titanium fixture implanted in the radial bone failed to osseointegrate and was removed five months after implantation. No infection was detected and the electrodes pertaining to this implant remained implanted (eight intramuscular electrodes). The implant system has a modular design with a series of connectors that allow for the electrodes or the titanium implants to be removed or exchanged without explanting the other components. The patient was allowed to continue using the prosthesis coupled to the ulna implant alone, but with careful loading. Four months after explantation, to allow for healing of tissues, a new titanium fixture was implanted. The new titanium fixture had a larger diameter to ensure contact with cortical bone. Six months after the implantation of the new fixture, the weight of the prosthesis was loaded equally in both the radial and ulna implants. The new fixture was not loaded immediately to allow for osseointegration to take place. Whereas the hand prosthesis could be electromechanically coupled to a single implant, distributing the weight to both implants reduces the risks of mechanical failures. Two fixtures also allow for a total of 16 electrode channels. The e-Abutment Screw of the ulna implant was replaced due to mechanical failure 3.5 years

after implantation. A potential cause for said failure could be that this implant had to carry the full weight of the prosthesis alone for approximately ten months while the other implant was replaced and became ready to load weight.

Discussion

Solutions for artificial limbs must be designed for use outside of research laboratories to confer real clinical benefit to people with limb loss. Here, we present the clinical implementation of a transradial neuromusculoskeletal prosthesis interfacing directly between the hand prosthesis and the nervous and skeletal systems of the user. Implanted electrodes with feedthrough connections through the titanium implant allowed for safe and stable acquisition of neuromuscular signals, resulting in bionic hand control that was suitable for long-term use in daily life.

After using the system at home for a year, the patient demonstrated a greater capacity for myoelectric control, specifically improving when gripping in different body positions, repetitive grasps and releases, and holding objects during motion (ACMC). This improved capacity suggests higher reliability and repeatability of the myoelectric signals acquired from the implanted electrodes, compared to surface electrodes mounted in a socket (14, 28, 29). Tests stimulating the cuffed nerve also showed longitudinally stable percepts evoked on the palm and fingers of the phantom hand (Supplementary Material), sensations which open the door for biomimetic feedback directly communicating tactile information from the sensorized bionic hand (33–35).

Experiential questionnaires suggest that quality of life improved as a result of using the neuromusculoskeletal prosthesis, with the EQ-5D-5L and Q-ULA both showing higher outcomes, and the reduced DASH score suggesting lower perceived disability. Likewise, the patient reported reduced intensity of stump and phantom limb pain.

Human-machine interfaces requiring surgical interventions carry additional risks over non-invasive solutions. Risks associated with the surgery itself, and the long-term potential risk of infections must be factored. Failed osseointegration in one implant was observed in this case and was resolved with a lager diameter implant. The other implant required the change of e-Abutment Screw after this broke in June 2022 (> 4 years after implantation), potentially due to the fatigue experienced when the patient only used one implant to load the prosthesis. Compromised soft-tissue and skeletal structures can complicate reconstruction procedures and the selection of suitable implants. All these aspects should be weighed against the functional and psychosocial benefits of patients (*36*).

In this work, we prioritized research on prosthetic control over the provision of sensory feedback as the former has been reported to be of higher priority for patients (*36*). In addition, the implementation of sensory feedback in daily life requires robust and reliable sensors in the prosthesis, as well as analogue and digital strategies to reduce the effect of stimulation artifacts interfering with myoelectric recordings (*37*, *38*). There was no commercially available multi-articulated hand prosthesis with embedded sensors that could be used for a reliable implementation of sensory feedback in daily life during this study. Our research priorities and the lack of readily available sensorized prosthetic hands have delayed the implementation of sensory feedback in daily life in this patient. However, we foresee this to change in the coming years with the advent of commercially available, multi-articulated and sensorized prosthetic hands.

Overall, we demonstrated in one patient the long-term viability and utility of a transradial neuromusculoskeletal prosthesis, its ability to improve control over a bionic hand, along with improved quality of life for the user.

Methods

Study Design

This case study investigated the in-human implementation of a transradial neuromusculoskeletal prosthesis. The study objectives were to assess the safety and functionality of the neuromusculoskeletal interface (measured by the functional assessments and engineering tests), as well as the effects on the quality of life of the patient after using the neuromusculoskeletal prosthesis in daily life (measured by questionnaires).

Patient

One patient (female, born 1973) took part in this study between September 2018 and April 2021. The patient sustained a traumatic injury leading to transradial amputation of the right hand. The study protocols were carried out in accordance with the declaration of Helsinki and approved by the Regional Ethical Review Board in Gothenburg (Dnr. 12-769). Signed informed consent was obtained before conducting the experiments.

Surgical procedures and neuromusculoskeletal interface

Osseointegrated implant. A skin flap was raised at the distal aspect of the residual limb and both the radius and ulna bones were identified and made even in length. For each bone, the medullary canal was opened and prepared for implantation using a procedure previously described (*39*). A fixture was then installed and soft tissues trimmed as described by Brånemark *et al*. (*40*) A lateral and medial access to the forearm allowed for drilling a 3.5mm hole in each bone, about 2 cm proximal to the fixture. An e-central screw (e-CS), an e-abutment screw, and an abutment were installed within each fixture (Figure 1). Through the cortical holes, both leads coming from the e-CS were retrieved and one was passed into the dorsal and the other into the volar compartment of the forearm.

Electro-neuromuscular constructs. All muscles in the proximal forearm were degenerated and some of them could not be properly identified. On the dorsal surface, the interosseous nerve stump was

isolated and the end-neuroma excised, making it available for transfer to a non-vascularized free muscle graft (also known as a regenerative peripheral nerve interface – RPNI (*41*)). Motor nerve stimulation revealed relatively good muscle contraction for the extensor carpi radialis (ECR), the extensor digitorum communis (EDC), and the supinator muscles. One epimysial and one intramuscular electrode were implanted in the ECR, one intramuscular electrode in the supinator, and one epimysial electrode in the EDC.

On the volar surface, the end-neuroma on the ulnar nerve was excised and the nerve split in two fascicles: one fascicle was used to innervate a non-vascularized muscle graft, and one was wrapped with a cuff electrode for sensory feedback. Only the flexor carpi ulnaris (FCU) and the pronator teres (PT) muscles showed signs of active contraction after motor branch stimulation. One epimysial and one intramuscular electrode were implanted in the FCU and one epimysial electrode into the PT. The median nerve was identified proximal to the elbow joint. The large end-neuroma was removed, and the nerve split in two fascicles then transferred to a non-vascularized muscle graft each. No muscle was deinnervated as only the distal nerve branches terminating in neuromas were used for reconstruction. The four non-vascularized muscle grafts were harvested from the vastus lateralis muscle on the right thigh with a dimension of 5x3x1.5 cm, and all of them were instrumented with intramuscular electrodes.

Neuromuscular electrodes. All muscular electrodes were unipolar. The intramuscular electrode contacts had a 1.27 mm diameter and 2 mm length, and the epimysial electrode contacts had a 2.2 mm diameter. The neural electrode was a 4 mm diameter self-sizing spiral cuff with three central contacts of 1 mm diameter each in a mixed-tripole configuration (*42*). We utilized two types of muscular electrodes because of the nature of the targets. Epimysial electrodes are exposed to less mechanical stress and therefore are expected to remain operational for longer (*43*). In addition, the epimysial electrode contacts tend to have larger surface area and therefore fibrous encapsulation is less detrimental than for intramuscular electrodes (*43*). On the other hand, intramuscular electrodes

are more selective and less affected by crosstalk, and thus preferable for signal source independence (*43*). We employed epimysial electrodes in the native muscles prioritizing longevity, but the free muscle grafts are not vascularized and therefore depend primarily on blood diffusing from surrounding tissue for survival. An epimysial electrode on such a relatively small and non-vascularized muscle would compromise diffusion and thus survival. This is the reason for using intramuscular electrodes in such targets. In addition, mechanical stress is greatly reduced in small free muscle grafts in comparison to larger native muscles. Regarding the neural interface, we utilized an extra-neural electrode primarily for safety and longevity (*43–45*). Neural electrodes have been used mostly to provide sensory feedback rather than for control (*18–22*).This is because of the much lower signal-to-noise ratio (SNR) obtained in comparison with muscular electrodes. Despite that we have shown that our chronically implanted extra-neural electrodes can be used to decode motor intention (*46*), this has not yet been implemented reliably in daily life owing to the SNR challenge.

Self-contained prosthesis

The self-contained prosthesis included a hand, an embedded controller, a wrist-shaped battery unit, and a mechatronic coupler connected to the neuromusculoskeletal interface. The patient was provided with a single-DoF hand (MyoHand Variplus Speed – Ottobock, Germany) and an advanced multi-DoF hand that allowed for different grasps (Mia Hand – Prensilia SRL, Italy) (*47*). The patient was free to use either prosthesis during daily life, however, the assessments to evaluate function were performed using the same single DoF hand to avoid potential bias due to the end effector. Prior to the intervention, the patient used the single DoF hand attached to her residual limb by a conventional socket and controlled by surface electrodes. She employed the most common control scheme in which an electrode placed on the hand flexors, and another one in the hand extensors, were used to close and open the hand, respectively (two-site direct control). After the intervention, myoelectric signals from intramuscular electrodes in the extensor carpi radialis longus and flexor carpi ulnaris were mapped to open and close the prosthetic hand, respectively. A sustained open

signal was used to switch between grasps when the multi-DoF hand was used. Pre-operative assessments were conducted with this prosthetic system in which the socket and surface electrodes were replaced by the neuromusculoskeletal interface in the post-operative assessments. Mechanical attachment was then made via the osseointegrated implants and control signals were recorded using the implanted electrodes. The same control scheme was maintained in the pre- and post-operative assessments.

Functionality, quality of life, and pain assessments

Prosthetic functionality was evaluated with the Assessment of Capacity for Myoelectric Control (ACMC)(*48*) and the Southampton Hand Assessment Procedure (SHAP)(*49*). Changes in quality of life, perceived disability, problems faced during prosthesis use, and pain related to amputation were measured using the EQ-5D-5L questionnaire (*50*), the Disabilities of the Arm Shoulder and Hand (DASH) questionnaire (*51*), the questionnaire for Upper Limb Amputation (Q-ULA)(*52*), and the questionnaire for Phantom Limb Pain Tracking (Q-PLPT)(*53*), respectively. These assessments were performed 6 weeks before and 123 weeks after the intervention.

The ACMC is an observational assessment evaluating a person's ability to perform pre-defined daily tasks including packing a suitcase and setting a table. Twenty-two different aspects of prosthetic use (for example grasping, holding, and releasing of objects) are scored on a 4-point rating scale with a maximum of 66 points attainable per task. A normed composite score between 0-100 can be obtained from the raw score via Rasch analysis, where a composite score above 57.2 is classified as "extremely capable". The SHAP consists of two parts: in the first, comprising 12 tasks, the participant grasps and relocates abstract-shaped objects (cylinders, tabs, spheres, etc.); in the second part, the participant performs 14 activities of daily living (ADLs), such as turning a door handle, picking up coins, and moving containers. The execution times of all 26 tasks are used to calculate the global Index of Function (IOF), a normed score where 100 or higher is associated with normal hand function.

The EQ-5D-5L questionnaire assesses the quality of a patient's life within five categories: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. An EQ-5D score was obtained by norming the five responses ranging between "no problems" and "extreme problems" using the Danish value set (*54*), as there is no Swedish EQ-5D-5L value set available yet. The DASH measures physical functions based on 30 questions, each rated on a 5-point Likert scale. The DASH score is a weighted sum of the questionnaire answers between 0 (no physical difficulties) and 100 (unable to perform physical functions with the arm/shoulder/hand). The Q-ULA assesses changes in, and problems faced during prosthesis use. The Q-ULA score is a weighted average of 30 questions rated on a 4-point Likert scale, where 0 means that the patient experiences no problems and 100 signifies extreme problems during prosthesis use and extreme reduction in quality of life. The Q-PLPT measures changes in phantom limb pain, stump pain, and how much the phantom limb pain interferes with daily life, each on a Likert scale between 0 (no pain/no interference) to 10 (extreme pain/full interference).

Throughout the duration of the study, the long-term electrical and functional stability of the implanted electrodes was periodically monitored by sending cathodic-first, rectangular, bipolar, asymmetric, charge-balanced, current-controlled pulses with known current and measuring the resulting voltage at each electrode via an oscilloscope, thereby calculating electrical impedance. Additionally, sensory acuity to neural stimulation was documented via a manual psychometric procedure to identify stimulation thresholds, and perception stability was tracked via somatotopic maps drawn by the participant detailing where elicited sensations were felt on the phantom hand.

Supplementary materials

Supplementary Figures S1-S15
Supplementary Movie S1

References

1.   P. J. Kyberd, C. Wartenberg, L. Sandsjö, S. Jönsson, D. Gow, J. Frid, C. Almström, L. Sperling,

Survey of upper-extremity prosthesis users in Sweden and the United Kingdom. *J Prosthet Orthot*. **19**, 55–62 (2007).

2.   K. Hagberg, R. Brånemark, Consequences of non-vascular trans-femoral amputation: a survey of quality of life, prosthetic use and problems. *Prosthet Orthot Int*. **25**, 186–94 (2001).

3.   U. Wijk, I. Carlsson, Forearm amputees' views of prosthesis use and sensory feedback. *J. Hand Ther.* **28**, 269–278 (2015).

4.   E. M. Janssen, H. L. Benz, J. H. Tsai, J. F. P. Bridges, Identifying and prioritizing concerns associated with prosthetic devices for use in a benefit-risk assessment: a mixed-methods approach. *Expert Rev. Med. Devices*. **15**, 385–398 (2018).

5.   P. Parker, K. Englehart, B. Hudgins, Myoelectric signal processing for control of powered limb prostheses. *J. Electromyogr. Kinesiol.* **16**, 541–8 (2006).

6.   F. R. Finley, R. W. Wirta, Myocoder studies of multiple myopotential response. *Arch. Phys. Med. Rehabil.* **48** (1967).

7.   K. Englehart, B. Hudgins, A robust, real-time control scheme for multifunction myoelectric control. *IEEE Trans Biomed Eng*. **50**, 848–54 (2003).

8.   M. Ortiz-Catalan, B. Håkansson, R. Brånemark, Real-Time and Simultaneous Control of Artificial Limbs Based on Pattern Recognition Algorithms. *IEEE Trans Neural Syst Rehabil Eng*. **22**, 756–764 (2014).

9.   D. D'Accolti, K. Dejanovic, L. Cappello, E. Mastinu, M. Ortiz-Catalan, C. Cipriani, Decoding of Multiple Wrist and Hand Movements Using a Transient EMG Classifier. *IEEE Trans. Neural Syst. Rehabil. Eng.* **31**, 208–217 (2023).

10.   J. M. Hahne, M. A. Schweisfurth, M. Koppe, D. Farina, Simultaneous control of multiple functions of bionic hand prostheses: Performance and robustness in end users. *Sci. Robot.* **3** (2018), doi:10.1126/scirobotics.aat3630.

11.   T. Kuiken, G. Li, B. A. Lock, R. D. Lipschutz, L. A. Miller, K. A. Stubblefield, K. B. Englehart, Targeted Muscle Reinnervation for Real-time Myoelectric Control of Multifunction Artificial Arms. *JAMA*. **301**, 619–28 (2009).

12.   P. F. Pasquina, M. Evangelista, A. J. Carvalho, J. Lockhart, S. Griffin, G. Nanos, P. McKay, M. Hansen, D. Ipsen, J. Vandersea, J. Butkus, M. Miller, I. Murphy, D. Hankin, First-in-man demonstration of a fully implanted myoelectric sensors system to control an advanced electromechanical prosthetic hand. *J. Neurosci. Methods*, 1–9 (2014).

13.   S. Salminger, A. Sturma, C. Hofer, M. Evangelista, M. Perrin, K. D. Bergmeister, A. D. Roche, T. Hasenoehrl, H. Dietl, D. Farina, O. C. Aszmann, Long-term implant of intramuscular sensors and nerve transfers for wireless control of robotic arms in above-elbow amputees. *Sci. Robot.* **4**, eaaw6306 (2019).

14.   E. Mastinu, F. Clemente, P. Sassu, O. Aszmann, R. Brånemark, B. Håkansson, M. Controzzi, C. Cipriani, M. Ortiz-Catalan, Grip control and motor coordination with implanted and surface electrodes while grasping with an osseointegrated prosthetic hand. *J. Neuroeng. Rehabil.* **16**, 49 (2019).

15.   P. P. Vu, A. K. Vaskov, Z. T. Irwin, P. T. Henning, D. R. Lueders, A. T. Laidlaw, A. J. Davis, C. S. Nu, D. H. Gates, R. B. Gillespie, S. W. P. Kemp, T. A. Kung, C. A. Chestek, P. S. Cederna, A regenerative peripheral nerve interface allows real-time control of an artificial hand in upper limb amputees. *Sci. Transl. Med.* **12**, eaay2857 (2020).

16.   P. Lukyanenko, H. A. Dewald, J. Lambrecht, R. F. Kirsch, D. J. Tyler, M. R. Williams, Stable, simultaneous and proportional 4-DoF prosthetic hand control via synergy-inspired linear interpolation: a case series. *J. Neuroeng. Rehabil.* **18**, 1–15 (2021).

17.   M. Ortiz-Catalan, R. Brånemark, B. Håkansson, J. Delbeke, On the viability of implantable electrodes for the natural control of artificial limbs: Review and discussion. *Biomed. Eng. Online*. **11**, 33 (2012).

18.   G. S. Dhillon, S. M. Lawrence, D. T. Hutchinson, K. W. Horch, Residual function in peripheral nerve stumps of amputees: implications for neural control of artificial limbs. *J Hand Surg*. **29**,

605–15; discussion 616-18 (2004).

19. S. Raspopovic, M. Capogrosso, F. M. Petrini, M. Bonizzato, J. Rigosa, G. Di Pino, J. Carpaneto, M. Controzzi, T. Boretius, E. Fernandez, G. Granata, C. M. Oddo, L. Citi, A. L. Ciancio, C. Cipriani, M. C. Carrozza, W. Jensen, E. Guglielmelli, T. Stieglitz, P. M. Rossini, S. Micera, Restoring natural sensory feedback in real-time bidirectional hand prostheses. *Sci. Transl. Med.* **6**, 222ra19 (2014).

20. D. W. Tan, M. A. Schiefer, M. W. Keith, J. R. Anderson, J. Tyler, D. J. Tyler, A neural interface provides long-term stable natural touch perception. *Sci. Transl. Med.* **6**, 257ra138 (2014).

21. T. S. Davis, H. A. C. Wark, D. T. Hutchinson, D. J. Warren, K. O'Neill, T. Scheinblum, G. A. Clark, R. A. Normann, B. Greger, Restoring motor control and sensory feedback in people with upper extremity amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves. *J. Neural Eng.* **13**, 036001 (2016).

22. L. Zollo, G. Di Pino, A. L. Ciancio, F. Ranieri, F. Cordella, C. Gentile, E. Noce, R. A. Romeo, A. Dellacasa Bellingegni, G. Vadalà, S. Miccinilli, A. Mioli, L. Diaz-Balzani, M. Bravi, K.-P. Hoffmann, A. Schneider, L. Denaro, A. Davalli, E. Gruppioni, R. Sacchetti, S. Castellano, V. Di Lazzaro, S. Sterzi, V. Denaro, E. Guglielmelli, Restoring tactile sensations via neural interfaces for real-time force-and-slippage closed-loop control of bionic hands. *Sci. Robot.* **4**, eaau9924 (2019).

23. P. Herberts, R. Kadefors, E. Kaiser, I. Petersen, Implantation of micro-circuits for myo-electric control of prostheses. *J Bone Jt Surg*. **50**, 780–791 (1968).

24. J. Hoffer, G. E. Loeb, Implantable electrical and mechanical interfaces with nerve and muscle. *Ann. Biomed. Eng.* **8**, 351–60 (1980).

25. R. B. Stein, D. Charles, J. A. Hoffer, J. Arsenault, L. A. Davis, S. Moorman, B. Moss, New approaches for the control of powered prostheses particularly by high-level amputees. *Bull. Prosthet. Res.* **17**, 51–62 (1980).

26. F. Clippinger, R. Avery, B. Titus, A sensory feedback system for an upper-limb amputation prosthesis. *Bull. Prosthet. Res.* **10–22**, 247–258 (1974).

27. F. W. Clippinger, J. H. McElhaney, M. G. Maxwell, D. W. Vaughn, G. Horton, L. Bright, Prosthetic sensory feedback lower extremity. *Newsl. Prosthetics Orthot. Clin.* **5**, 1–3 (1981).

28. M. Ortiz-Catalan, B. Hakansson, R. Branemark, An osseointegrated human-machine gateway for long-term sensory feedback and motor control of artificial limbs. *Sci. Transl. Med.* **6**, 257re6-257re6 (2014).

29. M. Ortiz-Catalan, E. Mastinu, P. Sassu, O. Aszmann, R. Brånemark, Self-Contained Neuromusculoskeletal Arm Prostheses. *N. Engl. J. Med.* **382**, 1732–1738 (2020).

30. H. Y. N. Lindner, A. Langius-Eklöf, L. M. N. Hermansson, Test-retest reliability and rater agreements of Assessment of Capacity for Myoelectric Control version 2.0. *J. Rehabil. Res. Dev.* **51**, 635–644 (2014).

31. S. Coretti, M. Ruggeri, P. McNamee, The minimum clinically important difference for EQ-5D index: A critical review. *Expert Rev. Pharmacoeconomics Outcomes Res.* **14**, 221–233 (2014).

32. F. Franchignoni, S. Vercelli, A. Giordano, F. Sartorio, E. Bravini, G. Ferriero, Minimal clinically important difference of the disabilities of the arm, shoulder and hand outcome measure (DASH) and its shortened version (quickDASH). *J. Orthop. Sports Phys. Ther.* **44**, 30–39 (2014).

33. E. Mastinu, L. F. Engels, F. Clemente, M. Dione, P. Sassu, O. Aszmann, R. Brånemark, B. Håkansson, M. Controzzi, J. Wessberg, C. Cipriani, M. Ortiz-Catalan, Neural feedback strategies to improve grasping coordination in neuromusculoskeletal prostheses. *Sci. Rep.* **10**, 11793 (2020).

34. G. Valle, A. Mazzoni, F. Iberite, E. D'Anna, I. Strauss, G. Granata, M. Controzzi, F. Clemente, G. Rognini, C. Cipriani, T. Stieglitz, F. M. Petrini, P. M. Rossini, S. Micera, Biomimetic Intraneural Sensory Feedback Enhances Sensation Naturalness, Tactile Sensitivity, and Manual Dexterity in a Bidirectional Prosthesis. *Neuron*. **100**, 37-45.e7 (2018).

35. J. A. George, D. T. Kluger, T. S. Davis, S. M. Wendelken, E. V. Okorokova, Q. He, C. C. Duncan,

D. T. Hutchinson, Z. C. Thumser, D. T. Beckler, P. D. Marasco, S. J. Bensmaia, G. A. Clark, Biomimetic sensory feedback through peripheral nerve stimulation improves dexterous use of a bionic hand. *Sci. Robot.* **4**, eaax2352 (2019).

36. A. Middleton, M. Ortiz-Catalan, Neuromusculoskeletal Arm Prostheses: Personal and Social Implications of Living With an Intimately Integrated Bionic Arm. *Front. Neurorobot.* **14** (2020), doi:10.3389/fnbot.2020.00039.

37. T. Keller, M. R. Popovic, Real-time stimulation artifact removal in EMG signals for neuroprosthesis control applications. *Proc. 6th Annu. IFESS Conf.*, 4–6 (2001).

38. E. J. Earley, A. Berneving, J. Zbinden, M. Ortiz-Catalan, Neurostimulation artifact removal for implantable sensors improves signal clarity and decoding of motor volition. *Front. Hum. Neurosci.* **16**, 1–12 (2022).

39. S. Jönsson, K. Caine-Winterberger, R. Brånemark, Osseointegration amputation prostheses on the upper limbs. *Prosthetics Orthot. Int.* **35**, 190–200 (2011).

40. R. Brånemark, Ö. Berlin, K. Hagberg, P. Bergh, B. Gunterberg, B. Rydevik, A novel osseointegrated, percutaneous prosthetic system for treatment of patients with transfemoral amputation: A prospective study of 51 patients. *Bone Jt. J.* **96**-**B**, 106–113 (2014).

41. P. P. Vu, A. K. Vaskov, Z. T. Irwin, P. T. Henning, D. R. Lueders, A. T. Laidlaw, A. J. Davis, C. S. Nu, D. H. Gates, R. B. Gillespie, S. W. P. Kemp, T. A. Kung, C. A. Chestek, P. S. Cederna, A regenerative peripheral nerve interface allows real-time control of an artificial hand in upper limb amputees. *Sci. Transl. Med.* **12**, 1–12 (2020).

42. M. Ortiz-Catalan, J. Marin-Millan, J. Delbeke, B. Håkansson, R. Brånemark, Effect on signal-to-noise ratio of splitting the continuous contacts of cuff electrodes into smaller recording areas. *J. Neuroeng. Rehabil.* **10**, 22 (2013).

43. M. Ortiz-Catalan, R. Brånemark, B. Håkansson, J. Delbeke, On the viability of implantable electrodes for the natural control of artificial limbs: Review and discussion. *Biomed Eng Online*. **11**, 33 (2012).

44. B. P. Christie, M. Freeberg, W. D. Memberg, G. J. C. Pinault, H. A. Hoyen, D. J. Tyler, R. J. Triolo, Long-term stability of stimulating spiral nerve cuff electrodes on human peripheral nerves. *J. Neuroeng. Rehabil.* **14**, 70 (2017).

45. K. A. Yildiz, A. Y. Shin, K. R. Kaufman, Interfaces with the peripheral nervous system for the control of a neuroprosthetic limb: a review. *J. Neuroeng. Rehabil.* **17**, 1–19 (2020).

46. B. Ahkami, M. Ortiz-Catalan, Extra-Neural Signals From Severed Nerves Enable Intrinsic Hand Movements In Transhumeral Amputations. *Sci. Rep.*, 1–7 (2021).

47. M. Controzzi, F. Clemente, D. Barone, A. Ghionzoli, C. Cipriani, The SSSA-MyHand: a dexterous lightweight myoelectric hand prosthesis. *IEEE Trans. Neural Syst. Rehabil. Eng.* **4320** (2016), doi:10.1109/TNSRE.2016.2578980.

48. L. M. Hermansson, A. G. Fisher, B. Bernspång, A. C. Eliasson, Assessmet of Capacity for Myoelectric Control: A new Rasch-built measure of prosthetic hand control. *J. Rehabil. Med.* **37**, 166–171 (2005).

49. C. M. Light, P. H. Chappell, P. J. Kyberd, Establishing a standardized clinical assessment tool of pathologic and prosthetic hand function: Normative data, reliability, and validity. *Arch. Phys. Med. Rehabil.* **83**, 776–783 (2002).

50. M. Herdman, C. Gudex, A. Lloyd, M. Janssen, P. Kind, D. Parkin, G. Bonsel, X. Badia, Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual. Life Res.* **20**, 1727–1736 (2011).

51. P. L. Hudak, P. C. Amadio, C. Bombardier, Development of an upper extremity outcome measure: The DASH (disabilities of the arm, shoulder, and head). *Am. J. Ind. Med.* **29**, 602–608 (1996).

52. K. Hagberg, R. Brånemark, O. Hägg, Questionnaire for Persons with a Transfemoral Amputation (Q-TFA): initial validity and reliability of a new outcome measure. *J. Rehabil. Res. Dev.* **41**, 695–706 (2004).

53. M. Ortiz-Catalan, R. A. Gudmundsdottir, M. B. Kristoffersen, A. Zepeda-Echavarria, K. Caine-Winterberger, K. Kulbacka-Ortiz, C. Widehammar, K. Eriksson, A. Stockselius, C. Ragnö, Z. Pihlar, H. Burger, L. Hermansson, R. A. Guðmundsdóttir, M. B. Kristoffersen, A. Zepeda-Echavarria, K. Caine-Winterberger, K. Kulbacka-Ortiz, C. Widehammar, K. Eriksson, A. Stockselius, C. Ragnö, Z. Pihlar, H. Burger, L. Hermansson, Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: a single group, clinical trial in patients with chronic intractable phantom limb pain. *Lancet*. **388**, 2885–2894 (2016).

54. C. E. Jensen, S. S. Sørensen, C. Gudex, M. B. Jensen, K. M. Pedersen, L. H. Ehlers, The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. *Appl. Health Econ. Health Policy*. **19**, 579–591 (2021).

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M.O.C., J.M., and R.B. designed the implant system. P.S. and R.B. performed the surgeries. E.M. and M.O.C. developed the electronic embedded system. F.C., L.C., M.C. and C.C. designed the multi-DoF hand prosthesis. M.O.C, J.Z., J.M., D.D., M.C., F.C., L.C., E.J.E., E.M. and C.C. defined the experimental protocol. J.Z., E.M., E.J.E., J.K., M.M.N and D.D. conducted the experiments. J.Z., E.J.E., and D.D. verified and analyzed the data independently. J.Z., E.J.E., and M.O.C. drafted the manuscript. All authors have access to all the data, revised, and approved the final manuscript.

Competing interests

J.Z., D.D., L.C., P.S., E.J.E., M.M.N., and S.J. declare no competing interests. E.M. and M.O.C. have consulted for Integrum AB. J.K., M.O.C. and R.B. hold shares of Integrum AB. M.C., F.C., and C.C. hold shares in Prensilia Srl. M.O.C. and R.B. are co-inventors on patent # US9579222B2 entitled "Percutaneous gateway, a fixing system for a prosthesis, a fixture and connecting means for signal transmission ", which is held by Integrum AB.

Data availability

All data associated with this study are present in the paper or the Supplementary Materials.