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Review article

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Neurotechnologies to restore hand functions

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Abstract

Reaching and manipulating objects are crucial tasks that allow proactive interaction with our surroundings. However, these functions are lost after neurological disorders or traumatic events that cause hand paralysis. Neuroprosthetic technologies are medical devices that can substitute or restore a damaged motor or sensory modality. In this Review, we discuss how advanced technological modules can be used to restore hand functions in subjects with paralysis. First, we illustrate how the subject's intended hand functions can be extracted by deciphering their cortical activity or residual body movements. Next, we describe how invasive and non-invasive electrical stimulation of neural or muscular structures can activate different hand muscles to restore functional movements. We then provide examples of 'brain-to-body' interfaces that can decode the hand motor intent from brain signals and activate muscles accordingly, allowing voluntary control of movements while bypassing the neurological issue. Finally, we discuss the future steps required for the clinical translation of these technologies.

Sections

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Key points

- Neuroprostheses based on decoding and stimulation of the nervous system can be used to restore hand functions.
- Voluntary hand control can be restored by bypassing the lesion using 'brain-to-body' interfaces (BBIs).
- Various invasive and non-invasive solutions exist to develop the BBI components needed to restore hand function.
- BBIs could potentially provide long-term restoration of hand function.

Introduction

Even the most mundane daily activities, such as putting on a shirt and buttoning it up, checking the weather forecast on the mobile phone, getting a sip of coffee or grabbing an umbrella involve diverse hand functions and grasp movements. The aim of researchers working in neuroprosthetics — the discipline concerned with the development of medical devices that substitute or restore damaged motor, sensory or cognitive functions — is to provide similar functions to individuals who have lost hand mobility caused by stroke, spinal cord injury (SCI) or amyotrophic lateral sclerosis. Currently, the most common solution for people with motor deficiency is to adapt tools to their specific needs; a voice-over control can be used to navigate through a mobile phone, an adapted cup and a straw enables a patient to drink a beverage. Since the early 2000s, brain–machine interfaces (BMIs), which are neuroprostheses that create a direct communication pathway between brain activity and an external device, have been proposed as a way to bypass the injured neural pathways[1] and allow people with severe motor deficiencies to control various devices. For example, a cortical implant can empower users to brain-control a tablet[2] or a unimanual[3] or bimanual[4] robotic arm for self-feeding.

However, the solution preferred by patients would be to restore their body functions rather than replacing them with an external device[5]. The restoration of hand movements using neuroprostheses and brain-to-body interfaces (BBIs), neuroprostheses that create an artificial link between brain commands and body actuation through electrical stimulation, is not new (Fig. 1a–c). Numerous studies have reported the recovery of hand opening and some types of power grasp (for example, lateral and palmar)[6–8]. Non-invasive BBIs are routinely used for neurorehabilitation purposes (particularly for hand restoration in patients with stroke[9,10]), and invasive BBIs have been used as assistive devices for patients with severe paralysis[11,12]. However, despite allowing restoration of a few coarse hand movements, BBIs have yet to recover the variety of power and precision grasps and single finger movements necessary for daily activities. Therefore, neuroprostheses are needed that can selectively and independently control individual fingers, provide multiple grasping movements, and are not prone to rapid fatigue (Fig. 1d). Furthermore, simultaneous decoding of multiple degrees of freedom (DoFs) and a better understanding of sensorimotor cortical processes for movement preparation, coordination and execution, are essential. Here, after an overview of the cortical, spinal and muscular functions in a normal human body, we describe the neurotechnological modules for motor decoding and movement restoration. We conclude by discussing how these modules can be integrated into neuroprostheses to restore voluntary hand control and how to facilitate their clinical translation.

Normal control of hand movements

The human hand is a complex biomechanical system with 27 DoFs[13], 6 in the wrist (1 for flexion–extension, 1 for radio-ulnar deviation, 1 for supination–pronation and 3 for translation in space), 5 in the thumb (3 for flexion–extension and 2 for abduction–adduction) and 4 in each of the other fingers (3 for flexion–extension and 1 for abduction–adduction) with some finger interdependence[14], which allow for a variety of shapes and functions. Although hand movements are very similar between humans and non-human primates (NHPs), human hand dexterity is unique, partly owing to its morphology: a higher thumb-to-finger-length ratio and a more complex muscular structure in the thumb than in NHPs allow higher flexibility in finger opposition and the ability to create forceful precision grips[15]. The collection of human hand movements can be divided into two main groups, namely prehensile and non-prehensile movements, used for grasping and pushing or lifting objects, respectively[16] (Fig. 2a). Prehensile movements are more prevalent[17,18] and have been studied more extensively. Prehensile movements have been systematically arranged into 33 grasp types based on hand configuration and object geometry, which can be reduced to 17 prototypical types when not considering object geometry[19]. Moreover, each grasp movement can be classified as power, precision or intermediate, based on whether large force, precision or a mixture of both is required. The occurrence of different grasp types in daily life has been extensively studied to determine their importance for neuroprosthetics and neurorehabilitation[20,21]. However, despite providing some general guidance — for example, the prevalence of lateral and medium wrap grasps — there is high variability in the frequency of grasp types across environments and subjects investigated[19]. Thus, neuroprostheses that restore a large set of hand movements are needed to benefit more patients in more contexts.

Anatomical pathway

Human hand movements are controlled by coordinated contractions of extrinsic and intrinsic hand muscles, located in the forearm and within the hand itself, respectively (Fig. 2b). Extrinsic muscles provide strength, whereas intrinsic muscles allow fine movements. These muscles contract owing to electrical signalling originating from motoneurons in the ventral horn of the spinal cord. The motoneurons travel out of the spinal cord in the spinal nerves at different levels to reach their target muscle, where they enter at a location called the motor point. The muscles of the hand are targeted by the spinal roots at the C5–T1 levels, according to a rostro-caudal somatotopy[22]: the more proximal the muscle, the more rostral the peak of the spinal motoneuron pool that innervates it, but with a high degree of overlap of the motoneuron pools across muscles. In the upper extremity, the C5–T1 spinal nerves first form the brachial plexus, where they reorganize into different nerve trunks to efficiently travel to different regions of the arm[23]. The nerve trunks that form in the brachial plexus and are responsible for hand function are the median nerve, which innervates most flexor and pronator muscles in the ventral forearm and some intrinsic hand muscles, the ulnar nerve, which innervates the flexor carpi ulnaris and the medial half of the flexor digitorum profundus as well as the majority of intrinsic hand muscles, and the radial nerve, which innervates extensor and supinator muscles in the forearm and hand[23–25]. Motoneuron axons travel within fascicles in these nerves. The density, diameter and functional topography of nerve fascicles depend on the distance from

the spinal cord[26]: more, smaller and better functionally partitioned fascicles emerge distally, as fibres innervating the same muscle organize in separate patches and eventually form a distinct fascicle to branch out of the nerve trunk towards the muscle.

Spinal motoneurons receive input from multiple neural pathways, that is, sensory afferents and supraspinal regions, either directly or through spinal interneurons[27,28]. Multiple cortical regions are involved in voluntary movements, where the primary motor cortex (Broadmann's area 4) mainly contributes to the execution of movements. Here, pyramidal cells in layer 5 of the primary motor cortex project to spinal interneurons and motoneurons and constitute about 30% of the corticospinal tract. Anatomical and evolutionary differences have led to the classification of two areas in the primary motor cortex that are thought to affect dexterous movements like those of the hand, namely the caudal and rostral regions[29–31]. Compared with caudal primary motor cortex, the rostral primary motor cortex is evolutionarily older, has primarily disynaptic connections with motoneurons through interneurons and is thought to use spinal cord mechanisms to control a wide range of motor behaviours. Caudal primary motor cortex is more developed in humans and apes, is characterized by monosynaptic connections to motoneurons and is thought to control highly skilled movements. A large area of human primary motor cortex, about 9 cm^2 (ref. 32), is associated with hand movements; although cortical representations for different fingers largely overlap[33], multiple studies support the hypothesis that finger somatotopy is present in this area[34,35].

Since the 1960s, investigators have asked how the motor system, with more than 30 muscles and 20 joints in the human hand contributing to motion production, reduces the burden of regulating the large number of variables available[36]. Despite the great number of muscles involved, most voluntary movements in vertebral species can be generated from the activation of relatively few muscle synergies[37]. In the human hand, postures and movements have been represented by the activation of a few joint, force or muscle synergies[38–42]. Whether these synergies are a fundamental property of neural motor control or whether they are an artefact of task structure is still debated[43]. Motor responses to cutaneous[44] and intraspinal stimulation[45,46] revealed that the spinal cord in vertebrates is organized into modules that generate specific patterns of muscle activation. Additionally, cortical stimulation in NHPs evokes complex movements[47]. Together, these findings have led to the idea that movement is generated by the activation of modular muscle synergies with the motor cortex determining the patterns of activation[37]. Nonetheless, evidence suggests that the motor cortex might be more involved and also encodes muscle synergies[31] and contributes to the flexible activation of motor units[48].

Motor control

Although anatomical pathways for human hand motion production are well described, how the motor cortex controls movement is still debated. The historical view of motor control in higher vertebrates has been that the cortex must take a neural representation of high-level parameters, such as movement direction or velocity, and convert that into commands for muscles through a series of transformations[49]. The classical approach has relied on trying to find the movement parameter that the motor cortex is representing by correlating extracellular intracortical recordings in primary motor cortex of animal models with a variety of movement parameters during movement tasks[50]. Ultimately, a multitude of variables represented in primary motor cortex have been found, ranging from movement direction[51] and instantaneous hand kinematics[52] to muscle activations[53]. However, no consensus has been reached on what the role of the motor cortex is in motor control.

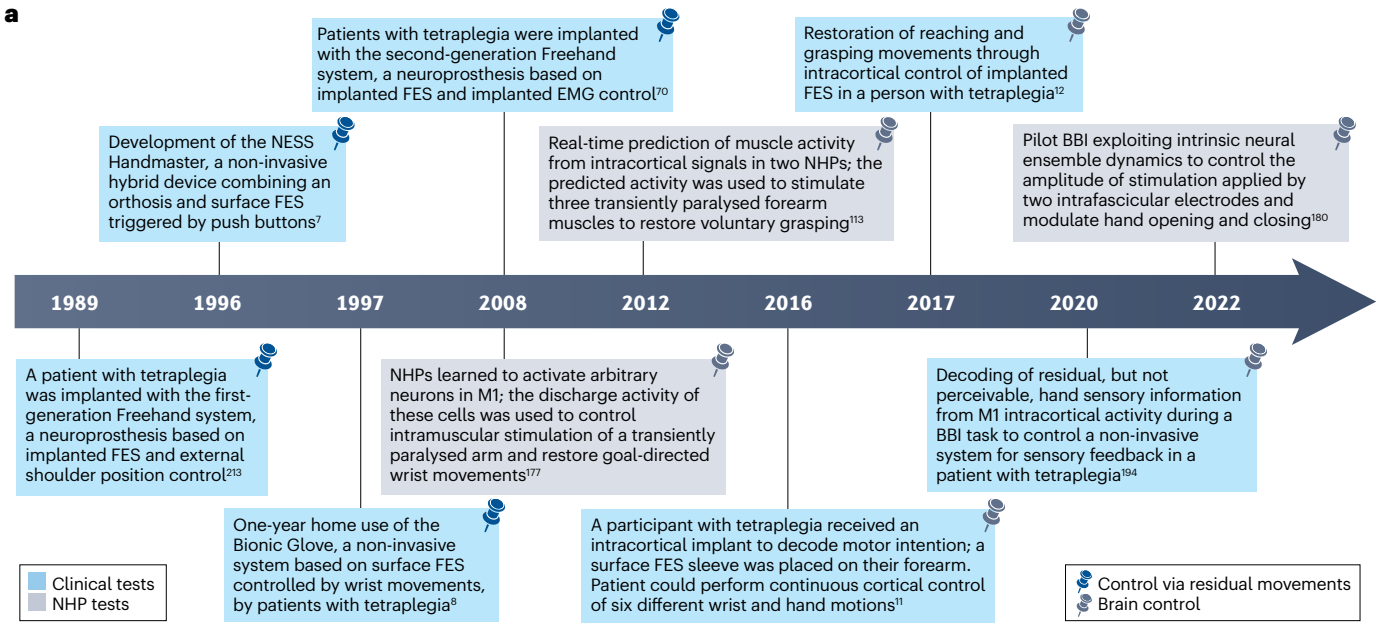
Alternatively, neurophysiology recordings in NHPs have pointed out heterogeneity in the parameters represented by individual neurons in primary motor cortex[50,54–57], suggesting that a paradigm shift away from representational modelling is needed to understand the encoding of movements. With the rise of microelectrode arrays and the ability to record from up to hundreds of neurons at the same time[58], research focus has shifted towards looking at the covariance of neurons activating in the motor cortex of NHPs to understand how they work together to compose movement-generating outputs. In this view, the role of neurons is not to represent any specific movement covariate; instead the primary motor cortex activity reflects a mixture of signals, some of which output to drive muscles, but many of which are internal processes composing those outputs[59]. Dimensionality-reduction methods have become widely used to visualize the covariance of neural activity[60,61], revealing various aspects of motor control, including preparatory activity[62], motor learning and plasticity[63–65], and the formation of descending motor commands[59,66,67]. One view is that a large amount of variance of neural activity resides in a low-dimensional space, which ensures robustness in movement execution[66]. This subspace might be preserved between different movements, with only a small amount of neural variance accounted for by movement-specific subspaces. These dynamics have been studied largely in upper arm movements in NHPs and, although they could also be applied to hand movements, the increased sensory feedback during hand movements points to different dynamics[68]. Therefore, a systematic evaluation of motor cortex dynamics during hand movements and the impact of sensory feedback is needed to understand whether these findings can be extended to hand movements.

Decoding intended hand movements

To estimate intended hand movements and restore a range of hand dexterity, various approaches can be taken. For example, discrete commands can be extracted, such as to perform grasping, to select a certain type of grasp, or to flex or extend a certain finger or group of fingers. Discrete commands can be substituted or combined with continuous control of single DoFs, such as the level of grasp or finger closure or force. Discrete decoding has been implemented using non-invasive interfaces with the body (decoding through residual body movements) or the brain (using electroencephalography, EEG). Higher decoding accuracy on several finger movements has been obtained with implantable electrodes placed on the surface of the brain (using electrocorticography, ECoG).

However, to restore hand dexterity for a larger spectrum of daily activities is more complex. In this case, the decoder should allow continuous and independent control of multiple DoFs. Although decoding all 27 DoFs of the hand is probably not necessary for functional performance in daily life, decoding at least 7 DoFs (flexion–extension of the wrist, flexion–extension and abduction–adduction of the thumb, and flexion–extension of the other four fingers) would allow graded control of a variety of prehensile and non-prehensile movements and recovery of many tasks. For more flexibility, abduction–adduction of the index finger, but also of the other fingers, adding 1 to 4 DoFs, could be considered. So far, continuous multi-DoF hand control has been obtained only with intracortical solutions, that is, using electrodes that penetrate the brain.

In this section we describe existing neurotechnologies that use various sources to decode hand movements. We present solutions based on residual body movements, EEG, ECoG and intracortical electrodes.



Residual body movement decoding

Most of the current clinical applications of neuroprostheses for hand-movement restoration rely on the user's residual body movements to provide motor commands. Body control sources can be distinguished into homologous and non-homologous solutions depending on whether they are part of the natural 'command chain' (that is, neuromuscular control pathway) of the hand, or not. Examples of non-homologous approaches include movements of the contralateral shoulder and button presses, used in the first-generation Freehand system (NeuroControl Corp., Valley View, TX, USA)[6] and the NESS H200

Fig. 1 | Evolution of neuroprostheses for voluntary hand control. a, Timeline of major events in the development of hand neuroprostheses. During the first pioneering phase, most hand neuroprostheses were based on residual body control implemented through non-invasive interfaces, allowing the command of a couple of degrees of freedom[7,8,70,214] Restoration of no more than two grasping tasks was achieved using muscle stimulation with surface, but also implanted electrodes. In the late 2000s, brain–body interfaces (BBIs) for grasping were demonstrated in non-human primates (NHPs)[114,179] and a few years later in two patients with tetraplegia[11,12]. Intracortical recordings were used to decode the motor intent to drive the stimulation applied through intramuscular or multi-pad surface electrodes, where simple functional tasks were restored in the subjects. In 2020, the BBI of one of the two implanted patients was integrated with a system for sensory feedback, resulting in substantial improvement in grasping performance[196]. Moreover, an intracortical BBI based on intrafascicular peripheral nerve stimulation with only two nerve implants was reported in a NHP[182]. **b**, Examples of commercial hand neuroprostheses based on residual body control. **c**, Examples of BBIs to restore grasping. **d**, The dream solution for BBIs would allow patients to regain high hand dexterity with small and portable external components. First, recording and decoding of brain signals is achieved using an embedded, fully implanted system (1)[206,215]. Next, the decoded motor intention is wirelessly transmitted to an external, portable control unit that computes the stimulation protocol based on the user command and the state of the arm (2). Then, stimulation parameters are wirelessly transmitted to an implanted pulse generator that sends electrical pulses to the neuromuscular system through chronically implanted electrodes (3)[70,152]. Finally, the user regains voluntary control of different power and precision grasps and single finger movements (4). EMG, electromyography; FES, functional electrical stimulation; iBCI, intracortical brain–computer interface. Part **b** is adapted from ref. 8, Elsevier, reprinted from ref. 139, Springer Nature Limited and image courtesy of Bioventus. Part **c** is reprinted from ref. 12, with permission from Elsevier, and adapted with permission from ref. 196, Elsevier.

(Bioventus LLC, Durham, NC, USA)[69], respectively, to select the desired type of grasping and its onset and offset. Despite non-homologous approaches being robust and easy to implement, they scale poorly in controlling multiple DoFs for more complex movements and increase the cognitive load.

A more intuitive, but not truly homologous, solution was implemented in the Bionic Glove[8], now commercialized as ReGrasp (Rehabtronics, Edmonton, Canada), whereby people with C6 tetraplegia controlled the onset and offset of grasping using the residual extension and gravity-induced flexion of the wrist, respectively. This technique resulted in a natural amplification of their already mastered tenodesis grasp, a passive grasp mechanism in which extension of the wrist leads to shortening of the finger flexors and thus to flexion of the fingers. This approach was later extended to the second-generation Freehand system[70], employing implanted electromyography (EMG) or kinematic wrist sensors[71]. The use of multi-muscle EMG signals recorded from the forearm and hand has been proposed as a truly homologous solution providing an increased control of dimensionality, that is, more DoFs can be controlled. Classification of hand postures has been performed using myoelectric pattern recognition in subjects with incomplete tetraplegia[72,73]. In addition, subthreshold muscle activity — detectable with EMG but without producing open movements — has been reported in most patients diagnosed with motor complete SCIs[74,75]. These low-level EMG signals were recorded with surface electrode arrays positioned on the forearm in a patient with complete SCI and used to discriminate between attempted single finger movements[76]. One limitation of homologous residual body control is that there is currently no robust solution to disentangle in real time the voluntary activity from that evoked by the neuroprosthesis without loss of data[77]. Moreover, it must be tailored to each patient and is not applicable when the residual kinematic and muscle activities are completely absent.

Brain decoding

A more generalizable solution would be to use neurotechnologies that decode hand movements from brain activity. Brain activity can be recorded using interfaces with different levels of invasiveness (transcutaneous, intracranial or intracortical; Fig. 3a), leading to different recording and decoding resolutions (Fig. 3b).

Non-invasive signals: EEG. The non-invasive (transcutaneous) solution using EEG has generated the largest number of human studies in the field. EEG signals have high temporal but low spatial resolution because they are based on the cumulative activity of many neurons. Therefore, to decode specific movements it is necessary to extract relevant features across time and electrodes. Frequency-related features are generally extracted using Fourier transform, wavelets or bandpass filtering, and it is common to see spatial features extracted through Laplacian filters, spatial patterns, principal component analysis and independent component analysis[78]. Sensorimotor-related rhythms commonly extracted are the mu band (8–12 Hz) and beta band (18–30 Hz), as these change in amplitude with overt movement, imagined movement and movement preparation.

EEG recordings have been used in healthy subjects and patients with tetraplegia for discrete decoding of hand movements. Linear discriminant analysis classifiers can decode the onset of grasping[79] and discriminate between two or three grasp types[80–85] and object affordances[85] using EEG signals over the motor cortex and fronto-parietal areas. Unfortunately, classification accuracy has never reached high values; that is, not exceeding 70% in binary classification. EEG signals have low amplitude and lack the specificity to decode motor intentions for the hand well above chance levels. Therefore, the accuracy of predicted movements might not be high enough to control a hand in daily life. In addition, EEG caps are cumbersome and require skill and time to be placed and calibrated, further limiting their acceptance for daily assistance.

However, EEG signals can also be used to trigger muscle stimulation[86] or to control an orthosis or exoskeleton[87] in a neurorehabilitation setting. A double-blind study with 32 patients with chronic stroke showed substantially higher motor improvement in the BMI group (the BMI was used to trigger an orthosis attached to the plegic limb) compared with a sham-BMI group after 4 weeks of training[88], as measured by the modified Fugl–Meyer assessment motor score[89], which assesses voluntary movement of the upper limb. In this case, the contingent link between brain activity and repetitive activation of the afferents is thought to promote a Hebbian-like plasticity mechanism (a form of synaptic plasticity caused by the causal relationship between pre- and post-synaptic activity), which might increase the excitability of motor circuits to a level that allows voluntary activation of preserved, functional corticospinal fibres[90]. The key element here is high temporal resolution such that the cortical motor command is synchronized with the afferent signal[90–92], rather than achieving 100% decoding accuracy.

Invasive signals: ECoG. In comparison with EEG, a higher spatiotemporal resolution and the elimination of external components can be

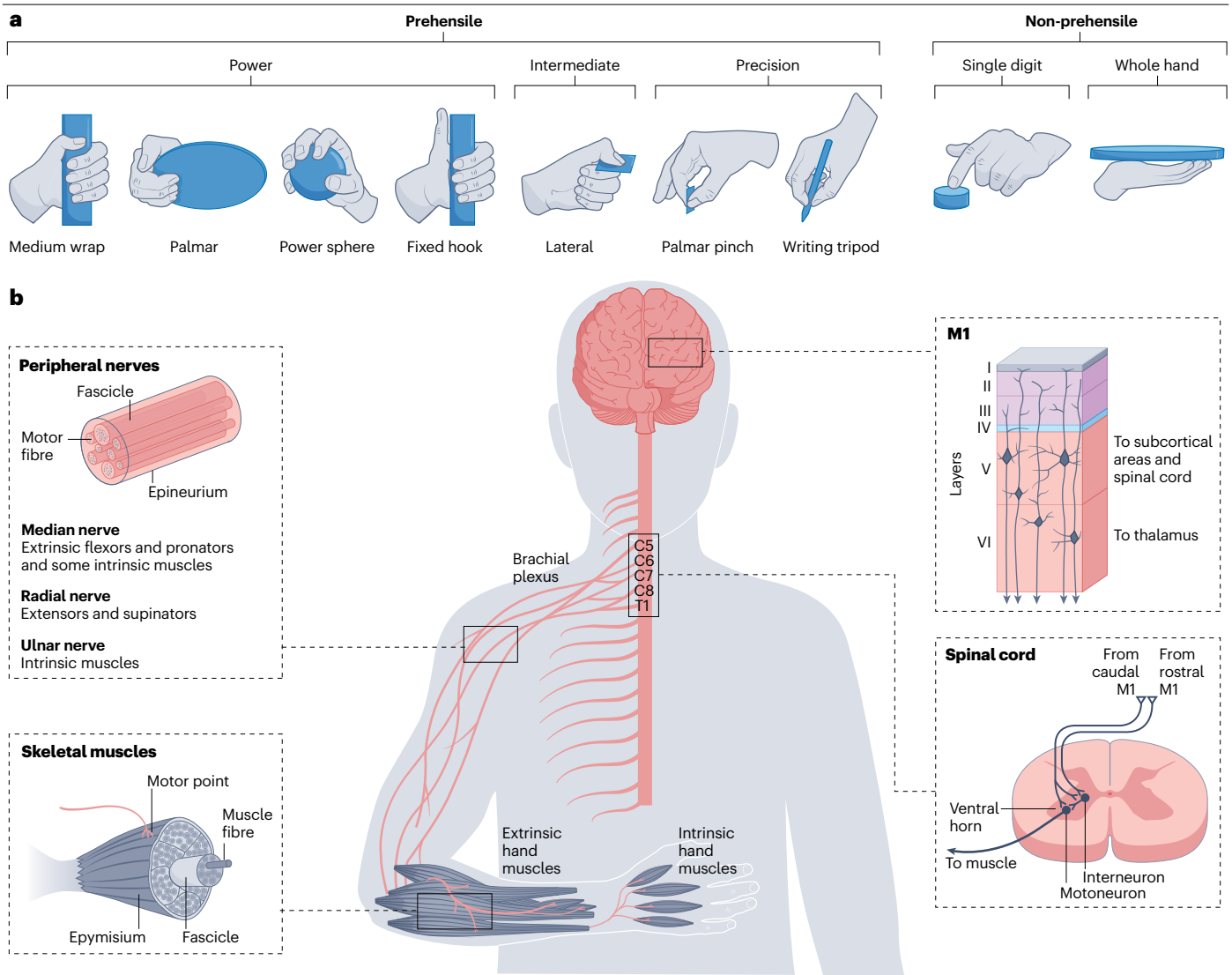


Fig. 2 | Normal hand movements and their anatomical pathway. a, Examples of prehensile and non-prehensile hand movements, used for grasping and pushing or lifting objects, respectively[16]. Prehensile movements are classified into power, precision and intermediate grasps[19]. Non-prehensile movements can involve single digits or the whole hand. **b**, Hand movements are generated by contracting extrinsic and intrinsic hand muscles, located in the forearm and in the hand, respectively. The skeletal muscle is composed of muscle fibres organized in fascicles, surrounded by a connective tissue called epymisium. The nerve motor branch enters the muscle belly at the motor point. Hand muscles are innervated by the median, radial and ulnar nerves, which form in the brachial plexus. A peripheral nerve is composed of motor fibres organized into fascicles, surrounded by a connective tissue called epineurium. Hand muscles are targeted by the C5–T1 spinal nerves. Spinal motoneurons, originating in the ventral horn of the spinal cord, receive input directly from cells originating in the caudal primary motor cortex (M1, which is composed of six layers) or from spinal interneurons, which in turn receive input from cells originating in the caudal and rostral M1. Large pyramidal cells in layer 5 send their axons to the spinal cord.

obtained by recording signals from the surface of the brain using ECoG. Because ECoG electrodes are large and far from the neurons in the cortical layer V projecting to the spinal cord, they still record the combined activity of many neurons. However, ECoG motor signals are more specific and have a larger frequency range of interest than EEG, with mu and beta rhythms still present and a higher-frequency gamma range that is thought to be related to the activity of single neurons[93].

ECoG recordings have been used to accurately classify up to five hand postures and single finger movements[94–97]. Moreover, ECoG activity has also been used to control prosthetic hands through online detection and classification of hand or finger movements[98,99]. These studies employ linear classifiers, such as linear discriminant analysis or support vector machines. Moreover, offline studies demonstrate accurate 1-DoF continuous hand control with ECoG. For example, linear decoders with nonlinear transforms at the output applied to ECoG recordings can predict single finger kinematics[100,101] and force[101]. Moving to completely non-linear methods, a convolutional neural network combined with a long short-term memory has been used for decoding

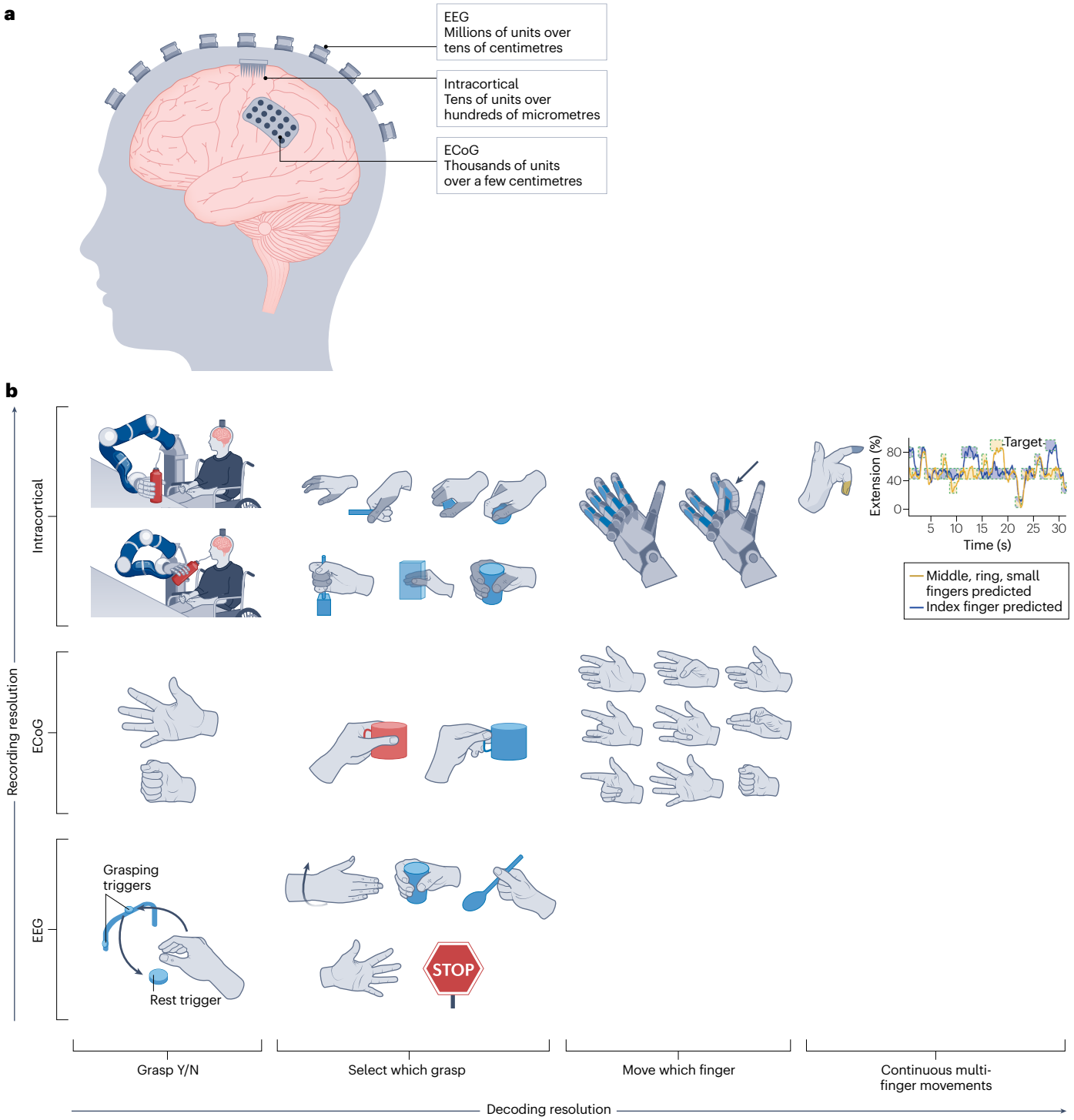


Fig. 3 | Interfaces and strategies to decode hand movements from brain activity. a, Brain signals can be recorded with transcutaneous (electroencephalography, EEG), intracranial (electrocorticography, ECoG) or intracortical electrodes, from the least to the most invasive interface, resulting in different levels of spatial resolution (number of recorded neurons, or units, and the covered area of cortical tissue). **b**, Classification of selected studies in terms of type of brain interface used and decoded information, such as the intention to grasp[79,97] (with 3D control of a robotic arm[104]), discrete grasps[83,95,107] discrete single finger movements[96,105] and continuous multi-finger kinematics[117]. Part **b** is adapted from ref. 104, Springer Nature Limited. Part **b** is adapted from ref. 107, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **b** is adapted with permission from ref. 105, Wolters Kluwer Health, Inc. Part **b** is adapted with permission from ref. 117, Elsevier. Part **b** is adapted from ref. 97. CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **b** is adapted with permission from ref. 95, Elsevier. Part **b** is adapted with permission from ref. 96, IOP. © [2015] IEEE. Reprinted, with permission, from ref. 79, adaptation permission from author. © [2019] IEEE. Reprinted, with permission, from ref. 83, adaptation permission from author.

single finger trajectories[102], with the convolutional layer replacing the feature extraction pipeline.

ECoG electrodes remain on the surface of the brain and cause little damage or foreign body response, which is thought to evoke longer electrode lifetimes and more consistent signals over time compared with more invasive approaches[103]. However, despite having great potential for clinical applications, it might be difficult to substantially increase the number of hand DoFs controlled by ECoG-based systems. The limited spatial separation of human cortical areas devoted to different fingers limits the specificity that can be reached using ECoG electrodes, which record the summation of the activity of many units.

Invasive signals: intracortical. The solution that has shown the highest levels of accuracy, control rate and dimensionality involves the recording of spikes through intracortical electrodes. Intracortical electrodes penetrate the cortex, recording from neurons micrometres away and allowing the spiking rate of single units or multi-units to be calculated, thus estimating the neural activation in highly localized areas. Since the early 2000s, intracortical multi-electrode arrays (Box 1) have been used for movement decoding because they allow large ensembles of neurons (100–400 units) to be recorded, which is necessary for dexterous control.

Discrete hand movements can be accurately decoded online and offline using intracortical signals. Linear discriminant analysis classifiers applied to intracortical activity can predict the grasping intention during 3D control of a robotic arm[104] or discriminate between single finger movements[105] in humans with tetraplegia. Similarly, support vector machines applied to intracortical signals could accurately classify four to six grip types offline[106] and allow switching between seven hand postures in a human BBI study[107]. Classification from intracortical recordings have also been performed using non-linear methods, specifically neural networks. Applied on a dataset from the 1990s, in which intracortical activity was recorded one electrode at a time from NHPs moving all five fingers individually[108], neural networks were reported to be particularly accurate at classifying which finger was moving[109,110], with nearly 100% success offline. Moreover, compared with a support vector machine, a deep neural network showed lower decline in accuracy and lower increase in response time when increasing the number of hand postures to classify[111].

Intracortical signals are also effective for continuous hand control. For example, an intracortical BMI reported continuous decoding of a hand grasp aperture using simple linear regression[112]. Similarly, linear control enabled modulation of the grasp aperture of a robotic hand to enable self-feeding in a patient with paralysis[3]. In this case, accuracy was improved using ridge regression to prevent overfitting[113], and in many of these linear-only approaches, part of the time history (typically 100–200 ms) of the signal is included to achieve a better fit. Extending to more DoFs, a linear decoder with one nonlinear transform at the output was used to predict EMGs of up to five hand muscles in a BBI for grasping in NHPs[114]. Intracortical signals can be used to decode not only the kinematics of the hand as a whole[115], but also of separate finger groups simultaneously[116,117], showing great potential for recovery of complete hand dexterity. The decoder applied in these studies is the Kalman filter, which was introduced in intracortical BMI studies of the 2000s and is still widely used, and which enables smoother and more controllable movements than traditional linear regression[118,119]

Box 1

Intracortical electrode technologies

Most intracortical brain–machine–interface (BMI) studies in humans and non-human primates (NHPs) have been performed using one or more Utah arrays, arrays of 100 microelectrodes on a 4 mm by 4 mm silicon substrate[216,217]. This device has remained the gold standard for decades, establishing a strong track record of long-term safety in dozens of patients[218]. However, this device causes substantial scarring in the immediate vicinity of the electrodes[219,220], resulting in a low neuronal yield per electrode, with 70% of arrays having a 40% or greater yield in the first 3 months but decreasing to 50% of arrays with such a yield at 1 year after implant[221], thereby limiting performance.

One strategy to solve this problem is to record from more channels and optimize power consumption by recording spiking activity features with lower power than the traditional spike threshold crossing rate[133,222]. There is also an emerging class of subcellular electrodes (<20 µm cross-sectional area) that cause minimal scarring and which can enable higher long-term neuronal yields than silicon arrays[215,223–225] using soft materials to match the mechanical properties of the brain[224,226–231]. However, approaches using soft materials usually require a stiff insertion shuttle to implant the electrode, which can cause damage during insertion. Subcellular electrodes can also be made out of stiff materials that do not require a shuttle such as metals[232,233], silicon carbide[234] or carbon fibre[235,236]. Even for traditional silicon probes, emerging devices have dramatically higher channel density than the Utah array; for example, the Neuropixel probe has 384 recording sites on a 10-mm-long 70 µm×20 µm cross-sectional shank, allowing for recording from hundreds of well-isolated neurons per probe[237]. Another approach is to minimize the foreign body response by coating the implanted electrodes with a neuroadhesive protein coating[238]. With hermetic feedthroughs (which allow electrical signal transmission without transfer of particles or fluids) getting smaller, miniaturized titanium ceramic packages[239] could soon be used in BMIs. Another approach to increase channel count could be achieved using 'neural dust', that is, submillimetre-sized electronic implants spread over large areas of cortex that wirelessly transmit neural data using ultrasound backscatter[240], transcutaneous radio-frequency links[241] and optical interfaces[242,243]. Unlike existing high-channel-count devices that record hundreds of intracortical signals but only from a few cortical locations, like the Neuropixel probe[237], neural dust would allow for single unit-level signals to be obtained across several centimetres of cortex. Moreover, these small electronic implants would eliminate the need for chronic dura openings or a percutaneous connector, allowing for more electrodes to be implanted with lower risk of adverse events to the patient.

From an algorithmic perspective, improved performance in continuous BMIs has emerged from refining rather than replacing linear models. For example, retraining parameters based on online data have been developed for 2D cursor movements[120,121], but can also improve accuracy when applied to decoding finger kinematics[116]. Neural networks were being explored for continuous control in the early 2000s[122], but their performance was not yet competitive with linear algorithms. After more than a decade of offline analysis of intracortical data using neural network methods, it is now clear that they can achieve a much better fit to kinematic data than their linear counterparts[123–125]. Moreover, the neural network field is constantly advancing, not only for increasing decoding accuracy but also for preventing overfitting, reducing training data and improving computation speed[126]. Neural networks are being tested for regression in online settings[127] using faster parallel computing and training paradigms[128,129] and regularization methods to prevent overfitting[130–132].

Currently, intracortical electrodes outperform ECoG in hand control in terms of accuracy, control rate and dimensionality, but at the cost of more invasive surgery and potentially less signal stability over time[103], which could affect decoder performance. There is ongoing effort to improve intracortical electrode electronics[133] and flexibility (Box 1) to increase the stability of the implants and to implement automatic, unsupervised recalibration methods to avoid the frequent collection of calibration data[134,135].

Restoring hand movements

Hand movements can be restored by applying electrical stimuli to the neuromuscular system at different distal–proximal levels using interfaces with various degrees of invasiveness. Here, we describe existing neurotechnologies and highlight their advantages and limitations — particularly as assistive devices — considering three critical aspects: the level of dexterity restored, the comfort of use and the potential for deployment (Fig. 4a). The level of restored dexterity refers to the degree that the neurotechnology allows users to perform a given motor task reliably, which, in turn, depends on selectivity, that is, the ability to recruit specific muscles, and resistance to fatigue. The latter is crucial because fatigue is generally developed more quickly with electrical stimulation than in natural movements for two main reasons. First, whereas physiologically a fused muscle contraction results from the asynchronous firing of multiple motor units at low frequency (~5 Hz), electrical stimulation activates motor units synchronously and thus requires a higher firing frequency (>20 Hz) to get a fused contraction[136,137]. Second, as opposed to natural movements, electrical stimulation tends to primarily recruit large-diameter motor fibres, which are fast-fatiguing, because they have a lower excitability threshold (a phenomenon called inverse recruitment)[138]. The comfort of use is influenced by the usability of the device, the setting-up time and the presence of visible components. Moreover, stimuli that target motoneurons usually result in activation of nearby sensory fibres, which could cause discomfort in patients with preserved sensations. Finally, the potential for deployment of the neurotechnology depends on its cost and the complexity of eventual surgical interventions.

Surface functional electrical stimulation

The most traditional technique to restore hand movements is transcutaneous functional electrical stimulation (FES), often referred to as surface FES. Conventional devices[7,8] make use of a few large electrodes (area of ~25 cm^2) positioned on the skin over the motor points of the targeted muscles and connected to an external stimulator (Fig. 4b). The electrodes, often integrated into a garment to facilitate donning and doffing, are spanned over the forearm to activate the extrinsic hand muscles, and over the thenar eminence to control the thumb. These devices generally allow recovery of two grasps, in this case, lateral and palmar.

Surface FES is non-invasive and inexpensive compared with techniques requiring surgery, and is thus easily deployable. Several devices are commercially available and used in clinical practice, such as the NESS H200 or the ReGrasp. Over the years, however, surface FES has become primarily a therapeutic intervention, referred to as functional electrical therapy (FET), instead of a tool for daily assistance[139]. Surface FES has poor selectivity because surface stimuli delivered from single large electrodes cannot selectively trigger the muscles that lie deep below the skin (for example, there is wrist interference when targeting the fingers[140]), nor are they suited to individually activating the small and closely spaced intrinsic hand muscles. Surface FES is also prone to rapid fatigue: the current source lies far from the motor fibres, so distance from the source has a negligible effect on the order of activation of motor units and the phenomenon of inverse recruitment is pronounced, causing the muscles to fatigue quickly[141]. Therefore, the dexterity provided by surface FES is limited. Moreover, the presence of a visible frame and the need to repeatedly position the electrodes and to eventually retune the parameters following donning and doffing reduce the surface FES's comfort of use. Furthermore, surface stimuli activate cutaneous sensory fibres, and the high currents required for muscle recruitment may cause discomfort in patients with intact sensation.

New surface FES devices based on multi-pad electrodes have been designed to alleviate some of these limitations[138]. With multiple pads that can be activated independently, these devices shape the electrical field to more selectively target muscles. Moreover, stimuli can be distributed over different muscle areas to promote the asynchronous activation of different motor units, thus delaying the onset of fatigue. Small pads (area of ~1.5 cm^2) can also target synergistic groups of intrinsic hand muscles, substantially enlarging the hand workspace[142] (Table 1). These new devices pave the way for more effective surface-FES-based assistance.

Implanted functional electrical stimulation

Another solution is to surgically place the electrodes intramuscularly or on the muscle epimysium (Fig. 4b), a technique known as implanted FES. The implanted FES-based Freehand system found great success among patients with SCI, counting more than 250 users[6]. The first-generation device comprised eight electrodes implanted in forearm muscles and in the thenar eminence, providing the user with lateral and palmar grasps[6]. Four additional stimulating channels were integrated into the second-generation system; two of them were implanted in intrinsic hand muscles to restore two additional grasps customized to the patient's needs[70,143] (Table 1). Besides the Freehand, few other devices based on implanted FES to elicit hand extension movements have been developed as therapeutic tools for stroke survivors[144,145].

Implanted FES can intrinsically provide greater dexterity than surface FES: selectivity is higher because, in principle, all muscles, including deep and small ones, can be targeted individually, and fatigue resistance is improved as the proximity of the current source to the motor fibres increases the impact of distance and thus reduces the influence of diameter size on the order of recruitment[146]. Moreover, the components are invisible, the electrodes are fixed and the parameters need only be retuned sporadically, thus increasing comfort

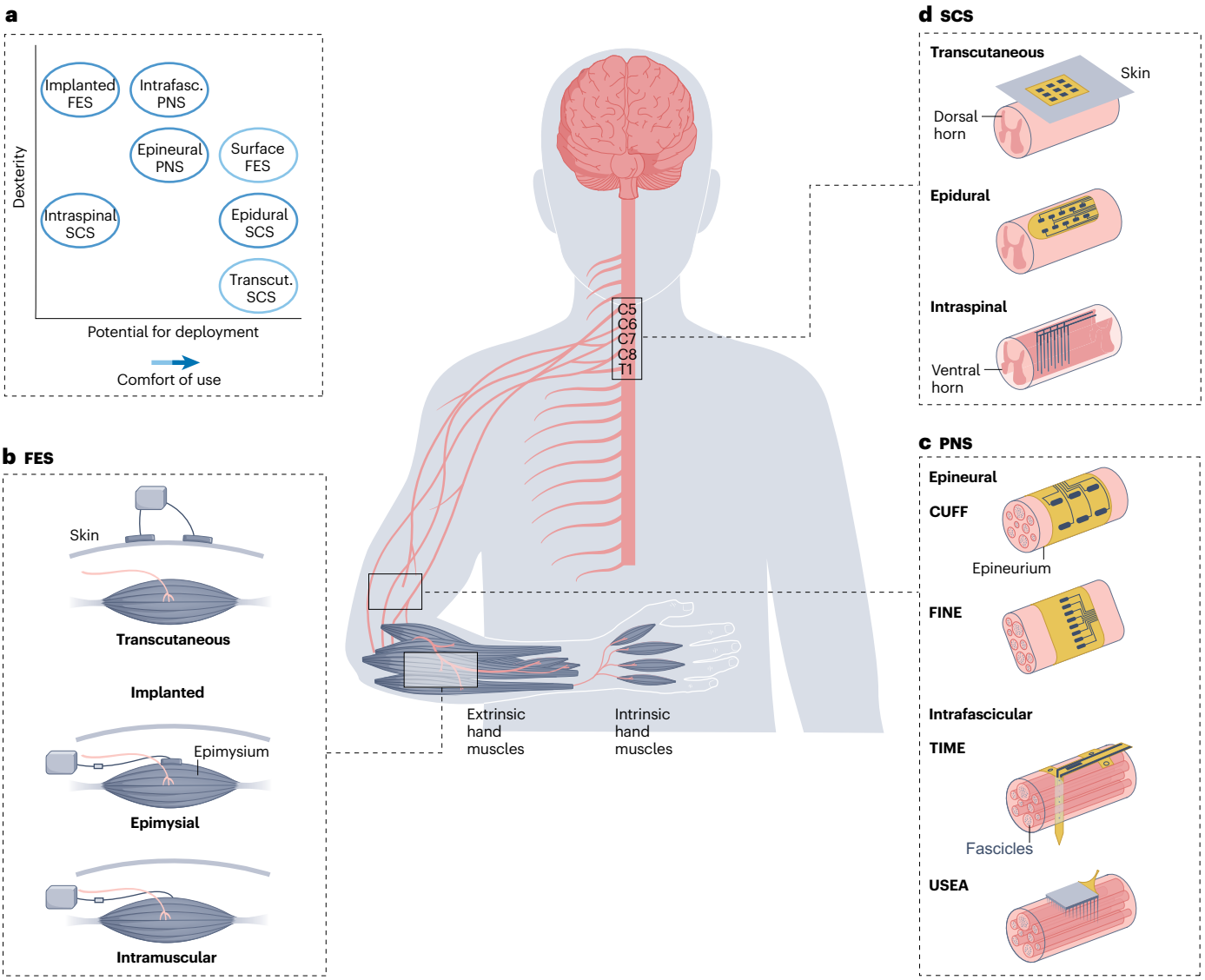


Fig. 4 | Neurotechnologies to restore hand functions. Hand functions can be restored by electrically stimulating different regions of the neuromuscular system using different interfaces. **a**, Dexterity versus potential for deployment and comfort of use for different strategies to restore hand functions. **b**, Functional electrical stimulation (FES) is performed using transcutaneous or implanted (epymisial or intramuscular) electrodes targeting the extrinsic and intrinsic hand muscles. **c**, Peripheral nerve stimulation (PNS) is applied through epineural electrodes, such as the cuff electrode and the flat interface nerve electrode (FINE), or intrafascicular electrodes, such as the transverse intrafascicular multichannel electrode (TIME) and the Utah slanted electrode array (USEA)[149], targeting the median, radial and ulnar nerves above their bifurcations. **d**, Spinal cord stimulation (SCS) is implemented using transcutaneous, epidural or intraspinal leads targeting the C5–T1 spinal nerves.

of use. Finally, stimulation through implanted electrodes has a lower intensity (around 25 mA) compared with surface electrodes (up to 120 mA)[139], reducing the risk of discomfort when nervous sensory fibres are activated. The main limitation concerns the potential for deployment: the technology is expensive and requires a long and extensive surgical intervention. Several distributed muscles must be accessed and implanted, and multiple long leads connecting the electrodes to the central unit must be routed appropriately, which becomes more complicated as functionality increases. To overcome this limitation, efforts are being made in developing wireless active implantable electrodes[147] or architectures based on distributed stimulators[148], which could considerably improve the practicality of this neurotechnology.

Peripheral nerve stimulation

An alternative approach is to stimulate the peripheral nerves above their bifurcations (Fig. 4c). Thanks to the somatotopy of the peripheral nervous system[26], multiple muscles can be triggered by a single nerve electrode that accesses motoneuron populations individually. A variety

of peripheral nerve interfaces have been designed[149] ranked in terms of their invasiveness, which in turn determines their selectivity. The main distinction is between epineural (that is, lying on the nerve surface) and intrafascicular (inserted into the nerve trunk) electrodes (Fig. 4c). To date, peripheral nerve stimulation (PNS) for selective hand muscle recruitment has been tested in NHPs with different interfaces and monopolar stimuli[150–152] and in people with tetraplegia using epineural electrodes and multipolar stimuli[153,154] (Table 1). Comparing preclinical studies, it appears that intrafascicular electrodes allow the selective recruitment of a greater number of muscles[152], probably because more central fascicles are less accessible with monopolar epineural PNS. Meanwhile, multipolar stimulation paradigms have been shown to more effectively spread the current delivered through epineural interfaces and increase selectivity[155]; thanks to this approach, up to three grasps were elicited in the subjects enrolled in clinical studies NCT03721861 and NCT04306328 (refs. 153,154) (Table 1).

Similar to implanted FES, PNS benefits from high comfort of use. Furthermore, PNS could provide the same selectivity as implanted FES, as long as all the different motoneuron populations are singularly accessed. This aspect depends on electrode geometry, implantation and nerve topography, which determine whether the electrical field can be shaped to recruit each motoneuron population without recruiting the other populations. To reduce inter-subject variability in performance and thus increase reliability, intrafascicular electrodes are inherently better than epineural because they allow targeted implantation. Insertion can be focused on penetrating relevant fascicles identified by intraoperative stimulation such that the electrode active sites are close to the motoneuron populations in each subject. Furthermore, experiments in rats demonstrate that fatigue resistance is higher when using intrafascicular electrodes than epineural electrodes owing to the closer proximity of the current source to the fibres, which weakens the phenomenon of inverse recruitment[156]. Moreover, in NHPs the force generated by intrafascicular stimuli can be sustained for the time necessary to perform functional tasks[152]. Therefore, intrafascicular PNS has the potential to provide similar dexterity to implanted FES and has a higher potential for deployment, because, at a comparable material cost, the surgery is less extensive and cabling is simplified thanks to the minimal number of implants concentrated in a single anatomical location (Fig. 4c).

Spinal cord stimulation

The last technique consists of electrically stimulating the spinal cord at the cervical level. The mechanism for generating movement is different from the neurotechnologies previously described: spinal cord stimulation (SCS) preferentially engages primary sensory afferents that run in the dorsal columns and roots, which in turn trigger motoneurons[157–160]. The cervical spine can be accessed with intraspinal, epidural or transcutaneous leads (Fig. 4d). Experiments in the early 2010s showed that intraspinal stimulation can evoke isolated reaching and grasping in NHPs[161] (Table 1). Later, epidural SCS, which became popular owing to its success in restoring locomotion[162], has been applied to reanimate the upper limb in NHPs[163], tetraplegic patients[164] and stroke survivors[165]. Tailored, laterally placed epidural electrodes can target specific dorsal roots, resulting in independent control of arm and hand muscle groups according to the rostro-caudal somatotopy of the spine[163,165] (Table 1), similar to the more invasive intraspinal stimulation. In parallel, transcutaneous SCS has shown success as a therapeutic intervention to promote upper limb recovery[166–170]. Furthermore, tuned stimuli allow some independence in the control of the arm and hand of healthy subjects with transcutaneous SCS[171,172], suggesting that further advances in surface electrode design might lead to selectivity similar to that of implanted electrodes.

Using SCS, motoneurons are mostly transynaptically activated, and their recruitment follows the natural order, so this

Table 1 | Neurotechnologies to restore hand functions

Stimulation method	Study type	Subjects	Evoked hand functions of selectively recruited hand muscles	Refs.
Surface FES	Clinical trial: NCT03199833	9 healthy subjects	Hand opening, lateral grasp, palmar grasp, power sphere grasp, tip pinch grasp and tripod grasp; not specified in how many subjects they have been obtained	142
Implanted FES	Clinical trials: NCT03898804, NCT03482310 and NCT02329652	13 patients with SCI at level C5 or C6, ASIA score A or B (15 arms implanted)	Hand opening in 15/15 arms, lateral grasp in 15/15 arms, palmar grasp in 15/15 arms, two additional customized grasps in the 13/15 arms implanted with two additional electrodes in intrinsic muscles	143
Multipolar PNS using cuff electrodes	Clinical trials: NCT03721861 and NCT04306328	10 patients with SCI at level C5, ASIA score A or B	Hand opening in 5/6 patients (1 patient did not have thumb extension), lateral grasp in 5/6 patients, palmar grasp in 5/6 patients and fixed hook grasp in 3/6 patients	153,154
Monopolar PNS using FINEs	Preclinical	6 healthy NHPs	Selectivity for 4/6 recorded muscles in 2/7 implants, selectivity for 3/6 recorded muscles in 1/7 implants and selectivity for 2/6 recorded muscles in 4/7 implants	151
Monopolar PNS using TIMEs	Preclinical	7 healthy NHPs	Hand opening, power sphere grasp, fixed hook grasp and lateral tripod grasp in 3/3 animals tested with burst stimulation	152
Monopolar PNS using USEAs	Preclinical	4 healthy NHPs	Hand opening, power sphere grasp, fixed hook grasp and inferior pincher; not specified whether they were obtained in all animals	150
Epidural SCS	Clinical trial: NCT04512690	2 stroke patients	Palmar grasp in 2/2 patients	165
Intraspinal stimulation	Preclinical	6 healthy NHPs	Palmar grasp in 6/6 animals	161

ASIA, American Spinal Cord Injury Association; FES, functional electrical stimulation; FINE, flat interface nerve electrode; NHP, non-human primate; SCS, spinal cord stimulation; SCI, spinal cord injury; TIME, transverse intrafascicular multichannel electrode; USEA, Utah slanted electrode array.

technique has – in theory – higher fatigue resistance than other neurotechnologies. In practice, rigorous quantification and comparison of fatigue is missing. In terms of comfort of use, the two implanted SCS solutions are preferred to transcutaneous SCS, which requires donning and doffing. Moreover, epidural SCS provoked non-painful sensations in the few patients treated[164,165] probably owing to intensities being in the range of 1–10 mA. Transcutaneous SCS has, instead, a higher intensity (up to 200 mA[173]) and requires parameter tuning and the use of waveforms with a 10-kHz carrier frequency[173] to avoid discomfort. The potential for deployment is high for transcutaneous SCS because it is non-invasive, but also for epidural SCS because its surgical procedure is well established (it is similar to epidural SCS for pain relief[174], performed in ~36,000 patients yearly in the USA[175]). The main limitation of SCS concerns selectivity: because the spinal motoneuron pools innervating the muscles of the hand spatially overlap[22], their singular control and the hand workspace are structurally limited with any spinal interface (Table 1). Therefore, we foresee that SCS will be used to assist reaching and coarse arm movements rather than fine hand functions.

Brain-to-body interfaces

Current solutions

In the previous sections we described the different ways of decoding the subject's intentions related to hand movements and of restoring these movements with different degrees of functionality. The two blocks can be used separately to control external devices[176–178] and to implement rehabilitation therapies for improving motor functions[139]. However, it would be of particular interest (even if more challenging) to combine them to restore the full chain of hand control, bypassing lesions and other damage to the nervous system.

The brain is the ultimate control source to target for an intuitive and generalizable hand control, which is why, since the late 2000s, after the commercial diffusion of neuroprostheses based on residual body control, much effort has been dedicated to the development of BBIs. Moreover, intracortical electrodes have been the best-performing interface for discrete classification, but more importantly, for decoding the motor intent on a continuous basis, which is fundamental to achieving natural hand control. Therefore, BBIs are increasingly being tested using intracortical decoding. Experiments with NHPs have shown the possibility of devising an intracortical BBI using implanted FES[179–181] or intrafascicular PNS[152,182] to restore wrist and hand tasks. This possibility has also been confirmed in two patients with tetraplegia using multichannel surface FES[11,107,183] or implanted FES[12]. Using the BBI, the two subjects could perform simple functional tasks, such as coffee drinking and self-feeding[12], grasp-pour-and-stir[11] and grasp-and-release of different objects[107]. Nonetheless, the question remains as to how we can take advantage of all the described modules to perform more complex tasks. In the next section, we list key enabling features that could enable BBIs to become viable clinical technologies and provide superior hand dexterity while being comfortable and safe.

Future challenges

The first challenge will be the integration of the neurotechnology blocks for motor decoding and movement restoration. Depending on the dexterity provided by the two blocks, different BBI solutions can be proposed. For a BBI that restores a set of grasps, the decoded grasp type could be simply translated into a predefined pattern of stimulation that evokes that grasp[11,107]. For a BBI that provides higher dexterity including continuous finger control, the use of a sequential decoding algorithm can instead be envisioned, for example, a two-layer hidden Markov model (HHM)[184]. The HHM would first discriminate between prehensile and non-prehensile movements and then decode either the type of grasp and its strength, or the kinematics of the fingers; predefined stimulation patterns would then trigger the grasp or fingers according to the decoded command.

Safety will be another key challenge; BBIs are a class apart from more classical assistive BMIs (that is, brain-controlled keyboard or tablet), because small errors can lead to serious consequences, which is why in prosthetic interaction with food and drink in the laboratory, researchers often do not use real water[11,185] and enact safety protocols when objects are held near the face[3,12]. Moreover, motor sequence in the real world involves posture, vision and attention changes, all of which affect neural activity even in the primary motor cortex[186]. For a system that is used in daily life, this might reveal a whole new level of safety concerns, for example, if the user attempts to drive a vehicle or operate power tools. To improve the performance and safety of future BBIs, additional elements such as closed-loop stimulation strategies and sensory feedback will be needed.

Most of the current neurotechnology modules for movement restoration are open loop, meaning that the controller works independently from the actual output state. However, muscle response can change during repeated stimulation owing to factors such as the onset of fatigue or the emergence of perturbations (for example, spinal reflexes in patients with SCI). Moreover, in SCS, the state of the limb can influence the effect of the stimuli on the produced movement[187]. Closed-loop stimulation could provide robustness and reliability while reducing the need for continuous user input[188]. Examples of closed-loop neuroprostheses for grasping have been implemented using feedback controllers that modulate the injected electrical charge in real time to maintain a target force based on EMG or force sensors[189,190]. Closed-loop methods should be standardized to have wider application. To this end, a better understanding of the relationship between stimulation parameters and motor output, the identification of stable and robust feedback signals, and the development of efficient control-policy algorithms are needed[191].

The performance and safety of BBIs would also benefit from sharing the control between the movement decoding and movement restoration blocks, that is, from providing some level of autonomy to the stimulation controller. A shared control strategy would consist of the integration of high-order commands, decoded by the subject's brain activity, and low-level commands sent by the stimulation controller[192]. Electronic skins[193] could be used for detecting relevant information about the hand's interaction with objects. This information could be used as input to the motor restoration block to perform low-level actions, such as 'economic' object securing, that is, to exert a force that is sufficient to prevent slippage but does not cause undue muscle fatigue. Alternatively, to avoid the use of external sensors that might reduce the residual sensitivity of the user, sensory information could be directly detected from the body's own sensory pathway[194]. In this context, in the late 1990s, two Freehand users were implanted with epineural electrodes to record thumb cutaneous receptor signals that the controller used to adjust the stimulation intensity to avoid object slippage[195]. Moreover, experiments in a patient with complete tetraplegia have shown that touch information can be decoded from intracortical recordings of residual, but not-perceivable sensory activity[196], uncovering another 'natural' sensing source for the implementation of shared control in various patient populations.

Finally, sensory information should be provided to the BBI user in the case of sensory impairment (for example, after a complete SCI).

Box 2

Translational considerations

Like the well-established cochlear implants[244] or deep brain stimulation[245], clinical and market translation of motor decoding and grasp restoration neurotechnologies will require substantial reduction in production, operation and maintenance costs. For example, unsupervised decoder-updating methods[135,246] will reduce the need for recalibration by external operators; optimization methods[247,248] and closed-loop algorithms[191,249] will speed up the process of parameter tuning for electrical stimulation (for motor restoration) and increase its fidelity; automatic failure detection[250] will improve maintenance; and standardization of data communication[251,252] will increase interoperability safety between different modules[251]. In general, following a modular design strategy[178] will reduce production costs, because the same module could be reused for different applications[178,253] For example, transverse intrafascicular multichannel electrodes have been used for sensory feedback restoration[254] and motor decoding[255] in amputee patients, as well as for movement restoration for people with paralysis at the preclinical stage[152]. A 'networked neuroprosthesis' system[148] allows different recording and stimulation modules to be combined to address different pathologies.

However, despite these foreseeable cost-related improvements, there are still numerous barriers to the deployment of neurotechnologies to low-resource settings and even to their broad usage in developed countries, including differences in healthcare systems dictated by financial or human resource limitations[256]. Preoperative management of implantable neurotechnologies is often a multidisciplinary effort, involving neurologists, neurosurgeons, therapists, psychologists and other clinical staff[257]. Neurosurgery could be prohibitively expensive for patients when it is not sponsored by government-based programmes or insurances[258]. Approaches based on standard surgical procedures have a better chance of deployment; epidural stimulation (proposed to restore coarse hand movements[165]) is a standard treatment for chronic pain (~36,000 patients are implanted yearly in the USA[175]) and the WIMAGINE wireless electrocorticography system shape has been adapted to a craniotomy with a 50-mm-diameter trephine[259]. The same rationale can explain the interest in an endovascular approach for brain implants, which uses interfaces implanted in brain blood vessels[260]. A strong argument can be made for the reimbursement of neurotechnologies restoring hand functions, as it could reduce the insurance costs for covered personal care. Furthermore, by increasing users' independence and mobility, these technologies could improve their productivity and employment; the employment rate of patients after SCI is currently only about 38% worldwide[261].

Sensation is a crucial component of hand motor control, therefore, supplementing vision with the information about the hand's state and its interaction with objects during movement execution is essential[197] to restore greater hand functionality. The importance of sensation was confirmed in two pilot human studies showing that the performance of a BMI[198] or a BBI[196] for grasping can substantially benefit from the integration of tactile sensory feedback. Two alternative approaches could be adopted to restore hand sensation, that is, biomimetic sensory feedback or sensory substitution[197]. On one hand, biomimetic feedback could be implemented by electrically stimulating a region of the hand sensory pathway that is not de-afferent after the neurological disease[197]. Examples include the spinal cord[199], the cuneate nucleus[200], the ventral posterolateral thalamus[201] and the somatosensory cortex[202]. On the other hand, the non-invasive electrical or mechanical stimulation of a substitutive region with intact sensation (for example, the arm[196]) could implement the sensory substitution.

Improvement of motor decoding and movement restoration blocks will also be necessary; one option is the creation of new solutions that combine existing neurotechnologies, according to the modular approach formalized in ref. 178. In this view, neuroprostheses are defined by three fundamental blocks (motor decoding, movement restoration and sensory feedback restitution) that rely on a set of neurotechnology modules performing specific functions (for example, motor decoding is defined by a recording module and a motor parameter extraction module). Following this approach, one can imagine new modules by recombining existing neurotechnologies. For example, for an effective trade-off between hand workspace dimensionality and number of implants, that is, to develop a more highly functional but also more easily deployable system, using different stimulation modules that work synergistically can be envisioned. For example, the extrinsic hand muscles could be targeted using PNS. Indeed, above the first nerve branches, motoneuron pools are well segregated or even in separated fascicles[26], and are thus easier to recruit selectively with neural interfaces. Concurrently, the intrinsic muscles, whose nerve fibres are packed more proximally[26], could be directly implanted with intramuscular leads. Moreover, synergistic use of existing motor decoding modules could help to solve a paradoxical situation: rapid improvement of the motor restoration modules allows the recovery of more DoFs than what can be decoded of the user's intentions. For example, implanted FES or PNS could restore single finger movements, but no technique can currently predict the position of the fingers that the user wants to move. Although intracortical recordings might solve this problem in the future, a short-term solution could be to exploit several existing modules: finger classification using ECoG recordings could select the finger, and decoding of residual EMGs could trigger the continuous movement of the chosen finger.

Furthermore, technological advances are needed to make BBIs clinically applicable (Box 2). So far, all the pilot BBI studies performed were based on external and bulky laboratory processing units, recording and stimulation systems, with a percutaneous connection wired to the implanted electrodes. For daily use, the system should have small and portable external components, which communicate wirelessly with the implants. Partially implantable (with wireless external power and control unit)[70,203] or fully implantable[148] neurotechnologies for motor restoration have been developed and one has been clinically approved: the partially implantable second-generation Freehand system (NCT00583804 and NCT00890916). However, only pilot studies of wireless[2,204] and portable[204] intracortical BMIs in humans have been

demonstrated, all based on the Utah array with percutaneous head-mounted pedestal connector. As for ECoG-based neurotechnologies for motor decoding, partially implantable portable devices are currently undergoing preclinical[205] or clinical (NCT02550522)[206,207] trials. Ultimately, regulatory approval requires recording and stimulation blocks to be evaluated as a complete system (Box 2).

Importantly, cases of abandoned patients — patients who have been implanted with a neurotechnology that has become non-functional and for which hardware replacement and/or software updates are not available any more — have been reported[208,209]. This problem needs to be addressed. For example, the explant process should be considered, allowing updates to future iterations of the hardware. The use of soft materials[210] could help in this regard. Others have proposed to include the costs of explantation in the cost of neuroprostheses[211,212]. Another option would be to set up a partner non-profit organization to cover for this eventuality. Technical standardization (for example, neurostimulator connectors[213]) could protect patients with implants from being abandoned, as some companies will inevitably go bankrupt and others should be able to take over patients who have already received implants. As such, neurotechnologies could follow the same standardization path as for pacemakers in the 1990s[212].

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References

1. Lebedev, M. A. & Nicolelis, M. A. L. Brain–machine interfaces: from basic science to neuroprostheses and neurorehabilitation. *Physiol. Rev.* **97**, 767–837 (2017).
2. Simeral, J. D. et al. Home use of a percutaneous wireless intracortical brain-computer interface by individuals with tetraplegia. *IEEE Trans. Biomed. Eng.* **68**, 2313–2325 (2021).
3. Collinger, J. L. et al. High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet* **381**, 557–564 (2013).
4. Handelman, D. A. et al. Shared control of bimanual robotic limbs with a brain–machine interface for self-feeding. *Front. Neurorobot.* **16**, 918001 (2022).
5. Collinger, J. L. et al. Functional priorities, assistive technology, and brain–computer interfaces after spinal cord injury. *J. Rehabil. Res. Dev.* **50**, 145–160 (2013).
6. Peckham, P. H. et al. Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: a multicenter study. *Arch. Phys. Med. Rehabil.* **82**, 1380–1388 (2001).
7. IJzerman, M. et al. The NESS Handmaster orthosis: restoration of hand function in C5 and stroke patients by means of electrical stimulation. *J. Rehabil. Sci.* **9**, 86–89 (1996).
8. Prochazka, A., Gauthier, M., Wieler, M. & Kenwell, Z. The Bionic Glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. *Arch. Phys. Med. Rehabil.* **78**, 608–614 (1997).
9. Biasiucci, A. et al. Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke. *Nat. Commun.* **9**, 2421 (2018).
10. Soekadar, S. R., Birbaumer, N., Slutzky, M. W. & Cohen, L. G. Brain–machine interfaces in neurorehabilitation of stroke. *Neurobiol. Dis.* **83**, 172–179 (2015).
11. Bouton, C. E. et al. Restoring cortical control of functional movement in a human with quadriplegia. *Nature* **533**, 247–250 (2016).
12. Ajiboye, A. B. et al. Restoration of reaching and grasping in a person with tetraplegia through brain-controlled muscle stimulation: a proof-of-concept demonstration. *Lancet* **389**, 1821–1830 (2017).
This article reports the intracortical control of implanted muscle stimulation, which restores grasping in a person with tetraplegia.
13. ElKoura, G. & Singh, K. Handrix: animating the human hand. *Proc. 2003 ACM SIGGRAPH/Eurographics Symp. on Computer Animation* 110–119 (ACM, 2003).
14. Martin, J. R., Zatsiorsky, V. M. & Latash, M. L. Multi-finger interaction during involuntary and voluntary single finger force changes. *Exp. Brain Res.* **208**, 423–435 (2011).
15. Nanayakkara, V. K. et al. The role of morphology of the thumb in anthropomorphic grasping: a review. *Front. Mech. Eng.* https://doi.org/10.3389/fmech.2017.00005 (2022).
16. Napier, J. R. The prehensile movements of the human hand. *J. Bone Jt Surgery Br.* **38**, 902–913 (1956).
17. Kilbreath, S. L. & Heard, R. C. Frequency of hand use in healthy older persons. *Aust. J. Physiother.* **51**, 119–122 (2005).
18. Gracia-Ibáñez, V., Sancho-Bru, J. L. & Vergara, M. Relevance of grasp types to assess functionality for personal autonomy. *J. Hand Ther.* **31**, 102–110 (2018).
19. Feix, T., Romero, J., Schmiedmayer, H., Dollar, A. M. & Kragic, D. The GRASP taxonomy of human grasp types. *IEEE Trans. Human Machine Syst.* **46**, 66–77 (2016).
20. Bullock, I. M., Zheng, J. Z., De La Rosa, S., Guertler, C. & Dollar, A. M. Grasp frequency and usage in daily household and machine shop tasks. *IEEE Trans. Haptics* **6**, 296–308 (2013).
21. Vergara, M., Sancho-Bru, J. L., Gracia-Ibáñez, V. & Pérez-González, A. An introductory study of common grasps used by adults during performance of activities of daily living. *J. Hand Ther.* **27**, 225–234 (2014).
22. Schirmer, C. M. et al. Heuristic map of myotomal innervation in humans using direct intraoperative nerve root stimulation: clinical article. *J. Neurosurg. Spine* **15**, 64–70 (2011).
23. Bollini, C. A. & Wikinski, J. A. Anatomical review of the brachial plexus. *Tech. Reg. Anesth. Pain Manag.* **10**, 69–78 (2006).
24. Jabaley, M. E., Wallace, W. H. & Heckler, F. R. Internal topography of major nerves of the forearm and hand: a current view. *J. Hand Surg. Am.* **5**, 1–18 (1980).
25. Boles, C. A., Kannam, S. & Cardwell, A. B. The forearm: anatomy of muscle compartments and nerves. *AJR Am. J. Roentgenol.* **174**, 151–159 (2000).
26. Delgado-Martínez, I., Badia, J., Pascual-Font, A., Rodríguez-Baeza, A. & Navarro, X. Fascicular topography of the human median nerve for neuroprosthetic surgery. *Front. Neurosci.* **10**, 286 (2016).
27. Porter, R. & Lemon, R. *Corticospinal Function and Voluntary Movement* (Oxford Univ. Press, 1995).
28. Lemon, R. N. An enduring map of the motor cortex. *Exp. Physiol.* **93**, 798–802 (2008).
29. Strick, P. L., Dum, R. P. & Rathelot, J.-A. The cortical motor areas and the emergence of motor skills: a neuroanatomical perspective. *Annu. Rev. Neurosci.* **44**, 425–447 (2021).
30. Witham, C. L., Fisher, K. M., Edgley, S. A. & Baker, S. N. Corticospinal inputs to primate motoneurons innervating the forelimb from two divisions of primary motor cortex and area 3a. *J. Neurosci.* **36**, 2605–2616 (2016).
31. Rathelot, J.-A. & Strick, P. L. Muscle representation in the macaque motor cortex: an anatomical perspective. *Proc. Natl Acad. Sci. USA* **103**, 8257–8262 (2006).
32. Roux, F.-E., Niare, M., Charni, S., Giussani, C. & Durand, J.-B. Functional architecture of the motor homunculus detected by electrostimulation. *J. Physiol.* **598**, 5487–5504 (2020).
33. Sanes, J. N., Donoghue, J. P., Thangaraj, V., Edelman, R. R. & Warach, S. Shared neural substrates controlling hand movements in human motor cortex. *Science* **268**, 1775–1777 (1995).
34. Beisteiner, R. et al. Finger somatotopy in human motor cortex. *Neuroimage* **13**, 1016–1026 (2001).
35. Dechent, P. & Frahm, J. Functional somatotopy of finger representations in human primary motor cortex. *Hum. Brain Mapp.* **18**, 272–283 (2003).
36. Bernshteĭn, N. A. *The Co-ordination and Regulation of Movements* (Pergamon Press, 1967).
37. Bizzi, E. & Cheung, V. C. The neural origin of muscle synergies. *Front. Comput. Neurosci.* **7**, 51 (2013).
38. Santello, M. & Soechting, J. F. Force synergies for multifingered grasping. *Exp. Brain Res.* **133**, 457–467 (2000).
39. Mason, C. R., Gomez, J. E. & Ebner, T. J. Hand synergies during reach-to-grasp. *J. Neurophysiol.* **86**, 2896–2910 (2001).
40. Thakur, P., Bastian, A. & Hsiao, S. Multidigit movement synergies of the human hand in an unconstrained haptic exploration task. *J. Neurosci.* **28**, 1271–1281 (2008).
41. Weiss, E. J. & Flanders, M. Muscular and postural synergies of the human hand. *J. Neurophysiol.* **92**, 523–535 (2004).
42. Bicchi, A., Gabiccini, M. & Santello, M. Modelling natural and artificial hands with synergies. *Phil. Trans. R. Soc. Lond. B* **366**, 3153–3161 (2011).
43. Tresch, M. C. & Jarc, A. The case for and against muscle synergies. *Curr. Opin. Neurobiol.* **19**, 601–607 (2009).
44. Tresch, M. C., Saltiel, P. & Bizzi, E. The construction of movement by the spinal cord. *Nat. Neurosci.* **2**, 162–167 (1999).
45. Tresch, M. C. & Bizzi, E. Responses to spinal microstimulation in the chronically spinalized rat and their relationship to spinal systems activated by low threshold cutaneous stimulation. *Exp. Brain Res.* **129**, 401–416 (1999).
46. Lemay, M. A. & Grill, W. M. Modularity of motor output evoked by intraspinal microstimulation in cats. *J. Neurophysiol.* **91**, 502–514 (2004).
47. Overduin, S. A., d'Avella, A., Carmena, J. M. & Bizzi, E. Microstimulation activates a handful of muscle synergies. *Neuron* **76**, 1071–1077 (2012).
48. Marshall, N. J. et al. Flexible neural control of motor units. *Nat. Neurosci.* **25**, 1492–1504 (2022).
49. Bizzi, E., Mussa-Ivaldi, F. A. & Giszter, S. Computations underlying the execution of movement: a biological perspective. *Science* **253**, 287–291 (1991).
50. Kalaska, J. F. From intention to action: motor cortex and the control of reaching movements. *Adv. Exp. Med. Biol.* **629**, 139–178 (2009).
51. Georgopoulos, A. P., Kalaska, J. F., Caminiti, R. & Massey, J. T. On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J. Neurosci.* **2**, 1527–1537 (1982).
52. Moran, D. W. & Schwartz, A. B. Motor cortical representation of speed and direction during reaching. *J. Neurophysiol.* **82**, 2676–2692 (1999).
53. Townsend, B. R., Paninski, L. & Lemon, R. N. Linear encoding of muscle activity in primary motor cortex and cerebellum. *J. Neurophysiol.* **96**, 2578–2592 (2006).
54. Churchland, M. M. & Shenoy, K. V. Temporal complexity and heterogeneity of single-neuron activity in premotor and motor cortex. *J. Neurophysiol.* **97**, 4235–4257 (2007).
55. Graziano, M. The organization of behavioral repertoire in motor cortex. *Annu. Rev. Neurosci.* **29**, 105–134 (2006).
56. Scott, S. H., Gribble, P. L., Graham, K. M. & Cabel, D. W. Dissociation between hand motion and population vectors from neural activity in motor cortex. *Nature* **413**, 161–165 (2001).
57. Scott, S. H. Inconvenient truths about neural processing in primary motor cortex. *J. Physiol.* **586**, 1217–1224 (2008).

58. Nicolelis, M. A. L. et al. Chronic, multisite, multielectrode recordings in macaque monkeys. *Proc. Natl Acad. Sci. USA* **100**, 11041–11046 (2003).
59. Churchland, M. M. et al. Neural population dynamics during reaching. *Nature* **487**, 51–56 (2012).
This study describes the neural population activity in motor cortex with a strong oscillatory component.
60. Kalaska, J. F. Emerging ideas and tools to study the emergent properties of the cortical neural circuits for voluntary motor control in non-human primates. *F1000Res* https://doi.org/10.12688/f1000research.17161.1 (2019).
61. Cunningham, J. P. & Yu, B. M. Dimensionality reduction for large-scale neural recordings. *Nat. Neurosci.* **17**, 1500–1509 (2014).
62. Kaufman, M. T., Churchland, M. M., Ryu, S. I. & Shenoy, K. V. Cortical activity in the null space: permitting preparation without movement. *Nat. Neurosci.* **17**, 440–448 (2014).
63. Sadtler, P. T. et al. Neural constraints on learning. *Nature* **512**, 423–426 (2014).
64. Golub, M. D. et al. Learning by neural reassociation. *Nat. Neurosci.* **21**, 607–616 (2018).
65. Oby, E. R. et al. New neural activity patterns emerge with long-term learning. *Proc. Natl Acad. Sci. USA* **116**, 15210–15215 (2019).
66. Russo, A. A. et al. Motor cortex embeds muscle-like commands in an untangled population response. *Neuron* **97**, 953–966.e8 (2018).
67. Shenoy, K. V., Sahani, M. & Churchland, M. M. Cortical control of arm movements: a dynamical systems perspective. *Annu. Rev. Neurosci.* **36**, 337–359 (2013).
68. Suresh, A. K. et al. Neural population dynamics in motor cortex are different for reach and grasp. *eLife* **9**, e58848 (2020).
69. Snoek, G. J., IJzerman, M. J., in't Groen, F. A., Stoffers, T. S. & Zilvold, G. Use of the NESS Handmaster to restore handfunction in tetraplegia: clinical experiences in ten patients. *Spinal Cord* **38**, 244–249 (2000).
70. Kilgore, K. L. et al. An implanted upper-extremity neuroprosthesis using myoelectric control. *J. Hand Surg.* **33**, 539–550 (2008).
This article reports the clinical validation of the second-generation Freehand system, a neuroprosthesis to restore grasping based on implanted muscle stimulation and myoelectric control.
71. Hart, R. L., Kilgore, K. L. & Peckham, P. H. A comparison between control methods for implanted FES hand-grasp systems. *IEEE Trans. Rehabil. Eng.* **6**, 208–218 (1998).
72. Liu, J. & Zhou, P. A novel myoelectric pattern recognition strategy for hand function restoration after incomplete cervical spinal cord injury. *IEEE Trans. Neural Syst. Rehabil. Eng.* **21**, 96–103 (2013).
73. Lu, Z., Stampas, A., Francisco, G. E. & Zhou, P. Offline and online myoelectric pattern recognition analysis and real-time control of a robotic hand after spinal cord injury. *J. Neural Eng.* **16**, 036018 (2019).
74. Sherwood, A. M., Dimitrijevic, M. R. & McKay, W. B. Evidence of subclinical brain influence in clinically complete spinal cord injury: discomplete SCI. *J. Neurol. Sci.* **110**, 90–98 (1992).
75. Heald, E., Hart, R., Kilgore, K. & Peckham, P. H. Characterization of volitional electromyographic signals in the lower extremity after motor complete spinal cord injury. *Neurorehabil. Neural Repair* **31**, 583–591 (2017).
76. Ting, J. E. et al. Sensing and decoding the neural drive to paralyzed muscles during attempted movements of a person with tetraplegia using a sleeve array. *J. Neurophysiol.* **126**, 2104–2118 (2021).
77. Osuagwu, B. A. C., Whicher, E. & Shirley, R. Active proportional electromyogram controlled functional electrical stimulation system. *Sci. Rep.* **10**, 21242 (2020).
78. McFarland, D. J. The advantages of the surface Laplacian in brain–computer interface research. *Int. J. Psychophysiol.* **97**, 271–276 (2015).
79. Randazzo, L., Iturrate, I., Chavarriaga, R., Leeb, R. & Del Millan, J. R. Detecting intention to grasp during reaching movements from EEG. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* **2015**, 1115–1118 (2015).
80. Jochumsen, M., Niazi, I. K., Dremstrup, K. & Kamavuako, E. N. Detecting and classifying three different hand movement types through electroencephalography recordings for neurorehabilitation. *Med. Biol. Eng. Comput.* **54**, 1491–1501 (2016).
81. Schwarz, A., Ofner, P., Pereira, J., Sburlea, A. I. & Müller-Putz, G. R. Decoding natural reach-and-grasp actions from human EEG. *J. Neural Eng.* **15**, 016005 (2018).
This article describes the decoding of reach-and-grasp movements from EEG.
82. Iturrate, I. et al. Human EEG reveals distinct neural correlates of power and precision grasping types. *NeuroImage* **181**, 635–644 (2018).
83. Müller-Putz, G. R. et al. Applying intuitive EEG-controlled grasp neuroprostheses in individuals with spinal cord injury: preliminary results from the MoreGrasp clinical feasibility study. In *2019 41st Ann. Int. Conf. IEEE Engineering in Medicine and Biology Society (EMBC)* 5949–5955 (IEEE, 2019).
84. Ofner, P. et al. Attempted arm and hand movements can be decoded from low-frequency EEG from persons with spinal cord injury. *Sci. Rep.* **9**, 7134 (2019).
85. Sburlea, A. I., Wilding, M. & Müller-Putz, G. R. Disentangling human grasping type from the object's intrinsic properties using low-frequency EEG signals. *Neuroimage Rep.* **1**, 100012 (2021).
86. Gant, K. et al. EEG-controlled functional electrical stimulation for hand opening and closing in chronic complete cervical spinal cord injury. *Biomed. Phys. Eng. Express* **4**, 065005 (2018).
87. AL-Quraishi, M. S., Elamvazuthi, I., Daud, S. A., Parasuraman, S. & Borboni, A. EEG-based control for upper and lower limb exoskeletons and prostheses: a systematic review. *Sensors* **18**, 3342 (2018).
88. Ramos-Murguialday, A. et al. Brain–machine interface in chronic stroke rehabilitation: a controlled study. *Ann. Neurol.* **74**, 100–108 (2013).
89. Fugl-Meyer, A. R., Jääskö, L., Leyman, I., Olsson, S. & Steglind, S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scand. J. Rehabil. Med.* **7**, 13–31 (1975).
90. Ethier, C., Gallego, J. & Miller, L. Brain-controlled neuromuscular stimulation to drive neural plasticity and functional recovery. *Curr. Opin. Neurobiol.* **33**, 95–102 (2015).
91. Mrachacz-Kersting, N., Kristensen, S. R., Niazi, I. K. & Farina, D. Precise temporal association between cortical potentials evoked by motor imagination and afference induces cortical plasticity. *J. Physiol.* **590**, 1669–1682 (2012).
92. McFarland, D. J. & Wolpaw, J. R. EEG-based brain–computer interfaces. *Curr. Opin. Biomed. Eng.* **4**, 194–200 (2017).
93. Buzsáki, G. & Wang, X.-J. Mechanisms of gamma oscillations. *Annu. Rev. Neurosci.* **35**, 203–225 (2012).
94. Miller, K. J., Zanos, S., Fetz, E. E., den Nijs, M. & Ojemann, J. G. Decoupling the cortical power spectrum reveals real-time representation of individual finger movements in humans. *J. Neurosci.* **29**, 3132–3137 (2009).
95. Pistohl, T., Schulze-Bonhage, A., Aertsen, A., Mehring, C. & Ball, T. Decoding natural grasp types from human ECoG. *Neuroimage* **59**, 248–260 (2012).
96. Chestek, C. A. et al. Hand posture classification using electrocorticography signals in the gamma band over human sensorimotor brain areas. *J. Neural Eng.* **10**, 026002 (2013).
This article describes the decoding of multiple hand postures from ECoG.
97. Pistohl, T. et al. Grasp detection from human ECoG during natural reach-to-grasp movements. *PLoS ONE* **8**, e54658 (2013).
98. Hotson, G. et al. Individual finger control of a modular prosthetic limb using high-density electrocorticography in a human subject. *J. Neural Eng.* **13**, 026017–026017 (2016).
99. Yanagisawa, T. et al. Real-time control of a prosthetic hand using human electrocorticography signals. *J. Neurosurg.* **114**, 1715–1722 (2011).
100. Flint, R. D., Rosenow, J. M., Tate, M. C. & Slutzky, M. W. Continuous decoding of human grasp kinematics using epidural and subdural signals. *J. Neural Eng.* **14**, 016005 (2017).
101. Flint, R. D. et al. The representation of finger movement and force in human motor and premotor cortices. *eNeuro* https://doi.org/10.1523/ENEURO.0063-20.2020 (2020).
102. Xie, Z., Schwartz, O. & Prasad, A. Decoding of finger trajectory from ECoG using deep learning. *J. Neural Eng.* **15**, 036009 (2018).
103. Schalk, G. & Leuthardt, E. C. Brain–computer interfaces using electrocorticographic signals. *IEEE Rev. Biomed. Eng.* **4**, 140–154 (2011).
104. Hochberg, L. R. et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature* **485**, 372–375 (2012).
105. Jorge, A., Royston, D. A., Tyler-Kabara, E. C., Boninger, M. L. & Collinger, J. L. Classification of individual finger movements using intracortical recordings in human motor cortex. *Neurosurgery* **87**, 630–638 (2020).
106. Carpaneto, J. et al. Continuous decoding of grasping tasks for a prospective implantable cortical neuroprosthesis. *J. Neuroeng. Rehabil.* **9**, 84 (2012).
107. Colachis, S. C. I. et al. Dexterous control of seven functional hand movements using cortically-controlled transcutaneous muscle stimulation in a person with tetraplegia. *Front. Neurosci.* **12**, 208 (2018).
108. Schieber, M. H. & Hibbard, L. S. How somatotopic is the motor cortex hand area? *Science* **261**, 489–492 (1993).
109. Hamed, S. B., Schieber, M. H. & Pouget, A. Decoding M1 neurons during multiple finger movements. *J. Neurophysiol.* **98**, 327–333 (2007).
110. Aggarwal, V. et al. Asynchronous decoding of dexterous finger movements using M1 neurons. *IEEE Trans. Neural Syst. Rehabil. Eng.* **16**, 3–14 (2008).
111. Skomrock, N. D. et al. A characterization of brain–computer interface performance trade-offs using support vector machines and deep neural networks to decode movement intent. *Front. Neurosci.* **12**, 763 (2018).
112. Carmena, J. M. et al. Learning to control a brain–machine interface for reaching and grasping by primates. *PLoS Biol.* **1**, e42 (2003).
113. Wodlinger, B. et al. Ten-dimensional anthropomorphic arm control in a human brain–machine interface: difficulties, solutions, and limitations. *J. Neural Eng.* **12**, 016011 (2014).
114. Ethier, C., Oby, E. R., Bauman, M. J. & Miller, L. E. Restoration of grasp following paralysis through brain-controlled stimulation of muscles. *Nature* **485**, 7398 (2012).
115. Irwin, Z. T. et al. Neural control of finger movement via intracortical brain–machine interface. *J. Neural Eng.* **14**, 066004 (2017).
116. Vaskov, A. K. et al. Cortical decoding of individual finger group motions using ReFIT Kalman Filter. *Front. Neurosci.* **12**, 751 (2018).
117. Nason, S. R. et al. Real-time linear prediction of simultaneous and independent movements of two finger groups using an intracortical brain–machine interface. *Neuron* **109**, 3164–3177.e8 (2021).
This article presents the decoding kinematics of multiple finger groups from intracortical signals.
118. Wu, W., Shaikhouni, A., Donoghue, J. R. & Black, M. J. Closed-loop neural control of cursor motion using a Kalman filter. *26th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* **2**, 4126–4129 (2004).
119. Kim, S.-P., Simeral, J. D., Hochberg, L. R., Donoghue, J. P. & Black, M. J. Neural control of computer cursor velocity by decoding motor cortical spiking activity in humans with tetraplegia. *J. Neural Eng.* **5**, 455–476 (2008).
120. Gilja, V. et al. A high-performance neural prosthesis enabled by control algorithm design. *Nat. Neurosci.* **15**, 1752–1757 (2012).
121. Orsborn, A. L. et al. Closed-loop decoder adaptation shapes neural plasticity for skillful neuroprosthetic control. *Neuron* **82**, 1380–1393 (2014).

122. Sanchez, J. C., Principe, J. C., Carmena, J. M., Lebedev, M. A. & Nicolelis, M. A. L. Simultaneus prediction of four kinematic variables for a brain–machine interface using a single recurrent neural network. *26th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* **2**, 5321–5324 (2004).
123. Pandarinath, C. et al. Inferring single-trial neural population dynamics using sequential auto-encoders. *Nat. Methods* **15**, 805–815 (2018).
124. Allahgholizadeh Haghi, B. et al. Deep multi-state dynamic recurrent neural networks operating on wavelet based neural features for robust brain machine interfaces. *Proc. NeurIPS 2019* https://proceedings.neurips.cc/paper_files/paper/2019/file/1e0feeaff84a19bf3936e693311fa66d-Paper.pdf (2019).
125. Glaser, J. I. et al. Machine learning for neural decoding. *eNeuro* https://doi.org/10.1523/ENEURO.0506-19.2020 (2020).
126. Gu, J. et al. Recent advances in convolutional neural networks. *Pattern Recogn.* **77**, 354–377 (2018).
127. Willsey, M. S. et al. Real-time brain–machine interface achieves high-velocity prosthetic finger movements using a biologically-inspired neural network decoder. *Nat. Commun.* **13**, 6899 (2022).
128. Mehrotra, P., Dasgupta, S., Robertson, S. & Nuyujukian, P. An open-source realtime computational platform (short WIP paper). *ACM SIGPLAN Not.* **53**, 109–112 (2018).
129. Santurkar, S., Tsipras, D., Ilyas, A. & Madry, A. How does batch normalization help optimization? In *Proc. NeurIPS 2018* (2018).
130. Srivastava, N., Hinton, G., Krizhevsky, A., Sutskever, I. & Salakhutdinov, R. Dropout: a simple way to prevent neural networks from overfitting. *J. Mach. Learn. Res.* **15**, 1929–1958 (2014).
131. Ioffe, S. & Szegedy, C. *Batch Normalization: Accelerating Deep Network Training By Reducing Internal Covariate Shift* (MLR Press, 2015).
132. Li, Y., Wei, C. & Ma, T. Towards explaining the regularization effect of initial large learning rate in training neural networks. *Proc. NeurIPS 2019* https://proceedings.neurips.cc/paper/2019/file/bce9abf229ffd7e570818476ee5d7dde-Paper.pdf (2020).
133. Even-Chen, N. et al. Power-saving design opportunities for wireless intracortical brain–computer interfaces. *Nat. Biomed. Eng.* **4**, 984–996 (2020).
134. Bishop, W. et al. Self-recalibrating classifiers for intracortical brain–computer interfaces. *J. Neural Eng.* **11**, 026001 (2014).
135. Jarosiewicz, B. et al. Virtual typing by people with tetraplegia using a self-calibrating intracortical brain–computer interface. *Sci. Transl. Med.* **7**, 313ra179 (2015).
136. Bickel, C. S., Gregory, C. M. & Dean, J. C. Motor unit recruitment during neuromuscular electrical stimulation: a critical appraisal. *Eur. J. Appl. Physiol.* **111**, 2399–2407 (2011).
137. Malešević, N. M. et al. A multi-pad electrode based functional electrical stimulation system for restoration of grasp. *J. Neuroeng. Rehabil.* **9**, 66 (2012).
138. Koutsou, A. D., Moreno, J. C., Del Ama, A. J., Rocon, E. & Pons, J. L. Advances in selective activation of muscles for non-invasive motor neuroprostheses. *J. Neuroeng. Rehabil.* **13**, 56 (2016).
This article reports the use of multi-pad electrodes improve selectivity and resistance to fatigue of transcutaneous FES.
139. Marquez-Chin, C. & Popovic, M. R. Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: a review. *Biomed. Eng. Online* **19**, 34 (2020).
140. Popović-Maneski, L. et al. Multi-pad electrode for effective grasping: design. *IEEE Trans. Neural Syst. Rehabil. Eng.* **21**, 648–654 (2013).
141. Vromans, M. & Faghri, P. D. Functional electrical stimulation-induced muscular fatigue: effect of fiber composition and stimulation frequency on rate of fatigue development. *J. Electromyogr. Kinesiol.* **38**, 67–72 (2018).
142. Crema, A. et al. A wearable multi-site system for NMES-based hand function restoration. *IEEE Trans. Neural Syst. Rehabil. Eng.* **26**, 428–440 (2018).
143. Kilgore, K. L. et al. Evolution of neuroprosthetic approaches to restoration of upper extremity function in spinal cord injury. *Top. Spinal Cord. Inj. Rehabil.* **24**, 252–264 (2018).
144. Merrill, D. R., Davis, R., Turk, R. & Burridge, J. H. A personalized sensor-controlled microstimulator system for arm rehabilitation poststroke. Part 1: System architecture. *Neuromodulation* **14**, 72–79 (2011).
145. Spensley, J. STIMuGRIP® a new hand control implant. In *2007 29th Ann. Int. Conf. IEEE Engineering in Medicine and Biology Society* 513 (IEEE, 2007).
146. Singh, K., Richmond, F. J. R. & Loeb, G. E. Recruitment properties of intramuscular and nerve-trunk stimulating electrodes. *IEEE Trans. Rehabil. Eng.* **8**, 276–285 (2000).
147. Becerra-Fajardo, L. et al. Floating EMG sensors and stimulators wirelessly powered and operated by volume conduction for networked neuroprosthetics. *J. NeuroEng. Rehabil.* **19**, 57 (2022).
148. Makowski, N. S. et al. Design and testing of stimulation and myoelectric recording modules in an implanted distributed neuroprosthetic system. *IEEE Trans. Biomed. Circuits Syst.* **15**, 281–293 (2021).
149. Yoshida, K., Bertram, M. J., Hunter Cox, T. G. & Riso, R. R. Peripheral nerve recording electrodes and techniques. In *Neuroprosthetics* Vol. 8 (eds Horch, K. W. & Dhillon, G. S.) 377–466 (World Scientific, 2016).
150. Ledbetter, N. M. et al. Intrafascicular stimulation of monkey arm nerves evokes coordinated grasp and sensory responses. *J. Neurophysiol.* **109**, 580–590 (2013).
151. Brill, N. A. et al. Evaluation of high-density, multi-contact nerve cuffs for activation of grasp muscles in monkeys. *J. Neural Eng.* **15**, 036003 (2018).
152. Badi, M. et al. Intrafascicular peripheral nerve stimulation produces fine functional hand movements in primates. *Sci. Transl. Med.* 13, eabg6463 (2021).
This article reports intrafascicular stimulation of peripheral nerves, which evokes multiple fine hand movements in NHPs.
153. Tigra, W. et al. Selective neural electrical stimulation restores hand and forearm movements in individuals with complete tetraplegia. *J. Neuroeng. Rehabil.* **17**, 66 (2020).
154. Azevedo-Coste, C. et al. Activating effective functional hand movements in individuals with complete tetraplegia through neural stimulation. *Sci. Rep.* **12**, 16189 (2022).
155. Dali, M. et al. Model based optimal multipolar stimulation without a priori knowledge of nerve structure: application to vagus nerve stimulation. *J. Neural Eng.* **15**, 046018 (2018).
156. Veltink, P. H., van Alsté, J. A. & Boom, H. B. Multielectrode intrafascicular and extraneural stimulation. *Med. Biol. Eng. Comput.* **27**, 19–24 (1989).
157. Gaunt, R. A., Prochazka, A., Mushahwar, V. K., Guevremont, L. & Ellaway, P. H. Intraspinal microstimulation excites multisegmental sensory afferents at lower stimulus levels than local alpha-motoneuron responses. *J. Neurophysiol.* **96**, 2995–3005 (2006).
158. Capogrosso, M. et al. A computational model for epidural electrical stimulation of spinal sensorimotor circuits. *J. Neurosci.* **33**, 19326–19340 (2013).
159. Hofstoetter, U. S., Freundl, B., Binder, H. & Minassian, K. Common neural structures activated by epidural and transcutaneous lumbar spinal cord stimulation: elicitation of posterior root-muscle reflexes. *PLoS One* **13**, e0192013 (2018).
160. de Freitas, R. M., Capogrosso, M., Nomura, T. & Milosevic, M. Preferential activation of proprioceptive and cutaneous sensory fibers compared to motor fibers during cervical transcutaneous spinal cord stimulation: a computational study. *J. Neural Eng.* https://doi.org/10.1088/1741-2552/ac6a7c (2022).
161. Zimmermann, J. B., Seki, K. & Jackson, A. Reanimating the arm and hand with intraspinal microstimulation. *J. Neural Eng.* **8**, 054001 (2011).
162. Wagner, F. B. et al. Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature* **563**, 65–71 (2018).
163. Barra, B. et al. Epidural electrical stimulation of the cervical dorsal roots restores voluntary upper limb control in paralyzed monkeys. *Nat. Neurosci.* **25**, 924–934 (2022).
This article shows that epidural electrical stimulation of the cervical spinal cord restores reaching and grasping in NHPs.
164. Lu, D. C. et al. Engaging cervical spinal cord networks to reenable volitional control of hand function in tetraplegic patients. *Neurorehabil. Neural Repair.* **30**, 951–962 (2016).
165. Powell, M. P. et al. Epidural stimulation of the of the cervical spinal cord for post-stroke upper-limb paresis. *Nat. Med.* **29**, 689–699 (2023).
166. Gad, P. et al. Non-Invasive activation of cervical spinal networks after severe paralysis. *J. Neurotrauma* **35**, 2145–2158 (2018).
167. Zhang, F. et al. Cervical spinal cord transcutaneous stimulation improves upper extremity and hand function in people with complete tetraplegia: a case study. *IEEE Trans. Neural Syst. Rehabil. Eng.* **28**, 3167–3174 (2020).
168. Inanici, F., Brighton, L. N., Samejima, S., Hofstetter, C. P. & Moritz, C. T. Transcutaneous spinal cord stimulation restores hand and arm function after spinal cord injury. *IEEE Trans. Neural Syst. Rehabil. Eng.* **29**, 310–319 (2021).
169. Chandrasekaran, S. et al. Targeted transcutaneous cervical spinal cord stimulation promotes upper limb recovery in spinal cord and peripheral nerve injury [Abstract]. *Brain Stimul.* **16**, P373 (2023).
170. Huang, R. et al. Minimal handgrip force is needed for transcutaneous electrical stimulation to improve hand functions of patients with severe spinal cord injury. *Sci. Rep.* **12**, 7733 (2022).
171. de Freitas, R. M. et al. Selectivity and excitability of upper-limb muscle activation during cervical transcutaneous spinal cord stimulation in humans. *J. Appl. Physiol.* **131**, 746–759 (2021).
172. Zheng, Y. & Hu, X. Elicited upper limb motions through transcutaneous cervical spinal cord stimulation. *J. Neural Eng.* **17**, 036001 (2020).
173. Gerasimenko, Y. et al. Transcutaneous electrical spinal-cord stimulation in humans. *Ann. Phys. Rehabil. Med.* **58**, 225–231 (2015).
174. Pollard, E. M. et al. The effect of spinal cord stimulation on pain medication reduction in intractable spine and limb pain: a systematic review of randomized controlled trials and meta-analysis. *J. Pain. Res.* **12**, 1311–1324 (2019).
175. Manchikanti, L. et al. Spinal cord stimulation trends of utilization and expenditures in fee-for-service (FFS) Medicare population from 2009 to 2018. *Pain Physician* **24**, 293–308 (2021).
176. Thakor, N. V. Translating the brain–machine interface. *Sci. Transl. Med.* **5**, 210ps17 (2013).
177. Borton, D., Micera, S., Millan, J. D. R. & Courtine, G. Personalized neuroprosthetics. *Sci. Transl. Med.* **5**, 210rv2 (2013).
178. Shokur, S., Mazzoni, A., Schiavone, G., Weber, D. J. & Micera, S. A modular strategy for next-generation upper-limb sensory-motor neuroprostheses. *Med* **2**, 912–937 (2021).
179. Moritz, C. T., Perlmutter, S. I. & Fetz, E. E. Direct control of paralysed muscles by cortical neurons. *Nature* **456**, 639–642 (2008).
180. Pohlmeyer, E. A. et al. Toward the restoration of hand use to a paralyzed monkey: brain-controlled functional electrical stimulation of forearm muscles. *PLOS One* **4**, e5924 (2009).
181. Ethier, C. & Miller, L. E. Brain-controlled muscle stimulation for the restoration of motor function. *Neurobiol. Dis.* **83**, 180–190 (2015).
182. Losanno, E. et al. Validation of manifold-based direct control for a brain-to-body neural bypass. Preprint at *bioRxiv* https://doi.org/10.1101/2022.07.25.501351 (2022).
183. Friedenberg, D. A. et al. Neuroprosthetic-enabled control of graded arm muscle contraction in a paralyzed human. *Sci. Rep.* **7**, 8386 (2017).

184. Kao, J. C., Nuyujukian, P., Ryu, S. I. & Shenoy, K. V. A high-performance neural prosthesis incorporating discrete state selection with hidden Markov models. *IEEE Trans. Biomed. Eng.* **64**, 935–945 (2017).
185. Vu, P. et al. Long-term upper-extremity prosthetic control using regenerative peripheral nerve interfaces. Preprint at *Res. Square* https://doi.org/10.21203/rs.3.rs-1578680/v1 (2022).
186. Schaffelhofer, S. & Scherberger, H. Object vision to hand action in macaque parietal, premotor, and motor cortices. *eLife* **5**, e15278 (2016).
187. Capogrosso, M. et al. Configuration of electrical spinal cord stimulation through real-time processing of gait kinematics. *Nat. Protoc.* **13**, 2031–2061 (2018).
188. Lynch, C. L. & Popovic M. R. Closed-loop control for FES: past work and future directions. *Proc. 10th Annu. Conf. Int. FES Soc.* 2–4 (2005).
189. Freschi, C. et al. Force control during grasp using FES techniques: preliminary results. *Proc. 5th Annu. Conf. FES Soc.* 17–24 (2000).
190. Ciancibello, J. et al. Closed-loop neuromuscular electrical stimulation using feedforward-feedback control and textile electrodes to regulate grasp force in quadriplegia. *Bioelectron. Med.* **5**, 19 (2019).
191. Wenger, N. et al. Closed-loop neuromodulation of spinal sensorimotor circuits controls refined locomotion after complete spinal cord injury. *Sci. Transl. Med.* **6**, 255ra133 (2014).
192. Lebedev, M. A. et al. Future developments in brain-machine interface research. *Clinics* **66**, 25–32 (2011).
193. Chen, H., Dejace, L. & Lacour, S. P. Electronic skins for healthcare monitoring and smart prostheses. *Annu. Rev. Control Robotics Autonomous Syst.* **4**, 629–650 (2021).
194. Haugland, M. & Sinkjaer, T. Interfacing the body's own sensing receptors into neural prosthesis devices. *Technol. Health Care* **7**, 393–399 (1999).
195. Haugland, M., Lickel, A., Haase, J. & Sinkjaer, T. Control of FES thumb force using slip information obtained from the cutaneous electroneurogram in quadriplegic man. *IEEE Trans. Rehabil. Eng.* **7**, 215–227 (1999).
196. Ganzer, P. D. et al. Restoring the sense of touch using a sensorimotor demultiplexing neural interface. *Cell* **181**, 763–773.e12 (2020).
This article reports the integration of sensory feedback in a brain-controlled neuroprosthesis for grasping in a person with tetraplegia.
197. Bensmaia, S. J., Tyler, D. J. & Micera, S. Restoration of sensory information via bionic hands. *Nat. Biomed. Eng.* https://doi.org/10.1038/s41551-020-00630-8 (2020).
198. Flesher, S. N. et al. A brain–computer interface that evokes tactile sensations improves robotic arm control. *Science* **372**, 831–836 (2021).
199. Yadav, A. P., Li, D. & Nicolelis, M. A. L. A brain to spine interface for transferring artificial sensory information. *Sci. Rep.* **10**, 900 (2020).
200. Loutit, A. J. & Potas, J. R. Restoring somatosensation: advantages and current limitations of targeting the brainstem dorsal column nuclei complex. *Front. Neurosci.* **14**, 156 (2020).
201. Heming, E., Sanden, A. & Kiss, Z. H. T. Designing a somatosensory neural prosthesis: percepts evoked by different patterns of thalamic stimulation. *J. Neural Eng.* **7**, 064001 (2010).
202. Flesher, S. N. et al. Intracortical microstimulation of human somatosensory cortex. *Sci. Transl. Med.* **8**, 361ra141 (2016).
203. Rowald, A. et al. Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. *Nat. Med.* **28**, 260–271 (2022).
204. Weiss, J. M., Gaunt, R. A., Franklin, R., Boninger, M. L. & Collinger, J. L. Demonstration of a portable intracortical brain–computer interface. *Brain Comput. Interf.* **6**, 106–117 (2019).
205. ABILITY. *Wyss Center* https://wysscenter.ch/advances/ability (2022).
206. Benabid, A. L. et al. An exoskeleton controlled by an epidural wireless brain–machine interface in a tetraplegic patient: a proof-of-concept demonstration. *Lancet Neurol.* **18**, 1112–1122 (2019).
207. Larzabal, C. et al. Long-term stability of the chronic epidural wireless recorder WIMAGINE in tetraplegic patients. *J. Neural Eng.* **18**, 056026 (2021).
208. Hansson, S. O. The ethics of explantation. *BMC Med. Ethics* **22**, 121 (2021).
209. Paralyzed again. *MIT Technology Review* https://www.technologyreview.com/2015/04/09/168424/paralyzed-again/ (2022).
210. Lacour, S. P., Courtine, G. & Guck, J. Materials and technologies for soft implantable neuroprostheses. *Nat. Rev. Mater.* **1**, 16063 (2016).
211. Sierra-Mercado, D. et al. Device removal following brain implant research. *Neuron* **103**, 759–761 (2019).
212. Abandoned: the human cost of neurotechnology failure. *Nature.com* https://www.nature.com/immersive/d41586-022-03810-5/index.html (2023).
213. North, R. B., Konrad, P. E., Judy, J. W., Ries, A. J. & Stevenson, R. Examining the need to standardize implanted stimulator connectors: NANS survey results. *Neuromodulation* **24**, 1299–1306 (2021).
214. Keith, M. W. et al. Implantable functional neuromuscular stimulation in the tetraplegic hand. *J. Hand Surg.* **14**, 524–530 (1989).
215. Musk, E. & Neuralink An integrated brain–machine interface platform with thousands of channels. *J. Med. Internet Res.* **21**, e16194 (2019).
216. Nordhausen, C. T., Maynard, E. M. & Normann, R. A. Single unit recording capabilities of a 100 microelectrode array. *Brain Res.* **726**, 129–140 (1996).
217. Normann, R. A. & Fernandez, E. Clinical applications of penetrating neural interfaces and Utah Electrode Array technologies. *J. Neural Eng.* **13**, 061003 (2016).
218. Bullard, A. J., Hutchison, B. C., Lee, J., Chestek, C. A. & Patil, P. G. Estimating risk for future intracranial, fully implanted, modular neuroprosthetic systems: a systematic review of hardware complications in clinical deep brain stimulation and experimental human intracortical arrays. *Neuromodul. Technol. Neural Interf.* **23**, 411–426 (2020).
219. Welle, C. G. et al. Longitudinal neural and vascular structural dynamics produced by chronic microelectrode implantation. *Biomaterials* **238**, 119831 (2020).
220. Szymanski, L. J. et al. Neuropathological effects of chronically implanted, intracortical microelectrodes in a tetraplegic patient. *J. Neural Eng.* **18**, 0460b9 (2021).
221. Sponheim, C. et al. Longevity and reliability of chronic unit recordings using the Utah, intracortical multi-electrode arrays. *J. Neural Eng.* **18**, 066044 (2021).
222. Nason, S. R. et al. A low-power band of neuronal spiking activity dominated by local single units improves the performance of brain–machine interfaces. *Nat. Biomed. Eng.* **4**, 973–983 (2020).
223. McNaughton, B. L., O'Keefe, J. & Barnes, C. A. The stereotrode: a new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records. *J. Neurosci. Methods* **8**, 391–397 (1983).
224. Luan, L. et al. Ultraflexible nanoelectronic probes form reliable, glial scar-free neural integration. *Sci. Adv.* **3**, e1601966 (2017).
225. Guitchounts, G., Markowitz, J. E., Liberti, W. A. & Gardner, T. J. A carbon-fiber electrode array for long-term neural recording. *J. Neural Eng.* **10**, 046016 (2013).
226. Liu, J. et al. Syringe-injectable electronics. *Nat. Nanotechnol.* **10**, 629–636 (2015).
227. Wang, X. et al. A parylene neural probe array for multi-region deep brain recordings. *J. Microelectromech. Syst.* **29**, 499–513 (2020).
228. McCallum, G. et al. Chronic interfacing with the autonomic nervous system using carbon nanotube (CNT) yarn electrodes. *Sci. Rep.* **7**, 11723 (2017).
229. Hanson, T. L., Diaz-Botia, C. A., Kharazia, V., Maharbiz, M. M. & Sabes, P. N. The 'sewing machine' for minimally invasive neural recording. Preprint at *bioRxiv* https://doi.org/10.1101/578542 (2019).
230. Chung, J. E. et al. High-density, long-lasting, and multi-region electrophysiological recordings using polymer electrode arrays. *Neuron* **101**, 21–31.e5 (2019).
231. Hong, G. & Lieber, C. M. Novel electrode technologies for neural recordings. *Nat. Rev. Neurosci.* **20**, 330–345 (2019).
232. Obaid, A. et al. Massively parallel microwire arrays integrated with CMOS chips for neural recording. *Sci. Adv.* **6**, eaay2789 (2020).
233. Ali, M. A. et al. Sensing of COVID-19 antibodies in seconds via aerosol jet nanoprinted reduced-graphene-oxide-coated 3D electrodes,". *Adv. Mater.* **33**, e2006647 (2021).
234. Frewin, C. L. et al. (Invited) silicon carbide as a robust neural interface. *ECS Trans.* **75**, 39 (2016).
235. Patel, P. R. et al. Insertion of linear 8.4 μm diameter 16 channel carbon fiber electrode arrays for single unit recordings. *J. Neural Eng.* **12**, 046009 (2015).
236. Welle, E. J. et al. Sharpened and mechanically durable carbon fiber electrode arrays for neural recording. *IEEE Trans. Neural Syst. RehabilitatiEng.* **29**, 993–1003 (2021).
237. Jun, J. et al. Fully integrated silicon probes for high-density recording of neural activity. *Nature* **551**, 232–236 (2017).
238. Golabchi, A., Woeppel, K. M., Li, X., Lagenaur, C. F. & Cui, X. T. Neuroadhesive protein coating improves the chronic performance of neuroelectronics in mouse brain. *Biosens. Bioelectron.* **155**, 112096 (2020).
239. Shah, K. et al. High-density, bio-compatible, and hermetic electrical feedthroughs using extruded metal vias. *Proc. Conf. 2012 Solid-State, Actuators, and Microsystems Workshop* (2012).
240. Seo, D. et al. Wireless recording in the peripheral nervous system with ultrasonic neural dust. *Neuron* **91**, 529–539 (2016).
241. Lee, J. et al. Neural recording and stimulation using wireless networks of microimplants. *Nat. Electron.* **4**, 604–614 (2021).
242. Lee, S. et al. A 250 μm×57 μm microscale opto-electronically transduced electrodes (MOTEs) for neural recording. *IEEE Trans. Biomed. Circuits Syst.* **12**, 1256–1266 (2018).
243. Lim, J. et al. 26.9 A 0.19×0.17mm^2 wireless neural recording IC for motor prediction with near-infrared-based power and data telemetry. In *2020 IEEE Int. Solid-State Circuits Conf. (ISSCC)* 416–418 (IEEE, 2020).
244. Zeng, F.-G. Celebrating the one millionth cochlear implant. *JASA Express Lett.* **2**, 077201 (2022).
245. Vedam-Mai, V. et al. Proceedings of the Eighth Annual Deep Brain Stimulation Think Tank: advances in optogenetics, ethical issues affecting DBS research, neuromodulatory approaches for depression, adaptive neurostimulation, and emerging DBS technologies. *Front. Hum. Neurosci.* **15**, 644593 (2022).
246. Schwemmer, M. A. et al. Meeting brain–computer interface user performance expectations using a deep neural network decoding framework. *Nat. Med.* **24**, 1669–1676 (2018).
247. Laferriere, S., Bonizzato, M., Cote, S. L., Dancause, N. & Lajoie, G. Hierarchical Bayesian optimization of spatiotemporal neurostimulations for targeted motor outputs. *IEEE Trans. Neural Syst. Rehabil. Eng.* **28**, 1452–1460 (2020).
248. Losanno, E. et al. Bayesian optimization of peripheral intraneural stimulation protocols to evoke distal limb movements. *J. Neural Eng.* **18**, 066046 (2021).
249. Müller, P., Del Ama, A. J., Moreno, J. C. & Schauer, T. Adaptive multichannel FES neuroprosthesis with learning control and automatic gait assessment. *J. Neuroeng. Rehabil.* **17**, 36 (2020).
250. Heiwolt, K. et al. Automatic detection of myocontrol failures based upon situational context information. In *2019 IEEE 16th Int. Conf. Rehabilitation Robotics (ICORR)* 398–404 (IEEE, 2019).
251. Chavarriaga, R., Carey, C., Luis Contreras-Vidal, J., McKinney, Z. & Bianchi, L. Standardization of neurotechnology for brain-machine interfacing: state of the art and recommendations. *IEEE Open. J. Eng. Med. Biol.* **2**, 71–73 (2021).
252. Paek, A. Y. et al. A roadmap towards standards for neurally controlled end effectors. *IEEE Open. J. Eng. Med. Biol.* **2**, 84–90 (2021).
253. Loeb, G. E. & Richmond, F. J. Turning neural prosthetics into viable products. *Front. Robot. AI* **8**, 754114 (2021).

254. Petrini, F. M. et al. Six-month assessment of a hand prosthesis with intraneural tactile feedback. *Ann. Neurol.* **85**, 137–154 (2019).
255. Cracchiolo, M. et al. Computational approaches to decode grasping force and velocity level in upper-limb amputee from intraneural peripheral signals. *J. Neural Eng.* **18**, 055001 (2021).
256. Zyl, C., Badenhorst, M., Hanekom, S. & Heine, M. Unravelling 'low-resource settings': a systematic scoping review with qualitative content analysis. *Br. Med. J. Glob. Health* **6**, e5190 (2021).
257. Zhang, C. et al. An international survey of deep brain stimulation utilization in Asia and Oceania: the DBS Think Tank East. *Front. Hum. Neurosci.* **14**, 2020 (2022).
258. Simon, C., Bolton, D. A. E., Kennedy, N. C., Soekadar, S. R. & Ruddy, K. L. Challenges and opportunities for the future of brain–computer interface in neurorehabilitation. *Front. Neurosci.* **15**, 2021 (2022).
259. Sauter-Starace, F. et al. Long-term sheep implantation of WIMAGINE®, a wireless 64-channel electrocorticogram recorder. *Front. Neurosci.* **13**, 2019 (2022).
260. Oxley, T. J. et al. Motor neuroprosthesis implanted with neurointerventional surgery improves capacity for activities of daily living tasks in severe paralysis: first in-human experience. *J. NeuroInterv. Surg.* **13**, 102–108 (2021).
261. Post, M. W. et al. Employment among people with spinal cord injury in 22 countries across the world: results from the International Spinal Cord Injury Community Survey. *Arch. Phys. Med. Rehabil.* **101**, 2157–2166 (2020).

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C.C. and M.M. wrote the sections on natural motor control and hand decoding. E.L., S.S. and S.M. wrote the sections on motor function restoration and brain-to-body interfaces. E.L., S.S. and S.M. also harmonized all the different sections, writing introductions and conclusions. All authors revised and approved the final version of the manuscript.

Competing interests
S.M. holds shares in the companies IUVO, GTX and Sensars Neurotechnologies, which are all developing neurotechnologies to restore the sensorimotor functions of people with disabilities. All other authors declare no competing interests.

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