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Editor's Summary

Helping the Brain Help Itself

In this Review, Courtine and colleagues describe "personalized neuroprosthetics" as the synergy between accurate diagnosis, integrated development of neurotechnology, and patient-specific treatment design, ultimately "to help the brain help itself" in nervous system disorders.

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ROBOTICS AND NEUROPROSTHETICS

Personalized Neuroprosthetics

David Borton,[1] Silvestro Micera,[2,3] José del R. Millán,[2] Grégoire Courtine[1]*

Decades of technological developments have populated the field of neuroprosthetics with myriad replacement strategies, neuromodulation therapies, and rehabilitation procedures to improve the quality of life for individuals with neuromotor disorders. Despite the few but impressive clinical successes, and multiple breakthroughs in animal models, neuroprosthetic technologies remain mainly confined to sophisticated laboratory environments. We summarize the core principles and latest achievements in neuroprosthetics, but also address the challenges that lie along the path toward clinical fruition. We propose a pragmatic framework to personalize neurotechnologies and rehabilitation for patient-specific impairments to achieve the timely dissemination of neuroprosthetic medicine.

HELP THE BRAIN HELP ITSELF

In the healthy neuromotor system, the development of intention and motor execution is a dynamic and highly distributed process that originates in the brain. The intended action is transmitted along the axonal "super highway" of the spinal cord to "smart circuits" that transform the descending command into coordinated patterns of muscle activation. A continuous stream of sensory and motor information is actively coalesced to ensure the accurate and sequenced execution of movement. The output of the motor cortex and brainstem motor regions is under the continuous influence of other structures of the brain, including the cerebellum and basal ganglia, which are essential for producing smooth movements. These contextual information streams form loops interacting with one another at key integration centers of the nervous system, such as the association cortices and the thalamus. Failures of function in one seemingly insignificant processing loop can, and often do, lead to marked consequences that induce transient or permanent deficits in cognitive ability and motor control. In Parkinson's disease (PD), the premature loss of dopaminergic transmission in the substantia nigra disturbs the basal ganglia loops and motor output circuitry of the brain, causing tremor, gait disturbance, rigidity, and deficits in cognitive function. Demyelination—the phenotype of multiple sclerosis (MS)—reduces the conductivity of axons, which alters their ability to convey information to distant circuits. Stroke, although focal in nature, induces complex and far-reaching effects on the central nervous system (CNS). Less subtle, but particularly palpable, is the marked consequence resulting from severe spinal cord injury (SCI), which, in extreme cases, can make a person completely unable to control the world around them.

Nervous system disorders have long-term health, economic, and social consequences. Despite the best available medical treatments, millions of individuals endure a long life with sensorimotor and cognitive deficits that markedly affect their quality of life. Transplantation of specific neuronal populations engineered by stem cell technologies has shown therapeutic efficacy in animal models of neurological disorders (*1*, *2*). Likewise, virus vectors enable manipulating the genetic constitution of neurons and other neural cells, holding promises to treat various CNS disorders (*3*). Nevertheless, the safe and efficacious translation of these approaches into curative treatments or interventions capable of repairing the injured human CNS remains challenging. Advances in fundamental brain science, neuroengineering, computational neuroscience, neurosurgery, neuropharmacology, and robotics have opened avenues for alternative, neurotechnology-intensive solutions to cellular and molecular therapies. This broad field of research—termed neuroprosthetics—taps into spared brain and spinal circuits to replace or restore sensorimotor functions.

Neuroprosthetic treatments are broadly divided into two categories. Replacement strategies leverage a sensing neural interface to extract dynamic information from cortical activity to generate effector control commands. Pioneering brain-machine interfaces (BMIs) [see related Perspective by Thakor, this issue (*4*)] for replacement of function have allowed nonhuman primates (NHPs) (*5*–*9*) and severely paralyzed persons (*10*–*13*) to operate sophisticated actuators, including robotic arms, to perform activities of daily living by using brain activity only. Restoration treatments exploit neuromodulation paradigms to regulate dysfunctional neuronal circuits with continuous electrical stimulation, neuropharmacology, or a combination of the two (*14*–*17*). Neuromodulation of the basal ganglia, spinal cord, retina, and auditory nerves is improving the lives of countless individuals with PD [deep brain stimulation (DBS)], chronic pain (spinal cord stimulation and intrathecal drug delivery), blindness (retinal prostheses) [see related Perspective by Zrenner, this issue (*18*)], or hearing disorders (cochlear implants), respectively.

The marriage of replacement and restoration neuroprosthetic strategies is occurring at a fast pace. An increasing number of brain-to-body interfaces are establishing electronic bridges to enable the direct neuromodulation of denervated spinal segments (*19*) and muscles (*8*) from cortical signals in animal models. Meanwhile, the efficacy and spectrum of neuromodulation treatments are quickly expanding with the design of closed-loop control systems that aim to adjust therapies based on individual circuitopathies and detected sensorimotor impairments (*20*, *21*). These advances in neuroprosthetics represent variations on the same theme: the need to capitalize on the intrinsic capacity of remaining neural circuits and their plasticity to restore function. In this Review, we describe the core principles and bourgeoning neurotechnology underlying the latest and contemplated achievements of neuroprosthetic treatments to replace, restore, and rehabilitate sensorimotor functions. Throughout the review, we also seek to share our vision on prospective innovations and current impediments to personalizing neuroprosthetic treatments for distinct neurological disorders to increase clinical efficacy and relevance. We have chosen limited but concrete examples to illustrate individualization in clinical settings. In closing, we address the challenges toward clinical fruition, but also provide a

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glimpse at the extraordinary potential of neuroprosthetics to improve the quality of life for people with neurological disorders. Our objective is to outline a practical framework for the design of personalized neuroprosthetic treatments "to help the brain help itself."

REPLACEMENT: A LITTLE "BIT" GOES A LONG WAY

Replacement strategies leverage interfaces with the brain, spinal cord, peripheral nerves, and muscles to "listen" to endogenous neuronal activity and then extract useful bits of information to control prosthetics. Controlled effectors range from computers to robotic limbs. Although there are many accepted and continuously growing terminologies, this approach primarily falls under the appellation BMIs. Neuroprosthetic technologies used today rely on an imperfect understanding of localized neuronal circuitry. Yet, these bits of information have enabled the design of potentially life-changing BMI systems.

Listening to the brain

Information in the cerebral cortex can be garnered from the unit action potential or spike and from field potentials (FPs) (Fig. 1A). The FP recorded by scalp electrodes is called the electroencephalogram (EEG). FPs recorded inside the skull, epidural or subdural, are called electrocorticograms (ECoGs), whereas intraparenchymal recordings of FP are termed local field potentials (LFPs). The early 20th century brought the first visualizations of brain activity through EEG, but only in 1969 did it become possible to directly interface a sensing electrode with a single neuron to achieve operant conditioning of cortical unit activity in NHPs and later in humans. In 1992, the field transitioned from single-neuron recording to neural population recording or multiple single units (MSUs). This breakthrough was made possible by the emergence of the microelectronic industry, including the silicon-based microelectrode brain array (MEA) (Fig. 1A).

The proliferation of high-density neural recordings allowed the discovery of core principles through which cortical networks can coordinate movement. For example, the identification of neural tuning relationships to upper limb dynamics led to BMI designs based on the mechanistic understanding of brain transfer functions and movement decoding (*9*). During the last two decades, an explosion of neural decoding achievements across spatial and temporal scales has enabled varying degrees of prosthetic control in NHPs. Multidimensional motor information pertaining to intention and execution has been extracted from neuronal ensemble modulation in the primary motor cortex (*6*, *7*, *22*), premotor cortex (*5*, *23*), and parietal areas (*24*). This decoding has enabled NHPs and humans to manipulate neuroprosthetic actions, ranging from continuous trajectories (*5*, *6*, *11*, *12*, *25*) to discrete states, such as directions (*26*), targets (*24*, *27*, *28*), and grasp aperture (*8*, *10*, *22*). NHPs have even been able to learn concurrent transformation functions, which highlighted the development of learning engrams, termed prosthetic memory (*29*). The more pertinent choice of recording instrumentation for neuroprosthetic designs or neurorehabilitation depends on the objective of the intervention. Although EEG signals may provide useful intent-related inputs (*13*), the single-neuron resolution of intracortical electrodes extracts the maximal amount of information (*4*).

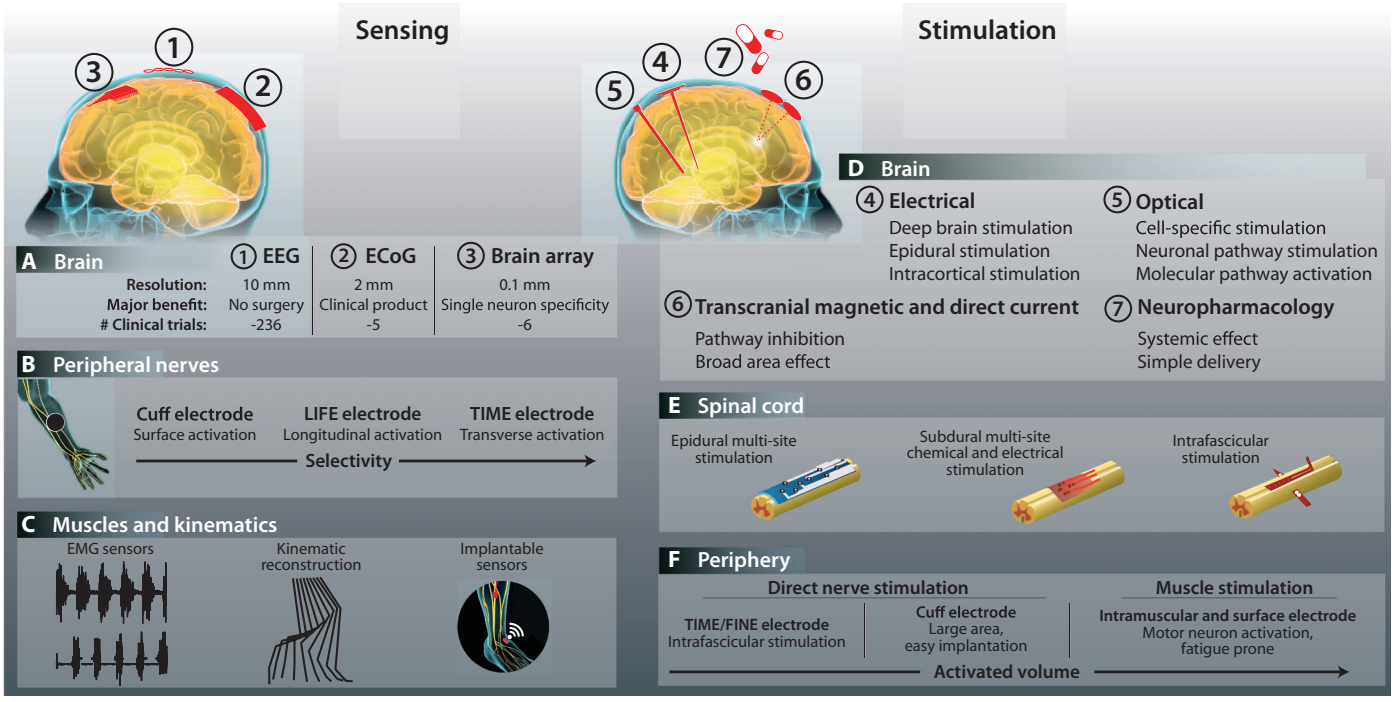

Fig. 1. Neuroprosthetic toolbox. Neurotechnologies are divided into two categories: sensing and stimulation interfaces. (**A** to **C**) Sensing devices are broken down into subcategories of various resolutions that are interfaced with the brain (A), peripheral nerves (B), muscles (C), and body kinematics (C). (**D** to **F**) Stimulation probes are divided into electrical, optical, and chemical classes that can recruit neurons in the brain (D), spinal cord (E), and periphery with various activation volumes and specificities (F). LIFE (longitudinal intrafascicular nerve electrode) excites a small area of the nerve cross section; TIME (transversal intrafascicular multichannel electrode) excites small populations of nerve fibers of different fascicles over the nerve cross section.

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ECoG systems play an intermediate role, providing potentially more stable signals because of spatial smoothing, yet maintaining a finer resolution than EEG recordings (*30*, *31*) (Fig. 1A).

Frontier achievements in BMI

Recently, two groups implanted percutaneous, chronic MEAs into the cortex of individuals with chronic paralysis (*11*, *12*). Both groups leveraged a population of neurons in a small patch of cortex to interpret the individual's intended motor action. This BMI enabled voluntary control of a robotic arm to perform seven-dimensional reach and grasp movements with remarkable fluidity and even safely bring a cup of coffee (*11*) or chocolate (*12*) from table to mouth—overcoming the technical and logistical challenges to bring a robotic system into the personal space. Current BMI developments seek to directly interface brain signals with other body parts. For example, brain-controlled stimulation of muscles restored grasping in NHPs with transient arm paralysis (*7*, *8*). Preliminary results using a highly sophisticated musculoskeletal model in a tetraplegic patient suggest that contemplated BMI-driven stimulation of muscles, nerves, or spinal cord may restore more naturalistic movements of prosthetic arms (*32*). This kind of sophisticated brain-to-body interfaces will critically rely on bio-inspired control structures (*12*), including low- and high-level neural information harvested from multiple brain regions. To this end, the Human Brain Project (http://www.humanbrainproject.eu/) and the BRAIN Initiative from the National Institutes of Health (http://www.nih.gov/science/brain/) may well expand the BMI landscape. Such funding opportunities aim to enable development of the technological and computational frameworks necessary to monitor neuronal ensemble modulation from multiple brain areas. These initiatives coupled with neurotechnological advances should help achieve superior, personalized prosthetic control.

Dynamic cortical activity

Translation of BMI breakthroughs into personalized devices usable in daily life will face the challenge of maintaining stability despite changing sources of control. Traditional understanding of neural tuning has proven more complex and variable than originally imagined. Studies have shown that motor cortex activity co-varies with a broad range of parameters of motor performance—from target location to joint motion, torque, and muscle activation patterns (*33*). Further, a stable representation in one frame of reference can change across behaviors, postures, and movements (*34*), highlighting the capacity of the cortex to hold dynamic information required for movement preparation and execution. This inherent information uncertainty and daily recording instability often demand recalibration of BMI control algorithms on a daily basis, which may not be conducive to a normal life-style.

Although procedures have been developed to seek long-term stability (*35*), such motor control complexity requires contextual and individualized adjustments to decoding solutions. New statistical frameworks have been proposed to explore the high-dimensionality of neural activity across environments and context, but only recently has implantable wireless neurotechnology been developed to enable collection of neural data for such analysis (*36*, *37*). At first sight, versatile encoding may appear inefficient and metabolically expensive. However, this flexibility may be critical to adjust motor behaviors to novel contexts while concurrently facilitating learning and generalization within shared neuronal networks. BMI researchers are seeking to harness context dependency and versatility of brain activity to their advantage using closed-loop decoder adaptation (CLDA) and machine learning. These developments are paving the way toward personalized BMI technologies.

Listening outside the brain

Few attempts have been made to chronically record from spinal circuits for prosthetic control. Spinal axonal and neuronal packing is extremely dense and heterogeneous. The uniform parallel distribution makes unit isolation difficult for chronic electrophysiology instrumentation. Instead, researchers have focused on extracting position and velocity information from muscle activity (*38*), peripheral nerve signals (*39*), and dorsal root ganglion (DRG) (*40*, *41*) (Fig. 1, A to C). The decoded information is integrated into closed-loop control systems where they serve as a motor command or as sensory feedback. For example, real-time decoding of sensory information from DRG has recently been used to control walking induced by functional electrical stimulation (FES) (*42*) or penetrating spinal electrodes (*41*) in anesthetized cats. Theoretically, these various sources of feedback signals could provide useful bits of information for controlling a neural prosthesis.

Writing into the brain

Replacement strategies have traditionally focused on reading out from the brain to control devices but, more recently, have sought to additionally write perceptions into the brain for replacement of sensation (*43*–*45*). Sensory feedback is necessary to achieve coordinated prosthetic control. Visual feedback is generally used to provide information on executed prosthetic action, but the addition of congruent kinesthetic information improves performance (*46*). These results suggest that integration of multifaceted sensory inputs will play an important role in augmenting neuroprosthetic control (Fig. 1, D to F) (*33*). Sensory substitution, including tactile feedback to body areas where patients retain somatosensory perception, is an immediate alternative to improve BMI performance (*47*). Direct intracortical microstimulation may be suitable to provide rich sensory feedback in real time (Fig. 1D) (*4*, *48*). However, constructive sensory percepts have been difficult to evoke owing to the uncertain neural activation fields from electrical simulation, the poor ability of animal models to report directly on quality of sensation, and the subjective nature of sensory input. NHPs have been able to explore a simulated environment with an avatar hand and to discriminate virtual objects on the basis of artificial feedback delivered through intracortical microstimulation of the primary somatosensory cortex (*43*). However, the provided feedback was binary, rather than graded and continuous. The optogenetic toolbox is providing a range of strategies to manipulate the activity of specific microcircuits (*49*), even of single neurons, while avoiding electrical stimulation artifacts that impede bidirectional BMI design. Various strategies are being explored to induce artificial sensory feedback with optogenetic stimulation (Fig. 1D). Despite the luring potential for translational medicine (*50*), the technical and regulatory hurdles that lie ahead along the path toward turning optogenetic neuromodulation therapies into a clinical reality are nontrivial (*51*).

Plugging into the peripheral nervous system

Multiple approaches have enabled restoration of sensation and active control of upper limb prosthesis in human amputees. Targeted reinnervation allowed redirection of cutaneous sensation from the amputated hand to the chest skin (*52*). Noninvasive stimulation of the reinnervated chest region with a dense electrode array provided tactile sensation with precise somatotopic organization. Likewise, intraneural peripheral electrodes have enabled some degree of specificity in the recruitment of

peripheral nerve afferents (Fig. 1F) (*53*, *54*). This technology has also been used to design neural interfaces in which grip information was decoded from electrical activity of forearm muscles [electromyography (EMG)] (Fig. 1B) (*53*) or motor nerves (Fig. 1F) (*39*). Bidirectional peripheral interfaces have a high potential to translate into useful system to restore neural control of a prosthetic hand while delivering rich sensory feedback in real time.

RESTORATION: A CONVERSATION WITH THE NERVOUS SYSTEM

Thousands of years ago, humans used electric eels to treat pain—one of the first documented uses of electricity to deliver therapy. Since then, advances in material science and charge storage and delivery have enabled more precise perturbations of the nervous system, including electrical, optical, and magnetic stimulation (Fig. 1D). In parallel, progress in neuropharmacology has yielded a wide range of chemical agents to alter the state of neuronal networks (Fig. 1D). This combined electrical and pharmacological toolbox has led to new medical practices to alleviate many symptoms resulting from neurological disorders. The challenge for the next generation of neuroprosthetic treatments is to initiate a productive conversation with the nervous system wherein devices not only deliver therapy but also continuously titrate themselves on the basis of neural states and detected motor impairments. These contemplated strategies are referred to as closed-loop neuroprosthetic system.

Electrically engaging effectors

FES of muscles provides safe and easy access to muscle effectors. Muscle FES remains one of the few clinically proven and effective prosthetic therapies that enable basic grasping, standing, bladder control, and movement rehabilitation (*55*). A safe and nonsurgical approach consists of delivering current through surface electrodes placed on the skin over the muscle to be stimulated (Fig. 1F). These electrodes are most effective for activating large and superficial muscles. However, muscle fibers are recruited in a nonphysiological order, which leads to rapid fatigue. Owing to skin's high resistance, FES can require high currents to actuate muscles, which is often uncomfortable for patients. Implanted FES electrodes avoid many of surface electrode limitations, but at the expense of complex surgical procedures. Nevertheless, even greater specificity has been achieved with peripheral nerve interfaces (Fig. 1F) (*38*). In particular, intrafascicular electrodes enabled access to intrinsic hand muscles that cannot be recruited independently using conventional FES (*56*). Complex reach-to-grasp movements have also been evoked in NHPs when delivering intraspinal microstimulation at specific locations of cervical segments (Fig. 1E) (*57*). However, there is no sufficiently detailed atlas to guide the placement of microwires to evoke distinct movement, which severely limits neuroprosthetic applications (*57*). Practical FES systems will have to solve the equation between variable muscle recruitment specificity, surgical complexity, and cost to personalize solutions that mediate meaningful benefits.

Reanimating the "spinal brain"

The spinal sensorimotor infrastructure has traditionally been viewed as an assembly of reflex subsystems and central pattern generators (CPGs) that produce automated and stereotypical motor activity in response to sensory input or descending command (*58*). The high degree of automaticity embedded in spinal circuits enables the execution of complex motor behaviors with considerable precision and without conscious thought (*59*). The spinal brain acts as a smart information-processing interface that integrates dynamic input from sensory ensemble and makes a decision on how to stably and continuously adjust motor output to meet environmental constraints (*59*). Despite these advanced properties, the markedly depressed state of the spinal cord after injury prevents the production of standing and walking. Consequently, much effort has been invested in developing paradigms to replace the missing sources of neuromodulation and excitation that are normally delivered to spinal sensorimotor circuits for coordinating movement. Electrical stimulation has been the primary strategy used to compensate for the interrupted source of spinal excitation after injury. Continuous electrical stimulations applied to the dorsal roots (*60*), over the dorsal aspect of the spinal cord (*16*), or directly into the ventral horn of lumbar segments (*41*) (Fig. 1E), have shown the ability to elicit standing and stepping patterns in animal models and humans with SCI (*16*, *59*), PD (*15*), and MS (*61*). In combination with monoamine agonists (*62*), epidural electrical stimulation of lumbosacral circuits has been able to restore full weight-bearing locomotion in rats with complete SCI (*17*). This electrochemical neuroprosthesis replaces the missing source of neuromodulation and excitation after the interruption of descending pathways, although the exact mechanisms remain unclear.

Neurotechnology and stimulation protocols are at the early stages of development. Empirical knowledge and visual observations have guided electrode positioning, as well as the selection of electrode configurations and stimulation parameters. Extensive mappings revealed that various locations and stimulation profiles are necessary to facilitate standing, stepping, and isolated movements (*16*, *59*). This manual tuning is impractical and suboptimal. These experiments emphasize the need to establish a mechanistic framework to personalize multisite stimulation algorithms and develop closed-loop control systems that take full advantage of this paradigm to facilitate movement in motor-impaired subjects.

Regulating brain function

Regulation of dysfunctional neuronal circuits with neuromodulation therapies has broadened the spectrum of treatment options for neurological disorders (*14*). For example, dopamine precursors (pharmacological modulation) and DBS (electrical modulation; Fig. 1D) of the basal ganglia circuitry have become commonly applied therapies to mitigate, independently and synergistically, many of the cognitive and motor symptoms associated with PD. The introduction of electrical currents into deep brain structures recruits a multiplicity of axonal, somatic, and dendritic elements—each with different functions, latencies, and propagative properties. The recruitment of neural structures depends on stimulation modality, charge densities, local synaptic arrangements, and stimulation profile. This plurality of mechanisms has led to elusive and contradictory hypotheses to explain the therapeutic impact of DBS (*14*). A catalog has been proposed wherein each of the individual elements in the constellation of symptoms maps onto specific neural subcircuits—termed symptomatotopy (*14*). Unfortunately, the ability to draw such a map is questionable—especially for human-specific disease phenotypes for which experimental data are lacking. According to ClinicalTrials.gov, there are nearly 100 ongoing clinical trials that are exploring the impact of DBS for reducing detrimental effects of many neurological disorders, including major depression disorder, obsessive-compulsive disorder, chronic pain, and dystonia. However, incomplete

understanding of disease circuitopathies and the inherently nonspecific nature of DBS are hindering the translation of these approaches (*14*). Today, electrodes for brain stimulation and recording take very few physical forms (*63*) and fail to leverage our understanding of neuromotor disorders to optimize efficacy. Novel electrode design and advanced current steering methods aim to increase the specificity and directionality of DBS to expand therapeutic flexibility. Nevertheless, the inherent limitations of electrical stimulation may prevent achieving personalization of DBS treatments.

Shedding light on brain circuits

The burgeoning field of optogenetics lends perspective on the mechanisms of therapeutic interventions, potentially leading to fundamentally new neuromodulation paradigms. The integration of optogenetic technologies into neuromodulation treatments is already bearing fruit, bringing new prosthetic tools, targets, and therapeutic interventions for neuromotor diseases (*21*, *49*, *50*, *64*). Refined delivery of light, cell-specific targeting methods and genetic control of expression enable well-controlled neural excitation or inhibition of brain, spinal cord, and peripheral nerves (*49*, *50*). However, clinical use of optogenetic technology relies on an enhanced understanding of how damaged neuronal circuits and their interconnections produce disease (circuitopathies), the identification of specific promoters to drive expression of light-sensitive channels, the safe delivery of optical stimulation, and, crucially, the safe and efficacious translation of gene therapy to humans. Moreover, the first attempt to implement the optogenetic toolbox in NHPs has revealed unexpected obstacles. Although optogenetic constructs robustly modulate neural activity in NHPs (*65*), optically induced behavioral effects have been only obtained in a few animal studies, under restricted conditions, and with limited scope (*66*, *67*). Despite the luring potential for transforming restorative medicine, and initiatives for commercial exploration (http://circuittx.com/), excitement must be tempered by objective reality. Numerous practical, technical, and regulatory hurdles lie in translating optogenetic neuromodulation therapies to common clinical practice (*51*).

Bringing the brain into the loop

Automated closed-loop control systems yield great potential to improve neuromodulation therapies by reducing titration latency and adjusting parameters to meet dynamic patient-specific needs (Fig. 2) (*20*). Industrial developments of clinically viable neuromodulation platforms provide tools to personalize stimulation algorithms on the basis of FP recordings from the brain (*36*). Epilepsy has been an early target for closed-loop neuromodulation where systems detect aberrant activity through ECoG or cortical MEAs and, based on a software-implemented control policy, deliver electrical (*68*) or optogenetic (*21*) stimulation to disturb aberrant network states. Closed-loop platforms serve as the foundation for further integration of biosignals to enhance patient-specific data collection. Moreover, the introduction of varying neuromodulation features offers the opportunity to alter the dynamic state of neuronal networks, which may aid in understanding diseased states of the nervous system. Optimal closed-loop control systems must incorporate policies between neural circuits and stimulation algorithms (co-adaptive) to reach maximum therapeutic effects.

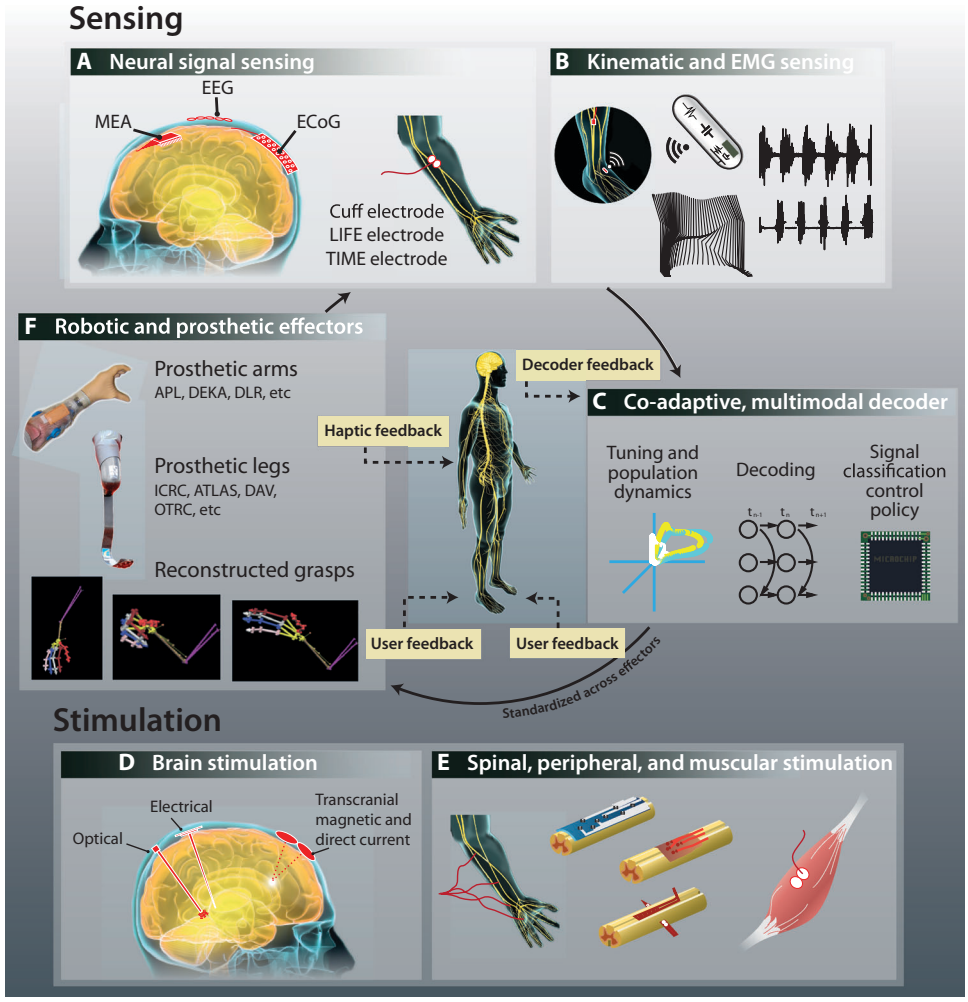

Fig. 2. Closed-loop neuroprosthetic design. (**A** to **F**) Motor intent extracted from the central and peripheral nervous system (A), informed by composite movement feedback (B), are processed through co-adaptive algorithms (C). This process builds control policies to deliver stimulation to the brain (D), spinal cord, peripheral nerves, and muscles (E), and/or to control robotics, smart prosthetics, or other assistive technologies (F). This system design includes natural and artificial feedback loops to the user and control policies. This marriage of BMIs and neuromodulation therapies through closed-loop control systems is occurring at a fast pace. Grasp reconstructions reproduced from (*22*) with permission. Prosthetic arm and leg obtained from Wikipedia Commons.

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WORKING HAND IN HAND

During most of the 20th century, neuroscientists shared Ramon y Cajal's conception of the adult CNS: "in the adult brain, nervous pathways are fixed and immutable; everything may die, nothing may be regenerated" (*69*). Today, however, structural and functional neuroplasticity of spared brain regions and their interconnections form the basis for functional recovery after insult. Traumatic injuries, cerebral infarction, and other sudden neural damage open a window of opportunity for increased neuroplasticity, which can mediate extensive restoration of sensorimotor functions after moderate CNS lesion. To enhance this remodeling, neuroprosthetic systems must maximize the engagement of neural systems during training and ensure that the brain works together with the spinal cord.

Activity-dependent neuroplasticity

The field of neurorehabilitation has long understood the implications of neuroplasticity for the design of activity-based interventions to increase recovery after neuromotor disorders. In the early 1980s, disruptive experiments first illustrated the power of activity-dependent neuroplasticity after injury. Despite the complete interruption of supraspinal input, intense daily training enabled the spinal cord of adult cats to learn to step on a motorized treadmill or to stand quietly for hours with full weight bearing (*70*). However, cats that had been trained to stand stepped very poorly. Inversely, cats that were trained to walk for hours on a treadmill had limited ability to stand. Task-specific activation of sensorimotor circuits selected and reinforced subsets of connections and neurons in a way that substantially improved the ability of the spinal brain to perform the practiced movement successfully (*59*, *70*). Functional and structural rearrangements through mechanisms of Hebbian neuroplasticity, local axonal growth, synapse formation, stabilization, and elimination have since been observed in the brain and spinal cord after various insults (*71*, *72*). Activity-dependent neuroplasticity at the systems level implies that the therapeutic effects of training will strongly depend on the following: (i) the type of practiced motor task, (ii) the availability of meaningful sensory information to shape the remodeling of neuronal circuits, and (iii) the presence of robust and coinciding activity throughout the brain and spinal cord during rehabilitation. These practical findings are steering the design of robotic interfaces and neuroprosthetic systems to augment the beneficial impact of neurorehabilitation, which we summarize below.

Robot-assisted training

Robotic engineering pioneered the application of devices to enhance activity-based neuroplasticity with training after insult (*73*, *74*). Although there are different views on the more suitable strategies for the design of rehabilitation robots (*75*), the objective of these interfaces is to enable adjustable and highly reproducible assistance of lower or upper limb movements during intensive task-specific training. Ideally, rehabilitation robots only require supervision from a physiotherapist who sets the parameters of the mechatronic structure to continuously challenge the patient's neuromuscular system. Robotic interfaces also monitor the patient's participation and performance, which provides a quantitative and objective evaluation of training outcome. These combined features have contributed to the popularity and success of rehabilitation robotics in the clinical setting, which led to the accelerated development of increasingly complex, multiple degree-of-freedom interfaces. However, since the first introduction of robotic devices for occupational medicine in the 1990s (*73*, *74*), exoskeletons and other training interfaces have failed to demonstrate superior capabilities to restore function compared to conventional therapy. For example, robot-assisted training delivered in the acute or chronic stage after a stroke can improve recovery of upper limb function, but performance has been in the best scenario equivalent to those obtained with manual guidance (*76*). Nevertheless, even more controversial is the potential benefit of exercise driven by a lower limb orthosis, which has repeatedly been questioned in comparative clinical trials involving multiple neurological disorders [see related Perspective by Goldfarb *et al.*, this issue (*77*)]. Despite important proofs of feasibility, robotic engineering has yet to leverage the disruptive potential of robotic technology to surpass conventional therapies. This challenge is giving birth to a new field of research merging neuroprosthetics and soft robotics, which has been termed "soft" neurorobotics.

Soft neurorobotics is a new class of rehabilitation interfaces that seeks to provide more natural, interactive, and safer robotic assistance through soft design. Engineers are integrating "softness" through three synergistic building blocks. First, they use soft materials, such as silicon rubber derivatives, to design wearable interfaces that are comfortable and lightweight, and whose ergonomic design is personalized through anthropometry. Second, they develop soft hardware, including soft actuators (*78*) and stretchable sensors (*79*), to enable compliant interactions between the user and the robotic interface. Third, they use soft control algorithms that integrate multilevel biological and neurological feedback to personalize the degree of assistance based on the current state of the limbs, the intended movement, and the physiological condition of the trained subject.

The first generation of compliant robotic interfaces has achieved softness through variable impedance control. For example, the use of series elastic actuators, which consist of an elastic element inserted between a conventional motor and the subject, allows the robotic interface to be entirely decoupled from the user—the robot becomes transparent (*80*). Compliant interactions enable the robot to act as a postural neuroprosthesis that continuously personalizes the amount of support and assistance on the basis of the performed task and subject-specific impairments. This type of robotic postural neuroprosthesis instantly restores unexpected motor control capacities in rats with partial SCI or stroke (*80*). Adaptive control algorithms are the main tools used to integrate softness in current rehabilitation robots. Instead of moving the limbs along predefined trajectories, robotic assistance is continuously adjusted to limb state (*81*), active subject participation (*75*), brain states (*82*), and bio-cooperation markers such as heart rate (*83*). Current rehabilitation robots require the user to adapt to the training paradigm through uncomfortable, rigid master-slave interactions. Although many obstacles remain, soft neurorobotics promises to personalize the rehabilitation environment to the anthropometric, physiological, and psychological features of the user to enhance remodeling of the brain and spinal cord with customized training.

Multisystem neurorehabilitation

Activity-based therapies are designed with the reasoning that the repetitive exposure to task-specific patterns of sensory input will reinforce the activated sensorimotor circuits to promote functional improvement. Although this approach is effective in individuals who retain the ability to engage motor circuits (*72*), training after more severe lesions that spare limited or no ability to engage residual function fails to promote useful neuroplasticity in sensorimotor pathways. What is the rationale

for this lack of efficacy? The answer may be deceptively simple: A critical threshold of activity may be necessary for neuronal circuits to respond to task-specific proprioceptive input. Several neuroprosthetic systems have shown the ability to manipulate neural activity directly within the brain and spinal cord, or indirectly through peripheral nerve or muscle stimulation, to promote active movement.

Application of these activity-enabling systems during training, termed multisystem neurorehabilitation (*17*), has led to long-lasting improvements of motor functions in animal models and humans with neuromotor disorders. For example, treadmill-based step training enabled by an electrochemical spinal neuroprosthesis mediated marked amelioration of locomotor capacities in severely paralyzed rats (*17*, *59*). Repeated practice under the presence of chemical and electrical spinal stimulations, which enabled a so-called functional state (*59*), triggered structural and functional remodeling of sensorimotor circuits, but only in the engaged spinal cord. Treadmill-restricted training failed to engage the brain, and no (or limited) activity-dependent neuroplasticity took place in spared descending pathways; in this condition, the spinal brain appears to work alone. Robot-assisted training paradigms that are designed to encourage the brain to communicate with the electrochemically enabled spinal cord instead restored supraspinal control over refined gait movements in rats with an SCI, leading to permanent paralysis (*17*). Recovery of voluntary locomotion relied on the ubiquitous remodeling of brain and spinal neuronal pathways. Similar results were obtained in a man with chronic paraplegia who pursued stand training enabled with electrical spinal cord stimulation (*16*). After several months, the patient regained the capacity to consciously control joint-specific movements of the leg, but only in the electrically enabled state. These experiments in animal models and humans with SCI illustrate the core principle of multisystem neurorehabilitation: provide neuroprosthetic systems to enable and encourage the use of spared, but functionally dormant, neuronal pathways and circuits to boost activity-dependent neuroplasticity and recovery.

Encouraging the brain to join the party

Activity-enabling systems have also been exploited to rehabilitate upper limb function, which more heavily relies on supraspinal contribution compared to gait control (*58*). Facilitation of arm and hand movements using FES systems, peripheral nerve stimulation, or intraspinal stimulation has promoted improvements of motor functions in animal models and in individuals with stroke and cervical SCI (*84*). However, carryover effects of training have been contingent on the presence of voluntary activation. These therapeutic strategies share the same conceptual framework as Hebbian learning: ensure that the exogenous recruitment of muscles—and evoked afferent feedback—temporally collides with a residual descending drive to trigger Hebbian-like neuroplasticity in the activated sensorimotor circuits (*19*, *57*). Consequently, the degree of neuroplasticity and recovery is likely to correlate with the strength and timing of the dialogue between spared and active brain and spinal circuitries. BMI technology offers the opportunity to incorporate brain signals into closed-loop stimulation algorithms to improve communication synchrony. For example, NHPs with a lateral hemisection SCI have learned to increase motor cortex LFP power to volitionally boost ongoing muscle activity with recurrent intraspinal stimulation to perform a force-matching task with their paretic upper limb (*85*). Likewise, preliminary evaluations in individuals with chronic stroke suggest that rehabilitation enabled by BMI-guided electrical stimulation of arm muscles may promote unexpected gains in function (Fig. 2, A and F) (*86*, *87*). In these applications, movement intention was derived from EEG signals, which contain a limited spectrum of prosthetic actions to train movement. However, restoration of a simple function may shift the functional state of the motor infrastructure, establishing the conditions for generalization of learning and improvement to more complex tasks.

For more skilled movements, MSU or ECoG recordings may provide sufficient degrees of freedom to engage hand and arm muscles in the context of rehabilitation training. The BMI toolbox enables monitoring motor attention during training to ensure active participation of the brain, which is essential to trigger activity-dependent neuroplasticity (*17*, *82*, *88*). Although preliminary, these studies are mapping the future of multisystem neurorehabilitation—bidirectional BMI technology to relay decoded intent to networked prosthetic systems (Fig. 2). The underlying objective is to ensure that the neuroprosthetic technology and spared neural systems work hand in hand to promote the maximum possible degree of neuroplasticity and functional recovery for each patient.

Unexpected mathematics

Multisystem neurorehabilitation exploits activity-dependent neuroplasticity to maximize recovery after injury, but the amount of spared neural connectivity restricts the therapeutic potential of such interventions. Plasticity-enhancing neurostimulation methods (*72*), nerve growth–promoting interventions (*89*, *90*), and stem cell technology (*91*) provide tools to soften this physical boundary and increase neuroplasticity with training. These strategies aim to replace damaged neural elements, which position them at the fringe of neuroprosthetics. Theoretically, rehabilitation in a growth-permissive environment is expected to increase functional recovery. However, the first combinatorial attempts in rat models of SCI have uncovered potentially detrimental synergies (*89*) and complex interactions (*90*) between task-specific exercise and plasticity-enhancing therapies. The type and quality of the practiced movements seem to determine the balance between beneficial and detrimental neuroplasticity (*89*, *90*). These preliminary results stress the importance of integrating robotic and neuroprosthetic systems to enable coordinated and powerful movement during training to steer the functional integration of newly formed circuits and regenerative axons into the spared neuromotor infrastructure. The combination of neuroprosthetic training and neuroregenerative strategies, which recruit distinct mechanisms, promises to be complex, but may be the key to improve recovery after the most severe forms of neuromotor impairment (Fig. 3).

FROM PERSONALIZED NEUROPROSTHETICS TO CLINICAL REALITY

Decades of technological developments have engendered a plurality of neuroprosthetic strategies to replace or restore impaired sensorimotor functions after neurological disorders. Concurrently, advances in imaging and clinical neurosciences have contributed to improving our understanding of circuitopathies, emphasizing the importance of patient-centered approaches in the design of therapies. However, these advances in neural prosthetics and neurology have yet to translate into common medical practice. The therapeutic toolbox at clinicians' disposal lacks reliable, safe, versatile, and meaningful neuroprosthetic options to help people with neuromotor disorders. Neuroprosthetic interfaces mainly remain confined to the stereotyped environments of

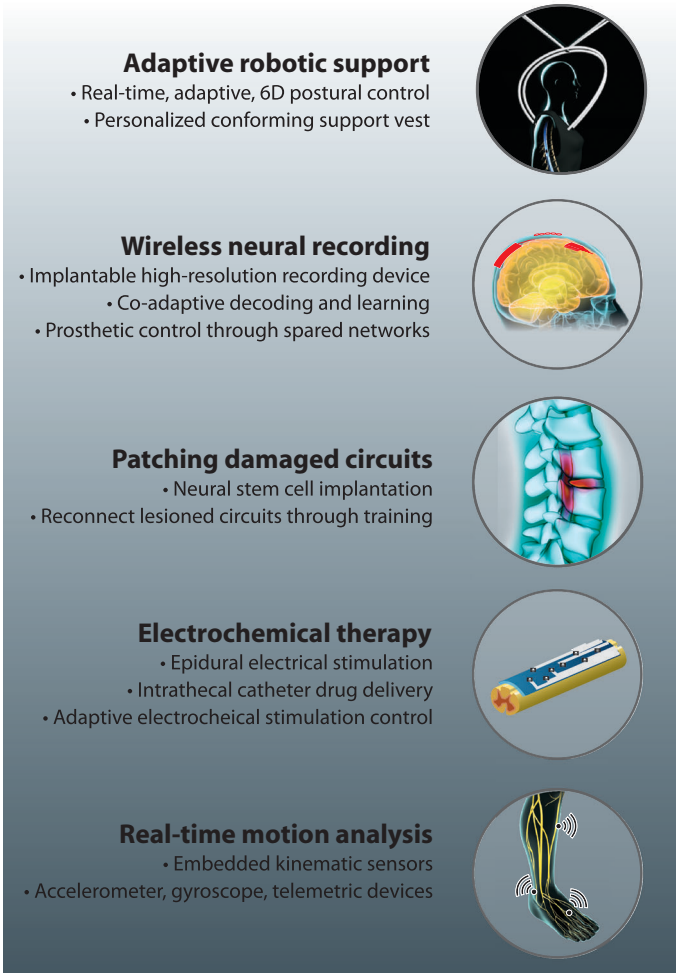

Fig. 3. Neuroprosthetic treatment integration. A panoply of neurotechnologies, neurorehabilitation paradigms, and neural repair interventions has shown efficacy to improve functional recovery after neuromotor disorders in animal models and humans. The next generation of treatments will integrate these paradigms to maximize recovery. Here, we specifically illustrate the putative combination of treatment paradigms for individuals with SCI.

sophisticated laboratories where skilled engineers must operate and continuously tune the technology. Dissemination of personalized neuroprosthetics among the patient population is contingent on several nontrivial clinical, technical, organizational, and regulatory hurdles—the resolution of which relies on the concerted efforts of world-class engineers, clinicians, therapists, funding agencies, and regulatory bodies (Fig. 4). We address some of these challenges.

Neuroprosthetics 2.0

Success in translational neuroprosthetics has been achieved primarily while working with severely paralyzed individuals. These achievements have demonstrated that current neurotechnologies are safe and may improve quality of life. The time has come to broaden the spectrum of targeted neurological impairments, specifically to evaluate the therapeutic effect of neuroprosthetic treatments in individuals with less-severe deficits than severely paralyzed persons, the latter being the typical subjects for early clinical investigations (*11*, *12*, *16*, *88*). For example, implementation of neuroprosthetic systems may uncover distinct treatment mechanisms for individuals with moderate versus severe SCI, including growth of new connections through variable volume of spared tissue (*17*). The potential risk-benefit ratio of surgical interventions for individuals with moderate deficits is high. Nevertheless, proof of efficacy in few subjects would suffice to trigger the deployment of such procedures in larger clinical populations. Inclusion of an educated patient's perspective in the decision-making process for treatment design may further accelerate widespread clinical use (Fig. 4). This step forward requires improved diagnosis platforms to identify the balance between high-risk, high-gain interventions and low-risk, but pragmatic and efficient, treatments that will maximize recovery for each patient (Fig. 4).

Currently, neurologists make these decisions on the basis of their day-to-day experience and collective wisdom. Data-mining techniques provide statistical tools to articulate this classification with objective markers gathered into multicenter database, to create evidence-based personalization of treatment design (*92*). For example, the Stanford, Harvard, and University of California, Los Angeles, hospitals are among the first to digitize patient records, allowing "Google search" across a patients' health history. Structural, functional, and electrophysiological analyses of brain and spinal neuronal networks are common practice in clinical centers. Likewise, technology exists to automatically collect high-resolution information from patients and to standardize functional assessments across clinical centers (Fig. 4). A few U.S. government– and EU government–funded initiatives have begun to implement systematic procedures for harmonizing data quality, standards, and best practices in brain and spinal injury research [for example, European Multicenter Study on Human Spinal Cord Injury (EMSCI; http://www.emsci.org/), the PD genetic association database (http://www.pdgene.org/), and the Alzheimer's association (http://www.alz.org/)]. Similar standardization must be implemented in robotic and neuroprosthetic system designs. Synergizing "big data," standardized protocols, and compatible technologies can serve three essential goals for personalized neuroprosthetics: (i) enable the training of therapists in common rehabilitative technologies, (ii) map patient-specific circuitopathies and potential for recovery to distinct combinations of neuroprosthetic technologies and individualized neurorehabilitation programs, and (iii) monitor evolution of disease states during training to continuously adjust neuroprosthetic systems and rehabilitation procedures to patient-specific features.

Relevant animal models

Most interventions developed in rodent models of neuromotor disorders have failed to translate into clinical therapies. The importance of neocortical networks and corticospinal projections for the control of movement has steadily increased during primate evolution. These discrepancies in the motor system of rodents versus primates have nontrivial consequences for disease etiology, mechanisms of recovery, and therapeutic design (*93*). For example, cortical stroke leads to minimal locomotor deficits in rats (*80*), whereas the same lesions have marked impact on gait in NHPs and humans (*72*). Moreover, neuroprosthetics rely on advanced microsystems that may be implanted temporally, or for a lifetime. Although preliminary evaluations and iterative adjustments of implanted devices are conveniently conducted in rodents, differences in size and immune responses between rodents and humans (*94*) preclude a direct translation to clinically usable devices. Consequently, for many applications, there is a critical need for conducting

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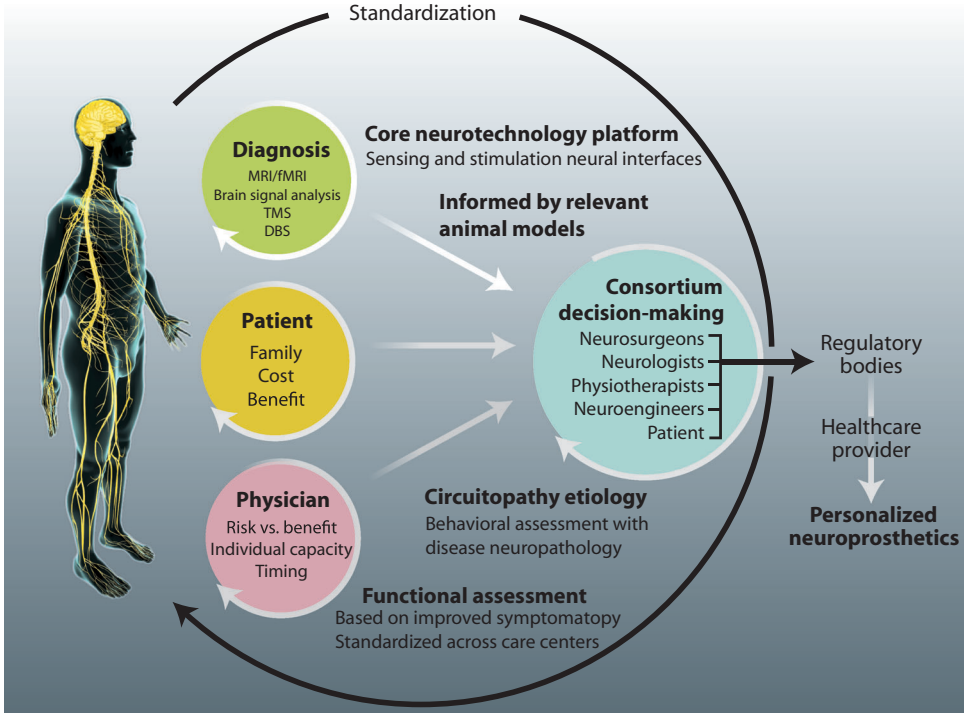

Fig. 4. Roadmap to personalize neuroprosthetics. The path toward personalization necessitates high-resolution disease diagnosis enabled by new core technology platforms and educated by animal models. Functional assessment by the physician attempts to bridge gap between behavioral and etiological source of pathology. An informed consortium of neuroscientists, neurologists, neuroengineers, neurosurgeons, and the patient makes decisions. Regulatory bodies and health care providers are the final enablers of neuroprosthetic technology. MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; TMS, transcranial magnetic stimulation.

translational work in NHPs to evaluate safety, optimize design, and demonstrate efficacy of therapeutic interventions. Despite the stigma associated with publicly funded primate research (*95*), we argue that there is much to gain with few, but well-designed, NHP studies (*96*) to accelerate the translation of promising interventions developed in rodents to viable therapies for humans (*93*).

Impediments to biologically tolerant devices

Neural engineers have developed sophisticated neural interfaces, but these devices have yet to reach the critical threshold to operate safely, chronically, and reliably to mediate long-lasting therapeutic benefits (*4*). This translational step is an underestimated challenge (*51*, *97*). The physical mismatch of materials at the metal-to-scalp or metal-to-electrolyte interface is a constant source of noise and signal degradation, which leads to decreased stability of inputs to decoders (*98*, *99*), and undesirable biological responses, including inflammation, edema, and higher risk of infection (*100*, *101*). Implanted neurosensing and neurostimulating devices must cope with these inherent error signals while behaving transparently to the host body (bio-tolerance). Achieving such transparency requires improved electrode materials to ensure long-term performance, in conjunction with embedded electronics that are wireless, autonomous, and reliable. For example, difficulties in maintaining high-fidelity neural recordings over years, along with decoder instability, continue to be key impediments in the translation of BMI systems to common medical practice. Neuro-attractive molecules combined with improved probe design may alleviate many of the obstacles for long-lasting neural interfaces (*101*). Current flexible device packaging processes for biocompatible polymeric insulation offer erratic dependability against the aggressive environment of the human body (*102*). Hence, most packaging schemes for chronic therapeutic use have been limited to solid titanium hermetic packages or equally rigid ceramics. Carefully designed polymers maximizing flexibility, bio-tolerance, and minimizing porosity may overcome many of the current implantable device packaging challenges, but they remain at the early stages of development (*103*).

Concerted efforts have been necessary to build implantable devices for real-time wireless transmission of tens of megabytes per second of neurophysiological information to external computational centers (*37*). However, their translation to use in humans remains elusive. Engineers seek to build optimized data and power transmission solutions for implantable medical devices. These developments have culminated in commercialized products and clinically available therapies, including pacemakers, DBS systems, and cochlear implants. However, real-time circuitopathy analysis requires spatiotemporally specific broadband recordings from hundreds, or even thousands, of output channels. The Federal Communications Commission (FCC) has recently allotted a dedicated radio spectrum for wearable medical device communication, termed MBAN (Medical Body Area Network). Nevertheless, the ever-growing need for high-rate medical data collection will require data transmission capabilities reaching orders of magnitude above the allotted rate. Cellular communication technology, advanced by both private and public funding, must be leveraged to meet these unprecedented demands (*104*).

The personal and institutional cost of doing business

Neuroprosthetic treatments rely on the integration of multiple technologies into one cohesive therapy. Regulatory pathways through the FDA (U.S. Food and Drug Administration) (http://www.fda.gov/CombinationProducts/) or EMA (European Medicines Agency) (http://www.ema.europa.eu, "hybrid medical product") for multisystem design are prohibitively expensive and combinatorially complex. For example, the clinical implementation of an electrochemical spinal neuroprosthesis to restore locomotion after SCI (*17*) would require ethical authorizations for the electrode array, implanted pulse generator, real-time control policies, implanted motion sensors, multicompartment drug delivery systems, and multicomponent chemical cocktails (Fig. 3). Although some of these components may be tested and validated individually, proof of efficacy may critically rely on their joint implementation. Nevertheless, can this be attained? Without corporate partners, a sound business model, and substantial therapeutic evidence in animal models, potentially useful neuroprosthetic systems remain stranded on

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the bench, unlikely to reach the bedside. The BRAIN initiative is a first step toward funding the conception and implementation of next-generation neuroprosthetic treatments. However, there is a critical lack of institutional funding to fill the gap between breakthroughs in animal models and large-scale clinical trials. Moreover, dissemination to common medical practice faces the bitter equation of high cost plus uncertain improvements in quality of life—a balance that may level differently for patients and health care providers.

THE FUTURE OF PERSONALIZED NEUROPROSTHETIC MEDICINE

Translation of neuroprosthetic technologies to clinical practice is imminent. This confidence arises from few, but powerful, neuroprosthetic treatments that are already improving the life of countless individuals (cochlear implants, retinal prosthesis, DBS, etc.), as well as inspiring breakthroughs in animal models and human case studies (for example, http://www.BrainGate2.org). Neuromotor disorders encompass multifaceted etiologies and phenotypes that necessitate individualized interventions. The field of neuroprosthetics has populated clinical centers and research laboratories with an abundance of neurotechnologies for diagnosis and treatments. Through standardization, existing and contemplated neurotechnologies could be assembled flexibly to personalize neuroprosthetic treatments for each patient and deficit, both in the clinic and at home. Compared to medical treatments based on drug delivery or surgery, neuroprosthetics necessitate the orchestrated contribution from neurosurgeons, neurologists, physiotherapists, and neuroengineers to conceive complex treatments centered on the patient. This transdisciplinary framework is only beginning to be applied (*105*). Through well-organized consortia combining synergistic diagnosis and technological platforms, neuroprosthetics may soon become a treatment option to improve the quality of life for individuals with neuromotor disorders. Although many obstacles remain, personalized neuroprosthetics offer a panoply of technology-intensive but pragmatic solutions "to help the brain help itself" that may be staring us in the face.

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Competing interests: D.B., S.M., J.d.R.M., and G.C. have patents filed on neuroprosthetic treatments, neuropharmacology, and implantable neural devices.

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