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The Evolution of Neuroprosthetic Interfaces

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ABSTRACT: The ideal neuroprosthetic interface permits high-quality neural recording and stimulation of the nervous system while reliably providing clinical benefits over chronic periods. Although current technologies have made notable strides in this direction, significant improvements must be made to better achieve these design goals and satisfy clinical needs. This article provides an overview of the state of neuroprosthetic interfaces, starting with the design and placement of these interfaces before exploring the stimulation and recording platforms yielded from contemporary research. Finally, we outline emerging research trends in an effort to explore the potential next generation of neuroprosthetic interfaces.

KEY WORDS: neural engineering, brain-machine interface, prosthetic, challenges, recording, stimulation

I. INTRODUCTION

Prosthetic devices have existed for millennia. The first prostheses were solely cosmetic, one of the earliest examples being an artificial Egyptian toe from the fifteenth century BC.[1] In the sixteenth century, these devices became more functional when Ambroise Paré engineered an artificial hand actuated by a system of springs and catches.[1,2] Prosthetic technology continues to evolve today due to improvements in our fundamental understanding of the body and advancements in biomedical engineering.[3,4] Pioneering work in the late 1960s by Fetz revealed that, given feedback, monkeys could learn to consciously control the firing rate of their own cortical neurons.[5] The next year, Humphrey *et al* found that recordings from neurons could be used to predict, and thus potentially drive, arm movements.[6] Subsequent groundbreaking studies demonstrated just that; in 1999, Chapin et al. showed that rats could control a robot arm's trajectory via recordings from the motor cortex.[7] These early works laid the foundation for the field of neuroprostheses, devices designed to interact with the nervous system and restore function. The subject has long since developed into a multi-disciplinary field to address losses of motility, sensation, and quality and ease of living due to injury or disease. For instance, the first commercially available cochlear implant was developed in 1972 based on early work by Djourno et al. nearly 20 years prior; it remains the most successful clinical neuroprosthesis.[8] Moreover, deep brain stimulation (DBS) has been a popular option for treating Parkinson's disease for nearly 30 years.[8,9] Perhaps the most technologically advanced upper-limb prosthesis, the DEKA arm, boasts numerous degrees of freedom (DoF) and a control scheme that allows for simultaneous coordination of multiple joints.[10–12] Similarly, the modular prosthetic limb developed in the Johns Hopkins' Applied Physics Lab has 26 total DoF and a distributed processor network for real-time motor coordination. Mechanically, these artificial limbs behave with comparable dexterity to their human counterparts.[10,13] However, many of these technological achievements have not transitioned well to clinical deployment. Upper-limb prosthesis rejection rates average 23–26% for adults, with varying rejection rates for different subtypes.[10,14,15] In fact, users generally prefer less advanced devices, attributing their choices to the low practicality and durability, unwieldiness, and lack of nonvisual or tactile feedback in more advanced prostheses.[10,16] Given these trends, prosthesis adoption does not appear driven by mechanical design or dexterity. Rather,

the limiting factor in current prosthetic systems is the quality of the *neuroprosthetic interface* (NI), defined here as any platform designed to facilitate communication between the nervous system and a prosthetic device.

Neuroprosthetic interfaces can record from and/or stimulate select areas of the nervous system, traditionally via electrodes placed near the cells or tissues of interest.[3,4,17] When localized to the central nervous system (i.e., the brain and spinal cord), such devices are referred to as brain–machine interfaces (BMIs) or brain-computer interfaces (BCIs).[3,18,19] For our purposes, "neuroprosthetic interface" encompasses both BMIs and interfaces outside the central nervous system (CNS), for instance, with the peripheral nervous system (PNS). An ideal interface would allow the user to directly control the output behavior of the prosthesis (e.g., the movement of an artificial arm) while receiving relevant sensory information from the device. This essentially recreates the control-feedback loop found in an intact limb, where the nervous system propagates information via electrical signals, or action potentials, throughout the body.[17,20,21] These signals provide output for controlled muscle contractions and input/feedback from sensory organs (e.g., texture, temperature, position), creating a bidirectional pathway through which we explore and manipulate our environment. It is generally accepted that introducing this input–output behavior in prosthetic devices would yield better, more natural integration with their users, thereby improving their practicality, adoption rates, and positive human impact.[22,23]

Broadly speaking, direct communication with the nervous system is one of the primary goals in neuroengineering to date.[17,24] Recording neural activity can reveal how the nervous system encodes information, as well as user intent such as motor commands.[19,25] Similarly, electrical stimulation (generally via current injection) can induce different neuronal behaviors depending on the type and intensity of stimulation, as well as the intended target. Stimulation of the subthalamic nucleus, for example, can reduce the tremors characteristic of Parkinson's disease.[21,26–28] Both recording and stimulation of the nervous system have clear clinical benefits; however, the complexity of the nervous system has made a clear best standard for neuroprosthetic interfaces difficult to determine.[18,29] The incomplete understanding surrounding nervous system repair and neural modulation exacerbates these difficulties.[17,28] The effects of electrical stimulation (and different patterns thereof) on neuronal activity are still undergoing extensive study.[30,31] Even more "well-established" strategies experience hurdles; for instance, although the incidence of hardware issues in DBS is low, a decline in verbal fluency is a common post-surgical complication.[32] Ongoing research efforts have become more interdisciplinary as the design challenges for NIs become better defined. Among them are biocompatibility, decoding neural information, spatial and temporal precision of recording and stimulation, signal fidelity, and chronic efficacy *in vivo*.[3,33–35] However, as clinicians, engineers, and researchers address these hurdles, NIs have been applied to controlling wheelchairs and computer programs, moving artificial limbs, and restoring basic sensory feedback.[17,36–43] Future NIs may even serve to improve and restore memory, with current research showing promise in rats and nonhuman primates.[44,45]

In this review, we present a broad overview of the development of neuroprosthetic interfaces. We begin by outlining the basic design constraints for a neuroprosthetic interface, as well as important considerations for NI placement (i.e., within the CNS or PNS). We then outline current NI strategies from the literature, emphasizing achievements and ongoing challenges in the field. These strategies range from noninvasive recording techniques to electrodes implanted directly within the brain, and each type of NI has advantages and disadvantages. These studies preface a discussion of promising areas of future development, in which researchers are exploring novel ways (e.g., ultrasound and infrared light) to stimulate and monitor the nervous system.

II. NI DESIGN OBJECTIVES

The specific application of an NI dictates its physical and functional parameters and introduces specific design constraints. In general, however, all platforms share the same goal: robust, clinically viable communication with the nervous system. This goal underlies the rationale for three universal design objectives that applies to all NIs: (1) biocompatibility, (2) high-resolution/selectivity, and (3) long-term reliability/stability. While the aesthetic of the interface (e.g., its appearance and size) does not apply as a design objective in the context of the goal described, it is worth mentioning as an important factor in us-

ers' comfort with and ultimate acceptance of a neuroprosthesis.

First, NIs must be biocompatible; that is, they must minimally disrupt the function of otherwise healthy tissue. This applies not only to their physical properties (e.g., material composition and stiffness), but any effects of their function. Stimulating electrodes, for example, must deliver safe amounts of current into the surrounding tissue without inducing irreversible redox reactions, which can damage both the electrode and the host.[21] Biocompatibility must be considered in the context of the target tissue because the response to a material is often dependent upon where it is implanted (e.g., brain versus peripherally). These safety thresholds are dependent on not only the electrode type and size but also the stimulation parameters (e.g., waveform, duty cycle, pulse frequency, and width); thus, they may well vary across different NIs, as indicated in a more in-depth review of stimulation thresholds by Cogan et al.[46] Equally important is the method of delivery into the body, if the device is to be implanted. Both short-term trauma (as seen in needle deliveries) and the longer-term foreign body response can adversely affect NI function.[35] A common problem in implantable, electrode-bearing NIs is encapsulation of the electrodes in fibrous tissue, which ultimately compromises the ability of the device to stimulate and record as impedances and other biophysical properties change.[33–35] Thus, both the interface and its delivery method must be designed with tissue reactivity in mind. Moreover, this biocompatibility should persist for a lifetime. Although this goal has yet to be fully realized, research achievements to date suggest it is far from infeasible; a 2010 study reported 7 years of recording from the monkey cortex with a microwire array. Visual prostheses have been implanted for more than 10 years in humans, and electrodes to correct foot-drop in patients with hemiplegia have been implanted for up to 12 years.[47–49] These and other longitudinal studies continue to provide invaluable insights into the long-term biocompatibility of NIs,

Second, the interface should be designed such that (1) interference from other tissues (either electrically active or non-electrically active) is minimized and (2) the target area is close enough for high-resolution spatial and temporal recording, and/or selective stimulation. The interface is dependent on both the placement of the NI and its ability to isolate the target signals from surrounding electrical activity. In many cases, smaller microelectrodes may be advantageous, with greater flexibility in placement and less contact with non-target cells. The precision with which an NI can stimulate or record from the target cells is integral to its functionality. Cochlear implants, for example, permit many individuals to perceive speech but not music; literature suggests that an increased number of active electrodes may aid in better melody recognition.[50–52] Moreover, there is often a tradeoff between recording/stimulation selectivity (i.e., the electrode proximity to the tissue) and the foreign body response to more invasive NIs (Fig. 1).

Finally, an ideal NI must exhibit consistent behavior once implanted, both physically and functionally. For instance, physically, NIs may experience micro-motion relative to the brain that could exacerbate a foreign body response and increase the distance between the electrode and the target neurons. Moreover, implanted NIs may suffer from wire breakage, delamination, and insulation breakdown over long periods of time *in vivo* (i.e., "wear and tear" issues).[34,53–55] These NIs can affect the consistency of recordings, meaning more invasive NIs must often be recalibrated regularly. From a functional standpoint, consistency often pertains to the impedance of the electrodes. Related to this finding, as noted above, astrocytes and macrophages surround NI electrodes post-implantation and increase the distance between the active recording/stimulation site and the target neurons.[56] This process may effectively increase impedance or change the phase and frequency response thereof, dropping the signal-to-noise ratio (impairing or eliminating recording capabilities) while increasing the amount of current needed to effectively stimulate the target. Even optogenetic stimulation (addressed in more detail below) may suffer, as gliosis may obstruct the transmission of light into tissue.[33–35] Moreover, the foreign-body response may result in a decreased neuronal density in the vicinity of the active region (potentially due to neuronal degeneration), further inhibiting NI function over time.[33,34,57,58] Interestingly, the presence of microglia has not been directly correlated with electrode performance, although other biotic factors (intraparenchymal bleeding, neurotoxic proteins) are currently being explored as potential contributors to chronic degradation in NI performance.[54,55,59] Hence, chronic NI function is directly tied to its biocompatibility. Arguably, maintaining reliable performance

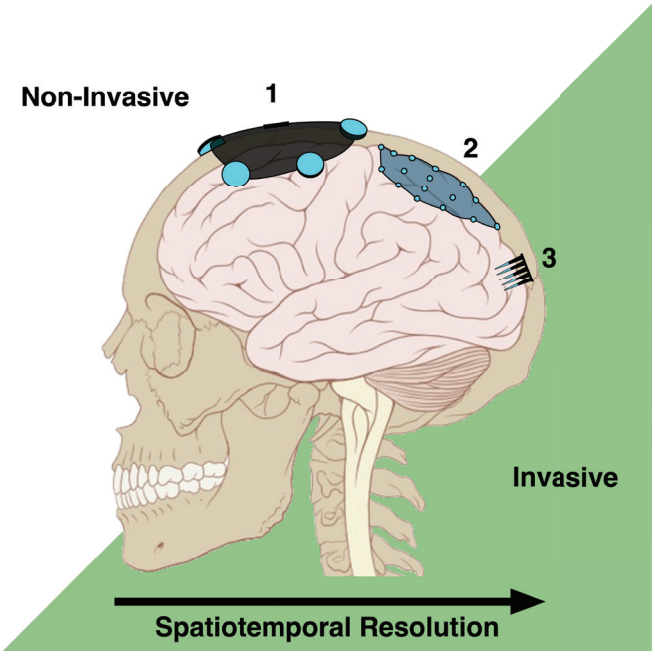

FIG. 1: Signal resolution and NI placement. In general, the more invasive the NI the higher the accessible spatial and temporal resolution. Scalp-mounted EEG electrodes (1) and ECoG electrodes under the dura (2) record gross cortical oscillations, while intracortical electrode arrays (3) can detect single-cell activity. (Adapted from Lynch & Jaffe, 2006.)

for the long term is the most important consideration for NIs and the most challenging obstacle to date.

III. NI PLACEMENT: CENTRAL OR PERIPHERAL?

Typically, NIs can be categorized by their location in the body; that is, whether they interact with the CNS (BMIs, as described above; spinal cord) or the PNS. We present a brief discussion of localization in the CNS versus PNS before exploring each in more depth.

A. CNS Versus PNS Placement

In the brain, recording BMIs offer levels of spatial resolution down to multi- or single-neuron (or unit) recordings.[19,60] Several groups have used these recordings of neural activity to drive motor commands. In 2006, Hochberg et al. reported motor cortex recordings for up to 11 months using an implanted microelectrode array in human spinal cord injury (SCI) patients, who could move computer cursors and robotic arms.[61] Since then, at least one patient with locked-in syndrome and two with amyotrophic lateral sclerosis (ALS) have been able to communicate using an intracortical NI linked to a computer.[62,63] Similarly, at least one human implanted with a microelectrode array has demonstrated cursor control for 1,000 days, nearly 3 years post-implantation.[64] Control signals recorded from the brain have been used to drive direct stimulation of intact, but paralyzed muscle groups in both non-human primates and, more recently, a quadriplegic human.[65,66] The high spatial resolution of these BMIs requires the implantation of electrodes in the otherwise non-injured brain. However, electrode implantation in the CNS may result in inflammation and fibrous encapsulation of the device, often leading to signal instability as previously outlined.[33,35] To decode commands from neural recordings, BMI software implements a learning algorithm to decode the user's intent from specific patterns of neural activity.[19] With extensive training and calibration, users can learn to modulate these patterns and control a target device. Such systems often require regular tuning and recalibration to account for the signal instability often encountered by more invasive BMIs, limiting utility and practicality.

As the end point of the brain's connection to the environment, the PNS presents an opportunity

to leverage the processing power of the CNS rather than straining to decipher it. For instance, PNS interfaces present the benefit of leveraging specialized brain networks and, in particular, spinal cord feedback loops to control and fine-tune movement. Using this approach, motor commands can be recorded directly from motor neurons/axons or the muscles they innervate. Myoelectric prostheses, for example, detect the electrical activity from residual muscles to drive motor commands. As the electrical signals from muscle have an amplitude several orders of magnitude larger than those of nerves, they can be detected through the skin (i.e., noninvasively), and are easier to record and decode. For these reasons, myoelectric prostheses are the most widely available advanced prosthetic system, although they present their own issues. Namely, they offer a limited number of command channels (open and close), and experience signal inconsistency due to skin movement and sweat interfering with the surface electrodes over time.[16] Implantable myoelectric sensors (IMES) are a potential alternative, eliminating the aforementioned issues to provide more consistent signal quality and greater number of control channels.[67–69] Early clinical trials show promise for IMES, with subjects performing more complex tasks with IMES-driven prostheses.[67] Similarly, afferent nerve fibers can be stimulated to deliver sensory information to the host, with stimulation of different neuronal subtypes resulting in different perceptions (e.g., pressure, texture, and proprioception).[70] Targeted muscle reinnervation (TMR) reroutes nerves to distinct muscle groups, leveraging the larger signal amplitudes of muscles to decode motor commands from surface recordings. Interestingly, multiple reports suggest that a similar approach (targeted sensory innervation) may provide sensory restoration by redirecting nerves to sensory nerve fascicles to innervate predefined areas of skin; post-innervation, the skin above the can be stimulated, recreating a sense of touch for the otherwise missing limb.[71–74]

NIs in the PNS may thus be subjected to less of the computational burden of signal interpretation than those in the CNS. However, the PNS presents its own challenges. The computational benefit of recording from the PNS (namely, that the signals come "processed" from the CNS for optimal movement control) is also its drawback: the signal may be stereotyped and require time and training to map to other types of control. Also, interference from surrounding musculature when making neural recordings, as well as signal from muscle being much coarser that that from single units (e.g., neurons or axons), limits the complexity of the command signal. Moreover, in patients in whom the pathway from the brain to the peripheral nerve is compromised (e.g., SCI or ALS patients), the PNS is not a viable location for the interface, although this can be circumvented by stimulating the PNS through commands recorded remotely from the brain.[66]

Finally, peripheral nerves must innervate a living target to survive and maintain useful activity. Following peripheral nerve injury, the distal axon segments undergo Wallerian degeneration and distal support cells provide a supportive environment for axon regeneration and reinnervation (see the 2011 review article by Pfister et al.).[75] However, this environment is temporary, and numerous conditions (among them the size of the injury, time needed for repair, and the condition of the proximal nerve segment) often prevent reinnervation of the distal segment before it degrades.[76,77] NIs that present a living target may better take advantage of placement in the PNS, conceptually similar to TMR noted above. Moreover, early stages of tissue-engineered "biohybrid" platforms are discussed later in the review.

There is no single best option for NI placement, as each comes with its own unique benefits and challenges. Often the particular deficit and/or desired efficacy of a device determines the location. However, the needs and condition of the patient often inform or provide constraints regarding where an NI would function best. Even given efficacy and patient-specific parameters, there may be more than one suitable site for NI implantation. With design objectives and placement options in mind, we now turn toward an overview of different NI strategies, as well as notable accomplishments and common issues in the field.

IV. CURRENT INTERFACES IN THE CNS

Generally speaking, BMIs extract and relay information from the brain or spinal cord to some output that "replaces, restores…or improves natural CNS output."[19] For instance, when disease and/or trauma compromise neuromuscular pathways, NI systems intercept neural activity directly from the sensorimotor cortex, bypassing the faulty pathways entirely.[25] Individuals with a diminished capacity

for voluntary movement (as seen in ALS, SCI, and similar conditions) can thus use BMIs to communicate and interact with their environment through an external device. Such subjects have controlled computer cursors in two-dimensional and three-dimensional spaces, have used computer applications, have browsed the Internet, and have moved motorized wheelchairs.[40,43,78–83] BMIs also see use in rehabilitation, with patients controlling robotic orthotics and muscle stimulators to reinforce or support movement.[84–87] Electrical stimulation of the spinal cord is also being explored to restore movement and coordination to muscles paralyzed from SCI.[88–90] Notably, Harkema et al. have demonstrated that epidural stimulation of the spinal cord in SCI patients can recruit local neural circuitry and give them the ability to stand with minimal support; at least one study participant regained some degree of conscious control over lower limb movement and bladder function.[91,92]

The most common BMIs can be described on a spectrum of invasiveness: generally, the more invasive the system, the higher the signal resolution (Fig. 1). The three most prominent recording methods in the CNS are scalp electroencephalography (EEG), electrocorticography (ECoG), which records from the cortical surface (also called intracranial EEG, or iEEG), and intracortical and depth electrodes. ECoG, intracortical electrodes, and depth electrodes also provide opportunities for stimulation and have led to the early development of bidirectional BMIs, that is, systems capable of both recording and stimulation to "close the loop" with direct sensory stimulation, rather than auditory or visual feedback. There is also a growing body of literature on transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), non-invasive techniques that can increase or decrease activity in specific cortical regions.[93] In the context of NIs, TMS and tDCS have been applied to improve motor learning, for example, when calibrating control schemes for a BMI.[93–95]

A. EEG

Originally developed in 1929 by Hans Berger, EEG uses electrodes placed on the scalp to detect oscillations from neural activity summed over different regions of the brain.[19,25] Researchers discovered that participants could learn to consciously affect these oscillations once provided with some form of feedback, usually visual or auditory cues.[96,97] This biofeedback, combined with EEG's noninvasiveness and simplicity, has made EEG the most common BMI for clinical use.[41] Current EEG arrays are designed to monitor specific types and frequencies of brain waves. With training, these waves can be used as command signals.[4,41,80,96,98,99] One set of examples includes event-related brain potentials (ERPs), which arise due to specific, task-dependent stimuli. The P300, for example, is an ERP that occurs when the user is presented with the item they were focusing on among other related items. For example, a P300-BCI for communication may present the user with different letters until the P300 is detected, indicating the user has seen the desired letter, and build up words sequentially.[98] Among their many applications, EEG-BMIs have been used to control computer programs, write text, move a computer cursor in three dimensions, direct powered wheelchairs, and trigger functional electrical stimulation of otherwise paralyzed muscles.[4,100–102]

Clinically, the noninvasiveness of EEG is beneficial, but it invariably limits the bandwidth of accessible brain activity. Although increased understanding of EEG signals and analysis techniques may somewhat reduce these limits, current spatial resolution is restricted to averages of neural activity across relatively large areas of the brain. Historically, the maximum transfer rate for EEG-BMI was believed to be approximately 2 words per minute, although Chen et. al. recently demonstrated a significant improvement to approximately 12 words per minute.[13,103] Other biopotentials arising from muscle activity (EMG), eye movement (EOG), and the filtering effect of the layers of tissue between the brain and the scalp electrodes can also confound the target signal, which is on the scale of microvolts.[4,101,104,105] Many EEG-BMIs require repeated calibration due to signal variation within and across experiments, although research into adaptive classification algorithms to address these issues is ongoing.[106,107] Overall, EEG remains a powerful and evolving tool in rehabilitation and assistive technology.[4,13,36,40,41,78,84,86,101,108–110]

B. ECoG/iEEG

For ECoG recordings, electrodes (usually embedded in a flexible grid) are placed underneath the skull, either above the dura mater (epidural) or un-

derneath it in direct contact with the cortical surface (Fig. 2).[41,97,111] Compared with EEG, ECoG offers higher spatial resolution, greater spectral frequency, and a generally improved signal-to-noise ratio.[112–114] These advantages have been leveraged in numerous studies demonstrating the potential of ECoG as a BMI with higher resolution than EEG and less of the immune response than seen by intracortical electrodes.[115] ECoG is most often seen in seizure intervention. During surgery, subdural arrays are used to record seizure activity, map the cortex, and target seizure foci before therapeutic resection; they may also be used to study the effects of DBS.[116,117] Achievements in ECoG-BMIs include computer cursor control in one, two, and three dimensions, using recordings of motor imagery to select different characters, and more recently, real-time control of a prosthetic limb with a movement prediction accuracy of 69.2 percent.[113,114,118,119] In 2013, the Fetz group reported successfully using an ECoG grid to elicit sensations by stimulating the somatosensory cortex in two human patients.[120] Although not as spatially specific as intracortical electrodes, differing stimulation frequencies and amplitudes were perceived as changes in the sensation's intensity.[120]

The benefits of ECoG stem from its proximity to the brain compared to scalp EEG: direct cortical contact eliminates the signal attenuation and filtering that result from recording through the skull. These advantages come at the cost of increased invasiveness, as ECoG requires surgery to expose the brain and position the electrodes.[19,97,114] As such, clinical studies have generally been limited to epilepsy patients already undergoing surgery for seizure intervention.[115] Clinical studies have shown that, with control schemes adopted from EEG, ECoG-BMIs require shorter learning periods while delivering comparable accuracy.[19,114] However, due to the above restrictions, these studies have historically been limited to short-term trials. The recently FDA-approved Neuropace system, which uses subdural electrodes to detect seizure activity, may provide opportunities for longer studies.[121] Whether these benefits persist over time remains to be seen, although a 2010 study by Chao et al. showed near-constant predictive accuracy over multiple months in monkeys.[122] Historically, ECoG has been considered "middle ground" on the spectrum of BMIs. The electrode placement allows recording of finer-scale activity than EEG without penetrating the blood-brain barrier, poten-

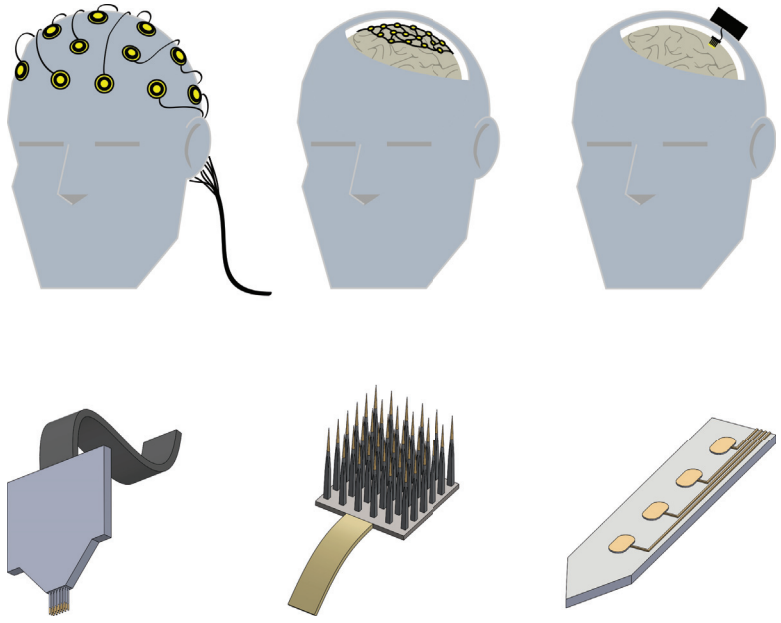

FIG. 2: Neuroprosthetic interfaces in the CNS. Top: Placement and invasiveness for prominent BMI approaches. Current interfaces interact with the CNS at the scalp (left), the brain surface (middle), or from within the brain (right). Bottom: Examples of intracortical/penetrating neural electrodes. Intracortical NIs may take the form of microwire assemblies (left), arrays (middle), or flat shanks with multiple active recording/stimulation sites (right; center ellipses portray active sites).

tially preserving long-term signal quality.[114,115,123] Active efforts to improve ECoG platforms include more flexible arrays, electrode miniaturization, and low-impedance electrode coatings—all designed to improve biocompatibility, signal resolution, and selectivity.[124] While these improvements are beneficial for NIs in general, craniotomies must be performed for the positioning of ECoG arrays on the brain. As such, human ECoG trials are primarily acute, and the ratio of risk to benefit for ECoG use may well vary depending on the patient. While the behavior of ECoG arrays over time in humans has not been fully elucidated, longer-term animal studies with subdural electrodes and the development of wireless, fully implantable ECoG devices show promise for ECoG as applied to NIs.[115,122,125–128] Significant progress must also be made in ECoG signal acquisition and analysis to account for the amplitude attenuation at higher frequencies (i.e., gamma bands, which can exceed 100 Hz) and to better capture signals from subcortical areas. These higher frequencies have been strongly correlated with critical cognitive and motor processes, and although still largely untapped, they may prove valuable in next-generation BCI systems.[114] In short, more detailed risk–benefit analyses must be conducted before accurate comparisons can be made.

C. Intracortical and Depth Electrodes

Electrodes implanted within the cortex offer the highest spatial and temporal resolution recording, and they are capable of recording single units (the action potentials of individual neurons) as well as field potentials (activity across several neurons).[97] Current intracortical electrodes include flat shanks and shank arrays with multiple electrically active sites, platform arrays with several fixed electrodes (e.g., the well-known Utah electrode array and its FDA-approved iteration in BrainGate trials), microwire assemblies, and DBS electrodes, which are implanted in subcortical structures (Fig. 1).[26,34,97,104,129] The high resolution and signal-to-noise ratio (SNR) of intracortical NIs compared with EEG and ECoG makes them ideal for the real-time detection required for smooth prosthesis control.[130] Moreover, strategic positioning of the active sites offers selective recording from different neuronal populations. Simultaneous recordings from cortical and subcortical regions have been performed in rodents, primates, and humans.[59] Beyond recording, intracortical and depth electrodes can be placed with high spatial specificity, making them ideal for directly stimulating specific areas of the brain. CNS stimulation can be applied to suppress epileptic seizures, mitigate symptoms of Parkinson's disease (as seen with DBS), and this procedure may be beneficial in treating certain psychiatric conditions.[26,28,35,131] Potential also exists for restoring sensory function using this technique. Several studies in non-human primates show that sensory information can be delivered via intracortical stimulation, often as part of a closed-loop BMI.[132–134] Perhaps one of the greatest examples of sensory restoration is that of cochlear implants, which are designed to stimulate the auditory nerve tonotopically. Worldwide, more than 100,000 people with hearing loss use cochlear implants to compensate for their impairments, and they can even hear and understand speech.[135] Similarly, retinal stimulation can elicit visual percepts in patients with vision loss.[136,137] Ongoing development of electrodes and stimulation parameters has provided basic letter recognition, orientation, and improved visual acuity in blind patients.[138–140] The first commercially approved retinal prosthesis, Argus II, has been shown to improve hand–eye coordination, mobility, and letter recognition, although the quality of these benefits varies as the stimulation complexity increases.[137,138,141]

The high spatiotemporal resolution of intracortical and depth electrodes is achieved through exposing and/or penetrating the brain, though these are significantly more invasive processes than those required for EEG or even ECoG. Moreover, the quality of intracortical recordings tends to degrade over long periods of time. While Hochberg et al. reported recordings from the motor cortex over 1 year post-implantation, they reported decreased signal amplitude and channel count.[61,97] Even when chronic recordings are attained, extremely labor-intensive recalibration has been necessary due to signal/spike drift from day to day. Studies on single-unit stability show that individual neurons may vary their firing patterns significantly across recordings; one such study reporting only 39% of the units remaining stable after 15 days.[142,143] Thus, arguably the most significant design problem for intracortical electrodes is the stability of the interface over both acute and chronic time scales.[33,34] This stability is hindered by a host of factors acting on a range of time scales. In the short term, the initial mechanical trauma of

electrode insertion and the presence of a foreign body lead to scar formation surrounding the implant, inflammation, and a decrease in neuron density surrounding the electrode.[33,53] Over time, implanted electrodes may suffer from mechanical failures (e.g., broken connectors, insulation fracture and delamination).[54,55,59] There may also be so-called micro-motion effects due to differences in mechanical properties between electrodes and brain tissue that become relevant due to head motion and/or pulsatile motion due to the patient's heartbeat. Electrode arrays fixed to the skull can also experience motion relative to the brain that may shift them away from optimal recording locations.[34,53,104,144] All of these factors can consequently affect signal quality during chronic implantation. However, the exact effects of the immune response on signal quality are ambiguous. Studies report high variability in both immune response and device functionality across and within several types of intracortical recording electrodes.[34,35] Strategies to overcome these biocompatibility and biostability challenges include finding insertion speeds to minimize initial trauma, delivering immunosuppressive and anti-inflammatory agents, incorporating bioactive molecules to encourage cell adhesion, and constructing electrodes from softer materials.[34,145–151] Additionally, downstream correction *in silico* may account for signal drift through auto-recalibration, as suggested by Bishop in 2014, or offset correction algorithms, as demonstrated by Homer et al.[152,153] Still, no consensus has been reached regarding the kind of cortical activity that is best for intracortical recordings. The benefits of capturing individual spikes versus the summed activity of several neurons (local field potentials, or LFPs) are still being compared. LFPs may be more stable, and they have been shown to yield similar performance to single-unit activity in predicting movement.[154,155] Finally, current BMIs are limited by the number of electrodes and active sites that can be incorporated onto one device, which in turn limits the number of distinct neural signals that may be desired for multidimensional input/output. The Argus II described above has 60 electrodes and covers 11˚ by 19˚ in the visual field, compared to the full field of human vision, which is roughly 180˚ by 135˚, including peripheral vision.[141,156,157] This limitation in NI bandwidth is a key target of the DARPA Neural Engineering System Design (NESD) initiative, which aims to record from and stimulate 1,000,000 and 100,000 neurons, respectively.[158]

D. Bidirectional Systems

Systems capable of simultaneous (or near-simultaneous) electrical stimulation and recording of neural activity are also being explored. Based on temporal and spatial proximity of the stimulation and recording region(s), this approach introduces the additional challenge of the electrical stimulation itself interfering with the quality of the recording; however, there have been several notable successes in bidirectional neural interfaces. In 2011, O'Doherty et al. implanted microwires into the primary motor and somatosensory cortices of monkeys. By stimulation of the latter cortex, they were able to provide tactile feedback as the monkeys directed a computer cursor (using motor cortex recordings) to explore different objects.[134] Alessandro Vato et al. demonstrated bidirectional BMI in rodents; early validation showed it capable of stimulating the brain upon detection of some target activity.[159] Vato et al. also demonstrated a bidirectional BMI algorithm that maps the state of an external device (e.g., position) into a series of electrical impulses while transforming recordings from the motor cortex into a tunable output force. Such a paradigm could conceivably be applied toward the operation of an artificial limb. The algorithm was tested against simulations of cortical neural data, proving robust results even when the data were artificially degraded to mimic declining BMI sensitivity.[160] Similarly, Dr. Fetz's research group at the University of Washington has conducted extensive research into linked microrecording-to-microstimulation systems.[161–163] Here, the Neurochip and its successor, the Neurochip 2, were designed to deliver intracortical stimulation upon detection of certain neural activity. Both platforms have been implanted in freely moving monkeys. As of 2011, the Neurochip 2 was able to record (via ECoG) and stimulate the motor cortex in a closed loop.[163]

Additionally, Brian Litt and other researchers have reported on extensive work in developing iEEG systems for seizure intervention.[164,165] One such device, the Neuropace RNS System, uses iEEG to record cortical activity and stimulates targeted regions to suppress epileptic seizures upon the detection of abnormal activity. Through careful feature selection and algorithm design and training on large datasets, these platforms can be tuned to detect precursor seizure activity specific to each participant. The RNS is FDA approved, although studies comparing the

behavior of closed-loop versus open-loop stimulation devices (which simply stimulate target regions regardless of cortical activity) are ongoing.[164–166]

E. Challenges in the CNS

There is a clear tradeoff between spatiotemporal resolution and invasiveness for CNS interfaces (see Figs. 1 and 2). Thus far, the output capabilities of noninvasive BMIs are limited by their resolution and the ability to account for variation in the target signal features; the latter requires extensive training to learn alternative, potentially non-intuitive control schemes.[83,106] Variability in performance accuracy across BMIs has been well documented; sources range from user fatigue and concentration to the type and severity of the user's disability.[4,98,167] Although EEG-BCIs have been used for gross motor commands, the narrow bandwidth and latency currently prevent real-time, fine movement control for prosthetic limbs.[4] While the tailored electrode placement of invasive BMIs allows for higher-resolution recording, the highly variable *in vivo* stability and long-term behavior of the current widely used technologies in the field still pose substantial developmental hurdles to their clinical adoption.[33,35]

Overall, intracortical electrodes will require significant improvements and further optimization before widespread use ensues. However, early studies in humans have shown that subjects implanted with intracortical arrays can operate computer applications and prosthetic devices, such as the DEKA Arm (reported by Hochberg et al. in 2012).[61,168] Additionally, the bandwidth of ECoG allows for the detection of key neural information related to motor intent and certain disorders without directly penetrating the blood–brain barrier. Moreover, advances in flexible electronics (e.g., thin-film electrodes) have yielded ECoG arrays that conform to the brain without compressing the tissue.[125,169–171] However, implanting these arrays requires large craniotomies for grid placement; thus, human trials with ECoG arrays have generally been limited to acute studies for patients already undergoing treatments (primarily for epilepsy), with a few recent trials in other patient populations.[119,172,173] More chronic studies have been performed in nonhuman primates. A 2011 study in rhesus macaques showed stable power spectra and evoked potentials over 8 weeks.[125] Thus, while ECoG-based BCIs may in time provide tangible benefits for NI users, the effects of chronic implantation on both interface function and the host brain must be further characterized.

V. CURRENT INTERFACES IN THE PNS

Peripheral nervous system interfaces (PNSIs) target the peripheral nerves located throughout the body for electrical stimulation and recording.[71,174] Like BMIs, peripheral interface research aims to recover bodily functions that are lost when trauma or disease-related damage occurs to the nerves supplying the area and/or the end targets themselves. Although peripheral nerves exhibit regenerative abilities when transected, this process is slow, and the target area may atrophy in the interim.[174] By recording the activity from the proximal nerve stumps, peripheral interfaces can provide motor commands for a neuroprosthesis; similarly, information can be translated into electrical impulses to stimulate the nerve, replicating tactile and proprioceptive sensation.[71,74,175–177] Challenges in the PNS overlap significantly with those in the CNS, namely, the tradeoff between signal selectivity and tissue disruption, although the fascicular organization of peripheral nerves can be leveraged here. Targeted muscle reinnervation, originally developed by Todd Kuiken, involves rerouting nerves to isolated portions of healthy muscle and using the resultant EMG signals to control prostheses.[72,178] While not directly contacting the PNS, TMR leverages the larger signal amplitude of EMGs, the ease of accessing muscle relative to the nervous system, and preexisting methods of recording muscle activity.[71,178] These benefits are crucial to the success of TMR, and several research efforts have demonstrated that patients undergoing TMR exhibit real-time multi-joint control of prosthetic limbs and perform daily tasks more naturally.[72,178] Ongoing clinical trials in TMR will likely lead to further improvements. Another approach is the regenerative peripheral nerve interface (RPNI), developed by Paul Cederna et al., wherein nerve fascicles are implanted into muscle grafts, each with its own electrode.[179] Although it is still being optimized, RPNI has proven viable for more than a year in a rodent model, with muscle reinnervation and consistently detectable muscle activity during implantation.[179–182]

Functional electrical stimulation (FES) is another application wherein peripheral nerves are

stimulated; clinical trials have proven FES useful in correcting foot-drop, regulating respiration, and restoring grasp for tetraplegics.[71,100,183] Stimulation of the PNS also has applications in regulating bladder dysfunction, incontinence, and has even been implicated in stroke protection in animal models and immune system modulation in at least one human study.[184–188] The NIH's SPARC initiative (Stimulating Peripheral Activity to Relieve Conditions) is focused on supporting these and similar research efforts in "peripheral neuromodulation," i.e., influencing organ function via stimulation of the PNS. As with BMIs, peripheral interfaces can be broadly differentiated by their invasiveness (Fig. 3).

A. Extraneural

Extraneural electrodes reside outside the epineurium (Fig. 3) and are the least invasive of the PNSIs. They take a number of forms, although they generally consist of a biocompatible insulator such as silicone containing at least two electrical contacts.[71,189] Some are sutured directly to the epineurium, while others are designed to wrap around or enclose the nerve. Cuff electrodes, the most widely investigated peripheral interface electrode, are favored for their ease of implantation and fascicular selectivity. Studies have demonstrated that certain cuff electrode designs can record and stimulate chronically, and they have already been used in relieving pain, managing incontinence via stimulation, and controlling hand-grasp prostheses, with some studies lasting several months.[190–193] Using multiple cuffs or several contacts within a cuff enables stimulation of different nerve fascicles. The somatotopic organization of axons within these fascicles allows for the selective, graded activation of distinct muscle groups in the upper limb.[3,194–198] A prevalent application of extraneural NIs is vagus nerve stimulation (VNS), an invaluable technique that has been clinically approved to treat symptoms of drug-resistant epilepsy and, more recently, chronic depression.[199,200] The therapeutic potential for VNS in Alzheimer's disease, migraines, heart disease, and other psychiatric conditions is also being explored.[200] Similarly, cuff electrodes have been implanted in human amputees, providing consistent tactile sensations throughout the "phantom" limb for more than a year,

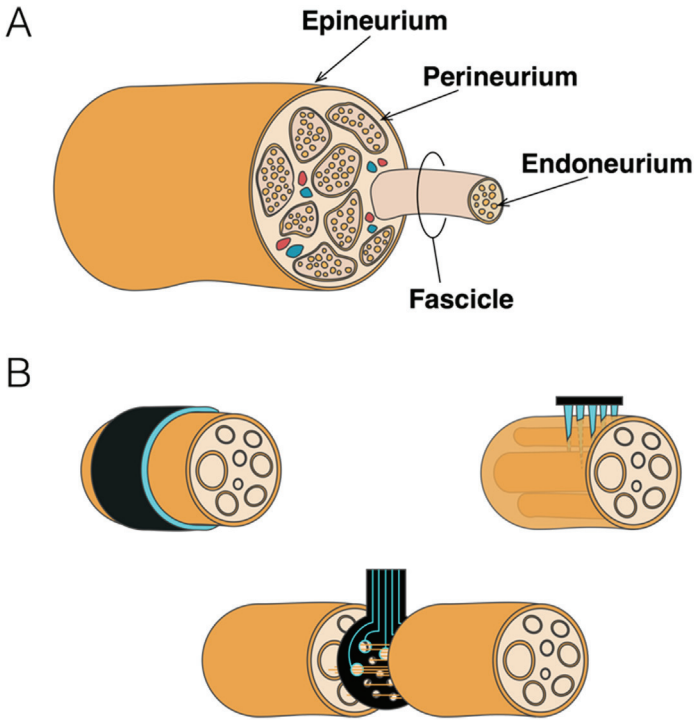

FIG. 3: NIs in the Peripheral Nerve. (A) General overview of peripheral nerve anatomy. Individual axons are bundled in endoneurium and in turn, into discrete fascicles, supplied via blood vessels embedded in the perineurium. Fascicles in turn are bundled and protected by the dense connective tissue of the epineurium. (B) Peripheral interface electrodes range from extraneural (upper left), to penetrating/intraneural (upper right), to regenerative (bottom).

yielding measured improvements in dexterity with their prostheses.[201] Flat-interface nerve electrodes (FINEs) increase the surface area of the target nerve and consequent selectivity by flattening it; the amount of damage was force dependent with no detectable damage below a certain threshold. Moreover, the flattening of the nerve increases the number of accessible fascicles near the epineurium.[71,202,203] Computational models of the FINE strongly suggest its potential for highly selective stimulation in FES applications; a theory since borne out by numerous animal and clinical trials.[204–206]

B. Intraneural

Intraneural electrodes penetrate the epineurium and generally the perineurium as well, contacting the target fascicles directly. Electrodes have been designed for both longitudinal and transverse insertion into the nerve, although longitudinal intrafascicular electrodes (LIFEs) are more common and have been implanted in human subjects.[71,176,207] The Utah array, originally developed for cortical applications, has also been adapted for experimental use to record from and stimulate peripheral nerves.[208] They experience higher selectivity and signal-to-noise ratios, as well as a lower stimulus current threshold (in general), as there is less leakage into neighboring tissues.[209] The selectivity is such that specific fascicles and portions of single fascicles can be independently stimulated.[210] Intrafascicular electrodes have been shown to record action potentials for months at a time in cats with minimal tissue reactivity, although due to their needle structure and penetration into the perineurium, they are capable of damaging the nerve and can elicit secondary inflammatory responses.[3,208,211,212] Some researchers have sought to mitigate these issues by replacing the metal wires with polymer filaments, which more closely match the stiffness of neural tissue and exhibit limited electrode drift.[71,213,214] An animal study has demonstrated that LIFEs can be used as part of a closed-loop system for controlling ankle position.[215] Further research and experimentation may allow for similar developments in humans. A feasibility study has already shown that LIFEs can record viable motor command signals and transmit stimuli encoding joint angle and force when implanted in the median nerve.[176] Similarly, a researcher volunteered to have a 100-electrode array implanted in his median nerve for approximately 3 months and experienced force feedback from the sensors of a prosthetic hand and controlled it in turn; however, only a fraction of the electrodes remained functional by the end of the study due to wire failure.[175] As with intracortical electrodes, the long-term stability of these devices must be further evaluated and improved upon.

C. Regenerative

Regenerative electrodes (commonly called sieve electrodes) are placed across transected nerves, allowing the regenerating nerve to extend axons through the electrode itself. Contacts around some of the holes allow for recording from and stimulation of axons and groups of axons. Several regenerative electrodes also possess guidance tubes for proper placement of the nerve trunk ends.[189] Sieve electrodes made from polyimide reduce (but do not eliminate) the compressive damage of more rigid materials like silicon, which can lead to axonopathy.[216] Moreover, polyimide electrodes have proven biocompatibility, with no detectable inflammation over 12 months of implantation in a rat study and similar results in others.[217,218] Recently, Gore et al. reported successful motor axon growth through a PDMS regenerative electrode in rats, with reinnervation of distal muscle confirmed through recording during locomotion.[219] However, a significant drawback with sieve electrodes is that the target nerve must be transected, which may cause some degree of cell death in the projecting spinal motor and dorsal root ganglia neurons as well as introduce often significant time periods for the axons to regenerate to appropriate targets. Moreover, post-transection, fascicular organization of the target nerve changes dramatically—smaller sensory and autonomic fibers regenerate through the sieve faster than larger (e.g., motor fibers), which in some cases may have diminished or absence of regrowth.[217,220,221] This process is reflected, for example, in a low degree of reinnervation seen in distal muscle.[217,220] Due to the invasiveness of the procedure and the time needed for the nerve to heal, research with regenerative electrodes has been limited mainly to animal studies.[189,221–226] However, some of these studies indicate that such electrodes may be chronically viable. Srinivasan et al. recorded action potentials from rats for up to 5 months post-implantation.[225] efforts to optimize sieve electrodes *in vivo* are ongoing, and pores ranging from 30 to 65

nm in diameter appear to best support nerve regeneration.[71,227,228] Similarly, Bellamkonda et al. noted that a pore length of 3 mm ensured that at least one node of Ranvier (where the action potential presents the largest detectable extracellular signal) would be in the NI.[225] Additionally, Kung et al. created a "regenerative peripheral nerve interface," wherein a transected nerve innervates distinct muscle units, each of which was paired with an electrode.[180] Thus far, the interface has yielded reliable behavior (i.e., recorded compound muscle action potentials from the muscle units) for up to 7 months in a rodent model.[180] Notably, studies have used polyethylene glycol (PEG) to reconnect damaged nerve fibers at the axonal level.[229–231] Immediately following trauma, PEG therapy has been shown to rapidly restore functional connections in animal models; as such, it may be a viable method to limit the damage of nerve transection and improve acute and chronic functionality of sieve electrodes.[229–233]

D. Challenges in the PNS

Extraneural electrodes must contend with the relatively large biopotentials of adjacent tissues such as EMG, although insulation like that seen in cuff electrodes at least partially mitigates this issue.[71,234] Extraneural selectivity is mainly limited to fascicles near the epineurium, where the electrode contacts the nerve. FINEs as described above increase electrical access to the deeper fascicles of the nerve. Also, the slowly penetrating interfasicular nerve electrode (SPINE) extends blunt electrical contacts into the epineurium without piercing the perineurium. However, SPINEs have only undergone acute studies, and their influence on the nerve over longer periods has not yet been investigated.[71,235] Intraneural and regenerative electrodes offer high selectivity and have been proven stable, some for months at a time. However, the stability of these electrodes must be further studied and optimized before clinical trials become widespread. Fibrous encapsulation of these electrodes is common, and while potentially beneficial for physical stability and maintenance of intimate contact, the resulting signal attenuation can lower the efficacy of implanted devices.[3] Additionally, the material properties of peripheral interface electrodes must be carefully tailored (as is the case with all electrodes), as overly rigid or tightly fitting electrodes can damage the nerve by compressing it or cutting off the blood supply.[71] This is a particularly important consideration in cases of nerve interface in motile limbs requiring sliding and often stretching of the nerve, as device "catch points" may lead to nerve injury and impede blood flow.

A related phenomenon is the loss of electrode functionality due to connection failure, which has generally been observed in longer studies.[175,236] This problem is also complicated by the range of motion experienced by peripheral tissues (i.e., limb movement), which necessitates the use of flexible materials that will remain in contact with the target area without damaging the nerve. As TMR uses surface EMG sensors to detect the rerouted motor commands, it must contend with the interference from movement and sweat, which negatively impact signal fidelity through the skin.[13]

Reverse recruitment is another issue facing PNSIs, notably for FES applications. In the intact neuromuscular pathway, motor units are activated in order of increasing size; that is, smaller axons become active before larger ones (i.e., the size principle). The more fatigue-resistant motor units are recruited before the fatigue-sensitive ones during normal muscle contractions.[174,237] However, muscles activated via FES often fatigue quickly due to violation of the natural size principle, with the early recruitment of the larger fibers due to nonspecific electrical stimulation of the nerve.[238–241] Some efforts to address this effect include varying stimulation intensities, frequencies, pulse widths, and "alternating" paradigms, wherein different fascicles are stimulated in sequence to avoid overtaxing any one group of motor units.[238,242,243] As with BMIs, evaluating and improving the long-term *in vivo* function of peripheral interfaces is crucial to harnessing their full potential.

VI. FUTURE INTERFACES: NOVEL PARADIGMS

A. Optogenetics

Optogenetics involves the incorporation of opsins, or light-sensitive ion channel proteins, into cells via transgenesis or viral vectors. Cells expressing these opsins are then subject to targeted stimulation by illumination that in turn leads to changes in membrane potential.[60,244] Once opsins are introduced, it is possible to stimulate targeted neurons with pulses of light rather than current injection. Stimulation can be inhibitory or excitatory depending on the current

passed through the channel, and selectivity has high spatial control; specific cell types can be targeted via transfection methods, and only transfected cells will be susceptible to optical stimulation.[60,245,246] Although optogenetics technology has been extensively developed for neuronal probing and control *in vivo*, recent efforts have been made to integrate optogenetics into neural interface technology. Current research in this area is focused on studying how best to implement this powerful tool for neural interfaces and on combining it with existing interface technologies.[247,248] Bryson et al. have demonstrated "orderly recruitment" of muscles innervated with light-sensitive motoneurons.[247,249–251] In this case, "orderly" refers to concordance with the size principle: the preferential recruitment of smaller muscle units before larger, more easily fatigued units. This specificity is physiologically advantageous but, as noted above, is currently unaccounted for in electrical stimulation. Additionally, optogenetic stimulation of the auditory nerve and retina has been realized, and optogenetic stimulation arrays are being developed for use in a closed-loop neuroprosthetic system.[245,248,252] Implanted nerve cuffs offer a potential method of long-term interface, and they are being investigated in animal studies.[249] Similarly, Steinberg et al. and others have begun exploring optogenetics as a therapeutic strategy for improving functional stroke recovery.[253–255] Optogenetics may even serve as a potential extension of current DBS, using light to selectively target neural circuitry.[256,257]

In a similar vein, neurons transduced with genetically encoded calcium indicators (GECIs) or voltage sensitive dyes (GEVSDs) can produce proteins that fluoresce during neuronal signaling.[258–260] These sensors enable the direct visualization of electrical activity in real time, providing an invaluable opportunity that has already been used to supplement and improve upon conventional recording methods.[59,169,258] The combination of optogenetics and GECIs in a closed loop has already been realized, with the GECI R-GECO1 and a channelrhodopsin allowing for reliable, simultaneous activation and imaging both *in vivo* and in *C. elegans* with little overlap.[261] It is feasible to consider that future neural interfaces will use optogenetics and calcium/voltage sensing to interact with neural tissue without physical contact or direct current injection. As with all NI platforms, optogenetics poses its own unique challenges. Host parenchyma must be transfected with adeno-associated or lentiviruses to express photoresponsive proteins, or *ex vivo* tranfected neurons must be injected into the brain (as described below). Additionally, light waveguides must be implanted in the brain in order to access deeper structures, and a fully implantable laser light system with sufficient power has yet to be developed (although LED optrodes can be used).[262] Finally, visible light cannot penetrate far into the brain before being scattered; this is being addressed with near-infrared (NIR) light, which can penetrate significantly deeper into tissue. Nanoparticles designed to absorb NIR light and in turn emit appropriate wavelengths to activate channelrhodopsins in target regions of the nervous system are being pursued.[263,264] Tsien et al. also demonstrated that channelrhodopsins sensitive to far-red light (above 600 nm) can be activated noninvasively because tissue absorbs and scatters such wavelengths less effectively than blue light.[265] Chronic function is also of concern because many optical probes are relatively rigid compared to the brain, and have experienced both glial encapsulation and reductions in signal quality over weeks to months, similar to other NI platforms.[266]

B. Magnetoencephalography (MEG)

Electrical activity induces magnetic fields that can be recorded via MEG. Similar to EEG, the magnetic fields can be consciously altered by users, allowing for real-time recording and control schemes based on these varying patterns, and there is evidence that MEG confers greater spatiotemporal resolution recording than EEG.[267,268] Thus far, MEG has been applied to control both virtual and physical prosthetic hands (alongside visual feedback of the hand's position) and drive the operation of virtual software by translating user-modified signals into computer mouse clicks.[267,269–271] The primary limiting factor for MEG in the context of NIs is the environment required; participants are placed in a magnetically shielded room and must remain still to avoid artifacts from body and head movements.

C. Ultrasound

A potential noninvasive stimulation and recording methodology is transcranial Doppler ultrasound (TCD), which measures cerebral blood flow velocities. Different states of mental activity can be reflected by changes in blood flow velocities, which

are then detected with TCD.[272] While TCD carries an inherent latency compared to other NIs (5–10 seconds between a change in mental state and the corresponding change in blood flow velocity), it is robust against electrical artifacts and is more portable than MEG.[272,273] Early research has shown TCD is fairly accurate in distinguishing distinct mental states (83–86% in a 2011 study by Myrden et al.), and it has been applied at least once to communicate via control of a virtual keyboard.[272,273] Ultrasound has also been used to evoke sensation through stimulation of peripheral nerves; moreover, neuropathic tissue has been shown as more responsive to ultrasound than healthy nerve, potentially offering a noninvasive way to identify neuropathic conditions.[274,275] Interestingly, focused ultrasound is also capable of inducing conduction block in peripheral nerves and is actively being explored as a potential treatment for pain and spasticity.[276–278]

D. Transcranial Magnetic Stimulation

TMS consists of magnetic pulses directed to the brain. By varying the parameters of the pulse train and the coils, specific areas of the cortex can be targeted for excitation or inhibition.[279,280] As a noninvasive technique, TMS has been an invaluable research tool for mapping the cortex, studying information processing, and investigating brain plasticity in humans.[279] Interestingly, TMS can elicit visual percepts in subjects through stimulation of the occipital cortex, providing a way to map and evaluate functional differences in the visual cortex for both seeing and blind subjects.[281,282] Within the context of NIs, TMS has been used in combination with EEG to "link" two human brains by delivering movement commands or phosphenes (perceptions of light caused by non-visual stimuli) to one participant based on recorded activity of the other.[283,284]

E. Infrared Nerve Stimulation

Extraneural optical nerve stimulation (also called infrared nerve stimulation, or INS) using pulses of infrared light has been suggested as an alternative method to interface with neural tissue.[285–289] INS utilizes low-energy, pulsed light to reliably stimulate neural structures. INS parameters (radiation wavelength, irradiation time, and energy) can significantly alter the light-tissue interaction, and the careful selection of parameters may provide a level of selectivity superior to that of electrical stimulation.[290] The feasibility, safety, and selectivity of INS have been well described and characterized in a number of animal models. Notably, fascicular infrared stimulation of the rat sciatic nerve elicited muscle responses with a selectivity previously only achieved with intraneural microelectrodes.[288] The development of INS-based interfaces may offer significant advantages over electrical stimulation; the wireless stimulation and high spatial resolution allowing for finer activation of the peripheral nerve. Recently, INS has been applied to the CNS, and has been shown to effectively evoke excitation and inhibition in the motor and somatosensory cortex, auditory and vestibular systems, cortical column, and the primary visual cortex in nonhuman primates.[285,291,292] Kuo et al. also reported on the stimulation of the subthalamic nucleus in a rodent model, with stimulation resulting in increased dopamine, suggesting that INS may be a potential therapeutic platform for Parkinson's disease and other dopamine-related conditions.[293] Finally, early trials in humans have shown that INS can be used to stimulate human dorsal root ganglia.[294] Although the research surrounding INS is promising, clinical applications of INS would require constant stimulation at 12–15 Hz, placing it above the upper threshold for injury.[295] An alternative to bypass these limitations has been proposed that combines INS with extraneural stimulation via nerve cuff.[296–298] This "electro-optical" paradigm uses INS to precondition the nerve, making it more excitable and amenable to electrical stimulation.[296–298]

Another point of concern is the mechanism(s) of action for INS. Research suggests a photo-thermal mechanism, wherein the absorption of photons heats the water in targeted neural tissue, generating a transient temperature gradient.[286] This gradient has been shown to generate depolarizing currents in neuronal membranes by increasing their capacitance.[299] However, the exact workings are still not fully known and are likely location-specific: INS of the cochlea, for example may involve a photo-mechanical (through thermal expansion) or photo-acoustic (via laser-induced stress waves) effect.[300]

F. Biohybrid Microsystems

The first "biohybrid" neural interface, devised by Kennedy et al., was a glass cone electrode contain-

ing neurotrophic factors to elicit ingrowth of host neurites.[110,301,302] In these so-called "neurotrophic electrodes," the activity of the neurites was recorded within the cone. Due to actual ingrowth and integration between the electrode and host neurites, it was believed that this strategy would provide a more stable interface. In another more recent approach, Mark Allen et al. constructed electrodes composed primarily of extracellular matrix (ECM), the network of proteins that surrounds cells *in vivo*.[303,304] As ECM is mechanically and biologically compliant with the brain, electrodes composed primarily of ECM may decrease the immune response and mechanical mismatch seen by traditional rigid, non-organic electrodes. Allen et al. fabricated collagen/Matrigel-based electrodes and implanted them in a rodent model, demonstrating multi-unit recordings over 5 weeks and reduced glial scarring compared with synthetic electrodes at 16 weeks.[303]

In alternative approaches, a number of research groups have begun creating advanced biohybrid neural interfaces by incorporating living cells and tissues into implantable devices.[29,39,305–307] These efforts are intended to improve the integration of implants with the host nervous system. One such approach involves coating intracortical electrodes with live cells, as explored by Purcell et al. in 2009 and de Faveri et al. more recently.[308,309] The results of Purcell et al suggested an initial "neuroprotective effect" from the neural stem cell–seeded electrodes, mitigating the tissue response 1 week post-implantation. However, increased neuronal loss was reported after 6 weeks, possibly due to the degradation of the hydrogel surrounding the cells.[308] De Faveri et al. coated microelectrodes with neurons and astrocytes within fibrin hydrogel, demonstrating high signal quality and a diminished astrocytic response up to 30 days post-implantation.[309] Electrochemical testing of the coated microelectrodes showed no significant changes in their impedance, attributed to water and ion absorption from the surrounding solution. The fibrin's small swelling profile and controllable thickness allowed de Faveri et al. to reach a signal-to-noise comparable to the bare microelectrodes for 85% of their cortical recordings, although the fibrin coating did result in an increased distance between the electrode and recording site.[309]

We are pursuing another biohybrid strategy for chronic BMI utilizing advanced micro-tissue engineering techniques to create the first biological "living electrodes." These living electrodes are composed of discrete population(s) of neurons connected by long engineered axonal tracts that penetrate the brain to a prescribed depth for integration with local neurons/axons, with the latter portion remaining externalized on the brain surface where functional information is gathered using less invasive means (e.g., ECoG). In this radical paradigm, only the biological component of these constructs penetrates the brain, thus attenuating a chronic foreign body response. This strategy is founded on the plasticity of both endogenous and tissue-engineered neural networks, whereby neurons have the intrinsic ability to sense (through dendritic inputs) and respond to (via axonally transmitted action potentials) local activity. Toward this end, we have developed three-dimensional micro-tissue–engineered neural networks (micro-TENNs).[310–313] By localizing the neuronal somata at one or both ends of hydrogel micro-columns, we are able to create long encapsulated axonal tracts within a miniature form factor *in vitro* that can then be precisely microinjected *en masse* into the brain. Initially, micro-TENNs have been developed for the physical reconstruction of long-distance neural circuitry lost due to trauma or disease (Fig. 4).[311–314]

More recently, we have applied similarly engineered axonal constructs to serve as living electrodes by synapsing with specific cortical regions and transmitting information in one or both directions (Fig. 5). Paired with an ECoG array, these micro-TENNs could relay information from the cortex to the surface and vice versa, eliminating the need for a non-organic chronic foreign body within the brain. Similarly, transducing the micro-TENNs with channelrhodopsins and/or genetically encoded calcium indicators would allow for targeted optical stimulation and recording as previously described. As living constructs, micro-TENNs offer a way to bypass the electrode size and number limitations of current NI platforms via "biological multiplexing";each micro-TENN axon can synapse with multiple host neurons, offering a powerful method to reach a multitude of neurons and several target regions with a single construct. Moreover, through careful selection of the neurons used to create micro-TENNs and customized cell- and tissue-engineering techniques, we may influence the specific host neuronal subtypes with which the living electrode neurons form synapses, thereby adding a level of specificity to lo-

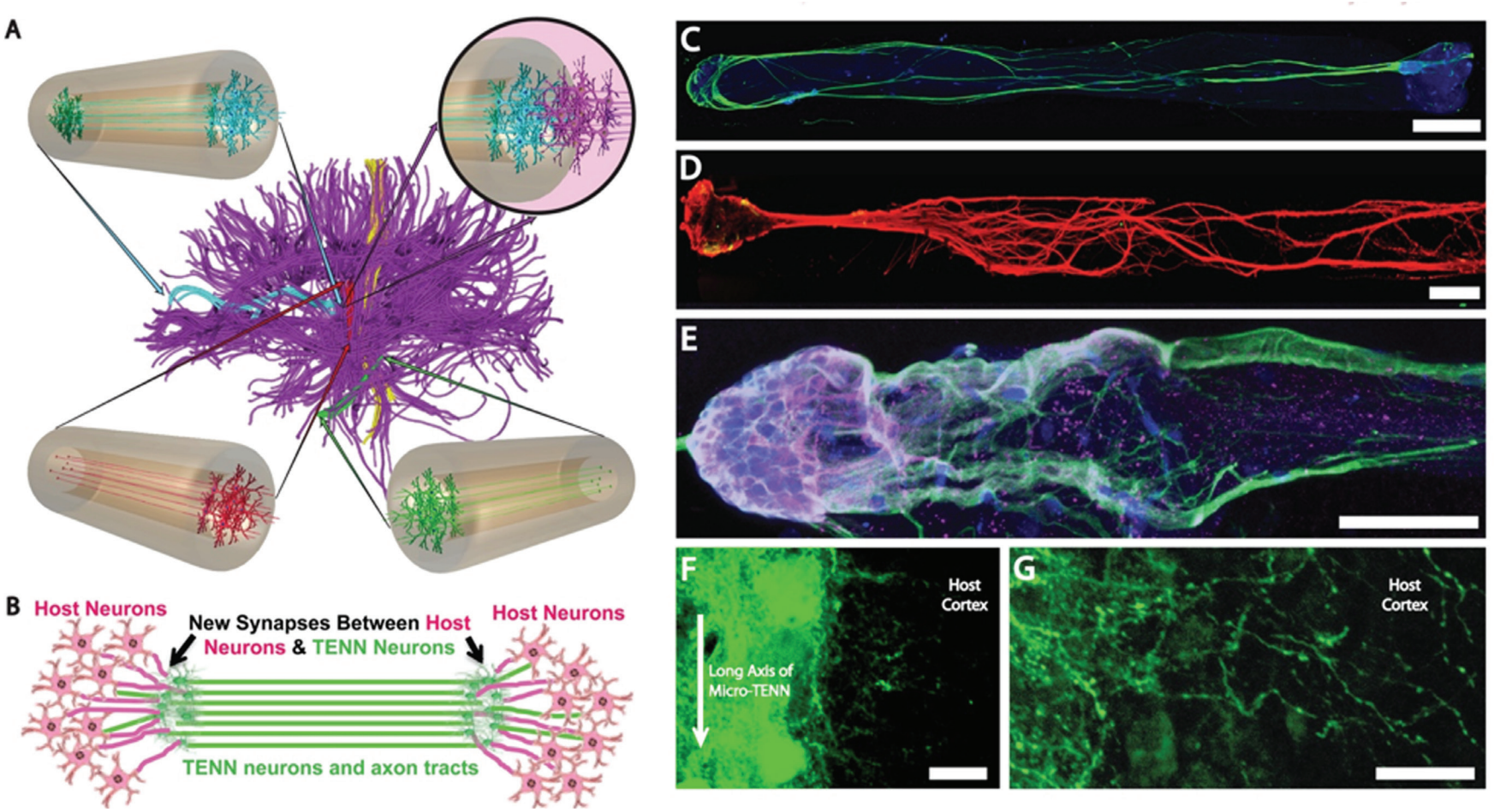

FIG. 4: Micro-tissue engineered neural networks (Micro-TENNs), consisting of discrete neuronal population(s) with long axonal tracts within a biocompatible micro-column. Micro-TENNs are used for the direct reconstruction of long-distance axonal pathways after CNS degradation. (A) Diffusion tensor imaging representation of the human brain demonstrating the connectome comprised of long-distance axonal tracts connecting functionally distinct regions of the brain. Unidirectional (red, green) micro-TENNs and bidirectional (blue) micro-TENNs can bridge various regions of the brain (blue: corticothalamic pathway, red: nigrostriatal pathway, green: entorhinal cortex to hippocampus pathway) and synapse with host axons (purple; top right). (B) Conceptual representation of a micro-TENN forming local synapses with host neurons to form a new functional relay to replace missing or damaged axonal tracts. (C) Confocal reconstruction of a bidirectional micro-TENN, consisting of two populations of neurons spanned by long axonal tracts within a hydrogel micro-column stained via immunocytochemistry to denote axons (b-tubulin III; green), and cell nuclei (Hoechst; blue). (D) Confocal reconstruction of a unidirectional micro-TENN consisting of a single neuron population (MAP2; green) extending axons (tau; red) longitudinally (adapted from (Cullen *et al*., 2012)). (E) Confocal reconstruction of a unidirectional micro-TENN, stained via immunocytochemistry to denote neuronal somata/dendrites (MAP2; purple), neuronal somata/axons (tau; green) and cell nuclei (Hoechst; blue). (F) Confocal reconstruction of a transplanted GFP^+ micro-TENN showing lateral outgrowth *in vivo*. (G) Confocal reconstruction showing GFP^+ processes extending from a transplanted micro-TENN into the cortex of a rat. Scale bars: 300 μm in C, 250 μm in D, 100 μm in E, 20 μm in F and G. (Reprinted from Struzyna LA, Harris JP, Katiyar KS, Chen HI, Cullen DK, with permission from the Editorial Office of Neural Regeneration Research, Copyright 2015.)

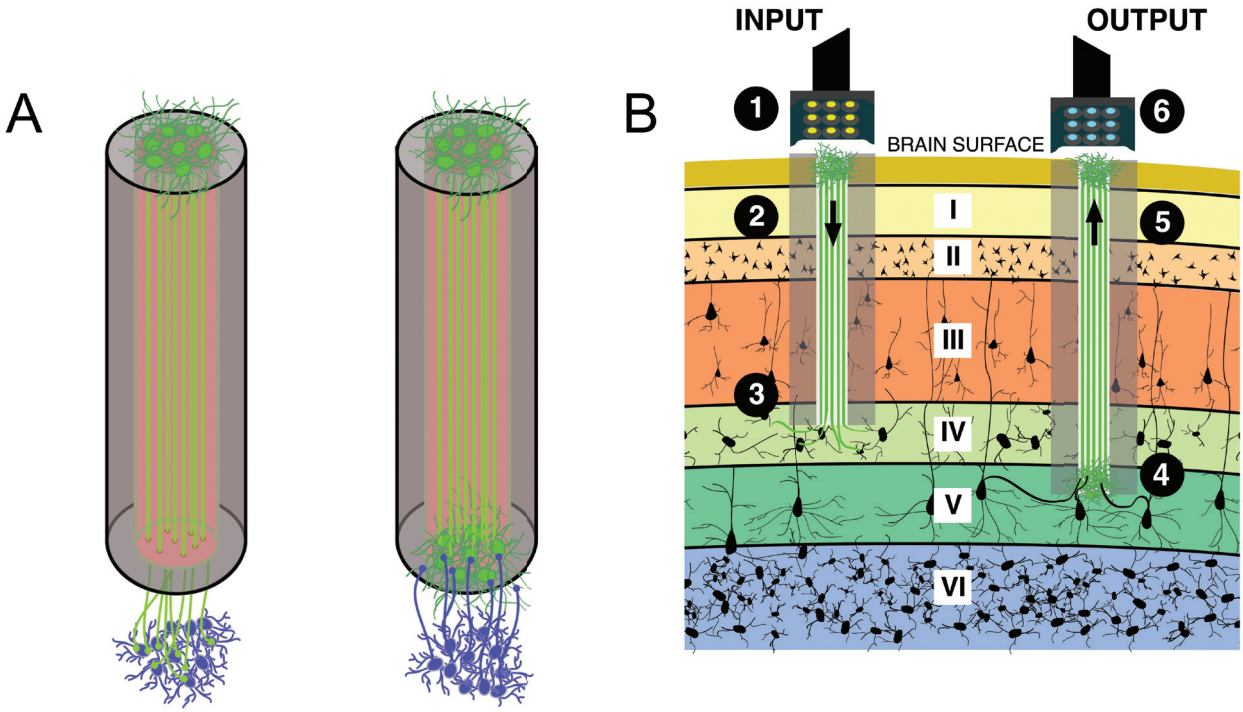

FIG. 5: Micro-TENNs as "living electrodes." (A) Unidirectional micro-TENNs (left) synapse with the host (blue cells) and deliver inputs to targeted cortical regions, while bidirectional micro-TENNs (right) may be synapsed by the host and transmit cortical activity. Relevant signal propagation denoted by arrows. (B) Conceptual schematic of the micro-TENNs as "living electrodes" *in vivo*. Left: Input paradigm. An LED array (1) optically stimulates a unidirectional micro-TENN with channelrhodopsin-positive neurons (2), which synapse with host Layer IV neurons (3). Right: Output paradigm. A microelectrode array (4) records from the neurons of a bidirectional micro-TENN (5), which are synapsed by host neurons from Layer V (6). Roman numerals denote cortical layers.

cal stimulation and recording that is not currently attainable with conventional NI systems. To date, micro-TENNs have been implanted in the rat brain, and neural survival, maintenance of axonal architecture, and synaptic integration with the host have been demonstrated.[310] Thus, in addition to serving as "living electrodes," these versatile constructs may serve as living scaffolds to promote regeneration of host axons along the micro-TENN axons or may physically "wire-in" to replace lost host circuitry.[314,315] Although it is actively being developed and tested, our biohybrid "living electrode" strategy may result in a neural interface with a specificity, spatial density, and long-term fidelity greater than that possible with artificial microelectronic or optical substrates alone.

In the PNS, biohybrid neural interfaces are also promising to enable robust integration between peripheral axons and electronics to drive the next generation of robotic prosthetic devices.[29,39,306] In the case of loss-of-limb, it is surgically advantageous to avoid implanting electrodes in the otherwise non-injured brain or spinal cord. Thus, as described previously for the case of TMR and RPNI, a neural interface with the peripheral nerves originally serving the lost limb would be ideal, as this is the final point of motor output and primary sensory input. However, PNS axons necessitate a living target for innervation, and residual muscle may not be available or may not provide the signal complexity for fine motor control. Therefore, we employ a blend of tissue engineering and micro-electrical techniques to facilitate direct integration with host axons to allow for complex command signals while enabling a vehicle for proprioceptive and other sensory feedback. We previously demonstrated that these tissue engineered constructs serve as a replacement end target and drive host axon regeneration into intimate contact with micro-electrodes.[39,306] Our current efforts are aimed toward testing the ability of these constructs to transmit electrical signals, and establishing the mechanism of action by which they allow for integration with host axons.

Collectively, our biohybrid approaches operate at the intersection of neuroscience and engineering to establish preformed implantable neural networks as a complimentary alternative to conventional hardware/electrode-based interfaces. Thus, these approaches potentially represent a paradigm-shift for chronic neural interface with the CNS or PNS.

VII. CONCLUSION

The nervous system connects the individual to their environment, and its breakdown is often physically and emotionally devastating. This is far from a rare issue—in 2010 more than 20% of the United States population reported having some disability, with the majority related to motor impairments in the upper or lower body.[316] Nearly 2 million people in the United States are amputees due to trauma or disease alone, with almost 200,000 people receiving amputations per year.[10,317] The Amyotrophic Lateral Sclerosis Association reports a prevalence of 30,000 ALS patients in the United States; the number of people living with other neuromuscular disorders is several orders of magnitude larger.[316,318] Fortunately, neuroprosthesis research has yielded a host of new technologies that can promote neural regeneration, enable communication, and restore mobility post-injury. These successes have their roots in multidisciplinary research, crossing disparate domains in engineering, neuroscience, and medicine. It follows that future interfaces will likely use some combination of both established and newly developed strategies to address the challenges faced by current interfaces—immunoreactivity, chronic stability, and selectivity, among others—to integrate more seamlessly with the human body. As NIs improve, prosthesis adoption will increase accordingly as patients feel more in tune with their devices. Concurrently, ongoing research in this space will lead to new applications and platforms for rehabilitation, therapeutics, and the restoration of quality of life.

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