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Brain-Machine Interfaces: Electrophysiological Challenges and Limitations

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ABSTRACT: Brain-machine interfaces (BMI) seek to directly communicate with the human nervous system in order to diagnose and treat intrinsic neurological disorders. While the first generation of these devices has realized significant clinical successes, they often rely on gross electrical stimulation using empirically derived parameters through open-loop mechanisms of action that are not yet fully understood. Their limitations reflect the inherent challenge in developing the next generation of these devices. This review identifies lessons learned from the first generation of BMI devices (chiefly deep brain stimulation), identifying key problems for which the solutions will aid the development of the next generation of technologies. Our analysis examines four hypotheses for the mechanism by which brain stimulation alters surrounding neurophysiologic activity. We then focus on motor prosthetics, describing various approaches to overcoming the problems of decoding neural signals. We next turn to visual prosthetics, an area for which the challenges of signal coding to match neural architecture has been partially overcome. Finally, we close with a review of cortical stimulation, examining basic principles that will be incorporated into the design of future devices. Throughout the review, we relate the issues of each specific topic to the common thread of BMI research: translating new knowledge of network neuroscience into improved devices for neuromodulation.

KEY WORDS: brain machine interfaces, deep brain stimulation, motor prosthesis, cortical stimulation, network neuroscience.

I. INTRODUCTION

Since Penfield's first studies using electrical stimulation of the brain, the possibility of altering neuronal function in a specific and predictable way to reverse disease or enhance function has motivated countless human and animal studies. Further pioneering work with subcortical stimulation introduced the idea of chronic, implantable stimulation devices to alter brain function.[1] Significant recent advances in our ability to directly monitor and stimulate neural circuits, coupled with a greater understanding of how activity within these circuits reflects and affects behavior and action, suggest that we have entered a new period of development in which devices that can diagnose and treat neurological disorders will become increasingly available.

The general principle guiding the development of these devices, known as brain-machine interfaces (BMI), is based on the past century of neuroscience research, which has demonstrated that neural function can be recorded, computationally modeled, and ultimately manipulated. Engineering efforts that take advantage of this wealth of knowledge are aimed at developing devices that can directly communicate with the human nervous system. The clinical successes realized in addressing cardiac

ABBREVIATIONS

BMI, brain-machine interface; DBS, deep brain stimulation; GPi, internal globus pallidus; GPe, external globus pallidus; STN, subthalamic nucleus; SN, substantia nigra; ATN, anterior thalamic nucleus; SANTE, stimulation of the anterior thalamus in epilepsy; VNS, vagal nerve stimulation; LC, locus coeruleus; EMG, electromyograph; LGN, lateral geniculate nucleus

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disorders, where devices such as pacemakers and implantable cardiac defibrillators have been developed to manipulate cardiac physiology through closed-loop stimulation, serve as a precedent for their neurological analogs.

The development of the next generation of BMIs, however, will critically depend on overcoming major scientific and engineering hurdles. For example, it has become clear that sensory and motor systems, let alone higher-level functions, involve multiple overlapping areas of the brain that coordinate activity together in a complex manner. Furthermore, major goals in engineering any such device include ensuring long-term recording stability in an in vivo environment, identifying optimal surgical implantation techniques to decrease tissue damage and consequent inflammation, and quantifying stimulation parameters that optimally manipulate neural activity in a controlled and predictable manner. Addressing these goals represents the focus of research for many groups working on the development of BMIs today.

The goal of this review is to render a sketch of a central problem of BMI: translating network neuroscience into more complex and effective devices capable of communicating directly with the central nervous system. We attempt to achieve this goal by examining the most successful of the devices presently used to interface with the human nervous system, and to describe how each addresses a different problem of interaction with a complex neural environment. The multidisciplinary nature of BMI research warrants a much more expansive exploration into areas such as tissue engineering, software algorithms, materials testing, and advanced modeling. We focus on lessons gleaned from experience with clinical devices, but our treatment of the problem is by no means exhaustive.

This review will begin by exploring the evidence describing the neurophysiologic mechanisms of deep brain stimulation and vagal nerve stimulation in an attempt to outline how some of the aforementioned challenges have been addressed. Describing the evidence for different theoretical explanations, from modulation of neuronal firing rates to the disruption of network synchrony, will lay the foundation for understanding how BMIs can one day be used to induce controlled neuronal activity and to elicit predictable behavior. Furthermore, exploring the physiological mechanisms underlying these open-loop devices will yield insight into how these BMIs can ultimately be engineered in a closed-loop system.

This review will continue by examining the development of motor and visual prostheses, two open-loop BMI systems whose long-term development will ultimately depend on the development of effective techniques of electrical stimulation. Exploring the world of motor prosthetics will shed light upon the various decoding schemes used to extract information from the nervous system. The next generation of motor prostheses will of course need to refine these methods of extraction as well as incorporate stimulation technology in a single closed-loop system. Visual prosthetics represent a more ambitious challenge, because they seek to actually recapitulate the neural circuitry itself before communicating that information to viable tissue. Hence, the challenge here lies not only in stimulation, but in developing computationally efficient algorithms for encoding.

Finally, this review will investigate some of the hypothesized mechanisms of cortical stimulation in order to return once again to one of the fundamental challenges facing BMIs: how to electrically stimulate neural tissue to appropriately convey information. Ironically, the neurophysiologic processes that underlie cortical stimulation are probably the most poorly understood, even though Penfield's work is over 50 years old.

II. DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE

II.A. Background

Deep brain stimulation (DBS) has been used to treat over 80,000 people worldwide since its development.[2] DBS was a significant advance in the development of early BMIs capable of communicating with and modulating the central nervous system.[3] DBS has been found to be especially effective in the treatment of Parkinson's disease and other movement disorders, although the role of DBS has

recently expanded to other neurological disorders.[4] The core clinical features of Parkinson's disease, a neurodegenerative disorder primarily affecting the dopamine-producing cells of the substantia nigra, are distinguished by resting tremor, bradykinesia, and rigidity.[5] Traditional neurosurgical approaches to the treatment of such disorders included thalamotomy, pallidotomy, and subthalamotomy; these fell out of favor because of complications, technical challenges, and the emergence of levadopa therapy in the 1970s. However, serendipitous intraoperative observations that high-frequency stimulation reversibly suppressed tremors led to the emergence of DBS for medically refractory Parkinson's and essential tremor.[6,7] DBS has a low side-effect profile: rates of hemorrhage from electrode placement are less than 1%, and the incidence of other severe complications is lower than for most cranial surgeries.[4,8] The most common complications are related to wound infection, skin erosion over the electrodes, or wire breakage. These occur at around 4% per electrode over its lifespan, which can be longer than 20 years for some patients.[8] A low-morbid implantation procedure and clinical effectiveness in an otherwise inexorable condition help explain why clinicians have sought to apply DBS to novel locations. Routine targets for intervention now include the ventral intermediate nucleus of the thalamus, globus pallidus, and the mainstay of therapy, the subthalamic nucleus.

Despite the clinical efficacy of DBS and 20 years of experience with the procedure, the precise neurophysiological mechanisms that underlie this first-generation BMI remain poorly defined. DBS for Parkinson's reflected rational BMI design to some degree: the circuitry of the basal ganglia was thought to be well understood. Electrical stimulation seemed like reversible lesioning initially. But subsequent investigations have failed to pinpoint the details of the mechanism by which DBS exerts its effects. The attempt to answer this question led to interesting new insights about the effects of stimulation on brain tissue, novel anatomic connections, and hitherto lightly regarded phenomena such as the role of pathological oscillatory activity in the basal ganglia. This question has practical implications for patient selection and the determination of stimulation parameters for DBS. The latter is currently an empirical procedure that can waste battery life and lead to a delay in achievement of clinical effectiveness. Identifying stimulation parameters is difficult because the space of possible combinations of voltage, current, pulse width, and waveform characteristics is large. A limit of 30 μC/cm of charge density is considered safe based on animal studies.[9] Standard Medtronic DBS electrode contacts have a surface area of 0.06 cm with an impedance of 500 Ω.[2] Stimulation is normally undertaken at a voltage of 1–3.5 V and a frequency greater than 50 Hz. Higher frequencies often elicit better clinical results, although they reduce battery life.[9] A setting of 130 Hz is common, achieving an average battery life of 5 years with typical current amplitude of 3 mA. Certain targets (e.g., globus pallidus) require higher current or higher voltage to achieve effective stimulation (Fig. 1).

What happens in the brain when these stimulation parameters are applied is not yet clear. A detailed examination of the theories that attempt to explain the effects of DBS is instructive, since future devices that rely on both cortical and subcortical stimulation will benefit from a resolution of this question. The interaction of stimulation effects with local and distant neuronal connectivity is demonstrated by data for subthalamic nucleus stimulation. We focus on this target, for which the most data exist.

II.B. Physiological Mechanisms of Deep Brain Stimulation Surgery

According to the accepted model of the basal ganglia, direct projections from the caudate and putamen (striatum) to the internal segment of the globus pallidus (GPi) are physiologically balanced against indirect connections from the striatum, via the external segment of the globus pallidus (GPe), to GPi. Inhibitory connections from GPi to the motor nucleus of the thalamus represent the net output of the basal ganglia. In this model, reciprocal connections between the subthalamic nucleus (STN) and the indirect pathway and dopaminergic inputs from the substantia nigra (SN) modulate the physiological

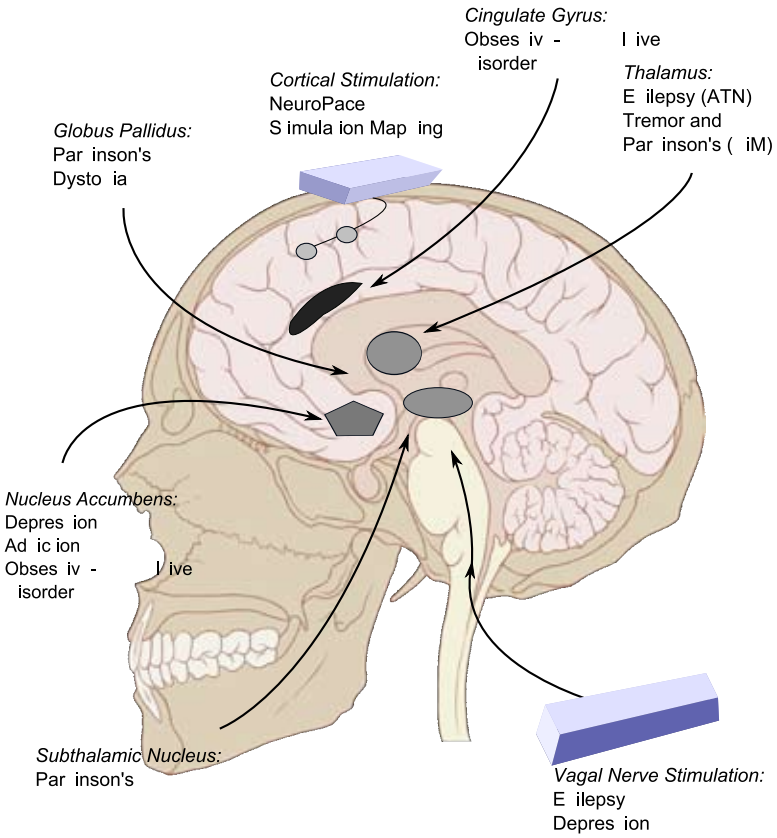

FIGURE 1. Sites of brain stimulation. Summary of targets for brain stimulation, with indications for each site listed below.

balance, and hence the activity, of the basal ganglia. In Parkinson's disease, degeneration of dopaminergic neurons in SN results in a shift in this balance to the indirect, inhibitory pathway, cascading into physiologic inhibition through connecting synapses to the thalamus and motor system beyond.

This classic model of basal ganglia circuitry is a useful point of departure for thinking about deep brain stimulation. Yet, attempts to understand the clinical effects of DBS based on the effect of stimulation on individual neurons has proven surprisingly difficult. There are currently four working hypotheses: (1) depolarization blockade,[10] (2) neurotransmitter depletion,[11] (3) synaptic inhibition,[12] and (4) modulation of basal ganglia network activity.[13]

1. Hypothesis I

The first hypothesis is centered on stimulation effects on ion channels. In vitro slice preparations from rodent-model Parkinsonian animals have been used to demonstrate that high-frequency stimulation induces cessation of spiking activity in STN neurons.[10] This effect is achievable in the presence of receptor blockade, suggesting it does not require afferent synaptic stimulation, and appears to be centered on sodium currents.

2. Hypothesis II

The hypothesis of synaptic failure due to neurotransmitter depletion posits that chronic high-frequency stimulation of STN cell bodies leads to efferent output, but that this rapidly depletes the synaptic terminal.[11] This has not been demonstrated unequivocally in STN in vitro or in vivo, and microdialysis findings contradict this theory.[14–16]

In patch clamp studies, STN neurons have

actually maintained their spiking output during high-frequency stimulation.[17,18] The stimulation locked the STN neurons into a pattern of firing separate from spontaneous activity and induced a time-locked firing of STN efferent target neurons in the GPi. Patch clamp studies can report oscillatory changes in membrane potential, but the act of creating a slice preparation necessarily eliminates the network dynamic effects of local field potentials. Therefore, extrapolating from slice preparations with limited numbers of neurons exposed to the stimulating electrode to the effects of macroelectrode stimulation may not be accurate.

3. Hypothesis III

In vivo studies have suggested a slightly different story. Electrical stimulation in primates has been shown to elicit changes in firing rates of neurons in efferent nuclei consistent with activation of neurons near DBS electrodes.[19] Recordings from the human globus pallidus during an implantation surgery have demonstrated uniform inhibition of GPi neurons with adjacent high-frequency microstimulation.[12] The relationship between the onset of stimulation and the inhibitory effect suggests that the time course was most consistent with activation of the afferent inhibitory axons that fell on the cell bodies of GPi neurons. The activity pattern was not consistent with depolarization blockade. This study presents the most compelling evidence for effects of stimulation on a population of neurons.

An important caveat to the findings of microstimulation studies (as in Dostrovsky et al.[12]) is that attempts to explain the clinical effectiveness of deep brain stimulation by analogy may be partially misguided. The charge per unit area delivered by typical microstim electrodes is similar to that of DBS macroelectrodes. But the total number of axons and cell bodies affected by macrostimulation is much greater, establishing the possibility of complicated interactions between neurons close to the stimulating electrodes and those further away. The total amount of charge delivered also makes it more likely that macroelectrodes are able to alter local field potentials established by larger ensembles of neurons. Microelectrode recordings from different basal ganglia sites in the setting of macroelectrode active stimulation would be especially enlightening in this regard, although it raises some technical challenges.

Ultimately, interpreting data about the neurophysiological effects of brain stimulation requires answering a seemingly straightforward question: does spiking activity increase or decrease in a brain structure that is being stimulated? In general, high-frequency stimulation (>50 Hz) seems to cause clinical effects similar to those elicited by lesioning procedures, suggesting that stimulation should decrease spiking. For STN, evidence is actually split on this matter. Data from human in vivo microelectrode recording does suggest that spiking activity decreases with high-frequency stimulation.[20,21] However, microdialysis data suggest that stimulation actually increases glutamate output from synaptic targets of STN neurons,[14–16] and animal data suggest that globus pallidus activity may actually increase with STN high-frequency stimulation,[19,22] consistent with an increase in STN output activity. Finally, direct recordings imply that single-unit activity may actually increase.[18]

4. Hypothesis IV

It may be the case that the effects of stimulation are heterogenous across different types of neurons and different regions. An alternative strategy for explaining the effects of DBS relies on local field potentials rather than alterations in single-unit activity within the direct/indirect paradigm. Field potentials are the summed effect of neuronal activity in a brain region generated by both local and distant populations. BMIs that rely on field potential modulation are appealing because they bypass the confounding effects of macroelectrode brain stimulation on single-unit activity. Given the complex effects of applying electrical current to groups of neurons in a three-dimensional space, field potential modulation may be the appropriate level of abstraction at which to consider and model the effects of brain stimulation. For DBS for Parkinson's, a compelling field potential theory centers on the disruption of pathological beta

band (12–20 Hz) synchrony by high-frequency STN stimulation.

II.C. Network Synchrony and Disruption

Human and primate data demonstrate that the basal ganglia of Parkinson's patients show a beta-band oscillation of substantially greater power than normal controls.[23–25] This oscillation, which is synchronous across different brain sites, is abolished in the period immediately before an individual initiates a movement, suggesting it contributes especially to the bradykinesia and rigidity that are the harbingers of worsening symptoms in the disease.[26] In *mptp*-induction models of Parkinson's in monkeys, the beta oscillation becomes more synchronous and powerful as the symptoms of the disease take hold in the treated animals.[23]

The beta-band oscillation is detectable over the motor cortex of Parkinson's patients, but not normal controls,[26,27] and the severity of freezing and bradykinesia are correlated with the power of the oscillation, strongly suggesting the role of the oscillation in the genesis of the negative symptoms of Parkinson's.[23] The beta oscillation entrains the spiking activity of STN neurons, and is coherent across both subthalamic nuclei bilaterally and with a beta-band oscillation in the globus pallidus.[28] Most notably, dopaminergic medication exhibits a dose-related attenuation of the beta oscillation in both STN and the globus pallidus.[29] High-frequency stimulation has been shown to disrupt beta-band synchrony oscillation in an effect that persists for a variable period after the termination of stimulation, but can last for over half an hour.[30]

All told, there is not yet a consensus on the role of the beta oscillation in pathogenesis for Parkinson's; some researchers believe it is an epiphenomenon related to some other underlying process and does not have a causal role. But theories based on disruption of beta synchrony are more consistent with existing data and clinical observations than those based on alterations in spiking activity. The mechanism by which stimulation disrupts beta synchrony is not immediately obvious; that may require a re-examination of single-unit neurophysiological data. With what is available, however, the evidence for the theory of beta synchrony disruption is certainly more consistent than the data regarding STN spiking activity and microdialysis, which show a mix of increased and decreased effect from stimulation.

It is our opinion that the stimulation of inhibitory afferents, as suggested by data from GPi,[12] is commensurate with the disruption of beta synchrony in the basal ganglia as a mechanism of action for DBS. It has been demonstrated theoretically and experimentally that reciprocal inhibition can establish oscillatory synchrony in recurrent loops of neurons, although this is strongest in the gamma band (for a review, see Wang[31]). With longer periods, beta oscillations are more likely to exhibit long-range synchrony across the structures of the basal ganglia. Both in vivo and in vitro studies may prove useful in elucidating this question.

III. BRAIN-MACHINE INTERFACES FOR EPILEPSY

The electrophysiological hallmark of seizure activity seen in epilepsy is abnormal excitability and synchronization of neuronal activity in the brain. For the 50 million patients affected by this disorder, the mainstay of therapy has been the use of anti-epileptic medication that prevents seizure activity through a variety of mechanisms by suppressing ion-channel activity. Despite maximal medical therapy, however, roughly one-third of patients with epilepsy suffer from persistent seizures.[32] Continued efforts to treat this neurological disorder medically over the past two decades have succeeded in improving the adverse effects of medication, but not in decreasing seizure frequency.

III.A. DBS for Epilepsy

1. Rationale

Based on the clinical successes enjoyed by DBS for movement disorders, and because at its essence, seizure activity in epilepsy represents pathological network activity, attention has recently been turned to using BMIs to address this neurological disorder. In principle, such devices should electrically modulate neuronal firing to disrupt pathological synchrony and reduce seizure activity. As with Parkinson's,

the relationship between synchrony and epilepsy is complicated. During an epileptic event, synchronization across different cortical and subcortical regions leads to tonic-clonic activity and loss of conscious awareness.[33] This is mostly in lower-frequency bands, although gamma-band (>34 Hz) activity seems to precede epileptic discharges. Synchronization appears to be more prevalent within rather than between cortical regions, even during generalized seizures.[34] Targets for DBS for epilepsy have so far focused on subcortical structures, for which stimulation is thought to disrupt the generation of more widespread synchronous networks.

Epileptic activity is thought to propagate through discrete and well-described anatomic locations in the brain. Although the circuit of Papez was initially implicated in emotional processing, this classic circuit has gained recent attention as a possible site of epileptic propogation.[35] The circuit of Papez links exiting fibers from the hippocampus to the mamillary bodies, which in turn project to the anterior nucleus of the thalamus. This nucleus communicates with the cingulate gyrus, which in turn projects to the hippocampus via the parahippocampal gyrus and entorhinal cortex.[36]

The mechanisms by which BMIs can attenuate seizure activity are likely similar to the mechanisms that underlie the success of DBS for movement disorders. If seizures propagate along known circuitry, then interrupting this circuit with electrical stimulation could potentially prevent the generation and propogation of seizure activity. DBS adopts this strategy. Vagal nerve stimulation also disrupts cortical EEG synchrony, but rather than preventing the propagation of an evolving seizure, it seems to reduce the onset of ictal activity. An examination of devices adopting this approach and currently under investigation may reinforce the notion that electrical stimulation may disrupt network activity in order to elicit clinical effects.

2. Anterior Thalamic Deep Brain Stimulation

The notion of chronic stimulation of subcortical structures to treat refractory epilepsy has a history beginning with the use of cerebellar hemispheric stimulation, although clinical efficacy for this approach was never proven in a randomized study.[37–40] The anterior thalamus was thought to play a role in kindling and epileptogenesis based upon imaging data showing volume loss in the anterior thalamic nucleus (ATN) with ongoing, poorly controlled seizure activity.[41–43] Animal data testing the ability of ATN stimulation to alter seizure activity demonstrated that it can delay the development of status epilepticus in rat models of epilepsy.[44–46] Low-frequency ATN stimulation elicits a synchronous response in cortical recording sites (a driving rhythm, part of the implantation procedure), while high-frequency parameters are used for clinically efficacious stimulation.[47]

These promising animal and anatomic underpinnings led groups to attempt small-scale implantation programs under local investigational institutional review boards.[48–50] The safety of these early trials prompted the ambitious SANTE (stimulation of the anterior thalamus in epilepsy) trial.[51] SANTE was a randomized, controlled trial that showed a significant seizure benefit for ATN stimulation that seemed to improve in the months that followed implantation. This led to FDA approval for ATN stimulation, adding it to the armamentarium for the treatment of refractory epilepsy.

SANTE specified localized onset, secondarily generalized epilepsy for inclusion in the trial, based on the theory that such seizures would recruit the ATN as they propagated through the cortex.[47,5] Electrographic seizure activity, by definition, includes high-amplitude, highly synchronous sub-gamma oscillatory activity that entrains multiple cortical areas.[34] Stimulation that successfully interrupts seizures disrupts this synchrony. Low-frequency stimulation has a clinically deleterious effect. What will prove most interesting, as with vagal nerve stimulation (VNS), is evidence of interictal changes in oscillatory activity, including gamma- and theta-band synchrony. It may be the case that there is an acute benefit from ATN stimulation due to the disruption of ongoing seizure activity, and a more chronic improvement in seizure response based on interictal desynchronization, as

TABLE 1. Vagal nerve stimulation trials

Study	N	Follow-up (months)	Improvement (median %)	>50% improved (% of pts)
Degiorgio 2000 [61]	195	12	45	35
Handforth 1998 [62]	196	3	28	24
Salinsky 1996 [63]	114	12	32	31
Morris 1999 [64]	114	38	25	31
Amar 1999 [65]	110	15	37	39

with VNS. As more patients undergo ATN DBS, data for this question should become available.

The future of subcortical stimulation to disrupt seizures hinges on the longevity of the effect observed in the SANTE trial. Morbidity rates during implantation and hardware failure will likely be similar to those reported for DBS for movement disorders.[4,8] If seizure reduction exceeds the ~40% rate reported for VNS, it may become the preferred therapy for medically refractory cases not amenable to surgical resection of tissue. The quality of life of epilepsy patients is directly proportional to seizure frequency, and given the mild side-effect profile of ATN stimulation this will likely govern the number of patients who ultimately undergo implantation.[52] ATN stimulation has led to several patients who became seizure free (14 patients seizure free for a median of 6 months), although the longevity of this result has not been established. Similarly, the seizure profile of patients who benefit most from ATN stimulation remains to be established. Its next application may be for patients with localized-onset seizures from foci near eloquent cortex.

III.B. Desynchronization and Vagal Nerve Stimulation

Similar to DBS for epilepsy, the mechanism of the effect of vagal nerve stimulation is not certain, but the low morbidity of the implantation procedure and the well-tolerated side-effect profile has led to the widespread adoption of VNS for cases of refractory epilepsy. Pioneering work in the 1980s (e.g., Terry[53]) led to several successful trials with sizable enrollments (see Table 1). The observation that mood symptoms seemed to improve in VNS patients, as well as the procedure's safety, has led to the application of VNS to novel domains such as depression, anxiety, Alzheimer's disease, and chronic migraine headaches (for a review, see Groves and Brown[54]). Efficacy of the procedure for epilepsy is limited: approximately half of patients achieve a 50% reduction in seizures after stimulation parameters are established. Patients with partial-onset epilepsy refractory to two or more medications are often referred for evaluation for VNS.[55,56] Late hardware complications, including infections and lead breakage, are more infrequent than for DBS (<5%), although patients are typically implanted at a younger age than with DBS for movement disorders, making the lifetime chance of such a complication slightly greater.[57,58] Follow-up surveillance for these occurrences now stretches over 20 years since VNS became widespread. Application of VNS to depression has been investigated, though significant benefit has been identified only in open-label trials.[59,60]

Vagal nerve stimulation may also achieve its clinical effects via network desynchronization. High-frequency, but not low-frequency vagal nerve stimulation can suppress interictal spiking activity, and VNS has been shown to increase REM sleep periods in both animals and humans.[66,67] Animal data have long suggested an immediate decrease in EEG synchrony following the initiation of VNS at 30 Hz.[68]

Investigations into the network activity seen in epilepsy have demonstrated that low-frequency synchronization with gamma-band desynchroniza-

tion occur in cortical regions immediately before the onset of seizure activity.[33,69] In humans, VNS seems to elicit a preferential decrease in low-frequency oscillatory coherence with a concomitant increase in gamma-band coherence both within and between the hemispheres.[70,71] The increase in gamma-band coherence may also account for the improvements in alertness and memory performance noted in patients following VNS implantation, although improvements in seizure control may account for this benefit separate from direct cognitive effects of nerve stimulation.[69,72]

The physiologic mechanism by which VNS leads to low-frequency EEG desynchronization is not clear. A possibility is that the solitary tract fibers stimulated by VNS may alter the activity of the locus coeruleus (LC). Vagal input to the LC has been demonstrated pharmacologically.[73] In animals, LC activation has been shown to decrease low-frequency oscillatory power and induce desynchronization.[74] This theory of VNS-mediated alterations in synchrony is commensurate with the attentional improvements that follow VNS, given the role of the LC in modulating alertness.

III.C. Closed-Loop Brain-Machine Interfaces for Epilepsy

1. Responsive Stimulation

While VNS and ATN DBS have yielded some clinical benefit, they are open-loop systems that offer constant one-way stimulation of the central nervous system.[47] A more nuanced approach commensurate with the next generation of BMIs would function to both detect and interrupt seizure activity, extending communication in both directions to achieve safer and more efficacious stimulation. This has been termed *responsive stimulation*, and it offers greater temporal specificity than open-loop systems because stimulation is delivered only when seizure activity is detected.[75] Theoretically, this allows more current to be delivered with less concern for chronic side effects. The first generation of such technologies is being developed and tested currently.

Cortical stimulation to achieve seizure interruption evolved from observations during macroelectrode stimulation mapping and from deep brain stimulation for epilepsy. Brief stimulation pulses delivered during a cortical afterdischarge were observed to interrupt ongoing epileptiform activity.[76] This fact, combined with data for the ability of ATN stimulation to interrupt seizure propagation, led to the design of a responsive stimulation system applied to patients undergoing preoperative intracranial EEG monitoring.[77] This approach consisted of an algorithm to identify incipient seizure activity, and to use that information to control a Grass S12 stimulator to deliver pulses to interrupt the seizure.

2. NeuroPace

The NeuroPace RNS system (NeuroPace, Mountain View, CA) uses these same principles in an implantable closed-loop device designed to disrupt seizure activity before it occurs.[78] Surface strip electrode contacts are placed over the cortex in an area of seizure activity. The device uses a learning algorithm to identify relevant features of an individual's seizures, and when it detects an oncoming seizure, it activates stimulation using an internally generated current. The details of the algorithm and the stimulation parameters have not been made public, but NeuroPace literature suggests that the parameters are derived empirically rather than based on common features of seizure activity across individuals.[78] Different areas of cortex in different patients seem to require unique parameters to achieve optimum seizure reduction. A phase III trial for NeuroPace is currently in its closing stages, and data should be available shortly.

Closed-loop systems offer advantages in that they can operate independent of subjective human control, have extended battery life, and possibly have a better side-effect profile compared to open-loop stimulation.[47] Grid microelectrode devices may offer improved signal detection and more refined stimulation options for seizure interruption.[79] Ultimately, the effectiveness of responsive neurostimulation depends on the ability of the detection system and analysis algorithm to accurately identify incipient seizure activity in the brain. This has proven difficult using surface encephalography,[80] although the improved spatial resolution and

high-frequency discernment of iEEG employed by NeuroPace seems to permit a degree of efficacious stimulation. With a sufficiently mild side-effect profile for the stimulation pulses intended to abort a seizure, the detection algorithm could be balanced in favor of sensitivity with less concern for specificity. This will likely be an idiosyncratic parameter depending on ictal onset zone. The use of subdural microelectrode (40 micron) arrays for improved detection of "mini-seizures" appears promising for seizure prediction.[81]

That the disruption of synchronous oscillatory activity may underlie the success of stimulation in Parkinson's and epilepsy suggests the possibility that other pathological conditions that involve abnormal synchrony may be targets for therapeutic intervention with DBS as well. There is evidence that oscillatory synchrony may be abnormally *diminished* in conditions such as schizophrenia, autism, and Alzheimer's disease.[82] For this reason, low-frequency, driving stimulation (as is used during site localization in ATN stimulation[47]) may be more appropriate than high-frequency stimulation. Noninvasive studies, such as magnetoencephalography, could be applied to patients with these conditions, specifically looking for possible sites amenable to alterations in brain synchrony.[83]

IV. MOTOR PROSTHESES

Neuromotor prosthetics comprise a set of medical devices designed to restore voluntary movement in paralyzed patients. They are a type of open-loop BMI in which signals are extracted from the central or peripheral nervous system, then decoded and used to control devices. Neural commands for voluntary movement are issued as electrical signals originating in primary motor cortex and can be recorded with varying degrees of fidelity and difficulty depending on the sensor technology employed. The goal is to detect signals that have the largest amount of information about movement that change as rapidly as the movement commands themselves change.

In motor disorders such as ALS, muscular dystrophy, and spinal cord injury, the individual can be cognitively normal and fully able to generate detailed movement plans using higher motor control structures. Likewise, in patients with congenital limb anomalies or who have suffered traumatic amputation of a limb, the nervous system may be completely normal up until the abnormal or missing extremity. Neuromotor prostheses either re-create actual lost function or generate a useful surrogate action to restore the ability of the person to interact with their environment.

Motor prosthetics comprise three primary components: a sensor which records a neural signal, a decoder which derives a voluntary control command from that signal, and an effector, in which the resulting command makes something physically happen in the world (Fig. 2). A variety of sensors, decoders, and effectors have been investigated for neuromotor prosthetics, and often distinct versions of each component can be mixed in different combinations.

Because patients can witness and experience the effect of their voluntary control, all neuromotor prosthetics are, in theory, considered closed-loop. This designation is somewhat specious given what a true closed-loop BMI—one that senses neural activity, independently processes information, and feeds stimulation back to the nervous system—ought to look like. Work is currently underway, however, to incorporate external tactile and direct cortical stimulation feedback to provide individuals with somatosensory and proprioceptive feedback in a manner more closely mimicking a healthy human motor control system.

IV.A. Decoding signals in residual nerve fibers, or adjacent muscle groups

In people who have lost a limb, or who have a degenerative muscle condition such as a dystrophy, one could argue that recording as distally as possible in the spinal cord or peripheral nervous system would be ideal. In principle, the more peripheral one gets from the brain, the more simple, and hence straightforward to decode, the mapping of neural activity to desired voluntary movement. However, in general, peripheral control signals yield only a single degree of freedom so if multiple joints need to be controlled they must be done sequentially rather than in parallel.

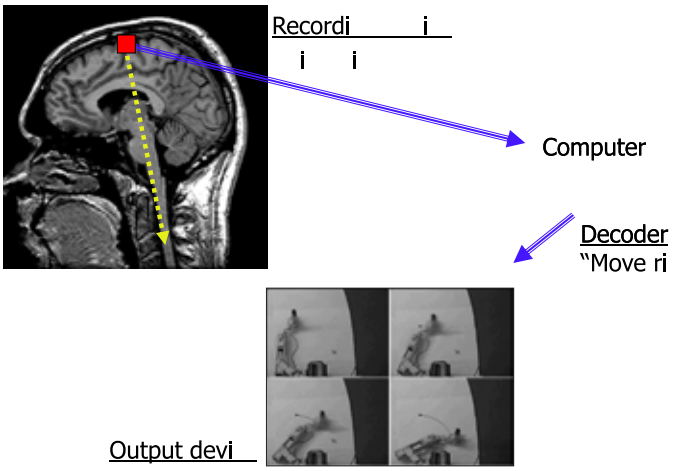

FIGURE 2. Components of a neuromotor prosthetic. A recording device, such as a set of implanted electrodes, captures neural activity while a person attempts or imagines a movement. Neural signals are amplified and processed and ultimately decoded by a computer algorithm that decodes the person's intent. Finally, the decoded control signal is used to actuate an output device, such as the robotic arm shown here.

Several control signals can be derived from the peripheral nervous system. Electrodes placed on the skin surface can capture electromyographic (EMG) activity: decoding algorithms ranging from simple amplitude threshold rules to neural networks have been employed to generate signals to drive robotic prosthetic limbs. Although noninvasive, EMG is hampered by the variability in signal to noise caused by changes in electrode placement and skin moisture. More invasive approaches are currently in development incorporating probes that penetrate within the nerve to chronically record and stimulate peripheral nerves,[84–86] but one of their major drawbacks is the need for microsurgery for implantation.

Targeted nerve re-innervation comprises a hybrid approach in which residual fibers are surgically transferred to novel muscle targets, such as the pectoralis major. Surface electrodes can record the EMG signal from the new target muscle, which acts as a natural biopotential amplifier of multiple, parallel distinct nerve signals.[87] Although this approach has offered the most impressive restoration of multi-degree-of-freedom control in human amputees, it suffers from the same drawbacks inherent in all noninvasive approaches, including skin breakdown, lower signal to noise, sensitivity to precise electrode positioning, and variable impedance from sweating.

Recently, an approach marrying chronically implanted microelectronics to the technique of using muscle as biopotential amplifier has been initiated: residual brachial plexus or peripheral nerve fibers are being coaxed with neurotrophic-factor-eluting silicon tetrode assemblies already seeded with autologous muscle tissue. Individual nerve fibers could thus contact a single muscle-silicon-probe target for a long-term biocompatible and biostable interface; the electronics would continually record the single myofiber activity and wirelessly transmit it to a decoding chip housed in a robotic prosthesis worn by the amputee.[88]

Another hybrid approach being explored is the use of engineered axons stretch-grown in vitro, with one end of the assembly cultured on a flat multielectrode array: once the axons are stretched to the desired length, the entire assembly is implanted just distal to residual nerve fibers in vivo. Preliminary tests have shown that such assemblies will interface chronically to the peripheral nervous systems in

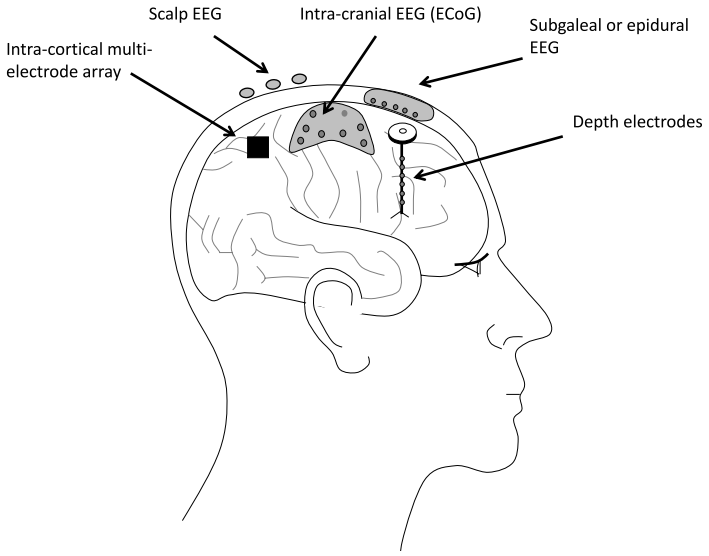

FIGURE 3. Examples of recording devices for brain-computer interfaces to restore movement. Scalp EEGs are noninvasive electrical sensors, whereas a range of chronically implantable devices exist to record neural activity. Only high-impedance electrodes on a multi-electrode array or microwires that may be affixed to a depth electrode can capture individual neuron action potentials; the majority of sensors capture local field potentials at various spatial resolutions.

animals and record neural signals. This approach leverages the features of axons being stretched ex vivo, thus bypassing the need of a patient's residual fibers to slowly regenerate long distances to find and link to a biostable electronic interface.[89]

IV.B. Decoding Signals in Motor Cortex

While motor prostheses that capture information from peripheral nerves offer an advantage in that the neural code at these distant sites is often relatively straightforward and easy to extract, deriving more variable and complex signals directly from central nervous system may offer distinct advantages. The precise feature which could be seen as a drawback—the rapid variability in how a particular area of motor cortex represents a distinct voluntary movement[90]—could also be envisioned as an advantage. With the proper decoding algorithm, an engineer could derive a much wider array of control signals from a single sensor with a much smaller footprint instead of having to record from a multiplicity of implanted sensors in the periphery. Furthermore, recording directly from the brain may be the only method to derive control signals in patients for whom the corticospinal pathway is damaged.

Although corticospinal tract neurons originate in a variety of cortical areas, including premotor, supplementary, and primary somatosensory cortices, the greatest density of this final-common-pathway of fine voluntary movement is found in primary motor cortex of the precentral gyrus. Just as electrical stimulation of primary motor cortex (M1) causes contralateral limb movement, so too recording from this area can provide a control signal. Over the past few decades, multiple laboratories around the world have developed a large toolbox of decoding algorithms to map activity recorded from sensors either on the scalp or implanted in the subdural space or within the brain to drive computers, communication devices, and effectors such as robotic arms or functional electrical stimulation of otherwise paralyzed muscles. Each sensor site (Fig. 3) and decoding approach has its own unique set of strengths and weaknesses.[91,92]

Whereas high-impedance probes implanted

into the brain can record the waveforms of action potentials of multiple, individual neurons, larger, lower-impedance probes can be used to capture the lower-frequency oscillatory activity representing the summed synaptic input in the dendritic fields of thousands of local neurons. In general, the further one moves a probe from the cortex, the lower the signal to noise and the larger the volume, and hence the population of neurons over which the electrical signal is summed. As with all BMI control signals, this phenomenon could be considered either an advantage or a drawback: on the one hand, signals derived from a larger population of neurons are more stable in their immunity to drop-out of particular individual neurons or precise placement of a sensor; on the other hand, they average away the distinct, parallel signals present in a given area of cortex.

Because of the ease and safety of placing scalp electrodes, a tremendous amount of work has been devoted to deriving as reliable as possible control signals from the EEG. These so-called EEG BMIs usually fall into one of four main categories. One uses features of evoked potentials in response to unexpected stimuli to determine what item in a large two-dimensional on-screen array a person is attending to.[93,94] Another approach requires participants to master voluntary feedback of cortical potentials to move computer cursors or select targets on a screen.[95–97] In a third approach, event-related desynchronization of a resting-state 8–12 Hz rhythm can be detected with real or imagined movements, offering a signal capable of controlling high-degree-of-freedom three-dimensional trajectories.[98] In a fourth approach, EEG signals can be artificially enhanced by presenting a person with a steady-state flickering stimulus, allowing a decoder to identify which stimulus a person is attending to and use this to make a selection or move a cursor.[99]

Not surprisingly, all the algorithms developed for scalp EEG can be deployed with intracranial electrodes as well. Every year, thousands of patients with pharmacologically intractable epilepsy are referred for phase III evaluation with implanted subdural grids and depth electrodes to help clinicians localize seizure activity. These patients, who are monitored post-operatively for several weeks, have volunteered for numerous studies in which cortical surface recordings have reliably been able to decode a variety of voluntary movements and use them to drive computer input in real time.[100–102]

A recent focus on decoding signals in the high-gamma range (50–200Hz) has generated excitement: free of the spatial filtering introduced by the skull, intracranial electrodes can record this higher-frequency activity with greater fidelity and spatial anatomic resolution than is possible on the scalp. Low-impedance electrodes machined at a smaller diameter and interprobe spacing than traditional subdural grid electrodes appear to be able to record from narrow columns of cortex and hence could afford more distinct, parallel input signals; these so-called micro-ECoG prototypes are just entering human trials at the time of this publication.[103] In addition, next-generation high-density multi-electrode grids with embedded active electronics on a dissolvable silk backing, which are flexible and can appose and conform to gyri, have just been tested in animal studies and may offer a promising alternative to rigid ECoG for chronic intracranial recording.[104]

To record the action potentials of individual neurons, probes implanted into the brain parenchyma are necessary. This class of sensor has long been considered the *ne plus ultra* because the ensemble activity of multiple, distinct neurons has been felt to be the richest and most detailed representation of fine, voluntary movement that a physical, artificial device can record. These sensors comprise one or more high-impedance electrodes in close physical proximity to the large layer V Betz cells of the primary motor cortex. An early form of this sensor was a pair of microwire electrodes affixed inside a small glass cone filled with neurotrophic factors; these cone electrodes were able to chronically record neural activity from the primary motor cortex of patients with brainstem strokes that had rendered them completely quadriplegic.[105]

In the past few years, several patients with spinal cord injury and ALS have been implanted with silicon multi-electrode arrays. Whereas the cone

electrodes had only a few channels and were fully implantable, using wireless infrared telemetry, the multi-electrode arrays comprise a 4×4 mm square with 100 electrodes (400-micron spacing) and have used percutaneous connectors affixed to the skull and exiting the scalp. For neuromotor prosthetics based on single-unit recordings, before decoding can occur the waveforms of raw voltage must be classified as action potentials or not. The need to record, amplify, multiplex, classify, and transmit these signals comprises an immense engineering challenge that only a handful of interdisciplinary laboratories have had success with.[106–108] Wireless prototypes capable of sending signals from this many channels at a 30-KHz sampling rate have just completed preliminary animal studies and would form the next step for human trials.

An alternative approach involves classifying the action potentials (also termed "spike sorting") in the implanted device itself. Instead of sending out a signal with a 30-KHz sampling rate, the waveforms are determined to be spikes or not in real time by the implanted device. Hence only the number and timing of spikes in a given time window need to be recorded and transmitted, dramatically decreasing the sampling rate for wireless transmission.[107]

Neuromotor prosthetics based upon multi-unit ensemble recording ultimately map spike times onto a movement control variable, such as intended position of the hand in three-dimensional space or a particular gesture; algorithms to achieve this mapping range from simple linear regression to neural networks, hidden Markov models, principle and independent component analyses, and Bayesian decoders with Kalman filters.[89,109–112] A variety of these techniques have been employed successfully in nonhuman primates and in human patients to generate real-time dynamic control signals; the fact that such a variety of distinct methods can all yield similar performance—and all based on recording just a sparse subset of 10 to 100 cells from a pool of millions of corticospinal neurons—suggests that the true mechanism by which primate motor cortex represents and engages complex, voluntary movement has a large degree of redundancy.

All of the sensor types discussed, from intracortical probes to scalp electrodes, have been incorporated into BMIs that have been used to drive powered wheelchairs, to control devices such as televisions, light switches, and prosthetic limbs, and for functional electrical stimulation of muscles (Fig. 4).[113–116] Given that a large number of permutations of distinct sensors and decoding algorithms have been successfully tested, the question arises how engineers and clinicians should go about selecting and developing a particular combination to the point where it could be deployed in patients on a larger scale.

V. VISUAL PROSTHESES

Inspired by the remarkable success of cochlear and brainstem implants in restoring audition to adults and children with profound sensorimotor loss, physiologists, engineers, and clinicians have been intent on duplicating this achievement in creating a visual prosthesis to restore vision to the blind. One of the pioneers of neuroengineering, James Brindley, tackled this problem as long ago as 1960 with wireless radio telemetry driven stimulators placed atop the visual cortex in a human patient.[117]

Despite these early promising proof-of-concept trials in human patients, success in creating a viable visual prosthetic has not been forthcoming. In a sense, developing a visual prosthesis represents a more ambitious goal than the previously discussed open-loop BMIs. In this case, information from the visual world would need to be extracted and translated to a neural code to be conveyed to viable neural tissue. This represents a challenge on two fronts: encoding of visual information and stimulation of neural tissue.

V.A. Retinal Devices

For patients who have an intact optic nerve but cannot transduce light to drive that nerve, such as in retinitis pigmentosa or macular degeneration, retinal prostheses represent the most obvious solution to restoring vision. By recording visual input, either on glasses-mounted cameras or with sensors in or on the eye itself, such a device can bypass a damaged retinal transduction system and

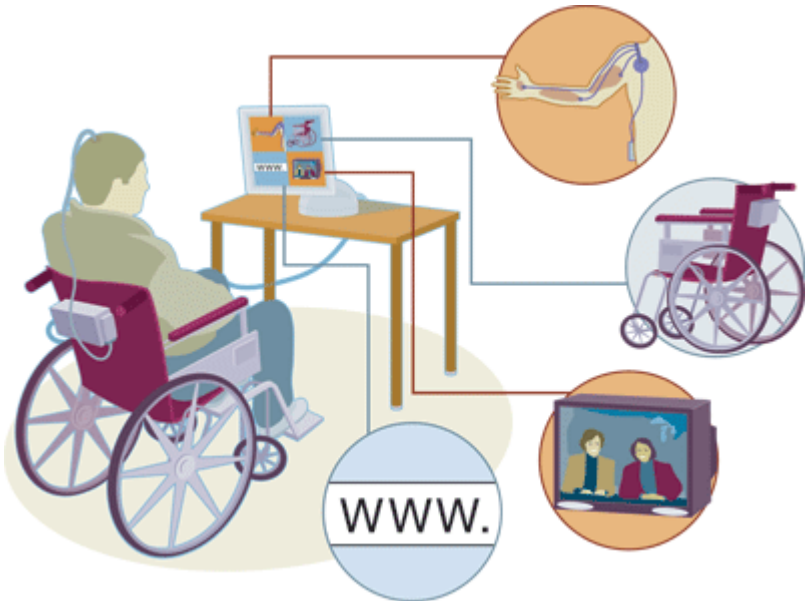

FIGURE 4. Potential outputs of a brain-computer interface for motor control. Once voluntary control signals are decoded from a neuromotor prosthetic, they can be dynamically assigned to control muscle stimulators, powered wheelchairs, household appliances, and computer applications such as Web browsing.

drive ganglion cells in the optic nerve to enable vision. This approach is analogous to the cochlear implant, which can bypass a damaged organ of Corti to directly drive the vestibulocochlear nerve. Tiny multi-electrode arrays have been fabricated and implanted chronically along the inner retinal surface in patients; these epiretinal implants drive the output ganglion cells to transmit signals out the optic nerve into the rest of the brain. Pilot clinical trials have shown that this device has restored the ability to navigate in the environment.[118]

After decussating at the optic chiasm, the major output of the optic pathways arrives at the lateral geniculate nucleus (LGN). This six-layered posterolateral thalamic structure encodes and transmits information about the entire contralateral visual field and hence exists as an ideal target for prosthetic vision restoration. Pilot studies in nonhuman primates have shown that reliable percepts can be induced with electrode arrays penetrating the LGN; human trials have not yet been planned.[119]

V.B. Visual Cortex Devices

Following upon the heels of Brindley and colleagues, several groups have been focusing on subdural and intracortical multi-electrode arrays in the primary visual cortex to restore vision. By communicating with higher-order visual centers in the brain, this approach offers both an advantage and a disadvantage. On the one hand, as in the motor prosthetic domain, such electrodes can easily access these areas of the cortex in order to induce neural activity representative of the visual scene. On the other hand, such an approach bypasses the complexities of visual processing that take place in the retina and lateral geniculate nucleus, and rely instead on a more simplified neural code that may not capture the nuances of visual information extracted by these structures.[117,120–123]

VI. CORTICAL STIMULATION

Cortical stimulation for motor, language, memory, and visual cortex mapping has been undertaken for

over 60 years. It has seen widespread application intraoperatively to guide surgery. Extraoperative mapping can also be performed using surface electrode contacts. The long, rich literature surrounding different parameters and philosophies for cortical brain stimulation is beyond the scope of this publication, but some interesting findings highlight the contrasts between cortical stimulation and the forms of stimulation previously discussed.

Three points are relevant. The first is that low-frequency, higher-amplitude stimulation (<20 Hz) appears to have functional effects similar to high-frequency stimulation (>50 Hz) in the cortex, counter to data in deep brain stimulation and vagal nerve stimulation, in which grossly different functional effects are elicited with high versus low frequencies.[124] The second point is that clinically useful stimulation has so far been limited to motor cortex, sensory cortex, visual cortex, and language cortex. Higher cognitive functions and memory cannot routinely be mapped via conventional methods.[125,126] The third point is that the animal literature contains several successful instances of microstimulation to achieve subtle insights into the functional properties of specific brain areas, from which we may derive lessons for examining higher cognitive function in humans and contemplating new technologies based on cortical stimulation.[127]

VI.A. Frequency for Stimulation

Cortical stimulation for functional mapping has been shown to be effective using low–frequency, high-current biphasic square-wave pulses (5 and 10 Hz), rather than the more conventional higher-frequency biphasic square-wave pulses (50 or 60 Hz).[124] The functional deficits and effects elicited were not statistically different from higher-frequency stimulation, and indeed fewer after discharges were initiated by the lower-frequency technique. This is important because afterdischarges are epileptiform spiking that follows stimulation, and they necessitate the cessation of stimulation at a particular site to avoid a more generalized seizure. It is noteworthy that the high-frequency stimulation seems to be more epileptogenic as compared to ATN or VNS, in which lower frequencies (<20 Hz) drive synchrony and associated epileptic activity. [47]

VI.B. Brain Functions Amenable to Stimulation Mapping

Cortical stimulation mapping is well understood for mapping motor function and language: at conventional stimulation parameters, biphasic square-wave stimulation delivered via bipolar contacts produces movement when motor cortex is stimulated, causes sensation when sensory cortex is stimulated, inhibits speech when receptive or productive speech areas are stimulated, and elicits phosphenes when visual cortex is stimulated. The effect of cortical stimulation on more complicated cognitive processes, however, is not well understood. Stimulation has yet to yield a reproducible system for mapping working and long-term memory, mainly because of the difficulty in testing different cortical sites at multiple different parameters.[125,128] Memory experiments require assessing recall frequency after the presentation of many items. Reliable testing is therefore extraordinarily time-consuming, and testing at multiple parameters (up to a threshold that elicits after-discharges) is prohibitive. Memory is not like speech or motor function: stimulating at one particular cortical site does not produce memory-arrest in the same manner as speech arrest.[125,128] Clinically useful memory mapping may ultimately require some pre-test knowledge about the properties of functional memory networks, obtained from passive analysis of EEG or iEEG data as subjects engage in memory tasks, apart from active stimulation.

VI.C. Lessons from Microstimulation

Cortical stimulation is more difficult than stimulation at subcortical sites such as the basal ganglia. The neuronal populations are more heterogenous, with a complex tangle of excitatory and inhibitory neuronal cell bodies and axons all receiving the effects of stimulation. Microstimulation is a very powerful tool to test hypotheses about the functional role of neurons that have been identified via microrecordings, but its utility for treating disease or enhancing cognitive function may be limited be-

cause its effects are predictable only in cortex with advantageous architecture.[127] Microstimulation in nonhuman primates is usually conducted at much higher frequencies than in human cortical mapping experiments (200 Hz, for example). Its application to human research will be facilitated by the introduction of 40-μm grid electrodes, which will permit better spatial resolution and more fine-grained stimulation.[79] Current macroelectrode contact stimulation may be too blunt to affect function in specific populations of neurons for functions more subtle than gross movement or speech comprehension. Applying cortical stimulation to problems such as memory and decision making may benefit from their introduction.

VII. CONCLUSION

The recent advances in neuroscience and engineering reviewed here suggest that viable brain-machine interfaces may emerge from the realm of science fiction into the reality of clinical medicine in the near future. First-generation BMI technology has realized significant clinical success in a wide variety of disorders, from Parkinson's disease and epilepsy to motor disorders. Yet despite their successes, these devices remain for the most part open-loop systems with as yet poorly understood mechanisms of action. The next generation of these devices will build upon this knowledge to incorporate more precise closed-loop electrical stimulation.

Modulation of network synchrony has emerged as a common feature underlying the success demonstrated with some of these first-generation BMIs. A search for new targets for DBS should involve identifying possible abnormal patterns of synchrony in patients with diseases such as Alzheimer's disease. Furthermore, future applications of brain stimulation will build on the success of NeuroPace by using more fine-grained signal analysis and newer algorithms to enhance or alter neuronal functioning in a closed-loop manner. Using smaller microgrid electrodes may allow human cortical stimulation to approximate some of the success that microstimulation in primates has achieved.

The developments realized in the world of motor prostheses are encouraging, but highlight the need to effectively decode neural signals in order to provide effective control signals. Major efforts currently underway seek to address how best to capture this information and will likely improve with technological advances in the ability to interface directly with the human nervous system. Ultimately, these motor systems will need to incorporate closed-loop feedback in the form of cortical stimulation in order to provide individuals with proprioceptive feedback that mimics the normal motor control system.

The question of using BMIs for higher-order cognitive functions becomes somewhat more complex as significant advances in understanding the neural circuits underlying these functions must first be realized. It is likely the case that these processes involve multiple areas of the brain in complex networks. Decoding these circuits poses the largest hurdle in moving BMIs to this domain, and nuanced stimulation algorithms at widespread cortical sites based upon this knowledge will likely be required to affect processes such as memory and decision making.

All told, the advances seen in the development of BMIs over the past decode represent an extraordinary achievement. That BMIs have been introduced and accepted into the standard lexicon of medical and engineering research is a testament to both their success and to their promise. The challenges in moving these devices to the next generation are immense, but with the wealth of research devoted to these issues, these challenges may be successfully navigated in the near future.

REFERENCES

1. Rosenow J, Das K, Rovit RL, Couldwell WT. Irving S. Cooper and his role in intracranial stimulation for movement disorders and epilepsy. Stereotact Funct Neurosurg. 2000;78(2):95–112.
2. Medtronic. Summary of DBS Usage Statistics; 2010. Available from: http://www.neurotechreports.com/pages/darpaprosthetics.html.
3. Benabid AL, Vercucil L, Benazzouz A, Koudsie A, Chabardes S, Minotti L, Kahane P, Gentil

M, Lenartz D, Andressen C, Krack P, Pollak P. Deep brain stimulation: what does it offer. Adv Neurol. 2003;91:293–302.
4. Halpern C, Hurtig HI, Jaggi JL, Grossman M, Won M, Baltuch GH. Deep brain stimulation in neurological disorders. Parkinsonism Relat Disord. 2007;13:1–16.
5. Siderowf AD. Parkinson's disease: clinical features, epidemiology, and genetics. Neurol Clin. 2001;19(3):565–78.
6. Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the Vim thalamic nucleus for bilateral Parkinson's disease. Appl Neurophysiol. 1987;50:344–6.
7. Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret J, de Rougemont J. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet. 1991;337:403–6.
8. Blomstedt P, Hariz M. Hardware-related complications of deep brain stimulation: a ten year experience. Acta Neurochir. 2005;147(10):1061–1064.
9. Kuncel AM, Grill WM. Selection of stimulus parameters for deep brain stimulation. Clin Neurophysiol. 2004;115(11):2431–2441.
10. Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated current in subthalamic neurons. J Neurophysiol. 2001;85:1351–6.
11. Urbano FJ, Leznik E, Llinas RR. Cortical activation patterns evoked by afferent axon stimuli at different frequencies: an in vitro voltage sensitive dye imaging study. Thalamus Relat Syst. 2002;1:371–8.
12. Dostrovsky JO, Levy R, Wu JP, Hutchison WD, Tasker RR, Lozano AM. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol. 2000;84:570–4.
13. Montgomery EB, Baker KB. Mechanisms of deep brain stimulation and future technical developments. Neurolog Res. 2000;22:259–66.
14. Breit S, Schulz JB, Benabid AL. Deep brain stimulation. Cell Tissue Res. 2004;318(1):275–288.
15. Windels F, Bruet N, Poupard A, Urbain N, Chouvet G, Feuerstein C. Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. Eur J Neurosci. 2000;12(11):4141–4146.
16. Windels F, Bruet N, Poupard A, Feuerstein C, Bertrand A, Savasta M. Influence of the frequency parameter on extracellular glutamate and g-aminobutyric acid in substantia nigra and globus pallidus during electrical stimulation of subthalamic nucleus in rats. J Neurosci Res. 2003;72(2):259–267.
17. Garcia L, D'Alessandro G, Fernagut PO, Bioulac B, Hammond C. Impact of high-frequency stimulation parameters on the pattern of discharge of subthalamic neurons. J Neurophysiol. 2005;94(6):3662.
18. Hashimoto T, Goto T, Hongo K. Neuronal responses to high-frequency stimulation in human subthalamic nucleus. Mov Disorders. 2009;24(12):1860–1862.
19. Hashimoto T, Elder CM, Okun MS, Patrick SK, Vittek JL. Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosci. 2003;23:1915–23.
20. Benazzouz A, Gao DM, Ni ZG, Piallat B, Bouali-Benazzouz R, Benabid AL. Effect of high-frequency stimulation of the subthalamic nucleus on the neuronal activities of the substantia nigra pars reticulata and ventrolateral nucleus of the thalamus in the rat. Neuroscience. 2000;99:289–95.
21. Tai C, Boraud T, Bezard E, Bioulac B, Gross C, Benazzouz A. Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridles neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. FASEB J. 2003;17(13):1820.
22. Anderson ME, Postupna N, Ruffo M. Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol. 2003;89:1150–60.
23. Weinberger M, Hutchison WD, Dostrovsky JO. Pathological subthalamic nucleus oscillations in PD: Can they be the cause of bradykinesia and akinesia? Exp Neurol. 2009;219(1):58–61.

24. Chen CC, Litvak V, Gilbertson T, Kuhn A, Lu CS, Lee ST. Excessive synchronization of basal ganglia neurons at 20 Hz slows movement in Parkinson's disease. Exp Neurol. 2007;205(1):214–221.
25. Brown P, Williams D. Basal ganglia local field potential activity: character and functional significance in the human. Clin Neurophysiol. 2005;116(11):2510–2519.
26. Kuhn AA, Williams D, Kupsch A, Limousin P, Hariz M, Schneider GH, Yarrow K, Brown P. Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. Brain. 2004;127(4):735.
27. Hauptmann C, Popovych O, Tass PA. Effectively desynchronizing deep brain stimulation based on a coordinated delayed feedback stimulation via several sites: a computational study. Biol Cybern. 2005;93(6):463–470.
28. de Solages C, Hill BC, Koop MM, Henderson JM, Bronte-Stewart H. Bilateral symmetry and coherence of subthalamic nuclei beta band activity in Parkinson's disease. Exp Neurol. 2009;221(1):260–266.
29. Weinberger M, Mahant N, Hutchison WD, Lozano AM, Moro E, Hodaie M. Beta oscillatory activity in the subthalamic nucleus and its relation to dopaminergic response in Parkinson's disease. J Neurophysiol. 2006;96(6):3248.
30. Bronte-Stewart H, Barberini C, Koop MM, Hill BC, Henderson JM, Wingeier B. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. Exp Neurol. 2009;217(1):1–3.
31. Wang XJ. Neurophysiological and Computational Principles of Cortical Rhythms in Cognition. Physiol Rev. 2010;90(3):1195.
32. Sillanpaa M, Schmidt D. Natural history of treated childhood-onset epilepsy: prospective, long-term population based study. Brain. 2006;129:617–24.
33. Jirsch J, Urrestarazu E, LeVan P, Olivier A, Dubeau F, Gotman J. High-frequency oscillations during human focal seizures. Brain. 2006;129(6):1593.
34. van Putten MJAM. Nearest neighbor phase synchronization as a measure to detect seizure activity from scalp EEG recordings. Journal of Clinical Neurophysiology. 2003;20(5):320.
35. Oikawa H, Sasaki M, Tamakawa Y, Kamei A. The circuit of Papez in mesial temporal sclerosis: MRI. Neuroradiology. 2001;43:205–10.
36. Papez JW. A proposed mechanism of emotion. Arch Neurol Psych. 1937;38:725–43.
37. Cooper IS, Upton A, Amin I. Chronic cerebellar stimulation (CCS) and deep brain stimulation (DBS) in involuntary movement disorders. Appl Neurophysiol. 1982;45(3):209.
38. Cooper I, Amin I, A M Riklan, Watkins S, McLellan L. Safety and efficacy of chronic cerebellar stimulation. Appl Neurophysiol. 1977–1978;40(2–4):124–134.
39. Van Buren JM, Wood JH, Oakley J, Hambrecht F. Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. J Neurosurg Pediatr. 1978;48(3).
40. Cooper I, Upton A. Therapeutic implications of modulation of metabolism and functional activity of cerebral cortex by chronic stimulation of cerebellum and thalamus. Biol Psychiatry. 1985;20(7):811.
41. Kimiwada T, Juhász C, Makki M, Muzik O, Chugani DC, Asano E, Chugani H. Hippocampal and thalamic diffusion abnormalities in children with temporal lobe epilepsy. Epilepsia. 2006;47(1):167–175.
42. Gutman DA, Holtzheimer PE, Behrens TEJ, Johansen-Berg H, Mayberg HS. A tractography analysis of two deep brain stimulation white matter targets for depression. Biol Psychiatry. 2009;65(4):276–282.
43. Tyvaert L, Chassagnon S, Sadikot A, LeVan P, Dubeau F, Gotman J. Thalamic nuclei activity in idiopathic generalized epilepsy: An EEG-fMRI study. Neurology. 2009;73(23):2018.
44. Mirski MA, McKeon AC, Ferrendelli J. Anterior thalamus and substantia nigra: two distinct structures mediating experimental generalized seizures. Brain Res. 1986;397(2):377–380.
45. Mirski MA, Ferrendelli JA. Anterior thalamic mediation of generalized pentylenetetrazol seizures. Brain Res. 1986;399(2):212–223.
46. Mirski M, Ferrendelli J. Interruption of the mam-

millothalamic tract prevents seizures in guinea pigs. Science. 1984;226(4670):72.
47. Lega BC, Halpern CH, Jaggi JL, Baltuch GH. Deep brain stimulation in the treatment of refractory epilepsy: update on current data and future directions. Neurobiology of Disease. 2009;38(3):354–360.
48. Upton A, Cooper I, Springman M, Amin I. Suppression of seizures and psychosis of limbic system origin by chronic stimulation of anterior nucleus of the thalamus. Int J Neurol. 1986;19–20:223–230.
49. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia. 2002;43(6):603–608.
50. Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N. Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia. 2004;45(4):346–354.
51. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, Osorio I, Nazzaro J, Labar D, The SANTE Group Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010;51(5):899–908.
52. Choi H, Sell RL, Lenert L, Muennig P, Goodman RR, Gilliam FG, Wong J. Epilepsy surgery for pharmacoresistant temporal lobe epilepsy: a decision analysis. JAMA. 2008;300(21):2497.
53. Terry RS, Tarver WB, Zabara J. The implantable neurocybernetic prosthesis system. Pacing Clin Electrophysiol. 1991;14(1):86–93.
54. Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev. 2005;29(3):493–500.
55. McLachlan RS. Vagus nerve stimulation for intractable epilepsy: a review. J Clin Neurophysiol. 1997;14(5):358.
56. Binnie C. Vagus nerve stimulation for epilepsy: a review. Seizure. 2000;9(3):161–169.
57. Smyth MD, Tubbs RS, Bebin EM, Grabb PA, Blount JP. Complications of chronic vagus nerve stimulation for epilepsy in children. J Neurosurg Pediatr. 2003;99(3):500–503.
58. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. J Clin Neurophysiol. 2001;18(5):415.
59. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, R. Howland, M. Kling, B. Rittberg, W. Burke, M.H. Rapaport, J. Zajecka, A., Nirenberg A, Husain M, Ginsberg D, Cooke G. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry. 2005;58(5):347–354.
60. George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry. 2005;58(5):364–373.
61. DeGiorgio C, Schachter S, Handforth A, Salinsky M, Thompson J, Uthman B, Howland R, Kling M, Moreno F, Rittberg B, Dunner D, Schwartz T, Carpenter L, Burke M, Ninari P, Goodnick P. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia. 2000;41(9):1195–1200.
62. Handforth A, DeGiorgio C, Schachter S, Uthman B, Naritoku D, Tecoma E, Henry T, Collins S, Vaughn B, Gilmartin R, V. S. Group. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology. 1998;51(1):48.
63. Salinsky MC, Uthman BM, Ristanovic RK, Wernicke J, Tarver WB. Vagus nerve stimulation for the treatment of medically intractable seizures: results of a 1-year open-extension trial. Arch Neurol. 1996;53(11):1176.
64. Morris 3rd G, Mueller W. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. Neurology. 1999;53(8):1731.
65. Amar AP, DeGiorgio CM, Tarver WB, Apuzzo MLJ. Long-Term Multicenter Experience with Vagus Nerve Stimulation for Intractable Partial Seizures. Stereotact Funct Neurosurg. 1999;73(1–4):104–108.

66. Piotr W, Bruce J, Michael C, Grant B, Lee H, Carmela T. The effect of vagal nerve stimulation on epileptiform activity recorded from hippocampal depth electrodes. Epilepsia. 2001;42(3):423–429.
67. Thompson J, Zaveri HPMcCarthy K, Carpentier A, Spencer S, Spencer D. Vagus nerve stimulation effects on intracranial EEG spectra recorded from cortex and thalamus. Epilepsia. 1999;40(Suppl 7):S138.
68. Magnes J, Moruzzi G, Pompeiano O. Synchronization of the EEG produced by low-frequency electrical stimulation of the region of the solitary tract. Arch Ital Biol. 1961;99:33–67.
69. Marrosu F, Santoni F, Puligheddu M, Barberini L, Maleci A, Ennas F, Mascia M, Zanetti G, Tuveri A, Biggio G. Increase in 20–50 Hz (gamma frequencies) power spectrum and synchronization after chronic vagal nerve stimulation. Clin Neurophysiol. 2005;116(9):2026–2036.
70. Vonck K, Van Laere K, Dedeurwaerdere S, Caemaert J, De Reuck J, Boon P. The mechanism of action of vagus nerve stimulation for refractory epilepsy: the current status. J Clin Neurophysiol. 2001;18(5):394.
71. Nemeroff CB, Mayberg HS, Krahl SE, McNamara J, Frazer A, Henry TR, George M, Charney D, Brannan S. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. Neuropsychopharmacology. 2006;31(7):1345–1355.
72. Chapotot F, Gronfier C, Jouny C, Muzet A, Brandenberger G. Cortisol secretion is related to electroencephalographic alertness in human subjects during daytime wakefulness. J Clin Endocrinol Metab. 1998;83(12):4263.
73. Jaseja H. EEG-desynchronization as the major mechanism of anti-epileptic action of vagal nerve stimulation in patients with intractable seizures: Clinical neurophysiological evidence. Med Hypotheses. 2009;74(5):855–856.
74. Samuels E, Szabadi E. Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part I: principles of functional organisation. Curr Neuropharmacol. 2008;6(3):254–85.
75. Sun FT, Morrell MJ, Wharen Jr RE. Responsive cortical stimulation for the treatment of epilepsy. Neurotherapeutics. 2008;5(1):68–74.
76. Lesser R, Kim S, Beyderman L, Miglioretti D, Webber W, Bare M, Cysyk B, Krauss G, Gordon B. Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. Neurology. 1999;53(9):2073.
77. Peters TE, Bhavaraju NC, Frei MG, Osorio I. Network system for automated seizure detection and contingent delivery of therapy. J Clin Neurophysiol. 2001;18(6):545.
78. Skarpaas TL, Morrell MJ. Intracranial stimulation therapy for epilepsy. Neurotherapeutics. 2009;6(2):238–243.
79. Van Gompel JJ, Stead SM, Giannini C, Meyer FB, Marsh WR, Fountain T, So E, Cohen-Gadol A, Lee K, Worrell G. Phase I trial: safety and feasibility of intracranial electroencephalography using hybrid subdural electrodes containing macro-and microelectrode arrays. J Neurosurg Pediatr. 2008;25(3).
80. Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. Brain. 2007;130(2):314.
81. Stead M, Bower M, Brinkmann BH, Lee K, Marsh WR, Meyer FB, Litt B, Van Gompel J, Worrell G. Microseizures and the spatiotemporal scales of human partial epilepsy. Brain. 2010;133(9):2369.
82. Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron. 2006;52(1):155–168.
83. Poza J, Hornero R, Abásolo D, Fernández A, Garcìa M. Extraction of spectral based measures from MEG background oscillations in Alzheimer's disease. Med Eng Phys. 2007;29(10):1073–1083.
84. Aoyagi Y, Stein RB, Branner A, Pearson KG, Normann RA. Capabilities of a penetrating microelectrode array for recording single units in dorsal root ganglia of the cat. J Neurosci Meth. 2003;128(1–2):9–20.
85. Dowden BR, Wilder AM, Hiatt SD, Normann RA, Brown NAT, Clark GA. Selective and grad-

ed recruitment of cat hamstring muscles with intrafascicular stimulation. IEEE Trans Neur Syst Rehabil Eng. 2009;17(6):545–552.
86. Rossini PM, Micera S, Benvenuto A, Carpaneto J, Cavallo G, Citi L, Cipriani C, Denaro L, Denaro V, Pino G, Ferrrei F, Guglielmelli E, Hoffmann K, Raspopovic S, Rossini L, Tombini M, Daria P. Double nerve intraneural interface implant on a human amputee for robotic hand control. Clin Neurophysiol. 2010;121(5):777–783.
87. Kuiken TA, Miller LA, Lipschutz RD, Lock BA, Stubblefield K, Marasco PD, Zhou P, Dumanian G. Targeted reinnervation for enhanced prosthetic arm function in a woman with a proximal amputation: a case study. The Lancet. 2007;369(9559):371–380.
88. Kuiken T, Kipke D. CNS Anatomy and TMR; 2009. Presented at the Workshop on Reliable Neural Interface Technology, DARPA, Arlington, VA. Available from: http://www.neurotechreports.com/pages/darpaprosthetics.html.
89. Kemere C, Santhanam G, Yu BM, Afshar A, Ryu SI, Meng TH, Shenoy K. Detecting neural-state transitions using hidden Markov models for motor cortical prostheses. J Neurophysiol. 2008;100(4):2441.
90. Brown TG, Sherrington C. On the instability of a cortical point. Proc R Soc Lond [Biol]. 1912;85(579):250–277.
91. Daly JJ, Wolpaw JR. Brain-computer interfaces in neurological rehabilitation. Lancet Neurol. 2008;7(11):1032–1043.
92. Donoghue JP. Bridging the brain to the world: a perspective on neural interface systems. Neuron. 2008;60(3):511–521.
93. Sellers E, Kubler A, Donchin E. Brain-computer interface research at the University of South Florida Cognitive Psychophysiology Laboratory: the P300 speller. IEEE Trans Neural Syst Rehabil Eng. 2006;14(2):221–224.
94. Townsend G, LaPallo B, Boulay C, Krusienski D, Frye G, Hauser C, Schwartz N, Vaughan T, Wolpaw J, Sellers E. A novel P300-based brain–computer interface stimulus presentation paradigm: Moving beyond rows and columns. Clinical Neurophysiology. 2010;121(7):1109–1120.
95. Schalk G, McFarland D, Hinterberger T, Birbaumer N, Wolpaw J. BCI2000: a general-purpose brain-computer interface (BCI) system. IEEE Trans Biomed Eng. 2004;51(6):1034–1043.
96. Wolpaw JR, McFarland DJ. Control of a two-dimensional movement signal by a noninvasive brain-computer interface in humans. Proc Natl Acad Sci, U S A. 2004;101(51):17849.
97. Kubler A, Nijboer F, Mellinger J, Vaughan T, Pawelzik H, Schalk G, McFarland D, Birbaumer N, Wolpaw J. Patients with ALS can use sensorimotor rhythms to operate a brain-computer interface. Neurology. 2005;64(10):1775.
98. Bradberry TJ, Gentili RJ, Contreras-Vidal JL. Reconstructing Three-Dimensional Hand Movements from Noninvasive Electroencephalographic Signals. J Neurosci. 2010;30(9):3432.
99. Zhu D, Bieger J, Molina GG, Aarts RM. A survey of stimulation methods used in SSVEP-based BCIs. Comput Intell Neurosci. 2010;2010:702357.
100. Schalk G, Miller K, Anderson N, Wilson J, Smyth M, Ojemann J, et al. Two-dimensional movement control using electrocorticographic signals in humans. J Neural Eng. 2008;5(1):75–84.
101. Hinterberger T, Widman G, Lal TN, Hill J, Tangermann M, Rosenstiel W, Scholkopf B, Elger C, Birbaumer N. Voluntary brain regulation and communication with electrocorticogram signals. Epilepsy Behav. 2008;13(2):300–306.
102. Miller KJ, Schalk G, Fetz EE, den Nijs M, Ojemann JG, Rao RPN. Cortical activity during motor execution, motor imagery, and imagery-based online feedback. Proc Natl Acad Sci, U S A. 2010;107(9):4430.
103. W. Wang, A. Degenhart, J. Collinger, R. Vinjamuri, G. Sudre, P. Adelson, D. Holder, E. Leuthardt, D. Moran, M. Boninger, A. Schwartz, D. Crammond, E. Tyler-Kabara, D. Weber. Human motor cortical activity recorded with Micro-ECoG electrodes, during individual finger movements. In: Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society; vol. 1; 2009. p. 586–589.
104. Kim D,JViventi J, Amsden J, Xiao J, Vigeland

L, Kim Y, Blanco J, Panilaitis B, Frechette E, Contreras D, Kaplan D, Omenetto F, Huang Y, Hwang K, Zakin M, Litt B, Rogers J. Dissolvable films of silk fibroin for ultrathin conformal bio-integrated electronics. Nature Mat. 2010;9(6):511–517.

105. Kennedy P, Andreasen D, Ehirim P, King B, Kirby T, Mao H, Moore M. Using human extracortical local field potentials to control a switch. J Neural Eng. 2004;1(2):72–77.
106. Borton D, Song Y, Patterson W, Bull C, Park S, Laiwalla F, Donoghue J, Nurmikko A. Wireless, high-bandwidth recordings from non-human primate motor cortex using a scalable 16-Ch implantable microsystem. In: Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. vol. 1. IEEE Engineering in Medicine and Biology Society; 2009. p. 5531.

107] Chestek C, Gilja V, Nuyujukian P, Kier R, Solzbacher F, Ryu S, Harrison R, Shenoy K. Hermes C: Low-power wireless neural recording system for freely moving primates. Proc IEEE International Symposium on Systems and Circuits. 2008. p. 1752–1755.

108. Farshchi S, Pesterev A, Nuyujukian P, Guenterberg E, Mody I, Judy J. Embedded Neural Recording With TinyOS-Based Wireless-Enabled Processor Modules. IEEE Trans Neural Syst Rehabil Eng. 2010 Jan;18(2):134–41.
109. Wu W, Shaikhouni A, Donoghue J, Black M. Closed-loop neural control of cursor motion using a Kalman filter. In: Conference Proceedings: Engineering in Medicine and Biology Society. vol. 2; 2004. p. 4126–4129.
110. Serruya MD, Hatsopoulos NG, Paninski L, Fellows MR, Donoghue JP. Brain-machine interface: Instant neural control of a movement signal. Nature. 2002;416(6877):141–142.
111. Taylor DM SA Tillery SI. Direct cortical control of 3D neuroprosthetic devices. Science. 2002;7(296):1817–8.
112. Santhanam G, Ryu SI, Yu BM, Afshar A, Shenoy KV. A high-performance brain–computer interface. Nature. 2006;442(7099):195–198.
113. Lauer RT, Peckham PH, Kilgore KL. EEG-based control of a hand grasp neuroprosthesis. Neuroreport. 1999;10(8):1767.
114. Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M, Caplan AH, Branner A, Chen D, Penn R, Donoghue J. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature. 2006;442(7099):164–171.
115. Pfurtscheller G, Muller GR, Pfurtscheller J, Gerner HJ, Rupp R. Thought-control of functional electrical stimulation to restore hand grasp in a patient with tetraplegia. Neuroscience Lett. 2003;351(1):33–36.
116. Galan F, Nuttin M, Lew E, Ferrez P, Vanacker G, Philips J, Philips J, Millán J. A brain-actuated wheelchair: Asynchronous and non-invasive brain-computer interfaces for continuous control of robots. Clin Neurophysiol. 2008;119(9):2159–2169.
117. Brindley G, Lewin W. The sensations produced by electrical stimulation of the visual cortex. J Physiol. 1968;196(2):479.
118. Caspi A, Dorn JD, McClure KH, Humayun MS, Greenberg RJ, McMahon MJ. Feasibility study of a retinal prosthesis: spatial vision with a 16-electrode implant. Arch Ophthalmol. 2009;127(4):398.
119. Pezaris JS, Reid RC. Demonstration of artificial visual percepts generated through thalamic microstimulation. Proc Natl Acad Sci U S A. 2007;104(18):7670.
120. Schmidt E, Bak M, Hambrecht F, Kufta C, O'rourke D, Vallabhanath P. Feasibility of a visual prosthesis for the blind based on intracortical micro stimulation of the visual cortex. Brain. 1996;119(2):507.
121. Srivastava N, Troyk P. Some solutions to technical hurdles for developing a practical intracortical visual prosthesis device. In: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. vol. 1; 2006. p. 2936.
122. Murphey DK, Maunsell JHR, Beauchamp MS, Yoshor D. Perceiving electrical stimulation of identified human visual areas. Proc Natl Acad Sci U S A. 2009;106(13):5389.

123. Normann RA, Greger BA, House P, Romero SF, Pelayo F, Fernandez E. Toward the development of a cortically based visual neuroprosthesis. J Neural Eng. 2009;6:035001.
124. Zangaladze A, Sharan A, Evans J, Wyeth DH, Wyeth EG, Tracy JI, Chervoneva I, Sperling M. The effectiveness of low-frequency stimulation for mapping cortical function. Epilepsia. 2007;49(3):481–487.
125. Ojemann GA. Organization of short-term verbal memory in language areas of human cortex: Evidence from electrical stimulation* 1. Brain Lang. 1978;5(3):331–340.
126. Ojemann GA. Brain organization for language from the perspective of electrical stimulation mapping. Behav Brain Sci. 2010;6(02):189–206.
127. Cohen MR, Newsome WT. What electrical microstimulation has revealed about the neural basis of cognition. Curr Opin Neurobiol. 2004;14(2):169–177.
128. Perrine K, Devinsky O, Uysal S, Luciano DJ, Dogali M. Left temporal neocortex mediation of verbal memory: Evidence from functional mapping with cortical stimulation. Neurology. 1994;44(10):1845–1850.