The Emerging World of Motor Neuroprosthetics: A Neurosurgical Perspective

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A MOTOR NEUROPROSTHETIC device, or brain computer interface, is a machine that can take some type of signal from the brain and convert that information into overt device control such that it reflects the intentions of the user's brain. In essence, these constructs can decode the electrophysiological signals representing motor intent. With the parallel evolution of neuroscience, engineering, and rapid computing, the era of clinical neuroprosthetics is approaching as a practical reality for people with severe motor impairment. Patients with such diseases as spinal cord injury, stroke, limb loss, and neuromuscular disorders may benefit through the implantation of these brain computer interfaces that serve to augment their ability to communicate and interact with their environment. In the upcoming years, it will be important for the neurosurgeon to understand what a brain computer interface is, its fundamental principle of operation, and what the salient surgical issues are when considering implantation. We review the current state of the field of motor neuroprosthetics research, the early clinical applications, and the essential considerations from a neurosurgical perspective for the future.

KEY WORDS: Brain computer interface, Brain machine interface, Electrocorticography, Electroencephalography, Neuroprosthetics, Single units

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During the past decade, the idea of machines that could be controlled by one's thoughts has emerged from the realm of fiction to one of serious scientific inquiry. The most common technical term for these types of devices is a brain computer interface (BCI). Other synonymous terms include motor neuroprosthetics, direct brain interface, brain machine interface, and neurorobotics. Most simply put, these are machines that create a new output channel from the brain other than the natural motor and hormonal commands. BCIs recognize some form of electrophysiological alteration in the brain of a subject and use these changes as signals to either communicate with or control some element of the outside world that is consistent with the intentions of that subject. Concrete examples of such applications would be some type of brain signal controlling a cursor on a computer screen, a prosthetic limb, or one's own limb. These types of devices hold tremendous promise for improving the quality of life of individuals who are cognitively intact yet motor impaired. This includes patients with spinal cord injury, stroke, neuromuscular disorders, and amputees. These are patients for whom, until now, the field of neurosurgery has not been able to offer any substantive intervention. Moreover, these populations are increasing in size and relevance because of the aging population and improved survival after stroke and trauma.

It is important to distinguish the emerging nature of these output BCIs, or devices that convert human intentions to overt device control, from those that translate external stimuli such as light or sound into internally perceived visual or auditory perceptions (i.e., input BCIs). There has been a rich and extensive experience in the sensory prosthetic field. To date, the most successful example of a sensory prosthetic is the cochlear implant. Cochlear implants are a therapeutic option for patients who lack the cochlear hair cells that transduce sound into neural activity but who have surviving auditory nerve fibers. In many cases, a cochlear prosthesis and associated speech processor can restore accurate speech reception to a person who otherwise has little or no auditory sensitivity. Indeed, many implant users routinely converse on the telephone (1). Cochlear implants have been in common clinical use for more than two decades, and more than 60,000 devices have been implanted (52). Auditory implants are also being extended to direct stimulation of the brainstem for those with dysfunctional cochlear nerves (e.g., neurofibromatosis-2) (57). To date, approximately 300 to 500 patients have been implanted with auditory brainstem implants (12, 40). Visual prosthetics are also making significant inroads into clinical viability. Prosthetics have been applied to every aspect of the visual system ranging from cortical implants (both surface and intraparenchymal electrodes) (3, 16–20, 71), to optic nerve stimulators (83), to retinal (both subretinal and epiretinal) implants (11, 32, 33, 87). Each of these platforms is undergoing various stages of clinical trials ranging from transient placement to chronic implantation. The most efficacious clinical platform, however, still has yet to be determined, as discussed by Margalit et al. (48).

Now, with the improved understanding of the electrophysiological underpinnings of motor related cortical function, rapid development of inexpensive and fast computing, and a growing awareness of the needs of the severely motor impaired, the notion of a practical and clinically viable BCI now is beginning to deserve serious consideration. It will be essential for the neurosurgical community to understand what these devices are and their implications for patient care. This will require a fundamental framework of how these systems operate, what the current BCI platforms and their limitations are, relevant issues when applied clinically, and what the important milestones are for their evolution toward entering standard neurosurgical practice.

This review will provide a reference to which neurosurgeons can refer to critically evaluate the emerging field of motor neuroprosthetics. We will discuss the critical features, function, and platforms of output BCIs; in addition, we will define the key surgical elements to be considered for an implantable BCI and then critically review the literature of the various platforms relative to these considerations.

Brain Computer Interface: Definition and Essential Features

In 2000, the First International Meeting on Brain Computer Interface Technology defined a BCI as "a communication system that does not depend on the brain's normal output pathways of peripheral nerves and muscles" (90). More simply, a BCI is a device that can decode human intent from brain activity alone to create an alternate communication channel for people with severe motor impairments (91). A real world example of this would entail a quadriplegic subject controlling a cursor on a screen with his or her electroencephalography (EEG) signal alone and unaided with the assistance or requirement of overt motor activity. It is important to emphasize this point. A true BCI creates a completely new output pathway for the brain. Wolpaw et al. (91), in their review of BCI interface technology, state this principle cogently: "A BCI changes electrophysiological signals from mere reflections of central nervous system (CNS) activity into the intended products of that activity: messages and commands that act on the world. It changes a signal such as an EEG rhythm or a neuronal firing rate from a reflection of brain function into the end product of that function: an output that, like output in conventional neuromuscular channels, accomplishes the person's intent. A BCI replaces nerves and muscles and the movements they produce with electrophysiological signals and the hardware and software that translate those signals into actions."

With a new output channel, the user must have feedback to improve the performance of how they alter their electrophysiological signals. Just as a child must learn how to walk or an athlete perfects certain movements, there must be continuous alteration of the subject's neuronal output (whether neuromuscular or electrophysiological) matched against feedback from their overt actions such that the subject's output can be tuned to optimize his or her performance toward the intended goal. Therefore, the brain must adapt its signals to improve performance, but also the BCI should be able to evolve to the changing milieu of the user's brain to further optimize functioning. This dual adaptation requires a certain level of training and learning curve both for the user and the computer. The better the computer and subject are able to adapt, the shorter the training that is required for control.

There are four essential elements to the practical functioning of a BCI platform (*Fig. 1*):

1) signal acquisition, the BCI system's recorded brain signal or information input.
2) signal processing, the conversion of raw information into a useful device command.
3) device output, the overt command or control functions that are administered by the BCI system.
4) operating protocol, the manner in which the system is turned on and off (91).

All of these elements play in concert to manifest the user's intention to his or her environment.

Signal acquisition is some real time measurement of the electrophysiological state of the brain. This measurement of brain activity is usually recorded via electrodes, but is by no means a theoretical requirement. These electrodes can be either invasive or noninvasive. The most common types of signals include EEG, electrical brain activity recorded from the scalp (24, 25, 28, 61, 79, 85), electrocorticography (ECoG) (42, 43), electrical brain activity recorded beneath the cranium (42, 43, 69), field potentials, electrodes monitoring brain activity from within the parenchyma (2), and "single units." microelectrodes monitoring individual neuron action potential firing (30, 35, 41, 82). *Figure 2* shows the relationship of the various signal platforms in terms of anatomy and population sampled. Other possible signals include magnetoencephalography, functional magnetic resonance imaging, positron emission tomography, and optical imaging. All of these types of signals, however, have either prohibitive equipment costs or

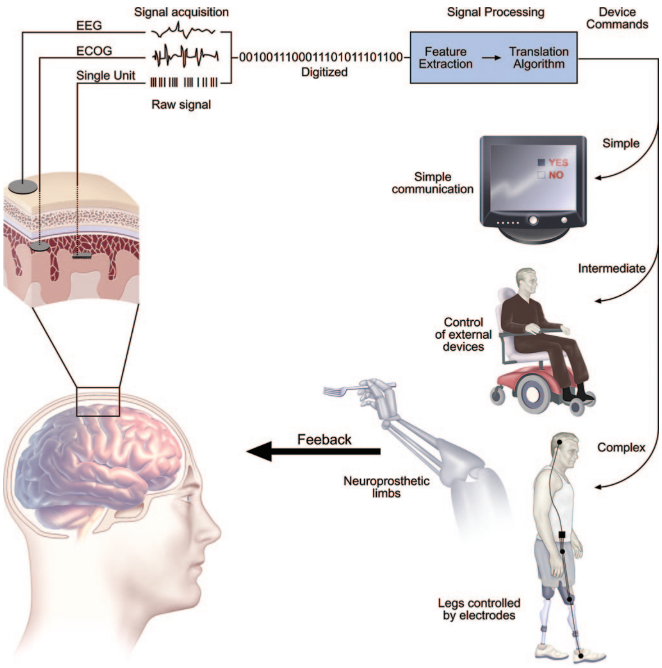

FIGURE 1. *Schematic showing the essential components of the BCI system. BCI replaces nerves, muscles, and the movements they produce with electrophysiological signals (i.e., EEG, electrocorticography, single unit action potentials) and hardware and software that translate those signals into actions. The essential elements to practical functioning of a BCI platform are as follows: 1) signal acquisition, the BCI system's recorded brain signal or information input. This signal is then digitized for analysis; 2) signal processing, conversion of raw information into a useful device command. This involves both feature extraction, determination of a meaningful change in signal, and feature translation. The conversion of that signal alteration to a device command; 3) device output, overt command or control functions that are administered by the BCI system. These outputs can range from simple forms of basic word processing and communication to higher levels of control such as driving a wheel chair or controlling a prosthetic limb. As a new output channel, the user must have feedback on their overt device output to improve performance of how they alter their electrophysiological signal. All these elements play in concert to make manifest user's intention to his or her environment.*

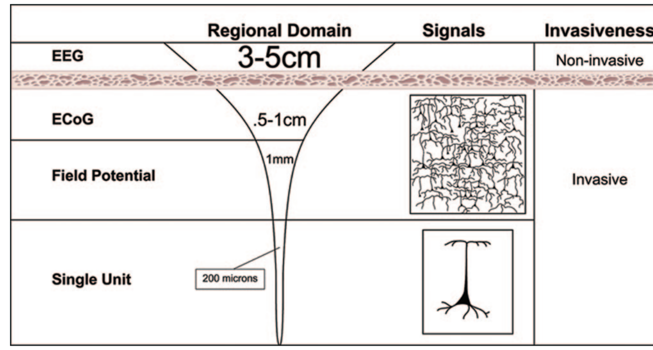

FIGURE 2. *Schematic showing the relationship of various signals used in BCI operation in regard to the area of the cortex distinguishable, neuronal population, and level of invasiveness. On one end of the spectrum, EEG is the least invasive while having the lowest signal fidelity because of a large regional signal domain. On the other hand, single unit monitoring has highest level of signal fidelity by monitoring single neuron action potentials, but is the most invasive of signal modalities because of a need for cortical penetration. These relationships govern the risk-benefit assessment in terms of what level of control is necessary against the level of risk in signal acquisition. The ideal platform has the least amount of risk in device application while maintaining a high level of complex information for device control.*

excessively slow time constants that do not make them practical currently. Once acquired, the signals are then digitized and sent to the BCI system for further interrogation.

In the signal processing portion of BCI operation, there are two essential functions: feature extraction and signal translational. The first pulls significant identifiable information from the gross signal, and the second converts that identifiable information into device commands. It is important to note that the process of converting raw signal into one that is meaningful requires a complex array of statistical analyses. These techniques can vary from assessment of frequency power spectra, event related potentials, and cross correlation coefficients for analysis of EEG/ECOG signals to directional cosine tuning of individual neuron action potentials (45, 53, 62). These statistical methods assess the probability that an electrophysiological event correlates with a given cognitive or motor task. As an example, after recordings are made from an EEG signal, the BCI system must recognize that a meaningful, or statistically significant, alteration has occurred in the electrical rhythm (feature extraction) and then associate that change with a specific cursor movement (translation). As mentioned above, it is important that the signal processing be dynamic such that it can adjust to the changing internal signal environment of the user. In regard to the actual device output, this is the overt action that the BCI accomplishes. As in the previous example, this can result in moving a cursor on a screen; other possibilities are choosing letters for communication, controlling a robotic arm, driving a wheelchair, or controlling some other intrinsic physiological process such as moving one's own limb or controlling bowel and bladder sphincters.

An important consideration for practical application is the overall operating protocol. This refers to the manner in which the user controls how the system functions. The "how" includes such things as turning the system on or off, controlling what kind of feedback and how fast it is provided, how quickly the system implements commands, and switching between various device outputs. These elements are critical for BCI functioning in the real world application of these devices. Currently, research protocols are very controlled in that all the parameters are set by the investigator. In other words, the researcher turns the system on and off, and he or she adjusts the speed of interaction or defines very limited goals and tasks. These are all things that the users will need to be able to do by themselves in an unstructured applied environment.

NEUROSURGICAL ISSUES OF BCIs

With the emergence of these neuroprosthetic technologies, the neurosurgical community should have a framework to evaluate these new systems as they apply to patients. This framework should ask the following six questions. Is the BCI safe? Is the system durable? Will the implant last in the patient for an extended period of time? Is it reliable? Will the BCI perform consistently for the subject? Does the BCI system have sufficiently complex control to be useful? Is the BCI suitable for the given patient population? And, has there been sufficient technical and practical demonstration of the systems efficacy? We will review the relevant issues and the implications of each of these questions.

In addition to the processing issues that define the requirements of a BCI system, there is a separate and distinct set of factors that a neurosurgeon must consider about a given platform when considering application toward a clinical population. The most fundamental issue is whether a BCI system is safe. First, surgical implementation must have acceptable clinical risk, and then, subsequently over time, the construct must be reliable and durable in its ability to acquire signals. Assessing the risks of initial surgical application is relatively straightforward because this will most likely involve variants of standard surgical practices. Likely equivalent types of technical procedures are the placement of deep brain stimulators, cortical stimulators for pain, and the placement of grid electrodes. What will require closer scrutiny is the construct's likelihood for ongoing function. This can be affected by how the construct is designed (i.e., will the construct break down in a couple years?) and how the patient responds to the construct histologically (i.e., will scar formation prohibit signal acquisition after a period of time?). If the device has a short half-life, this will necessitate removal and reimplantation around areas of eloquent cortex. Because of the inherent risk of reoperation, unnecessarily short time frames for device replacement could potentially increase the risk of injury to those regions.

Beyond issues of safety, there are performance-related factors that must be considered for a BCI to have practical application. These issues include complexity of control and levels of speed and accuracy. How complex the control afforded by a given BCI can be assessed by how many degrees of freedom (DOF) of control there are. DOF refer to how many processes can be controlled in parallel. This can also be thought of in terms of dimensions in space. For a BCI to be clinically viable, such that it can truly enable a motor impaired individual to meaningfully engage in his or her environment, it will likely require a minimum of three-dimensional control, or three DOF. One-dimensional control, or one DOF, allows for binary interaction (e.g., yes or no) or proportional control (e.g., move left fast or to the right slowly). Two-dimensional control (two DOF) allows for moving a cursor on a screen along an x and y axis. This level of control, although an improvement from no ability to communicate, is still limited. Three-dimensional control, however, provides a substantive improvement in enabling the BCI user. This level of control translates to a subject controlling an object in three-dimensional space (such as a basic robotic arm) or controlling an object in two-dimensional space with a parallel switch command function (i.e., controlling a computer mouse with a "click" function). This type of control would allow a given patient to either perform such tasks as operating a Windows based computer, directing a wheel chair (with a brake function), or performing very basic operations of a prosthetic limb in three-dimensional space. For truly more physiological approximations of limb function, such as controlling a robotic arm for an amputee or inducing the paralyzed limb to move in a coordinated fashion, this would require many more DOF. As an example, controlling a prosthetic arm in a fashion that approximates normal human use would require a minimum of seven DOF (i.e., three at the shoulder, one at the elbow, one in the forearm, and two at the wrist).

The overall performance of a BCI system is assessed by its speed and accuracy. These are important considerations for a human BCI, which will need to operate at a rate acceptable for the user to interact in real world situations and also be able to function with a minimum of errors that could potentially lead to dangerous situations (e.g., making a wrong turn with a wheelchair, failure to ask for help, misdirecting a prosthetic limb, etc.) These variables are incorporated into a single value known as the rate of information communicated per unit time, or bits per minute or bit rate (66). The bit rate of a BCI system must increase as the complexity of choices increases. Therefore, more information must be communicated when choosing between four choices compared with two. As a corollary, the information necessarily increases from one DOF to two DOF and so on. Also, in regard to rate of information transfer, it is not simply how many choices are made in a given period of time, it is how many choices are made correctly. Accuracy has a significant impact on information transfer. As an example, a BCI system that is 90% accurate in a two-choice system conveys the same amount of information as a BCI system that is 65% accurate in a four-choice system (66). The current bit rate for human BCI systems are approximately 25 bits/minute (90). This translates to a very basic level of control: being able to answer yes and no, very simple word processing, etc. The information transfer rate for an effective BCI system that reliably and quickly responds to the user's environment will need to be higher. Which bit rate will be appropriate will depend on the task and the patient.

Patients who may benefit from a neuroprosthetic may be very different in regard to both their clinical needs and their optimal platform. Patients with spinal cord injury, amyotrophic lateral sclerosis (ALS), amputations, and stroke may all have some type of motor impairment, but they may require very different device outputs relevant to their clinical situation. A spinal cord injury patient may optimally benefit from a device that allows the individual to control some type of motorized wheel chair or allows he or she to control their bowel and bladder sphincter tone. An ALS and locked-in stroke patient, however, might have needs primarily related to communication. An amputee may need very fine control of a prosthetic limb. Moreover, these patients may vary as to what type of signal and implant platform may work best given their pathology. A motor cortical related implant may be optimal for a subject with cord dysfunction or amputation but may not work well in an ALS or stroke patient where that part of the brain may not be normal. Therefore, it is vital that the patient population and its underlying pathology be taken into consideration for the type of platform to be used and the functions it provides.

In a final summation, as research and new advances in the motor neuroprosthetic field emerge, one must be able to distinguish between technical demonstrations and practical demonstrations of BCI function. A technical demonstration refers to the first time that something is technically possible. Examples of these include when Fetz and Finocchio (26), in 1971, first demonstrated that one degree of control could be obtained from the operant training of a monkey to alter the firing rate of a single neuron, or when single DOF control in human BCI systems was further demonstrated by Wolpaw et al. (94), in 1991, using EEG signals and then by Leuthardt et al. (43), in 2004, with ECoG. These are exciting demonstrations of what is possible. The next step in application toward the patient must be a demonstration in real world use. Accomplishing BCI control is very different in real world scenarios with multiple distractors and uncontrolled variables and objectives than that of more restricted experimental conditions. A current example of this is revealed in some of the single unit-based systems developed by Donoghue that are now being commercialized by the company Cyberkinetics (74). In 2002, Serruya et al. (75), using microelectrode arrays in monkeys, were able to achieve two-dimensional control. The highest standard to date is three-dimensional control, which was accomplished by Taylor et al. (82), in 2002, through the use of microelectrode arrays in primates. When applied clinically to the first human subject, preliminary reports seem to indicate that control has been somewhat limited despite optimal results in previous primate paradigms (23). Whether this is because the subject is in a less controlled environment, a limitation of the signals acquired, or simply because of the early nature of the human trials is not clear at this point and requires further investigation.

CURRENT BCI PLATFORMS

There are currently three types of platforms that currently have potential for near-term clinical application. They differ primarily in the signal that they use for control, namely, EEG, single unit recording, and ECoG. Each has feature profiles that give them advantages and disadvantages regarding their utility for an applied setting. The signal platform, its history, and their strengths and weaknesses as they relate toward patients are reviewed below.

EEG-based Systems

Human BCI experience has, until recently, been confined almost entirely to EEG recordings, and studies have mainly evaluated the use of sensorimotor rhythms, slow cortical potentials (SCPs), and P300 evoked potentials derived from the EEG (39, 70, 91).

Sensorimotor Cortex Rhythms

In awake individuals, primary sensory or motor cortical areas typically display 8 to 12 Hz EEG activity when they are not processing sensory input or producing motor output (27, 29, 37, 56). This idling activity, called μ rhythm when recorded over sensorimotor cortex, is thought to be produced by thalamocortical circuits (56). The β rhythm is typically associated with 18 to 26 Hz β rhythms. Although some of these β rhythms are harmonics of μ rhythms, some are separable by topography or timing from μ rhythms and thus seem to be independent EEG features (50, 58, 59). Several factors originally suggested that μ or β rhythms could be useful for BCI-based communication. These rhythms are associated with those cortical areas that are most directly connected to the brain's normal motor output pathways. Movement or preparation for movement is typically accompanied by a decrease in μ and β activity over sensorimotor cortex, particularly contralateral to the movement. Most relevant for BCI operation, this decrease in activity also occurs with imagined movements and does not require actual movement (50, 64). Thus, these changes can occur independently of activity in the brain's normal output channels of peripheral nerves and muscles and could therefore serve as the basis for a BCI. *Figure 3A* shows representative results from a BCI using sensorimotor cortex rhythms. People, including those with ALS or spinal cord injury (39), have learned to control μ or β amplitudes in the absence of movement or sensation and can use this control to move a cursor to select letters or icons on a screen or to operate a simple orthosis (63). Two-dimensional cursor control and mouse-like sequential reach and select control have also been demonstrated and have achieved speed and accuracy approaching that reported for monkeys with implanted electrodes (51, 92, 93).

Slow Cortical Potentials

SCPs are slow changes in EEG potentials that are centered at the vertex and occur over periods of several seconds. Negative SCPs are usually associated with movement and other functions involving cortical activation, whereas positive SCPs are usually associated with reduction in such activations (4, 67). Elbert et al. (24) have shown that people can learn to control SCP amplitude. *Figure 3B* shows the typical topography and time course of this phenomenon, which provides the basis for a BCI that Birbaumer et al. (5, 6) and Kubler et al. (38) refer to as a "thought translation device (TTD)." This system has been tested extensively in people with late-stage ALS and has proved able to supply basic communication capability (39) and control over simple Internet tasks. The fact that it has proven able to function for users who have almost no remaining voluntary movement is strong evidence that this system does not depend on neuromuscular function.

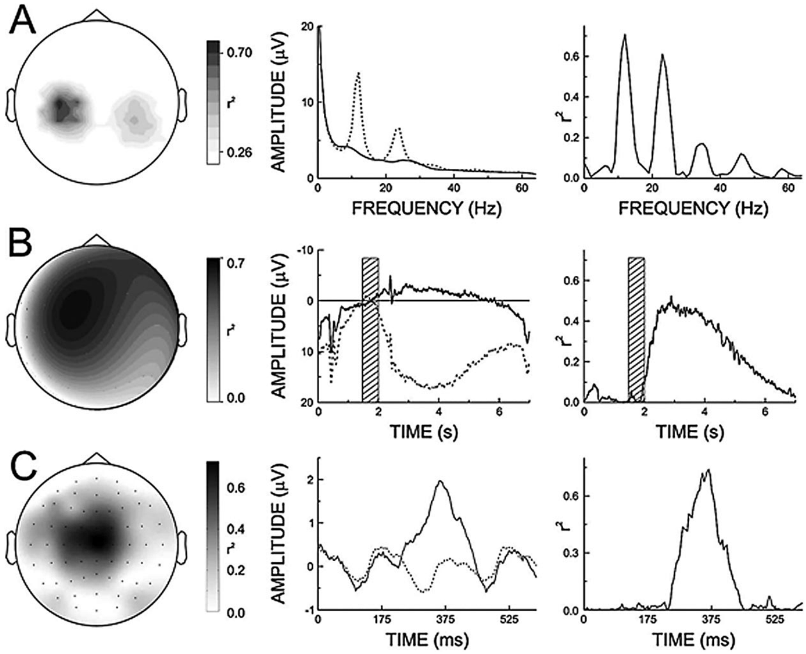

FIGURE 3. *Schematic showing three EEG brain signals used for BCIs in humans.* A, *sensorimotor rhythm control of cursor movement.* Left, *topographical distribution on the scalp (nose on top) of control (measured as r^2, proportion of single-trial variance that is caused by the target position) calculated between the top and bottom target positions for the 3 Hz band centered at 12 Hz.* Middle, *voltage spectra for the location over the left sensorimotor cortex (i.e., C3) for cursor movement up (*dashed line*) and down (*solid line*).* Right, *corresponding r^2 spectrum for the top versus bottom targets. The user's control is sharply focused over sensorimotor cortex and in μ and β rhythm frequency bands.* B, *SCP control of cursor movement.* Left, *topographical distribution of SCP control, calculated between two tasks of producing cortical negativity (*top target*) or positivity (*bottom target*).* Center, *time courses of EEG at vertex for negativity task (*solid line*) and for positivity task (*dashed line*).* Right, *corresponding r^2 time course calculated between the two conditions.* C, *P300 control of spelling program.* Left, *topographical distribution of P300 potential at 340 ms after stimuli, measured as r^2 for the stimuli including versus, but not including the desired character.* Center, *time courses at vertex of voltages for stimuli including (*solid line*) or not including (*dashed line*) the desired character.* Right, *corresponding r^2 time course (70).*

P300 Evoked Potentials

Infrequent or particularly significant auditory, visual, or somatosensory stimuli, when interspersed with routine stimuli, typically evoke a positive potential in the EEG that peaks at approximately 300 ms and is centered over parietal cortex (21, 80). This P300, or "oddball," potential distinguishes the brain's response to infrequent or significant stimuli from its response to routine stimuli. Donchin et al. (22) and Farwell and Donchin (25) have used P300 potentials as the basis for a BCI. The BCI system flashes letters or other symbols in rapid succession. The stimulus that the user wants produces a P300 potential. By detecting this P300, the BCI system learns the user's choice. With this method, people (including those with ALS) can use a simple word-processing program. Because the amplitude of the P300 evoked by a specific stimulus in the BCI protocol depends mainly on whether the user wants to select it, this P300-based communication does not seem to require any neuromuscular control. At the same time, however, it is not yet entirely clear whether P300 amplitude in this setting depends to some extent on the user's ability to fixate gaze on the desired selection. *Figure 3C* shows representative results from a P300-based BCI. The BCI system flashes letters or other symbols in rapid succession. The stimulus that the user wants produces a P300 potential. By detecting this P300, the BCI system learns the user's choice. With this method, people (including those with ALS) can use a simple word-processing program (73).

In summary, the EEG-based paradigms are noninvasive and have been the basis for most BCI studies in humans to date. Numerous studies have shown that, using EEG, healthy and motor impaired individuals can control devices without using muscles. Currently, the National Institute of Neurological Disorders and Stroke is sponsoring a study titled "Moving a Paralyzed Hand Through Use of a Brain-Computer Interface." The study is seeking to enroll 30 patients who are either healthy or have a chronic stoke history with a residual, severe, unilateral paresis. The goal of the study will be to use an EEG-based BCI system to control a hand orthosis (54). There are, however, no companies that are currently attempting to market a BCI platform using EEG. There are some practical considerations that need to be met regarding clinical application of EEG-based BCIs. Because of the external nature of signal acquisition, brain signals acquired with this method are susceptible to external forces (i.e., electrode movement) and signal contamination (i.e., interference generated by muscle movements or the electrical environment). A representative example of an EEG BCI setup is shown in *Figure 4*. In addition, because signals are quite removed from the sources within the brain, EEG signals have less fidelity and spatial specificity and a limited frequency detection (<40 Hz), which seems to result in prolonged user training for higher levels of control. Furthermore, it is possible that these spatial and frequency limitations also prohibit the complexity of movements that can be supported by EEG. From a practical standpoint, external monitoring from EEG electrodes placed in a cap or fixed to the skin are unlikely to provide long-term solutions for individuals who need to be continuously monitored or are significantly impaired such that they can not manipulate their electrodes should they migrate. Given the limitations of this signal platform, its clinical impact seems to be restricted to short-term applications with those patients who are totally paralyzed and who require very basic levels of control.

Single Unit-based System

The ability of animals to modulate the activity of a single neuron in their brain for control has been known since the

FIGURE 4. *Example of an EEG-based BCI platform. Notable elements include the electrode cap worn (*asterisk*) by the subject and the viewer screen (*double asterisks*) for which the subject controls the cursor on the screen (BCI computer not shown) by various EEG signals and signal processing methods (i.e., sensorimotor rhythms, SCP, or P300 paradigm) (89).*

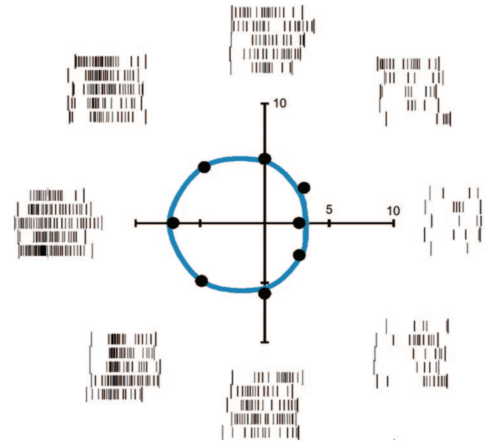

FIGURE 5. *Cosine tuning in a primary motor (M1) cortical neuron. The outer raster data shows spiking activity of a single M1 neuron during 2-dimensional center-out reaching task to eight peripherally located targets by a rhesus monkey. The monkey made five reaches to each target. Spike times were aligned by movement onset, and an average firing rate histogram was made for each target. The resulting eight average firing rates were square-root transformed and plotted on radial graph (inset,* black dots*, units are square root of spikes per second). The processed firing rates are well fit by standard cosine function (*blue line*) (53).*

1960s and was first performed in nonhuman primates in the early 1970s (26). These early studies were limited to one-dimensional control; however, in the 1980s, Georgopoulos et al. (30) developed a method of decoding three-dimensional hand movement direction from a population of neurons in primary motor cortex of nonhuman primates. By serially recording the single-unit activity from 50 to 200 individual neurons during a repeated reaching task, an accurate prediction of average hand movement direction was made post hoc. During the 1990s, neurophysiologists refined and enhanced these neural decoding methods to include prediction of both three-dimensional direction and speed (i.e., hand velocity) (53, 72), but could not implement them in real time until the technology for recording multiple single units simultaneously had been developed. In the late 1990s, several groups were having success in recording chronic, single-unit action potentials from a number of neurons simultaneously, which culminated in a number of studies in the early 2000s showing elegant multidimensional real time BCI control (75, 82, 88).

The proximal arm area of primary motor cortex is the dominant structure targeted for BCI control via single-unit activity. The firing rate activity of approximately 50% of the neurons in this area of the brain encode hand velocity via a cosine tuned receptive field. *Figure 5* illustrates the cosine tuning property of motor cortical neurons, as modified by Moran and Schwartz (53). In this example, a monkey was trained to make reaching movements from a center location to eight equally spaced peripheral targets (30, 53). The outer portion of the figure shows the spike rasters for five repeated reaches to each target. For reaches to the left, the neuron fired maximally, whereas reaches in the opposite direction resulted in a minimal firing rate. For intermediated directions, the neuron modulated its activity based on the relative angle between the preferred direction of the neuron (i.e., movement direction where neuron fired maximally) and the hand movement direction. By calculating the firing rate of the neuron during the reaction and movement time of each reach direction and plotting it on a radial graph (*Fig. 5*, center), it can be shown that the data are well fit by a cosine function. The advantage of the cosine tuning model is that a fairly simple linear decoding method can be used to predict hand movement velocity from a population of cosine tuned neurons (30). Because the cosine function is the basis for vector math (i.e., dot products), a prediction of where the subject is going to move its hand can be made by scaling the preferred directions of a number of simultaneously recorded motor cortical neurons by their instantaneous activity and summing the scaled vectors together. This process has been classically called the population vector algorithm first proposed by Georgopoulos et al. (30) and is the basis for all linear decoding methods used in single-unit BCI research.

There have been some limited trials in which single neuronal firing has been used in quadriplegic subjects to achieve control. The results thus far are too limited to make any definitive conclusions. Two modalities have been attempted. The earliest by Kennedy and Bakay (35), in 1998, attempted to monitor the firing of several neurons in a terminal ALS patient through the use of an electrode construct in which neurites were induced to grow within a surgically implanted glass cone electrode that contained neurotrophic factors (*Fig. 6*). This same glass cone electrode construct was then implanted in Brocas speech cortex for the purpose of enhancing speech by identifying the various electrical signal changes associated with various phonemes (34). The current company involved in the development of this construct is Neural Signals, Inc., Atlanta, GA. To date, the group has implanted this device into

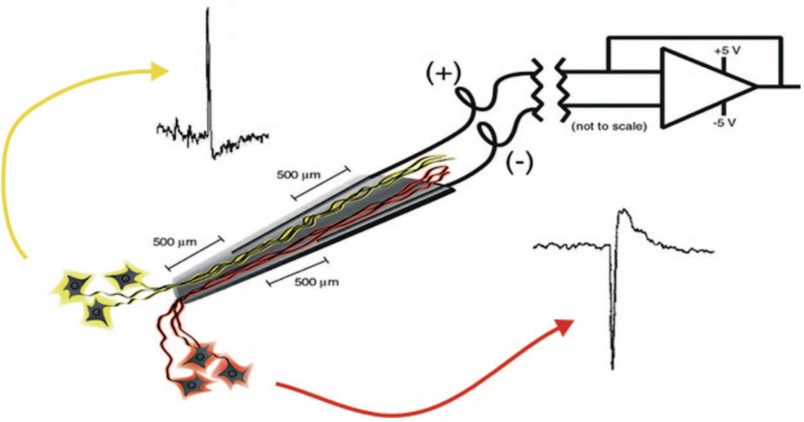

FIGURE 6. *Schematic showing glass cone electrode schematic. Once an electrode is placed between the gyrii in Area 4 (primary motor cortex, M1), the tissue surrounding the electrode sprouts neurites, which are directed into and through the cone of the electrode by neurotrophic factor. Inside the insulated glass cone are two wires insulated with just the tip of conducting wire exposed. Signals closer to one wire produce a waveform in relation to the pole of the electrode (yellow neurites produce electric signal different from red neurites). Internal electronics contain an amplifier tied to an induction coil for power. These are cemented onto the cranium under the scalp. The external electronics consist of a modified analog receiver used to catch the transmitted signal and pass it to a bioamplifier, Hi-8 tape deck, and oscilloscope. The induction unit forces the current through the outside coil placed over the internal induction coil to power the implant. For signal processing, the bioamplifier relays signals to a Datawave patch panel, where signals are digitized and analyzed for various waveform characteristics. These spikes are sorted into clusters of similar spikes. An analysis computer is tied to a patient computer running Windows and reads events sent from the analysis computer. These events are based on what type of spike is detected by analysis software. Depending on which event is read by the patient machine, the cursor moves in a variable direction and amount.* Courtesy of Dr. Phillip Kennedy of Neural Signals, Inc.

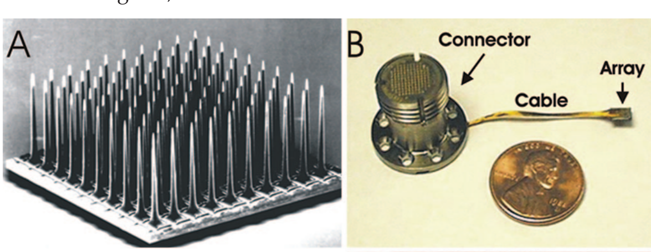

FIGURE 7. *Single unit BCI system.* A, *a "Utah array" consists of 10 × 10 array of microelectrodes.* B, *the array is then attached by cable that transmits the signals to the connector. The size is shown relative to a penny.* C, *the connector is then externalized through the skin and connected via an external cable to the signal processor with an associated patient and technician monitor (not shown).* Courtesy of Cyberkinetics.

eight subjects. They are not currently enrolling any further subjects pending the results from the current enrollees. The second approach has been through the population vector algorithm described above and the use of electrode arrays that monitor 10s to 100 cortical motor neurons simultaneously. This type of construct was first implanted in a spinal injured quadriplegic in 2004 (74). The company involved with the development of this signal platform is Cyberkinetics (Foxborough, MA). Refer to *Figure 7* for an example of electrode array and hardware set up. They have currently implanted four patients and are open for further recruitment of subjects.

From a control systems point of view, the best signal for BCI control has been achieved with multiple, single-unit action potentials recorded in parallel directly from cerebral cortex. No other experimental BCI modality to date has provided as good a control in terms of accuracy, speed, and DOF than single-unit data. Unfortunately, with current microelectrode technology, obtaining long-term stability of single-unit recordings has proven difficult at best. Current single-unit recordings techniques require insertion of a recording electrode into the brain parenchyma. In consideration of the highly vascular nature of the brain, it is impossible to implant such a device without severing blood vessels and, therefore, inducing a reactive response around the implant site (81). Astrocytes and other glial tissue begin to encapsulate the implanted microelectrode via a standard foreign body response. Over time, the microelectrode is essentially electrically insulated from the surrounding tissue and can no longer discriminate action potentials (84). Unlike stimulating neuroprosthetics electrodes (e.g., deep brain stimulator for Parkinson's), increasing stimulation current to counter encapsulation is not an option. Once encapsulated, single-unit isolation cannot be reversed on the implanted electrodes. From a clinical point of view, it should give a neurosurgeon significant pause to implant microelectrodes into the brain of patients knowing that they will only provide a year of BCI control. In considering that these constructs are prone to scarring and would be implanted in eloquent regions of cortex, repetitive procedures could have significant detrimental effects to the brain and the patient's long-term functional and cognitive status. Invasive BCI electrodes, therefore, need a prolonged life span to warrant the risks of an intracranial procedure.

To date, current single-unit microelectrodes have long-term biocompatibility issues leading to limited life spans. However, there are several groups developing new biomaterials as well as slow-release drug delivery systems that could significantly decrease encapsulation of implanted microelectrodes and make single-unit recordings practical in the future. For instance, cross linking an anti-inflammatory agent such as dexamethasone to a hydrogel coating on the microelectrode might theoretically reduce the initial injury response of implantation (76). Likewise, incorporating microfluidic channels on microelectrodes could allow for chronic drug delivery to the implant site to not only control reactive responses in the surrounding tissue but enhance neural growth around the electrode to increase information content. Unfortunately, these studies are just beginning, and there will be years of testing before this technology is suitable for the clinic. Although single-unit recordings are ideal from a neural control point of view, the technology needed to obtain long-term recordings is still controversial, and until new technologies improve microelectrode durability, single-unit BCI will remain largely in the research domain for now.

ECoG-based Systems

ECoG as a signal platform has emerged over the last several years as a possible candidate for a clinically viable BCI system. ECoG is a measure of the electrical activity of the brain taken from beneath the cranium. This signal can be either subdural or epidural, but is not a signal taken from within the brain parenchyma itself. It has not been studied extensively until recently because of the limited access of subjects. Currently, the only manner to acquire the signal for study is through the use of patients requiring invasive monitoring for localization and resection of an epileptogenic focus. See *Figure 8* for a representative example of an experimental setup.

The experimental approach was developed on the basis of current understanding of sensorimotor rhythms and on the methodology of current EEG-based BCIs that use these rhythms (95). Sensorimotor rhythms comprise mu (8–12 Hz), beta (18–26 Hz), and gamma (>30 Hz) oscillations (36, 65, 94). As mentioned earlier, the lower frequencies of μ and β are thought to be produced by thalamocortical circuits, and they change in amplitude in association with actual or imagined movements (31, 44, 62, 68). Higher frequencies (>30 Hz), or γ rhythms, are thought to be produced by smaller cortical assemblies (47). BCIs based on EEG oscillations have focused exclusively on μ and β rhythms because γ rhythms are inconspicuous at the scalp (60). In contrast, γ rhythms as well as μ and β rhythms are prominent in ECoG during movements (31, 47, 60, 68).

Until recently, the signal was assumed to be very similar to that of EEG in regard to the amount and type of information it could convey. This, however, was not true; the signal itself is quite different. The ECoG signal is much more robust compared with EEG signal: its magnitude is typically five times larger (0.05–1.0 versus 0.01–0.2 mV for EEG) (7), its spatial resolution as it relates to electrode spacing is much finer (0.125 versus 3.0 cm for EEG) (28, 78), and its frequency bandwidth is significantly higher (0–200 Hz versus 0– 40 Hz for EEG). When analyzed on a functional level, many studies have revealed that higher frequency bandwidths, unavailable to EEG methods, carry highly specific and anatomically focal information about cortical processing (13–15, 77). *Figure 9* shows a representative example of the focal nature of γ frequency changes. ECoG's superior frequency range is attributable to two factors. First, the capacitance of cell membranes of the overlying tissue combined with their intrinsic electrical resistance constitutes a low-pass (resistance capacitance) filter that largely eliminates higher frequencies from the EEG (78). Second, higher frequencies tend to be produced by smaller cortical assemblies (37). Thus, they are more prominent at elec-

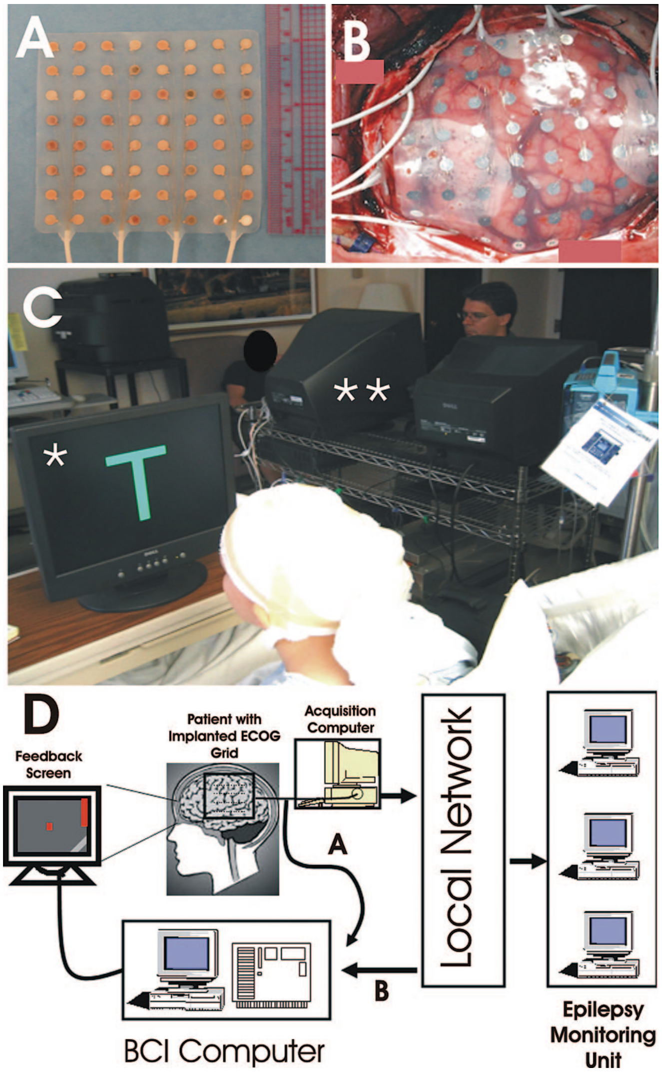

FIGURE 8. *Example of an ECoG based BCI platform.* A, *a standard 64 electrode grid 8 × 8 cm in size.* B, *an intraoperative picture of the grid placed over sensorimotor cortex.* C, *photograph of the subject involved in BCI operation. Notable elements are the feedback screen in front of the subject* (asterisk*) and the BCI computer* (double asterisk*).* D, *schematic diagram of the ECoG BCI system. Once the patient has a subdural grid surgically implanted for the purposes of seizure monitoring, the ECoG signal is routed to a standard acquisition computer. This signal is then sent to a local network for which signal tracings may be viewed for clinical purposes. For the purpose of BCI operation, the signal is split either directly from the patient* (A) *or taken in real time off the network* (B) *(43). The signal is then sent to the BCI computer where the raw signal is analyzed in real time to detect whether a meaningful alteration has occurred in the electrical rhythm that is statistically significant (feature extraction) and then associates that change with a specific device command (translation). In this example, the device command is controlling the movement of a cursor on the feedback screen.*

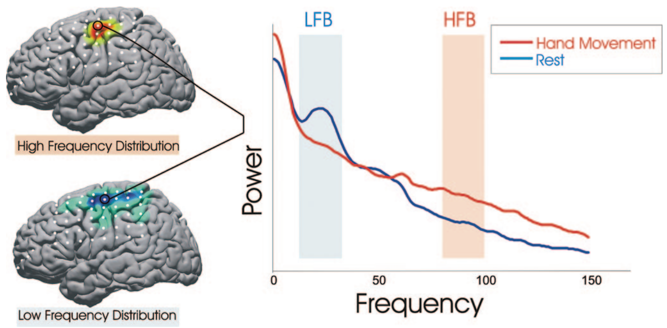

FIGURE 9. *The difference between the anatomic distribution of lower frequencies (α and β rhythms) compared with higher frequencies (γ rhythms).* Left, *two brains mapped in standardized Talairach space.* Top, *brain represents a high-frequency distribution (high-frequency band (HFB), 75–100 Hz) of power changes associated with hand movement when compared against rest.* Bottom, *brain represents a low-frequency distribution (low frequency band (LFB), 8–30 Hz) of power changes associated with hand movement in the same patient. The subdural electrodes (*white dots*).* Right, *a frequency power spectra plot depicting power change versus frequency for two conditions of hand movement versus rest taken from the same electrode. In LFB, 8 to 30 Hz, there is a drop in power for hand movement when compared against rest, which is broadly distributed. In HFB, 75 to 100, there is an increase in power with hand movement when compared with rest, which is much more focal in nature. LFB is detectable by both EEG and ECOG, whereas HFB, which is much more focal, can only be detected with ECOG. This has important implications when looking for independent signals to use for device control. γ rhythms are more easily separable than those of lower frequencies.*

trodes that are closer to cortex than EEG electrodes and thereby achieve higher spatial resolution (78).

Recent studies have cogently demonstrated its effectiveness as a signal in BCI application. Leuthardt et al. (43), in 2004, revealed the first use of ECoG in closed loop control. Over brief training periods of 3 to 24 minutes, four patients mastered control and achieved success rates of 74 to 100% in one-dimensional tasks. In additional experiments, the same group found that ECoG signals at frequencies up to 180 Hz accurately reflected the direction of two-dimensional joystick movements (43). Soon after, Schalk et al. (69), in 2004, demonstrated two-dimensional online control using independent signals at high frequencies inconspicuous to that appreciable by EEG. In addition, Leuthardt et al. (42), in 2005, demonstrated that ECoG control using signal from the epidural space was also possible. All these studies combined show the ECoG signal to carry a high level of specific cortical information that can allow the user to gain control very rapidly.

Beyond the technical demonstration of ECoG BCI feasibility, there is some pathological and clinical evidence to support the implant viability of subdural-based devices. There is an extensive body of literature investigating the tissue response to intraparenchymal cortical electrodes and their associated signal prohibitive reactive gliotic sheaths (81, 84). Although more limited, the studies that have been performed investigating nonpenetrating subdural placed electrodes, however, have been more encouraging. In cat and dog models, long-term subdural implants showed minimal cortical or leptomeningeal tissue reaction while maintaining prolonged electrophysiological recording (10, 46, 49, 96). In clinical studies, the use of subdural electrodes as implants for motor cortex stimulation have been shown to be stable and effective implants for the treatment of chronic pain (8, 9, 55). In addition, preliminary work using the implantable Neuropace device for the purpose of long-term subdural electrode monitoring for seizure identification and abortion has also been shown to be stable (86).

ECoG is a very promising intermediate BCI modality because it has higher spatial resolution, better signal-to-noise ratio, wider frequency range, and lesser training requirements than scalp-recorded EEG and at the same time, has lower technical difficulty, lower clinical risk, and probably superior long-term stability than intracortical single-neuron recording. Although a clinical trial has not been begun to date, this feature profile and recent evidence of the high level of control with minimal training requirements in human subjects shows potential for real world application for people with motor disabilities.

CONCLUSION

It is an exciting time within the field of motor neuroprosthetics. Currently, research is only beginning to crack the electrical information encoding the information in a human subject's thoughts. Even with this basic level of understanding, significant strides have been made to show that understanding this "neural code" can have significant impact in augmenting function for those with various forms of motor disabilities. Each of the reviewed signal platforms has the potential to substantively improve the manner in which patients with spinal cord injury, stroke, cerebral palsy, and neuromuscular disorders interact with their environment. Each platform also has unique hurdles that they will need to overcome. For EEG and ECoG, increasing the complexity of control is critical, whereas for single-unit platforms, demonstrating implant durability is of pivotal concern. In consideration of the rapid progression of these technologies over the past 5 years and the concomitant swift ascent of computer processing speeds, signal analysis techniques, and emerging ideas for novel biomaterials, these issues should not be viewed as obstacles but rather as milestones that will be achieved. The order in which these milestones will be accomplished remains to be seen. As research in this field begins to transition from basic scientific and engineering research to one of clinical application, it will herald in a new era of restorative neurosurgery. The field of neurosurgery will have the potential to move from a purely ablative approach to one that also encompasses restorative techniques. In the future, a neurosurgeon's capabilities will go beyond the ability to remove offending agents such as aneurysms, tumors, and hematomas to prevent the decrement of function. Rather, he or she will also have the skills and technologies in the clinical armamentarium to engage the nervous system to restore abilities already lost.

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COMMENTS

For much of its history, neurosurgery has been "limited" by the idea that the adult nervous system does not have the ability to repair itself. This has placed obvious constraints on the scope of therapeutic possibilities for our field. Over the course of the past few years, there has been tremendous interest in a "biological" solution to surmount these limitations, with considerable effort and financial resources devoted to "restorative neurosurgery." These efforts have taken the form of stem cell research and attempts to "engineer" cells at the molecular level. In this review, the authors remind us that perhaps a less "biological" approach may ultimately play a role in restoring function to the damaged nervous system. The field of neuroprosthetics is rapidly expanding, and its capabilities, which are intimately dependent upon computational power, will surely broaden with the increasing influence of new technological paradigms such as nanotechnology. This review is timely and of obvious relevance to neurosurgeons.

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Leuthardt et al. provide a general overview of the idea of neuroprosthetics. This new field involves the use of a brain computer interface (BCI) with which electrical impulses from the brain parenchyma are transformed into usable data to overcome, for example, an acquired or congenital neurological deficit. The idea of a paraplegic patient simply using their thoughts to control a mechanical wheelchair, or better yet, to walk with robotic leg braces, is very appealing. The possibilities for such a technology are seemingly limitless. However, in its current state, there are some issues that must be dealt with. The authors point out many of the hurdles that must be overcome. For example, implanted depth electrodes develop surrounding gliosis, which essentially renders them useless after a period of time. While research into new biomaterials may provide answers to inflammatory reactions of the brain, one must also consider plasticity reactions of the brain. BCI systems must be made to adapt as existing neural connections are used in novel ways. The authors also mention the idea of feedback. This can be accomplished by combining both input and output BCIs. This could be used, for example, to input proprioceptive information to the sensory cortex, while outputting commands to a robotic appendage from the motor cortex. Regardless of the current technological issues, this article gives neurosurgeons an introduction to a field in which we will undoubtedly see a rapid expansion of in the not too distant future.

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The idea of the expansion of brain functions and their interaction with the world outside the body is always considered in the human being history. Plato, in *The Republic*, used, for the first time, the word cybernetic to signify the interface between each man and the governance of people. In 1834, André-Marie Ampère included "cybernètique" in his classification of human knowledge.

The study of the communication and control of regulatory feedback between human and machines was born around the Second World War and the intersection between neurology and electronic network theory became a powerful vogue idea between 1948 and the 1970s. The organic life form interfaced with technological devices strongly stimulates many cultural fields, generates a great debate in the philosophy of mind, telecommunication engineering, and many cult movies produced in the past 20 years (*Terminal Man*, *Blade Runner*, *Minority Report*, *Matrix*) always considered the interface brain-machine under control of the machine.

The development of neuroprosthetics includes deep brain stimulation to improve movement disorders or psychiatric disease, but neuroprosthetics based on the BCI go beyond the imagination of most writers. Interface with visual cortex could build up visual prosthesis, but the interaction with the retina, hippocampus, and cochlea are just a few examples of possible implants.

There is the awareness that clinical application of BCI has only started, and I am quite sure that improvement of computer technology and knowledge of brain activity will make feasible the clinical application of BCI on severely impaired patients. So far the electroencephalography-based systems represent a promising way to develop an interface to provide a better quality of life. Actually, we don't know which patient affected by acute lateral sclerosis or spinal cord injury will benefit from BCI, and, to select the ideal patient, a first attempt using scalp electroencephalography could be a promising suggestion. Another issue consists of the brain structure to be used for BCI; if the scalp electroencephalogram is one term of the system, it should be stressed that the μ activity is not constant and rarely recorded (the 8-12 Hz activity is the α rhythm typical of the occipital region). Even when a motor response of a robotic arm is requested, the BCI does not necessarily have to be linked to a pericentral activity. For instance, a λ activity should be used. The use of the single unit-based system is very attractive, but, unfortunately, is still theoretical and poses heavy limitations. The problems of a long-term function of such a method is real and the single unit approach should be considered after the resolution of the electrode encapsulation phenomenon. From this point of view, the placement on the cortex of strip or grids seems to be the ideal solution. The activity recorded is clear, has fewer artifacts, and its possible application should included on a demanding system to control seizures. Also, the subcutaneous placement of the cable connected to the grid and a subclavicular telemetry device allows safe and easy daily use of the BCI.

Electrocochleography seems to be very attractive, but the cortico-cortical evoked potential is a challenging alternative. Researchers have to realize that the high definition of the language, visual, and motor areas by this technique allows broad neuronal network detection.

The greatest advantage of the clinical application of BCI justifies accepting the risk faced from more invasive procedures. It must be remembered that, in epilepsy surgery, the preoperative evaluation by the placement of grids on the brain surface has proven to be a very low-risk methodology.

In my opinion, it must be remembered that BCI is not the only solution: the research on restorative neurosurgery focused on stem cells, gene therapy, and neurotrophic factors supporting brain structures, are reporting promising results.

In conclusion, the present report is particularly interesting because of the clinical perspective of the possibility of translating a neural input by an effect independent of any peripheral systems and the insight into what may be the future of behavioral science for the neurosurgical audience. The authors have provided us with a new perspective in the field of neurosurgery, particularly in restorative neurosurgery.

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Leuthardt et al. present us with a review of the current state-of-the-art in man-machine interfaces. Focusing on output BCIs intended to restore motor control, they paint an optimistic picture of how these devices may restore function to our patients incapacitated by permanent neurological injuries. Although this technology is still in its infancy, it is certainly likely that useful neuroprosthesis will become available long before neurorestorative strategies, such as stem cell therapies, and neurosurgeons will likely be playing a significant role in the development and implementation of such technology.

Nevertheless, many hurdles remain in this area. The authors are correct in stating that the fidelity and quality of electrical signals would be highest with implantable BCIs, such as cortical or single-unit systems. For these implantable devices, local tissue reactions and scarring can significantly dampen the extraction of electrophysiologic data, and, as the authors point out, the ability to revise such operations needs to be considered. Next-generation devices will have to be composed of truly inert biomaterials or use biological strategies to prevent these phenomena. Other problems relate to the need for BCIs to reliably translate complex electrophysiological data sets into a variety of meaningful signals to reproduce normal human motor function. Ultimately, technological advancements will likely overcome these and other hurdles. The authors have provided a commendable introduction to this exciting and important emerging field.

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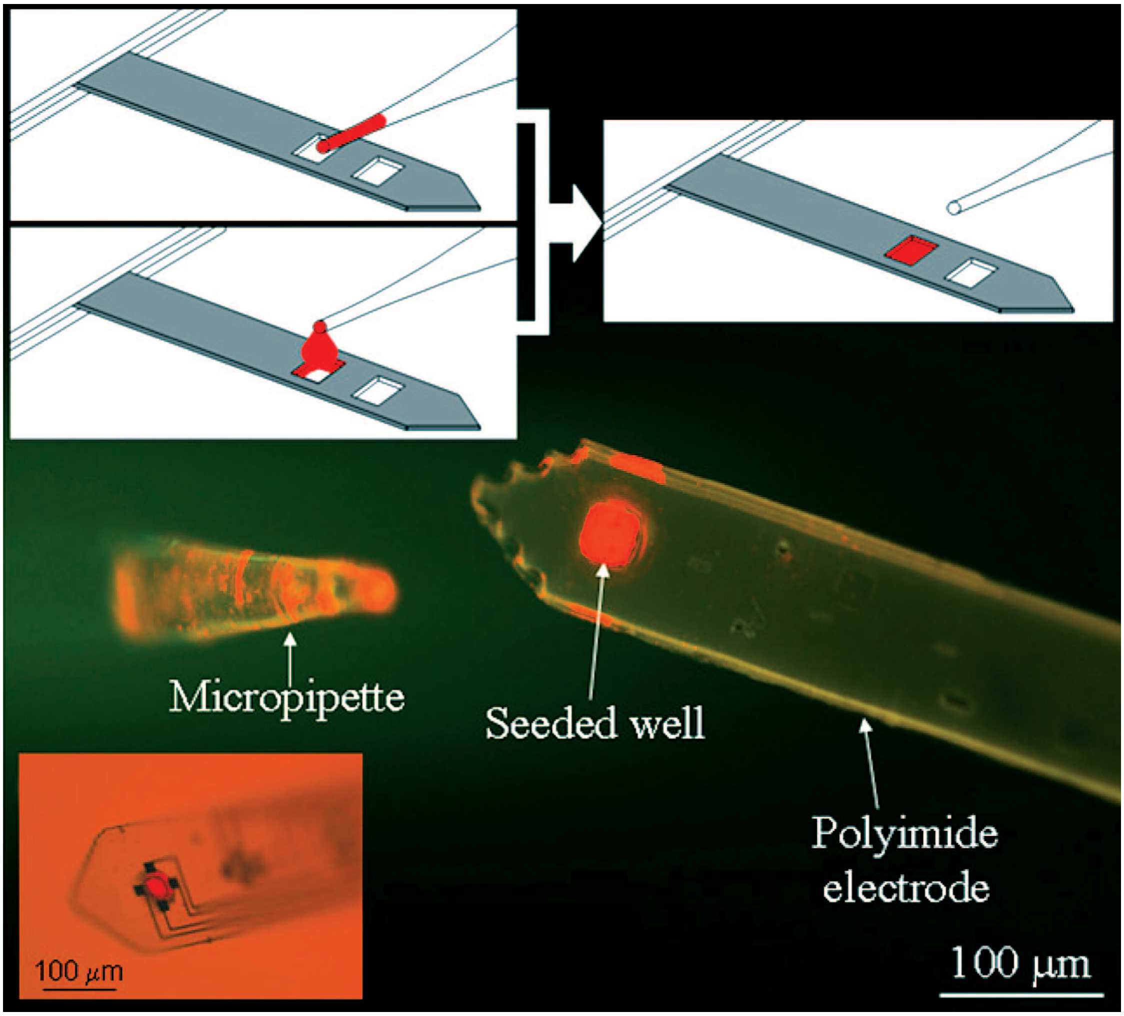

Microdrug delivery techniques for minimizing inflammatory responses to the implantation of neural prosthetic devices. *Figure illustrates wells micromachined into the shank (device substrate) of a micro-electro-mechanical system (MEMS)-based neural probe. These wells (rectangular or elliptical, 20–60 μm wide, 7–20 μm deep) allow for the integration of hydrogels infused with bioactive molecules with the intended neural target. (Williams JC, Holecko MM, Massia SP, Rousche P, Kipke D: Multi-site incorporation of bioactive matrices into MEMS-based neural probes.* **J Neural Eng** *2:L23–L28, 2005.)*