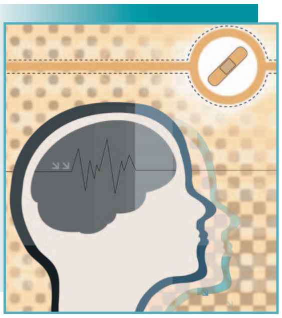

Sensors for Brain-Computer Interfaces

Options for Turning Thought into Action

**BY LEIGH R. HOCHBERG
AND JOHN P. DONOGHUE**

Brain-computer interfaces (BCIs) hold the promise to restore mobility and independence to persons with paralysis. In spinal cord injury, brainstem stroke, and a host of neuromuscular disorders, the intact brain is "disconnected" from its intact target (such as a limb or the facial musculature), preventing mobility and—in locked-in syndrome [1] and severe amyotrophic lateral sclerosis (ALS)—precluding even meaningful verbal communication. If it becomes possible to discern the movement intention of someone with paralysis—reliably, safely, and in real time—it would then be possible to provide not only a robust new method of communication but eventually the ability to gain control over a prosthetic limb or, by connecting to additional technologies, one's own limbs. In this review, we survey several methods for revealing neural activity in the human brain and their potential for re-enabling mobility in persons with severe paralysis.

Sensors, Decoders, and Actuators

Figure 1 summarizes the approach used to construct a BCI. It is worth noting that the nomenclature in this young field has not yet been settled upon: brain-machine interfaces, neural prosthetics, brain-communicator interfaces, human neuromotor prostheses, and other monikers are used somewhat interchangeably. A BCI is actually a system comprising a sensor, a neural decoder or translator, and some form of actuator to carry out an action.

The *sensor* is dedicated to discerning, either indirectly or directly, changes in neural activity related to the intent to influence (or move) an external device, the *actuator* (which, in the noninjured person, is the limb itself). Possible sensors include functional magnetic resonance imaging (fMRI) systems, near-infrared (NIR) systems, magnetocencephalography (MEG), electroencephalography (EEG), electrocorticography (ECoG), and microelectrode-based intracortical neurophysiology. Proposed actuators include a cursor on a computer screen (to operate the computer and its software), a motorized wheelchair, a semiautonomous robot, a prosthetic limb, or a functional electrical stimulation (FES) device that could reanimate a paralyzed limb. Between the sensor and actuator lies the *decoder*, which receives neural data recorded by the sensor, discerns the user's intention, and converts that intention into a command signal for the actuator. (The important science of signal processing/decoding is reviewed elsewhere in this issue). In designing a complete BCI system, the choice of sensor, decoder, and actuator are interdependent. For example, if the goal is to discern the intention to turn a switch on or off, the type of sensor and its location in or around the brain may be different than if the goal is real-time control of a multiarticulated limb while looking elsewhere and speaking (something humans without paralysis do without hesitation). We focus here on sensors being considered for human BCI use, with an emphasis on the use of intracortical recording technologies, which appear to meet most effectively the combined need for high fidelity, small size, and the potential to restore independence to persons with severe paralysis.

Macro Scale Sensors: Functional Magnetic Resonance Imaging; Near-Infra Red Imaging

Blood-oxygen-level-dependent (BOLD) functional MRI (fMRI) has provided new insights into human cerebral function. This technique, which measures the delayed local hemodynamic response to neural activity (believed to be the result primarily of changes in local field potentials [2]), has been used to explore cortical and subcortical structures involved in voluntary movement and motor learning [3]–[6]. Real-time BCIs can be constructed by providing fMRI-based feedback related to the intensity of activation of different cortical areas [7]. In one fMRI-based BCI study [8], healthy subjects were trained to imagine four different mental tasks, the performance of which could be independently classified by observing BOLD activity throughout the brain. Participants were then able to perform these four mental tasks in order to control the movement of a cursor in four directions. However, generation of each cursor movement took more than 2 min. Although this slow response time, coupled with the current large size, temporal resolution, and indirect functional correlation of MRI, precludes its use as a practical BCI for persons with paralysis, fMRI studies may help to guide the location of sensors used in other BCI applications.

NIR imaging uses light-emitting diodes (optodes) attached to the scalp to record changes in cortical hemodynamics and oxygenation linked to neural activity [9], [10]. Harnessing the slow vascular response that can be recorded by NIR

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systems, a single optode was recently used to distinguish between two states of motor intention with a temporal resolution of approximately 20 s [11]. Faster vascular responses (in the range of 100 ms) have also been explored; it is possible that an extracranial, subdural, or intracortical application of this technology could be useful in the development of a BCI. More invasive optical recordings, which provide fast and potentially information-rich neural activity, may be feasible, though not yet as a portable device.

High Temporal Resolution, Low Spatial Resolution: Electroencephalography

Considerable progress has been made in the development of electroencephalography (EEG)-based systems for improved communication or prosthetic control [12], [13]. (For the reader's convenience, a table listing some of the laboratories pursuing human or nonhuman primate BCI research is available at http://donoghue.neuro.brown.edu/bcilabs/bcilabs.htm; see also Vaughan et al., 2003 [12] for a recent review.) A ubiquitous diagnostic tool in clinical neurophysiology, EEG uses multiple (2–128) scalp electrodes (sensors) to record a wide range of signals generated by synchronous changes in postsynaptic potentials emanating from thousands of (or more) neurons—mostly cortical pyramidal cells oriented perpendicular to the skull's surface [14]. These synchronies are divided into different frequency ranges within the 0.3–20+ Hz range (divided into delta, theta, alpha, and beta bands), with higher frequencies (gamma frequencies) somewhat less discernable due to the strong low-pass filtering effects of the volume conductors between the brain and scalp (including meninges, CSF, and skull; see electrocorticography below). Most EEG-BCIs rely upon the user's ability to learn to modulate the amplitude of a specific EEG frequency band (EEG$_{\text{MOD}}$) at one or more electrode locations, while others take advantage of evoked potentials, the nonvoluntary synchronous subcortical/cortical responses to an external stimulus (EEG$_{\text{EP}}$).

As a potential communication system for persons with severe paralysis, the P300-based BCI is unique in its use of an EEG$_{\text{EP}}$ that appears approximately 300 ms after the presentation of an "oddball" stimulus. For example, if a single audible tone is repeatedly presented to a subject and then interrupted by a different tone, the appearance of that novel stimulus will generate a P300 response. Similarly, when presented with a computer monitor displaying an alphabet grid whose rows and columns flash at random, the P300 is generated only when the letter being attended (the oddball/correct stimulus) is illuminated. Despite the limitations imposed by the typically very small signal-to-noise ratios (SNR)—mainly slow speed resulting from the need for repeated illumination of both incorrect and correct letters until the stimulus-triggered P300 signal reaches statistical significance—this system has the distinct advantage over EEG$_{\text{MOD}}$ of not requiring "learning" and can provide a communication system which requires only that the user be able to attend to a specific stimulus by visual fixation [15]–[17].

Most other EEG-BCI systems [18]–[22] allow subjects to control a computer cursor or other devices by modulating ongoing slow cortical potentials, mu- (alpha rhythms centered over the sensorimotor cortex) or beta-rhythm amplitude. Over the past 15 years, these systems have provided a communication platform for persons with advanced ALS and cerebral palsy as well as two-dimensional (2-D) control of a computer cursor in a radial, center-out task in persons with

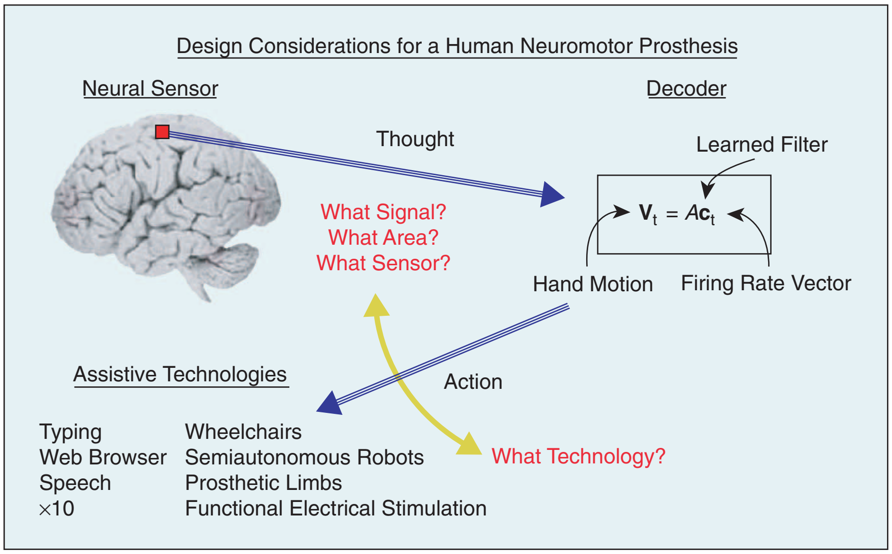

Fig. 1. The design of a brain-computer interface (BCI). BCIs consist of a sensor, a decoder, and an actuator (effector). For persons with paralysis, the effector could be any number of assistive devices (such as a prosthetic limb), the choice of which will influence which sensor and decoding system are most appropriate. Common sensors for BCIs under development include scalp-based EEG electrodes, subdural electrodes, and intracortical electrode arrays. The decoder illustrated here takes motor cortex neuronal activity ("firing rate") and converts it, through a mathematical "filter," to intended hand motion.

Individual patients may select future BCI systems for practical, cosmetic, or other reasons independent of bit rate or even objective efficacy.

paraplegia [23]. In addition, the BCI2000 program [24] (http://www.bci2000.org) has produced a common toolbox of actuators (including cursor control, spelling tasks, and 2-D robotic arm control) with which different sensor/decoder systems can be tested and compared.

EEG-BCIs do not require surgery, and thus provide one benchmark to which more invasive BCIs can be compared. While relatively noninvasive, EEG-BCIs have several limitations, including 1) the need for extensive training before adequate actuator control is obtained [23], [25]; 2) considerable setup time for each session (including the requirement for a technician or caregiver to prepare the scalp sites for good electrode contact, properly place and later remove the electrodes or electrode cap, and clean the skin); 3) the potential for harmful skin breakdown if electrode leads remain on the scalp for extended periods of time; 4) the implied requirement for focused attention on the ongoing task to the exclusion of other activities (such as talking or redirecting gaze); 5) limited information transfer rates [12]; and, 6) limited potential to scale systems to provide control signals for simultaneous upper- and lower-extremity prostheses (i.e., to re-enable all missing limb actions). Furthermore, EEG systems require the use of a surrogate signal for control of an external device rather than the still-available, natural neural command signals for the missing action. In other words, specific mental processes unrelated or loosely related to controlling the actuator are co-opted for the purpose of BCI control; this would seem to preclude engaging those mental processes for their original purpose during BCI use. By analogy, tongue-based control switches are currently available for use by persons with tetraplegia, but these devices cannot be used while simultaneously speaking. In the development of a BCI to re-enable independent limb control, this use of surrogate signals would seem to be a disadvantage. Finally, while these systems have been helpful to persons with progressive motor neuron disease, and further improvements in EEG-BCIs may provide helpful communication tools for persons with locked-in syndrome, there have not yet been reports of successful EEG-BCI-enabled communication by persons who were already locked-in when training on these systems began. It is the need for faster, multidimensional control which has motivated the development of more invasive BCIs. In our opinion, however, the risks associated with intracranial/intracortical BCIs (such as those described below) are best justified if their anticipated benefits sufficiently exceed those of EEG-BCIs.

Intracranial Electrodes

For EEG-BCIs, scalp, skull, meninges, and cerebrospinal fluid each contribute to attenuation of the ultimate signal generator: neurons. By recording transcranially from a metal bone screw placed through the outer and inner table of the skull (the screw head can also protrude through the scalp), it is possible to record EEG-type signals with improved SNR characteristics. This was recently demonstrated by Neural Signals, Inc. in two patients with ALS [26] and holds potential as a minimally invasive BCI. We loosely define “minimally invasive” as having a low potential for infection and where contact or disruption of neural tissue and vasculature is also minimal.

Electrodes placed beneath the dura, on the surface of the brain, provide electrocorticography signals (ECoG), which are similar to EEG in that they both indicate synchronous, volume-averaged, low-pass filtered, neural activity. ECoG has the advantage of wider spectral and spatial characteristics than scalp EEG recordings [27], [28], and ECoG can record all frequencies at a greatly improved SNR. Grids or strips of subdural electrodes are used in patients with medically refractory epilepsy; careful localization with such electrodes is used to guide subsequent surgery to remove or otherwise isolate the seizure focus and to spare adjacent eloquent cortex. Movement-related ECoG signals have been well studied [29], and recent ECoG-BCI experiments [30], performed in patients with epilepsy already undergoing clinically-indicated intracranial recordings, have demonstrated the ability to gain one-dimensional, closed-loop control over a cursor by using motor-imagery-induced neural activity; open-loop classification of two-dimensional tasks from ECoG recordings also has been demonstrated [27]. The ability of ECoG to record signals from smaller assemblies of neurons and to take related advantage of higher-frequency rhythms holds potential for improved BCIs. ECoG, however, is limited by the need for a craniectomy (large portions of the skull are removed for current epilepsy monitoring indications, though smaller craniotomies could be made for a specific ECoG-BCI indication in the future) and the subdural placement of ECoG electrodes. Neither preclinical nor human evidence of ECoG’s ability to record safely or effectively for extended periods of time is yet established; long-term ECoG studies are currently being conducted in Tuebingen. Subdural strips or grids remain in place for rarely more than three weeks, with recordings occasionally complicated by hemorrhage, infection, infarction, cerebral edema, or death [31]. The removal of a subdural grid and subsequent replacement with a new grid (a potential asset for any in-dwelling medical device) is rarely performed secondary to inflammation of the meninges. The use of smaller and fewer ECoG electrodes may reduce many of these complications, as may transcranial systems. Thus, it remains unclear whether ECoG is either more safe or less invasive than intracortical recordings.

Cerebral neuronal activity is the ultimate signal generator for all BCIs.

Intracortical Recording and Preclinical Studies

Cerebral neuronal activity is the ultimate signal generator for all BCIs, and the arm-hand area of the primary motor cortex (M1) may be ideally suited to provide cortical control of a multiarticulate prosthetic device [32]–[34]. Decades of single-cell recordings in monkeys, as well as neuronal pair and ensemble interactions discovered with newer recording technologies [35]–[39], have revealed that many features of voluntary motor control are encoded in the neuronal discharge of primate M1 [40]. Such features include movement dynamics (e.g., force, joint impedance), kinematics (e.g., direction, velocity), and "higher level" variables such as target-dependent activity [41]. Movement commands are localized into distinct face, arm, and leg regions on each side of the brain. The ability to analyze the simultaneous activity of multiple cortical neurons during the preparation and production of movement [42], not only in M1 but in other cortical areas, presents the potential to record chronically from the cortex of persons with paralysis and to use these recordings for the direct, real-time control of a prosthetic device [43]–[45]. At least five laboratories [46]–[50], including our own, have now demonstrated the ability for a monkey to perform useful behavioral tasks simply by using the neural signals recorded from electrodes chronically implanted in its brain. In these tasks, monkeys were trained to play simple "video games" using a standard joystick or manipulandum to control a computer cursor or other output. Electrodes were then placed chronically into motor areas of the brain, allowing cortical recordings to be correlated to motor activities. After building decoders (e.g., linear filters, artificial neural networks) that mapped this neural activity to the motor output, the joystick was then "disconnected," and these (neurologically intact) monkeys quickly learned that they could still control the computer cursor by direct neural output. Such experiments provided preclinical "proof of principle" for subsequent clinical trials in persons with paralysis.

Clinical Trials of Intracortical BCIs

The first type of intracortical BCI (iBCI) implanted into humans was the "cone"—or "neurotrophic"—electrode, which contains two electrode wires in a glass enclosure [51]. Patients with near complete paralysis secondary to ALS, brainstem stroke, and mitochondrial myopathy have received this electrode, which has been implanted into the motor cortex [52], [53]. By modulating action potentials or local field potentials generated by the axons, which have grown into the enclosure, patients demonstrated control over the vertical or horizontal excursion of a computer cursor, which re-enabled the ability to control a keyboard-type display; the flexion of a "cyberdigit" was also achieved [54]. While the interval between the "go" cue and response (e.g., flexion of cyberdigit) was 5 s or longer, the ability for persons with paralysis to gain external device control with even a single pair of implanted electrodes made clear the potential for clinically useful human iBCIs.

Based upon work conducted in the Donoghue laboratory [46], [55], and following eight years of device development and testing in monkeys, a 4 mm × 4 mm sensory (array) of 100 silicon microelectrodes ([35], Cyberkinetics, Inc.) is now being tested in pilot clinical trials of a brain-computer interface system in humans with spinal cord injury, brainstem stroke, or muscular dystrophy. By simultaneously recording local field potentials and action potentials from an ensemble of neurons in the arm-hand area of the motor cortex, it is hoped that real-time control over an external device can be provided to persons with severe paralysis. The initial goal of this pilot trial of the BrainGate Neural Interface System is to demonstrate the safety and feasibility of computer cursor control. Preliminary results from the first participant, a 25 year old with traumatic C4 ASIA A spinal cord injury, have been encouraging [56], including rapid ability for *continuous* cursor control. A similar pilot trial for persons with amyotrophic lateral sclerosis has been approved as well.

Intracortical electrode arrays and iBCIs have numerous advantages. First, they can record directly from the same cortical location(s) which provided the substrate for voluntary movement before neural injury or degeneration. This implies a greatly reduced need to "learn" new strategies for device control, as the neural activity evoked by intended or imagined limb movement can be converted, in a timescale of less than 200 ms, to related movement of an external device. Second, by harnessing signals from the motor cortex in particular, it is anticipated that neuromotor prosthesis control can remain relatively independent of other motor or cognitive activities, as does natural limb action, thereby allowing a person with paralysis to control an external device while looking around the room and talking. Third, by incorporating both dynamic and kinematic variables known to be encoded in cortical neuronal activity, it may be possible to use these same signals to direct the position, velocity, and force applied by a prosthetic limb or (using evolving functional electrical stimulation techniques [57], [58]) to re-enable control over one's own limb. Finally, the array's tiny size, surface location, minimal penetration by very fine electrodes, and limited surgical procedure would classify the implant as minimally invasive, by our definition.

The current human trials utilize a single multichannel electrode array. While considerable neural information can potentially be extracted, it is likely that recordings taken from multiple arrays placed over a wider expanse of motor cortex (including, e.g., the contralateral arm or leg M1

An increasing number of laboratories are focusing their efforts on BCI development, and measures to evaluate the relative benefits of each system will be useful.

cortex) might provide even greater user flexibility. It is also worth mentioning that iBCIs may be useful not only for persons with paralysis but also for those with limb amputation. Intracortical neurotechnologies also may be useful in rehabilitation after stroke by helping to re-engage areas of the cortex partially isolated by neighboring or subcortical infarction. While clinical and neuroprosthetic research indications will continue to guide the placement of intracortical electrodes, their placement will also provide an unprecedented opportunity to observe basic neurophysiologic mechanisms of learning, memory, and motor control, which could previously only be examined in animal models.

We and others have wondered whether intracortical electrode recording surfaces must lie in layer V, the principal output layer from motor cortex to the spinal cord, in order to be useful. While large pyramidal cells in layer V generate larger amplitude signals and are thus comparatively easier to record, these large cells have not always been the ones recorded from in the nonhuman primate work that formed the basis for the current clinical trials, and there is no particular reason to believe that it will be easier to modulate voluntarily the activity of layer V cells than pyramidal cells in layer II/III. It is unclear whether the arrays being used in the current BrainGate clinical trials, which have 1-mm-long electrodes, are recording from cells in layer III or V. The intriguing question about which layer(s) may be ideal for iBCI control might be tested directly in the future by using electrodes with vertically oriented, closely spaced recording surfaces or other configurations not currently available for humans. In addition to the Cyberkinetics array, several additional intracortical sensors are being developed for potential iBCI use [35], [36], [38], [59]–[64]. While certain electrodes have been shown to record for years in nonhuman primates [65], longevity will be an ongoing issue, as electrodes appear to generate varying degrees of intracortical and meningeal tissue reaction, which may or may not significantly interfere with recording over time, especially if they must function for many decades. It is also important to recognize that implant materials may have varying tolerance to the dynamic biological environment [66]. Ultimately, there may be many ideal cortical and subcortical locations and designs for these arrays, which will only be determined by continued, careful animal and human studies.

Intracortical BCIs require neurosurgical placement and thus carry small but unavoidable risks associated with surgery (including stroke, hemorrhage, infection, and complications from anesthesia). However, experience with central nervous system implants continues to expand, and deep brain stimulators—with stimulating electrodes inserted through approximately 65 mm of cortical and subcortical tissue until they reach their target structure—have been placed in more than 25,000 persons with movement disorders with considerable success. Like early cardiac pacemakers and deep brain stimulators, iBCIs currently utilize externalized connectors that limit patient mobility and maintain a break in skin integrity where they protrude; more desirable, but more complex implantable systems that use telemetry or infrared communication to transmit neural signals to extracorporeal (or other internal) devices are under development. The first in-human iBCIs now being tested, like EEG-BCIs, currently require substantial equipment and the assistance of a trained technician. Both miniaturization and automatization of amplification/decoding processes are challenging but feasible. These advances are critical steps towards a fully implantable and portable system that can potentially provide great benefit to persons with paralysis.

Can Information Transfer Rates Be Used to Compare BCIs?

An increasing number of laboratories are focusing their efforts on BCI development, and measures to evaluate the relative benefits of each system will be useful. In comparing the merits of various BCIs, the information transfer (bit) rate [67] is often considered to be a significant yardstick to compare disparate systems. While useful for evaluating how well discrete selections are made by a user employing a particular BCI, there are important limitations of this metric. The goal of information rate calculations is to compare the speed and accuracy of different input systems (i.e., sensors and decoders). Such comparisons demand that the same actuator (test effector) be used in each comparison, as even slight differences between tasks limits the utility of further comparison. For example, in the standard “center-out” task in which a cursor is centered in a screen and the user must move the cursor to one of several peripheral targets, it is difficult to compare tasks in which initial contact (<1 ms) with the target is scored as a “hit,” when another task requires that the user remain within the target boundary for hundreds of milliseconds. This scenario also alludes to a second issue with information rate calculations: they are dependent upon the test effector (often presented on a video display). The BCI2000 initiative provides an important effort toward ensuring equivalent effectors when making such comparisons. A principal goal of BCI research is not only to re-enable communication and to provide discrete environmental control but to permit persons with paralysis to reanimate their own limbs in the same, *continuous* manner achieved by individuals without paralysis. While bit rate calculations can be helpful benchmarks and stimulate productive competition among laboratories, care should be applied if extrapolating or comparing information rates from BCIs with nonidentical effectors.

Furthermore, individual patients may select future BCI systems for practical, cosmetic, or other reasons independent of bit rate or even objective efficacy.

Outlook

Toward the pursuit of "turning thought into action," the ideal BCI will provide complete independence, requiring neither assistance from a caregiver nor daily oversight by a trained technician. Efforts should be made to develop BCIs for which training is relatively rapid and acceptable to users [68]. Persons with tetraplegia place high priority on the restoration of arm and hand function, and toward that goal, systems for the intracortical control of multiarticulate prosthetic limbs are now being designed. For persons with locked-in syndrome and other severe communication impairments, BCIs may provide useful communication systems within the next few years. Minimizing or eliminating the need for caregiver/technician assistance with these systems will be crucial to their success. BCIs have largely been developed and maintained by university- or government-supported researchers; myriad regulatory, commercial, reimbursement, and product support considerations must be satisfied before the transition from laboratory bench to patient bedside is fully achieved. The scale of this translational effort is formidable. While a brief comparison of sensors has been provided, the continued development of different BCI systems remains critical. Not only will advances in signal processing and decoding be fostered by both the independent and cooperative efforts of multiple laboratories, but BCIs ultimately offered to patients may well include intracortical, intracranial, and extracranial sensors or a combination of these. The interdependence between sensors, decoders, and actuators underscores the importance of early and thoughtful BCI design choices, which will result from extensive collaboration among physicians, therapists, neuroscientists, computer scientists, biomedical engineers, and, most importantly, the patients and research participants whose experience and insights must continue to guide our efforts.

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