Bridging the Brain to the World: A Perspective on Neural Interface Systems

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Neural interface (NI) systems hold the potential to return lost functions to persons with paralysis. Impressive progress has been made, including evaluation of neural control signals, sensor testing in humans, signal decoding advances, and proof-of-concept validation. Most importantly, the field has demonstrated that persons with paralysis can use prototype systems for spelling, "point and click," and robot control. Human and animal NI research is advancing knowledge about neural information processing and plasticity in healthy, diseased, and injured nervous systems. This emerging field promises a range of neurotechnologies able to return communication, independence, and control to people with movement limitations.

Rapid growth and development at the intersection of neuroscience, computer science, engineering, and medicine has allowed the creation of revolutionary neurotechnologies to evaluate and treat nervous system disorders and to restore lost neural functions. Available neurotechnologies can relieve symptoms of Parkinson's disease through electrical stimulation of deep brain structures and restore hearing by stimulating auditory nerve fibers. Neural interface (NI) systems that sense neural signals, also called brain computer interfaces (BCIs), are early-stage neurotechnologies designed to restore control, communication, and independence to persons with paralysis when the motor control structures are disconnected from muscle output. When motor pathways fail NIs offer a physical bridge for movement intention to reach the external world by detecting neural signals that reflect desired actions and transforming them into commands for action, bypassing muscles and damaged neural structures. The emerging neurotechnology field has moved quickly in recent years to demonstrate that people with paralysis can use an NI to perform potentially useful functions. Practical NI systems are not yet widely or commercially available, but many of the critical barriers to success are being tackled.

Although the roots of NIs can be traced back well into the last century, scientific as well as public interest in the potential for NI technology was ignited by demonstrations of monkeys substituting neural signals from their motor cortex for hand motions (Serruya et al., 2002; Taylor et al., 2002). Using neural signals in place of arm motion, able-bodied monkeys moved computer cursors to accomplish goal-directed actions. This proof of concept was soon followed by the launch of a pilot clinical trial in which humans with longstanding tetraplegia demonstrated the ability to use motor cortex activity immediately to operate computer software and control a robotic arm (Hochberg et al., 2006). Each of these studies, and many complementary studies, was based on a novel approach in which arm movement intentions were captured from the spiking patterns of a population of cortical neurons in motor cortex. During this same period, both the level of interest and accomplishments in a then nearly parallel effort using field potential (FP)-based NI technologies also accelerated. Humans with severe paralysis demonstrated the ability to use FP-NI systems, based on scalp-based electroencephalogram (EEG) sensors, for applications ranging from letter-by-letter spelling (Kubler et al., 2005; Wolpaw et al., 2002) to 2D cursor control (McFarland et al., 2008).

By reaching these major milestones, NI systems have come to a threshold of being able to substantially alter the functional capabilities of persons who have any of a wide range of movement limitations. However, NIs in any form must be sufficiently reliable, beneficial, and easy to use for them to become widely adopted and commercially attractive. Both engineering and fundamental scientific issues remain, but considerable progress made so far has helped codify the major obstacles remaining to create a practical human NI system. These initial advances have focused debate and motivated considerable research necessary to realize this entirely new way to help those with movement limitations. The field has also stimulated inquiry into the nature of neural signals and neural coding, investigation of neural implant safety, innovative engineering of "smart" microscale implantable systems, and cross-field discussion of issues and needs of those with movement limitations. The fervor of activity has attracted a number of basic laboratories to engage in multidisciplinary research; shaped scientific meetings and journals (see, e.g., IEEE Trans. Neural Syst. Rehabil. Eng. volume 14:2); evoked vigorous dialog, especially over the use of invasive and noninvasive technologies; and garnered much public and media attention. The move from preclinical to pilot clinical trials has provided a solid example of translational success in neuroscience. Finally, the emergence of NI systems has promoted useful dialog regarding the ethics of communicating directly with the brain, working with a potentially vulnerable user population, and managing conflict of interest when attempting to move scientific and engineering discovery into commercial distribution. All of these can be seen as healthy signs of an emerging area that presents formidable challenges. Many review articles on the various designs and types of NI systems are now available (e.g., J. Physiology volume 579:3). Instead of re-reviewing these reports, the goal of this perspective is to provide a current point of view from one immersed in the field—first, to attempt to identify and clarify some major current key issues, and second, to provide personal impressions

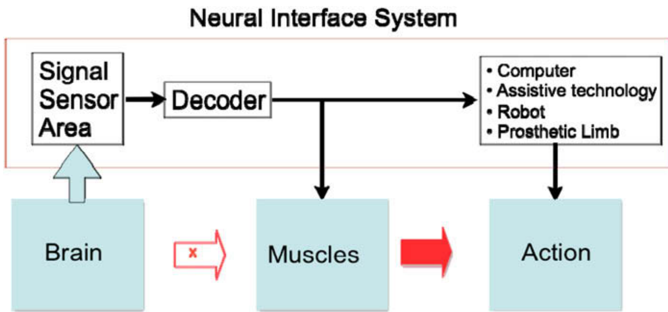

Figure 1. Design of a Neural Interface System
Disconnection of signals carrying movement intention to muscles is "bridged" by detecting signals that are either direct representations of movement or indirect substitutes for that signal. Each signal type requires the selection of a sensor and the area from which that signal is obtained. Neural signals are decoded into a command that is used to operate a range of devices to effect actions. In addition to physical systems, the signal could be routed to the muscles and, via muscle stimulators, reconnect the brain to the muscles to restore voluntary action.

of the future of NI systems. Topics are presented as contemporary questions frequently raised in the current NI community.

What Is an NI System and Whom Is It Intended to Benefit?

Nearly all in the field will agree that one major goal of NI research is to create a bridge from the brain to the outside world—a kind of replacement part, or prosthesis, for the motor system. A system that senses brain signals may have other roles in evaluating disease states, for example to predict seizure onset in epilepsy, or to guide therapy; these important potential uses of an NI are outside the scope of this perspective. Opinions vary on the target population for NI devices. Concepts for NIs range from an externally driven, reliable, brain-activated switch for a person who is totally unable to move or speak, to an implanted system that provides direct brain-actuated dexterous limb movement for someone with limb paralysis. The design and implementation of these visions share common features but also present independent problems that lead down divergent paths.

However simple or elaborate, a functional NI system is potentially of enormous value for individuals with movement limitations. Many disorders leave the cerebral mechanisms for volitional movement intact, but disconnect motor signals from the muscles, preventing normal movement and, in the worst cases of complete "locked in" paralysis, blocking all forms of communication as well. Paralysis originates in diverse ways that include: injury to descending motor pathways in the spinal cord, brainstem, or cerebrum through stroke or trauma (spinal cord injury [SCI], cerebral palsy); degenerative disorders that lead to the loss of motor neurons (such as amyotrophic lateral sclerosis [ALS]) or motor pathways (e.g., multiple sclerosis); degenerative disorders of the muscle (muscular dystrophy); or limb loss. This range of conditions limiting useful movement affects hundreds of thousands in the US alone. An NI offers a physical means to reconnect action intentions to the world, as illustrated in Figure 1.

A note on nomenclature is valuable because multiple sets of terminology to name NIs exist. BCI can mean either brain computer interface or brain-controlled interface. The former reflects the idea that neural output, normally meant to control muscles, is now directed at controlling a computer; the latter reflects the fact that the interface is being run directly from the brain without the usual somatic intermediaries. Additionally, neural signals may not go to a computer, but to a machine like a robot; hence the term brain machine interface (BMI) is used. By contrast, NIs may control a range of assistive technologies that are not computers or "machines," such as a push-buttons, so terms that reflect function as a replacement part, such as neural prosthesis or neuromotor prosthesis (NMP), have also been used. Here, I have adopted the term NI system as a general name to encompass the range of these neurotechnologies.

There is widespread agreement that any NI requires three major components (Figure 1): (1) a sensor to detect neural signals, (2) a signal processor that converts neural activity into a command related to a desired action, and (3) a device to effect action, often called an assistive technology (AT) in the clinical realm. Ongoing concerns relate mainly to the first two areas, including the optimal types of signals and sensors and the ability to obtain them, decoding approaches, and the necessary capabilities of the control signal. At this point, there has been less attention paid by the NI research community toward explicit AT needs, but this likely reflects the relatively early stage of the field and the substantial challenges of going from neural signals to a command signal. A stable and reliable control signal can be readily applied to many useful ATs. Thus, despite still having various designations, the overall concept of providing a link from neural signals as a means to compensate for loss of control is seen as the central principle that unifies this field.

NI Classification: Direct and Indirect Systems

There is not general agreement on how to categorize various emerging types of NI systems, and this reflects the diversity of technologies being developed. Systems may be grouped by the nature of the control signal, sensor location, or output form. One constructive classification method stems from the cerebral processes that the particular NI system engages to provide control: (1) indirect NIs—those systems that co-opt neural events not intrinsically or originally related to intended movement in order to achieve action and (2) direct NIs—those that attempt to control action by using those neural events that underlie the intended movements. Thus, an indirect NI provides a surrogate (replacement) output, because the source of control comes from a signal that substitutes for the missing motor command. Learning to raise or lower the amplitude of an EEG signal over the auditory cortex to activate a switch (Wilson et al., 2006) would be one clear example of an indirect NI system, because this signal is not ordinarily directly coupled to movement. One subtype of indirect NI involves learning to associate the power or amplitude of a brain rhythm with a desired action. For example, learned suppression of a cortical rhythm reflecting attention could substitute for action of the hand on a computer mouse. Through a decoder and simple hardware one could couple the amount of attentional suppression to upward movement of computer cursor on a monitor so that cursor motion is achieved

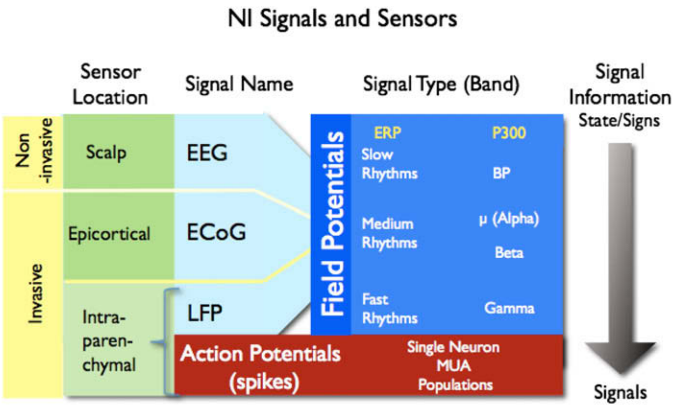

Figure 2. Signals and Sensors for Neural Interface Systems
Two broad classes of electrical potentials are being evaluated as signal sources for neural interface (NI) systems: field potentials (FP, darker blues) and action potentials (spikes, red). FPs include slow potentials, such as the Bereitschaft potential (BP); medium rhythms that include μ and beta SMRs; and fast gamma rhythms. Event-related potentials (ERPs) are triggered events such as the P300. FPs may be recorded (light blue) from single or multiple sites on the scalp as the EEG, directly above the brain as the ECoG, and within the brain as the local field potential (LFP). FP bandwidth, signal-to-noise, or sampling area is influenced by distance from the brain and electrode size, shape, and number. All but the EEG recordings require invasive methods to place sensors. Spikes can only be recorded within the brain parenchyma. Spikes originate from single neurons but can also be recorded as local mixtures of spiking neurons (MUA, multiunit activity); population signals are obtained by combining information from spikes from different neurons or MUA channels. FP signals carry information (arrow to right) that appears to represent brain states or signs of underlying subthreshold and threshold processes, while spikes are signals that carry specific details of action such as hand velocity in space.

without the user engaging hand movement circuitry. Instrumental conditioning or biofeedback-like training is used to form an arbitrary association between whatever modulates the brain signal and the desired action for this learned form of indirect control. A second subtype of indirect system is based on capturing event-related potentials (ERPs) that respond to a time-locked event, which signals the user's intent. The clearest and most successful example of this type of indirect NI is the P300 evoked potential system, in which control is derived from amplitude differences in this response to attended and nonattended computer-flashed stimuli (Birbaumer, 2006). The P300 response can be used, without learning, to select one attended character within a larger matrix of characters to create a spelling device (Figure 4). Research on indirect systems is driving inquiry into the various types of brain rhythms and the ability of humans to learn to control them, as well as the nature of ERPs related to cognitive and other events.

By contrast, a *direct* NI system attempts to reconnect the neural spiking patterns related to movement, say for the arm, directly back to a device that carries out arm-like functions (Donoghue et al., 2007). Thus, arm movement control signals used to guide hand movement for mouse control of a computer cursor are instead used to guide the cursor directly from the brain. Consequently, a direct NI control signal does not require any initial learning because it maps neural activity related to the intended motor feature directly to the desired action. There has been a major emphasis on arm function for direct NI systems because neural control of the arm in nonhuman primates at the single and neuron population is comparatively well-understood and because restoration of arm-like functions, such as point and click actions of a computer mouse, is both enabling and highly desired by those with tetraplegia (Anderson, 2004). Direct systems, which necessarily intercept movement commands from only one part of a distributed motor control system, rely on a very limited sample of ongoing processes captured at an intermediate stage. Learning, either by the human or decoders, is therefore likely to play a critical part in optimizing direct NI function and in compensating for missing or disconnected parts of the motor system. An implicit assumption for a direct NI is that control would be more natural and intuitive because it begins with the signal ordinarily used to perform a particular missing action (i.e., hand motor commands to achieve hand-like actions). Success in testing this idea will be discussed below.

What Are the Most Useful Signals for NIs?

One contentious but key issue is selecting the optimal neural signal to provide control. In its ideal form, the neural control signal would achieve the quality of the communication link between the brain and the able body. Greater information content, speed of transfer (information rate), reliability, and signal accessibility are features that influence optimal neural signal selection. Lack of fundamental knowledge concerning the nature of neural signals and information coding in the brain, as well as insufficient human NI experience, limits our ability to judge how much control potential there is in various neural signals, although small samples are unlikely to provide elaborate control without support from physical systems.

Divergent opinions on the best signal sources have emerged based on the main classes of neural signals. Two broad types of electrical potentials form important information carrying modes or signs of information processing in the nervous system (Bullock, 1997; Figure 2): action potentials (spikes) and FPs. Both classes are currently used as NI control sources, and the field has divided, to some degree, along the lines of those using FP, largely in humans, and those using spike-based systems in animal models and, more recently, humans. It is widely held that action potentials, or spikes, are the major neural information-carrying mode of the nervous system, and would thus seem to be the richest source of movement information. Most agree that information is largely carried by spike rate (number of spikes in a specific interval or a related function). The vast majority of systems neurophysiologists investigate information codes at the level of spikes from single cells and, to a lesser extent, evaluate additional information conveyed by populations of spiking neurons. It is not surprising then that researchers from this background form the base of those working on direct NI systems, which are considered direct because they use spikes.

The amount of movement information available from spiking activity is impressive. Hand velocity, position, forces, and goals, among other variables, can all be gleaned from single cells in motor cortex (Scott, 2008). Higher information levels, such as upcoming plans for hand motion, can be decoded from parietal and frontal neuron spiking (Achtman et al., 2007; Pesaran et al., 2006; Scherberger and Andersen, 2007). Recording many cells at once adds information distributed across heterogeneous populations and reduces noise (information variability) by averaging across neurons (e.g., Maynard et al., 1999). The number of neurons required for a reasonably reliable reconstruction of hand motion is remarkably small. For example, about 50 cells in the MI arm area can provide a very good estimate of hand motion in 2D or 3D space (Serruya et al., 2002; Taylor et al., 2002; Carmena et al., 2005). Consequently, there has been great interest in using signals from populations of a few dozen neurons, now technically feasible to gather, as control signals for direct NI systems. The mixed signal, when many spikes are intermingled together from a single site, is called multiunit activity (MUA), which is thought to represent averaged spiking of a local population. MUA is also a spiking signal of interest for NI applications because it reduces the technical demands of isolating single neurons on each electrode, although MUA is just beginning to be studied in this domain (Stark et al., 2008).

FPs are the other type of neural electrical potential that is used to obtain control signals. FPs are more complex than spikes, in that they reflect the flow of transmembrane currents, usually of synaptic origin, summed across groups of neurons of varying size, frequency, and spatial distribution. While the recognition of FPs as an information-carrying signal is long standing, the recent surge in NI interest has renewed and accentuated study into the nature, origin, and significance of FPs and their relationship to spiking. FPs are both signals and signs (Bullock, 1997) of underlying neural processes that generally reflect brain states, such as stages of sleep or alertness or higher cognitive processes. A comprehensive discussion of the many subtypes and sources of these signals is not possible here; only a brief explanation of the type of control signals possible from FP and recent advances in their use in NI will be presented (for additional perspectives see Clinical Neurophys. volume 117:3; Birbaumer, 2006; Vaughan et al., 2006).

A schema to organize common types and subbands of signals relevant to NI control is shown in Figure 2. In this context, FPs include two major subgroups: (1) rhythmic signals that can be grouped as slow, medium, or fast, and (2) ERPs, which are responses triggered by a time-locked event. All three rhythms have been used as NI control signals. Slower cortical potentials (<1 Hz), which might not actually be rhythms but slow potential shifts, were among the first successfully used for NI control in humans (Birbaumer et al., 2006). These slowly modulating potentials may last seconds, such as the Bereitschaft or readiness potential (BP or RP), which is linked to an impeding self-paced movement. Humans can learn to modulate slow potentials volitionally for continuous, single-dimension control (Iversen et al., 2008). Faster FP rhythms have received increasing attention in recent years, because they seem to carry more information and require less learning than slow rhythms, as tested in NI applications. Medium-range rhythms include μ (8–12 Hz, over Rolandic cortex or the similar band, but potentially different; alpha elsewhere) and beta (12–20 Hz or higher) rhythms. Medium rhythms, particularly those over sensorimotor cortex (SMR), are now actively being tested as an NI control signal (McFarland et al., 2008) in part because humans can learn to modulate their amplitude by imagining various types of movement. The higher range and broad gamma band (>30 Hz to ~100 Hz) are only recently being carefully evaluated with intracranial recordings because they are heavily filtered in more common scalp recordings. Middle and high bands appear to carry distinctly different information (Belitski et al., 2008). Beta oscillations appear in primary motor cortex (MI) in able-bodied monkeys (Baker et al., 2003; Donoghue et al., 1998; Murthy and Fetz, 1996) and in humans with paralysis (Hochberg et al., 2006), where they, rather than spiking patterns, mark the transition from preparation to intended action. By contrast, gamma rhythms are correlated with aspects of spiking as shown in visual (Belitski et al., 2008) and parietal cortex (Andersen et al., 2004), suggesting that they might provide specific forms of information (Womelsdorf and Fries, 2006) useful for NI movement applications. Beyond rhythms, FPs include ERPs. ERPs signify large-scale potential shifts in neuronal populations that can be elicited and modulated by various external or internal events. As noted earlier, the P300 has been intensively investigated for NI applications.

FP can radiate considerable distances, especially in the lower frequencies, and can therefore be recorded electrically outside as well as inside the head, unlike spikes. FP recorded by scalp electrodes is called the EEG; FP recorded inside the skull, close to the cortical surface (above or below the dura) is the electrocorticogram (ECoG); and the FP recorded intraparenchymally is the local field potential (LFP). The ease of recording FP at the scalp has made the EEG attractive as a signal source to create, test, and develop NI systems using humans in a number of laboratories, and has allowed them to be usefully adopted by persons with paralysis (Vaughan et al., 2006). EEG systems have drawbacks as potential sensors and FP signal sources for NIs that include limited bandwidth (loss of higher frequencies due to scalp filtering), significant noise and environmental artifact (muscle contamination), the need for an able-bodied person to attach sensors to the scalp, variability in sensor contact over time, tethering to instruments, and appearance issues. However, efforts to enhance signals, reduce sensor application problems, and deal with tethering issues are underway (Farshchi et al., 2004).

ECoG provides a lower noise signal of higher bandwidth and power, particularly in the gamma range, because filtering by the scalp is reduced (Schalk et al., 2008). ECoG sensors, if implanted and wireless, potentially eliminate many of the drawbacks of EEG signals, but a long-term ECoG recording system, FDA approved for NI use, is not currently available. Presently the main opportunity to study human ECoG-based control occurs in conjunction with short-term placement of subdural grids in candidates for epilepsy surgery. These grids usually have many relatively large (~4 mm) electrodes (see Figure 4), regularly arranged in a silastic sheet that covers large aspects of the cortical surface for mapping in order to plan surgical resections. Recordings made over cortex with this grid allow experimental investigation of the person's abiltity to control FP bands for NI purposes. This test bed for humans has advanced understanding of ECoG signals for NI control and is becoming a more widespread development platform for indirect NIs. Most noteworthy is the fact that humans using ECoG-derived signals can learn to control SMRs within a single session, compared with the need for many months of training with EEG-derived FPs (Schalk

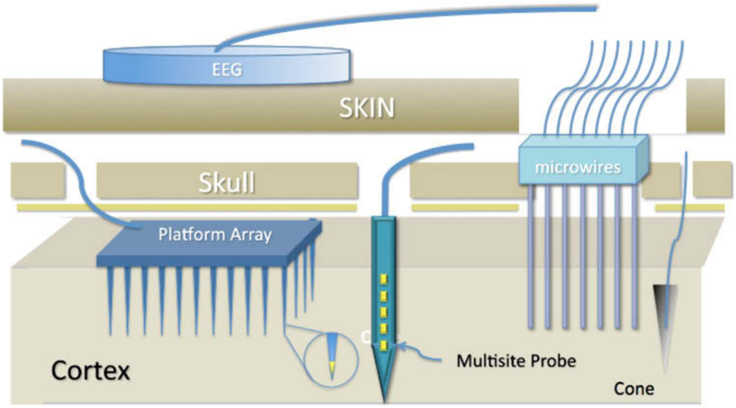

Figure 3. Intracortical Sensor Types Compared with a Common Surface EEG Electrode
Three main types of intraparenchymal (intracortical) sensors now in use are illustrated: platform array, an array of electrodes emanating from a substrate that rests on the cortical surface; multisite probe, with contacts along a flattened shank; and microwire assemblies, consisting of fine wires. Cone electrodes are a form of microwire placed within a glass cone that is open at its end. Cellular elements grow into the cone to establish contact with the wire. Platform arrays and microwires, in their present form, record from an exposed conductive tip (enlargement, yellow), while multisite probes record from many sites along their length. Only cone electrodes and platform arrays are currently being evaluated in human trials (see text for details).

et al., 2008). LFPs are being pursued because these higher-resolution FP signals might be able to provide information contained in spiking populations, but with fewer of the technical demands (see following section). In addition, LFPs can be recorded simultaneously with spikes (by different bandpass filtering), so that both signals could be used together, thus expanding the information that could be used for NI control. Direct evaluation of LFP signal in NIs is limited; Philip Kennedy and colleagues have demonstrated that a tetraplegic human could learn to use LFP amplitude for control (Kennedy et al., 2004).

Are Invasive Technologies Justified? Are They Feasible?

An ongoing debate in the NI field has centered on concerns of whether invasive sensors, which are required to obtain spiking or FPs from ECoG or LFPs, can provide sufficiently stable and reliable signals to warrant the risks of neurosurgical placement and the long-term presence of a foreign body. Safety is the first concern for any NI being developed. The questions of safety and invasiveness are currently raised by some to argue that only indirect, EEG-based systems are reasonable and acceptable for NI users. However, it is often not recognized outside the clinical community that there is already substantial, FDA-approved use of implantable neurological devices in humans, with a low incidence of complications. In one example, there are now more than 30,000 people with deep brain simulators (www.medtronic.com/physician/activa/history.html), in which mm scale electrodes are implanted centimeters deep into the brain to provide subthalamic nucleus stimulation that reduces symptoms of Parkinson's disease. Thus, placing sensors onto or just into the brain's surface (Figure 3) would not appear to present a safety concern beyond that associated with other implanted devices. In support of this view, there are >2500 days of experience in four participants with an intracortical array in the BrainGate pilot trial we are conducting, suggesting that this sensor may have an acceptable safety profile for an implanted device, although this represents a very limited sample from a study still in progress.

A second concern relates to the ability of sensors to provide signals over the long term. Invasive electrical recordings may be subject to tissue reaction, motion, and breakdown, although current evidence from at least some sensors indicates that long-term recording is possible despite these real issues. Spikes are recorded in the extracellular space only by placing a small conductor surface near enough to a neuron to detect the brief ~1 ms electrical field generated when a spike occurs. Since spikes can be detected only at distances significantly smaller than 150 μm from cell of origin (Buzsaki, 2004), motion tolerance is limited. There are several types of multisite spike sensors being evaluated in animal models. Existing multielectrode sensors include: microwires, planar silicon probes, and platforms with microelectrode arrays (Figure 3). Microwires are assemblies of insulated fine wire usually rigidly affixed to the skull; planar Si probes are manufactured with semiconductor precision to provide multiple sites along a flat, tapered shank; platform arrays contain a set of typical microelectrodes emerging from a flat platform that rests on the cortical surface (Donoghue, 2002). Each of these sensors has characteristic design and materials features that may influence their stability and longevity. But these are initial-stage sensors. It is widely recognized that sensor reliability needs to be improved and better sensors developed. Only cone electrodes, in which microwires are encased in a glass cone, from Neural Signals, Inc, (Deluth, GA) and the platform array made by I2S Implantable Microsystems (Salt Lake City, UT), are being evaluated in humans at this time.

Studies in monkeys routinely report declines in the number of channels recorded and the signal quality over periods of many months, as well as day-to-day changes in the number of neurons observed (see Donoghue et al., 2004; Schwartz et al., 2006 for discussion). The causes of these declines have not been adequately determined. Tissue reaction around an intracortical microelectrode is widely cited as the major impediment to long-lasting recording and data clearly show that electrode penetration leads to a number of concerning tissue responses. Of major reported concern is a layering of glial cells around recording surfaces that could prevent signal capture. Immediate and chronic tissue responses to electrode implants have been carefully delineated (Shain et al., 2003; Szarowski et al., 2003; Yuen et al., 1987), but general conclusions have been drawn by comparing studies in which species, electrode size, shape and assembly design (e.g., platforms or single probes), coating material, insertion type, surgical procedures, manufacturing techniques (lab or commercial), and quality control have differed substantially. Can results based on placing a blunt-tipped microwire coated with Teflon, inserted slowly, and fixed to the skull be realistically compared to those from a conical-shaped electrode array coated with parylene, emerging from a platform, inserted quickly, floating on the arachnoid surface (Figure 3)? Each type of sensor is very likely to have a unique tissue response profile influenced by insertion, tissue reaction, micromotion, its foreign materials, tethering from cables, etc. Most importantly, evaluations of tissue response effects on the ability to record electrical potentials have largely been lacking. A mild tissue reaction—even if chronic—may be acceptable if neural signals are reliably obtained for years without otherwise compromising health. Less emphasis has been given to biostability issues, which may be a significant reason why success rates vary for spike sensors. The body provides a harsh environment. Implantation of biostable sensors, impervious to leaks, breakage, and chemical degradation while robust against mechanical forces is a major challenge that is only beginning to be addressed.

Our experience is entirely with a 4 × 4 mm platform of 100 parylene-coated Si microelectrodes in which the platform rests on the arachnoid surface. Suner et al. (2005) showed with this array in monkeys that more than 80% of the original data channels continued to provide signals after 1 year of monitoring. Others monitored for less time, but many months, also showed similar signal retention. This same array type in humans (Hochberg et al., 2006; Truccolo et al., 2008) has provided spike recordings from MI cortex well over 1 year after implantation, although with a decline in channel count and signal size. However, signal declines we have observed appear to be mainly related to physical failures of the implant or insulation leaks that shunt signals, rather than gliosis. Further, signals obtained after more than 2 years are sufficient for the one participant now being tested to perform accurate point and click computer cursor control (Kim et al., 2007). Further clinical study will determine whether useful signals can be recorded for many years. Philip Kennedy's glass cone electrodes, a very different technology, have also been able to record long-term, in this case by capitalizing on the tissue injury response to induce neurite ingrowth to recording wires (Kennedy and Bakay, 1998).

Thus, the prospects for using invasive systems seem promising, but not without challenges. The combined data from animals and humans suggest that safety problems for implantable systems will not exceed those of established implantable neurotechnologies. Results from humans and animals demonstrate the potential for years of spike and LFP recording sufficient for a useful NI device. In order to get large numbers of signals to the outside, implantable systems will require sophisticated internal signal processing and wireless transmission, which adds to the challenge of invasive sensors. Implantable microsystems for this purpose are very complex devices because they must be small, produce little heat, not leak, and process and transmit large amounts of data. While the challenges of creating small-scale microelectronic sensors impervious to the internal environment, and well-tolerated by the body for decades, are substantial, sensor systems suitable for this purpose are being developed (Song et al., 2005, 2007).

What Brain Area Provides Optimal Neural Control Signals?

Motor cortex has been a successful source of control signals for both FP- and spike-based NI systems. The MI has been a major target of investigation for spiking NI because there is so much known about the relationship of its activity to arm movement (Georgopoulos, 1991). Information about arm trajectory in space can be readily recovered from MI spiking in able-bodied monkeys, allowing cursor control as if a computer mouse were being moved by the hand (Serruya et al., 2002; Taylor et al., 2002). Further, a population of MI neurons from a single 4 × 4 mm, 100 electrode BrainGate array generally placed within the precentral arm region array in humans with tetraplegia can provide both cursor motion signals related to imagined arm actions and a click signal, based upon imagined hand squeeze (Kim et al., 2007). These findings show that a small MI arm area patch can provide simultaneous information about both the arm and hand that is useful as an NI control signal. It might also be possible to extend volitional control to both arms and legs by placing sensors bilaterally in MI arm and leg representations.

The collection of other motor control areas could provide additional, different or more flexible control signals. Shenoy and colleagues (Achtman et al., 2007; Santhanam et al., 2006) have shown that premotor cortex (PM) in monkeys contains information about target goals that can be decoded as discrete selections, akin to keyboard entry, during movement planning. Combining continuous control signals from MI and key press activity from PM could allow the emulation of typing, pointing, and clicking actions for efficient operation of the usual input devices of a computer. Parietal cortex spiking contains information about upcoming movement and, when combined with simultaneously recorded LFPs, various epochs of planning and action can be delineated (Andersen et al., 2004). Thus, future NI systems may gain considerably greater function if they employ multiple sensors placed in a variety of cortical areas and use both FP and spike signals for control. It appears likely that control capabilities of multiarea sensors will be evaluated in animal models in the near term.

How Much Information Can Be Derived from Neural Signals?

Decoding neural signals for NI use is a key step in transforming patterns of neural activity into useful control signals. Decoding aims to produce stable, information-rich signals as quickly as they are achieved in the normally operating nervous system. This challenge has attracted major interdisciplinary interest, both to understand the nature of neural signals (by showing what is contained in them) and to develop useful control signals for NI applications. Virtually every readily identifiable method of decoding information has been attempted in both FP and spike signals (for further discussion see Paninski et al., 2007; Schwartz et al., 2006; Serruya et al., 2003; Srinivasan et al., 2007; Truccolo et al., 2005; Wu et al., 2006).

Decoding efforts have focused on creating two types of control signals: (1) continuous state classifiers, to allow ongoing control as might be needed to move a cursor or wheelchair around in space, and (2) discrete state classifiers, to make specific selections such as a button press or typing keystrokes. For continuous control, a goal is to extract information about one or more dimensions to move an effector, such as a robot arm or cursor, from one place to another. By learning to modulate different SMR bands independently, 2D continuous control can be decoded into a usable signal for an indirect NI system (McFarland et al., 2008). Using spikes in a direct NI, three dimensions of hand motion can be recovered from spiking patterns in MI arm area neurons (Taylor et al., 2002). For discrete decoding, a goal is to identify how many different selections might be obtained. ERP systems typically are used to make binary choices based on FP amplitude differences. For example, a P300 decoder works in humans by classifying observed FP response differences. The item in a set with the largest average response, the one attended by the user, is selected. A discrete decoder using the richer information in spikes is able to differentiate among a large number of selections, potentially to achieve key selections that could enable typing at rates of ~15 words/min (Santhanam et al., 2006).

Combining discrete and continuous classifiers adds further control. Simple state selection (decoding a click by classifying hand squeeze) has already been combined with continuous state decoding of imagined or attempted reaching to achieve point and click control for a direct, spike-based NI in a person with tetraplegia (Kim et al., 2007). Point and click actions can also be decoded using an indirect EEG NI, in which learned 2D modulation of the SMR is coupled with a subsequent click selection learned from another EEG signal (McFarland et al., 2008). In an animal model, Schwartz and colleagues have also demonstrated the use of a continuous state-decoded spike signal to guide a complex robot arm in 3D space, and a discrete decoder coupled to close a gripper that allowed a monkey to use the robot to reach and grasp food (Velliste et al., 2008).

Decoding remains at a level where neural signals do not provide the same control, reliability, or speed possible as for able-bodied people. Efforts are ongoing to improve speed and accuracy in the face of limited and variable neural signal information. Classification with a slow rhythm or P300 system is very time-consuming, taking seconds to tens of seconds per choice, and is more error prone, although new decoding schemes have improved accuracy (Krusienski et al., 2008). Moving a cursor to a location on a screen to select an icon using spiking-based decoding also currently takes several seconds; actions can now be achieved with very high accuracy, but this level of performance is not always reliable (Kim et al., 2007). These poorly understood sources of variability are, at present, critical areas needing attention, and will likely be the subject of many studies in coming years. One approach to improve performance adds burden onto the computer, so that it deals with deficiencies in the neural control signal, but this performance increase by fixed algorithms comes at the cost of flexibility. Thus, with a single switch, using existing technology, a robotic arm could be driven automatically to pour water into a glass and bring it close to one's mouth, but the ability to deal with any unexpected obstacle would require additional computational abilities and technology not yet available. Adaptive decoding is an approach that adjusts to unreliable neural signals and is now being implemented (Helms Tillery et al., 2003; Wu and Hatsopoulos, 2008).

The total effective output of an NI system, has yet to have a widely accepted method for direct comparison across systems. Establishing performance metrics is an essential step toward meaningful discussions of recording, decoding and, ultimately, total NI system function. Information extracted by a decoder can be measured in ways that range from information bits to surveys of user satisfaction. A single measure may give poor estimates of decoding success. For example, it is possible to decode the SMR well enough to achieve 2D cursor control with a click (McFarland et al., 2008). However, this control requires high attentional demands, considerable training of the user to gain control over the neural signal, and participation of the decoder in the task by terminating the control epoch and re-centering the cursor every time a target is achieved. Similarly, 2D control with a click can also be decoded from MI using spiking signals. This control is continuous, does not require explicit patient training beyond a few minutes long filter-building epoch, and necessitates no special attentional demands (Kim et al., 2007). Therefore, comparing the total amount of information simply at the level of achieving point and click, without accounting for these other differences, is problematic to communicate overall efficacy to both the research and user communities. While it is difficult to compare the amount of information in the FP and spiking systems, these two NI systems have viable point and click decoding approaches that could provide a choice of invasive or noninvasive system for persons with limited movement.

Will NI Systems Function in Individuals with Paralysis?

Although numerous studies in intact primates have advanced NI research, ultimately the system must work in persons who have long-standing paralysis or even ongoing degenerative disease such as ALS. Indirect, FP-NI systems were tested early on in humans with tetraplegia (Birbaumer, 2006). Successful use of NI systems in this population, based upon slow and middle rhythms and on the P300, demonstrates that these rhythms and ERPs are preserved and controllable in tetraplegia, including late stage ALS (Iversen et al., 2008). However, there is concern that indirect signals may fail at end stages of the fully locked-in state (Birbaumer, 2006). Development of direct NIs has largely been performed in able-bodied monkeys. Based on current concepts of plasticity and injury response, humans with tetraplegia, irrespective of its cause, could have lost the potential to control neural activity or even lack functional neural activity after motor areas were disconnected from the body (Enzinger et al., 2008). Kennedy (Kennedy and Bakay, 1998) first showed that a person with severe paralysis could engage neuron spiking by intention. Pilot clinical studies have now further demonstrated that years after SCI or stroke, MI spiking as well as LFP activity remains and both signals can be immediately modulated by intention or attempts to move (Hochberg et al., 2006; Truccolo et al., 2008). These findings are remarkable in at least two aspects. First, SCI damages MI axons, which could result in their inactivity or cell loss. Second, plasticity after lack of use or injury would be expected to produce marked restructuring of the cortex, perhaps by having other areas take over the former arm motor cortex (Donoghue et al., 1990; Sanes et al., 1990). Remarkably, participants in our study with tetraplegia from sources as varied as SCI, pontine stroke, or ALS have been able to engage MI activity immediately upon the request to imagine arm actions. Although the generality of these findings need to be confirmed, it is very promising that the neural substrate to provide complex NI control has been obtained. Thus, both FP and spiking signals useful for NIs remain long after onset of paralysis in injury or

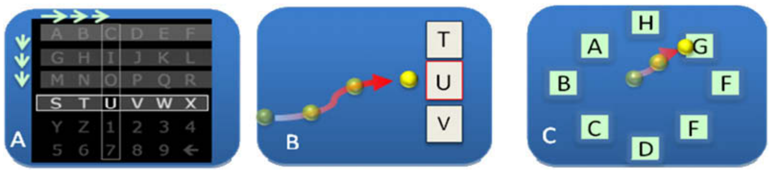

Figure 4. Three Types of NI Spellers

(A) P300 speller in which rows and then columns are flashed successively and the P300 ERP is monitored. The unique response to one row and one column predicts that the letter at the intersection "U" is being attended. Several repeats are necessary to make an estimate from averaged responses.

(B) A 1D speller. A computer displays three possible letter choices and moves the cursor from left to right across the screen. The upward movement of the cursor is controlled by the learned modulation of the amplitude of an FP rhythm.

(C) A 2D NI. In this case the cursor can be moved anywhere on the screen either by learned modulation of two FP SMRs or by decoding spiking patters of a direct NI. In the present instantiation of learned SMR control, the cursor must be replaced at the center by the computer after each trial, while the direct NI allows continuous control, including return to the center under the control of the user. In either of these cases letters could be replaced by icons that could indicate more complex choices, such as a desire for food or a drink. Yellow dot represents the cursor under neural control.

degenerative diseases. It is significant that controllable MI spiking signals remain, at least in single test participants, years after stroke (Kim et al., 2007; Truccolo et al., 2008), suggesting that the very large population of individuals with stroke-related impairments might benefit from NI technology. However, human demonstrations of retained activity are limited in number; therefore, further studies will be essential to understand the range of capabilities that remains in these various disorders.

What Types of Devices Are Possible to Control?

With sufficiently rich and reliable signals, various types of physical systems could be used to allow greater control and independence in humans with paralysis. These include computers, other commonly useful technologies, robots, or muscles themselves.

Computer Interfaces

Computers are ordinarily operated by pointing (mouse) actions, as well as discrete selections (keystrokes and mouse clicks). Computer operation achieving both of these functions has been demonstrated. A P300 BCI allows computer-based letter selections, albeit slowly, for spelling, an approach that is being tested in persons with severe paralysis unable to communicate verbally. Importantly this system has been able to achieve nearly 80% correct classification at a rate of about 2/min in persons with ALS (Nijboer et al., 2008). Cursor control has become a gold standard in demonstrating the achievement of brain control. In most cases monkeys or humans have used cursor control to reach targets on a screen that mimic paradigms used to study motor control. With simple continuous cursor control, humans have been able to operate an FP-based speller that places letters or words on a computer screen (Figure 4). In one version, a cursor sweeps across the screen under computer control and is then moved up (0.5D) or up and down (1D) under neural control to end on one choice. Nearly fully paralyzed persons have been able to spell using a 1D slow-rhythm FP system (Kubler et al., 2005) or LFPs through an implanted electrode (Kennedy et al., 2004). In both cases control was difficult and the device was error-prone, very slow, and effortful. Cursor actions are improved using SMR-EEG systems, which have shown control sufficient to move a cursor in 2D to one of four targets, and then click using a discrete classification of another EEG signal (McFarland et al., 2008). This approach, which has not yet been advanced to persons with tetraplegia, required extensive training, computer oversight to adapt to signal changes and to recenter the cursor after each target is obtained, and considerable attention of the user. With this NI, users reached their target on 59%–88% of trials. Using ECoG-based SMR modulation, 2D cursor control was in about the same range, but impressively, learning could be achieved within a single session (Schalk et al., 2008). These findings indicate that basic computer operations could be achieved using either invasive or noninvasive indirect NIs.

Our recent work with the BrainGate NI system has shown that persons with tetraplegia can operate computer software with a direct NI based on multineuron spiking from MI (Hochberg et al., 2006). In demonstrations a participant moved a cursor to icons to use simple custom email programs and played video games (videos: www.nature.com/nature/focus/brain/experiments/videopage4.html). The attentional demands for this direct NI system appeared to be low, in that other natural actions, such as head motion or speech, could occur while the cursor was being controlled. Importantly, no learning was required: spike-based control was available immediately after a decoding filter was created. Using simple linear decoders the cursor moved to targets, but wobbled and was difficult to stabilize over an icon. Nevertheless, one participant studied across five sessions successfully reached >73% (up to 95%) of screen targets. It is noteworthy that error did not decline systematically across sessions, suggesting that learning is not being automatically engaged for control improvement. Advances in decoding have now improved computer control considerably so that a person with tetraplegia (from a pontine stroke) can reliably place a cursor under continuous control onto any of eight small targets, stop, and a click with 96%–100% success rate over three sessions (Kim et al., 2007), effectively mimicking computer mouse control. This system still shows within- and between-day control variability that is suboptimal for everyday computer use, but this level of control is potentially useful even in its present form. Overall the levels of successful control of a computer cursor suggest that persons with tetraplegia could operate typical computer software with few modifications to accomplish everyday actions in a natural way.

Assistive Technologies

Pointing or discrete selections can be used to operate a wide range of ATs that could significantly enhance independence, control, and quality of life for persons with tetraplegia. Real or virtual switches on a computer screen can be coupled to any electrical device through readily available technology. In our pilot trial, for example, participants have demonstrated the ability to use commercial interfaces to control lights, fans, and a television by making button selections on a computer-based AT system (Hochberg et al., 2006). Because both FP and spike-based NI systems are capable of switch function, they should be able to operate many ATs. With larger numbers of selections and greater dimensional control, choices could be more numerous and made faster (Figure 4).

Robots

One of the more captivating demonstrations of NI technology has been the demonstration of neural control of various kinds of robots. In any early closed loop spike-based system, rats controlled a lever arm that delivered a water tube (Chapin et al., 1999). One participant in our pilot clinical trial used a simple robot arm to grasp a piece of candy and deliver it to a technician (Hochberg et al., 2006) via a control interface displayed on a screen. In a more recent demonstration of spike-based NI systems, an able-bodied monkey used a robot arm to feed itself (Velliste et al., 2008). In this case, the monkey remapped neural activity formerly related to arm movements to actions of the robotic arm, without a control interface intermediary. These studies demonstrate that direct NIs can be adapted to the complexities of a dynamical, physical system to establish arm-like control that may be useful in operating assistive robots that subserve useful functions.

What Is the Future of NI?

The rapid rise of the NI field in the last decade and the early success of several technologies in humans indicate that NI research will become an established subfield of neuroscience and neuroengineering, potentially creating a wide set of neurotechnologies that will be coupled invasively or noninvasively to the nervous system. These systems hold the great potential to improve the lives of those with limited movement abilities. Early devices with modest capabilities, such as spelling control, are emerging for severely affected persons, but once established, it is my opinion that performance will readily be extended to allow and encompass many activities of daily living now requiring caretakers. A complete indirect NI system, called BCI 2000, is being made generally available for researchers to improve or elaborate this BCI and for persons with paralysis (Vaughan et al., 2006). This effort will accelerate development of indirect NI and availability to a wider user group. The overall rate of advancement and growing interest in NI research suggests that the quality of control will continue to improve for both direct and indirect systems. Two types of invasive systems, ECoG using SMR and direct NIs, appear to be able to provide multidimensional control with many advantages over EEG-based systems. These invasive systems will receive greater emphasis in the next years. Spike-based systems appear to have the advantage of not making substantial attentional demands, requiring no learning (at least for initial use), being under more natural control, and ultimately being more expandable to multiple discrete and continuous control signals. It is likely that these differences will be more closely examined and used to drive more rapid development of the most promising systems. This will lead to a number of human trials of different NI pilot devices. Automation, miniaturization, and the development of a fully implantable, wireless system, which are essential advances, are likely to be achieved in the near term through engineering advances, better decoding and adaptive control strategies, and enhanced understanding of the underlying signals.

Beyond connecting the brain to machines, computers, or other physical devices, restoration of brain-to-muscle function is also a realistic possibility. Neural signals coupled to implanted FES systems could provide motor commands capable of driving paralyzed arm muscles, thus creating a physical nervous system that would restore movement. Although the NI components still require development, stimulation systems to drive muscles already exist and are being used by persons with SCI to gain arm and leg function (Peckham and Knutson, 2005). Recovering complex limb control is an ambitious, longer-term possibility, but even restoring simple actions that allow limited reach and grasp would be a marked advance toward the top priority of those with tetraplegia from SCI (Anderson, 2004). Meeting more basic goals such as an effective communication interface for a person fully locked in provides an important new life choice for these individuals. NI may follow the course of cardiac pacemakers, which went from a primitive device with large, technician-controlled external components to a sophisticated implantable technology incorporating intelligent signal processing within a few decades (Jeffrey, 2001).

Connecting directly to the brain raises ethical issues when one can "eavesdrop" on internal neural processes related to intentions. Because the choice of accepting this technology in research trials is determined by the potential user, after lengthy and carefully considered informed consent, there are not overarching ethical concerns at the current time about these clinical applications. Trial participation requires the use of established regulatory processes with oversight to ensure an informed decision. By contrast, ethical dilemmas could emerge if capabilities include the unlikely ability to read out details of internal thoughts or to augment cognitive abilities (Serruya and Kahana, 2008). These science-fiction-esque possibilities, nevertheless, need to be carefully monitored, with diligent but sensible oversight and guidance from the scientific community as well as regulatory authorities and ongoing discussions with future users.

The full translation of NI technology to users is difficult and costly. Early attempts to move this neurotechnology from laboratory to users has been influenced by the entry of commercial entities, which is the usual route for providing medical devices on a large scale. I have participated in this process through Cyberkinetics Neurotechnology Systems, Inc., an NI technology development company I cofounded (makers of the BrainGate system). Cyberkinetics added substantial funding and commercialization insight to make possible the complex move of NI technology to human pilot clinical trials. This entry raises the dilemma of objective evaluation competing with financial interests. Management of this process requires balanced and rational oversight to attain successful translation to those who need these medical devices, which is not easily achieved. Efforts by academic groups to make the noninvasive BCI system available outside of a commercial scheme has aided both in helping persons and advancing the technology while testing another model for technology transfer that may or may not be viable. The appearance of a commercially or noncommercially available system for persons with paralysis will not mark the end of NI development, nor will it block the creation of competitive systems. As with the development path of cardiac pacemakers, NIs are on a trajectory of ongoing improvements and advancements leading to new ways to restore independence, control, and communication for the broad spectrum of persons with paralysis. The study of neural signals in humans, especially at the spiking and LFP level, complemented by animal models, will also radically expand our understanding of neural processing and its changes in disease. The appearance of the first widely available (and useful) NI system will be an important landmark showing the successful translation of substantial intellectual, temporal, and financial investment in science and engineering into a clinical breakthrough with great significance to humans with movement limitations.

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REFERENCES

Achtman, N., Afshar, A., Santhanam, G., Yu, B.M., Ryu, S.I., and Shenoy, K.V. (2007). Free-paced high-performance brain-computer interfaces. J. Neural Eng. *4*, 336–347.

Andersen, R.A., Musallam, S., and Pesaran, B. (2004). Selecting the signals for a brain-machine interface. Curr. Opin. Neurobiol. *14*, 720–726.

Anderson, K.D. (2004). Targeting recovery: priorities of the spinal cord-injured population. J. Neurotrauma *21*, 1371–1383.

Baker, S.N., Pinches, E.M., and Lemon, R.N. (2003). Synchronization in monkey motor cortex during a precision grip task. II. effect of oscillatory activity on corticospinal output. J. Neurophysiol. *89*, 1941–1953.

Belitski, A., Gretton, A., Magri, C., Murayama, Y., Montemurro, M.A., Logothetis, N.K., and Panzeri, S. (2008). Low-frequency local field potentials and spikes in primary visual cortex convey independent visual information. J. Neurosci. *28*, 5696–5709.

Birbaumer, N. (2006). Breaking the silence: brain-computer interfaces (BCI) for communication and motor control. Psychophysiology *43*, 517–532.

Birbaumer, N., Weber, C., Neuper, C., Buch, E., Haapen, K., and Cohen, L. (2006). Physiological regulation of thinking: brain-computer interface (BCI) research. Prog. Brain Res. *159*, 369–391.

Bullock, T.H. (1997). Signals and signs in the nervous system: the dynamic anatomy of electrical activity is probably information-rich. Proc. Natl. Acad. Sci. USA *94*, 1–6.

Buzsaki, G. (2004). Large-scale recording of neuronal ensembles. Nat. Neurosci. *7*, 446–451.

Carmena, J.M., Lebedev, M.A., Henriquez, C.S., and Nicolelis, M.A. (2005). Stable ensemble performance with single-neuron variability during reaching movements in primates. J. Neurosci. *25*, 10712–10716.

Chapin, J.K., Moxon, K.A., Markowitz, R.S., and Nicolelis, M.A. (1999). Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex. Nat. Neurosci. *2*, 664–670.

Donoghue, J.P. (2002). Connecting cortex to machines: recent advances in brain interfaces. Nat. Neurosci. 5 (*Suppl*), 1085–1088.

Donoghue, J.P., Suner, S., and Sanes, J.N. (1990). Dynamic organization of primary motor cortex output to target muscles in adult rats. II. Rapid reorganization following motor nerve lesions. Exp. Brain Res. *79*, 492–503.

Donoghue, J.P., Sanes, J.N., Hatsopoulos, N.G., and Gaal, G. (1998). Neural discharge and local field potential oscillations in primate motor cortex during voluntary movements. J. Neurophysiol. *79*, 159–173.

Donoghue, J.P., Nurmikko, A., Friehs, G., and Black, M. (2004). Development of neuromotor prostheses for humans. Suppl. Clin. Neurophysiol. *57*, 592–606.

Donoghue, J.P., Nurmikko, A., Black, M., and Hochberg, L.R. (2007). Assistive technology and robotic control using motor cortex ensemble-based neural interface systems in humans with tetraplegia. J. Physiol. *579*, 603–611.

Enzinger, C., Ropele, S., Fazekas, F., Loitfelder, M., Gorani, F., Seifert, T., Reiter, G., Neuper, C., Pfurtscheller, G., and Muller-Putz, G. (2008). Brain motor system function in a patient with complete spinal cord injury following extensive brain-computer interface training. Exp. Brain Res. *190*, 215–223.

Farshchi, S., Mody, I., and Judy, J.W. (2004). A TinyOS-based wireless neural interface. Conf. Proc. IEEE Eng. Med. Biol. Soc. *2004*, 4334–4337.

Georgopoulos, A.P. (1991). Higher order motor control. Annu. Rev. Neurosci. *14*, 361–377.

Helms Tillery, S.I., Taylor, D.M., and Schwartz, A.B. (2003). Training in cortical control of neuroprosthetic devices improves signal extraction from small neuronal ensembles. Rev. Neurosci. *14*, 107–119.

Hochberg, L.R., Serruya, M.D., Friehs, G.M., Mukand, J.A., Saleh, M., Caplan, A.H., Branner, A., Chen, D., Penn, R.D., and Donoghue, J.P. (2006). Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature *442*, 164–171.

Iversen, I.H., Ghanayim, N., Kubler, A., Neumann, N., Birbaumer, N., and Kaiser, J. (2008). A brain-computer interface tool to assess cognitive functions in completely paralyzed patients with amyotrophic lateral sclerosis. Clin Neurophysiol. *119*, 2213–2223.

Jeffrey, K. (2001). Machines in Our Hearts: The Cardiac Pacemaker, the Implantable Defibrillator, and American Health Care (Baltimore: Johns Hopkins University Press).

Kennedy, P.R., and Bakay, R.A. (1998). Restoration of neural output from a paralyzed patient by a direct brain connection. Neuroreport *9*, 1707–1711.

Kennedy, P., Andreasen, D., Ehirim, P., King, B., Kirby, T., Mao, H., and Moore, M. (2004). Using human extra-cortical local field potentials to control a switch. J. Neural Eng. *1*, 72–77.

Kim, S.-P., Simeral, J.D., Hochberg, L.R., Donoghue, J.P., Friehs, G.M., and Black, M.J. (2007). Multistate decoding of point and click control signals from motor cortical activity in a human with tetraplegia. Proceedings of the 3rd International IEEE/EMBS Conference on Neural Engineering, 486–489.

Krusienski, D.J., Sellers, E.W., McFarland, D.J., Vaughan, T.M., and Wolpaw, J.R. (2008). Toward enhanced P300 speller performance. J. Neurosci. Methods *167*, 15–21.

Kubler, A., Nijboer, F., Mellinger, J., Vaughan, T.M., Pawelzik, H., Schalk, G., McFarland, D.J., Birbaumer, N., and Wolpaw, J.R. (2005). Patients with ALS can use sensorimotor rhythms to operate a brain-computer interface. Neurology *64*, 1775–1777.

Maynard, E.M., Hatsopoulos, N.G., Ojakangas, C.L., Acuna, B.D., Sanes, J.N., Normann, R.A., and Donoghue, J.P. (1999). Neuronal interactions improve cortical population coding of movement direction. J. Neurosci. *19*, 8083–8093.

McFarland, D.J., Krusienski, D.J., Sarnacki, W.A., and Wolpaw, J.R. (2008). Emulation of computer mouse control with a noninvasive brain-computer interface. J. Neural Eng. *5*, 101–110.

Murthy, V.N., and Fetz, E.E. (1996). Synchronization of neurons during local field potential oscillations in sensorimotor cortex of awake monkeys. J. Neurophysiol. *76*, 3968–3982.

Nijboer, F., Sellers, E.W., Mellinger, J., Jordan, M.A., Matuz, T., Furdea, A., Halder, S., Mochty, U., Krusienski, D.J., Vaughan, T.M., et al. (2008). A P300-based brain-computer interface for people with amyotrophic lateral sclerosis. Clin. Neurophysiol. *119*, 1909–1916.

Paninski, L., Pillow, J., and Lewi, J. (2007). Statistical models for neural encoding, decoding, and optimal stimulus design. Prog. Brain Res. *165*, 493–507.

Peckham, P.H., and Knutson, J.S. (2005). Functional electrical stimulation for neuromuscular applications. Annu. Rev. Biomed. Eng. *7*, 327–360.

Pesaran, B., Nelson, M.J., and Andersen, R.A. (2006). Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning. Neuron *51*, 125–134.

Sanes, J.N., Suner, S., and Donoghue, J.P. (1990). Dynamic organization of primary motor cortex output to target muscles in adult rats. I. Long-term patterns of reorganization following motor or mixed peripheral nerve lesions. Exp. Brain Res. *79*, 479–491.

Santhanam, G., Ryu, S.I., Yu, B.M., Afshar, A., and Shenoy, K.V. (2006). A high-performance brain-computer interface. Nature *442*, 195–198.

Schalk, G., Miller, K.J., Anderson, N.R., Wilson, J.A., Smyth, M.D., Ojemann, J.G., Moran, D.W., Wolpaw, J.R., and Leuthardt, E.C. (2008). Two-dimensional movement control using electrocorticographic signals in humans. J. Neural Eng. *5*, 75–84.

Scherberger, H., and Andersen, R.A. (2007). Target selection signals for arm reaching in the posterior parietal cortex. J. Neurosci. *27*, 2001–2012.

Schwartz, A.B., Cui, X.T., Weber, D.J., and Moran, D.W. (2006). Brain-controlled interfaces: movement restoration with neural prosthetics. Neuron *52*, 205–220.

Scott, S.H. (2008). Inconvenient truths about neural processing in primary motor cortex. J. Physiol. *586*, 1217–1224.

Serruya, M.D., and Kahana, M.J. (2008). Techniques and devices to restore cognition. Behav. Brain Res. *192*, 149–165.

Serruya, M.D., Hatsopoulos, N.G., Paninski, L., Fellows, M.R., and Donoghue, J.P. (2002). Instant neural control of a movement signal. Nature *416*, 141–142.

Serruya, M., Hatsopoulos, N., Fellows, M., Paninski, L., and Donoghue, J. (2003). Robustness of neuroprosthetic decoding algorithms. Biol. Cybern. *88*, 219–228.

Shain, W., Spataro, L., Dilgen, J., Haverstick, K., Retterer, S., Isaacson, M., Saltzman, M., and Turner, J.N. (2003). Controlling cellular reactive responses around neural prosthetic devices using peripheral and local intervention strategies. IEEE Trans. Neural Syst. Rehabil. Eng. *11*, 186–188.

Song, Y.K., Patterson, W.R., Bull, C.W., Beals, J., Hwang, N., Deangelis, A.P., Lay, C., McKay, J.L., Nurmikko, A.V., Fellows, M.R., et al. (2005). Development of a chipscale integrated microelectrode/microelectronic device for brain implantable neuroengineering applications. IEEE Trans. Neural Syst. Rehabil. Eng. *13*, 220–226.

Song, Y.K., Patterson, W.R., Bull, C.W., Borton, D.A., Li, Y., Nurmikko, A.V., Simeral, J.D., and Donoghue, J.P. (2007). A brain implantable microsystem with hybrid RF/IR telemetry for advanced neuroengineering applications. Conf. Proc. IEEE Eng. Med. Biol. Soc. *2007*, 445–448.

Srinivasan, L., Eden, U.T., Mitter, S.K., and Brown, E.N. (2007). General-purpose filter design for neural prosthetic devices. J. Neurophysiol. *98*, 2456–2475.

Stark, E., Drori, R., and Abeles, M. (2008). Motor cortical activity related to movement kinematics exhibits local spatial organization. Cortex, in press. Published online July 10, 2008. 10.1016/j.cortex.2008.03.011.

Suner, S., Fellows, M.R., Vargas-Irwin, C., Nakata, G.K., and Donoghue, J.P. (2005). Reliability of signals from a chronically implanted, silicon-based electrodearray in non-human primate primary motor cortex. IEEE Trans. Neural. Syst. Rehabil. Eng. *13*, 524–541.

Szarowski, D.H., Andersen, M.D., Retterer, S., Spence, A.J., Isaacson, M., Craighead, H.G., Turner, J.N., and Shain, W. (2003). Brain responses to micro-machined silicon devices. Brain Res. *983*, 23–35.

Taylor, D.M., Tillery, S.I., and Schwartz, A.B. (2002). Direct cortical control of 3D neuroprosthetic devices. Science *296*, 1829–1832.

Truccolo, W., Eden, U.T., Fellows, M.R., Donoghue, J.P., and Brown, E.N. (2005). A point process framework for relating neural spiking activity to spiking history, neural ensemble, and extrinsic covariate effects. J. Neurophysiol. *93*, 1074–1089.

Truccolo, W., Friehs, G.M., Donoghue, J.P., and Hochberg, L.R. (2008). Primary motor cortex tuning to intended movement kinematics in humans with tetraplegia. J. Neurosci. *28*, 1163–1178.

Vaughan, T.M., McFarland, D.J., Schalk, G., Sarnacki, W.A., Krusienski, D.J., Sellers, E.W., and Wolpaw, J.R. (2006). The Wadsworth BCI Research and Development Program: at home with BCI. IEEE Trans. Neural Syst. Rehabil. Eng. *14*, 229–233.

Velliste, M., Perel, S., Spalding, M.C., Whitford, A.S., and Schwartz, A.B. (2008). Cortical control of a prosthetic arm for self-feeding. Nature *453*, 1098–1101.

Wilson, J.A., Felton, E.A., Garell, P.C., Schalk, G., and Williams, J.C. (2006). ECoG factors underlying multimodal control of a brain-computer interface. IEEE Trans. Neural Syst. Rehabil. Eng. *14*, 246–250.

Wolpaw, J.R., Birbaumer, N., McFarland, D.J., Pfurtscheller, G., and Vaughan, T.M. (2002). Brain-computer interfaces for communication and control. Clin. Neurophysiol. *113*, 767–791.

Womelsdorf, T., and Fries, P. (2006). Neuronal coherence during selective attentional processing and sensory-motor integration. J. Physiol. (Paris) *100*, 182–193.

Wu, W., and Hatsopoulos, N.G. (2008). Real-time decoding of nonstationary neural activity in motor cortex. IEEE Trans. Neural Syst. Rehabil. Eng. *16*, 213–222.

Wu, W., Gao, Y., Bienenstock, E., Donoghue, J.P., and Black, M.J. (2006). Bayesian population decoding of motor cortical activity using a Kalman filter. Neural Comput. *18*, 80–118.

Yuen, T.G., Agnew, W.F., and Bullara, L.A. (1987). Tissue response to potential neuroprosthetic materials implanted subdurally. Biomaterials *8*, 138–141.