The Development of Brain-Machine Interface Neuroprosthetic Devices

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Summary: The development of brain-machine interface technology is a logical next step in the overall direction of neuroprosthetics. Many of the required technological advances that will be required for clinical translation of brain-machine interfaces are already under development, including a new generation of recording electrodes, the decoding and interpretation of signals underlying intention and planning, actuators for implementation of mental plans in virtual or real contexts, direct somatosensory feedback to the nervous system to refine actions, and training to encourage plasticity in neural circuits. Although pre-clinical studies in nonhuman primates demonstrate high efficacy in a realistic motor task with motor cortical recordings, there are many challenges in the clinical translation of even simple tasks and devices. Foremost among these challenges is the development of biocompatible electrodes capable of long-term, stable recording of brain activity and implantable amplifiers and signal processors that are sufficiently resistant to noise and artifact to faithfully transmit recorded signals to the external environment. Whether there is a suitable market for such new technology depends on its efficacy in restoring and enhancing neural function, its risks of implantation, and its long-term efficacy and usefulness. Now is a critical time in brain-machine interface development because most ongoing studies are science-based and noncommercial, allowing new approaches to be included in commercial schemes under development. **Key Words:** Brain-machine interface, brain-computer interface, prosthesis, electrode, EEG.

INTRODUCTION

The simple conceptual underpinnings of brain-machine interface (BMI) neuroprosthetic devices hide their underlying complexity. In patients who have a failure of communication between neural structures (or output to the external environment) due to illness, stroke, or injury, BMI neuroprosthetic devices would be expected to functionally replace the biological signal-transmission modality with a technological one.[1–4] For example, a patient with failure of communication between the brain and extremities due to a spinal cord injury might be outfitted with a BMI neuroprosthetic device that reads signals directly from the motor cortex, uses these signals to control the activity of a prosthetic upper extremity, and returns appropriate feedback signals to the sensory cortex to allow for closed-loop control of a robotic arm.[5] As with the natural limb, the ideal BMI neuroprosthetic device would allow the seamless translation of thoughts into actions in a manner completely natural and transparent to the user, because motor control (and motor learning) are innately subconscious events. There are other applications of BMI neuroprosthetic devices. In addition to motor neuroprosthetics, one might imagine devices for communication through speech or electronic mail, or for sensory modalities such as hearing or vision, or potentially for higher-order processes such as learning and memory. Conceptually, any function that the brain or nervous system serves could be implemented if appropriate signals could be harnessed and directed, either within or outside the body.

Neuroprosthetic devices to enhance nervous system function have been conceptualized for some time in the scientific literature, popular culture, and science fiction. Neuroprosthetic enhancement may take the form of functional improvement in a disease state in which residual function is below normal or an abnormal symptom arises, or of functional augmentation of the normal state

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where additional capability is desired. In this regard, electrical interaction with the central and peripheral nervous systems have been developed most extensively using cardiac pacemaker technologies to primarily evoke sensory stimulation.

Since the 1960s, electrical stimulation has been applied to the sensory thalamus, peri-aqueductal gray regions, and dorsal spinal cord for the relief of pain. The current generation of sensory input devices includes cochlear stimulation for hearing restoration, spinal cord stimulation for pain, and visual system stimulation for blindness. The conceptual underpinnings of each device rest on the concept of directly evoking artificial signals within sensory pathways to emulate naturally generated ones. After decades of development, systems such as deep brain stimulators (DBS) for movement disorders (i.e., tremor, Parkinson's disease, and dystonia) are in widespread clinical use because of their simple engineering design and ease of implantation.

The idea of implantable, functioning BMI sensorimotor neuroprosthetic devices has been prominently featured in science fiction. For example, the highly popular 1970s television series, *Six Million Dollar Man*, featured an injured astronaut restored to health with a "bionic" right arm, left eye, and legs that provided superhuman strength, vision, and speed. Such imaginings belie the substantial advances in robotics, materials science, computation/signal processing, and systems neuroscience that are still required to produce a device that is capable of performing even the simplest motor tasks, such as reaching or grasping. What is quite remarkable, however, is that recent advances in each of these areas of research have allowed the development of prototype neuroprosthetic BMI devices for humans and nonhuman primates that are capable of performing simple tasks in the laboratory environment.[6–10] The technological underpinnings of these recent advances and the challenges that lie ahead are the topic of this review.

FUNDAMENTAL COMPONENTS OF BMI NEUROPROSTHETIC DEVICES

To successfully translate thoughts into actions, a BMI motor neuroprosthetic device would be required to incorporate several discrete functions. These include detection of an appropriate "brain intent" signal in some real-time modality, rapid extraction of the signal from the available data (in the face of noise), communication of that signal to some form of internal or external actuator device, and then feedback on the task to determine whether and how precisely the "brain intent" command was actually performed. Each of these steps often emulates rather widespread steps occurring within the human nervous system and encompassing all normal brain function.

Signal detection

The initial stage is signal detection. A sensor measures changes in a physiological variable at a timescale relevant to the task to be performed. The flow of information in the brain may be observed through diverse physiological changes, any of which might be used to drive a BMI neuroprosthetic device. Such changes might include neurotransmitter concentration gradients measured with voltammetric electrodes, blood-flow changes detectable with functional MRI, or magnetic fields produced by ionic current flows. At the present time, technological advances in signal processing are perhaps best at sensing and processing the electrical fields produced as a result of action-potential neuronal discharges. Electrical signals in the brain may be detected at the level of individual units (single-unit recordings), small populations of neurons in a region (multi-unit recordings and local field potentials), or large populations of neurons over several square centimeters of cortex (electrocorticography and electroencephalography). Studies examining each of these signals individually and in combination have been performed, with differing electrode geometries that influence the types of signals recorded. Each type of signal is more or less discrete, and in focusing in on specific neuronal signals, the larger picture of "brain intent" may be inherently lost, or alternatively, if only high-level signals are decoded, then critical specific information may be missing, making it impossible to reconstruct the control signal in sufficient detail.

Information extraction

Once a signal has been detected, it must be interpreted to determine its information content. Depending on the location of the sensor, the time of recording with respect to an action, and the nature of the signal itself, the information contained within the same signaling modality may be highly variable. For example, signals that are recorded in a specific brain region and with respect to a reaching or grasping task may reflect the following: several potential planned movements under consideration by the subject, coordination of the multiple muscle contractions of a single movement, proprioceptive information, or unrelated neural activity constituting background noise. Understanding the identity and nature of signals associated with motor activity is an ongoing area of active research. Likewise, the recorded signals may be related only indirectly to the actual signals, particularly if the specific generator of the needed control signal is damaged and only an associated brain region is suitable for recording. In this scenario, learning at the brain or device level may be required to approximate the desired but unavailable signal and to infer intent.

Neuroprosthetic actuators

Once information related to the task has been extracted from the collected signals, the intended action must be implemented though an actuator. In the case of spinal cord injury, command signals may be used to drive a computer interface,[6,11,12] to move a robotic arm[6,8] or perhaps to externally stimulate the patient's own peripheral nerves or muscles.[13] The degree of sophistication in the actuator critically depends on the nature and rate of information flow. Although low bit rates of information flow may be quite useful in rate-independent communication applications, a much higher rate of information flow is required to produce a functional motor neuroprosthetic with real-time applications. Furthermore, just as natural movements are shaped not only by the motor cortex, but also by additional circuits in the basal ganglia, cerebellum, and spinal cord, neuroprosthetic command signals may require additional interpretation and modulation at the actuator, depending on the granularity of the available signal and the actual device intelligence.

Feedback and adaptation

In any motor control system, errors in measurement, in interpretation, and in execution may be introduced at any stage of the signaling and output process. Hence, for robust and accurate performance, feedback compensation of errors must play an important role in system design. This is particularly true in the injured brain, where the initial signal may necessarily not be the most direct one, and extrapolation may be needed on signal execution to approximate what may be the "real" intended control. As mentioned, there may be some feedback present in the actuator itself, whereby comparisons may be performed between the command signal and the executed action. For example, a prosthetic hand can include a slip detector for local control of grasping to maintain effective grip, but higher level control to signal or trigger release is still needed.

By contrast, in many current implementations of BMI, motor neuroprosthetic devices, feedback, and error correction occur through the subject's observation of a cursor position with respect to a target position. Here the feedback loop is completed by the patient's own visuomotor sensory apparatus. At the unconscious level, the subject may eventually rewire neuronal circuits to improve overall system performance. Between these two implementations, one might consider adaptation and correction based on direct electrical or mechanical stimulation of the nervous system.

SPECIFIC IMPLEMENTATION OF BMI NEUROPROSTHETIC COMPONENTS

Signal detection

Four major types of electrical signals are currently under investigation for use in neuroprosthetic devices: (1) single-unit or multi-neuron recordings, (2) local field potentials (LFPs), (3) electrocorticography (ECoG), and (4) EEG. Each signal modality lies along a spectrum in terms of invasiveness and information content.

Single-unit recordings. The fundamental unit of neural activity is the action potential discharge of individual neurons. To record single-unit activity, a sufficiently small probe must be placed into the brain parenchyma at the location of interest. Because of the larger size of the neuronal cell body, signals from these structures are detected preferentially to those from much narrower individual axons. The flow of current into the neuronal soma or axon with each action potential has a return path through the conductive extracellular fluid. This produces a current dipole that produces an extracellular electrical field potential. The magnitude of the potential depends on the amount of current flow, the conductance of the extracellular space, the distance of the recording electrode to the dipole, and the orientation of the dipole with respect to the electrode. Single-unit recording electrodes (ranging in size from submicron up to 30 to 50 μm) may record potentials of several hundred microvolts from variably sized cortical neurons, and depending on proximity, from multiple neurons simultaneously. To record from multiple neurons in a single region of the brain, recording electrodes are often organized into multi-electrode spatial arrays. When signals from two or more independent neurons contribute to the output of a single recording electrode, these may be differentiated on the basis of the action-potential waveform using signal processing software. Recording bandwidth to allow for clear resolution of action-potential waveforms is in the range of 300 to 5000 Hz. Information in neuronal firing may be encoded in the interpulse interval or the overall rate of firing. To minimize stochastic variation, firing events are typically binned over 20 to 100 ms and are summed together, depending on average action-potential firing frequency. Hence, the effective signal bandwidth is in the range of 10 to 50 Hz for individual neurons.

Electrode arrays may be produced from silicon using microfabrication techniques[14] or assembled from microwires.[15] Microwire assemblies comprise individual 30 to 50 μm diameter tungsten or other metal wires coated with Teflon (DuPont, Wilmington, DE) or polyimide insulation. The wires may be mounted on a circuit board to form a rectangular grid in which the microwires are located 200 to 500 μm apart. The lengths of each wire can be adjusted up to a centimeter or more, depending on the rigidity of the material. In a typical configuration, the circuit boards forming an array are mounted directly to the skull, fixing the wire in position. Using this technology, in some cases, stable recordings have been achieved in nonhuman primates for up to several years after electrode implantation. However, due in part to the free-ranging activity of primate subjects, a slow and typically steady decline in active units is commonly encountered, particularly since these arrays are often attached to the skull rather than the more mobile brain surface, to allow for easier external attachment to recording electronics.

With the evolution of sophisticated micro-fabrication techniques, silicon chip technology offers another attractive approach for electrode array design.[16] Silicon arrays may be configured as shanks, each with a number of recording sites along each shank.[17] To produce such an array, guided boron diffusion into a silicon wafer is performed to define the shape and thickness of the device. After this step, layers of insulating material, conductive interconnects, and additional surface insulation are applied. Recording sites are established by etching the top-most layer of insulation and depositing iridium metal. Finally, the undoped silicon is removed. With this approach, length and shank geometry can be adjusted according to the target tissue, although this is generally limited to a maximum of 1.0 to 1.5 mm in total depth. Because the brain moves relative to the skull, which may account for some of the loss of neuronal activity over time, probes can be designed with a flexible ribbon cable connector, such that they sit on the surface of the brain, moving with each venous pulsation. An alternative configuration is to use similar techniques to produce a three-dimensional 10×10 array of needle microelectrodes on a 4×4 millimeter base.[16] These arrays possess the theoretical advantage that initial signal-processing electronics may be manufactured into the same piece of silicon, possibly allowing for improved signal-to-noise ratio. The disadvantage of the three-dimensional array is that the maximal needle length with current micro-fabrication technology is limited to 2 mm or so, an inadequate distance to reach layer V neurons in many areas of the human cerebral cortex. Recently this technology has been applied to human use, which is discussed as follows.[6] Long-term survival of signals continues to be a challenge. Likewise, with a fixed spacing array, many of the contacts are silent because neurons are not necessarily in proximity, severely limiting the capability for recording a large number of neurons simultaneously.

The greatest challenge facing proponents of the single-unit recording is the longevity of the signals, due to micro-instability at the electrode-brain interface, the inherent fragility of the neurons, cortical pulsations, and irregular spacing of neurons. One strategy that may help to address this challenge is the use of neurotrophic agents to encourage neurons to interface more stably with electrode assemblies.[18–20] In addition, the development of carbon nanotube technologies appear to have potential to help to establish biologically advantageous connections to neurons with improved electrical properties.[21] Other areas of improvement include the incorporation of microfluidics into silicon-based devices. Currently, there are few options for stable, long-term recording arrays that can meet the required biocompatibility standards for materials implanted into the brain (e.g., use of platinum/iridium electrode coatings), severely limiting even highly preliminary testing of these devices for human use.

Local field potentials, EEG, and ECoG. Electrical fields produced by individual neurons sum to produce local field potentials. These LFPs may be measured with the same microelectrodes used to measure single-unit activity. By convention, large-amplitude, high-frequency spike waveforms are electronically filtered out of the LFP signal. In tissues where multiple neurons are firing in concert, recorded LFPs reflect cellular electrophysiological activity occurring approximately 50 to 350 μm from the tip of the electrode, and slower ionic events from 0.5 to 3 mm from the tip of the electrode. Importantly, when neurons fire asynchronously, the electrical fields that they generate may cancel, eliminating the net LFP signal. Hence, the LFP signal indicates the degree of coordinated activity among multiple local neurons in a region of the brain.

Although LFPs sample the activity of groups of neurons within millimeters of the recording electrode in the tissue of interest, ECoG and EEG integrate the activity of neurons acting in concert over much larger areas at the cortical surface and scalp, respectively (i.e., perhaps thousands to millions of neurons). Electrodes on the brain or scalp surface are much further removed from neurons than microelectrodes inserted into brain tissue. As a result, the signals recorded are of far lower amplitude than single-unit recordings, and these display much less specific-time resolution. ECoG and EEG electrodes are typically several millimeters in size, and they sample neurons over several square centimeters of cortex depending on the design. All commercially available ECoG/EEG electrodes were specifically designed for epilepsy monitoring over a large brain surface rather than for focal detection of neuronal activity within a specific gyrus, but grid electrodes for optimal spacing to detect brain activity can be constructed, usually with 1 mm electrodes, spaced 1 to 2 mm apart, in a tight array, suitable for a single gyrus.

LFPs, ECoG, and EEG require progressively larger populations of synchronously active neurons to generate a signal, resulting in several advantages and disadvantages for this modality of recording. As individual neurons are highly stochastic and the loss of individual neurons in a population may be frequent, field potential recordings are likely to be more robust than single-unit recordings. Likewise, since microscopic motion is less important, and since electrodes on the surface of the brain avoid any inherent local brain damage, the neuronal responses of these larger electrodes are more stable over time. In addition, because signals are integrated over larger brain regions, the electrode design for these signals may be less invasive in the case of surface cranial

EEG, and the electronics are simpler due to lowered bandwidth requirements. However, with this increased integration, the spatial resolution of the signals is considerably lower, and likely the information content is also more limited.

Several categories of field-potential signals have proven useful in neuroprosthetic applications. These include sensorimotor rhythms, slow cortical potentials, and P300 evoked potentials. Sensorimotor rhythms between 8 to 12 Hz (μ-rhythm) and 18 to 26 Hz (β-rhythm) are believed to arise from thalamocortical loops, and they are reduced in activity during real and imagined movements. Slow cortical potentials are EEG oscillations at frequencies below 1 Hz. Movement and other forms of cortical activation result in negative slow cortical potentials, whereas reduced activity is associated with positive cortical potentials. P300 evoked potentials are positive deflections in voltage that occur in the parietal cortex some 300 ms after presentation of a significant stimulus. The evoked potential does not occur in response to routine stimuli. Subjects have been able to control these field-potential signals with training. However, with direct cortical surface recording, much higher frequency responses (up to 500 Hz) can be used to infer brain activity, allowing both a faster response time as well as more direct linkage to ongoing neuronal responses.

Information extraction from the signal. The signal detection modality, be it single-unit recordings, LFPs, ECoG, or EEG, is only the medium for information about the task of interest and the brain's actual intent. Pristine signals with low or uninterpretable information content are not useful to a neuroprosthetic application, just as an empty but high-performance delivery vehicle is not useful to a person expecting a shipment. Hence, information content of the signal rather than signal bandwidth (with consideration of errors) is of greatest importance to BMI applications. Each signal form has its proponents, and perhaps the best way to assess their utility lies in an examination of how these devices have performed so far. A common scheme to rate information content (as in Shannon bits/second) has so far eluded the field, because the various type of information extracted and used are highly disparate and difficult to quantify.

Information and devices using single-unit signals. A great deal is known about the information content of single-unit activity in various regions of the brain. As the principal substrate for information content in neural signals, a substantial fraction of studies in systems neuroscience involve the responsive properties of individual neurons during tasks. Single-unit activity has been described in motor planning, reward, face perception, discriminative touch sensation, and a broad range of additional scenarios. In the typical experiment, subjects perform a specific motor or cognitive task, single-unit recordings are made, and correlations between task performance and neural activity are explored.

In some cases, a mathematical relationship may be uncovered between the performance of a task and neural activity. For example, directionality of movement has been related to some motor-cortex neuronal firing rates through a cosine tuning function.[22] In neuroprosthetic applications, the paradigm is typically one of constructing a model based on repeated performances of a specific task so that the response characteristics of individual neurons are defined.[23] Once the model is trained, patterns of neuronal activity are interpreted to match these patterns to specific tasks from the past. In addition to interpreting the natural function of single-units and using them to drive prosthetic devices, an important potential factor for the efficacy of a single-unit based neuroprosthetic device arises from the plasticity of the brain. Subjects have been trained through an operant-conditioning paradigm to control the rate of arbitrary cortical neurons.[24] This feature of plasticity may be potentially used to drive a neuroprosthetic device.[25]

Motor neuroprosthetic devices using single-unit recordings have been demonstrated in both animal and human subjects. In 1999, Chapin et al.[26] reported a neuroprosthetic robotic application that used signals recorded from the motor cortex to enable a rat to obtain a water reward. Multi-neuron signals recorded from the rat cortex were converted into signals for one-dimensional robot arm control. In this paradigm, animals with significant numbers of recorded neurons (e.g., 25 units) were able to use these brain-derived signals to position the robot arm and obtain water. In 2000, Wessberg et al.[27] demonstrated real-time prediction of hand movement with ensembles of cortical neurons in nonhuman primates. Using microwire arrays, a large population of neurons in the pre-motor, primary motor, and posterior parietal cortical areas were recorded as the subjects performed motor tasks. These recordings produced real-time predictions of one- and three-dimensional arm movement trajectories, which then could be used for real-time control of a robotic arm performing similar movements.

In 2002, studies by Serruya et al.[28] and Taylor et al.[7] demonstrated real-time neuroprosthetic device control in primates. In Serruya et al.,[28] primate subjects were able to use motor cortical neuronal outputs recorded with a silicon-based array to move a computer cursor to arbitrary positions in a 14-degree target region in real time. Taylor et al.[7] reported a paradigm in which nonhuman primate subjects moved a cursor from a center-start position to one of eight targets arranged in three-dimensional space. Cell-tuning properties changed when used for brain-controlled movements, allowing fewer neurons to drive task performance. In 2003, Carmena et al.[8] reported neuroprosthetic real-time control of a robotic arm for reaching and grasping in primates. This study demonstrated neuronal plasticity and learning in multiple cortical areas during task performance, as well as indicating that the same population of recorded neurons may be able to control different tasks, such as both reaching and grasping.

Promising developments in work with nonhuman primates have encouraged limited study of BMI neuroprosthetic applications in humans. Kennedy and Bakay[29] pioneered efforts to produce an implanted BMI neuroprosthetic, implanting a patient with "locked-in" syndrome due to amyotrophic lateral sclerosis with a neurotrophic cone electrode.[30] This initial patient was able to control the amount of neural activity recorded from the electrode. A second patient was able to control a computer cursor.[12] In the intraoperative setting, Patil et al.[31] demonstrated that signals obtained from the thalamus and subthalamic nucleus could be used to predict force-task performance from signals recorded in these deep-brain structures. Signals recorded from subcortical targets demonstrated information capable of predicting patient activity during a force-production task with properties similar to those observed in nonhuman primate studies.

Recently, Donoghue, et al.[4] and Hochberg, et al.[6] reported successful implantation of a silicon-based cortical array in a patient with tetraplegia. The patient was implanted with a 96-channel, silicon-based microelectrode array in the motor hand area. During the 6 months after implantation, after which adequate unit recordings were lost, the subject used imagined movements to control the degree of unit activity. This activity could then be harnessed to control a cursor during a center-out task to perform simple computer and appliance control tasks and to drive the control of a simple robotic arm. In these experiments, the information available from the electrode, the stability over time of the information, and the training time were limited, which severely curtailed the tasks that could be controlled.

Information and devices using LFPs, ECoG, and EEG. Field potential signals integrate the activity of regional neurons acting in concert. Synchronous signals, often in the form of oscillatory behavior, may be locally observed (LFPs) at the cortical surface (ECoG) or at the scalp (EEG). The potential to harness these signals noninvasively have made them an attractive source of information for cortical neuroprosthetic devices. Prototype devices have been developed using both ECoG and EEG, but as add-on research during invasive epilepsy studies in general, rather than using dedicated high-density grid electrodes appropriate to signal recording.[32,33] Although single-unit-based neuroprosthetic devices typically use models to interpret the function of neurons and then drive models to perform similar tasks, field-potential based recordings are based on subject conditioned control of field-potential signals.

Slow cortical potentials are also subject to operant control in subjects with intact function of motor and pre-motor cortical and subcortical structures. By controlling slow cortical potentials after letters or words were spoken or presented by a computer, Birbaumer et al.[34] developed a spelling device for the paralyzed. Patients were able to produce from 0.15 to 3 letters per minute using this device. Sensorimotor rhythms over a region of cortex are reduced when a subject imagines movement of a limb corresponding to that region, which may increase when movement of a different limb is imagined.[35] Sensorimotor mu and beta rhythms have been used to control the movement of a cursor on a screen to one of eight random locations within 10 seconds.[9] A similar paradigm has been used to allow control of reaching and grasping in high spinal cord-lesioned patients.[36–38] In general, the information content from these devices is limited to a few choices per minute, but cursor control on a computer screen can be achieved.

Feedback and adaptation

To achieve widespread application, neuroprosthetic devices must achieve goals of both speed and accuracy. Error correction must be automatic or require minimal user effort. As in natural activities, a neuroprosthetic device use should approach an unconscious level with use, functioning as an additional appendage or inherent attachment. These two processes of feedback and intelligent adaptation, acting in concert, are likely to play important roles in the next stages of neuroprosthetic development.

Feedback paradigms in neuroprosthetics. At present, visuomotor feedback is the predominant form of feedback control available to users of current neuroprosthetic designs. For example, in a field-potential based application for communication, subjects select letters through a series of binary decisions, choosing among groups of letters displayed on a screen, until a letter is chosen after five decision steps and two correction/confirmation steps.[39] In single-unit based motor neuroprosthetic applications, human and primate subjects receive visual indications of the accuracy of their movements in real time.[6–8]

However, in the natural state, a wide range of feedback modalities are used to increase the accuracy of a desired movement. In the central movement circuits of the brain, command signals present in motor cortex are modulated by diverse inputs from the nonpyramidal portions of the motor system, such as the basal ganglia and cerebellum, as well as proprioceptive inputs routed through the thalamus. It has been noted that the characteristic movements induced in single-unit neuroprosthetic applications based on signals detected in the motor cortex are reminiscent of patients who have neurological deficits in nonpyramidal motor subsystems.[40] Natural movements also benefit from feedback processes in spinal reflex regulatory arcs and in proprioceptive feedback through sensory pathways.

Current paradigms to provide nonvisuomotor feedback to neuroprosthetic devices is limited both scientifically and technologically. Although associations between cortical motor activity and proprioceptive sensory modalities have been described,[41] the ability to introduce sensory information directly to the cortex (or thalamus) is limited. In humans, sensory and motor signals have been carefully studied in both sensory and motor thalamus during neurosurgical procedures for movement disorders and pain. However, stimulation has resulted in only poorly formed sensory percepts, although sensations could be evoked from nonfunctioning amputated limbs.[42] However, even an artificial sensory precept can be graded, resulting in, for example, a graded description of gripping force.

Formation of a clear precept may not be required for neuroprosthetic applications. As an example, patients with profound hearing loss may receive a cochlear implant device in which auditory neurons are directly stimulated. Although the generated sensations are far from normal hearing, patients are often able to retrain their minds to the point that they experience the sensory stimuli as a form of hearing. Along these lines, cortical microstimulation delivered to primary somatosensory cortex though chronically-implanted microelectrode arrays has been used to direct nonhuman primate task selection, suggesting that multi-electrode microstimulating electrodes may provide a potential mechanism to introduce a neuroprosthetic sensory feedback path.[43] Likewise, thalamic microstimulation may successfully emulate multiple aspects of movement and pressure, if provided in an appropriate spatial and temporal sequence.

Neural adaptation to neuroprosthetic devices. In addition to feedback mechanisms of error-correction, adaptation of the neural circuitry to the device, or built-in adaptation of the circuitry as a form of learning, are likely to be critical features allowing neuroprosthetic devices to achieve a degree of use similar to the natural limb. At the conscious level, primates can seemingly arbitrarily convert their neural activity into task performance. Several lines of evidence suggest that the activity of individual neurons is likely to be quite plastic. In what are now considered classic studies, Fetz and colleagues[44] demonstrated that arbitrarily selected neurons are subject to rate control during an operant conditioning paradigm. In primate studies, training of individual neurons to a specific task have been observed.[8] Finally, in a human application of a prototype BMI neuroprosthetic device, the subject was able to control devices in different scenarios with conscious control, suggesting rapid plasticity in the function of the individual units.[6] With the addition of feedback mechanisms, the robust quality of the device is likely to be improved.

In many instances the cortical area available for electrode implantation may not be ideal for the function of interest, particularly if there has been damage to the primary cortical region (as in the case of speech deficits or weakness after a cortical stroke). Thus, the task required may be relatively novel for the implanted region of cortex and significant learning and neural adaptation may be required to perform the task at all with signals recorded from that region. In this instance there may no electrophysiological data available to train a model relating cortical activity to task performance, as is commonly used in preclinical experiments. The correlation between the intention and the cortical activity will be initially undefined, complicating the training process considerably. Alternative methods of training would be required to initiate the task, and then with appropriate feedback and adaptation the hope would be that cortical plasticity would mould the commands for the desired task from the available (less than appropriate) signals available from the implanted, secondary brain regions.[45]

CHALLENGES FOR DEVELOPMENT OF CLINICAL BMI DEVICES

Particularly for motor neuroprosthetic systems, preclinical studies to control a robotic arm from motor cortical multi-electrode arrays show considerable feasibility. Multiple laboratories have demonstrated complex control paradigms in four dimensions (i.e., three planar dimensions and time) of a directly visualized prosthetic arm in suitably trained nonhuman primates.[1,7,27,28,46–49] However, considerable obstacles remain to be overcome prior to clinical implementation of such a system. Extension to more comprehensive human functional restoration or enhancement, particularly in communication and speech, represents considerable further challenges.

Signal detection

Apart from a single commercially available silicon-based microelectrode array (produced by Cyberkinetics Neurotechnology Systems, Inc., Foxborough, MA), no other recording electrode has Food and Drug Administration (FDA) approval for clinical trials for a BMI device.[6,16] Although platinum/iridium (Pt/Ir) microwires have been used short-term in humans successfully,[31] there is no version available or under consideration for long-term or permanent implantation. Most of the recording devices used in the nonhuman primate experiments have not been designed for human use, particularly in terms of the use of biocompatible materials (such as Pt/Ir rather than tungsten or steel), and in terms of construction suitable for long-term stability in a biological environment. Other multi-electrode recording arrays in development for possible human use include a Pt/Ir floating microelectrode array mounted on a ceramic substrate and a ceramic multi-contact electrode (produced by MicroProbe, Inc., Gaithersburg, MD).[50]

Other potential options include long-term ECoG electrodes. These are usually Pt/Ir strips designed to be placed on the surface of the brain for short-term diagnostic use. Exceptions include an ECoG electrode used as the sensing element for a seizure-control device (currently in FDA-approval trials by NeuroPace, Inc., Mountain View, CA), and the off-label use of spinal epidural stimulating electrodes (from Medtronics, Inc., Minneapolis, MN, or Advanced Neuromodulation Systems, Inc., Plano, TX). Although the use of these electrodes appears promising for eventual use in a BMI device, no devoted clinical trials have been performed yet to assess their real utility.[32,33] Hence, apart from the development of a new electrode and performance of all required studies for FDA approval, a process which often takes years, few available recording devices are currently available for initial BMI clinical trials. Whether BMI neuroprosthetic systems will remain a commercially attractive product for corporations and venture capital funds to support additional development and FDA approval remains to be seen.

Another missing element are multichannel amplifiers, both suitable for implantation and sufficiently sensitive for detection of either neuronal or ECoG signals. Such signals are usually heavily contaminated by artifacts, environmental noise, and muscle activation on the scalp. On the order of 100 channels of output are needed to support a functional multi-electrode array, providing a sobering constraint given the number of channels that are required to achieve a reliable functional restoration or enhancement. Because it is not currently possible to directly export 100 or more channels of a real-time analog signal across the scalp with any wireless or optical mode, some inherent data compression must be performed locally in the amplifiers/processing system. The technical challenge will be to reduce the data to a bandwidth, which is feasible for transmission that still retains useful information content. All current neuroprosthetic systems, such as deep brain stimulation and cochlear stimulation, rely upon implanted information processing circuitry. Apart from the EEG amplifiers (built into the Neuropace, Inc. system), no implanted amplifiers are currently available. Alternatively, it may be possible to develop a full bandwidth electrical socket connection for long-term use across the scalp, using sintered titanium waterproof connectors (as has been developed for one cochlear stimulation module), but wireless connections remain the most popular design goal for implantable electrical systems. Multiple questions remain, including how many channels will be required, how to mate the circuitry to the recording device for long-term stability, the type of adaptive processing needed in implanted computational devices, and how to export the signal to an external receiver for subsequent use.

Information extraction

Information content (in terms of suitable instructions to control the actuators) depends strongly on the type of brain signal gathered by the signal detection devices, the bandwidth, frequency and multiplicity of the devices, and the level of inherent noise and artifact. At the present time, although single-unit based devices offer theoretical advantages in terms of rates of information flow bandwidth, field-based systems have not yet been significantly outperformed by these devices in humans. In many instances, the suitability of the electrophysiological data from the brain may be less than optimal, particularly if the device must be located outside of the primary functional cortical or subcortical region of interest (such as in the case of stroke). In this scenario, training and adaptation may be critical for even rudimentary functional performance. In addition, the need for reliability requires that the accuracy of extracted information be confirmed. However, assessing the accuracy of a prediction of intended action from extracted information is nontrivial, because an independent measure of intention is not available.

Once these initial theoretical questions are addressed, then the physical design of the information processing hardware becomes a critical subsequent step. Information processing may occur within an implanted amplifier with signal processing hardware or as an external device. Information processing within the implanted hardware allows for data compression and lowered transmission bandwidth. However, then the processing algorithms may be more difficult to modify. External systems require a much richer information stream for processing, with accompanying increased bandwidth requirements. Furthermore, for clinical systems, FDA regulations typically require that all software, whether implanted or external, be fixed for clinical trial use. Hence, choosing the specific information extraction paradigm is a key design question for all BMI devices.

Developing an appropriate training paradigm also forms a critical challenge for information extraction. The ideal training paradigm for optimal ongoing use of a clinical BMI neuroprosthetic device will likely be very different from that optimized for nonhuman primate training. If the subject is naïve to the task, as is the case for clinical application, then different training approaches may be needed just to get the patient started. Communication tasks may also require a very different training paradigm, although some EEG-based studies have provided guidance for possible implanted BMI systems.[40,51–53] Sufficient training will be required to allow the subject to subconsciously operate the BMI device as with a natural appendage, or the device may prove too clumsy for effective use.

Neuroprosthetic actuators

Information driving the execution of an intentional action depends on the design of the actuator itself. For example, although multiple robotic arms exist, with varying similarity to the natural limb, each requires a different command stream to perform a given action. Less challenging may be a virtual output on a computer, such as one driving a voice synthesizer or software for composing electronic mail. Such devices have been extensively developed for communication and motor enhancement. Therefore, the greatest challenge is the design of a control channel from the brain to the device, with sufficiently wide informational bandwidth to allow for useful function of the neuroprosthetic device.

Feedback and adaptation

Up to the present time, the primary form of feedback available for BMI neuroprosthetic devices has been visual. However, visual feedback fails to reliably guide tasks in many real-world instances. For example, an opaque glass or cup could be empty or full, but visual recognition would not reveal the current state. This would complicate the task of holding the glass or cup without a sensor to detect the weight appropriately and sufficiently for grip. For example, many robotic systems have force sensors in grippers, which could communicate force or pressure for either local control (to increase pressure to prevent slippage) or long-loop brain control. Thus, some form of somatosensory feedback is important, but how to provide this information to the brain as a relevant, easily understood clue remains controversial. One possibility is a haptic (touch) interface, where skin pressure or vibration frequency can be used to transmit information. Nerves normally controlling arm sensation have been rerouted to the chest or neck, where direct pressure on the re-innervated skin can topographically signal the brain for pressure in a robotic arm. Based on the high tolerance of implanted DBS systems, a thalamic sensory electrode (or microstimulation array) could be used in the sensory thalamus to provide a graded and spatially accurate sensation appropriate to the arm region, for example, to clue the brain as to the position of or pressure on an upper-extremity prosthesis.[42,54] Thus, there are many levels possible to insert feedback sensory signals into the brain relevant to the actuator and functional goal, including the skin, peripheral nerves, or the brain itself. The relative usefulness of each of these various approaches will need to be tested.

In addition to relying upon sensory feedback to refine and tune neuroprosthetic command signals, adaptation might be implemented in the actuator itself, in decoding and detection software, or left to plasticity and adaptive learning in the brain itself. For example, in the case of a motor actuator, an intermediate goal may be satisfied by intrinsic intelligence within a prosthetic arm (to prevent slippage), but the long-term goal of letting go of a cup or glass will likely require a direct command from the brain itself. All of this adaptation will need to be fixed in hardware and/or software for clinical implementation in a trial format. Hence, considerable preliminary testing will be required to choose between available approaches.

CONCLUSIONS

BMI neuroprosthetic technology is likely to change considerably during its evolution from preclinical to clinical studies. The eventual goal is to develop a BMI neuroprosthetic device that will allow the seamless translation of thoughts into actions in a manner completely natural and transparent to the user. Over the past 40 years, BMI development has moved from the realm of science fiction to rudimentary, yet promising devices in the clinical setting. However, many prerequisites for further development remain unsatisfied, posing considerable challenges. These include an understanding of the neural codes underlying intention and action, the development of a biocompatible electrode with the ability to deliver long lasting, low-noise signals from relevant regions of brain, and the development of operative techniques to implant a device in a human reliably and safely, to mention a few. However, perhaps the largest unanswered question relates to commercial attractiveness and marketability. The research and development costs of a functional BMI neuroprosthetic are enormous. Only time will tell whether there is sufficient commercial interest to successfully overcome the multifactorial challenges in the path of clinical BMI development.

REFERENCES

1. Schwartz AB, Cui XT, Weber DJ, Moran DW. Brain-controlled interfaces: movement restoration with neural prosthetics. Neuron 2006;52:205–220.
2. Leuthardt EC, Schalk G, Moran D, Ojemann JG. The emerging world of motor neuroprosthetics: a neurosurgical perspective. Neurosurgery 2006;59:1–14; discussion 11–14.
3. Lebedev MA, Nicolelis MA. Brain-machine interfaces: past, present and future. Trends Neurosci 2006;29:536–546.
4. Donoghue JP, Nurmikko A, Black M, Hochberg LR. Assistive technology and robotic control using motor cortex ensemble-based neural interface systems in humans with tetraplegia. J Physiol 2007;579:603–611.
5. Nicolelis MA. Actions from thoughts. Nature 2001;409:403–407.
6. Hochberg LR, Serruya MD, Friehs GM, et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature 2006;442:164–171.
7. Taylor DM, Tillery SI, Schwartz AB. Direct cortical control of 3D neuroprosthetic devices. Science 2002;296:1829–1832.
8. Carmena JM, Lebedev MA, Crist RE, et al. Learning to control a brain-machine interface for reaching and grasping by primates. Plos Biology 2003;1:193–208.
9. Wolpaw JR, McFarland DJ. Control of a two-dimensional movement signal by a noninvasive brain-computer interface in humans. Proceedings of the National Academy of Sciences of the United States of America 2004;101:17849–17854.

10. Birbaumer N, Kubler A, Ghanayim N, et al. The thought translation device (TTD) for completely paralyzed patients. IEEE Trans Rehab Eng 2000;8:190–193.
11. Birbaumer N, Hinterberger T, Kubler A, Neumann N. The thought-translation device (TTD): neurobehavioral mechanisms and clinical outcome. IEEE Trans Neural Syst Rehabil Eng 2003;11:120–123.
12. Kennedy PR, Bakay RA, Moore MM, Adams K, Goldwaithe J. Direct control of a computer from the human central nervous system. IEEE Trans Rehabil Eng 2000;8:198–202.
13. Peckham PH, Keith MW, Kilgore KL, et al. Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: a multicenter study. Arch Phys Med Rehabil 2001;82:1380–1388.
14. Kipke DR. Implantable neural probe systems for cortical neuroprostheses. Conf Proc IEEE Eng Med Biol Soc 2004;7:5344–5347.
15. Kralik JD, Dimitrov DF, Krupa DJ, Katz DB, Cohen D, Nicolelis MA. Techniques for long-term multisite neuronal ensemble recordings in behaving animals. Methods 2001;25:121–150.
16. Rousche PJ, Normann RA. Chronic recording capability of the Utah intracortical electrode array in cat sensory cortex. J Neurosci Methods 1998;82:1–15.
17. Vetter RJ, Williams JC, Hetke JF, Nunamaker EA, Kipke DR. Chronic neural recording using silicon-substrate microelectrode arrays implanted in cerebral cortex. IEEE Trans Biomed Eng 2004;51:896–904.
18. Kennedy PR, Kirby MT, Moore MM, King B, Mallory A. Computer control using human intracortical local field potentials. IEEE Trans Neural Syst Rehab Eng 2004;12:339–344.
19. Kennedy PR, Bakay RAE, Moore MM, Adams K, Goldwaithe J. Direct control of a computer from the human central nervous system. IEEE Trans Rehab Eng 2000;8:198–202.
20. Kennedy PR, Bakay RAE. Restoration of neural output from a paralyzed patient by a direct brain connection. Neuroreport 1998;9:1707–1711.
21. Nguyen-Vu TDB, Chen H, Cassell AM, Andrews RJ, Meyyappan M, Li J. Vertically aligned carbon nanofiber architecture as a multifunctional 3-D neural electrical interface. IEEE Trans Biomed Eng 2007;54:1121–1128.
22. Georgopoulos AP, Kettner RE, Schwartz AB. Primate motor cortex and free arm movements to visual targets in three-dimensional space. II. Coding of the direction of movement by a neuronal population. J Neurosci 1988;8:2928–2937.
23. Sanchez JC, Principe JC, Carmena JM, Lebedev MA, Nicolelis MA. Simultaneus prediction of four kinematic variables for a brain-machine interface using a single recurrent neural network. Conf Proc IEEE Eng Med Biol Soc 2004;7:5321–5324.
24. Fetz EE, Finocchio DV. Operant conditioning of specific patterns of neural and muscular activity. Science 1971;174:431–435.
25. Fetz EE. Real-time control of a robotic arm by neuronal ensembles. Nat Neurosci 1999;2:583–584.
26. Chapin JK, Moxon KA, Markowitz RS, Nicolelis MAL. Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex. Nat Neurosci 1999;2:664–670.
27. Wessberg J, Stambaugh CR, Kralik JD, et al. Real-time prediction of hand trajectory by ensembles of cortical neurons in primates. Nature 2000;408:361–365.
28. Serruya MD, Hatsopoulos NG, Paninski L, Fellows MR, Donoghue JP. Instant neural control of a movement signal. Nature 2002;416:141–142.
29. Kennedy PR, Bakay RA. Restoration of neural output from a paralyzed patient by a direct brain connection. Neuroreport 1998;9:1707–1711.
30. Kennedy PR. The cone electrode—a long-term electrode that records from neurites grown onto its recording surface. J Neurosci Methods 1989;29:181–193.
31. Patil PG, Carmena JM, Nicolelis MA, Turner DA. Ensemble recordings of human subcortical neurons as a source of motor control signals for a brain-machine interface. Neurosurgery 2004;55:27–35; discussion 35–28.
32. Leuthardt EC, Miller KJ, Schalk G, Rao RP, Ojemann JG. Electrocorticography-based brain computer interface--the Seattle experience. IEEE Trans Neural Syst Rehabil Eng 2006;14:194–198.
33. Leuthardt EC, Schalk G, Wolpaw JR, Ojemann JG, Moran DW. A brain-computer interface using electrocorticographic signals in humans. J Neural Eng 2004;1:63–71.
34. Birbaumer N, Ghanayim N, Hinterberger T, et al. A spelling device for the paralysed. Nature 1999;398:297–298.
35. Pfurtscheller G, Neuper C. Motor imagery activates primary sensorimotor area in humans. Neurosci Lett 1997;239:65–68.
36. Pfurtscheller G, Guger C, Muller G, Krausz G, Neuper C. Brain oscillations control hand orthosis in a tetraplegic. Neurosci Lett 2000;292:211–214.
37. Pfurtscheller G, Muller GR, Pfurtscheller J, Gerner HJ, Rupp R. "Thought"—control of functional electrical stimulation to restore hand grasp in a patient with tetraplegia. Neurosci Lett 2003;351:33–36.
38. Muller-Putz GR, Scherer R, Pfurtscheller G, Rupp R. EEG-based neuroprosthesis control: a step towards clinical practice. Neurosci Lett 2005;382:169–174.
39. Obermaier B, Muller GR, Pfurtscheller G. "Virtual keyboard" controlled by spontaneous EEG activity. IEEE Trans Neural Syst Rehabil Eng 2003;11:422–426.
40. Wolpaw JR. Brain-computer interfaces as new brain output pathways. J Physiol 2007;579:613–619.
41. Buneo CA, Andersen RA. The posterior parietal cortex: sensorimotor interface for the planning and online control of visually guided movements. Neuropsychologia 2006;44:2594–2606.
42. Davis KD, Kiss ZH, Luo L, Tasker RR, Lozano AM, Dostrovsky JO. Phantom sensations generated by thalamic microstimulation. Nature 1998;391:385–387.
43. Fitzsimmons NA, Drake W, Hanson TL, Lebedev MA, Nicolelis MA. Primate reaching cued by multichannel spatiotemporal cortical microstimulation. J Neurosci 2007;27:5593–5602.
44. Fetz EE. Operant conditioning of cortical unit activity. Science 1969;163:955–958.
45. Gage GJ, Ludwig KA, Otto KJ, et al. Naive coadaptive cortical control. J Neural Eng 2005;2:52–63.
46. Lebedev MA, Carmena JM, O'Doherty JE, et al. Cortical ensemble adaptation to represent velocity of an artificial actuator controlled by a brain-machine interface. J Neurosci 2005;25:4681–4693.
47. Andersen RA, Musallam S, Pesaran B. Selecting the signals for a brain-machine interface. Curr Opin Neurobiol 2004;14:720–726.
48. Donoghue JP, Hochberg LR, Nurmikko AV, Black MJ, Simeral JD, Friehs G. Neuromotor prosthesis development. Med Health R I 2007;90:12–15.
49. Laubach M, Wessberg J, Nicolelis MA. Cortical ensemble activity increasingly predicts behaviour outcomes during learning of a motor task. Nature 2000;405:567–571.
50. Moxon KA, Leiser SC, Gerhardt GA, et al. Ceramic-based multisite electrode arrays for chronic single-neuron recording. IEEE Trans Biomed Eng 2004;51:647–656.
51. Birbaumer N. Breaking the silence: Brain-computer interfaces (BCI) for communication and motor control. Psychophysiology 2006;43:517–532.
52. Birbaumer N, Cohen LG. Brain-computer interfaces: communication and restoration of movement in paralysis. J Physiol 2007;579:621–636.
53. Birbaumer N, Weber C, Neuper C, Buch E, Haapen K, Cohen L. Physiological regulation of thinking: brain-computer interface (BCI) research. Prog Brain Res 2006;159:369–391.
54. Kiss ZH, Davis KD, Tasker RR, Lozano AM, Hu B, Dostrovsky JO. Kinaesthetic neurons in thalamus of humans with and without tremor. Exp Brain Res 2003;150:85–94.