these differences aside, we focus below on how BMIs function and perform. We also highlight recent pilot clinical trials with people with paralysis.

### Subjects Can Type Messages Using Communication BMIs

To investigate how quickly and accurately a communication BMI employing a discrete decoder and preparation activity can operate, monkeys were trained to fixate and touch central targets and prepare to reach to a peripheral target that could appear at one of several different locations on a computer screen. Spikes were recorded using electrodes implanted in the premotor cortex. The number of spikes occurring during a particular time window during the preparation epoch was used to predict where the monkey was preparing to reach (Figure 39–7A). If the decoded target matched the peripheral target, a liquid reward was provided to indicate a successful trial.

By varying the duration of the period in which spike counts are taken and the number of possible targets, it was possible to assess the speed and accuracy of target selections (Figure 39–7B). Decoding accuracy tended to increase with the period in which spike counts are taken because spiking noise is more easily averaged out in longer periods.

An important metric for efficient communication is information transfer rate (ITR), which measures how much information can be conveyed per unit time. A basic unit of information is a bit, which is specified by a binary value (0 or 1). For example, with three bits of information, one can specify which of $2^3 = 8$ possible targets or keys to press. Thus, the metric for ITR is bits per second (bps). ITR increases with the period in which spike counts are taken, then declines. The reason is that ITR takes into account both how accurately and how quickly each target is selected. Beyond some point of diminishing returns of a longer period, accuracy fails to increase rapidly enough to overcome the slowdown in target-selection rate accompanying a longer period.

Overall performance (ITR) increases with the number of possible targets, despite a decrease in decoding accuracy, because each correct target selection conveys more information. Fast and accurate communication

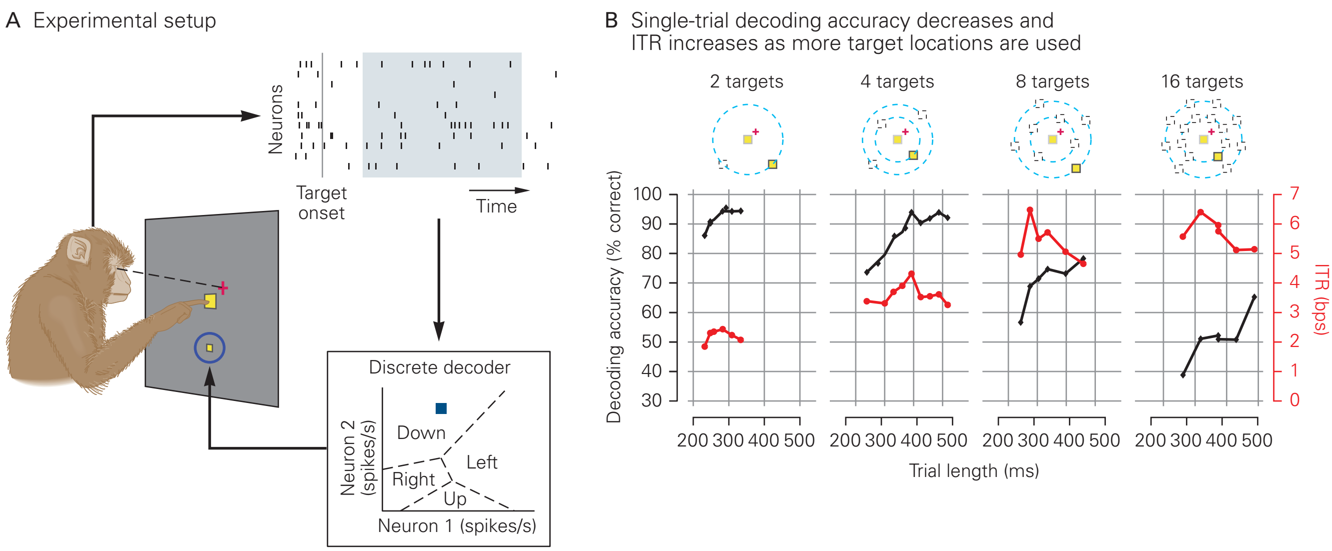


**Figure 39–7** A communication brain–machine interface can control a computer cursor using a discrete decoder based on neural activity during the preparation epoch.

**A.** After a monkey touched a central target (**large yellow square**) and fixated a central point (**red +**), a peripheral target (**small yellow square**) appeared and the monkey prepared to reach to it. Spike counts were taken during the preparation epoch and fed into a discrete decoder. The duration of the period in which spike counts are taken (ie, width of **light blue** shading) affects decoding performance and information transfer rate (**ITR**) (see panel **B**). Based on the spike counts (**blue square**), the discrete decoder guessed the target the monkey was preparing to reach to.

**B.** Decoding accuracy (**black**) and information transfer rate (**ITR, bits/s; red**) are shown for different trial lengths and numbers of targets. Trial length was equal to the duration of the period in which spike counts were taken (varied during the experiment) plus 190 ms (fixed during the experiment). The latter provided time for visual information of the peripheral target to reach the premotor cortex (150 ms), plus the time to decode the target location from neural activity and render the decoded target location on the screen (40 ms). (Adapted, with permission, from Santhanam et al. 2006.)

has been demonstrated in BMIs with this design based on a discrete decoder applied to preparatory activity. The ITR of this BMI is approximately 6.5 bps, which corresponds to approximately two to three targets per second with greater than 90% accuracy.

Recent studies have also investigated how quickly and accurately a communication BMI employing a continuous decoder and execution activity can operate. Two different types of continuous decoders were evaluated: a standard Kalman filter decoding movement velocity (V-KF) and a recalibrated feedback intention-trained Kalman filter (ReFIT-KF). The V-KF was calibrated using the neural activity recorded during actual arm movements (ie, open-loop control). The ReFIT-KF incorporated the closed-loop nature of BMIs into decoder calibration by assuming that the user desired to move the cursor straight to the target at each time step.

To assess performance, both types of decoders were used in closed-loop BMI control (Figure 39–8A). Monkeys were required to move a computer cursor from a central location to eight peripheral locations and back. A gold standard for performance evaluation was established by having the monkeys also perform the same task using arm movements. The ReFIT-KF outperformed the V-KF in several ways: Cursor movements using ReFIT-KF were straighter, producing less movement away from a straight line to the target; cursor movements were faster, approaching the speed of arm movements (Figure 39–8B); and there were fewer (potentially frustrating) long trials.

Given its performance benefits, the ReFIT-KF is being used in clinical trials by people with paralysis (Figure 39–8C). Spiking activity was recorded using a 96-channel electrode array implanted in the hand control area of the left motor cortex. Signals were filtered to extract action potentials and high-frequency local field potentials, which were decoded to provide "point-and-click" control of the BMI-controlled cursor. The subject was seated in front of a computer monitor and was asked, "How did you encourage your sons to practice music?" By attempting to move her right hand, the computer cursor moved across the screen and stopped over the desired letter. By attempting to squeeze her left hand, the letter beneath the cursor was selected, much like clicking a mouse button.

BMI performance in the clinical trials was assessed by measuring the number of intended characters subjects were able to type (Figure 39–8D). Subjects were able to demonstrate that the letters they typed were intended by using the delete key to erase occasional mistakes. These clinical tests showed that it is possible to type at a rate of many words per minute using a BMI.

### Subjects Can Reach and Grasp Objects Using BMI-Directed Prosthetic Arms

Patients with paralysis would like to pick up objects, feed themselves, and generally interact physically with the world. Motor BMIs with prosthetic limbs aim to restore this lost motor functionality. As before, neural activity is decoded from the brain but is now routed to a robotic arm where the wrist is moved in three dimensions (x, y, and z) and the hand is moved in an additional dimension (grip angle, ranging from an open hand to a closed hand).

In one test of a robotic arm, a patient with paralysis was able to use her neural activity to direct the robotic arm to reach out, grab a bottle of liquid, and bring it to her mouth (Figure 39–9). The three-dimensional reaches and gripping were slower and less accurate than natural arm and hand movements. Importantly, this demonstrated that the same BMI paradigm originally developed with animals, including measuring and decoding signals from motor cortex, works in people even years after the onset of neural degeneration or the time of neural injury.

BMI devices directing prosthetic arms and hands are now able to do more than just control three-dimensional movement or open and close the hand. They can also orient the hand and grasp, manipulate, and carry objects. A person with paralysis was able to move a prosthetic limb with 10 degrees of freedom to grasp objects of different shapes and sizes and move them from one place to another (Figure 39–10). Completion times for grasping and moving objects were considerably slower than natural arm movements, but the results are encouraging. These studies illustrate the existing capabilities of prosthetic arms and also the potential for even greater capabilities in the future.

### Subjects Can Reach and Grasp Objects Using BMI-Directed Stimulation of Paralyzed Arms

An alternative to using a robotic arm is to restore lost motor function to the biological arm. Arm paralysis results from the loss of neural signaling from the spinal cord and brain, but the muscles themselves are often still intact and can be made to contract by electrical stimulation. This capacity underlies functional electrical stimulation (FES), which sends electrical signals via internal or external electrodes to a set of muscle groups. By shaping and timing the electrical signals sent to the different muscle groups, FES is able to move the arm and hand in a coordinated fashion to pick up objects.

Laboratory studies in monkeys have demonstrated that this basic approach is viable in principle.

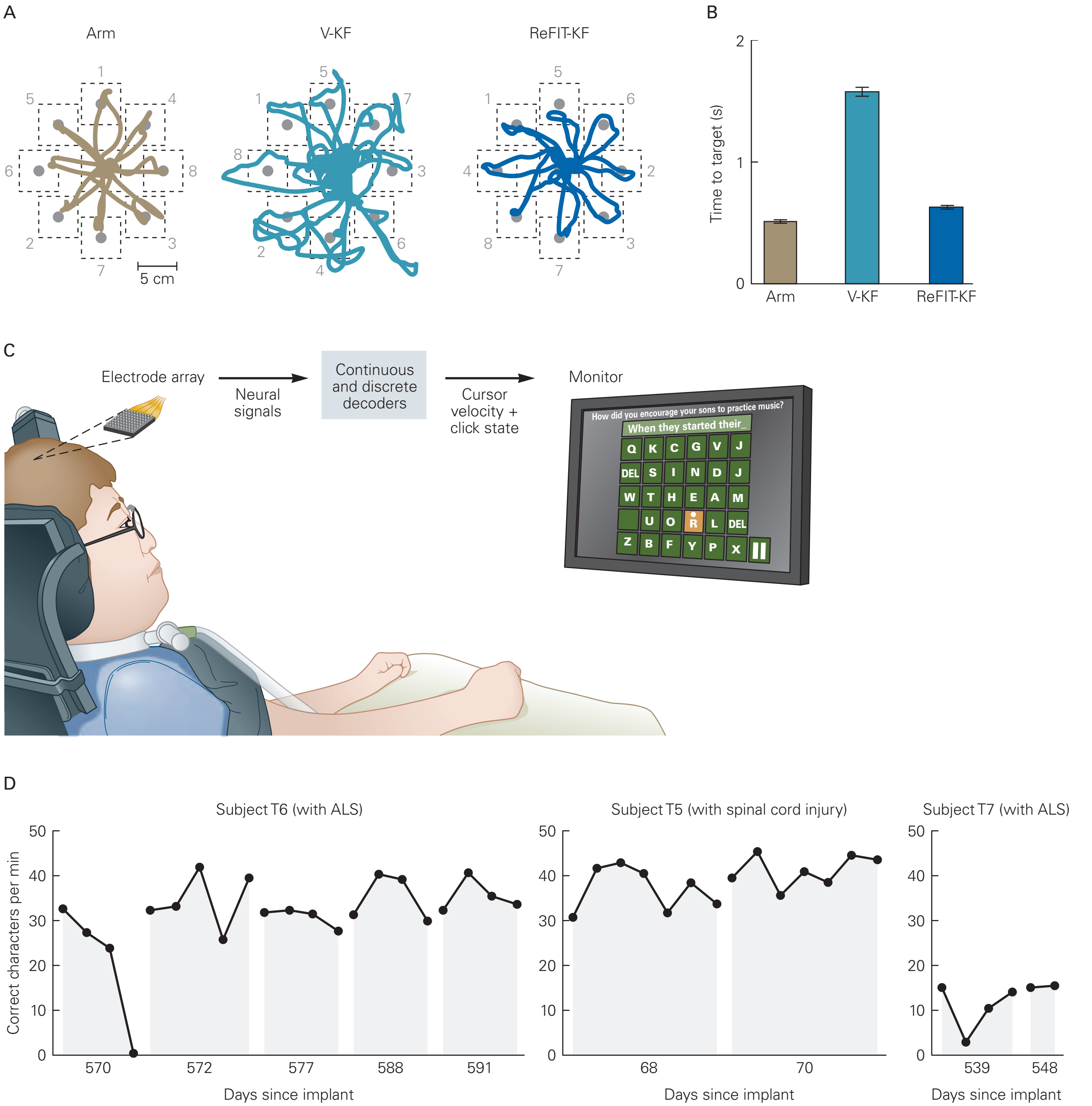


**Figure 39–8 A communication brain–machine interface (BMI) can control a computer cursor using a continuous decoder based on neural activity during the execution epoch.**

**A.** Comparison of cursor control by a monkey using its arm, a standard decoder that estimates velocity (BMI with Kalman filter decoding movement velocity [**V-KF**]), and a feedback intention-trained decoder (BMI with recalibrated feedback intention-trained Kalman filter [**ReFIT-KF**]). Traces show cursor movements to and from targets alternating in the sequence indicated by the numbers shown. Traces are continuous for the duration of all reaches. (Adapted, with permission, from Gilja et al. 2012.)

**B.** Time required to move the cursor between the central location and a peripheral location on successful trials (mean ± standard error of the mean). (Adapted, with permission, from Gilja et al. 2012.)

**C.** Pilot clinical trial participant T6 (53-year-old female with amyotrophic later sclerosis [**ALS**]) using a BMI to type the answer to a question. (Adapted, with permission, from Pandarinath et al. 2017.)

**D.** Performance in a typing task for three clinical trial participants. Performance can be sustained across days or even years after array implantation. (Adapted, with permission, from Pandarinath et al. 2017.)

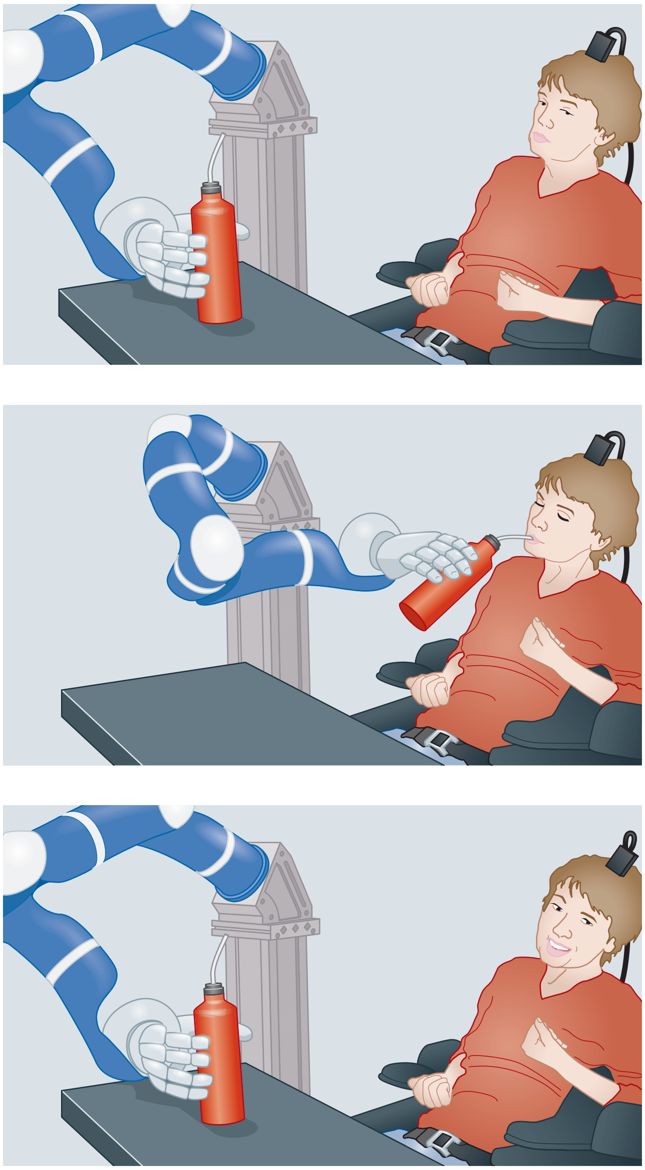

**Figure 39–9 A subject with paralysis drinks from a bottle using a robotic arm controlled by a motor brain–machine interface using a continuous decoder.** Three sequential images from the first successful trial show the subject using the robotic arm to grasp the bottle, bring it to her mouth and drink coffee through a straw, and place the bottle back on the table. (Adapted from Hochberg et al. 2012.)

It is implemented by calibrating a continuous decoder to predict the intended activity of each of several of the muscles, transiently paralyzed with a nerve block. These predictions are then used to control the intensity of stimulation of the same paralyzed muscles, which in turn controls motor outputs such as a grip angle and force. This process in effect bypasses the spinal cord and restores some semblance of voluntary control of the paralyzed arm and hand. Similar results have recently been demonstrated in patients with paralysis using either externally applied or fully implanted state-of-the-art FES electrodes. Intracortically recorded signals from motor cortex were decoded to restore movement via FES in a person with upper spinal cord injury (Figure 39–11). The subject was able to achieve control of different wrist and hand motions, including finger movements, and perform various activities of daily living.

## Subjects Can Use Sensory Feedback Delivered by Cortical Stimulation During BMI Control

During arm movements, we rely on multiple sources of sensory feedback to guide the arm along a desired path or to a desired goal. These sources include visual, proprioceptive, and somatosensory feedback. However, in most current BMI systems, the user receives only visual feedback about the movements of the computer cursor or robotic limb. In patients with normal motor output pathways but lacking proprioception, arm movements are substantially less accurate than in healthy individuals, both in terms of movement direction and extent. Furthermore, in tests of BMI cursor control in healthy nonhuman primate subjects, the arm continues to provide proprioceptive feedback even though arm movements are not required to move the cursor. BMI cursor control is more accurate when the arm is passively moved together with the BMI cursor along the same path, rather than along a different path. This demonstrates the importance of "correct" proprioceptive feedback. Based on these two lines of evidence, it is perhaps not surprising that BMI-directed movements relying solely on visual feedback are slower and less accurate than normal arm movements. This has motivated recent attempts to demonstrate how providing surrogate (ie, artificial) proprioceptive or somatosensory feedback can improve BMI performance.

Several studies have attempted to write in sensory information by stimulating the brain using cortical electrical microstimulation. Laboratory animals can discriminate current pulses of different frequencies and amplitudes, and this ability can be utilized to provide proprioceptive or somatosensory information in BMIs by using different pulse frequencies to encode different physical locations (akin to proprioception) or different textures (akin to somatic sensation). Electrical microstimulation in the primary somatosensory cortex can be used by nonhuman primates to control a cursor on a moment-by-moment basis without vision. In these subjects, the use of electrical microstimulation

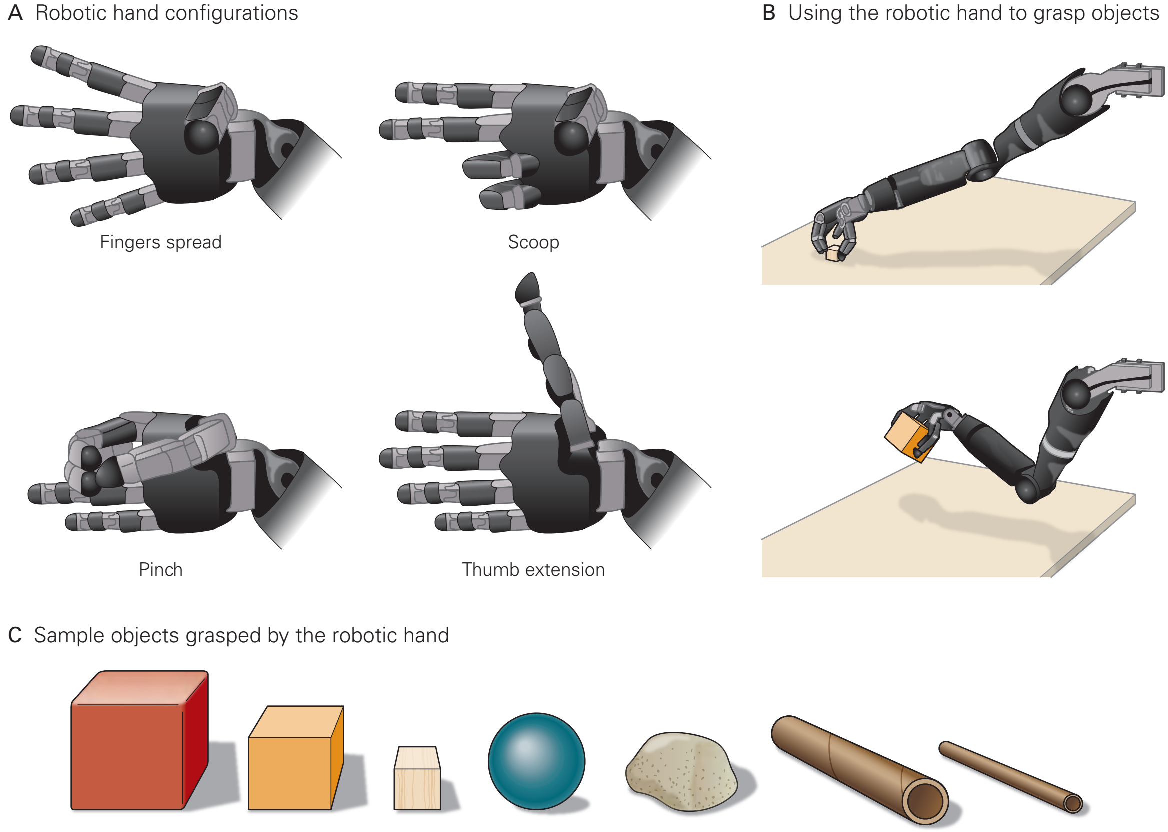


**Figure 39–10 A motor brain–machine interface (BMI) can control a prosthetic arm with 10 degrees of freedom.**

**A.** Examples of different hand configurations directed by the BMI. The 10 degrees of freedom are three-dimensional arm translation, three-dimensional wrist orientation, and four-dimensional hand shaping.

**B.** A subject uses the prosthetic arm to pick up an object and move it.

**C.** Objects of different shapes and sizes are used to test the generalization ability of the BMI. (Adapted from Wodlinger et al. 2015.)

and visual feedback together led to more accurate movements than either type of sensory feedback alone.

Furthermore, electrical microstimulation in the primary somatosensory cortex can also be used to provide tactile information. Nonhuman primates moved a BMI-directed cursor under visual feedback to hit different visual targets, each of which elicited a different stimulation frequency. Subjects learned to use differences in the stimulation feedback to distinguish the rewarded target from the unrewarded targets. This demonstrates that electrical microstimulation can also be used to provide somatosensory feedback during BMI control.

Finally, surrogate somatosensory information was delivered via electrical microstimulation to a person with paralysis and compromised sensory afferents. The person reported naturalistic sensations at different locations of his hand and fingers corresponding to different locations of stimulation in the primary somatosensory cortex.

## BMIs Can Be Used to Advance Basic Neuroscience

BMIs are becoming an increasingly important experimental tool for addressing basic scientific questions about brain function. For example, cochlear implants have provided insight into how the brain processes sounds and speech, how the development of these mechanisms is shaped by language acquisition, and how neural plasticity allows the brain to interpret a few channels of stimulation carrying impoverished auditory information. Similarly, motor and communication BMIs are helping to elucidate the neural mechanisms underlying sensorimotor control. Such scientific findings can then be used to refine the design of BMIs.

The key benefit of BMIs for basic science is that they can simplify the brain's input and output interface with the outside world, without simplifying the complexities of brain processing that one wishes to study.

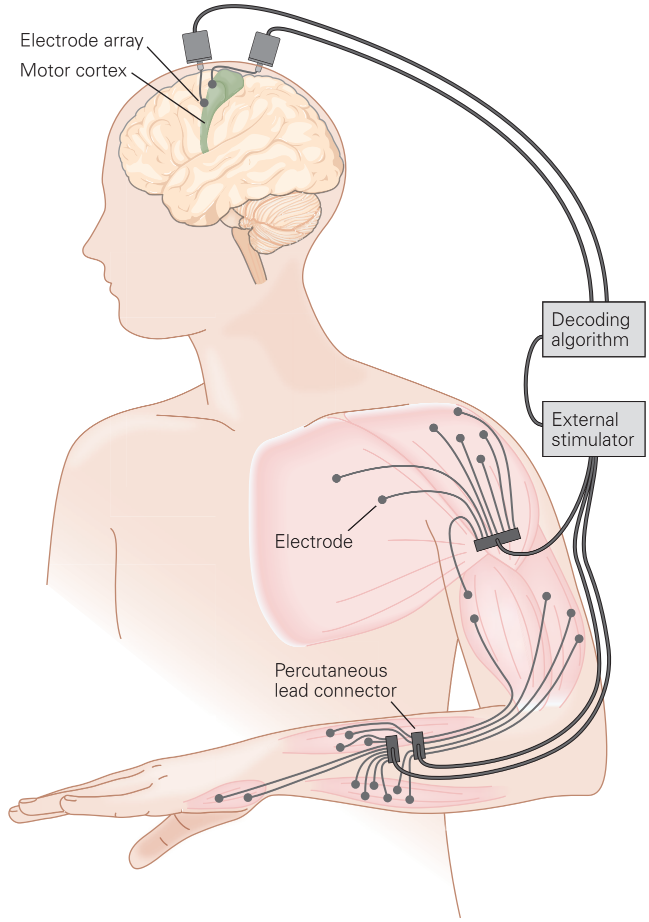


**Figure 39–11 A motor brain–machine interface (BMI) can control the muscles of a paralyzed arm using a continuous decoder and functional electrical stimulation.** Neural activity recorded in the motor cortex is decoded into command signals that control the stimulation of deltoid, pectoralis major, biceps, triceps, forearm, and hand muscles. This enables cortical control of whole-arm movements and grasping. Muscle stimulation is performed through percutaneous intramuscular fine-wire electrodes. (Adapted, with permission, from Ajiboye et al. 2017. Copyright © 2017 Elsevier Ltd.)

To illustrate this point, consider the output interface of the brain for controlling arm movements. Thousands of neurons from the motor cortex and other brain areas send signals down the spinal cord and to the arm, where they activate muscles that move the arm. Understanding how the brain controls arm movement is challenging because one can typically record from only a small fraction of the output neurons that send signals down the spinal cord, the relationship between the activity of the output neurons and arm movements is unknown, and the arm has nonlinear dynamics that are difficult to measure. Furthermore, it is usually difficult to determine which recorded neurons are output neurons.

One way to ease this difficulty is to use a BMI. Because of the way a BMI is constructed, only those neurons that are recorded can directly affect the movement of the cursor or robotic limb. Neurons throughout the brain are still involved, but they can influence the cursor movements only indirectly through the recorded neurons. Thus, in contrast to arm and eye movement studies, one can record from the entire set of output neurons in a BMI, and BMI-directed movements can be causally attributed to specific changes in the activity of the recorded neurons. Furthermore, the mapping between the activity of the recorded neurons and cursor movement is defined by the experimenter, so it is fully known. This mapping can be defined to be simple and can be easily altered by the experimenter during an experiment. In essence, a BMI defines a simplified sensorimotor loop, whose components are more concretely defined and more easily manipulated than for arm or eye movements.

These advantages of BMIs allow for studies of brain function that are currently difficult to perform using arm or eye movements. For example, one class of studies involves using BMIs to study how the brain learns. The BMI mapping defines which population activity patterns will allow the subject to successfully move the BMI-directed cursor to hit visual targets. By defining the BMI mapping appropriately, the experimenter can challenge the subject's brain to produce novel neural activity patterns.

A recent study explored what types of activity patterns are easier and more difficult for the brain to generate. They found that it was easier for subjects to learn new associations between existing activity patterns and cursor movements than to generate novel activity patterns. This finding has implications for our ability to learn everyday skills. A second class of studies involves asking how the activity of neurons that directly control movement differ from those that do not directly control movement. In a BMI, one can choose to use only a subset of the recorded neurons (the output neurons) for controlling movements. At the same time, other neurons (the nonoutput neurons) can be passively monitored without being used for controlling movements. Comparing the activity of output and nonoutput neurons can provide insight into how a network of neurons internally processes information and relays only some of that information to other networks.

Using this paradigm, a recent study recorded neural activity simultaneously in the primary cortex and striatum and designated a subset of the M1 neurons as the output neurons for controlling the BMI. They found that, during BMI learning, M1 neurons that were most relevant for behavior (the output neurons) preferentially increased their coordination with the striatum, which is known to play an important role during natural behavior (Chapter 38). Identifying output versus nonoutput neurons in a study using arm or eye movements would be challenging.

## BMIs Raise New Neuroethics Considerations

A growing number of biomedical ethics considerations centered on the brain have arisen from the dramatic expansion in our understanding of neuroscience and our capabilities with neurotechnology. These advances are driven by society's curiosity about the functioning of the brain, the least-well understood organ in the body, as well as the desire to address the massive unmet need of those suffering from neurological disease and injury. The use of BMIs raises new ethical questions for four principal reasons.

First, recording high-fidelity signals (ie, spike trains) involves risk, including the risks associated with initial implantation of the electrodes as well as possible biological (immunological or infectious) responses during the lifetime of the electrodes and the associated implanted electronics. Electrodes implanted for long periods currently have functional lifetimes on the order of many months to a few years, during which time glial scar tissue can form around the electrodes and electrode materials can fail. Efforts to increase the functional lifetime of electrodes range from nanoscale flexible electrodes made with new materials to mitigating immunological responses, as is done with cardiac stents.

For these reasons, patients considering receiving implanted recording technologies will need to evaluate the risks and benefits of a BMI, as is the case for all medical interventions. It is important for patients to have options, as each person has personal preferences involving willingness to undergo surgery, desire for functional restoration and outcome, and cosmesis—be it while deliberating cancer treatment or BMI treatment. BMIs based on different neural sensors (Figure 39–2) have different risks and benefits.

Second, because BMIs can read out movement information from the brain at fine temporal resolution, it seems plausible that they will be able to read out more personal and private types of information as well. Future neuroethics questions that may arise as the technology becomes more sophisticated include whether it is acceptable, even with patient consent, to read out memories that may otherwise be lost to Alzheimer disease; promote long-term memory consolidation by recording fleeting short-term memories and playing them back directly into the brain; read out subconscious fears or emotional states to assist desensitization psychotherapy; or read out potential intended movements, including speech, that would not naturally be enacted.

Third, intracortical write-in BMIs, similar to DBS systems currently used to reduce tremor, may one day evoke naturalistic spatial-temporal activity patterns across large populations of neurons. In the extreme it may not be possible for a person to distinguish self-produced and volitional neural activity patterns from artificial or surrogate patterns. Although there are numerous therapeutic and beneficial reasons for embracing this technology, such as reducing tremor or averting an epileptic seizure, more dubious uses can be envisioned such as commandeering a person's motor, sensory, decision making, or emotional valence circuits.

Finally, ethical questions also involve the limits within which BMIs should operate. Current BMIs focus on restoring lost function, but it is possible for BMIs to be made to enhance function beyond natural levels. This is as familiar as prescribing a pair of glasses that confer better than normal vision, or overprescribing a pain medication, which can cause euphoria that is often addictive. Should BMIs be allowed, if and when it becomes technically possible, to move a robotic arm faster and more accurately than a native arm? Should continuous neural recordings from BMIs, covering hours, days, or weeks, be saved for future analysis, and are the security and privacy issues the same or different from personal genomics data? Should BMIs with preset content be available for purchase, for example, to skip a grade of mathematics in high school? Should an able-bodied person be able to elect to receive an implanted motor BMI? While the safe and ethical limits of such sensory, motor, and cognitive BMI treatments might seem readily apparent, society continues to wrestle with these same questions concerning other currently available medical treatments. These include steroids that enhance musculature, energy drinks (eg, caffeine) that enhance alertness, and elective plastic surgery that alters appearance.

Although many of these ideas and questions may appear far-fetched at present, as mechanisms of brain function and dysfunction continue to be revealed, BMI systems could build on these discoveries and create even more daunting ethical quandaries. But equally important is the immediate need to help people suffering from profound neurological disease and injury through restorative BMIs. In order to achieve the right balance, it is imperative that physicians, scientists, and engineers proceed in close conversation and partnership with ethicists, government oversight agencies, and patient advocacy groups.

## Highlights

1. Brain–machine interfaces (BMIs) are medical devices that read out and/or alter electrophysiological activity at the level of populations of neurons. BMIs can help to restore lost sensory, motor, or brain processing capabilities, as well as regulate pathological neural activity.
2. BMIs can help to restore lost sensory capabilities by stimulating neurons to convey sensory information to the brain. Examples include cochlear implants to restore audition or retinal prostheses to restore vision.
3. BMIs can help to restore lost motor capabilities by measuring the activity from many individual neurons, converting this neural information into control signals, and guiding a paralyzed limb, robotic limb, or computer cursor.
4. Whereas motor BMIs aim to provide control of a robotic limb or paralyzed limb, communication BMIs aim to provide a fast and accurate interface with a computer or other electronic devices.
5. BMIs can help to regulate pathological neural activity by measuring neural activity, processing the neural activity, and subsequently stimulating neurons. Examples include deep brain stimulators and antiseizure systems.
6. Neural signals can be measured using different technologies, including electroencephalography, electrocorticography, and intracortical electrodes. Intracortical electrodes record the activity of neurons near the electrode tip and can also be used to deliver electrical stimulation.
7. To study movement encoding, one usually considers the activity of an individual neuron across many experimental trials. In contrast, for movement decoding, one needs to consider the activity of many neurons across an individual experimental trial.
8. A discrete decoder estimates one of several possible movement goals from neural population activity. In contrast, a continuous decoder estimates the moment-by-moment details of a movement from neural population activity.
9. The field is making substantial progress in increasing the performance of BMIs, measured in terms of the speed and accuracy of the estimated movements. It is now possible to move a computer cursor in a way that approaches the speed and accuracy of arm movements.
10. In addition to controlling computer cursors, BMIs can also guide a robotic limb or a paralyzed limb using functional electrical stimulation. Developments from preclinical experiments with able-bodied, nonhuman primates have subsequently been tested in clinical trials with paralyzed people.
11. Future advances of BMI will depend, in part, on developments in neurotechnology. These include advances in hardware (eg, neural sensors and low-power electronics), software (eg, supervisory systems), and statistical methods (eg, decoding algorithms).
12. An important direction for improving BMI performance is to provide the user with additional forms of sensory feedback in addition to visual feedback. An area of current investigation uses stimulation of neurons to provide surrogate sensory feedback, representing somatosensation and proprioception, during ongoing use.
13. Beyond helping paralyzed patients and amputees, BMI is being increasingly used as a tool for understanding brain function. BMIs simplify the brain's input and output interfaces and allow the experimenter to define a causal relationship between neural activity and movement.

14. BMIs raise new neuroethics questions, which need to be considered together with the benefits provided by BMIs to people with injury or disease.

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Byron M. Yu

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