

Neural Interface Technology for Rehabilitation: Exploiting and Promoting Neuroplasticity

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- Brain-computer interface • Neural interface • Neuroplasticity
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The primary goal of rehabilitation is to restore physical, psychological, and social functions and improve the quality of life for individuals with various motor, sensory, or cognitive impairments. Although treatment options vary from pharmacologic agents to physical exercise, this review article focuses on neural interface technology, also called neuroprosthetics, which functions by directly interacting with the nervous system either electrically or magnetically. More than 200 years ago, Luigi Galvani documented that leg muscle contraction can be elicited by electrical stimulation of the femoral nerve.^{1,2} However, it is only in the last several decades that neural interface technology started to receive increasing attention from biomedical engineers, neuroscientists, and clinicians, largely due to great advances in electronic medical devices and system neuroscience research. The US Food and Drug Administration (FDA) approved cochlear implants (CIs) for treating hearing loss in 1984 and deep brain stimulators (DBS) for treating Parkinson disease in 2000.³ The National Institutes of Health currently holds a biannual Neural Interface Conference with the goal of bringing industry partners, clinicians, and researchers together to discuss key issues and future directions related to neural interface technology.⁴

This review classifies neural interface devices and systems into 2 categories, neural recording systems and neural stimulation systems, based on the direction of information flow. Neural recording systems retrieve information from the nervous system through electrophysiological recording methods, such as electroencephalography (EEG) and microelectrode recording of single-neuron activities. Neural stimulation systems feed information into the nervous system by electrically or magnetically activating or inhibiting neural activity. These 2 categories represent a simplified classification scheme, as certain neural interface devices, such as implantable responsive neurostimulators for epilepsy treatment, are capable of neural recording and stimulation.^{5,6} As the term neural interface technology covers a broad range of devices and systems, it is a daunting task to provide a detailed and informative discussion on each device and system in 1 review article. Many books, special journal issues, and review articles are excellent references for neural interface technology.^{7–15} Hence, this article reviews neural interface technology from 3 unique perspectives: (1) neural interface systems that are currently under active research but have not yet reached clinical practice, to illustrate not only what has been accomplished but also what will be accomplished in the near future; (2) neural interface technology with systems that the authors have directly worked with in their rehabilitation research and clinical practice to provide a first-hand view of neural interface technology; (3) neural interface technology in association with neuroplasticity, a foundation for neurologic rehabilitation, demonstrating that those 2 concepts work symbiotically to improve the quality of life for individuals with disabilities (**Fig. 1**). Neuroplasticity will help those individuals to make better use of their neural interface devices,^{16–19} and neural interface technology can also promote neuroplasticity for functional recovery.^{7,20}

NEURAL INTERFACE TECHNOLOGY FOR NEURAL RECORDING

This section focuses on the application of neural interface technology to support brain-computer interface (BCI) devices. The primary goal of BCI technology is to establish a direct communication pathway between the brain and external devices enabling faster and more intuitive communication and control for individuals with motor disabilities caused by stroke, spinal cord injury (SCI), limb amputation, and degenerative neurologic disorders. In this sense, BCI is a type of assistive technology, and what differentiates it from traditional assistive devices is that user commands are extracted directly from brain activity without the need for users to exert any overt

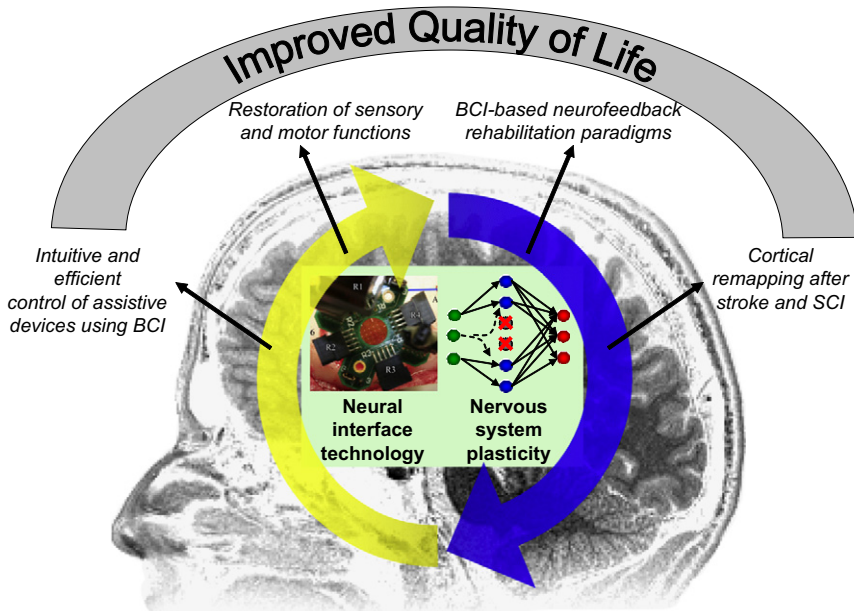


Fig. 1. The symbiotic relationship between neural interface technology and nervous system plasticity. Their close interaction leads to increased efficacy of neural interface devices and improved functional recovery of the nervous system, which eventually leads to better quality of life. The neural interface technology is exemplified by a photo of a microelectrode array for cortical surface recording. A schematic of a three-layer neural network models nervous system plasticity. When a group of neurons in the intermediate layer were damaged as a result of neurologic disorders (red "x") such as stroke, the input layer neurons (green dots) develop or strengthen connections (dashed lines) with spared neurons (blue dots) in the intermediate layer promoting functional recovery. (Courtesy of Dr. Justin Williams, University of Wisconsin-Madison, Madison, WI, USA, and James A. Hokanson, University of Pittsburgh, Pittsburgh, PA, USA.)

movement. BCI systems, with the capability to provide real-time feedback of neural activity, have also received considerable attention as rehabilitation tools for stroke and SCI patients.^{7,20} The goal is to induce neuroplasticity through the operation of BCI devices for functional recovery instead of using BCI systems permanently as assistive technology. In a typical BCI setup, multiple channels of neural signals are recorded simultaneously and fed into a decoding module. The decoding module then processes and decodes neural signals in real time to extract a BCI signal that can be used to control movement of a computer cursor or other external devices, such as a robotic arm or a communication aid.

Three factors are critical for the success of BCI applications. The first is the neural substrate (ie, neural activities), which encode a certain type of information that can be decoded as a BCI control signal. Many BCI applications were developed based on cortical representations of movement.^{19,21,22} Motor system neurophysiology studies have shown that activity of motor cortical neurons is modulated by movement, and that firing rates of a population of motor cortical neurons can be used to predict hand movement direction, speed, and position.^{23–30} This provides a neural substrate for extracting movement signals from the brain. The second factor for success is cortical plasticity induced by training through biofeedback. When subjects are trained to operate a BCI system, visual or other sensory feedback of the decoded movement

is presented to subjects in real time. It has been observed that, over time, modulation of recorded neural signals is enhanced as user performance improves.^{16–19} Neuroplasticity induced through BCI training not only helps BCI operation itself but also has the potential to promote functional recovery after damage to the nervous system from stroke and SCI.³¹ The third factor is an appropriate neural recording method that has sufficient spatial and temporal resolution to take full advantage of the aforementioned neural substrates and neuroplasticity. Various neural recording modalities have been used in BCI systems, including microelectrode recording of single-neuron activity,^{19,21,22,32,33} subdural electrocorticography (ECoG),^{34,35} scalp EEG,^{36,37} magnetoencephalography (MEG),³⁸ and functional magnetic resonance imaging (fMRI).³⁹ Depending on the targeted application, different BCI systems may have different requirements for the neural recording method. For example, a BCI system that acts as an assistive device needs to be portable, potentially fully implantable, and has the capability to record highly specific neural activity from a small cortical area. In contrast, portability may be less critical for a BCI system that serves as a rehabilitation tool if it can offer whole-head coverage with reasonable spatial and temporal resolution noninvasively, such as an MEG-based BCI system.

BCI as Assistive Technology

Considerable progress has been made using various neural recording methods, such as microelectrode recording of single-unit activities and scalp EEG.^{19,21,22,33,40} Each recording modality has its own advantages and disadvantages. Single-unit recording requires craniotomy and surgical insertion of microelectrode arrays into the cortex, and it has been suggested that microelectrode recording may lack long-term reliability due to foreign body reaction.¹⁵ In addition, single-unit recording typically requires sophisticated hardware and software systems. To capture the occurrence of spikes associated with action potentials, advanced data acquisition hardware with a high sampling rate (typically 25,000–50,000 Hz) is required. However, it offers the highest spatial and temporal resolution and can extract BCI control signals with multiple degrees of freedom with high accuracy. Researchers have demonstrated that nonhuman primates can achieve high-precision control of robotic arms to perform a self-feeding task,²² and clinical trials in human subjects are currently underway to test the safety and efficacy of BCI systems based on microelectrode recording of neuronal activity.²¹ At the other end of the spectrum, scalp EEG can be recorded noninvasively with much simpler recording systems (eg, sampling rate can be less than 1000 Hz), but it has a low spatial resolution (30 mm)⁴¹ and a low signal-to-noise ratio, especially at higher frequencies (>60 Hz) due to signal attenuation caused by the skull. It has been demonstrated that subjects can control the movement of a two-dimensional cursor with EEG by modulating their sensorimotor rhythm (10–30 Hz),⁴⁰ but extensive training is often required.

In parallel with the work of other groups using microelectrode recording and scalp EEG, the authors have been developing BCI systems using ECoG and micro-ECoG. ECoG (sometimes also called intracranial EEG) recently received considerable attention as a promising modality for BCI application.^{34,35} ECoG recordings are often performed for patients with intractable epilepsy for presurgical brain mapping and seizure foci localization. Patients' ECoG signals are recorded continuously for epilepsy monitoring, and those signals can be split off and fed into a second neural recording system for BCI research. Because its electrodes are placed inside the skull, ECoG preserves a wide range of high-frequency components (40–200 Hz) of the electrical field potential generated by neuronal activities. Several groups of researchers, including the authors, found that the power of high-frequency bands

increases significantly during movement, and varies systematically with movement direction (**Fig. 2**).^{34,42} The high-frequency band of ECoG signals encodes desired movement direction, similar to the high-frequency band of local field potential signals recorded in animal studies.⁴³ Thus, ECoG potentially contains rich information for extracting BCI control signals. Several studies have shown that human subjects can achieve effective control of cursor movement within a short period of time with ECoG (**Fig. 3**).^{34,35,42}

Implantation of these standard subdural ECoG grids typically requires a craniotomy that exposes a large portion of cortical surface. For BCI applications, such an invasive craniotomy is impractical and can be avoided with a new technique called micro-ECoG. A micro-ECoG electrode grid can be described as a miniature version of the regular ECoG grids with smaller electrodes and closer spacing between electrodes. Micro-ECoG grids can record neural activity from a localized cortical volume with high spatial and temporal resolution, which makes it possible to extract even richer and more specific information from micro-ECoG signals for controlling BCI devices. Furthermore, a micro-ECoG grid can easily be implanted through a small burr hole in a minimally invasive surgery, and it can be placed on top of the dura mater. By leaving the dura intact, risks of various complications, such as infection, can be significantly reduced. Previously, the Cleveland Clinic Foundation group reported no serious complications from epilepsy monitoring using epidural electrodes, and there was zero instance of purulent wound infection from 500 epidural electrodes inserted.⁴⁴

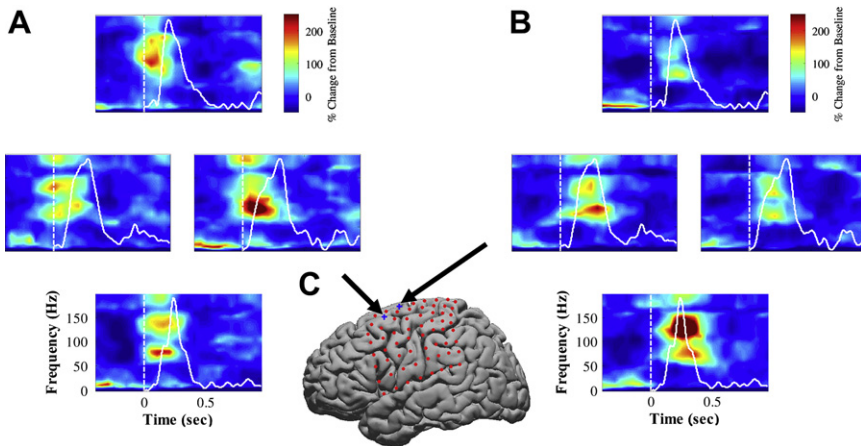


Fig. 2. Movement modulation of ECoG signals recorded from 2 representative subdural ECoG electrodes above the motor cortical area as the subject performed a center-out movement with a two-dimensional cursor controlled by a joystick. (A, B) Each panel shows 4 spectrograms arranged corresponding to cursor movement direction (up, down, left, and right). Time 0 represents movement onset (also marked with white vertical lines). Color represents percent change from baseline. Solid white curves are cursor velocity profiles. (C) Locations of subdural ECoG electrodes. A grid of 64 electrodes (red dots) covers the left frontal and parietal cortical areas. The 2 electrodes the responses of which are depicted in (A) and (B) are marked with blue "+" signs and black arrows. For the high-frequency band, there is a significant increase in power during movement. Furthermore, the high-frequency band power differs across 4 different movement directions, with a strong activation for rightward movement in (A) and downward movement in (B).

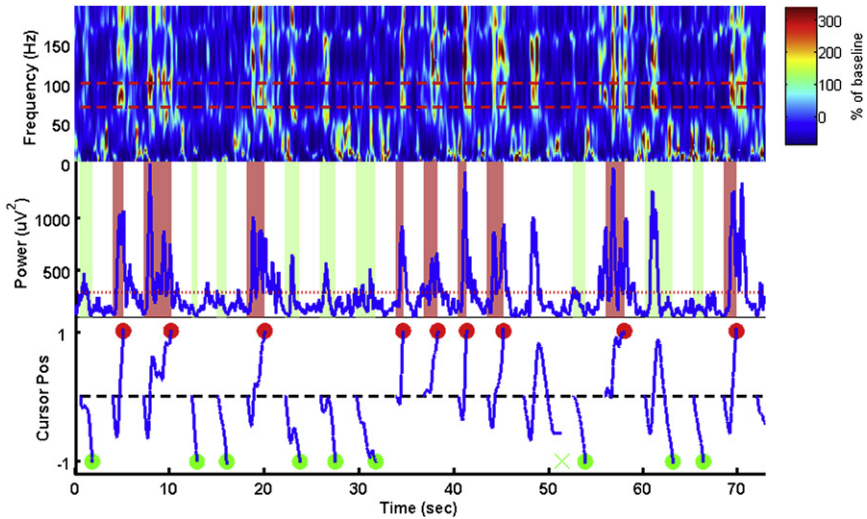


Fig. 3. Real-time control of one-dimensional computer cursor movement using an ECoG channel. (*Top*) The time-frequency plot of the ECoG signal. Color represents percentage change from baseline. The red dashed lines mark the frequency band used to control the cursor (70–100 Hz). (*Middle*) Instantaneous power of the 70 to 100 Hz band (*blue curve*) and its baseline power (*red line*). (*Bottom*) Vertical cursor position plotted as a function of time (*blue curve*). The cursor always started from the center of the screen at the beginning of each trial. The red and green dots indicate the time and cursor vertical position when a top or a bottom target was hit. “x” indicates an unsuccessful trial. For this subject, an accuracy of 73% was achieved within the first 10 minutes of the brain-control session; the chance level was 50%.

Hence, micro-ECoG recording may provide high-quality neural recording with low clinical risks, making it a desirable platform for developing clinical BCI devices.

With approval from the Institutional Review Board at the University of Pittsburgh, the authors recently conducted a micro-ECoG study in a human subject undergoing subdural ECoG recording for the purpose of epilepsy monitoring. A micro-ECoG grid with 14 recording electrodes was implanted over the motor cortical area, and the high-frequency band of neural signals recorded from this micro-ECoG grid showed significant modulation by hand movement, including individual finger movement⁴⁵ and grasping/pinching movement of the hand.⁴⁶ Modulation of micro-ECoG signals by hand movement offers a neural substrate that is critical to the success of a BCI system intended to restore volitional control of finger movement. During the experiment, the subject achieved real-time control of one-dimensional cursor movement within 30 minutes. Offline analysis showed that hand posture (open vs closed) can be predicted accurately using micro-ECoG signals and that individual finger movement can be decoded with an accuracy of 73% (chance level 20%).⁴⁵

The capability to decode hand movement from micro-ECoG recording has great clinical significance. Loss of hand function leads to difficulties in simple daily tasks, such as grooming, feeding, and dressing, and it significantly affects quality of life. In addition to high-level SCI patients, many individuals with hand function impairments caused by other neurologic disorders, such as stroke,⁴⁷ may benefit from this technology. A large number of stroke patients have upper limb paresis on admission to hospital (60%–70%)⁴⁸ and 55% to 75% of stroke survivors have limited upper-extremity function.^{49,50} Our study suggests that it is possible to develop a minimally invasive implantable BCI device based

on micro-ECoG recording to provide control signals for prosthetic hands or functional electrical stimulators to reanimate paralyzed hands.

For all the BCI systems mentioned above, regardless of the neural signal (single-unit activity, EEG, ECoG, and so forth), when a subject operates a BCI system, neuroplasticity plays a critical role. Through closed-loop training with real-time feedback of cursor or robotic arm movement, BCI systems induce neuroplasticity that greatly facilitates BCI control.^{16–19} Meanwhile, neuroplasticity induced by BCI not only benefits BCI operation itself, but may also potentially facilitate functional recovery. In the next 2 sections, the goal of using BCI devices changes from simply operating the device to serving as a tool for stroke and SCI rehabilitation.

BCI as a Rehabilitation Tool

In addition to controlling assistive devices that can replace or augment impaired functions, BCI technology can also facilitate the restoration of function through neuroplasticity.^{7,20} Traditional therapies for restoring motor function focus on forced use of the impaired limb. Most notably, constraint-induced movement therapy and electromyogram (EMG)-based biofeedback have proven to be fairly successful strategies for improving muscle strength and performance of activities of daily living.^{51–55} However, the success of these therapies depends on the patient having a moderate degree of residual function to start with. In the case of SCI or severe hemiplegia, alternative therapies for restoration of function need to be explored. In particular, this article focuses on research that seeks to engage neuroplasticity using BCI as a neurofeedback tool to elicit changes along the corticospinal pathway.

Neurofeedback is a technique in which an individual learns to voluntarily modulate, or change, his or her brain activity.^{56,57} Current clinical applications of neurofeedback include the treatment of epilepsy, anxiety, and, more recently, attention deficit hyperactivity disorder (ADHD).^{56–59} Users are provided with real-time feedback of some feature of their neural activity, often the amplitude of oscillatory signals originating within the cortex. Based on this feedback, the individual learns to control the neural signal of interest. Voluntary modulation of sensorimotor rhythm amplitude is often learned through neurofeedback to control a BCI device. It is well established that neuroplasticity can be induced, and that control of voluntary modulation can be improved, with BCI training.^{16,17,19,21,31,38,60} In addition to improving brain control of external devices, such as computer cursors and robotic arms, neuroplasticity induced by BCI training may also directly facilitate motor function recovery. Many previous studies have shown that functional recovery is often associated with cortical activity returning to a state close to that of an unimpaired individual.^{61–63} BCI training through neurofeedback can directly influence cortical activity and potentially restore a normal cortical activation pattern, which could have a positive effect on downstream neuromuscular systems.

A recent study investigated the feasibility of restoring movement using BCI training in chronic stroke patients.^{20,31} In that study, subjects learned to modulate their brain activity to control an orthosis that opens and closes the hand. Eight participants with chronic hand weakness secondary to stroke underwent training focused on modulating sensorimotor rhythm amplitude as measured by MEG. MEG sensors over the sensorimotor region that were activated during imagery of movement of the paralyzed hand were selected as control channels for the MEG-based BCI. Motor imagery and observation, for example, of an individual performing the intended task, represent powerful inductors of cortical plasticity.^{64–67} Sensorimotor rhythm amplitude controlled the vertical position of a computer cursor and the subjects tried to hit a top or bottom target. In addition, the same neural signals were coupled to control

of the hand orthosis. The orthosis guided the hand into an open or closed position depending on the sensorimotor rhythm amplitude relative to a predetermined threshold. After 3 to 8 weeks of training, these 8 patients were able to achieve an average success rate of 72% for the 2-target task. Although this success rate may seem modest, it should be noted that most of these patients were able to achieve control with MEG sensors above the sensorimotor areas ipsilateral to their subcortical stroke lesions. No significant changes in gross hand motor function were measured for any of the patients. Hand function improvement was not expected in those patients, as they started the study with a 0/5 score on the Medical Research Council scale with completely paralyzed hands. To further improve the efficacy of this neurofeedback paradigm, particularly in patients who retain some level of hand motor function, BCI can be combined with functional neuromuscular stimulation to generate brain-controlled muscle contraction. The famous Hebb rule for neuroplasticity is often summarized as “the neurons that fire together, wire together”.^{68,69} Temporally coupled motor cortex activation, muscle contraction, and somatosensory feedback may promote neuroplasticity for motor functional recovery based on similar principles.

A Comprehensive Rehabilitation Approach Combining Action Observation, Motor Imagery, and BCI Neurofeedback

The authors believe that the feasibility and effectiveness of a BCI-based neurofeedback paradigm can be further enhanced by combining BCI-based neurofeedback with 2 additional training paradigms: action observation and motor imagery. Action observation training is based on the concept of a human mirror neuron system (MNS). Neurons in the human MNS fire when individuals act and when they observe the same action performed by another person.^{70–73} These neurons “mirror” the behavior, as if the observers are themselves acting. The human MNS plays a critical role for motor learning, action imitation, action understanding, speech, and social interaction.^{71,74} In addition to the classic human MNS, including the inferior parietal lobule, ventral premotor cortex, and the caudal part of the inferior frontal gyrus,^{75,76} multiple human and animal studies have also shown that the motor cortex demonstrates congruent activities during action observation and action execution.^{75,77–79} Just like action observation, motor imagery, or the imagined movement of a body part, can also activate multiple sensory and motor cortical areas. Motor imagery is believed to be a covert stage of action execution that draws on cortical areas that are typically involved in motor planning and execution, such as the supplemental motor area, premotor cortex, and the primary motor cortex (M1).^{80,81}

Action observation and motor imagery can elicit a certain degree of motor cortical activity in the absence of overt movement. They offer clinicians opportunities to directly activate cortical areas that cannot be activated otherwise, such as cortical areas representing a paralyzed limb. They may be able to strengthen neural pathways that remain intact, and also facilitate activation of motor cortical areas. Multiple studies have demonstrated that action observation and motor imagery can elicit sensorimotor cortical activity and, at least temporarily improve motor functions of paralyzed limbs after stroke and SCI.^{82–84} As discussed in the last section, a BCI-based neurofeedback training paradigm has the potential to promote neuroplasticity and functional recovery. A comprehensive rehabilitation approach that merges BCI neurofeedback, action observation, and motor imagery will bring even greater benefits to patients than using any of those paradigms alone. First, action observation and motor imagery will facilitate BCI training. They allow a BCI system to optimize its decoding algorithm to extract motor-related information from cortical activity without overt movement from patients. They also offer an intuitive way for patients to learn to voluntarily

modulate their cortical activity to operate a BCI system. Enhanced performance in BCI operation will make the neurofeedback paradigm more effective, potentially improving motor function recovery. Second, BCI systems can at least partially provide real-time feedback of actions that a patient is imagining, making motor imagery training more engaging and effective than simple motor imagery without any feedback.

The authors are currently developing such a rehabilitation paradigm to enhance motor cortical modulation in individuals with tetraplegia. In the case of incomplete SCI, it is our goal to maximize the amount of information transferred through remaining corticospinal pathways to enhance residual function. For others, maximizing voluntary control of cortical modulation may increase the effectiveness of BCI technology and future spinal cord regeneration therapies. Preliminary studies investigated motor cortical activity in able-bodied volunteers and individuals with tetraplegia during action observation and action execution, with a primary focus on hand motor function. The study was approved by the Institutional Review Board at the University of Pittsburgh. Results from 2 participants are reported here. One participant was a 29-year-old man with no history of neuromuscular disease, and the other was a 34-year-old man with a C7-level complete SCI that occurred 15 years before his participation in this study. A whole-head 306-channel MEG system (Elekta Neuromag) was used to record cortical activity noninvasively while subjects performed simple hand movements under 4 different conditions:

- 1) Observed: participants watched a video of the movements while they remained resting.
- 2) Imitated: participants performed the movements along with the video presentation.
- 3) Imagined: participants imagined performing the movements in response to a visual cue.
- 4) Overt: participants overtly performed the specified movement in response to a visual cue.

The time sequence and visual feedback provided during the experimental paradigm are shown in **Fig. 4**. Two different hand movements were tested: (1) grasping an object; (2) tapping an object with the finger tips using wrist flexion and extension. A total of 40 repetitions were collected using a randomized block design for each “condition × movement” combination.

The power of sensorimotor rhythm (10–30 Hz) was used as an indicator of motor cortical activation. Time-frequency plots averaged over all repetitions from

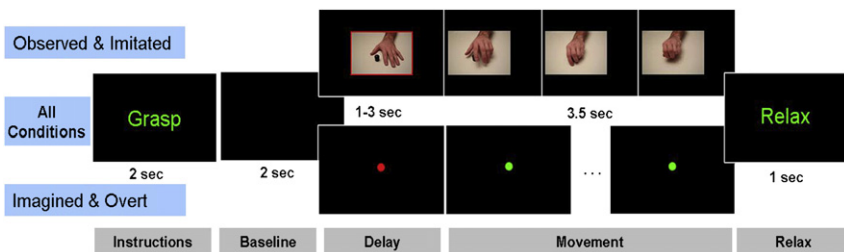


Fig. 4. The behavioral tasks used to study cortical activity during action observation, imitation, motor imagery, and overt movement. For all conditions an instruction slide specifies a “grasp” or “tapping” trial and is followed by a 2-second baseline period. For the observed and imitated conditions, a movie of the specified movement is shown following a brief delay period. For the imagined and overt conditions, movement time is indicated by the fixation dot turning from red to green. “Relax” signals the end of the trial.

a representative MEG channel above the motor cortex are shown in **Fig. 5**. In general, similar results were obtained from the able-bodied subjects and the subjects with SCI. For the overt and the imitated conditions, the power of sensorimotor rhythm decreased preceding movement, followed by a “rebound” (power increase). However, differences in cortical activation between those 2 subjects were noted, particularly in the imagined condition. The able-bodied subject showed a stronger decrease in sensorimotor rhythm power during the delay period and a clear post-movement rebound. A shortened period of power decrease was observed in the subject with tetraplegia, whereas the rebound occurred immediately at movement onset and was earlier than that seen in the able-bodied subject. For both subjects, the observed condition led to similar cortical activation as the overt condition, although to a lesser degree. These preliminary results provide strong support for pursuing a rehabilitation paradigm that combines MEG-based BCI and neurofeedback training with action observation and motor imagery. Future research is targeted to determining whether this new training paradigm can increase activation of the motor cortex and whether or not this translates to actual functional improvements.

NEURAL INTERFACE TECHNOLOGY FOR FUNCTIONAL NEURAL STIMULATION

Neural stimulation allows us to directly modulate activity of the nervous system. Compared with neural recording devices, to a certain degree, neural stimulation devices have had more success in being translated from basic research into clinical practice with a profitable market to support an active medical device industry in this domain.⁸⁵ Neural stimulation devices have benefited many patients with sensory, motor, and other neurologic disorders.^{13,14} Just like BCI applications, successful neural stimulation applications also rely on 3 factors: neural substrate, neuroplasticity, and the appropriate neural stimulation technique. CIs are an example.⁸⁶ Their neural substrate is the tonotopic organization of the basal membrane and the auditory nerve. Stimulating electrodes are inserted along the auditory nerve to elicit neural activities that represent the different frequency components of sound. Neuroplasticity again plays a critical role, as even the most advanced CI devices currently being marketed only have about 16 electrodes to represent a limited number of frequency components of sound, but neuroplasticity induced by extensive training, especially in early childhood, allows CI users to learn to discriminate various sounds, understand speech, and even enjoy music.⁸⁷

Neural stimulation technology can be used to replace specific sensorimotor functions or treat other neurologic and psychiatric disorders. Restoration of motor function is often targeted using functional electrical stimulation (FES).⁸⁸ In FES, nerve fibers innervating specific muscles are stimulated to activate their target muscle in a controlled fashion. Substantial work has been done in this area, with the aim of restoring walking or upper limb function. The most recent and exciting advance in this area is the combination of BCI with FES, whereby motor cortical activity is used to directly control FES devices to reanimate paralyzed limbs, bypassing the diseased neural pathway (eg, the spinal cord).^{89,90} Another application of neural stimulation is the restoration of sensory function. As mentioned earlier, the cochlear implant is one of the most successful neural interface technologies, and it has significantly improved the quality of life for many individuals with deafness. Neural interface devices to restore vision are also being investigated in research laboratories and start-up medical device companies.^{91–93} Neural stimulation targeted to modulate cortical and subcortical activities is being used to treat neurologic and psychiatric disorders such as epilepsy, Parkinson disease, and depression.^{13,14}

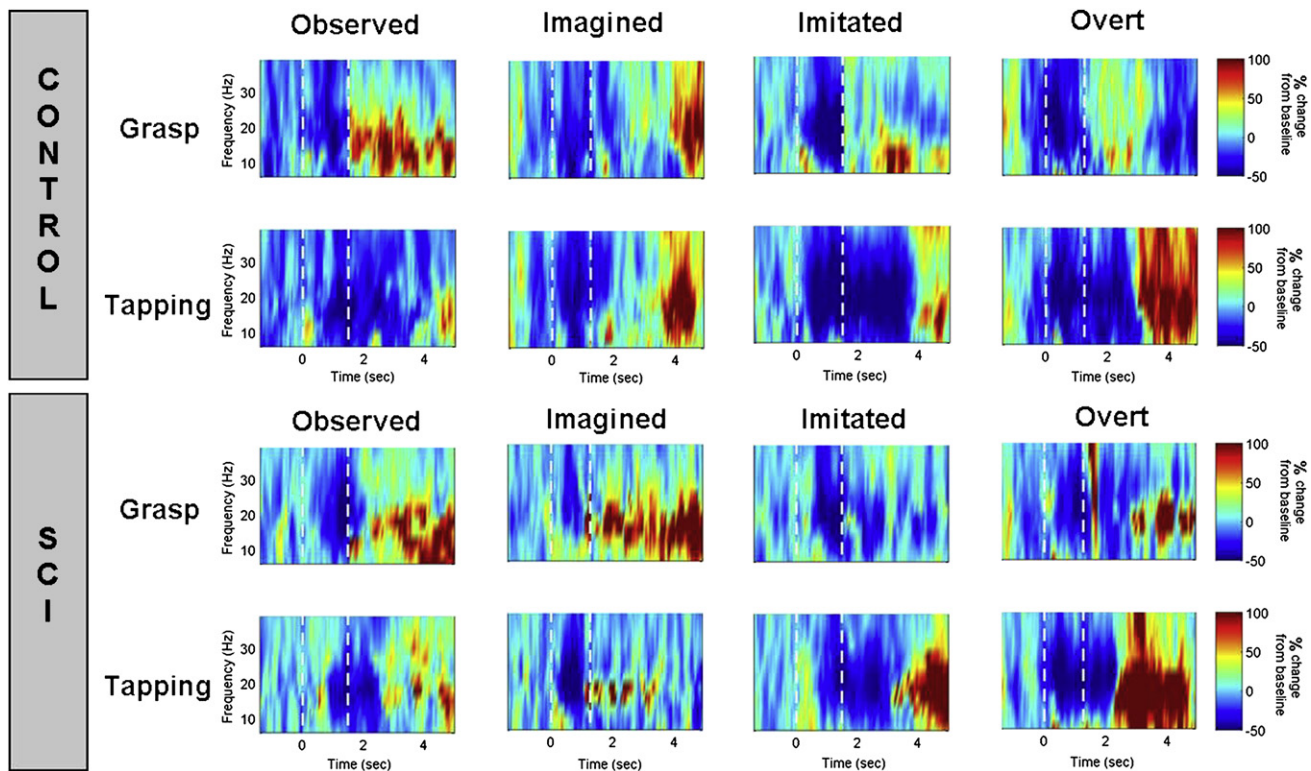


Fig. 5. Frequency band power modulation over time for 2 movements (grasp and tapping) under 4 conditions (observed, imagined, imitated, and overt) compared between a control subject (*top panel*) and a subject with tetraplegia (*bottom panel*). A single representative sensor over the contralateral sensorimotor cortex is pictured. Percent change in power from baseline (resting) is plotted for frequencies ranging from 4 to 40 Hz. The white dotted line at time = 0 seconds indicates the start of the delay period. The second white dotted line at time = 1.5 seconds indicates the start of the movement period. A characteristic decrease in power before movement followed by a “rebound” was observed for both subjects in the imitated and overt conditions. The same activation pattern was observed at a lower intensity for observed and imagined movements.

Just like BCI devices that can serve as assistive technology or as rehabilitation tools, neural stimulation technologies are being investigated for their potential to promote long-term neuroplasticity for rehabilitation applications. Given the capabilities of neural recording and stimulation, neural interface technology has the potential to promote neuroplasticity based on Hebbian learning by artificially associating activities of 2 separate sites within the nervous system. For example, Fetz's group demonstrated that motor cortical reorganization can be induced by coupling the action potentials of 1 motor cortical neuron (neural recording site) with electrical stimulation of another motor cortical neuron (neural stimulation site).⁹⁴ The following section provides a brief but informative sample of neural stimulation technology, focusing on neural stimulation for restoring somatosensation and cortical stimulation for stroke rehabilitation.

Neural Stimulation as Assistive Technology for Restoring Somatosensation

Somatosensory feedback is needed for motor planning, movement control, and activity modification. A prosthetic limb that is able to provide sensory information to its user may allow for greater functional performance. Sensory feedback can be provided as either a substitution or replacement of normal sensation.¹⁵ Sensory substitution involves delivering sensory information through a pathway or modality (ie, eye, ear, or skin) different from the pathway through which this type of sensory information is normally delivered or experienced.⁹⁵ Sensory substitution typically takes a noninvasive approach. An example of sensory substitution would be a prosthetic hand vibrating at its contact point on the residual limb to indicate grip force being applied. Several review articles have examined electrotactile and vibration methods of sensory feedback.^{96,97} Users have indicated that it may be challenging to respond to more than 1 source of sensory input using this feedback design. For example, a prosthetic hand may provide force feedback of hand opening or closing through vibration, but usually not both.⁹⁸ A drawback to electrotactile stimulation is pain induced at high levels of stimulation,⁹⁹ which is a particular concern due to the common presence of phantom limb pain in persons with amputation.

In contrast to sensory substitution, sensory replacement engages, as much as possible, the neural pathways normally involved in sensory reception and processing via somatosensory neural interfaces (SSNIs). SSNIs involve stimulation of an individual's nervous system to deliver information directly to a user's neural networks supporting perception and feedback control. A prosthetic hand utilizing an SSNI may directly stimulate the nervous system of the user to provide sensations of touch and position of the prosthetic hand. Direct stimulation of the nervous system more closely approximates sensation that is experienced by an unimpaired individual and also offers the potential to relay a greater "bandwidth" of information. Stimulation can occur anywhere in the nervous system, from the most peripheral elements to central structures including the somatosensory cortex via penetrating or surface electrodes of various types.

Electrical stimulation of peripheral nerves to provide sensory feedback to a prosthetic user has been investigated for several decades.^{100,101} The last decade has seen the development of implantable electrodes capable of delivering stimulation to nerves through multiple channels, thus providing more specific and richer sensory feedback.¹⁰² Among the electrode systems reviewed by Riso in 1999,¹⁰² longitudinally inserted intrafascicular electrodes have since been refined and can be used for individual finger sensory input.¹⁰³ This system has been used to provide feedback of grip force and joint position to individuals with upper limb amputation at or below elbow level while controlling a robotic arm.¹⁰⁴ This system allows the user to adjust

the position of the robot arm with no visual feedback from the unit. More investigation is needed to see if chronic systems based on this technology are feasible, because concerns regarding the stiffness of the implanted metal filaments relative to the surrounding nerve tissue have been raised.¹⁰²

Central stimulation of neural elements is also a possibility to provide sensory feedback for prosthetic applications. Work by Weber and colleagues in cats indicates that penetrating electrodes inserted into the dorsal root ganglion (DRG) can be used for sensory recording and sensory stimulation.¹⁰⁵ Cortical responses seen from DRG stimulation are similar to those seen with physiologic motion. Given the access to neural architecture and large action potentials visualized when recording from it, the DRG is an excellent structure to consider for neural prosthetic applications. Spinal cord stimulation, although commonly performed for pain management,¹⁰⁶ may be another potential approach for providing neuroprosthetic sensory feedback. A similar scenario presents itself in the case of the thalamus, which, like the spinal cord, has been investigated for stimulation for pain control.¹⁰⁷ Cortical stimulation for sensory feedback has been investigated through a variety of methods including intracortical microstimulation,¹⁰⁸ transcranial magnetic stimulation,^{109,110} and transcranial direct current stimulation (tDCS),¹¹¹ and are likely routes of continued research.

Neural Stimulation as a Rehabilitation Tool for Promoting Neuroplasticity

In addition to directly replacing or supplementing lost motor and sensory functions, neural stimulation may be able to promote neuroplasticity for rehabilitation by directly modulating activity of the nervous system.^{112,113} Earlier studies have shown that motor cortical representation of limbs can be altered through intracortical microelectrical stimulation in animals¹¹⁴ and in humans through direct noninvasive cortical stimulation.¹¹⁵ Recent studies using animal stroke models have shown that upper limb function can be improved after cortical surface electrical stimulation.¹¹⁶ These studies led to clinical trials of the first fully implantable cortical surface electrical stimulation device aiming to improve upper-extremity function.^{113,117} Stimulating electrodes were implanted epidurally above M1, and the electrodes were tunneled underneath the skin to the chest and connected to a subclavicular pulse generator.¹¹³ Focal high-frequency stimulation (eg, 50 or 100 Hz) was applied to the motor cortex. Several small-scale studies examined the changes in upper limb function, measured as the Fugel-Meyer score, following invasive cortical stimulation.¹¹³ Subjects who received cortical stimulation along with motor training showed higher Fugel-Meyer scores than those who only received motor training at 12 weeks post-implant.¹¹³ However, a larger-scale phase III clinical trial recently reported contradictory results, showing little difference in motor function improvement between motor training alone and combined motor training and cortical stimulation.¹¹⁸ In their 2009 article,¹¹⁸ Plow and colleagues discussed various factors that need to be further investigated and controlled for in future studies using invasive cortical stimulation, such as localization of cortical stimulation sites, descending pathway viability, and differences between animal and human studies. It was also suggested that noninvasive cortical stimulation will provide important insights into the efficacy of invasive cortical stimulation.

Noninvasive cortical stimulation can be performed using repetitive transcranial magnetic stimulation (rTMS) and tDCS.¹¹² At least 2 approaches have been explored using these noninvasive stimulation techniques.¹¹² One approach is to directly enhance motor cortical excitability of the stroke-affected hemisphere using ipsilesional cortical stimulation, which is also the approach taken by the implantable electrical cortical stimulators.¹¹² The other approach is to reduce interhemispheric inhibition

from the intact to the affected hemisphere by stimulating the hemisphere contralateral to stroke lesion. Both approaches have been shown to improve motor performance for stroke survivors, and motor function improvement was greater when cortical stimulation was coupled with motor training than when using cortical stimulation alone.^{113,119} Previously, it was reported that improvement in motor performance typically only lasts for a limited period of time after cortical stimulation (e.g., less than an hour).¹¹³ However, a recent study demonstrated that anodal tDCS led to prolonged motor skill enhancement over multiple days by potentially acting on motor skill consolidation mechanisms.¹²⁰ Although clinical protocols of cortical stimulation, either invasive or noninvasive, still need to be refined and their efficacy needs to be further investigated, noninvasive cortical stimulation using rTMS has been applied to modulate the excitability of a targeted cortical area to study various sensorimotor and cognitive functions. The rest of this section reviews in detail the effects of rTMS on cortical excitability and the potential mechanisms underlying these effects, which will eventually guide clinical application of cortical stimulation.

rTMS is a novel and painless way to stimulate the human brain noninvasively with the purpose of modulating the functions of the stimulated cortical regions or interconnected areas. Several studies have examined the effects of rTMS on the excitability of the hand¹²¹ and leg^{122,123} motor representations in M1. The duration of aftereffects of rTMS over M1 is often between 15 and 60 minutes, and depends on stimulation parameters such as the number of pulses applied, rate of application, and intensity of each stimulus. In some cases, the stimulus intensity used is below the threshold for evoking a muscle twitch in relaxed muscles, so that any effects observed could not be attributed to sensory input produced by movement. In this regard, stimulation of M1 at a subthreshold intensity and at a frequency of 1 Hz for about 25 minutes (1500 total stimuli) reduced the size of the motor evoked potentials (MEPs) evoked in finger muscles for the next 30 minutes.¹²⁴ Stimulation at frequencies higher than 1 Hz tends to increase rather than decrease cortical excitability. The aftereffects of rTMS also depend on the pattern of the individual TMS pulses. For example, Huang and collaborators¹²⁵ used theta-burst stimulation (TBS), a protocol in which three 50-Hz pulses are applied regularly 5 times per second for 20 to 40 seconds. In this protocol, low intensities of stimulation produce suppression of MEP size and if each TBS burst is applied for only 2 seconds, followed by a pause of 8 seconds and then repeated, the aftereffect becomes facilitatory.

Several studies have documented that rTMS induces adaptations in cortical neuronal circuitries.^{121,126–128} In this regard, high-frequency subthreshold rTMS can reduce short-interval intracortical inhibition in the stimulated M1.^{121,129} Although the cellular mechanisms of aftereffects of rTMS are not yet understood, some hypotheses have been postulated. It has been proposed that operating mechanisms include changes in the effectiveness of synapses between cortical neurons (long-term depression [LTD] and long-term potentiation [LTP] of synaptic connections). Like LTP/LTD, there is evidence from pharmacologic interventions that the aftereffects of rTMS depend on the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor, as they are blocked by a single dose of the NMDA-receptor antagonist dextromethorphan.¹³⁰ Another example is the use of an NMDA-receptor antagonist that can block the suppressive and facilitatory effect of some rTMS protocols.^{131–133} Another study demonstrated that aftereffects of rTMS on M1 excitability disappear when MEPs are tested in actively contracting muscle rather than at rest.¹³⁴ In this study the investigators suggested that rTMS was to some extent changing the level of excitability of the resting corticospinal system, rather than changing the effectiveness of transmission at synapses within the cortex. It is possible that both effects occur to different degrees depending on the parameters of rTMS.

In humans and nonhuman primates, corticospinal cells exert modulation over a large group of spinal interneurons.¹³⁵ Therefore, it is possible that activating corticospinal neurons by rTMS may also induce changes in spinal neuronal circuitries. Perez and collaborators¹²² applied 15 trains of 20 pulses at 5 Hz at intensities between 75% and 120% of the resting motor threshold of the tibialis anterior muscle and reported a decrease in the size of the soleus H-reflex at stimulus intensities ranging from 92% to 120% of the resting motor threshold. In this study the investigators demonstrated that rTMS increased the level of presynaptic inhibition at the terminals of Ia afferent fibers but did not change the level of disynaptic reciprocal Ia inhibition. At rTMS frequencies of 1 Hz, changes have also been reported in spinal cord reflexes. Valero-Cabré and colleagues¹³⁶ applied 600 pulses of 1-Hz rTMS at 90% of the resting motor threshold of the flexor carpi radialis (FCR) muscle and reported a lasting decrease in threshold and an increase in size of the FCR H-reflex. It is possible that a different stimulation frequency will have a different effect on spinal cord excitability.

Studies on able-bodied volunteers and stroke survivors have demonstrated that rTMS can noninvasively modulate motor cortical excitability and influence motor functions in a controlled fashion. Furthermore, the other form of noninvasive cortical stimulation, tDCS, can also modulate motor and cognitive functions in a polarity-specific manner in health and disease, and facilitate the design of sham interventions.^{137–139} However, better understanding of the effects and underlying mechanism of cortical stimulation techniques is needed to provide scientific guidance for future clinical trials aiming to promote neuroplasticity and functional recovery using invasive or noninvasive cortical stimulation.

SUMMARY

This article reviews neural interface technology and its relationship with neuroplasticity. Two types of neural interface technology are reviewed, highlighting specific technologies that the authors work with directly: (1) neural interface technology for neural recording, such as the micro-ECoG BCI system for hand prosthesis control, and the comprehensive rehabilitation paradigm combining MEG-BCI, action observation, and motor imagery training; (2) neural interface technology for functional neural stimulation, such as somatosensory neural stimulation for restoring somatosensation, and noninvasive cortical stimulation using rTMS and tDCS for modulating cortical excitability and stroke rehabilitation. The close interaction between neural interface devices and neuroplasticity leads to increased efficacy of neural interface devices and improved functional recovery of the nervous system. This symbiotic relationship between neural interface technology and the nervous system is expected to maximize functional gain for individuals with various sensory, motor, and cognitive impairments, eventually leading to better quality of life.

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