Brain–computer interfaces in neurological rehabilitation

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Recent advances in analysis of brain signals, training patients to control these signals, and improved computing capabilities have enabled people with severe motor disabilities to use their brain signals for communication and control of objects in their environment, thereby bypassing their impaired neuromuscular system. Non-invasive, electroencephalogram (EEG)-based brain–computer interface (BCI) technologies can be used to control a computer cursor or a limb orthosis, for word processing and accessing the internet, and for other functions such as environmental control or entertainment. By re-establishing some independence, BCI technologies can substantially improve the lives of people with devastating neurological disorders such as advanced amyotrophic lateral sclerosis. BCI technology might also restore more effective motor control to people after stroke or other traumatic brain disorders by helping to guide activity-dependent brain plasticity by use of EEG brain signals to indicate to the patient the current state of brain activity and to enable the user to subsequently lower abnormal activity. Alternatively, by use of brain signals to supplement impaired muscle control, BCIs might increase the efficacy of a rehabilitation protocol and thus improve muscle control for the patient.

Introduction

Motor recovery is not possible at present for patients with progressive diseases, such as amyotrophic lateral sclerosis (ALS), multiple sclerosis, or Parkinson's disease, or for many patients with severe trauma due to stroke, cerebral palsy, or injury to the spinal cord or brain. Although some innovative rehabilitation strategies have shown potential in randomised controlled trials,[1–5] available rehabilitation methods do not restore normal or near normal motor function and quality of life in most patients. Therefore, it is important to develop more effective alternative methods for people with motor disabilities.

Recently, there has been much interest in developing brain–computer interface (BCI) technology to help improve the quality of life and to restore function for people with severe motor disabilities. There are two ways that BCI systems can facilitate rehabilitation in people in whom disease or trauma has abolished or severely impaired muscle control. The first strategy is straightforward and has already been the focus of a considerable body of research. BCI systems can substitute for the loss of normal neuromuscular outputs by enabling people to interact with their environment through brain signals rather than through muscles.[6] Thus, for example, a person can use electrophysiological signals such as electroencephalographic (EEG) activity or cortical neuronal activity to indicate "yes" or "no" to control a cursor on a computer screen or to control a neuroprosthetic arm. The second use of BCI technology is more complex and has only recently started to be studied. BCIs might restore motor function by inducing activity-dependent brain plasticity to restore more normal brain function; they could help to guide brain plasticity by affecting motor learning, for example, by demanding close attention to a motor task or by requiring the activation or deactivation of specific brain signals.

The recent, rapid growth of BCI research and development efforts suggests the confluence of four factors. The first is the increased understanding of the characteristics and possible uses of brain signals gained from extensive research in animals and human beings over the past decades. The second factor is the recognition that activity-dependent plasticity occurs throughout the CNS and across the lifespan, and thus can have a substantial influence in determining the (positive or negative) functional effects of disease and trauma. The third factor is the widespread availability of powerful low-cost hardware and software programs for recording and analysing brain signals during real-time online activities. The final factor is the increased societal interest and appreciation of the serious needs and impressive potential of people with severe motor disabilities.

This Review describes the principles of BCI technology and discusses the current status and future prospects of BCI methods for providing non-muscular control and communication to people with severe motor disabilities. The status and future prospects of BCI methods for inducing and guiding brain plasticity to restore effective neuromuscular function to people with severe motor disabilities will also be reviewed.

BCI technologies

BCI systems enable a new real-time interaction between the user and the outside world. Signals that indicate the brain activity of the user are translated into an output (eg, cursor movement). The user receives feedback on this output, which in turn affects the user's brain activity and influences subsequent output. Therefore, if a person uses a BCI to control a neuroprosthetic arm, the position of the arm after each movement will influence the person's intent for the next movement and affect the brain signals that encode that intent. A system that simply records and analyses brain signals and does not provide the results of the analysis to the user in a real-time interactive way is not a BCI. Figure 1 shows the main components of a BCI system. The description of BCI methods (see below) can be applied to BCIs that either substitute for or enhance neuromuscular output.

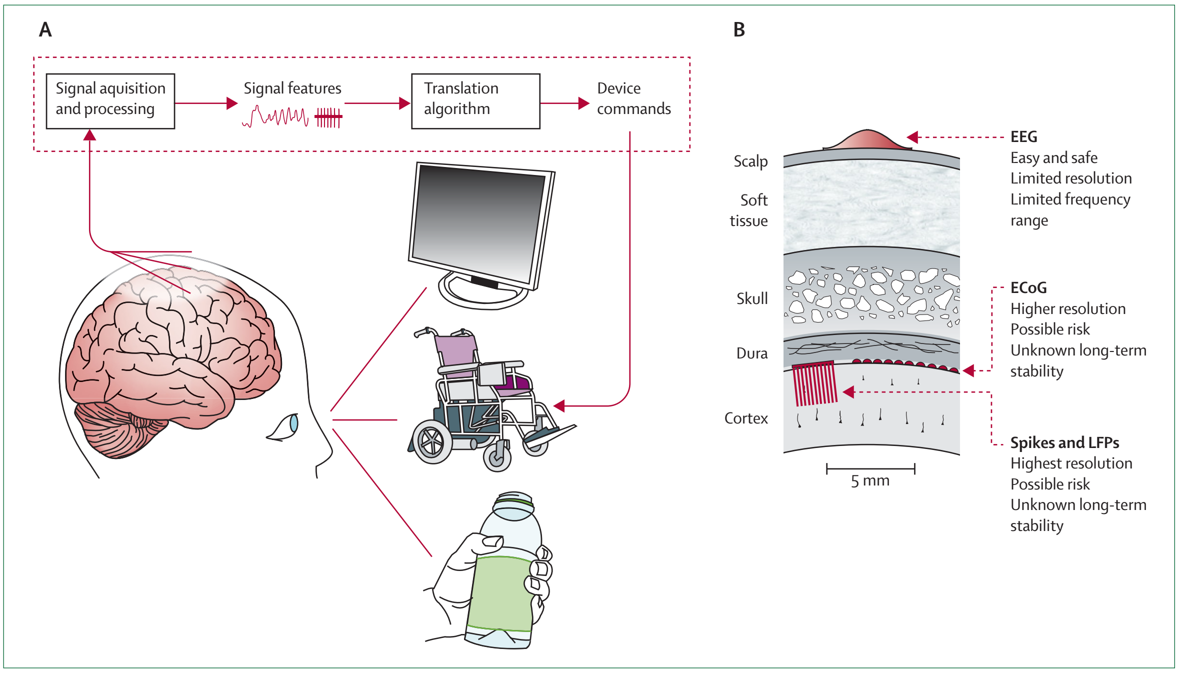

Figure 1: **Overview of a BCI system**
(A) Design and operation of a BCI system. Electrophysiological signals that indicate brain activity are obtained from the scalp, the cortical surface, or within the brain and are analysed to derive particular signal features (such as amplitudes of event-related potentials, EEG rhythms, or firing rates of single neurons). These features are translated into commands that operate an output device, such as a word-processing program, a wheelchair, or a neuroprosthetic limb. Adapted from Wolpaw JR et al,[6] with permission from Elsevier. (B) Recording locations for electrophysiological signals used by BCI systems. EEG activity is recorded using electrodes on the scalp. ECoG activity is recorded using electrodes on the cortical surface. Action potentials from single neurons or LFPs are recorded using electrode arrays implanted in the motor cortex or in other brain areas. Adapted from Wolpaw JR et al,[7] with permission from Cambridge University Press. LFP=local field potential.

Brain signals for BCIs

Brain signals can be detected and measured in many ways; these include the use of methods for recording electrical or magnetic fields, functional MRI, PET, and functional near-infrared imaging (fNIR). At present, magnetoencephalography, functional MRI, and PET are not suitable for widespread everyday use owing to their complex technical requirements, expense, and limited real-time capabilities. Only electrical field recording and possibly fNIR[8,9] are likely to be of practical value for clinical use in the near future.

Figure 1 shows that the electrical fields that result from brain activity can be recorded at the scalp (EEG activity), at the cortical surface (electrocorticographic [ECoG] activity), or within the brain (local field potentials or neuronal action potentials [spikes]). Each method has its own advantages and disadvantages. EEG recording is simple and non-invasive, but has limited topographical resolution and frequency range. In addition, EEG recordings are susceptible to contamination from electro-oculographic or electro-myographic activity from cranial muscles. ECoG and intracortical methods have better topographical resolution and wider frequency ranges, but implantation of electrode arrays on the cortical surface or within the brain is needed. Concerns about safety, the risk of tissue reaction, and long-term recording stability still need to be addressed.

The ultimate practical value of each of these methods will depend on which communication and control applications can be supported and on the extent to which the disadvantages can be overcome. The problem in determining the comparative value of non-invasive (ie, EEG) methods, moderately invasive (ie, ECoG) methods, and more invasive (ie, intracortical) methods has not yet been resolved. Although it is possible that practical, stable, and safe methods for the long-term recording of signals within the brain will soon be available, the speed and precision of communication and control that are possible with intracortical recording might not be much higher than is possible with less invasive methods.[10] At present, it seems probable that different recording methods will be useful for different applications, different users, or both. Careful and comprehensive assessments of the characteristics and capabilities of each of the alternatives are crucial. Experience of BCI research in human beings has so far primarily involved non-invasive EEG-based investigations.[6] There are a few reports of short-term ECoG studies:[11] so far, only limited data are available from people who have had intracortical electrode implants,[12–14] and most intracortical BCI data have been obtained from animal studies (primarily from monkeys).[15–20]

Signal processing

BCI technology is used to record and analyse brain signals to determine the output that is desired by the user (eg, which letter to select for spelling a word, which direction to move a cursor, and so on). This signal processing stage has two phases. The first phase is feature extraction, which is the measurement of the characteristics of the signals that encode the output. These features can be simple measures, such as the amplitudes of particular evoked potentials (eg, P300) or of particular rhythms (eg, sensorimotor rhythms) in the EEG, or the firing rates of individual cortical neurons, or they can be more complex measures, such as spectral coherences. To provide effective BCI performance, the feature-extraction component of the signal processing stage needs to focus on features that encode the relevant output (eg, the letter the user wants for spelling a word) and needs to extract those particular features accurately.

The second phase of BCI signal processing is the translation of these signal features into device commands using a translation algorithm. Brain signal characteristics such as rhythm amplitudes or neuronal firing rates are translated into commands that specify outputs, such as letter selection, cursor movement, or prosthesis operation. Translation algorithms can be simple (eg, linear equations) or complex (eg, neural networks, support vector machines).

An effective translation algorithm ensures that the user's range of control of the chosen features enables selection of the entire range of device commands. For example, the characteristic feature might be the amplitude of a 21–24 Hz β-rhythm in the EEG recording over the left sensorimotor cortex, which the user can vary over a range of 1–5 μV. Therefore, if the application is designed for a horizontal cursor movement, the translation algorithm must ensure that the 1–5 μV range enables the user to move the cursor to both the right and left edges of the screen. Furthermore, the algorithm must accommodate spontaneous variations in the user's range of control, such as those due to diurnal change or fatigue. Finally, the translation algorithm should also be able to accommodate and advance improvements in the control of the user. Thus, if the user's range of control improves from 1–5 μV to 1–8 μV, the algorithm should use this improvement to increase the speed and precision of cursor movement.

The ability of BCI technology to accommodate and facilitate adaptations of the system to the user and of the user to the system is crucial. Thus, the ability of the translation algorithm to continually adjust for spontaneous adaptations and for other changes in the signal features is important. New algorithms must be evaluated online (ie, in real-time use) as well as offline (ie, through analysis of past data) so that the effects on BCI performance of the adaptive interactions of the new algorithm with the user can be determined. Online evaluation should take place over short-term and long-term periods, because important adaptive interactions often develop gradually. Furthermore, simple algorithms (eg, linear equations[21]) have an inherent advantage because the essential ongoing adaptation of the algorithm to the user is typically simpler and more effective than for the more complex algorithms, such as neural networks[22] or support vector machines.[23] Simple algorithms should be replaced by more complex alternatives only if online and offline evaluations suggest that they provide superior long-term support without continual and arduous recalibration procedures.[24]

Learning to use BCIs

Plasticity in neurons and synapses of the CNS supports the learning of new information and the acquisition of new skills. Adaptive changes occur in neurons and synapses throughout the CNS from the cortex to the spinal cord[25,26] in initial development and across the lifespan.[27–29] The cognitive abilities and motor skills that indicate the intent of a person (eg, speaking, walking, or playing the piano) are acquired and maintained by these normal and ongoing adaptations in the CNS.

When the pathways for normal motor function are interrupted, BCIs can use brain signals as an alternative channel for communication or device control, or potentially as a way to influence brain plasticity processes that could induce recovery of normal motor control. The process of learning to operate a BCI device depends on principles of neural plasticity that are similar to those for a conventional learning process. In this case, the learning system is composed of two adaptive controllers: the brain of the BCI user and the BCI software. The BCI user produces brain signals that encode his or her intent and the BCI system brings about translation of these brain signals into commands that carry out the desired action. For example, people learning to use a sensorimotor rhythm-based BCI system typically begin by using various kinds of motor imagery to modify rhythm amplitudes. As training proceeds, the actual or imagined movements become less important, the use of a BCI system becomes more automatic (similar to conventional muscle-based skills), and the user controls the cursor with brain signals alone, without muscle activity. Virtual reality environments might be useful in facilitating control of these applications.[30]

Therefore, the effective use of a BCI is a skill that both the user and the system acquire and maintain. The user encodes intent within brain signal features that the BCI can measure, and the BCI measures these signal features and translates them into output commands. The ongoing dependence on the mutual adaptation of the user to the system and the system to the user is a basic principle of BCI operation. Proper management of this adaptation is one of the most difficult and important challenges of BCI research and development.

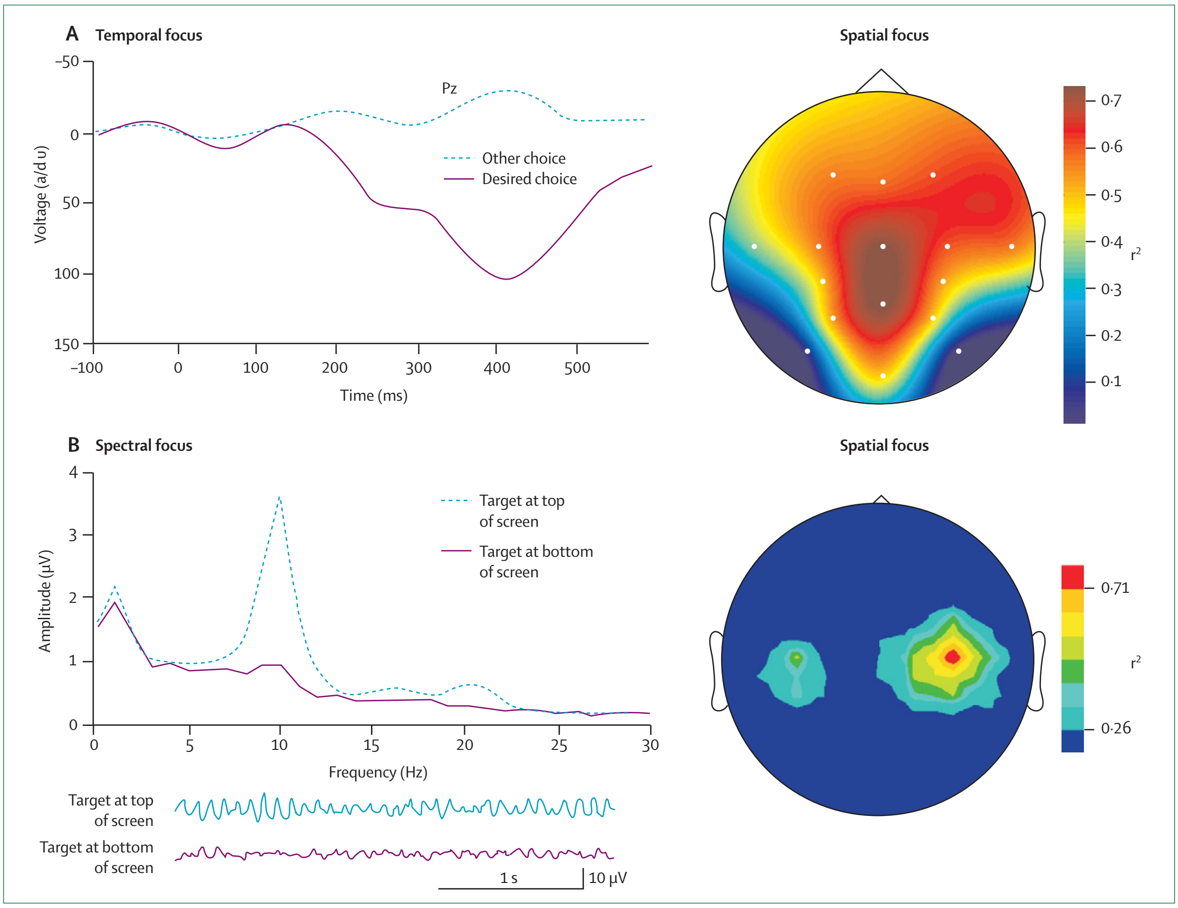

Figure 2: **EEG-based BCI systems**

(A) P300 event-related potential BCI.[31,32] A matrix of possible selections are shown on a screen. Scalp EEG signals are recorded over the centroparietal cortex while these selections flash in succession. The left panel shows that only the selection desired by the user will evoke a large P300 potential (ie, a positive potential about 300 ms after the flash). Adapted from Donchin E et al,[33] with permission from the Institute of Electrical and Electronics Engineers. The right panel shows involvement of the centroparietal cortex. (B) Sensorimotor rhythm BCI.[6,21,34,35] Scalp EEG signals are recorded over the sensorimotor cortex. Trained users control the amplitude of a 8–12 Hz μ-rhythm (or a 18–26 Hz β-rhythm) to move a cursor to a target at the top or bottom of the screen, or to targets at intermediate locations on the screen. The left panel shows the frequency spectra (top) for targets at the top and bottom of the screen and that this user's control is focused in the μ-rhythm frequency band. In addition, the left panel shows sample EEG traces (bottom) and that the μ-rhythm is prominent with the target at the top of the screen and minimal with the target at the bottom of the screen. Adapted from Wolpaw JR et al,[36] with permission from the Institute of Electrical and Electronics Engineers. In the right panel, scalp topography indicates that control is focused over the right sensorimotor cortex. Users who are well trained with BCI systems can also control movement in two or three dimensions.

BCIs for communication and device control

As described above, three types of BCI technologies have been developed on the basis of different brain signal recording methods: scalp recordings (EEG-based BCIs); cortical recordings (ECoG-based BCIs); and recordings of neuronal action potentials or local field potentials within the brain (intracortical BCIs). Here, we review these types of BCI technologies, their potential users, and their applications.

EEG-based BCIs

Three kinds of EEG-based BCI technologies have been tested in human beings. These types of BCIs are distinguished by the particular EEG features that they use to determine the user's intent. Figure 2A shows an EEG-based BCI[31,33] that focuses on the P300 event-related brain potential. The P300 signal appears in the EEG recording over central cortical areas about 300 ms after a salient or attended stimulus. In most P300-based BCI technologies described so far, the stimulus is visual. In the typical P300 BCI format, letters, numbers, or other visual stimuli are arranged in a matrix, and the rows and columns of the matrix flash in rapid succession while the user focuses attention on the item that he or she wishes to select. Only the row and column that contain the specific item will produce a P300 potential. By recognising this P300 potential, the BCI system can determine the user's selection. At present, this BCI method can enable users to communicate at rates of 20–30 bits/min.[37,38] In combination with appropriate software (eg, word prediction), this system can support word processing at rates of up to 2–4 words/min. Even though these

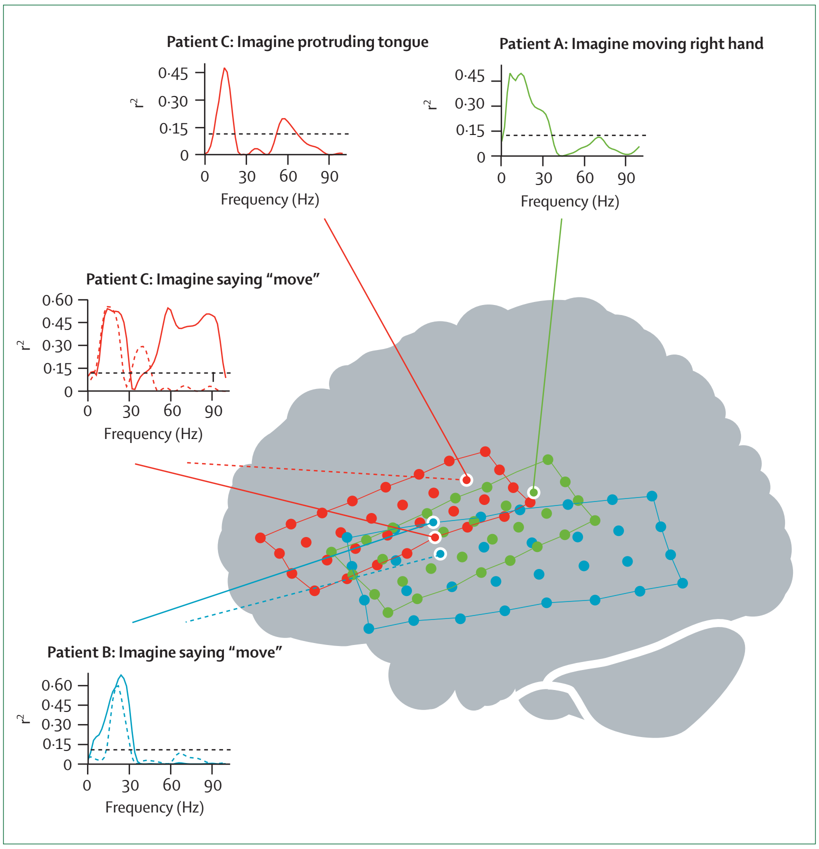

Figure 3: **An ECoG-based BCI**
ECoG control of vertical cursor movement using specific motor imagery to move the cursor up and rest (ie, no imagery) to move it down. The electrodes used for control are circled and the spectral correlations of their respective ECoG activity with target location (ie, top or bottom of screen) are shown. The specific imagined actions used are indicated. The significant levels of control achieved with different kinds of imagery are apparent (the dashed horizontal lines indicate significance at p=0·01). The solid and dotted r^2 spectra shown for patients B and C correspond to the sites indicated by the dotted and solid line locators, respectively. Modified from Leuthardt EC et al,[11] with permission from the Institute of Physics.

communication rates are low, by restoring the ability for independent communication, a P300-based BCI can greatly improve the quality of life of the user and of family members and caregivers.[39] Continuing improvements in stimulation formats and brain signal analysis are likely to increase these communication rates substantially in the future.

Figure 2B shows a BCI system using sensorimotor rhythms.[21,22,34,35,40–43] These rhythms are 8–12 Hz (μ) and 18–26 Hz (β) oscillations in the EEG signals recorded over sensorimotor cortices. μ-rhythm and β-rhythm amplitudes typically change with movement, sensation, and during motor imagery. Results from BCI studies have shown that people can learn to control μ-rhythm or β-rhythm amplitudes in the absence of any movement or sensation, and can use this control to move a cursor to select letters or icons on a screen or to operate a simple orthotic device. Both one-dimensional and two-dimensional cursor control,[21] and even three-dimensional cursor control,[44] can be achieved. Similar to P300-based BCIs, sensorimotor rhythm-based BCIs can support basic word processing or other simple functions. These systems might also support multidimensional control of the movements of a neuroprosthetic limb or a device such as a robotic arm. At present, the speed and precision of the multidimensional movement control achieved in human beings by sensorimotor-rhythm-based BCIs[21,44] equals or exceeds that achieved so far with invasive methods.[12,14] An EEG-based BCI can also recognise and use slow cortical potentials (SCPs), which last from 300 ms to several seconds.[45–47] In normal brain function, negative SCPs accompany preparatory depolarisation of the underlying cortical network, whereas positive SCPs are thought to reflect cortical disfacilitation or inhibition. With substantial training, control of SCPs to produce positive or negative voltage shifts can be learnt and used for basic word processing and other simple control tasks, such as accessing the internet.[45–47]

Available P300-based, sensorimotor rhythm-based, or SCP-based BCIs rely mainly on visual stimuli and visual feedback. Thus, although they do not depend on eye movements, they do need the user to be able to see and to maintain gaze. People who are severely disabled might not have the visual acuity or gaze stability needed to see the visual stimuli associated with BCI use, particularly if the stimuli change rapidly. Thus, BCI systems that use auditory rather than visual stimuli would be preferable, or even crucial, for some users, and such systems are being investigated.[48]

ECoG-based BCIs

Figure 3 shows a BCI system that uses sensorimotor rhythms in ECoG signals from electrode arrays on the cortical surface to implement a desired action.[11,49] ECoG recordings include μ-rhythms and β-rhythms, as well as the higher frequency gamma (30–200 Hz) rhythms, which are small or not visible in EEG recordings. With adequate electrode spacing, ECoG recordings can be used to detect activity limited to only a few mm² of cortical surface. At present, ECoG studies have been limited to short-term experiments in patients who were temporarily implanted with electrode arrays before surgery for epilepsy.[11,49] The results from these studies show sharply focused ECoG activity associated with movement and sensation and with motor imagery. Furthermore, the use of motor imagery to influence ECoG rhythm amplitudes to control cursor movements can be learnt with only a few minutes of training.

Some characteristics of ECoG-based BCI technologies suggest that they might provide substantially better communication and control than do EEG-based BCIs. One characteristic is the speed of learning of the user, which seems to be faster than that typically found with sensorimotor rhythms in scalp-recorded EEGs; furthermore, ECoG-based BCIs have a superior topographical resolution and wider spectral range than EEG-based BCIs, and an absence of contamination from electromyographic, electro-oculographic, or other non-brain signals. Widespread use of ECoG-based BCIs will need the development of fully implanted systems (ie, systems that use telemetry and thus do not have wires passing through the skin) and definitive evidence that these systems can function safely and reliably for many years.

Intracortical BCIs

Figure 4 shows a multi-electrode array for intracortical recording and the placement of the array within the motor cortex. Results from intracortical BCI studies in monkeys and, to a lesser extent, in human beings, show that single-neuron activity recorded from multi-electrode arrays can be used to move a cursor in one, two, or three dimensions.[12,13,15–20] Local field potentials, which can be detected by these arrays and indicate nearby synaptic and neuronal activity, might be able to provide similar multidimensional cursor control.[50] The standard approach in intracortical single-neuron and local field potential studies has been to define the neuronal activity that accompanies standardised limb movements, to use this activity for simultaneous control of comparable cursor movements, and to show that neuronal activity alone can control cursor movements without actual limb movements. As shown in figure 4, the relation between neuronal activity and cursor movements can change over time; ideally, neuronal activity adapts over training sessions to improve cursor control. This adaptation, as with the adaptations seen with EEG-based and ECoG-based BCI technologies, shows the need for the initial and continuing mutual adaptation of the system to the user and the user to the system.

The main concerns that must be dealt with before intracortical BCI technologies can be used clinically include the following: long-term safety; the stability and duration of the signals; tissue reactions to the implanted electrodes; the long-term usefulness of the signals; and the extent to which the control capabilities of the device (eg, for control of a neuroprosthetic limb) can exceed those of less invasive BCI systems. With regard to this last concern, a comparison of two videos[51,52] indicates that a non-invasive EEG-based BCI that uses sensorimotor rhythms[51] can provide cursor control that is similar in speed and accuracy to that achieved with intracortical methods.[52]

Potential users

At present, BCI technologies are likely to be useful mainly for people for whom conventional assistive communication methods are not effective, because severe motor disabilities will preclude their use of voluntary muscle control on which conventional methods depend. Those most likely to benefit include people with ALS who decide to accept artificial ventilation to prolong life as the disease progresses, children and adults with severe cerebral palsy who do not have useful muscle control, patients with brainstem strokes who have only minimal eye movement control, individuals with severe muscular dystrophies or peripheral neuropathies, and possibly people with acute disorders causing extensive paralysis (eg, Landry-Guillain-Barré syndrome). People with slightly less severe disabilities, such as patients with high cervical spinal cord injuries, might also prefer BCI technology to conventional assistive communication methods because conventional methods require use of their remaining voluntary muscle control (eg, methods that depend on gaze direction or electromyographic activity of facial muscles). The extent to which future BCI technologies can benefit people with less severe disabilities will depend on the speed and precision of the control that the BCI systems can provide and on the reliability and convenience of the BCI technology.

The specific BCI methods that are most effective for people with different disabilities might vary according to individual needs or brain signals affected as a result of the particular underlying CNS abnormality.[53] For example,

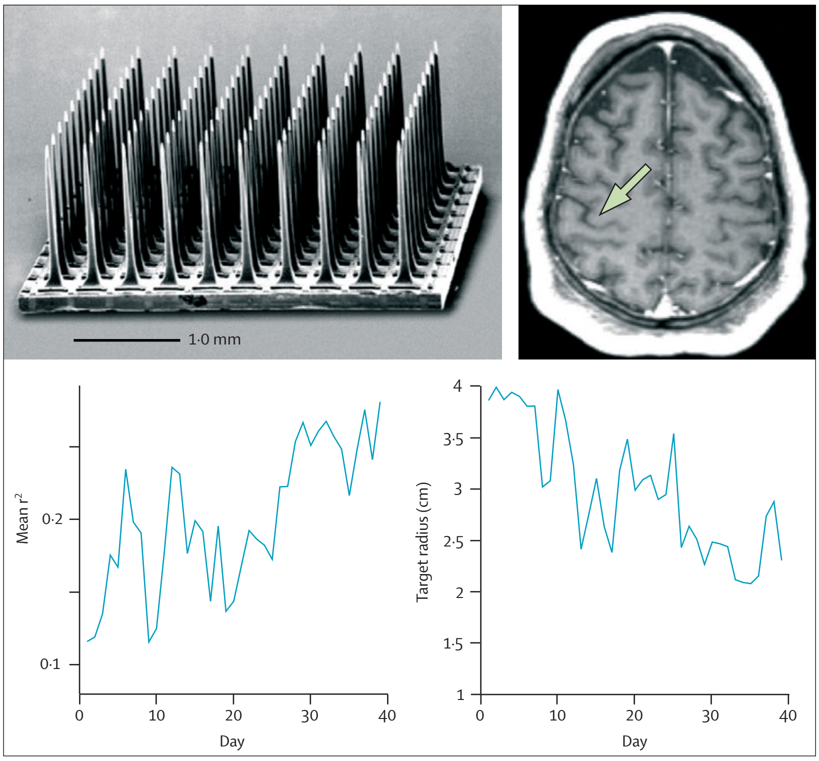

Figure 4: **Intracortical BCIs**

The top left panel shows an example of an array of 100 microelectrodes that would be chronically implanted in the motor cortex of a human being to record neuronal action potentials and local field potentials to control a cursor or other device. The top right panel shows the placement of an array in the motor cortex of a human being (arrow). Adapted from Hochberg LR et al,[14] with permission from Macmillan Publishers Ltd. The bottom panel shows control of three-dimensional cursor movements by individual neurons in the motor cortex of a monkey. In the left graph, improvement over daily training sessions is shown, measured as the average correlation of the firing rate of a single cortical neuron with target direction. In the right graph, the resulting improvement in motor function is shown, measured as the mean target radius required to maintain a 70% target hit rate. As the firing rates of the neurons that are controlling cursor movement become more strongly correlated with target direction, the size of the target can be reduced. Reproduced from Taylor DM et al,[17] with permission from the American Association for the Advancement of Science.

the pathology in the motor cortex that can occur in patients with ALS or the subcortical damage that is present in patients with severe cerebral palsy might impair the generation or control of sensorimotor rhythms or single-neuron activity (although available data suggest that this might not be true for ALS[54]). In these patients, other brain signals (eg, P300 potentials or neuronal activity from other brain areas) might be effective alternatives.

Many other factors might considerably affect the success of BCI applications. For example, the decision to adopt a BCI system and use it in everyday life might depend on concerns such as the convenience and complexity of the steps required for applying and removing electrodes and for accessing the BCI applications, or the user's appearance while operating the BCI.

Applications

BCI technologies have many possible applications, ranging from simple to complex. Simple BCI applications have been validated in the laboratory and are in limited clinical use. These include systems for answering "yes" or "no" to questions, managing basic control of the user's environment (eg, lights and temperature), controlling a television, or opening and closing a hand orthosis. These simple systems can be configured for basic word processing, sending emails, accessing the internet, or operating a motorised wheelchair. Such basic BCI applications might enable people who are almost totally paralysed (ie, "locked-in") to have a higher quality of life that can also be productive. Many studies have indicated that, with proper supportive care and the capability for basic communication, severely paralysed patients can have what they regard to be a reasonable quality of life and are only a little more likely to be depressed than are people without motor disabilities.[54–57] Some people who are severely disabled currently use EEG-based BCI systems for important purposes in their daily lives—for example, a neuroscientist with ALS has used a BCI system to run his National Institutes of Health-funded research programme since 2006.[58]

BCI technologies might also support more complex applications such as the operation of a robotic arm or a neuroprosthetic limb that provides multidimensional movement to a paralysed limb. Although many efforts are focusing on developing invasive BCI systems for these complex uses,[11–13,15–20,49] non-invasive EEG-based BCIs might also serve these purposes.[21,44] The future importance of such BCI applications will depend on their capacities, practicality, and reliability, their acceptance by particular groups of users, and on the extent to which they have substantial advantages over conventional assistive technology.

Careful assessment is needed to establish the practical value of BCI technologies to restore communication and control: the long-term reliability of BCIs, the extent to which people use them in their daily lives, and whether use improves mood, quality of life, and productivity of the user need to be proven. Specific applications that focus on each user's individual needs, desires, and physical and social environments will need to be configured frequently, particularly in the early stages of development of a BCI. Although the cost of BCI equipment is modest, current systems require substantial and ongoing technical support, which is very expensive and available only from a few research groups. Therefore, BCI systems are not available to most potential users at present. Widespread dissemination of BCI systems to those who would benefit from them will depend on the extent to which the need for continuing technical support can be minimised—BCI systems need to be easy to set up, easy to use, and easy to maintain if they are to have a substantial salutary effect on the lives of people with severe motor disabilities.

BCIs for restoring normal CNS function

Since the first description of EEG by Berger,[59] these brain signals have been used mainly for clinical diagnosis and for investigating brain function. At the same time, there have been investigations into the therapeutic use of EEG signals. For example, in work first initiated several decades ago, training people to control EEG features was studied as an intervention to decrease seizure frequency in people with epilepsy, to ameliorate attention-deficit hyperactivity disorders, or to treat other disorders.[60–65] These studies have focused mainly on producing long-term unidirectional changes (ie, an increase or decrease in particular EEG features) rather than on producing the rapid bi-directional changes needed for the real-time control of a BCI system. The history and current status of these efforts are dealt with elsewhere.[60–65] We focus on a new potential BCI therapeutic initiative that has begun only in the past several years and is generating substantial interest—the use of EEG-based BCI protocols to improve volitional motor control that has been impaired by trauma or disease.

When developing new methods to restore motor function, it is important to use available scientific evidence and target the impairment or pathology as directly as possible.[66] The most credible, evidence-based framework for creating an effective motor re-learning intervention after brain injury is that of activity-dependent CNS plasticity.[25–29] In an intact nervous system, activity-dependent CNS plasticity results in learning that changes motor function. Activity-dependent CNS plasticity is not limited to the healthy nervous system and can occur with trauma or disease; this plasticity can include changes at synaptic, neuronal, and circuit levels.[67–81] Stroke is followed by extensive plasticity in the cortex and elsewhere, as has been shown in animals[25,29,82–86] and in human beings.[87–94] After CNS disease or damage (such as after stroke), activity-dependent plasticity can positively or negatively affect the nervous system. Plasticity might lead to the restoration of more normal motor function but if repetitive abnormal movements are made, activity-dependent plasticity might solidify or even exacerbate abnormal motor function.

For successful restoration of CNS function, interventions that induce activity-dependent brain plasticity must be properly identified and targeted.[66] Current standard care approaches to restoring motor function focus on interventions at the periphery of the body, specifically the upper and lower limbs. The expectation is that repetitive movement practice will influence activity-dependent CNS plasticity that restores more normal function. By contrast, BCI-based approaches use EEG signals (or other direct measures of brain activity) to encourage and guide CNS plasticity to improve motor function.

Two BCI-based motor learning strategies are under study. The first strategy, similar to the early studies with BCI technologies to reduce seizure frequency, is to train patients to produce more normal brain activity (eg, as measured by specific EEG features; figure 5A). The hypothesis is that by influencing CNS plasticity that produces more normal activity, more normal CNS function will be restored and thus motor control will improve. The second strategy uses brain activity to activate a device that assists movement (figure 5B); by improving motor function, this movement is postulated to produce sensory input that induces CNS plasticity and leads to restoration of normal motor control (figure 5C).

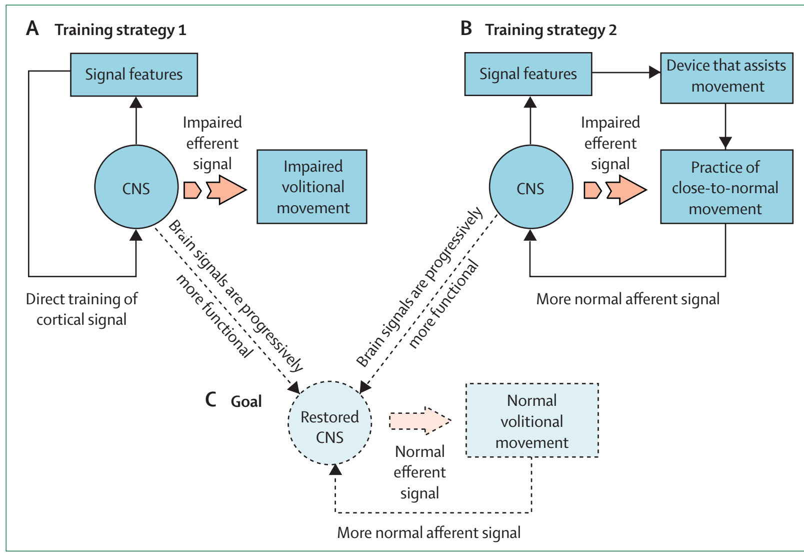

Figure 5: **Two BCI-based training strategies to encourage and guide CNS plasticity to improve motor function**
(A) This training strategy translates specific features of brain activity into an action (eg, cursor movement) and uses that action as feedback to train patients to produce more normal brain activity. The hypothesis is that the plasticity that produces this more normal activity will also restore more normal CNS function and will therefore improve motor control. (B) This training strategy uses specific features of brain activity to activate a device that assists movement that can compensate for the patient's impaired neuromuscular control during motor tasks. The hypothesis is that, by improving motor function, this assistance will produce sensory input that induces CNS plasticity to restore more normal motor control. (C) The first strategy aims to normalise brain activity with the expectation that this will be accompanied by improved motor function, whereas the second strategy uses brain activity to assist practice of more normal neuromuscular control with the expectation that the more normal sensory input produced by the better motor function will induce plasticity that improves neuromuscular control.

Training of brain signal characteristics

The plausibility of the first strategy (figure 5A) is supported by extensive evidence from animals and human beings (summarised above). These studies show that appropriate conditioning regimens can change brain signal features, including features of EEG, ECoG, or single-neuron activity.[11,17,19,21,95] In animals, motor recovery after stroke is associated with structural and functional changes, such as neurite outgrowth in the intact region immediately surrounding the infarct,[67,68] increased synaptogenesis,[68] and increased axonal sprouting.[69] Neuronal functional changes, such as increased excitability[70] and sequential expression of growth-promoting genes associated with axonal sprouting,[71] are also seen in these animals (including in older animals[72]). Similar mechanisms of neuronal plasticity seem to occur in human beings.[73–76] Larger infarcts, and more severe persistent motor deficits in particular, are likely to be associated with abnormal changes in activity to the non-lesioned hemisphere.[73] Changes can occur in regions distant from the infarct and include hyperexcitability of neurons in both hemispheres,[77] reorganisation of cortical sensory and motor maps,[78,79] sprouting of abnormal connections and new connections among cortical areas,[80] and re-routing of normal intrahemispheric and interhemispheric connections among motor regions.[81] Some studies have provided new insights into neural learning mechanisms and processes, describing processes such as the "training neuron" array, which can teach another array of neurons to become activated,[96] and the modulation of complex pathways in real-time (eg, pain perception[97]). These studies might help to refine training protocols, adding to earlier evidence for the principles of motor learning practice of closer to normal movements,[83] focused attention,[98] repetition of desired movements,[99–102] and training specificity.[103] By inducing changes in the features of brain activity, BCI protocols might be able to guide this plasticity to promote recovery of motor function.

So far, early results are promising: preliminary studies have shown that individuals who have had a stroke could gain control of specific EEG features.[104–106] In an associated study of three individuals who had survived a stroke,[107] Daly and co-workers recorded EEG activity while the patients planned and undertook a reaching task with the arm that had been affected by the stroke. EEG data were obtained before and after a motor learning training regimen. Cortical planning latency and cortical signal amplitude on EEG were measured during preparation for the reaching task. These EEG features improved in parallel with improvement in motor activity. However, so far, there is no information on whether training a patient to produce more normal brain signal features will improve motor function that involves the same areas that produce those signals.

Control of brain signals to activate a device that assists movement

The second training strategy (figure 5B) uses brain signals to activate a device that assists movement. This strategy is supported by evidence that practising or observing movements that are as close to normal as possible might help to improve motor function,[83,108,109] and help to guide newly sprouting axons to the appropriate cortical regions.[110] After brain injury, normal movement is often not possible and, therefore, other means to practise more normal movements are needed. Several randomised controlled trials have indicated that assistance of movement by functional electrical stimulation through surface electrodes can substantially improve upper limb function in individuals who have been mildly to moderately[3,4] or severely[2] impaired by stroke. Another promising approach is to combine movement training with robotic devices that assist movement.[2] Although these methods have proven to be effective in individuals affected by stroke with moderate or severe deficits, not all patients improved, and, in those patients who did improve, normal motor control was not regained in all individuals.[2–5]

Furthermore, the improvement in motor control that was shown entailed the high cost of many therapy sessions that needed close attention of staff; thus, alternative approaches, such as a BCI-based method, would be attractive. Brain signals might be used to activate a device that assists functional electrical stimulation or assists robotics that would enable practice of a movement that is closer to normal. BCI assistance would initially be configured to depend on the generation of a more normal brain signal. Although preliminary studies have provided variable results, taken together these studies suggest that this approach could be successful in some patients.[104,106,111,112]

Efforts to use BCI support to encourage and guide the restoration of motor function after brain injury are just beginning, and several gaps in our understanding need to be resolved. These unknown factors include the extent to which patients have detectable brain signals that can support one or both of the training strategies (figure 5); which brain signal features are best suited for use in restoring motor functions and how these features can be used most effectively; and what the most effective formats are for the BCIs aimed at improving motor functions (eg, what guidance should be provided to the user to maximise training that produces beneficial changes in brain signals). The eventual value of BCI technologies for improving motor function in individuals who have strokes or other neurological disorders depends on adequate answers to these questions.

Expectations for the future

EEG-based BCIs have begun to provide basic communication and motor control abilities to people with severe motor disabilities, such as patients with ALS who decide to accept long-term ventilation. The effect of these simple non-invasive BCI technologies will depend on further improvements in the ease and convenience of their daily use and on whether the need for continuing technical support can be further reduced. Both non-invasive and invasive BCI technologies are being developed and are likely to improve substantially in their capabilities for communication and control. Their future potential and importance will depend on what functions they can provide (eg, control of neuroprostheses), and the safety, convenience, and reliability of their long-term use.

BCI systems might also help to restore motor function after stroke or in other chronic CNS traumatic injuries or disease. They might be used to translate brain signals into outputs that can induce and guide activity-dependent CNS plasticity to promote the return of useful motor function. These efforts, which have just begun, mainly depend on the characteristics and strength of the relation between brain activity indicated by signal features (eg, EEG rhythms or single-neuron firing rates) and effective motor function. Improvements in our understanding of this relation will enable us to predict the extent of the potential success and eventual applications of BCI technology in rehabilitation protocols.

Search strategy and selection criteria

References for this Review were identified from searches by the authors done over the past 25 years, as well as through exhaustive searches of Ovid Medline and PubMed by use of the search terms "brain–computer interface", "BCI", "brain–machine interface", and "BMI", both alone and in combination with each of the following search terms: "communication", "environment control", "device control", "robot", "prosthetic", "prosthesis", "FES", "functional electrical stimulation", and "stimulator", from January 2000 until April 2008. Only papers published in English were reviewed. The final reference list was generated on the basis of relevance to the topics covered in this Review.

Contributors

Both authors contributed equally in preparing and revising the drafts of this Review. JRW provided figures 1 and 2, and JJD provided figure 3.

Conflicts of interest

JJD is a consultant to a company that develops medical devices (pro bono at the time of publication). JRW is co-author of several patents related to BCI technology. At the time of publication, these patents had not produced any income.

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References

1 Daly JJ, Roenigk K, Holcomb J, et al. A randomized controlled trial of functional neuromuscular stimulation in chronic stroke subjects. *Stroke* 2006; **37:** 172–78.

2 Daly JJ, Hogan N, Perepezko EM, et al. Response to upper-limb robotics and functional neuromuscular stimulation following stroke. *J Rehabil Res Dev* 2005; **42:** 723–36.

3 Ring H, Rosenthal N. Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation. *J Rehabil Med* 2005; **37:** 32–36.

4 Alon G, Sunnerhagen KS, Geurts AC, Ohry A. A home-based, self-administered stimulation program to improve selected hand functions of chronic stroke. *NeuroRehabilitation* 2003; **18:** 215–25.

5 Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA* 2006; **296:** 2095–104.

6 Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. Brain-computer interfaces for communication and control. *Clin Neurophysiol* 2002; **113:** 767–91.

7 Wolpaw JR, Birbaumer N. Brain-computer interfaces for communication and control. In: Selzer M, Clarke S, Cohen L, Duncan PW, Gage F (eds). Textbook of Neural Repair and Rehabilitation: Volume 1, Neural Repair and Plasticity. Cambridge: Cambridge University Press, 2006: 602–14.

8 Sitaram R, Zhang H, Guan C, Thulasidas M, Hoshi Y, Ishikawa A, et al. Temporal classification of multichannel near-infrared spectroscopy signals of motor imagery for developing a brain-computer interface. *Neuroimage* 2007; **34:** 1416–27.

9 Naito M, Michioka Y, Ozawa K, Ito Y, Kiguchi M, Kanazawa T. A communication means for totally locked-in ALS patients based on changes in cerebral blood volume measured with near-infrared light. *IEICE Transactions on Information and Systems* 2007; **E90-D:** 1028–37.

10 Rokni U, Richardson AG, Bizzi E, Seung HS. Motor learning with unstable neural representations. *Neuron* 2007; **54:** 653–66.

11 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.

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 Kennedy PR, Bakay RA. Restoration of neural output from a paralyzed patient by a direct brain connection. *Neuroreport* 1998; **9:** 1707–11.

14 Hochberg LR, Serruya MD, Friehs GM, et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* 2006; **442:** 164–71.

15 Serruya MD, Hatsopoulos NG, Paninski L, Fellows MR, Donoghue JP. Instant neural control of a movement signal. *Nature* 2002; **416:** 141–42.

16 Taylor DM, Tillery SI, Schwartz AB. Information conveyed through brain-control: cursor versus robot. *IEEE Trans Neural Syst Rehabil Eng* 2003; **11:** 195–99.

17 Taylor DM, Tillery SI, Schwartz AB. Direct cortical control of 3D neuroprosthetic devices. *Science* 2002; **296:** 1829–32.

18 Musallam S, Corneil BD, Greger B, Scherberger H, Andersen RA. Cognitive control signals for neural prosthetics. *Science* 2004; **305:** 258–62.

19 Carmena JM, Lebedev MA, Crist RE, et al. Learning to control a brain-machine interface for reaching and grasping by primates. *PLoS Biol* 2003; **1:** E42.

20 Chapin JK, Moxon KA, Markowitz RS, Nicolelis MA. Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex. *Nat Neurosci* 1999; **2:** 664–70.

21 Wolpaw JR, McFarland DJ. Control of a two-dimensional movement signal by a noninvasive brain-computer interface in humans. *Proc Natl Acad Sci USA* 2004; **101:** 17849–54.

22 Kostov A, Polak M. Parallel man-machine training in development of EEG-based cursor control. *IEEE Trans Rehabil Eng* 2000; **8:** 203–05.

23 Fatourechi M, Ward RK, Birch GE. A self-paced brain-computer interface system with a low false positive rate. *J Neural Eng* 2008; **5:** 9–23.

24 Muller KR, Anderson CW, Birch GE. Linear and nonlinear methods for brain-computer interfaces. *IEEE Trans Neural Syst Rehabil Eng* 2003; **11:** 165–69.

25 Nudo RJ. Mechanisms for recovery of motor function following cortical damage. *Curr Opin Neurobiol* 2006; **16:** 638–44.

26 Wolpaw JR, Tennissen AM. Activity-dependent spinal cord plasticity in health and disease. *Annu Rev Neurosci* 2001; **24:** 807–43.

27 Ziemann U, Ilic TV, Pauli C, Meintzschel F, Ruge D. Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *J Neurosci* 2004; **24:** 1666–72.

28 Kempermann G, Kuhn HG, Gage FH. Genetic influence on neurogenesis in the dentate gyrus of adult mice. *Proc Natl Acad Sci USA* 1997; **94:** 10409–14.

29 Foster TC, Dumas TC. Mechanism for increased hippocampal synaptic strength following differential experience. *J Neurophysiol* 2001; **85:** 1377–83.

30 Leeb R, Friedman D, Muller-Putz GR, Scherer R, Slater M, Pfurtscheller G. Self-paced (asynchronous) BCI control of a wheelchair in virtual environments: a case study with a tetraplegic. *Comput Intell Neurosci* 2007; **2007:** 79642.

31 Sellers EW, Kubler A, Donchin E. Brain-computer interface research at the University of South Florida Cognitive Psychophysiology Laboratory: the P300 Speller. *IEEE Trans Neural Syst Rehabil Eng* 2006; **14:** 221–24.

32 Farwell LA, Donchin E. Talking off the top of your head: toward a mental prosthesis utilizing event-related brain potentials. *Electroencephalogr Clin Neurophysiol* 1988; **70:** 510–23.

33 Donchin E, Spencer KM, Wijesinghe R. The mental prosthesis: assessing the speed of a P300-based brain-computer interface. *IEEE Trans Rehabil Eng* 2000; **8:** 174–79.

34 Muller-Putz GR, Scherer R, Pfurtscheller G, Rupp R. EEG-based neuroprosthesis control: a step towards clinical practice. *Neurosci Lett* 2005; **382:** 169–74.

35 Pfurtscheller G, Neuper C, Muller GR, et al. Graz-BCI: state of the art and clinical applications. *IEEE Trans Neural Syst Rehabil Eng* 2003; **11:** 177–80.

36 Wolpaw JR, McFarland DJ, Vaughan TM. Brain-computer interface research at the Wadsworth Center. *IEEE Trans Rehabil Eng* 2000; **8:** 222–26.

37 Serby H, Yom-Tov E, Inbar GF. An improved P300-based brain-computer interface. *IEEE Trans Neural Syst Rehabil Eng* 2005; **13:** 89–98.

38 Lenhardt A, Kaper M, Ritter HJ. An adaptive P300-based online brain-computer interface. *IEEE Trans Neural Syst Rehabil Eng* 2008; **16:** 121–30.

39 Sellers EW, Vaughan TM, McFarland DJ, et al. Brain-computer interface for people with ALS: long-term daily use in the home environment. Society for Neuroscience, San Diego, CA, USA. November 2007 (Abstract 414.5). Available at http://www.abstractsonline.com/viewer/viewAbstract.asp?CKey={024A3B7C-151C-4882-AD39-791772961CF0}&MKey={FF8B70E5-B7F9-4D07-A58A-C1068FDE9D25}&AKey={3A7DC0B9-D787-44AA-BD08-FA7BB2FE9004}&SKey={08E855C0-E4D9-473F-A152-8671E2CE33B7}.

40 Roberts SJ, Penny WD. Real-time brain-computer interfacing: a preliminary study using Bayesian learning. *Med Biol Eng Comput* 2000; **38:** 56–61.

41 Wolpaw JR, McFarland DJ, Vaughan TM, Schalk G. The Wadsworth Center brain-computer interface (BCI) research and development program. *IEEE Trans Neural Syst Rehabil Eng* 2003; **11:** 204–07.

42 Wolpaw JR, McFarland DJ. Multichannel EEG-based brain-computer communication. *Electroencephalogr Clin Neurophysiol* 1994; **90:** 444–49.

43 Wolpaw JR, McFarland DJ, Neat GW, Forneris CA. An EEG-based brain-computer interface for cursor control. *Electroencephalogr Clin Neurophysiol* 1991; **78:** 252–59.

44 McFarland DJ, Sarnacki WA, Wolpaw JR. Electroencephalographic (EEG) control of three-dimensional movement. Society for Neuroscience, Washington, DC, USA. November 2008. Abstract 778.4. Available at http://www.abstractsonline.com/viewer/viewAbstract.asp?CKey={CD433551-1B3F-48F0-9FD0-3DE3D157AE87}&MKey={AFEA068D-D012-4520-8E42-10E4D1AF7944}&AKey={3A7DC0B9-D787-44AA-BD08-FA7BB2FE9004}&SKey={FA317E68-3331-4F94-B0D9-6FA70986F1E4}.

45 Kubler A, Neumann N, Kaiser J, Kotchoubey B, Hinterberger T, Birbaumer NP. Brain-computer communication: self-regulation of slow cortical potentials for verbal communication. *Arch Phys Med Rehabil* 2001; **82:** 1533–39.

46 Birbaumer N, Kubler A, Ghanayim N, et al. The thought translation device (TTD) for completely paralyzed patients. *IEEE Trans Rehabil Eng* 2000; **8:** 190–93.

47 Birbaumer N, Ghanayim N, Hinterberger T, et al. A spelling device for the paralysed. *Nature* 1999; **398:** 297–98.

48 Nijboer F, Furdea A, Gunst I, et al. An auditory brain-computer interface (BCI). *J Neurosci Methods* 2008; **167:** 43–50.

49 Schalk G, Miller KJ, Anderson NR, et al. Two-dimensional movement control using electrocorticographic signals in humans. *J Neural Eng* 2008; **5:** 75–84.

50 Pesaran B, Pezaris JS, Sahani M, Mitra PP, Andersen RA. Temporal structure in neuronal activity during working memory in macaque parietal cortex. *Nat Neurosci* 2002; **5:** 805–11.

51 Wolpaw JR, McFarland DJ. Control of a two-dimensional movement signal by a noninvasive brain-computer interface in humans. Supplementary material, movie 1. *Proc Natl Acad Sci USA* 2004; **101:** 17849–54 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=15585584; accessed March 3, 2008).

52 Hochberg LR, Serruya MD, Friehs GM, et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Supplementary material, video 1. Center-out task. *Nature* 2006; **442:** 164–171 (http://www.nature.com/nature/journal/v442/n7099/suppinfo/nature04970.html; accessed March 5, 2008).

53 Chin CA, Barreto A. The integration of electromyogram and eye gaze tracking inputs for hands-free cursor control. *Biomed Sci Instrum* 2007; **43:** 152–57.

54 Kubler A, Nijboer F, Mellinger J, et al. Patients with ALS can use sensorimotor rhythms to operate a brain-computer interface. *Neurology* 2005; **64:** 1775–77.

55 Robbins RA, Simmons Z, Bremer BA, Walsh SM, Fischer S. Quality of life in ALS is maintained as physical function declines. *Neurology* 2001; **56:** 442–44.

56 Maillot F, Laueriere L, Hazouard E, Giraudeau B, Corcia P. Quality of life in ALS is maintained as physical function declines. *Neurology* 2001; **57:** 1939.

57 Simmons Z, Bremer BA, Robbins RA, Walsh SM, Fischer S. Quality of life in ALS depends on factors other than strength and physical function. *Neurology* 2000; **55:** 388–92.

58 Vaughan TM, McFarland DJ, Schalk G, et al. The Wadsworth BCI Research and Development Program: at home with BCI. *IEEE Trans Neural Syst Rehabil Eng* 2006; **14:** 229–33.

59 Berger H. [Über das electrenkephalogramm des menchen]. *Archiv für Psychiatrie Nervenkrankheiten* 1929; **87:** 527–70.

60 Walker JE, Kozlowski GP. Neurofeedback treatment of epilepsy. *Child Adolesc Psychiatr Clin N Am* 2005; **14:** 163–76.

61 Monderer RS, Harrison DM, Haut SR. Neurofeedback and epilepsy. *Epilepsy Behav* 2002; **3:** 214–18.

62 Sterman MB, Egner T. Foundation and practice of neurofeedback for the treatment of epilepsy. *Appl Psychophysiol Biofeedback* 2006; **31:** 21–35.

63 Strehl U, Trevorrow T, Veit R, et al. Deactivation of brain areas during self-regulation of slow cortical potentials in seizure patients. *Appl Psychophysiol Biofeedback* 2006; **31:** 85–94.

64 Monastra VJ, Lynn S, Linden M, Lubar JF, Gruzelier J, LaVaque TJ. Electroencephalographic biofeedback in the treatment of attention-deficit/hyperactivity disorder. *Appl Psychophysiol Biofeedback* 2005; **30:** 95–114.

65 Angelakis E, Stathopoulou S, Frymiare JL, Green DL, Lubar JF, Kounios J. EEG neurofeedback: a brief overview and an example of peak alpha frequency training for cognitive enhancement in the elderly. *Clin Neuropsychol* 2007; **21:** 110–29.

66 Daly JJ, Ruff RL. Construction of efficacious gait and upper limb functional interventions based on brain plasticity evidence and model-based measures for stroke patients. *Scientific World Journal* 2007; **7:** 2031–45.

67 Ng SC, de la Monte SM, Conboy GL, Karns LR, Fishman MC. Cloning of human GAP-43: growth association and ischemic resurgence. *Neuron* 1988; **1:** 133–39.

68 Stroemer RP, Kent TA, Hulsebosch CE. Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. *Stroke* 1995; **26:** 2135–44.

69 Carmichael ST, Wei L, Rovainen CM, Woolsey TA. New patterns of intracortical projections after focal cortical stroke. *Neurobiol Dis* 2001; **8:** 910–22.

70 Schiene K, Bruehl C, Zilles K, et al. Neuronal hyperexcitability and reduction of GABAA-receptor expression in the surround of cerebral photothrombosis. *J Cereb Blood Flow Metab* 1996; **16:** 906–14.

71 Carmichael ST, Archibeque I, Luke L, Nolan T, Momiy J, Li S. Growth-associated gene expression after stroke: evidence for a growth-promoting region in peri-infarct cortex. *Exp Neurol* 2005; **193:** 291–311.

72 Li S, Carmichael ST. Growth-associated gene and protein expression in the region of axonal sprouting in the aged brain after stroke. *Neurobiol Dis* 2006; **23:** 362–73.

73 Cramer SC, Shah R, Juranek J, Crafton KR, Le V. Activity in the peri-infarct rim in relation to recovery from stroke. *Stroke* 2006; **37:** 111–15.

74 Cramer SC, Nelles G, Benson RR, et al. A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke* 1997; **28:** 2518–27.

75 Teasell R, Bayona NA, Bitensky J. Plasticity and reorganization of the brain post stroke. *Top Stroke Rehabil* 2005; **12:** 11–26.

76 Jaillard A, Martin CD, Garambois K, Lebas JF, Hommel M. Vicarious function within the human primary motor cortex? A longitudinal fMRI stroke study. *Brain* 2005; **128:** 1122–38.

77 Redecker C, Luhmann HJ, Hagemann G, Fritschy JM, Witte OW. Differential downregulation of GABAA receptor subunits in widespread brain regions in the freeze-lesion model of focal cortical malformations. *J Neurosci* 2000; **20:** 5045–53.

78 Frost SB, Barbay S, Friel KM, Plautz EJ, Nudo RJ. Reorganization of remote cortical regions after ischemic brain injury: a potential substrate for stroke recovery. *J Neurophysiol* 2003; **89:** 3205–14.

79 Gharbawie OA, Gonzalez CL, Williams PT, Kleim JA, Whishaw IQ. Middle cerebral artery (MCA) stroke produces dysfunction in adjacent motor cortex as detected by intracortical microstimulation in rats. *Neuroscience* 2005; **130:** 601–10.

80 Dancause N, Barbay S, Frost SB, et al. Extensive cortical rewiring after brain injury. *J Neurosci* 2005; **25:** 10167–79.

81 Napieralski JA, Butler AK, Chesselet MF. Anatomical and functional evidence for lesion-specific sprouting of corticostriatal input in the adult rat. *J Comp Neurol* 1996; **373:** 484–97.

82 Chu CJ, Jones TA. Experience-dependent structural plasticity in cortex heterotopic to focal sensorimotor cortical damage. *Exp Neurol* 2000; **166:** 403–14.

83 Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* 1996; **272:** 1791–94.

84 Jones TA, Chu CJ, Grande LA, Gregory AD. Motor skills training enhances lesion-induced structural plasticity in the motor cortex of adult rats. *J Neurosci* 1999; **19:** 10153–63.

85 Nelles G, Jentzen W, Jueptner M, Muller S, Diener HC. Arm training induced brain plasticity in stroke studied with serial positron emission tomography. *Neuroimage* 2001; **13:** 1146–54.

86 Biernaskie J, Corbett D. Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. *J Neurosci* 2001; **21:** 5272–80.

87 Umphred DA. Neurological rehabilitation. St. Louis, MO, USA: Mosby, 1995.

88 Traversa R, Cicinelli P, Bassi A, Rossini PM, Bernardi G. Mapping of motor cortical reorganization after stroke. A brain stimulation study with focal magnetic pulses. *Stroke* 1997; **28:** 110–17.

89 Carey JR, Kimberley TJ, Lewis SM, et al. Analysis of fMRI and finger tracking training in subjects with chronic stroke. *Brain* 2002; **125:** 773–88.

90 Newton J, Sunderland A, Butterworth SE, Peters AM, Peck KK, Gowland PA. A pilot study of event-related functional magnetic resonance imaging of monitored wrist movements in patients with partial recovery. *Stroke* 2002; **33:** 2881–87.

91 Marshall RS, Perera GM, Lazar RM, Krakauer JW, Constantine RC, DeLaPaz RL. Evolution of cortical activation during recovery from corticospinal tract infarction. *Stroke* 2000; **31:** 656–61.

92 Liepert J, Uhde I, Graf S, Leidner O, Weiller C. Motor cortex plasticity during forced-use therapy in stroke patients: a preliminary study. *J Neurol* 2001; **248:** 315–21.

93 Johansen-Berg H, Dawes H, Guy C, Smith SM, Wade DT, Matthews PM. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain* 2002; **125:** 2731–42.

94 Neumann-Haefelin T, Moseley ME, Albers GW. New magnetic resonance imaging methods for cerebrovascular disease: emerging clinical applications. *Ann Neurol* 2000; **47:** 559–70.

95 Fetz EE. Operant conditioning of cortical unit activity. *Science* 1969; **163:** 955–58.

96 Jackson A, Mavoori J, Fetz EE. Long-term motor cortex plasticity induced by an electronic neural implant. *Nature* 2006; **444:** 56–60.

97 deCharms RC. Reading and controlling human brain activation using real-time functional magnetic resonance imaging. *Trends Cogn Sci* 2007; **11:** 473–81.

98 Singer R, Lidor R, Cauraugh JH. To be aware or not aware? What to think about while learning and performing a motor skill. *Sport Psychologist* 1993; **7:** 19–30.

99 Butefisch C, Hummelsheim H, Denzler P, Mauritz KH. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand. *J Neurol Sci* 1995; **130:** 59–68.

100 Dean CM, Shepherd RB. Task-related training improves performance of seated reaching tasks after stroke. A randomized controlled trial. *Stroke* 1997; **28:** 722–28.

101 Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased cortical representation of the fingers of the left hand in string players. *Science* 1995; **270:** 305–07.

102 Pascual-Leone A, Torres F. Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. *Brain* 1993; **116:** 39–52.

103 Plautz EJ, Milliken GW, Nudo RJ. Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. *Neurobiol Learn Mem* 2000; **74:** 27–55.

104 Birbaumer N, Cohen LG. Brain-computer interfaces: communication and restoration of movement in paralysis. *J Physiol* 2007; **579:**621–36.

105 Buch E, Weber C, Cohen LG, et al. Think to move: a neuromagnetic brain-computer interface (BCI) system for chronic stroke. *Stroke* 2008; **39:** 910–17.

106 Daly JJ, Cheng RC, Hrovat K, et al. Feasibility and accuracy of EEG-BCI system control during imposed upper limb motor tasks and relax conditions by stroke survivors. Society for Neuroscience, Washington, DC, USA, November 2008. Abstract 712·9. Available at http://www.abstractsonline.com/viewer/?mkey=%7BAFEA068D%2DD012%2D4520%2D8E42%2D10E4D1AF7944%7D.

107 Daly JJ, Fang Y, Perepezko EM, Siemionow V, Yue GH. Prolonged cognitive planning time, elevated cognitive effort, and relationship to coordination and motor control following stroke. *IEEE Trans Neural Syst Rehabil Eng* 2006; **14:** 168–71.

108 Iacoboni M, Koski LM, Brass M, et al. Reafferent copies of imitated actions in the right superior temporal cortex. *Proc Natl Acad Sci USA* 2001; **98:** 13995–99.

109 Rizzolatti G, Fogassi L, Gallese V. Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat Rev Neurosci* 2001; **2:** 661–70.

110 Carmichael ST, Chesselet MF. Synchronous neuronal activity is a signal for axonal sprouting after cortical lesions in the adult. *J Neurosci* 2002; **22:** 6062–70.

111 Hill NJ, Lal TN, Schroder M, et al. Classifying EEG and ECoG signals without subject training for fast BCI implementation: comparison of nonparalyzed and completely paralyzed subjects. *IEEE Trans Neural Syst Rehabil Eng* 2006; **14:** 183–86.

112 Daly JJ, Cheng RC, Hrovat K, Litinas KH, Rogers JM, Dohring ME. Development and testing of non-invasive BCI + FES/robot system for use in motor re-learning after stroke. International Functional Electrical Stimulation Society, Freiburg, Germany, September 2008. Paper 5·5. Available at http://www.ifess2008.de/NR/rdonlyres/31C92C70-AAB8-4A0E-AF21-828F81251C8D/27648/IFESS_2008_final.pdf.