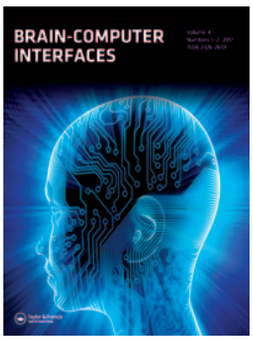

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Therapeutic applications of BCI technologies

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ABSTRACT

Brain-computer interface (BCI) technology can restore communication and control to people who are severely paralyzed. There has been speculation that this technology might also be useful for a variety of diverse therapeutic applications. This survey considers possible ways that BCI technology can be applied to motor rehabilitation following stroke, Parkinson's disease, and psychiatric disorders. We consider potential neural signals as well as the design and goals of BCI-based therapeutic applications. These diverse applications all share a reliance on neuroimaging and signal-processing technologies. At the same time, each of these potential applications presents a series of unique challenges.

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Rehabilitation; brain-computer interface; plasticity

Introduction

Brain-computer interfaces (BCIs) translate specific features of signals recorded from the brain into outputs that allow the user to act on the world without the participation of peripheral nerves and muscles [1]. BCI research has used a variety of brain signals to provide communication and control options [2]. BCI technology might also be used to improve rehabilitation of sensorimotor function after stroke and provide therapeutic paradigms for other disorders of the nervous system [3–6]. Potential applications might involve pathology due to stroke, degenerative diseases, developmental disorders, and other acquired disorders. Targeted functions could include motor, cognitive, emotional, and perceptual disorders. The purpose of the present survey is to consider issues relevant to the development of such technologies. These issues include a consideration of the therapeutic paradigms that have been proposed, the types of brain signals that might be employed, the goals of therapy, and some of the disorders of the nervous system that might be targeted.

To date much of the interest in BCI technologies has involved possible uses in the rehabilitation of motor function following stroke [6]. This may be due in part to prior research in the BCI literature that was concerned with development of methods to restore motor function for communication and environmental control [1]. However, many other possibilities exist [5], some of which will be considered in what follows, such as Parkinson's disease and psychiatric disorders.

BCI paradigms for therapy and rehabilitation

Application of BCI technologies to neurorehabilitation requires the design of BCI user tasks that provide a means for neuroplasticity to promote improved function. Design considerations include the targeted goal, whether real-time feedback is provided, whether the user is engaged in a sensory, cognitive, emotional, or motor task, and how brain activity is conceptualized (i.e. whether it is viewed as a static or dynamic process). A number of distinct paradigms have been proposed to date. These include neurofeedback, EEG-based imagery enhancement, closing the sensorimotor loop, training motor preparation, and state-dependent training.

Neurofeedback protocols have been used for many years to treat a variety of disorders. Perhaps the most common application of neurofeedback is for the treatment of attention-deficit hyperactivity disorder (ADHD) [7]. Neurofeedback involves recording EEG activity and providing feedback in the form of some visual or auditory stimulus based on the presence of a predetermined EEG feature [8]. No additional task is required of the user. Huster et al. [9] have described neurofeedback as most likely representing the earliest application of BCIs. They

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suggest that the primary difference with more recent BCIs designed for communication and control applications is in terms of the extent of EEG data processing. Neurofeedback protocols implicitly assume that the effects of training persist as a permanent trait-like condition. However, whether or not users actually gain control of the target EEG feature is not typically demonstrated in most neurofeedback studies [10]. This is understandable given the potential difficulty of doing controlled comparisons when training is in one direction only (i.e. to only increase or decrease the EEG feature in question). In contrast, the use of multiple states with most BCI communication applications provides a controlled within-subject comparison [11].

BCI methods have also been used to enhance motor imagery. The rationale for this approach is that motor imagery may provide an effective means of therapy for stroke-related dysfunction [12]. However, brain lesions may impair imagery [13] so that methods to facilitate imagery might enhance recovery. BCI-facilitated motor imagery involves providing various forms of feedback based on sensorimotor rhythms (SMRs) while users are given the task of imagining movement of affected limbs [14,15]. Enhanced motor imagery training assumes that motor imagery involves some of the same neural systems as are involved in actual movement.

A related BCI-based method proposed for rehabilitation of motor deficits following stroke involves closing the sensorimotor loop [16,17]. Here SMR desynchronization is rewarded by the operation of an orthosis that produces actual movement of the affected limb. The rationale for this approach is that activation of motor areas will be associated with the proprioceptive feedback produced by limb movement. This will then lead to sensory cortex excitation which is also interconnected with the motor cortices. Several explanations have been provided for the effects of closing the sensorimotor loop including Hebbian learning [18] and priming of subsequent physiotherapy [17].

BCI technology can also be used to train users to produce task-appropriate states prior to movement [19,20]. With this paradigm users learn to modulate SMRs in advance of the target motor task. This approach assumes that advanced preparation facilitates subsequent motor performance. Therapeutic benefit can then result from the performance of the facilitated motor behavior and also from the user potentially learning task-appropriate preparatory responses.

Task-appropriate brain states can also be produced without training by making trial-initiation contingent on the desired brain state [21–23]. In contrast to the methods previously discussed, this approach does not provide feedback for the BCI user to learn control of the targeted brain state. It only assumes that the task-appropriate brain state facilitates performance which in turn leads to persistent change due to enhanced neural plasticity.

Table 1 shows a summary of the main features of the methods discussed. As can be seen in the table, the paradigms differ with respect to the goal of training, whether feedback is presented, the nature of associated behavioral tasks if any, and the manner in which brain states are conceptualized. For example, a common goal of the neurofeedback approach is to normalize brain features through the use of feedback [24]. The neurofeedback approach does not include a behavioral task in addition to brain-state-dependent feedback control and assumes that the effects of training a brain state persist for a relatively long time following training. In contrast, the goal of state-dependent training is to activate task-related brain areas based on pre-trial activity. No feedback-based learning is required but the BCI user does engage in the targeted behavioral task. State-dependent training assumes that brain states are dynamic since this procedure depends on moment-to-moment fluctuations in state.

Which of these paradigms will work best for rehabilitation of brain disorders is currently an empirical question. No doubt it depends on characteristics of brain activity, such as whether or not these represent static traits or transient configurations of labile networks. As noted by Vernon [25], an implicit assumption underlying neurofeedback is that the training procedure will lead to long-term changes in the EEG outside of the training context, which will be associated with changes in behavior. Vernon [25] concludes that evidence for these assumptions is generally lacking. Some methods may be broadly applicable beyond motor deficits. For example, state-dependent training should be applicable to a wide range of functions while closing the sensorimotor loop may be more restricted. In addition, these methods may vary in ease of implementation. For example, state-dependent training does not require extensive training of the BCI user in brain-state feature control. However, this method may be problematic for those who are impaired to the extent that they cannot produce the target behavior.

Table 1. Characterization of several rehabilitation paradigms using BCI technology.

Paradigm	Goal	Feedback	Behavioral task	Concept of brain state
Neurofeedback	Normalize brain state	Yes	None	Static
EEG-based imagery enhancement	Enhance imagery	Yes	Imagery	
Close sensorimotor loop	Pair intention with sensory feedback	Yes	BCI control of orthosis or FES	
Train motor preparation	Activate task-appropriate brain areas	Yes	Criterion task	Reactive
State-dependent training	Activate task-appropriate brain areas	No	Criterion task	Reactive

Selection of an appropriate brain signal is an issue facing all of the methods discussed so far, and possibly other paradigms not considered here. These paradigms also differ in how signal selection has been done to date. The neurofeedback approach assumes an elaborate system of associating specific EEG features to specific functions and provides feedback accordingly [24]. Empirical support for these systems is minimal. Selection of features for motor recovery by the other methods is generally based on the well-established association of SMRs with motor function [26] but is much more limited in scope.

Even for the well-characterized motor system, much remains to be learned about the role of its various parts in terms of the signals generated and their potential relevance for rehabilitation. This becomes an even greater issue when considering other domains of neural control, such as emotion regulation. For example, most prior investigations of neural signals associated with emotion have involved averaging results across trials and subjects. Prediction of emotional responses on individual trials, a prerequisite for BCI-based feedback, is more challenging [27]. At the same time, there is great potential for modifying the activity of brain regions that could result in therapeutic benefit, provided that we acquire the necessary knowledge. However, attaining the therapeutic goal also requires knowledge of the principles of motor learning.

Elements of training that are important for motor learning and recovery

There are common principles of motor learning that should be considered regardless of whether the technologies applied are BCI systems or other technologies such as robotics or functional electrical stimulation. These include intention, attention, productive practice, progression of practice, repetition, functional relevance of task practice and training specificity [28], generalization, and dose [28,29].

Intention refers to possessing the motivation to perform the motor task and conceptualizing the execution of the task. Since conceptualizing the task is critical, BCI re-training of motor coordination can helpfully provide a visual representation of the task to assist the user in generating a cognitive representation of the desired movement. BCI can assist in more normally shaping a correct cognitive representation of the intended task by providing feedback regarding the desired goal versus the performance. Feedback can operate to refine the detail of the cognitive representation of the intention. Additionally, BCI can provide a creative and interesting BCI graphic user interface which may serve to motivate practice.

Attention refers to how closely and/or how long one focuses on the therapeutic task. For motor skill acquisition (i.e. brain plasticity) to occur, attending to the task is critical, which has been demonstrated by positive evidence [30]. These studies were unable to report a clinically significant improvement in motor control or function. In fact, some have shown that focusing attention, itself, can change neural activity [31]. The use of brain signals in a neural feedback paradigm could capture the imagination and focus attention of the user like no other type of feedback; that is, with BCI, the user understands that they are 'seeing' that they have produced some aspect of their own brain signal on the feedback screen. Even though they may not be able to move their fingers volitionally, they can see the production of a brain signal that is correlated with their intention to move; they can understand from this phenomenon that they have produced a brain neural signal operating from the desired intention, regardless of whether the brain signal is yet driving finger movement. This new information could be highly motivating for a patient to continue to practice the intention to move, which is required for control of volitional movement. An extreme example of attention impairment is the neglect syndrome after stroke. We are not aware of any information in the literature regarding the use of BCIs for retraining motor function for those with neglect, rendering it a topic to consider.

Training specificity can refer to training the desired coordinated movement, and is required to induce brain plasticity [32]. Productive practice of the desired movement refers to motor practice that is as close to the normal movement as possible, which is required for brain plasticity [33,34]. Productive practice is assigned at exactly the most efficacious challenge point [29]. That is, if one repeats a very easy movement, nothing new is learned; if one repeats a movement that is so difficult that performance is degraded substantially, then poor coordination will be learned, rather than the desired performance. The process of selecting a productive practice paradigm for a given session is a process of testing a hierarchy of difficulty until the most productive challenge point is identified for practicing that movement. For those with neural injury or disease, progression of practice is conducted in much the same manner, using finely incremented progression of difficulty beginning from ability to activate the desired muscle(s) and progressing through mass limb movements to isolated joint movement control [29]. Criteria for progression of practice to an incrementally more difficult movement can include the following: number of repetitions performed perfectly at the less-difficulty level; amount of coordination degradation at a given level of difficulty in terms of kinematics, kinetics, abnormal co-contractions; and type and degree of compensatory movements employed.

Repetition of practice refers to practicing the desired movement, which is critical to the brain plasticity that drives motor skill acquisition [35–38]. Recently, many have documented the lack of necessary repetition in standard clinical practice for stroke survivors and others. Notably, the nature of the repetition is critical, with practice of progressively more and more approximation to the desired coordination [28,39]. Repetition is necessary in order to progress to the next highest level of difficulty in the learning of motor control. In recent work [40,41], the number of repetitions was reported, respectively, for 13.6 h, 20.0 h, and 26.3 h of therapy for mildly/moderately impaired chronic stroke survivors, along with the findings that no increased use of the impaired limb was recorded at home and there was no significant difference in this across the three groups of different dosage (hours of treatment). In contrast, and though no 'home use measure' was used, other work [29,42] has shown that even more impaired (moderately/severely) chronic stroke survivors could exhibit recovery of coordinated limb movements and activities of daily living (e.g. picking up the knife and fork and cutting the meat). A notable difference between the two Lang papers versus this last-mentioned work is that the number of treatment hours for the McCabe/Daly reports [29,42] was 300 h of motor training for isolated joint movements, task component practice, and task practice. Notably then, duration of treatment is critical, as is the content of treatment.

In the absence of these principles, recovery of normal coordinated motor skill is not attainable: 'If an intervention includes practice of abnormal movements, unfocused attention, or too few repetitions, motor skill acquisition is unlikely to occur. In fact, one of the greatest difficulties for stroke survivors is the inability to produce volitional movements that are close to normal and that can be practiced repeatedly. Therefore, one of the critical hallmarks of an efficacious intervention is a method to practice close-to-normal movements repetitively, fulfilling the motor learning principles required to induce the brain plasticity needed to drive more normal movement' [32,p.2034]. We can differentiate between coordinated joint movements versus complex function tasks (i.e. activities of daily living) which are composed of multiple coordinated joint movements. Because recovery of coordinated joint movements may not mean recovery of full complex functional task performance, it is important in research studies to include homogeneous measures of activities of daily living, including complex functional tasks, such as feeding oneself with utensils or dressing oneself. In current clinical practice, compensatory strategies are taught, when it is thought that the limits of therapeutic response have been reached within the limited availability of therapy in the current healthcare milieu. Obviously, if current clinical practice is unable to restore normal coordination, compensatory strategies are preferable to nothing. However, this unfortunate state of current clinical practice is evidence for the need to develop more efficacious interventions, such as BCI applications.

BCI technology can be applied using the necessary motor learning principles for inducing brain plasticity for motor recovery. In order for BCI technology to prove feasible for motor learning, it must first be easily used, with high accuracy of user control of the brain signal gained within the first few training sessions. Somewhat discouragingly, a number of studies early on showed that many sessions could be required in order for some users to gain control of EEG-based BCI brain signals [43]. A second feasibility requirement is that BCI technology must support and facilitate practice of progressively more normal movement. On a positive note, some have shown that these two requirements can be met, especially if EEG-based BCI is paired with a practice-assist device that facilitates active repetitive practice of progressively more normal joint movements. Figure 1 shows that an EEG-based BCI, paired with surface functional electrical stimulation (FES), can be controlled within the first several sessions and at a high accuracy by chronic stroke survivors [5]. The FES system can be titrated in difficulty, as can the motor task assigned, together satisfying the principle of productive practice. A combined BCI/FES system may be more engaging than FES by itself, which satisfies the attention principle of motor learning. We can note that FES does not produce a physiologically normal muscle contraction in several regards; therefore, for best results, as soon as volitional muscle activation emerges, FES should be titrated to the lowest level needed for practice and then eliminated altogether, as volitional muscle contraction improves. BCI has also been paired with other

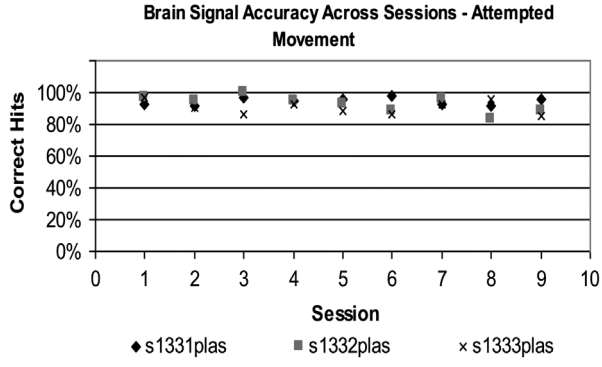

Figure 1. Accuracy of sensorimotor rhythm (SMR) control across nine training sessions for three subjects performing the imagined wrist/hand task (A), the attempted wrist/hand task (B), or the relaxation task (C). In A and B, accuracy is high throughout, almost always falling in the range 80–100%. In C, accuracy is slightly lower but remains in the range 70–100% except for 2 of the 27 sessions. Modified from [4].

technologies, such as robotics and transcranial direct current stimulation (tDCS; e.g. [44]).

Potential neural features to train for motor learning and recovery

There are a number of brain signal features that are candidates for use in BCIs for motor re-learning. The motor-related cortical potential (MRCP), the EEG slow wave associated with motor tasks, has signal characteristics that may lend it to useful application in BCIs, including latencies (timing features) and signal amplitude (Figure 2). This feature has been successfully employed to induce plasticity in stroke patients by Mrachacz-Kersting et al. [45]. Known differences for stroke survivors and healthy adults include abnormally prolonged latency and elevated amplitude (Figure 3; [46]). Given the correlation between motor coordination and either MRCP signal amplitude or latencies (Figure 4), there is the potential that feedback along those lines could be beneficial. Feedback for the user could include information to the user regarding EEG signal timing or signal amplitude. Signal timing may be the best choice if temporal aspects of coordination are trained. However, spectral power is the most frequently selected BCI feedback signal and is derived from the power of specified bands of EEG signal frequencies that are activated during event-related desynchronization (ERD); spectral power may be the feedback signal of choice in the case of initial inability to produce the movement or the entire joint movement. Figure 5 shows a brain map generated from spectral power at 21–24 Hz at the CP3 and CP6 electrode locations, during the motor event of attempted index finger extension.

There are unanswered questions regarding whether a single location of feedback from EEG signals is best versus multiple channels of feedback and whether the feedback should be different for different motor tasks. Figure 6 shows a brain map of multiple channels of information, as well as the difference between eccentric versus concentric muscle contractions. Signal amplitude was higher and earlier for eccentric versus concentric muscle contractions [47]. These refinements in brain signal feedback have the potential to improve the application of BCIs.

Another potential BCI variable is EEG signal brain connectivity between brain regions or connectivity between EEG signal and electromyographic signal (EMG). Figure 7 provides information regarding the difference between healthy adult EEG/EMG connectivity and that of stroke survivors. Therein may lie an additional potential signal for use in BCI.

Recent attention has been paid to the MRI brain measure of functional connectivity during a functional task (fcMRI). To date, connectivity parameters have

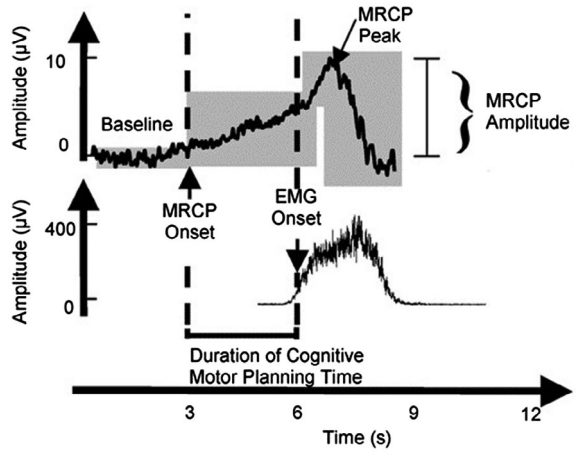

Figure 2. Schematic example of motor-related cortical potential (MRCP), electromyographical signal (EMG), and event identification. Onset MRCP is identified as signal deviation at least 1 std from the resting state mean for at least 100 ms. Onset of motor activity is identified from EMG signal deviation at least 1 std from the resting state mean for at least 100 ms. Planning time is calculated as the difference in the two latencies' onset. MRCP amplitude is the value of the MRCP peak minus the mean resting value.

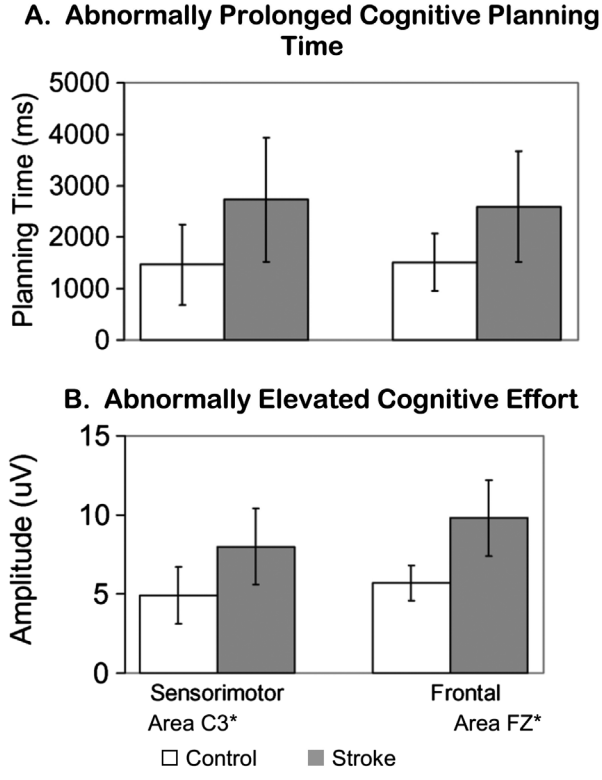

Figure 3. For both A and B, horizontal axis is cortical electrode location: C3 for sensorimotor area or Fz for frontal area. (A) Vertical axis is planning time in milliseconds, during a shoulder/elbow reach task. In both sensorimotor and frontal regions, cognitive planning time was abnormally prolonged for stroke (shaded bars) versus healthy controls (white bars). (B) Vertical axis is amplitude of cortical signal. In both sensorimotor and frontal regions, amplitude was abnormally elevated for stroke (shaded bars) versus healthy controls (white bars). Reprinted from [46].

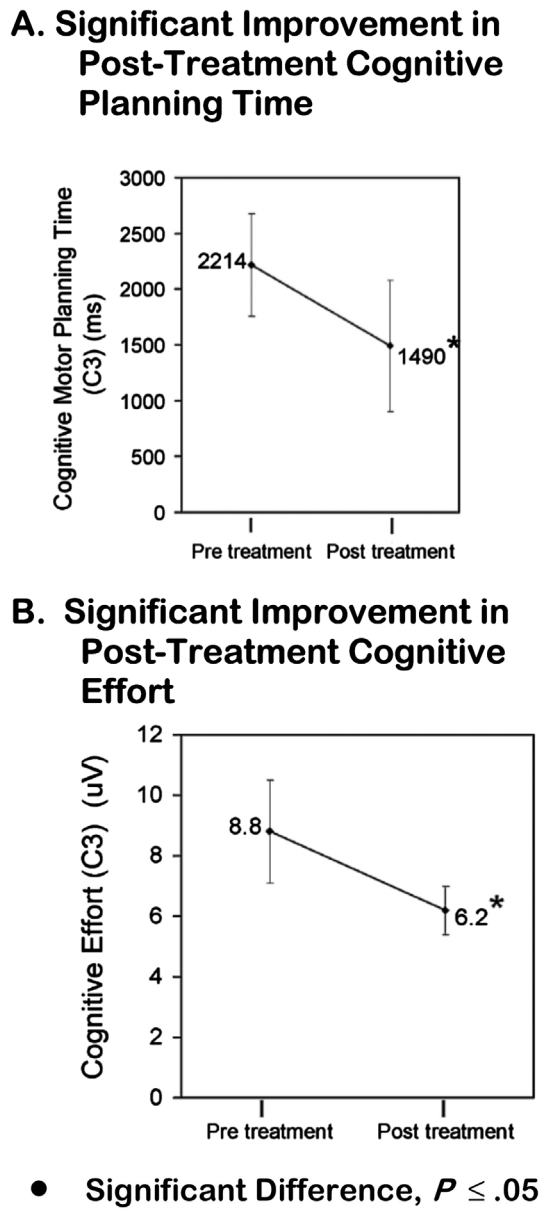

Figure 4. (A). Use of EEG-based MRCP latency measures to show difference in pre- versus post-treatment planning time (due to the small case series, caution should be used in interpreting results; this is an example, only). (B). Use of EEG-based MRCP signal amplitude to show difference in pre- versus post-treatment signal amplitude (due to the small case series, caution should be used in interpreting results; this is an example, only). Signal was measured at the C3 electrode, during shoulder/elbow reach. Reprinted from [46].

demonstrated varying results with regard to correlation with recovery of hand-motor outcome [48]. However, others have presented evidence that fcMRI for the inter-hemispheric connectivity in the somatomotor network and the dorsal attention network may hold important information regarding behavioral impairment versus intra-hemispheric connectivity within either the lesioned or unaffected hemisphere [49]. A connectivity-based approach may emerge in coming years as a viable BCI signal.

Even given the well-established association of SMRs with movement, there are still additional issues in selecting features for BCI systems. For example, within the context of use of transcranial magnetic stimulation, Plow et al. [50] discuss the issue of whether ipsilesional or contralesional areas should be targeted. They suggest that this might depend on the extent of a patient's lesions. A similar issue is present in spinal cord injury where crossed and uncrossed pathways can be affected to varying extents. BCI-based methods could also be used to enhance the activity of specific brain sites that might best participate in recovery. That the CNS does not always produce an optimal solution to damage is well illustrated by the success of constraint therapy [51].

Also within the context of TMS applications to rehabilitation, Chouinard and Paus [52] note that there are multiple components of the motor system that could serve as targets for activation, in addition to Brodmann's area 4. Indeed, Dum and Strick [53] have described contributions to the pyramidal track from premotor and cingulate motor areas. While axons from these sites are generally smaller, they nonetheless contribute a substantial portion of the pyramidal track. In addition, Dum and Strick [54] have noted that the distinction between premotor and primary motor areas is not as clear as is often supposed. Such considerations are of importance in light of the fact that the exact neural circuitry generating the SMRs is not precisely known. As the hand area of the primary motor cortex lies mainly on the anterior bank of the central fissure [55], it would not be expected to provide a clear projection to central areas of the scalp.

The advantage of the EEG signal is that it possesses high resolution in terms of time. The disadvantage is that it possesses very low resolution in terms of location of the signal. Therefore, some have begun theorizing whether other brain signals may be useful in motor learning. The disadvantages of functional magnetic brain imaging (fMRI) are as follows: very low resolution of time, extremely high noise sensed auditorily; a non-functional position is required (supine); and the required bore is physically confining, which reduces the options of functional task performance and can produce a claustrophobic sensation in some individuals. The advantage of fMRI is that it possesses more precision in localization of inferred brain activity versus the EEG signal. There are a number of signal features that could be considered in attempting to construct an fMRI-based BCI. Two conventional variables are volume of activation within specified brain regions and intensity of activation (Figure 8). Given the correlation between motor dysfunction and either volume of brain activation or intensity of brain activation (Figure 8), those fMRI signal features may be candidates for BCI use. A third variable is the centroid, which is a weighted variable accounting for both location and intensity of signal.

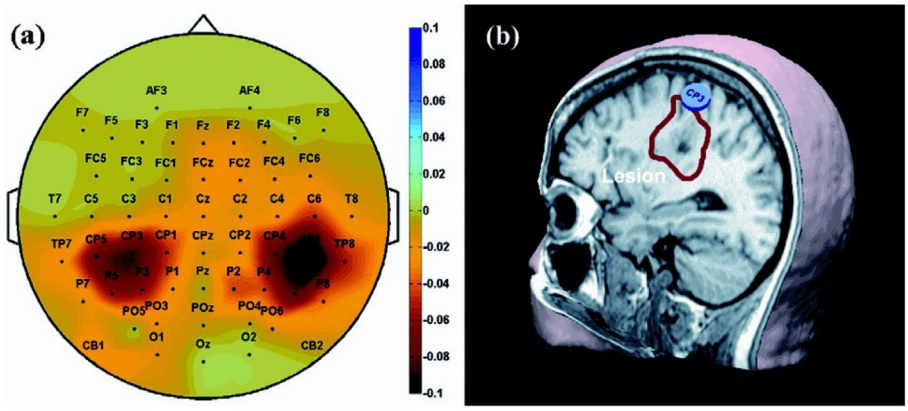

Figure 5. Example of EEG-derived spectral power and signal feature selection for BCI system. (a) Brain signal at CP3 and CP6 electrodes at 21 to 24 HZ produced a usable signal for motor training. This level of brain activity is illustrated according to R^2, which is a measure without units, and the vertical bar shows the range of R^2. The brain map shows signed $R^2 = -.10$ (at 21–24 Hz) for the CP3 electrode region during attempted right finger extension (shown by the more dense color region in the left, lesioned hemisphere). In the right hemisphere, the signed R^2 value was −.12 (at 21–24 Hz) for the CP6 electrode (right, non-lesioned hemisphere. (b) Relationship of the CP3 electrode to the left hemisphere lesion (red-outlined region). In this case, the lesion from stroke was in the left hemisphere, resulting in right arm coordination impairment. Therefore, brain training was needed for the left hemisphere, targeted to enhance function in the paretic right arm. For the BCI system, we selected the CP3 electrode in the left hemisphere and at the frequency band of 21–24 Hz, because of its proximity to the normal region of control for the right arm and the fairly robust signal in that power spectrum (with permission from [114], Figure 2).

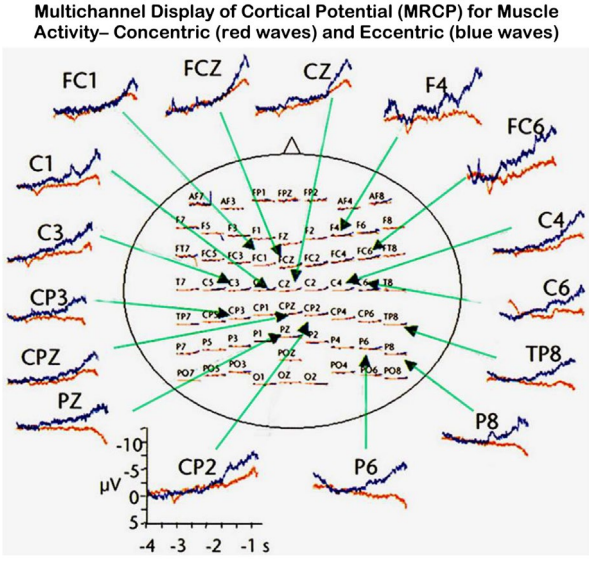

Figure 6. MRCP signal amplitude is higher and earlier for eccentric vs concentric muscle contractions. F, frontal; C, central; P, parietal; T, temporal; O, occipital; Z, middle; Reprinted from [47].

Figure 9 provides an example of the difference between healthy adults and some stroke survivors whose centroid lies beyond the range of normal individuals. The question arises as to whether recovery is driven by the movement of the centroid to within the range shown by healthy adults [115]. Otherwise, of course, this signal feature would not be helpful in motor re-training. Some have attempted to answer the question regarding the nature of brain signal features and their changes that drive recovery of motor function. There has been some controversy in the literature regarding whether recovery is driven by enhancement or a reduction of volume of brain activation [56] driving recovery of upper limb function. Table 2 shows the change in brain activation patterns for a sample of 23 stroke survivors, during recovery in response to chronic-phase treatment. Results showed that recovery is partially predicted by level of baseline dysfunction, but across individuals there is a unique pattern of change in brain patterns in response to treatment, and the type of change (increase or decrease in volume of activation) can differ within a given individual, across his/her brain regions [57]. For example, in Table 2, for the M1 row, there were 14 individuals who showed an increase in volume of activation in response to treatment and during recovery (Strategy 2, columns); in contrast and in the same M1 row, there were 9 individuals who showed a decrease in volume of activation in response to treatment and during recovery (Strategy 1 columns). Strategy 2 individuals began with greater dysfunction, according to the longer AMAT mean time shown in the M1 row for the Strategy 2 individuals versus the AMAT mean time shown in the M1 row for the Strategy 1 individuals, who required a shorter amount of time for the functional tasks of the AMAT. In other words, those with greater baseline impairment used Strategy 2, enlarging volume of brain activation with motor recovery; and those with less baseline impairment reduced or focused their brain activation patterns [57] in response to treatment and as they recovered. And it gets even more complicated, with each individual likely possessing a unique pattern

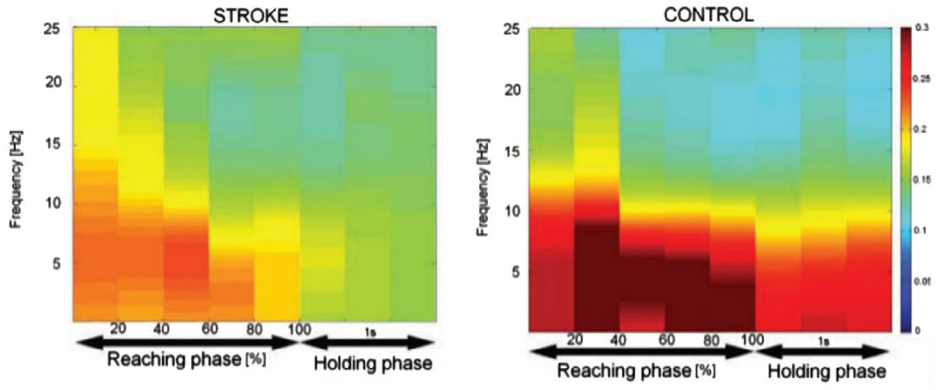

Figure 7. EEG-EMG connectivity. Group-averaged corticomuscular coherence between brain regions (columns) and muscles (rows) of the blue graphs. EEG signal was from parietal, central, frontal, left whole brain (non-lesioned side for stroke) and right whole brain (lesioned side for stroke). EMGs were from anterior deltoid, triceps brachii, and biceps brachii muscles. Rows of blue plots: for each of the three muscles, the upper row shows coherence with the scalp areas for the controls and the lower row for stroke. For each plot in each row or column, the *y*-axis is signal frequency, the *x*-axis is time, and the color bar indicates the level of coherence (red, higher level; blue, lower level). The figure shows that stroke patients had no significant corticomuscular coherence at the higher-frequency band (30–50 Hz). (For more detailed interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.) With permission from [47].

of increase or decrease in volume of activation across 12 regions of interest studied (Table 2; we can note the different numbers of individuals, shown down the column of ROIs for Strategy 2; that is, one given individual did not adhere to either Strategy 1 or 2 across their own ROIs, as they recovered motor function). Thus, the selection of a useful fMRI signal feature is quite difficult at this point.

Voluntary control of basal ganglia activity in Parkinson's disease

A BCI may be used to condition specific brain signal features. Volitional modulation of brain signal features, or the plasticity induced by control acquisition itself, modifies the state of the central nervous system. If the features are chosen such that the BCI-induced CNS state change includes changes to neural circuits that also participate in dysfunctional behaviors then it is expected that BCI training will modify behavior. Thus, for BCIs with therapeutic applications, it is important to select brain signal features that are related to the dysfunction.

In Parkinson's disease (PD), good candidate brain signal features are apparent. PD presents with pathological oscillations in the beta frequency band (14–30 Hz) in recordings from several nodes in the basal ganglia thalamo-cortical network [58–60]. Beta power is correlated with parkinsonian symptom severity and the beta power reduction during levodopa or deep brain stimulation therapy is correlated with symptom improvement [61,62]. Additionally, the degree to which spiking or high-frequency power is phase-locked to the beta oscillation (i.e. phase amplitude coupling, or PAC) is even more highly correlated with disease state and is more responsive to levodopa and DBS therapies than beta power [63,64].

At the Ottawa Hospital, PD patients scheduled for DBS surgery are given the opportunity to participate in a research program to investigate if volitional modulation of beta power or PAC magnitude is possible and if acquired control affects motor performance. During the standard-of-care DBS electrode implantation procedure, neuronal spiking activity and LFPs are monitored from multiple microelectrodes as they are driven along a linear trajectory to the stimulation target. We pause the microelectrodes descent in the putative subthalamic nucleus (STN) to perform the BCI experiment.

Participants use tracked motion controllers and a commercial virtual-reality head-mounted display to perform three tasks. First, each participant performs many trials of a three-dimensional center-out task in which they must use overt reaching to move the cursor to one of several targets. Preliminary analysis of our data from a few participants reveals correlations between spontaneously varying STN beta power and motor performance, confirming previous studies [65]. Second, each participant must control the color of a virtual sphere to match the cued color by modulating STN beta power or PAC. The participant is instructed to imagine stiff parkinsonian movements to turn the sphere orange and ease of movement to turn the sphere blue, but also that they are free to use any mental strategy that they feel is effective. To date, 6 participants have performed at least 20 trials each using STN beta power as the color-control feature. Preliminary analyses of these BCI control data suggest that participants are able to generate appropriate brain signals after approximately

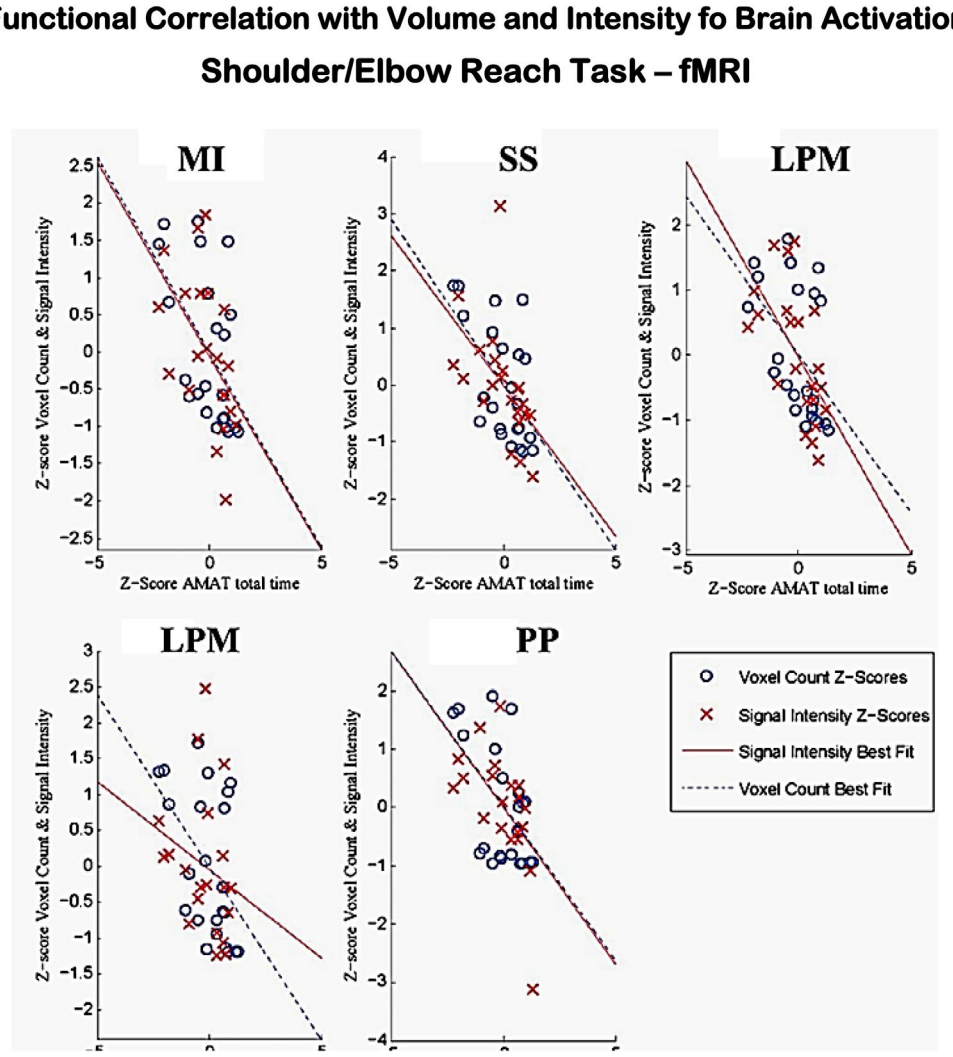

Figure 8. For 23 stroke survivors and five regions of interest (ROI's), correlations are shown between upper limb motor function task performance (Arm Motor Abilities Test (AMAT)) and each of two different brain measures during a shoulder/elbow reach task. Brain measures are shown as either brain volume of activation (from fMRI BOLD signal, voxel count, shown as the symbol 'o') or intensity of brain activation (from fMRI BOLD signal, amplitude, shown as the symbol 'x'). Correlations ranged from .43 to .75. The AMAT is composed of 13 complex upper limb functional tasks such as picking up a knife and fork and cutting meat, buttoning a sweater, and combing hair) (with permission from [115]).

Notes: M1, primary motor; SS, somatosensory; LPM, lateral premotor; SMA, supplementary motor area; PP, posterior parietal area; AMAT, Arm Motor Abilities Test (timed and summed for 13 complex functional tasks requiring shoulder/elbow movements, converted to *z*-score); O, voxel count score derived from fMRI during shoulder/elbow functional reach task, for each of the relevant ROIs shown, converted to *z*-score; X, signal intensity derived from fMRI during shoulder/elbow functional reach task, for each of the relevant ROIs shown, *z*-score.

12 trials (Figure 10). Third, in ongoing studies, we combine the attempted color control and center-out task to test the hypothesis that motor performance correlates with volitionally controlled brain signal features just as it does with spontaneously varying brain signal features.

If the data support this hypothesis then this will motivate the development of enhanced therapeutic strategies for PD patients. Researchers in the Starr lab at UCSF have promising preliminary results demonstrating acquired volitional control of beta power from the DBS electrode in the STN in a few participants with DBS stimulators that allow for chronic signal acquisition and feedback (Activa PC+S, Medtronic, USA). It might also be possible to use PD-related brain signal features recorded non-invasively from the scalp [66].

However, it should not be taken for granted that the best signals to use in a therapeutic BCI are those with the strongest correlation with disease state. Similarly, we should be careful not to choose signals simply because they enable accurate volitional control. It is possible that the best signals to use in a therapeutic BCI (i.e. those that best induce disease-relevant adaptive plasticity) have unobvious relationships to the disease state and no intuitive mental task to modulate them. More research is needed

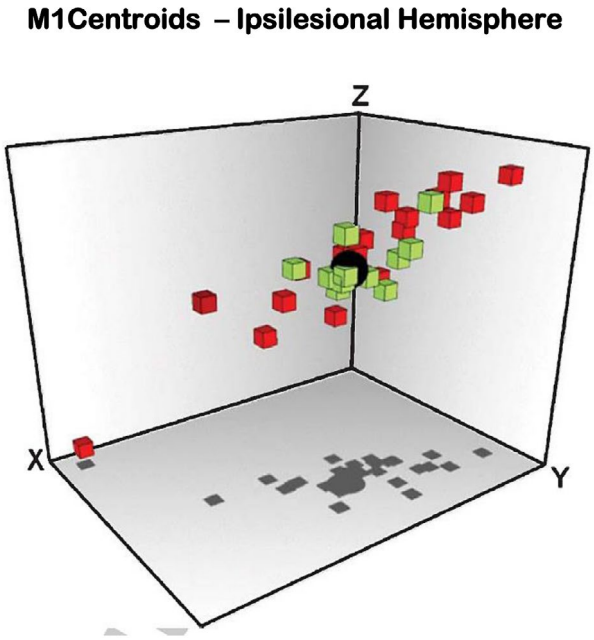

Figure 9. The left hemisphere M1 *centroids (ipsilesional hem*isphere) for all study subjects (healthy control (green cubes) and stroke (red cubes) subjects) in relationship to the average control group centroid (black sphere), during a functional reach task and fMRI data acquisition. The actual location within M1 for the sphere (average control centroid) in MNI coordinates is as follows: med/lat, $x = -31$; ant/post $y = -26$; caudal/rostral $z = 61$; the relative Euclidean distances between the individual squares and the sphere are within relative scale to each other. The 'walls' of the figure are provided to give visual assistance to the 3-D effect, and are not intended to be in a particular scale. Reprinted from [115].

to build frameworks to help understand the relationships between brain signals, their underlying neurophysiology, and the plasticity concomitant with their use as a control signal in a BCI. Computational models and animal models may provide great insight in this regard.

Application of BCIs as an intervention in psychiatric disorders

Psychiatric disorders are a major cause of disability in the United States, as well as in the rest of the world [67,68]. Treatments, although available for many psychiatric conditions, remain limited in their effectiveness and efficacy and a significant number of patients remain treatment resistant [69,70], or suffer from serious side effects [71,72]. Mainstream treatments include pharmacological interventions (e.g. selective serotonin reuptake inhibitors [SSRIs] for mood and anxiety disorders) or behavior-modification strategies (e.g. cognitive behavioral therapy [CBT] for psychosis and mood disorders). Nevertheless, there is a critical need for further development of novel treatments with increased disease-specific effectiveness and efficacy.

Recent advances in brain function monitoring and functional neuroimaging have provided researchers and clinicians with an opportunity to specifically sense brain activity associated with aberrant function or behavior, identify impairments in underlying neural substrates, and modulate their activity to improve brain function. For example, the EEG technique provides a temporally sensitive and clinically translatable mode of inspecting psychopathological aberrations in brain activity. Using real-time EEG neurofeedback, the EEG activity may be modified [73], based on specific principles of operant conditioning [74], whereby users are able to up-regulate a preferred state or behavior and down-regulate undesired ones to produce cognitive remediation [75]. Indeed, the EEG neurofeedback technique is now increasingly employed for therapeutic purposes across a range of neurological, psychiatric, and psychological conditions [76].

Technical advances in EEG signal processing have led to the development of the brain-computer interface (BCI), which offers original rehabilitation and therapeutic solutions [1,4]. By providing feedback of the user's

Table 2. Two separate strategies of brain change driving recovery, dependent upon baseline dysfunction level [57].

Strategy 2 (▲activation) = Lower functioning at baseline
Strategy 1 (▼ activation) = Higher functioning at baseline

		Strategy 2fMRI activation increased		Strategy 1 fMRI activation decreased or unchanged		
Regionofinterest		*N*	Baseline AMATMean (SD)	*N*	Baseline AMATMean (SD)	*p** value
Ipsilesional	M1	14	1927.4 (429)	9	1230.8 (749)	.01
	AS	8	1753.7 (418)	15	1602.0 (765)	NS
	S1	13	1914.9 (444)	10	1316.6 (756)	.03
	SII	11	1866.0 (484)	12	1461.2 (754)	NS
	LPM	11	1919.3 (462)	12	1412.3 (734)	NS
	SMA	11	1928.7 (466)	12	1403.7 (725)	.05
Contralesional	M1	11	1889.9 (492)	12	1439.3 (736)	NS
	AS	7	1754.4 (448)	16	1611.2 (741)	NS
	S1	10	1933.0 (491)	13	1440.8 (707)	NS
	SII	9	1754.4 (438)	14	1590.8 (777)	NS
	LPM	10	1897.4 (461)	13	1468.1 (740)	NS
	SMA	11	2043.3 (347)	12	1298.6 (684)	.004

*Wilcoxon rank sum test. Corrected for multiple tests. NS, not significant.

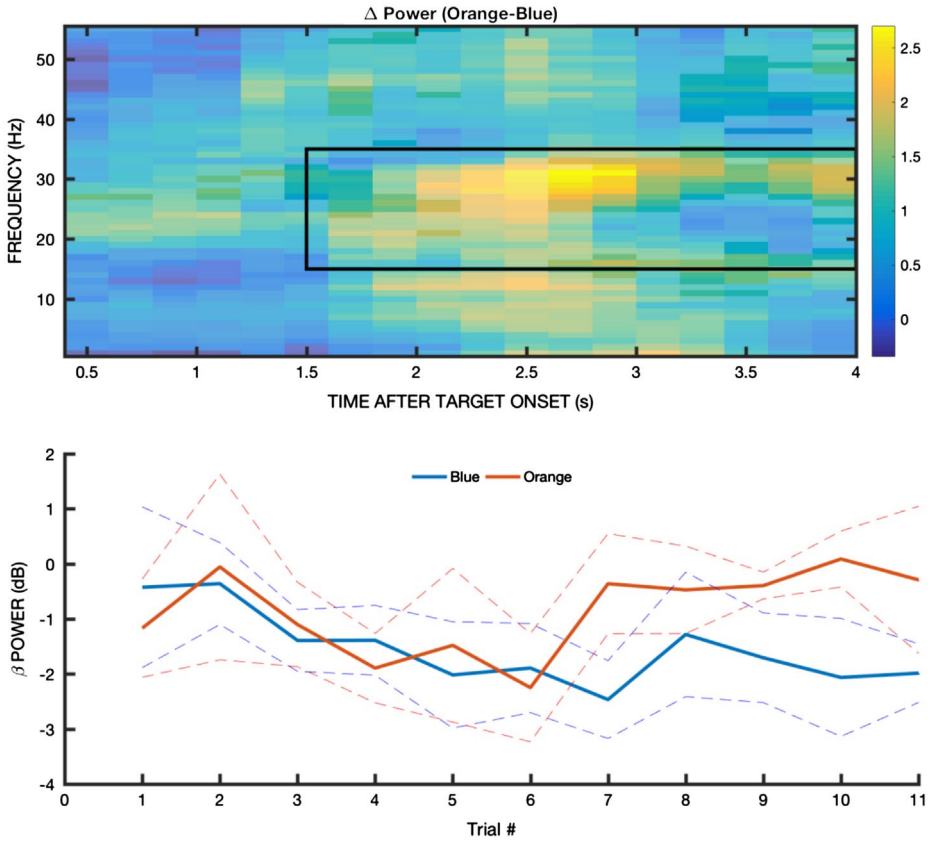

Figure 10. Six participants attempted volitional modulation of subthalamic beta-band oscillatory power; they were instructed to increase power to turn a sphere orange and to decrease power to turn a sphere blue. Top: difference of spectrograms (last five orange trials – last five blue trials) averaged across the six participants. The colored bar is in dB. Bottom: average power from the time-frequency window indicated in the top panel for each trial. The solid line is the mean across participants and the dashed line is the mean +/– the standard error. Beta power appeared to diverge between 'Orange' and 'Blue' cued trials after six trials of each class.

own brain activity in real time that are associated with specific neural states, BCIs reinforce the targeted brain states or dynamic modulations for achieving behavioral gains [75,77,78]. Despite the recent surge in BCI research for neurobehavioral modulation and previous reports of reduced disease symptoms, EEG neurofeedback has not been widely adopted as a therapeutic modality. The scientific community appears to be divided about the efficacy of neurofeedback, especially in psychiatric disorders, perhaps because of methodological limitations of studies reporting its efficacy. Here, we briefly discuss the current landscape of EEG neurofeedback studies in attention-deficit/hyperactivity (ADHD), mood and anxiety, and substance use disorders.

Attention-deficit/hyperactivity disorder

EEG neurofeedback training for ADHD is recognized as a Level 1 ('best support') intervention by the American Academy of Pediatrics. Neurofeedback training for ADHD typically involves enhancing beta (12–20 Hz) while inhibiting theta (4–7 Hz) activity [79]. Some studies have also shown comparable effects of modulating slow cortical potentials in improving ADHD symptoms [80,81]. Meta-analyses on the usefulness of EEG neurofeedback in ADHD have reported increased effect sizes in youth with ADHD [82–84], especially for the inattention dimension [82,83], compared to controls in open [84] as well as blinded [83] randomized trials. Importantly, neurofeedback efficacy for the inattention dimension was correlated with the number of training sessions [82] and seemed to be maintained over time [85]. Comparison between the neurofeedback training and pharmacological treatment effects showed that medication was more effective in improving clinical symptoms [86,87] or cognitive function [88], and neurofeedback was more effective for improving academic performance [89].

Mood disorders

The evidence of neurofeedback training efficacy for mood disorders, especially the major depressive disorder (MDD), is still emerging. In MDD, EEG data show relatively higher left than right alpha (8–13 Hz) activity

on frontal recording sites, also known as frontal alpha asymmetry [90–93]. Reducing the alpha asymmetry by increasing alpha in the right hemisphere has been reported to alleviate depressive symptoms in recently conducted pilot studies [94–97]. However, more rigorous studies with higher sample sizes and appropriate controls are required to validate the effectiveness of neurofeedback in mood disorders.

Anxiety disorders

EEG neurofeedback training in generalized anxiety disorder (GAD) [98,99] and obsessive-compulsive disorder (OCD) [100] has shown increased effectiveness compared to relaxation biofeedback and 'placebo' neurofeedback, respectively. However, it is unclear whether neurofeedback has any therapeutic effect in alleviating disease-specific symptoms in anxiety disorders. Thus, future studies, especially those that compare the neurofeedback results with those from mainstream techniques such as cognitive behavioral therapy, are required to further ascertain the specificity and efficacy of neurofeedback training in anxiety disorders.

Substance use disorders

EEG neurofeedback has been used in substance use disorders for decades, with the first study conducted in 1977 by Passini et al. [101], who used alpha conditioning to show reduced anxiety and improvement in personality measuring scales in alcoholics. The neurofeedback training protocol for substance use disorders has since evolved and now uses a combination of beta augmentation with theta suppression along with alpha/theta training [102]. This neurofeedback regimen has shown reduced drug-seeking symptoms, improved neurophysiological indices, and longer abstinence [103–107].

Despite the therapeutic promise shown by the aforementioned studies, neurofeedback is yet to be adopted as a dependable intervention for psychiatric disorders, primarily due to its nonspecific effects and outcomes. For example, some of the effects seen in patients with substance use disorders may well be due to the high comorbidity with ADHD [105]. However, this presents a unique window of opportunity where BCIs can play a significant role. BCI-inspired machine learning techniques and co-adaptive algorithms can be developed [108,109] to specifically classify disease-specific brain activity which can then be modulated and monitored with real-time neurofeedback. Moreover, the classifier set can be constrained further to drive specificity. For example, to train drug-addicted individuals to cognitively control the feeling of drug-craving, the feature space might be restricted to event-related potentials (for example the late positive potentials that have been shown to be sensitive to motivated attention to drug cues [110]) or stimulus-induced spectral perturbations in the theta range, which has been implicated in emotion appraisal [111]. However, constraining the feature set might also hamper performance accuracy in these BCIs. User-specific optimization of these BCI-based neurofeedback algorithms is also critical to adapt feedback to the user's workload and effort [112,113] and minimize user frustration.

Interim conclusion

In sum, BCI-based EEG neurofeedback presents an exciting new direction for personalized intervention in individuals with psychiatric disorders. Although the EEG neurofeedback training is beginning to show therapeutic promise, more placebo-controlled randomized and blinded studies are required to evaluate alternative methodologies and determine efficacy in different psychiatric conditions. BCI-based machine learning techniques can guide the specificity and sensitivity of this technique for a more targeted interventional approach. Lastly, there is a critical need to compare the outcomes of this intervention with those from mainstream pharmacological and cognitive-behavioral interventions to provide comparative metrics that will further guide evidence-based clinical decision-making.

Conclusions

There are many possible neural pathologies that might be treated with BCI-related technologies. However, it is not known at present how best to use these and what specific neural signals might be employed. This area is only just beginning to be explored and at this point it may be best for researchers to consider many different possibilities. The present discussion has introduced some issues, but these are by no means exhaustive.

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