Neuroimaging-based approaches in the brain–computer interface

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Techniques to enable direct communication between the brain and computers/machines, such as the brain–computer interface (BCI) or the brain–machine interface (BMI), are gaining momentum in the neuroscientific realm, with potential applications ranging from medicine to general consumer electronics. Noninvasive BCI techniques based on neuroimaging modalities are reviewed in terms of their methodological approaches as well as their similarities and differences. Trends in automated data interpretation through machine learning algorithms are also introduced. Applications of functional neuromodulation techniques to BCI systems would allow for bidirectional communication between the brain and the computer. Such bidirectional interfaces can relay information directly from one brain to another using a computer as a medium, ultimately leading to the concept of a brain-to-brain interface (BBI).

Communication between the brain and its surroundings

Computer devices and computer-controlled machines have become an indispensable element of daily life. The control commands for these devices are typically generated by motion of the extremities, eyes or vocal cords. Various approaches have been taken to develop techniques that circumvent these typical input routines. Such techniques are particularly beneficial for individuals who are incapable of providing mechanical control commands, including those with severe neuromuscular disorders, spinal injuries, or limited mobility in the extremities. The brain–computer interface (BCI) or the brain–machine interface (BMI; noted as 'BCI' herein), also referred to as 'direct neural interface', is a hardware and software system that provides a direct communication link between the neural activity of the brain and computer hardware/software components, without the involvement of peripheral nerves and muscles.

The concept of the BCI was first introduced in the early- to mid-1970s by using electrical activity from the surface of the scalp, as detected by electroencephalography (EEG), to generate control commands for electronic devices and computers [1]. Owing to the technical advancement of implantable microelectrodes and processing electronics, direct neural recordings from the lateral geniculate nuclei in the thalamus of cats was applied to reproducibly reconstruct visual images shown to them [2,3]. More recently, a needle microelectrode array was implanted onto the cortical surface of quadriplegic patients to detect electrical spikes and changes in the field potential from the somatomotor areas of the brain. As a result, neural firing patterns associated with a motor imagery task successfully created multi-dimensional computer cursor movement after closed-loop training [4]. A similar concept, which is based on the direct recording/decoding of cortical activity to control the directional movement patterns in a computer, has been used to provide robotic limb function for primates [5]. Electrocorticography (ECoG) utilizes signal detection from an array of surface electrodes that are implanted over the dura [6] and has been used to characterize brain activity for the purpose of BCI [7,8].

These invasive methods inevitably carry risks associated with surgical procedures, thus generating the need for noninvasive approaches to gain wider acceptance in neurotherapeutics and to increase the future commercial potential of BCI. Accordingly, noninvasive neuroimaging modalities are gaining momentum in the research arena for BCI systems. In this review article, we aim to review current and emerging modalities and their basic operating principles behind neuroimaging-based BCI.

Overview of the modalities used for BCI

Functional imaging modalities are listed in Table 1, along with information related to signal detection, temporal and spatial resolutions, and portability as well as approximate cost. EEG, magnetoencephalography (MEG) and functional MRI (fMRI) constitute the most active areas of investigation for BCI systems, whereas near infrared spectroscopy (NIRS) and functional transcranial Doppler sonography (fTCD) are emerging as potential modalities for BCI applications. Nuclear imaging techniques, such as single photon emission computed tomography and positron emission tomography, also offer information on regional functional activity in the brain through the detection of photons (e.g. gamma rays) that are emitted by radioactive tracers sensitive to specific metabolic mechanisms in the brain. However, these techniques require the injection of radioactive pharmaceutical agents, which prohibits repeated measurement in humans and, consequently, discourage widespread use for BCI applications. Accordingly, these methods are excluded from further discussion in this review.

Signal detection

EEG

EEG measures differences in electric potential on the scalp that are generated by neural activity, which is typically the sum of excitatory and inhibitory postsynaptic potentials of

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Table 1. Current and potential neuroimaging-based BCI/BMI modalities

Type	Signal source	Temporal resolution	Spatial resolution	Portability	Price range (USD)[a]
EEG	Electrical potentials associated with cortical activity	High (ms or better)	Coarse; currently on the order of a few cm^3.	Portable	~\$200–\$50 000
MEG	Magnetic fields associated with neuronal activity	High (ms or better)	Coarse; limited spatial localization, but currently better than EEG.	Not portable	\$2–3 million
fMRI	BOLD changes in susceptibility-weighted MR signal	Low (1–2 s); limited by hemodynamic delays	Good; on the order of 64 mm^3.	Not portable	>\$1 million
NIRS	BOLD changes in absorption spectrum of near-infrared light	Medium (hundreds of ms); limited by hemodynamic delays	Coarse; currently on the order of 1 cm^3 and limited depth penetration (maximal sensitivity at the cortical surface).	Portable	>\$20 000
fTCD	Blood flow velocity associated with neuronal activity	Medium (tens of ms)	Low; limitation of characterizing perfusion state via large blood vessels.	Portable	~\$5000

[a]Typical ranges for experimental set-up.

thousands or millions of cortical neurons [9]. The ensembles of neurons transmitting neurological signals across their synapses act as electric dipoles and generate measurable potential at the scalp surface with magnitude typically $<100\ \mu V$ (Figure 1). EEG is susceptible to both radial and tangential dipole sources relative to the scalp surface, with more sensitivity to sources in cortical gyri than in sulci [9]. Multi-channel arrays, conventionally comprising 64–128 electrodes [10], allow for simultaneous recording of EEG activity from the entire surface of the scalp. Localization of the source EEG activities is then estimated by solving the 'inverse problem' based on the temporal and spatial features of detected EEG activity and conductivity/scattering modeling of the anatomy [11]. However, the technique suffers from a marginal spatial resolution owing to the finite number of detectors (EEG electrodes) and the nonlinear characteristics of detected EEG scalp potentials arising from inhomogeneous thickness, geometry and conductivity of underlying skull/brain tissue [12]. Nonetheless, EEG has excellent temporal resolution (milliseconds or better), good portability and an inexpensive set-up cost.

MEG

A superconducting quantum interference device (SQUID), which is extremely sensitive to magnetic disturbance created during neuronal activity, can be used for signal detection around the scalp (Figure 1). The negligible cerebral magnetic fields [approximately one-billionth of the magnitude of the magnetic field of the earth (~0.5 gauss)] can be measured feasibly by SQUID sensors [10]. Modern MEG devices typically comprises helmet-shaped sensor arrays of more than 300 SQUIDs that are systematically arranged to cover the entire scalp. A synchronized activity of tens of thousands of neurons results in MEG signals on the order of 50–500 fT [13]. MEG principally detects the tangential component of the cerebral sources [14]; therefore, it is more susceptible to sulcal activity and less sensitive to dipole sources lying on gyral surfaces at the same depth. MEG source mapping, which involves the inverse problem similar to EEG [15], suffers from the lack of accurate spatial resolution in spite of its ability to measure neural activity in real-time. Furthermore, MEG requires dedicated shielding from electromagnetic interference (EMI) and is less beneficial in terms of portability, as compared with EEG.

fMRI

fMRI has surfaced as one of the major tools used for noninvasive characterization of brain function with superior spatial resolution (on the order of 2–3 mm cubic voxels) and has offered new opportunities for relaying information on regional brain activity and its possible regulation for the BCI. fMRI was developed in the early 1990s, exploiting the ability to detect changes in local cerebral blood volume, cerebral blood flow and oxygenation levels during neuronal activation [16]. The most widely used fMRI technique is based on the detection of local blood oxygenation level dependent (BOLD) signal contrast during neuronal activation using susceptibility-weighted (often referred to as T_2*-weighted) MR sequences, such as echo planar imaging (EPI), that are sensitive to changes in local magnetic susceptibility (Figure 1). Owing to inherently low BOLD signal contrast (1–4% difference between activation signal and baseline signal level) [17], a series of susceptibility-weighted images covering the whole or part of the brain is repeatedly acquired during block-based or event-related behavioral or cognitive tasks.

To extract the spatial and temporal information from the activation with respect to individual tasks, several statistical methods are applied to the time series of the MR signals on a voxel-by-voxel basis [18]. These methods typically include univariate analyses based on the general linear model [18] or multivariate analyses, such as independent component analysis (ICA) [19]. The resulting probability map of activation is typically thresholded and overlaid on high-resolution anatomical images. fMRI is generally performed using clinical MRI scanners (~3 T); however, ultra-high-field (UHF) human body scanners (>7 T) are becoming more commercially available for potential BCI applications. fMRI has a temporal resolution on the order of 1–2 s, which is further confounded by physiological delays in hemodynamic responses (approximately 4–5 s). The high susceptibility to head motion artifacts also requires compliance from the subject being imaged [20].

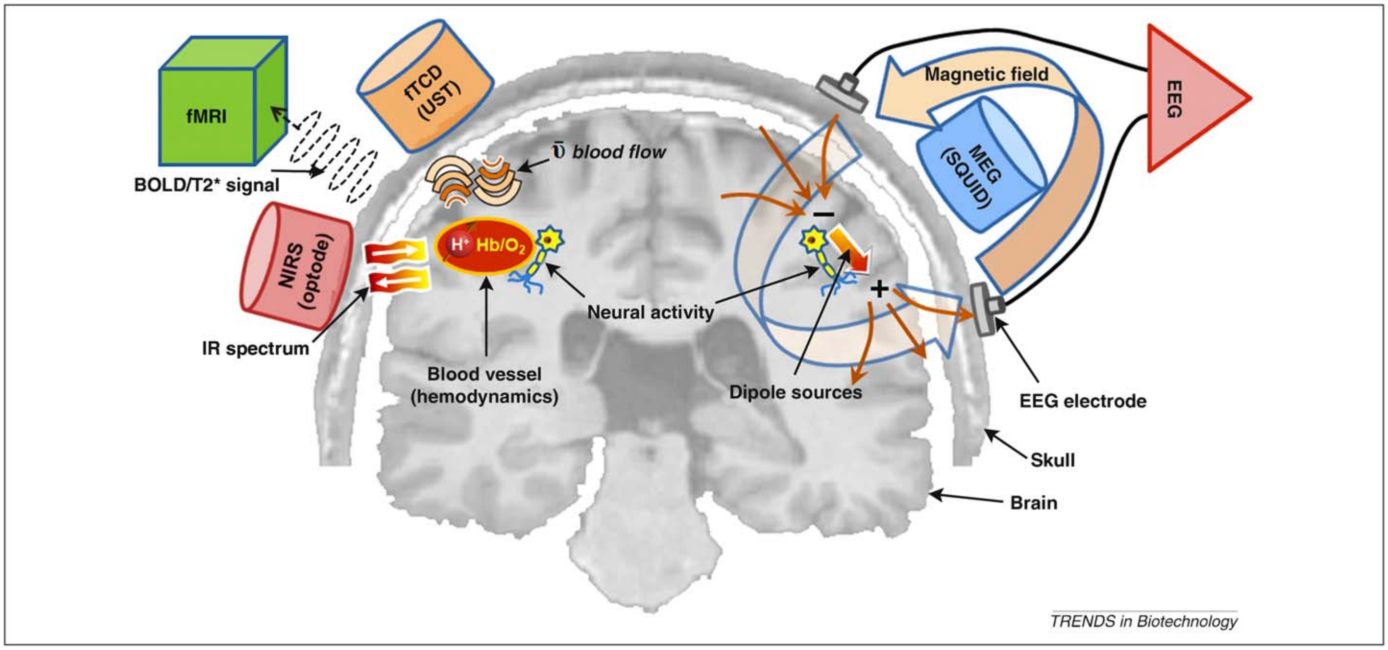

Figure 1. Schematic diagram of brain signal detection mechanisms. EEG measures the electrical potential differences on the scalp that are generated by cortical neural activity. Neurons transmitting neurological signals across their synapses act as dipole sources. MEG detects the magnetic fields associated with such neuronal activation by SQUID sensors. fMRI measures the hemodynamic responses, particularly magnetic dynamics of protons (H^+) related to neural activity; its technique is principally based on the detection of local BOLD signal contrast during neuronal activation. Using multiple arrays of optodes, NIRS characterizes changes in the intensity of attenuated near-infrared (IR) light (owing to scattering or absorption), resulting from changes in concentration between oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) during local neural activity. fTCD is based on ultrasound Doppler imaging, developed to measure the velocity of blood flow in major cerebral arteries by the ultrasound transducer (UST).

NIRS

Within the near-infrared spectrum (~630–1300 nm), light can penetrate the skull and reach considerable depth (1–3 cm from the skull surface) [21] to allow investigation of cerebral metabolism [22] (Figure 1). NIRS characterizes alternations in the intensity of attenuated light (owing to scattering and absorption) at different wavelengths resulting from changes in oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) concentrations during local neural activity [22]. Quantification of cortical neural activity is accomplished by applying multiple arrays of NIRS sensors (optodes) around the scalp, whereas the depth information can be estimated by time-of-flight distributions of the detected infrared light [23]. Although the spatial resolution of NIRS is still marginal (on the order of 1 cm [22]) and requires further refinement, NIRS can be made portable with a price range similar to that of EEG systems (Table 1). NIRS is a recently developed neuroimaging technique for the assessment of functional activity in cortical regions of the brain, and there has been growing interest in applying NIRS to BCIs [24].

fTCD

Arguably the most recent addition to the techniques considered for BCI applications, fTCD is based on ultrasound Doppler imaging, which was initially developed to measure the velocity of blood flow in major cerebral arteries [25]. Blood flow velocity is measured by detecting the ultrasonic wave frequencies reflected by flowing blood (Figure 1), often using the same transducer that generated the original sound wave. Because sound waves are both scattered and absorbed by the skull, administration of the ultrasound beam through a 'sonication window' (such as the thin temporal bone) is necessary; however, individual variability in skull thickness might hinder its applicability to the general population. The fTCD method has limited depth penetration, and the examination is constrained to the major vessels. Therefore, it currently provides information on hemispheric changes at the level of perfusion to major cerebral arteries. For example, the hemispheric dominance in blood flow during the performance of a language task (such as word generation, which is typically left-dominant) can be detected by fTCD [25] and concurrently interpreted to generate appropriate binary computer commands.

Principles and common features

Neuroimaging-based BCI methods share common operating features across the different modalities. Comparative schematics for conventional human-machine interfaces (HMI) are shown in Figure 2. During the execution of a motor task, specific areas of the brain are activated (e.g. hand motor area) and the neural signal is transmitted to the appropriate muscle groups via descending motor pathways in the peripheral nervous system (PNS). The muscle movement is then relayed to conventional HMIs, such as a keyboard or a computer mouse, to generate a specific input command for the computer or machine to execute. The operation performance is fed back to the operator via sensory feedback, thus enabling a closed-loop adaptation of the motor activity (i.e. for motor learning).

BCI replaces involvement of the descending motor pathways, PNS and muscles in the execution of motor tasks. First, functional data from the brain are acquired using different neuroimaging modalities. Then, the detected signals are routed to a set of rule-based algorithms to link the state of temporal and spatial characteristics of brain activity to specific machine input commands. These commands are often aided by a machine-learning algorithm to

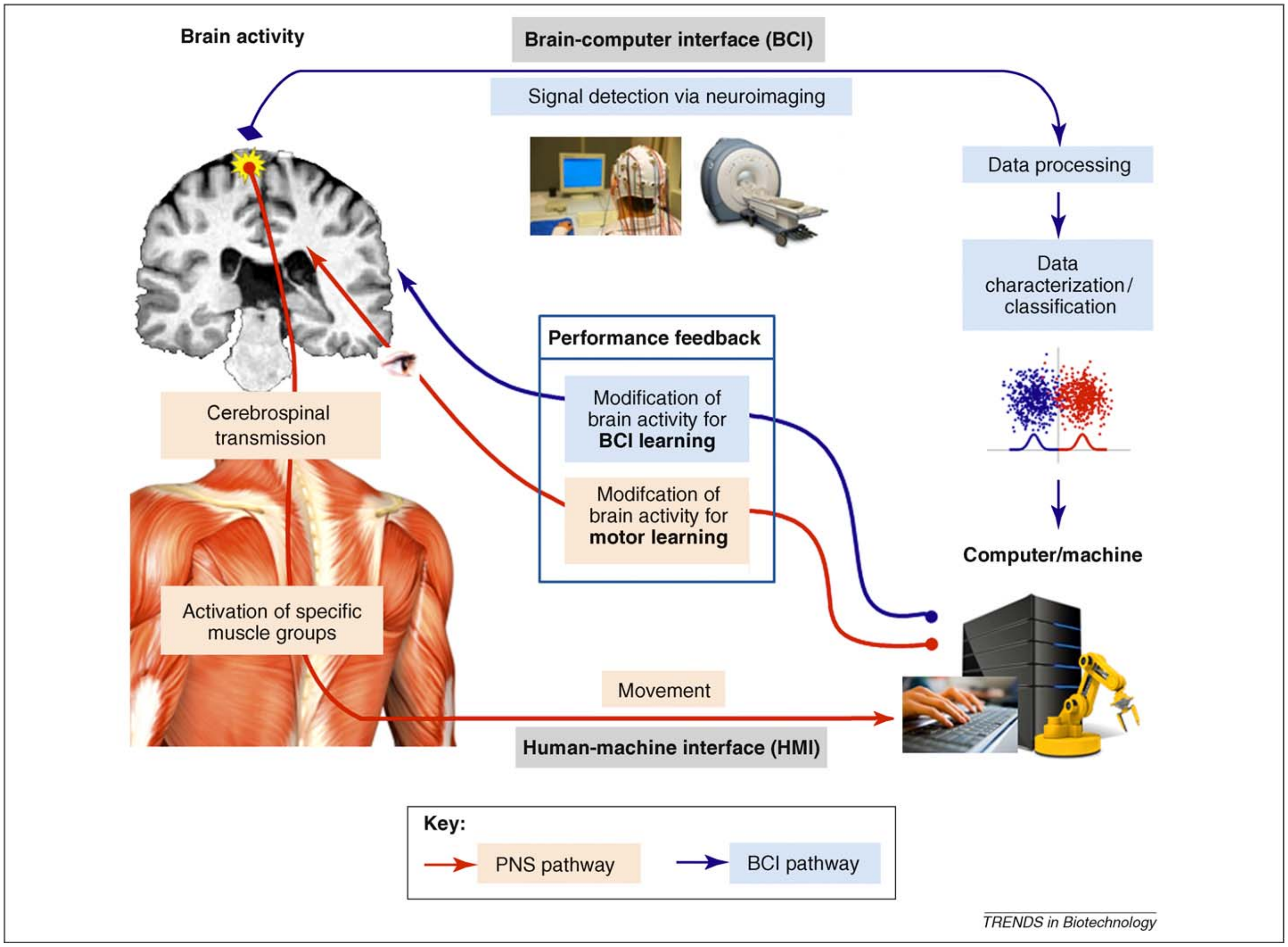

Figure 2. Comparative schematics of peripheral nervous system (PNS) and BCI pathways. Neuroimaging-based BCI techniques share common operating features of sensorimotor physiology. For instance, an individual activates the motor cortex for hand movement, and the neural signal is transmitted to the appropriate muscle groups via the descending motor pathway. The muscle movement is eventually executed and relayed to the conventional human-machine interface (HMI), such as a keyboard, to generate a specific input command for the computer or machine. BCI circumvents the involvement of PNS and muscles through the detection, analysis and classification of brain activity. Modification of brain activity is accomplished via feedback signals from operation performance (center), either by sensory feedback (particularly visual, as indicated by the eye) for motor learning in HMI, or by feedback training for BCI learning, known as 'neurofeedback'.

improve the accuracy of prediction or classification [26,27]. The process often involves the repeated acquisition of functional data from a subject to optimize the performance of the machine-learning algorithm. The input commands for the computer/machine are then transferred to the computer; the overall task performance (such as accuracy and speed) is often relayed back to the individual as sensory feedback to allow the user to regulate the state of specific brain function to achieve better performance. Through these processes, the user consolidates the modified brain activation strategy for the BCI.

This feedback training, also known as 'neurofeedback' [28,29], occurs during the BCI procedure and can be applied to modify a person's behavior-associated brain activity, resulting in a desirable cognitive outcome or behavior (Figure 3). The process is mediated by the modification of the level of cortical activation and subsequent learning of the concurrent task strategy. With further practice/training, this iterative process continues until the neural activity can be adjusted to a targeted level via neural plasticity. Clinical applications of such training cover a wide spectrum of neuropsychiatric conditions including pain modulation [28], attention [30] or addiction control [31]. A more detailed review of the modality-specific examples of BCIs is presented below. The advantages and disadvantages of each modality for BCI/BMI are listed in Table 2.

EEG-based BCI

The P300 component of event-related potentials (positive deflection at approx. 300 ms post-stimulus) has often been used as an electrophysiological cue to control BCIs owing to its association with categorical stimulus-evaluation processes [32]. For example, a user focuses attention successively on alphabetic characters he/she wishes to communicate, and the computer detects the P300 that is elicited when matrix-elements containing the chosen character are presented [33]. In addition to P300, slow cortical potentials [34] and steady-state visual-evoked potentials [35] have also been used as electrophysiological correlates in EEG-based BCIs. From the viewpoint of frequency components, the presence of event-related synchronization (ERS) and desynchronization (ERD) in contralateral sensorimotor μ (8–12 Hz) and β (18–26 Hz) rhythms has been observed both before and during movement [36,37] or

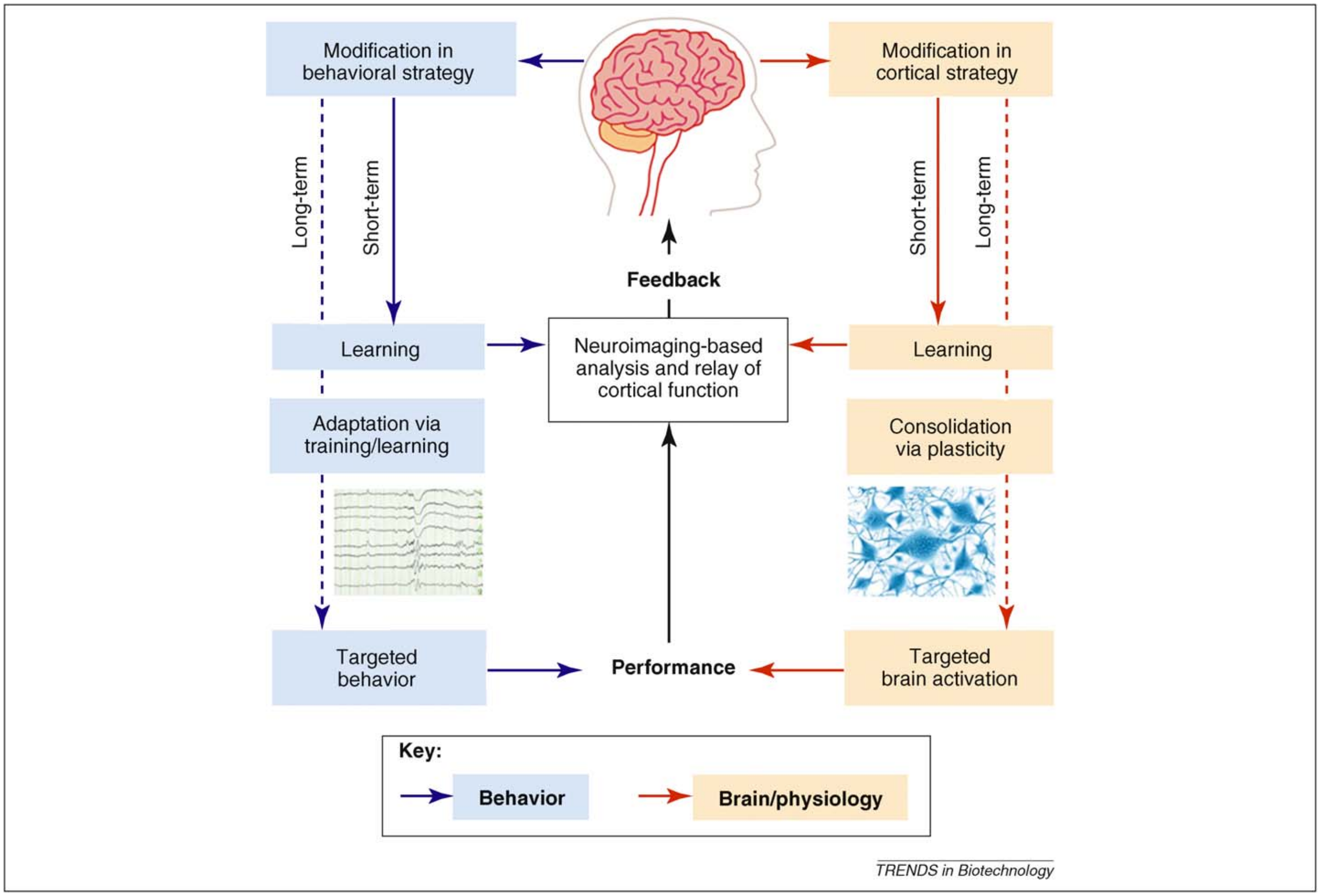

Figure 3. Comparison of BCI adaptation and neural plasticity neural plasticity and BCI adaptation via feedback modification or training. To overcome the inter-individual variability with respect to spectro-temporal features and spatial patterns of brain signals, advanced techniques of machine-learning have also been introduced for BCIs to automatically adapt to the specific brain activity of each user (blue pathways). The feedback training occurs to modify individuals' behavior-associated brain activity, resulting in a desirable cognitive outcome or behavior. Through the machine-learning technique, the need for subject training can be minimized. Similarly, the sensorimotor feedback process in the nervous system is also mediated by the modification of the level of cortical activation and subsequent learning of the concurrent task strategy. With further practice/training, this iterative process continues until the neural activity can be adjusted to a targeted level via neural plasticity (red pathways).

Table 2. Comparison of different neuroimaging-based BCI/BMI modalities

Type	Advantages	Disadvantages
EEG	• Good portability and affordability • Excellent temporal resolution applicable for real-time BCIs • Good availability of paradigms and computational algorithms for BCI applications compared with other modalities owing to a relatively long developmental history	• Imperfection in spatial localization, marginal spatial resolution • Involvement of inconvenient procedures during the placement of electrodes • Difficulties in maintaining good electrode–scalp contact and achieving long-term use of electrodes
MEG	• Excellent temporal resolution applicable for real-time BCIs • Superior spatial resolution and functional localization compared with EEG	• Limited portability • High set-up and maintenance costs • Requires dedicated electromagnetic shielding
fMRI	• Excellent spatial resolution • Data acquisition covering the entire brain volume • Excellent source localization – advantageous for identification of function-specific loci	• Limited temporal resolution associated with the inherent hemodynamic delay • Limited portability • High set-up and maintenance costs • Safety precaution required for ferromagnetic materials • Requires dedicated electromagnetic shielding
NIRS	• Good portability and affordability • Metabolic specificity depending on IR spectrum response • Uses corrosive-free sensors (e.g. optodes)	• Limited temporal resolution associated with the inherent hemodynamic delay • Optode size (requires spaces for both emitting and detecting IR light sources) • IR light occlusion by hair
fTCD	• Good portability • Ability to characterize the state of brain perfusion • Potential to actively modulate spatially-localized neuronal activity as computer-to-brain interface (CBI)	• Difficulties in transcranial delivery of the ultrasound • Difficulties in adjustment of sonication path/focus • Currently constrained to targeting large vessels

during motor imagery [38] and has subsequently been utilized to generate BCI commands.

The EEG signals that are obtained from the multichannel arrays manifest high-order spatiotemporal features that need to be classified for generation of the corresponding BCI commands. Accordingly, several classification methods have been applied to EEG-based BCIs using algorithms based on linear classifiers and nonlinear Bayesian classifiers (a comprehensive review of classifier types provided in Refs. [39,40]). Furthermore, adaptation of these machine-based classifiers to the real-time computation environment is actively being developed [26] and includes the investigation of multivariate classification techniques.

Nevertheless, EEG-based BCIs currently face unsolved challenges. Inherently, they have a poor spatial resolution associated with an inverse problem, and thus have to rely on computational methods to localize the source of activation [11]. In addition, owing to the variance in spontaneous EEG activity, a sufficient training phase is required before users can effectively generate BCI commands [41]. To overcome the substantial variability between individuals with respect to spectrotemporal features and spatial patterns of brain signals, advanced techniques of machine-learning have also been introduced for BCIs to automatically adapt to the specific brain activity of each user (Figure 3) [42]. Through the machine-learning technique, it has been demonstrated that the need for subject training can be minimized [43].

MEG-based BCI

MEG has been utilized in the field of real-time BCI because of its ability to instantly measure and compute magnetic field perturbation as a result of neuronal activity. MEG signals are magnetic 'counterparts' of EEG signals; therefore, MEG-based BCIs employ similar data processing strategies used in EEG-based BCIs [44]. Using the modulatory property of posterior α rhythm activity in MEG, it has been noted that the four target orientations of covert spatial attention (represented as four squares located at the top, right, bottom and left of the central fixation cross on the screen) could be reliably classified with up to 69% accuracy, without the need for lengthy and cumbersome subject training [45]. In an effort to improve classification techniques, the use of a temporal evolution of regularized classifiers has been suggested [46], and a linear Bayesian support vector machine (SVM) has been employed [47]. Furthermore, using synthetic aperture magnetometry (SAM) and a four-direction classification scheme, 95–97% classification accuracy for motor tasks and 86–87% classification accuracy for motor imagery tasks have been observed [48]. This promises a reliable, high performance, two-dimensional (2D) BCI from single-trial detection of natural human movement intentions. In the context of clinical applications, it has been reported that chronic stroke patients restored hand function using MEG-based BCI training [49].

Although MEG might be too bulky and expensive to become a convenient BCI modality for everyday use, magnetic fields are less attenuated or distorted by the skull and scalp than electric fields. As a result, MEG signals are less affected by the unknown physical properties of the skull than EEG signals [50]. Accordingly, reconstruction of MEG signals yields better spatial resolution than EEG (approx. threefold in terms of 3 dB roll-off points for forward/inverse filters [15]). For example, MEG can detect a sensorimotor rhythm with adequate spatial resolution to distinguish the movement of a single finger [51]. In addition, MEG can provide a consistent feedback experience and faster learning of μ rhythm control for participants [52] owing to its better signal-to-noise ratio than EEG. Nonetheless, MEG-based BCI would benefit from further improvement during the source localization process.

fMRI-based BCI

With the emergence of techniques to allow fast data processing and characterization, real-time fMRI (rtfMRI) [53] or near-real-time processing of fMRI data [54] has provided a medium by which individuals can receive information on the state of their own brain activity on-line. As a result, an individual can gain a degree of voluntary control of the regulation of region-specific cortical activation, thus enabling BCI. For example, the range of reported BCI tasks includes the regulation of activity in the sensorimotor areas during hand motor tasks [54] and in rostral-ventral/dorsal parts of the anterior cingulate cortex associated with the regulation of affective states or pain [28,53]. Furthermore, the activation in human auditory areas has been regulated based on selective auditory attention [55,56], whereas the activation in the sensorimotor cortex was enhanced during hand imagery tasks [57], confirming the observations of the earlier work [58]. The feasibility of rtfMRI-based BMI was also recently demonstrated [59], whereby 2D movement of a robotic arm was controlled by the regulation (and concurrent detection) of regional cortical activations in the primary motor areas. In this study, the participants engaged in right- and/or left-hand motor imagery tasks, and the BOLD signals originating from the corresponding hand motor areas were then translated into horizontal or vertical robotic arm movement.

Automated interpretation and classification of fMRI data is an emerging research field in the fMRI-BCI community to characterize underlying cognitive processes with minimal human intervention. Recent studies have addressed the concept of automatic pattern classification of fMRI data acquired from multiple sensory, motor and cognitive performances. Although variations in data processing schemes and region-of-interest selection exist [60], commonly adopted procedures include the automatic extraction of spatial and temporal features of activation maps using a machine learning algorithm, such as SVM or linear discriminant analysis techniques [60,61]. Furthermore, the accuracy of the classification varies greatly depending on the nature of the task and timing, from 53% [60] to 90% [62]. During these procedures, however, identification of the brain areas that are consistently and exclusively activated for a given task improves classification efficiency [61].

NIRS-based BCI

NIRS signals have been studied in relation to cognitive functions, suggesting their potential applicability to BCI devices [63]. During overt and covert hand movements, the contralateral hemispheric NIRS response was observed [64]. Furthermore, using motor imagery with a NIRS system, 89% correct classification of right and left hand imagery tasks has been observed [63]. NIRS can also detect the hemodynamic responses corresponding to the P300 component [65], and therefore potentially generates P300-related BCI commands without the use of EEG. The convincing belief of the applicability of NIRS to BCIs is reinforced by recent studies in which binary subjective preference was evaluated on a single-trial basis of NIRS signals during decision-making tasks, with an average accuracy of 80% [66]. Likewise with other modalities used in BCIs, pattern recognition techniques, such as SVM and the hidden Markov model (HMM), have also been introduced to classify NIRS signals [63].

NIRS promises to be a potent device for future BCIs owing to its flexibility of use, portability, metabolic specificity, high sensitivity in detecting small substance concentrations and affordability [64]. Compared with EEG, NIRS requires neither conductive gel nor corrosive electrodes, making it suitable for extended use [67]. However, major challenges of NIRS-based BCIs include the inherent latency of the hemodynamic response (on the order of several seconds), resulting in slow operation of NIRS-based BCIs and an inability to characterize the signals from subcortical regions [63]. To improve the feasibility of NIRS-based BCIs, the influence of respiration and blood pressure on hemodynamic response has to be reduced and higher spatial resolution needs to be attained [67].

Box 1. 'Real-world' applications of noninvasive BCI

BCI technology has been applied to several 'real-life' scenarios, with the primary goal of helping individuals with severe motor-disability as a result of amyotrophic lateral sclerosis (ALS), stroke, accidental injuries and other neuromuscular disorders. An estimated 50 000–60 000 people worldwide suffer from ALS [81] and approximately 15 million people worldwide suffer from stroke each year [82]; as such, noninvasive BCI technology will provide many of these individuals with an opportunity to achieve an enhanced quality of life.

ALS is a devastating disease that is characterized by progressive muscle weakness and atrophy owing to degeneration of the motor neurons. ALS eventually leads to a 'locked-in' state, whereby there is no external communication from the patient [77]. As an example of BCI application, four ALS patients have learned to control the movement of a computer cursor through EEG-based BCI (mediated by the detection of the sensorimotor rhythms) during a motor imagery task [78]. Similarly, P300-component based BCI has been tested on healthy volunteers to control a wheelchair outfitted with navigation capability [79]. Another real-life example of BCI could be found from improved rehabilitation outcome of a stroke-victim through a combination of EEG–MEG BCI-based training with goal-directed active physical therapy [80].

When used in the context of neurofeedback, BCI has ameliorated several neurological conditions, such as epilepsy [83] and chronic pain [28,84], as well as cognitive-psychiatric disorders, including attention-deficit hyperactivity disorder [85] and anxiety [86]. For instance, with the emergence of the fMRI-based BCI neurofeedback technique and its use in the management of chronic pain [28], individuals who suffer from chronic pain could potentially receive its benefits. It is also notable that efforts are being made to apply BCI technologies to operate simple personal communication (e.g. word processing, email, speech synthesizing) and environmental control (e.g. home automation) devices [87], with potential for future use in consumer electronics.

Concluding remarks and future implications

The ability to control computers and machines directly via thought processes in a noninvasive manner will undoubtedly offer various facets for clinical applications, ranging from the provision of control options for paralyzed individuals to potential neurorehabilitation via feedback training (Box 1).

There are ongoing efforts to increase the accuracy and flexibility of classification methods of neuroimaging data for BCI applications by combining/complementing data from multiple modalities. For example, the spatiotemporal characteristics of the BOLD signal from fMRI training can be correlated with specific EEG signal patterns that are associated with task training [68]. These patterns can be used as a supplement in subsequent training sessions. The combination of EEG and rtfMRI training data can be used to provide information that might not be easily obtained by fMRI alone, such as a high-speed, temporal sequence of activation/deactivation of brain activity. In doing so, it is important to account for the artifacts that an MRI environment produces in an EEG signal. For instance, ballistocardiogram artifacts, which arise from changes in electrical potential associated with subtle scalp motion or cranial/brain perfusion in the middle of a strong magnetic field, appear as low-frequency, periodic signals synchronized with cardiac pulsation [69]. Various filtering methods based on subtraction or adaptive filtering cued by the electrocardiography and electrooculography activity [69] and ICA [70] have been developed and are being investigated for EEG-fMRI integration.

In addition to these multi-modal approaches in BCI, it is important to note that the current concept of BCI has been formed around a unidirectional control mechanism in the sense that control information flows from the brain to a computer/machine. Therefore, one might argue that the means for computer-to-brain interface (CBI) should be created to realize a bidirectional interface between the brain and the computer. A method that enables the controlled modulation of regional brain activity will offer a new window of opportunity for creating various clinical applications ranging from functional brain mapping to the treatment of numerous brain-related disorders.

Invasive techniques, such as vagus nerve stimulation and deep brain stimulation, can provide a means for controlled neuromodulation [71]. As a potential alternative to these invasive procedures, transcranial magnetic stimulation (TMS) is employed to modulate cortical activity through the induction of current on the cortical surfaces by applying strong magnetic fields over the scalp; however, TMS lacks spatial specificity and has a limited depth of penetration [72].

Focused ultrasound (FUS) techniques might overcome some of these limitations and offer potential solutions for noninvasive CBI. Advancement in FUS technology now allows for a noninvasive and spatially accurate delivery of acoustic energy (and concurrent deposition of thermal or mechanical energy) to a small tissue region [73]. Owing to the ability to deposit steerable mechanical energy on small areas of the brain in a noninvasive manner, the FUS-mediated functional modulation of local brain regions has been suggested [74]. Through demonstration in recent animal models [75], highly localized reversible modulation was achieved by pulsed FUS sonication at the motor and visual areas, operating in low acoustic intensity, under the intensity used by most clinical ultrasound imagers, which is <720 mW/cm^2 spatial-peak temporal average intensity [76]. Application of these new techniques to various BCI methods might eventually complete the interface between the brain and the computer, thus leading to the development of a 'brain-to-brain interface' (BBI), in which neural activities from different individuals are linked and mediated by computers. The potential utilities of such systems remain to be investigated.

References

1 Vidal, J.J. (1973) Toward direct brain-computer communication. *Annu. Rev. Biophys. Bioeng.* 2, 157–180
2 Stanley, G.B. *et al.* (1999) Reconstruction of natural scenes from ensemble responses in the lateral geniculate nucleus. *J. Neurosci.* 19, 8036–8042
3 Butts, D.A. *et al.* (2007) Temporal precision in the neural code and the timescales of natural vision. *Nature* 449, 92–95
4 Hochberg, L.R. *et al.* (2006) Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* 442, 164–171
5 Taylor, D.M. *et al.* (2002) Direct cortical control of 3D neuroprosthetic devices. *Science* 296, 1829–1832
6 Shenoy, P. *et al.* (2008) Generalized features for electrocorticographic BCIs. *IEEE Trans. Biomed. Eng.* 55, 273–280
7 Vansteensel, M.J. *et al.* (2010) Brain-computer interfacing based on cognitive control. *Ann. Neurol.* 67, 809–816
8 Hill, N.J. *et al.* (2006) 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.* 14, 183–186
9 Niedermeyer, E. and Lopes da Silva, F.H. (1999) *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields*, Lippincott Williams & Wilkins
10 Babiloni, C. *et al.* (2009) Fundamentals of electroencephalography, magnetoencephalography, and functional magnetic resonance imaging. *Int. Rev. Neurobiol.* 86, 67–80
11 Grech, R. *et al.* (2008) Review on solving the inverse problem in EEG source analysis. *J. Neuroeng. Rehabil.* 5, 25
12 Chauveau, N. *et al.* (2004) Effects of skull thickness, anisotropy, and inhomogeneity on forward EEG/ERP computations using a spherical three-dimensional resistor mesh model. *Hum. Brain Mapp.* 21, 86–97
13 Murakami, S. and Okada, Y. (2006) Contributions of principal neocortical neurons to magnetoencephalography and electroencephalography signals. *J. Physiol.* 575, 925–936
14 Nunez, P.L. (1986) The brain's magnetic field: some effects of multiple sources on localization methods. *Electroencephalogr. Clin. Neurophysiol.* 63, 75–82
15 Bradshaw, L.A. *et al.* (2001) Spatial filter approach for comparison of the forward and inverse problems of electroencephalography and magnetoencephalography. *Ann. Biomed. Eng.* 29, 214–226
16 Belliveau, J.W. *et al.* (1991) Functional mapping of the human visual cortex by magnetic resonance imaging. *Science* 254, 716–719
17 Gati, J.S. *et al.* (1997) Experimental determination of the BOLD field strength dependence in vessels and tissue. *Magn. Reson. Med.* 38, 296–302
18 Friston, K. *et al.* (1995) Statistical parametric maps in functional imaging: a general linear approach. *Hum. Brain Mapp.* 2, 189–210
19 Esposito, F. *et al.* (2003) Real-time independent component analysis of fMRI time-series. *Neuroimage* 20, 2209–2224
20 Yoo, S.S. *et al.* (2005) Head motion analysis during cognitive fMRI examination: application in patients with schizophrenia. *Neurosci. Res.* 53, 84–90
21 Okada, E. *et al.* (1997) Theoretical and experimental investigation of near-infrared light propagation in a model of the adult head. *Appl. Opt.* 36, 21–31
22 Taga, G. *et al.* (2007) Effects of source-detector distance of near infrared spectroscopy on the measurement of the cortical hemodynamic response in infants. *Neuroimage* 38, 452–460
23 Wabnitz, H. *et al.* (2010) Time-resolved near-infrared spectroscopy and imaging of the adult human brain. *Adv. Exp. Med. Biol.* 662, 143–148
24 Birbaumer, N. *et al.* (2006) Physiological regulation of thinking: brain-computer interface (BCI) research. *Prog. Brain Res.* 159, 369–391
25 Bishop, D.V. *et al.* (2009) An efficient and reliable method for measuring cerebral lateralization during speech with functional transcranial Doppler ultrasound. *Neuropsychologia* 47, 587–590
26 Müller, K.R. *et al.* (2008) Machine learning for real-time single-trial EEG-analysis: from brain-computer interfacing to mental state monitoring. *J. Neurosci. Methods* 167, 82–90
27 Blankertz, B. *et al.* (2008) The Berlin Brain–Computer Interface: accurate performance from first-session in BCI-naive subjects. *IEEE Trans. Biomed. Eng.* 55, 2452–2462
28 deCharms, R.C. *et al.* (2005) Control over brain activation and pain learned by using real-time functional MRI. *Proc. Natl. Acad. Sci. U. S. A.* 102, 18626–18631
29 Yoo, S.S. *et al.* (2008) Neurofeedback fMRI-mediated learning and consolidation of regional brain activation during motor imagery. *Int. J. Imaging Syst. Technol.* 18, 69–78
30 Gevensleben, H. *et al.* (2009) Distinct EEG effects related to neurofeedback training in children with ADHD: a randomized controlled trial. *Int. J. Psychophysiol.* 74, 149–157
31 Trudeau, D.L. (2000) The treatment of addictive disorders by brain wave biofeedback: a review and suggestions for future research. *Clin. Electroencephalogr.* 31, 13–22
32 Donchin, E. and Coles, M.G.H. (1988) Is the P300 component a manifestation of context updating? *Behav. Brain Sci.* 11, 357–374
33 Farwell, L.A. and Donchin, E. (1988) Talking off the top of your head: toward a mental prosthesis utilizing event-related brain potentials. *Electroencephalogr. Clin. Neurophysiol.* 70, 510–523
34 Birbaumer, N. *et al.* (1990) Slow potentials of the cerebral cortex and behavior. *Physiol. Rev.* 70, 1–41
35 Vialatte, F.B. *et al.* (2010) Steady-state visually evoked potentials: focus on essential paradigms and future perspectives. *Prog. Neurobiol.* 90, 418–438
36 Pfurtscheller, G. *et al.* (1997) Foot and hand area mu rhythms. *Int. J. Psychophysiol.* 26, 121–135
37 Babiloni, C. *et al.* (2004) Alpha event-related desynchronization preceding a go/no-go task: a high-resolution EEG study. *Neuropsychology* 18, 719–728
38 Pfurtscheller, G. *et al.* (2006) Mu rhythm (de)synchronization and EEG single-trial classification of different motor imagery tasks. *Neuroimage* 31, 153–159
39 Besserve, M. *et al.* (2007) Classification methods for ongoing EEG and MEG signals. *Biol. Res.* 40, 415–437
40 Lotte, F. *et al.* (2007) A review of classification algorithms for EEG-based brain-computer interfaces. *J. Neural. Eng.* 4, R1–R13
41 Iversen, I. *et al.* (2008) Conditional associative learning examined in a paralyzed patient with amyotrophic lateral sclerosis using brain-computer interface technology. *Behav. Brain Funct.* 4, 53
42 Müller, K.R. *et al.* (2004) Machine learning techniques for brain-computer interfaces. *Biomed. Eng. (Biomedizinische Technik)* 49, 11–22
43 Blankertz, B. *et al.* (2006) The Berlin Brain-Computer Interface: EEG-based communication without subject training. *IEEE Trans. Neural Syst. Rehabil. Eng.* 14, 147–152
44 Pfurtscheller, G. and Lopes da Silva, F.H. (1999) Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin. Neurophysiol.* 110, 1842–1857
45 van Gerven, M. and Jensen, O. (2009) Attention modulations of posterior alpha as a control signal for two-dimensional brain-computer interfaces. *J. Neurosci. Methods* 179, 78–84
46 Zhdanov, A. *et al.* (2007) Inferring functional brain States using temporal evolution of regularized classifiers. *Comput. Intell. Neurosci.* 52609
47 Montazeri, N. *et al.* (2009) MEG based classification of wrist movement. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2009, 986–989
48 Battapady, H. *et al.* (2009) Single trial detection of human movement intentions from SAM-filtered MEG signals for a high performance two-dimensional BCI. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2009, 524–527

49 Birbaumer, N. and Cohen, L.G. (2007) Brain-computer interfaces: communication and restoration of movement in paralysis. *J. Physiol.* 579, 621–636
50 Salmelin, R. *et al.* (1995) Functional segregation of movement-related rhythmic activity in the human brain. *Neuroimage* 2, 237–243
51 Braun, C. *et al.* (2000) Differential activation in somatosensory cortex for different discrimination tasks. *J. Neurosci.* 20, 446–450
52 Mellinger, J. *et al.* (2007) An MEG-based brain-computer interface (BCI). *Neuroimage* 36, 581–593
53 Weiskopf, N. *et al.* (2004) Principles of a brain-computer interface (BCI) based on real-time functional magnetic resonance imaging (fMRI). *IEEE Trans Biomed Eng.* 51, 966–970
54 Yoo, S.S. and Jolesz, F.A. (2002) Functional MRI for neurofeedback: feasibility study on a hand motor task. *Neuroreport* 13, 1377–1381
55 Yoo, S.S. *et al.* (2007) Functional magnetic resonance imaging-mediated learning of increased activity in auditory areas. *Neuroreport* 18, 1915–1920
56 Yoo, S.S. *et al.* (2006) Increasing cortical activity in auditory areas through neurofeedback functional magnetic resonance imaging. *Neuroreport* 17, 1273–1278
57 Yoo, S.S. *et al.* (2007) Reproducibility of trial-based functional MRI on motor imagery. *Int. J. Neurosci.* 117, 215–227
58 deCharms, R.C. *et al.* (2004) Learned regulation of spatially localized brain activation using real-time fMRI. *Neuroimage* 21, 436–443
59 Lee, J.H. *et al.* (2009) Brain-machine interface via real-time fMRI: preliminary study on thought-controlled robotic arm. *Neurosci. Lett.* 450, 1–6
60 Cox, D.D. and Savoy, R.L. (2003) Functional magnetic resonance imaging (fMRI) 'brain reading': detecting and classifying distributed patterns of fMRI activity in human visual cortex. *Neuroimage* 19, 261–270
61 Lee, J.H. *et al.* (2009) Automated classification of fMRI data employing trial-based imagery tasks. *Med. Image Anal.* 13, 392–404
62 Mourao-Miranda, J. *et al.* (2005) Classifying brain states and determining the discriminating activation patterns: Support Vector Machine on functional MRI data. *Neuroimage* 28, 980–995
63 Sitaram, R. *et al.* (2007) Temporal classification of multichannel near-infrared spectroscopy signals of motor imagery for developing a brain-computer interface. *Neuroimage* 34, 1416–1427
64 Coyle, S. *et al.* (2004) On the suitability of near-infrared (NIR) systems for next-generation brain-computer interfaces. *Physiol. Meas.* 25, 815–822
65 Kennan, R.P. *et al.* (2002) Simultaneous recording of event-related auditory oddball response using transcranial near infrared optical topography and surface EEG. *Neuroimage* 16, 587–592
66 Luu, S. and Chau, T. (2009) Decoding subjective preference from single-trial near-infrared spectroscopy signals. *J. Neural. Eng.* 6, 016003
67 Bauernfeind, G. *et al.* (2008) Development, set-up and first results for a one-channel near-infrared spectroscopy system. *Biomed. Tech. (Berl.)* 53, 36–43
68 Diehl, B. *et al.* (2003) Mapping of spikes, slow waves, and motor tasks in a patient with malformation of cortical development using simultaneous EEG and fMRI. *Magn. Reson. Imaging* 21, 1167–1173
69 Bonmassar, G. *et al.* (2002) Motion and ballistocardiogram artifact removal for interleaved recording of EEG and EPs during MRI. *Neuroimage* 16, 1127–1141
70 Briselli, E. *et al.* (2006) An independent component analysis-based approach on ballistocardiogram artifact removing. *Magn. Reson. Imaging* 24, 393–400
71 Hoy, K.E. and Fitzgerald, P.B. (2010) Brain stimulation in psychiatry and its effects on cognition. *Nat. Rev. Neurol.* 6, 267–275
72 Fregni, F. *et al.* (2007) Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. *Lancet Neurol.* 6, 188–191
73 Jolesz, F.A. *et al.* (2005) MR imaging-controlled focused ultrasound ablation: a noninvasive image-guided surgery. *Magn. Reson. Imaging Clin. N. Am.* 13, 545–560
74 Gavrilov, L.R. *et al.* (1996) Application of focused ultrasound for the stimulation of neural structures. *Ultrasound Med. Biol.* 22, 179–192
75 Yoo, S.S. *et al.* (2009) Non-invasive regional modulation of brain function by focused ultrasound. In: Society for Neuroscience, pp. 1719, #105.111
76 AIUM Clinical Standards Committee (2004) How to interpret the ultrasound output display standard for higher acoustic output diagnostic ultrasound devices: version 2. *J. Ultrasound Med.* 23, 723–726
77 Nijboer, F. *et al.* (2008) A P300-based brain-computer interface for people with amyotrophic lateral sclerosis. *Clin. Neurophysiol.* 119, 1909–1916
78 Kübler, A. *et al.* (2005) Patients with ALS can use sensorimotor rhythms to operate a brain-computer interface. *Neurology* 64, 1775–1777
79 Rebsamen, B. *et al.* (2010) A brain controlled wheelchair to navigate in familiar environments. *IEEE Trans. Neural Syst. Rehab. Eng.* 2010 May 10. [Epub ahead of print]
80 Broetz, D. *et al.* (2010) Combination of brain-computer interface training and goal-directed physical therapy in chronic stroke: a case report. *Neurorehabil. Neural Repair* 2010 Jun 2. [Epub ahead of print]
81 Debove, C. *et al.* (2001) The Rilutek ® (riluzole) Global Early Access Programme: an open-label safety evaluation in the treatment of amyotrophic lateral sclerosis. *Amyotrop. Lateral Scler. Other Motor Neuron Disord.* 2, 153–158
82 WHO (2007) World Health Report (from the World Health Organization)
83 Walker, J.E. (2010) Using QEEG-guided neurofeedback for epilepsy versus standardized protocols: enhanced effectiveness? *Appl. Psychophysiol. Biofeedback* 35, 29–30
84 deCharms, R.C. (2008) Applications of real-time fMRI. *Nat. Rev. Neurosci.* 9, 720–729
85 Arns, M. *et al.* (2009) Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. *Clin. EEG Neurosci.* 40, 180–189
86 Hammond, D.C. (2005) Neurofeedback with anxiety and affective disorders. *Child Adolesc. Psychiatr. Clin. N. Am.* 14, 105–123 vii
87 Vaughan, T.M. *et al.* (2006) The Wadsworth BCI Research and Development Program: at home with BCI. *IEEE Trans. Neural Syst. Rehabil. Eng.* 14, 229–233