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Opinion

Harnessing Prefrontal Cognitive Signals for Brain–Machine Interfaces

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Brain–machine interfaces (BMIs) enable humans to interact with devices by modulating their brain signals. Despite impressive technological advancements, several obstacles remain. The most commonly used BMI control signals are derived from the brain areas involved in primary sensory- or motor-related processing. However, these signals only reflect a limited range of human intentions. Therefore, additional sources of brain activity for controlling BMIs need to be explored. In particular, higher-order cognitive brain signals, specifically those encoding goal-directed intentions, are natural candidates for enlarging the repertoire of BMI control signals and making them more efficient and intuitive. Thus, here, we identify the prefrontal brain area as a key target region for future BMIs, given its involvement in higher-order, goal-oriented cognitive processes.

Trends

As new directions for BMIs, cognitive BMI paradigms have various advantages, challenges, and future potential applications.

The ability to decode higher-order, goal-oriented cognitive signals from the prefrontal cortex provides new possibilities for goal-directed BMI technology that recognizes the user's intention.

As a complement to traditional approaches, the exploitation of cognitive signals may help overcome the limitations of the existing state-of-the-art BMI systems.

The direct decoding of goal-directed intentions can intuitively control BMI devices without goal-irrelevant, indirect thinking (i.e., independent of the final actuator or feedback modality).

Cognitive BMI approaches may help rehabilitate or augment the cognitive capabilities of patients with prefrontal dysfunctions.

Brain–Machine Interfaces: An Overview

BMIs, or brain–computer interfaces (BCIs), are a type of communication technology that links humans and devices by decoding the user's brain signals. This decoding process aims at inferring, in real time, the user's intention (e.g., move a prosthetic arm towards the right) based on measured neural activity patterns. The inference is based on models of task-specific patterns associated with different intentions (e.g., the differential activity in the left and right motor-related areas of the brain can be used to decode intentions to move the left or right hand). As BMI technology becomes more refined, its applicability in different environments increases, ranging from clinical use to general consumer electronics. For example, BMIs have been proposed for humans with motor deficits [1,2] as well as for able-bodied individuals with regard to gaming, human–machine interactions, and driving [3–6]. BMIs are an advanced biotechnology with widespread interest and numerous potential applications.

To generate appropriate BMI commands, the brain signals recorded from multiple channels are processed to extract meaningful features (Figure 1). In this context, features are processed signals that optimally reflect specific characteristics of a designated mental task. For instance, hand movements are known to induce spatiotemporal patterns at specific frequencies in the motor cortex of the contralateral hemisphere. These features, which carry information about the user's intentions, are then sent to a decoder [7,8] that translates the current brain activity pattern into commands to be performed by the device. Despite impressive progress in the field, multiple outstanding challenges need to be overcome before these technologies can be widely used in both clinical and consumer settings [9]. These challenges include improving the reliability of decoding, and endowing the decoding engine with adaptive capabilities, which will enable the BMI to be used long-term without explicit recalibration [10,11]. Improvements in

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the training paradigms and feedback [12], as well as the development of more robust and wearable signal acquisition devices [13], will also be required.

Currently, the most critical impediment to using BMI technology outside of the laboratory is that a large percentage of prospective end-users are unable to control the BMI because they experience difficulties in learning to modulate their brain signals. In a study involving 24 end-users, some with severe motor deficits, only 50% of the participants were able to control the BMIs after less than 10 days of training [2]. As we review below, current BMI paradigms usually decode primary sensory- or motor-related brain processes that, while critical for interaction, only represent a subset of all the processes taking place during goal-oriented interactions. It follows that BMIs could be greatly improved by enlarging the repertoire of brain signals to be exploited. In particular, we propose that decoding cognition-related signals might produce BMIs that are more robust and that could be controlled in a more intuitive manner compared with existing paradigms.

BMI Recording Techniques and Paradigms

There are two types of recording technique used in BMIs: invasive and non-invasive. Invasive techniques allow for the direct recording of high-quality brain electrical signals, despite the risk of infection inherent to the surgical procedure. For example, the activity of individual neurons can be recorded using microelectrode arrays implanted in the brain [**multi-unit activity** (MUA); see Glossary] [14–17]. BMIs can also utilize the concerted activity of differentially sized neuronal populations depending on the position of the electrodes, which can be implanted in the brain [**local field potential** (LFP)] [18] or on the surface of the brain [**electrocorticography** (ECoG)] [19].

Meanwhile, **electroencephalography** (EEG) [20] is a non-invasive technique that records the synchronous activity of thousands of cortical neurons using electrodes placed on the scalp. These invasive and non-invasive electrophysiological techniques have complementary advantages. Thus, a combination of technologies may be necessary to achieve the ultimate goal of long-term, reliable control of neuroprostheses [21]. Compared with EEG, other non-invasive neuroimaging modalities are fraught with limitations. **Magnetoencephalography** (MEG) devices are still too bulky to become a convenient BMI modality for everyday use. Moreover, **functional magnetic resonance imaging** (fMRI) and **near-infrared spectroscopy** (NIRS) result in slow BMI operation, owing to the inherent physiological latencies of the hemodynamic responses that they measure.

In general, BMI paradigms are divided into two types: (i) externally stimulated paradigms that decode brain responses to stimuli; and (ii) internally induced paradigms based on self-initiated mental tasks [20,22]. An example of the first type of paradigm is the use of the **P300** signal. This component is a large positive modulation of the EEG signal, involving the frontal and parietal areas, that peaks at approximately 300 ms after stimulus onset [23]. It is usually detected during the categorical stimulus evaluation processes. P300-based BMIs [24,25] have high detectability in most users and a relatively short latency, yielding fast communication. However, the P300 signal only reflects processes that are related to the presented stimulus, and does not carry broader information about the user's intention. Alternatively, several steady-state visual evoked potential (SSVEP)-based BMIs have also been proposed [26,27]. The SSVEP is a physically driven, brain electrical oscillatory response in the visual cortex at the exact same frequency of an externally flickering stimulus. The highest performance in SSVEP-based BMIs is achieved when users fixate on the flickering target, thereby being inappropriate for users who do not have proper gaze control [27], or for long-term users due to eye fatigue [28].

Glossary

Electrocorticography (ECoG): an intracranial measurement technique in which electrical activity is recorded directly from the surface of the cerebral cortex. ECoG utilizes a flexible, closely spaced subdural/epidural grid or strip of electrodes to record cortical activity. Compared with non-invasive techniques, it avoids signal distortion introduced by the skull and intermediate tissue. Hence, ECoG has both high temporal (millisecond scale) and high spatial (millimeter scale) resolution. Since a craniotomy is required to implant the electrode grid, ECoG is generally only applied to clinical patients.

Electroencephalography (EEG): measures differences in the electric potential representing the sum of the excitatory and inhibitory postsynaptic potentials from thousands or millions of cortical neurons. EEG is typically measured non-invasively using multichannel arrays, conventionally comprising 64–128 electrodes, placed on the scalp.

Functional magnetic resonance imaging (fMRI): a non-invasive neuroimaging technique that uses pulse sequences generated by a MRI scanner. The most widely used fMRI technique relies on the detection of local hemoglobin-based changes in blood-oxygen-level-dependent signal contrast during neuronal activation. This technique is characterized by high spatial resolution, but low temporal resolution owing to an inherently delayed metabolic response.

Local field potential (LFP): a massed electrophysiological signal obtained by the summed extracellular electrical potential recorded by intracranial electrodes. The local electrical potential is generated from multiple nearby neurons within a small volume of local neuron groups. The LFP signal (frequency $<$500 Hz) captures a multitude of neuronal processes, such as synchronized synaptic potentials and membrane currents.

Magnetoencephalography (MEG): utilizes a superconducting quantum interference device (SQUID) that is extremely sensitive to the magnetic disturbances created during neuronal activity. This device can be used to non-invasively detect the magnetic field signals around the scalp (~50–

The second type of BMI paradigm relies on the volitional modulation of brain rhythms, in particular those associated with motor tasks. One such endogenous signal is the **slow cortical potential** (SCP) [29]. For example, a slow, negative cortical potential (i.e., 'readiness potential') reflecting internally generated intentions to move a limb can be observed in the corresponding motor area before movement onset [30]. SCP-based BMIs were among the first BMIs to exploit the correlates of human voluntary intentional movement [31]. Although SCPs can be decoded on a single-trial basis, the decoding may take up to several seconds owing to the slow dynamics of SCP. Besides SCPs, BMIs also exploit brain activity linked to the execution or imagination of movements. Invasive approaches typically decode kinematic information (hand position or velocity) from neuronal spikes or LFPs [14,16,17,19]. Non-invasive approaches have extensively used motor-related spectral EEG modulations in the mu (8–13 Hz) and beta (14–30 Hz) rhythms over the sensorimotor cortex as features for BMIs [20]. Compared with approaches based on evoked responses, this type of approach usually requires longer training periods and exhibits lower accuracy. Nevertheless, some users, including those with disabilities, have achieved proper proficiency in BMI control skills (i.e., the ability to voluntarily modulate the brain rhythms used by the decoder) after only a few training sessions [1], and were able to demonstrate reliable control of these BMI devices [2,3,32–34].

Use of Goal-Oriented BMIs to Overcome Current Limitations

Previous studies on almost all types of BMI paradigm have demonstrated that participants, including those with severe motor deficits [2,16,17,25,31,34,35], can successfully learn to use a variety of brain-controlled devices [1]. Unfortunately, before BMI technology can be used outside the laboratory, several limitations need to be overcome.

First, the number of brain signals currently used by BMIs is limited, and the signals are principally derived from the primary sensorimotor cortex (i.e., activated by mental motor imagery) or the posterior-parietal and occipital cortices (i.e., elicited by processing specific stimuli). However, these signals only reflect a subset of the underlying processes that occur during goal-oriented interactions. The sensorimotor or posterior-parietal/occipital signals used by current BMIs are often linked to a specific characteristic of the chosen paradigm (e.g., the stimulus modality or presentation rate). Thus, the decoding accuracy of the BMI may decrease whenever the setup changes. Therefore, other brain activity features need to be harnessed as BMI control signals, especially for patients with damage to the primary sensorimotor cortex, or posterior-parietal/occipital cortices, or in cases where the signals derived from these regions are not reliable. We posit that higher-order cognitive brain signals, which encode goal-directed intentions instead of details on how to reach it, are natural candidates for enlarging the repertoire of BMI control signals. Moreover, the usage of goal-directed signals may enable us to achieve complex tasks intuitively, by delegating low-level details of their execution to intelligent devices (i.e., shared control) [33] and, critically, may allow for generalization over different operating conditions [36]. In the concept of 'goal-directed intentional brain activity', there could be two types of goal-directed tasks. One type is dependent on the output device (e.g., opening a window is specific to the window), and the other is independent of the output device (e.g., intended movement trajectories can be generalized to a variety of devices). Although the implementation of the goal-directed intention will depend on each case, the analysis of brain signals to recognize such an intention is similar.

Indeed, a BMI can function in two different ways; it can control a process or it can select a goal [37,38]. A BMI can control the details of the process to accomplish the user's intention. For instance, it can specify each step of the movement sequence that brings the output device to the goal. To do this effectively, the brain should provide information of all the complex high-speed interactions with the device as the movement proceeds. Alternatively, in the goal-selection approach, the BMI simply communicates the users' goal, and the movement is

500 fT) that are generated by neural activity. Modern MEG devices typically use helmet-shaped sensor arrays of more than 300 SQUIDs that are systematically arranged to cover the entire scalp.

Multi-unit activity (MUA): in MUA, extracellular electrical signals (in terms of action potentials) are recorded from multiple neurons simultaneously. The MUA (frequency >1000 Hz) portion of the recording represents the spiking of local neurons. To record from a local network of neurons, microelectrodes can be arranged in a grid-shaped array, which can also be implanted to obtain *in vivo* recordings.

Near-infrared spectroscopy (NIRS): light in the near-infrared spectrum (~630–1300 nm) can penetrate the skull. This light can be used to non-invasively investigate cerebral metabolism. NIRS identifies alterations in the intensity of attenuated light at different wavelengths that result from changes in the oxyhemoglobin and deoxyhemoglobin concentrations during local neural activity.

P300: an evoked EEG response to rare and relevant stimuli. It is one of the most frequently used event-related potentials for EEG-based BMIs. The signal is characterized by a positive EEG peak, usually observed at approximately 300 ms post stimulus during context-updating processes. For instance, in the classic matrix speller paradigm, elements in the matrix (rows or columns) are highlighted in a random order. When the user focuses their attention on a desired character, the P300 component will be elicited when the matrix elements containing that character are presented (Figure 1, main text).

Prefrontal cortex (PFC): a central component in the brain network supporting cognitive/attentional control, sensory input, and motor output. PFC is located anterior to the (pre)motor cortex in the frontal lobes, and can be divided into ventromedial and dorsolateral regions, each of which exhibits reciprocal connectivity with different posterior and subcortical brain areas. Anatomically and functionally selective PFC subregions have been associated with distinct forms of control.

Slow cortical potentials (SCPs): slow changes in the voltages recorded over the sensorimotor accomplished by neuroprosthetic controllers [37]. Given that the first approach requires effective management of the complex high-speed interactions between the BMI output and the sensory inputs, it places greater mental demands on the BMI than does goal selection. It has been previously reported that goal selection shows better BMI performance (in accuracy, speed, and information transfer rate) than does process control [38].

Additionally, BMI operational protocols often require users to perform mental functions that are not directly related to the task goal. For example, to move a bar on the monitor towards the right, users are typically trained to imagine a movement of the right hand, rather than to directly think of moving the bar to the right. By contrast, the goal-directed strategy has the potential to provide more natural control. As with any goal-selection approach, a goal-directed BMI decodes a subject's intention from cortical signals and delegates actual control of the process to the downstream apparatus [37]. Decoding goal-directed intentional brain activity could produce BMI operational strategies that are more intuitive, and ones that subjects might be able to acquire more easily.

cortex, which precede actual or imagined movement or cognitive tasks. It has been suggested that positive SCPs accompany mental inhibition, whereas negative SCPs are associated with mental preparation. Early SCP-based BMIs required users to learn how to voluntarily modulate these rhythms through operant conditioning, which required long training periods. More recently, the focus has shifted towards exploiting the functional role of movement-related SCPs. Thus, naturally elicited SCPs are being used to decode the onset of self-paced movement intentions of both able-bodied subjects and patients with stroke.

Advances in Cognitive BMI Technology

Higher cognitive functions, such as planning to achieve goals and evaluating the course of actions, are independent of the low-level details of how actions are executed, and of the sensory modalities conveying the status of the task under consideration. This is one of the fundamental differences between the proposed cognitive BMI and other sensorimotor and externally triggered sensory paradigms. A second difference is the loci of the corresponding neural signals. While classical BMI paradigms record signals from the frontocentral and parieto-occipital areas (Figure 1), cognitive BMIs should exploit neural signals from more diverse areas, ranging from rather specific parietal and frontal areas to complex prefrontal networks. Table 1

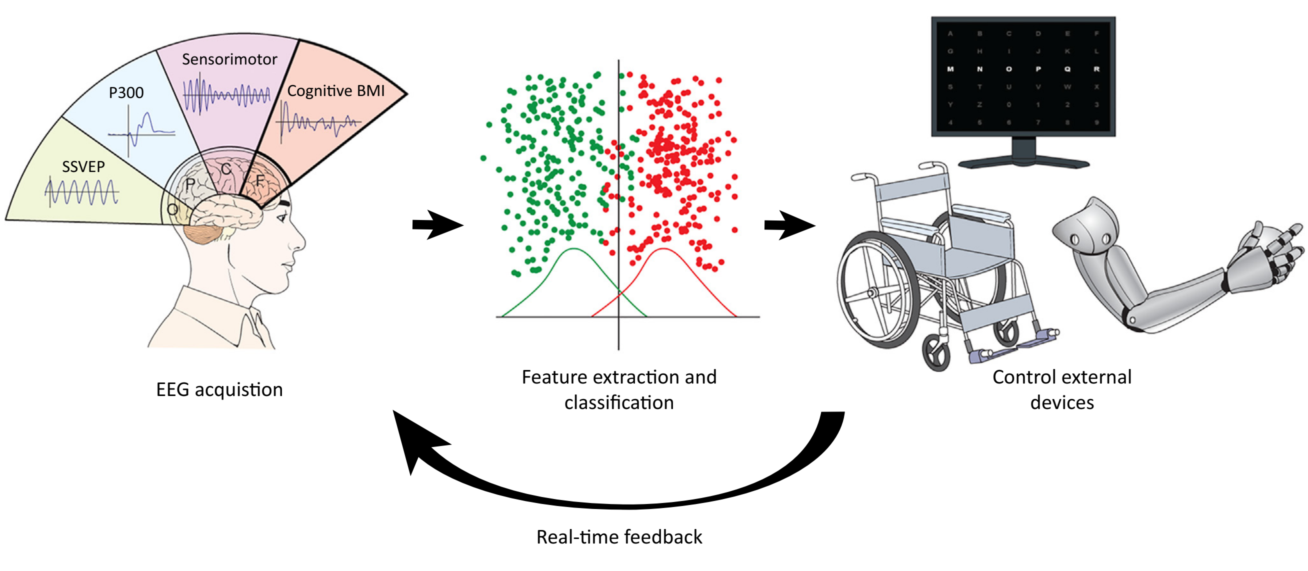


Figure 1. Electroencephalography (EEG)-based Brain–Machine Interface (BMI) Technology and its Categorical Paradigms. This schematic flow is a simplified conceptual structure of BMI technology. To obtain a control signal for BMIs, EEG signals are recorded from the relevant cortical areas [i.e., occipital steady-state visual evoked potentials (SSVEPs), noted as 'O'; parietal P300, noted as 'P'; central sensorimotor activity, noted as 'C'; and frontal and prefrontal cognitive rhythms, noted as 'F']. These frontal and prefrontal cognitive rhythms are newly proposed control signals for cognitive BMIs. Then, machine-learning techniques find pertinent features in the recorded EEG, which are sent to a classifier to determine the user's intention in real time. The BMI control signals cause a change in the environment (e.g., movement of a wheelchair or change in the position of a prosthetic arm), and this information can be used to provide real-time feedback to BMI users so that they can learn to better modulate their EEG activity and convey better mental commands. Eventually, this feedback could be exploited to adapt the parameters of the classifier in an ongoing closed-loop BMI system.

Table 1. Comparative Advantages and Disadvantages of Prefrontal and Sensorimotor BMIs

Prefrontal BMI	Sensorimotor BMI
Advantages	
• Uses goal-directed brain signals • Uses intuitive BMI commands; no need for arbitrary mental tasks (indirect thinking) • Allows combinations of BMI signals to be used across frontal and other brain regions • Potential concomitant therapeutic or rehabilitative effects for cognitive disorders • Spare utility when primary sensorimotor cortices are damaged	• Relatively well-established research field • Less elaborate signal processing is required • Relatively prompt signal processing for communication • Use of sensorimotor approaches for motor rehabilitation
Disadvantages	
• Newly developed research field • Exploits signals from a relatively complicated frontal cognitive network compared with the primary sensorimotor cortices • Elaborate signal processing is required to extract the spatially accurate cognitive information from raw brain signals	• Limited number of BMI control signals • Often relies on arbitrary mental tasks (goal-irrelevant thinking), leading users to adopt non-intuitive control strategies • Impasse when primary sensorimotor cortices are damaged

lists several advantages and disadvantages of the new cognitive BMI approach (Box 1) and of the existing sensorimotor BMI approach.

To date, while a large number of sensorimotor BMI studies have been conducted, only a few have focused on cognitive BMIs, although recently there has been growing attention to this approach. As shown in Table 2, studies investigating cognitive BMIs have used various recording modalities and targeted diverse areas, decoding different kinds of high-order, goal-directed intentions. One example of a cognitive BMI is decoding the goal of upcoming movements from neural activity that occurs before movement onset. For this purpose, BMIs can exploit signals based on EEG readiness potentials [39], ECoG recordings in the dorsolateral prefrontal cortex (DLPFC) [40], and MUA in the parietal reach region (PRR) of the posterior parietal cortex (PPC) [15]. For instance, Musallam and colleagues [15] showed that the expected value of reward could be decoded from MUA in the PRR, an area involved in transforming sensory inputs into action plans, whose activity exhibits directional selectivity. Aflalo and colleagues [35] found that PRR activity provided reliable information about reaching the goals and trajectories of a human with tetraplegia. Importantly, they demonstrated that decoding was cue independent and that some goal-selective neurons showed no bias with respect to which arm the subject imagined using. Other studies have targeted the DLPFC or the **PFC** in general. Vansteensel and colleagues [41] reported that the position of a computer cursor could be moved to a target by modulating the gamma ECoG activity in the left DLPFC, while Ryun and colleagues [42] observed that two types of movement (hand grasping and elbow flexion) could be predicted before movement onset by using prefrontal ECoG signals. Collectively, these invasive studies revealed the neurophysiological underpinnings of cognitive BMIs, and reinforced the feasibility of cognitive BMI technology.

In parallel, there have been increasing attempts to develop non-invasive cognitive BMIs in humans using EEG [43,44] and NIRS techniques [45]. For instance, Wang and Makeig [44] investigated whether non-invasive EEG signals recorded from the human PPC can be used to decode intended movement direction. They recorded whole-head EEG with a delayed saccade-or-reach task and found direction-related modulation of event-related potentials in the PPC. The decoding of these components yielded an average accuracy of 80.25% in binary

Table 2. Overview of Cognitive BMI Studies[a]

Signals	Participants	Experimental protocol	Performance	Refs
Invasive Approaches				
Frontal and Prefrontal Cortex				
Subdural ECoG in left DLPFC	Humans with intractable epilepsy ($N = 3$)	1D Computer-cursor movement control (two tasks: serial subtractions versus rest); several ~4-min runs (28–29 trials/run)	Online decoding; average correct hits: 78.3% (up to 91%)	[41]
MUA in medial-frontal area	Humans with intractable epilepsy ($N = 12$)	Onset of upcoming self-paced movements (Libet protocol [78])	Offline cross-validation accuracy >80% (30% of data used as a testing set)	[79]
Subdural ECoG in PFC, premotor, supplementary, and primary sensory-motor areas	Humans with intractable epilepsy ($N = 6$)	Decoding self-paced movement types: grasping of elbow flexion (68–138 trials)	Offline decoding accuracy: 74% (fivefold cross-validation)	[42]
Parietal Cortex				
MUA in PRR	Monkeys ($N = 3$)	Decoding-cued reaching goal location; 250 and 275 trials (four and six targets, respectively)	Online decoding accuracy: 40.8% and 31.3% (four and six targets, respectively)	[15]
MUA in PRR and PPC	Monkeys ($N = 2$)	Cued reaching task. Up to 25 daily sessions for offline training followed by up to 17 days of brain control sessions	Offline trajectory reconstruction: coefficient of determination (R^2) up to 0.61 (average across days). Online reaching success rate: up to 85.2% after 10 training days	[80]
MUA in left PPC	Human with tetraplegia ($N = 1$)	Goal and trajectory of imagined movements; online decoding used to control robot arm trajectories	Online accuracy of goal decoding: >90%	[35]
Non-Invasive Approaches				
Frontal and Prefrontal Cortex				
Error-related EEG potentials (frontocentral areas)	Healthy volunteers, no BMI experience ($N = 2$)	Simultaneous motor-imagery and error-potential decoding. 1D cursor control	Online recognition rate of correct single trials: 84.7%	[81]
Error-related EEG potentials (frontocentral areas)	Healthy volunteers ($N = 12$)	Monitoring of 1D and 2D movements of an external device (cursor control, simulated, and real robot arm); approximately 350 trials per subject	Online decoding accuracy: 72.5–74.3%	[36]
Motor-related EEG cortical potentials	Healthy controls (ME: $N = 15$; MI: $N = 10$) Stroke patients (AM: $N = 5$)	ME/MI of self-paced ankle movements: ME, AM: three test runs of 5 min duration each MI: two test runs of 5 min duration each	Offline decoding. Average TPR: healthy: ME: 82.5% and MI: 64.5%; stroke: AM: 55%	[82]
Motor-related EEG cortical potentials	Healthy volunteers ($N = 9$)	ME/MI of self-paced ankle movements; 15–20 trials for each condition	Online average TPR: ME: 84%, MI: 75%.	[83]

Table 2. (continued)

Signals	Participants	Experimental protocol	Performance	Refs
			Detection latency: ME: 235 ms; MI: 396 ms	
Slow cortical potentials in frontocentral areas	Healthy volunteers (*N* = 4)	Self-paced reaching and grasping tasks (400 trials per subject)	Offline detection of grasping intention: 70%. Decoding latency: 62 ms before grasping onset	[84]
NIRS signals in PFC	Healthy volunteers (*N* = 21)	Computer-cursor movement control (fivefold cross-validation of 50 trials)	Offline decoding accuracy: 65.5%	[45]
Parietal Cortex				
Movement-related temporoparietal EEG signals	Healthy volunteers (*N* = 4)	Cued delayed saccade/reaching task; three possible targets (900 trials overall)	Offline decoding accuracy: 80.3% (tenfold cross-validation)	[44]
Movement-related EEG slow cortical potentials in frontal and parietal areas	Healthy controls (*N* = 2); stroke patients (*N* = 3)	Cued self-paced reaching task; four possible targets (80 trials/target)	Offline decoding accuracy (fivefold cross-validation): healthy: 76%; stroke: 47% (chance: 25%)	[39]

[a]Abbreviations: AM, attempted movement; ME, movement execution; MI, movement imagination; *N*, number of participants; TPR, true positive rate.

single-trial EEG classification (left versus right). These results indicate that, in the PPC, neuronal activity associated with different movement directions can be distinguished even in a non-invasive manner and, thus, non-invasive cognitive BMIs are feasible.

Prefrontal Activity as a Source of Cognitive Signals

Using goal-directed intention recognition may help advance BMI technology (Figure 2), and activity in the PFC appears to be an ideal candidate for achieving this aim. The PFC is central to executive control (i.e., cognitive/attentional control of behavior), and the dynamic integration of sensory input, internal states, and motor output [46]. These higher-order cognitive functions, including planning and evaluating ongoing actions, are independent of action-execution processes, and of the sensory modalities that provide feedback on the current task [47]. Consequently, their correlates in the PFC remain robust across different tasks and feedback modalities. This is illustrated in the case of error-related potentials and reaching information (generated in the anterior cingulate and parietal cortices, respectively), shown to be consistent across different experimental paradigms. We posit that, because neural activity related to higher-order cognitive processes is a natural and intuitive neural correlate of goal-directed intentions, the decoding of these signals may lead to the seamless and efficient operation of complex brain-controlled devices (such as neuroprostheses and avatars), and to breakthroughs in communication and environmental control speeds.

The PFC comprises those parts of the frontal lobes that are located anterior to the motor and premotor cortices, and anatomically comprises the dorso-/ventrolateral PFC, dorso-/ventromedial PFC, and anterior PFC [48]. The DLPFC has reciprocal connections with brain regions for motor control (basal ganglia, premotor cortex, and supplementary motor cortex), performance monitoring (cingulate cortex), and nonemotional sensory processing (parietal/occipital association areas). Meanwhile, the ventromedial PFC has reciprocal connections with brain regions for emotional processing (amygdala), memory (hippocampal formation), and higher-order sensory processing (inferior temporal visual association areas) [49]. The existence of dissociable PFC

Box 1. Neural Correlates of Cognitive Processes

Anticipation and Movement Preparation

Slow activity modulations in cortical motor areas have been found to occur in the moments preceding self-paced voluntary movements, known as the readiness potential or motor-related cortical potential [29,78]. A similar slow negative EEG deflection (contingent negative variation) appears in central areas when subjects anticipate future events predicted by a warning stimulus [85]. Recently, the idea of decoding these slow cortical potentials (SCPs) has gained traction as a means of predicting a subject's upcoming actions. Indeed, SCPs have been used to predict the onset and direction of self-paced upper- and lower-limb movements using both invasive [15,35,40,79] and non-invasive techniques [39,82,83,86]. BMIs that use SCPs to predict the onset and direction of limb movements differ from those that rely on SCP modulation [29], because the former utilize the naturally elicited SCP and its functional correlates, while the latter require subjects to learn a new arbitrary skill via neurofeedback, which may necessitate long training periods.

Error-Related Potentials

Performance monitoring is crucial for learning and adapting behavior. Multiple studies have identified brain responses in the medial frontal cortex that are elicited by monitoring the performance of action-related processes [87,88]. These signals are evoked by the subject's own errors, as well as by unexpected feedback or errors during BMI interaction [43]. Modulation of neural activity in the theta frequency band (4–8 Hz) has been shown to correlate with error awareness, and this activity appears to originate in the anterior cingulate cortex. Importantly for BMI applications, these signals can be consistently measured using scalp EEG and reliably decoded on a single-trial basis [36,43,81].

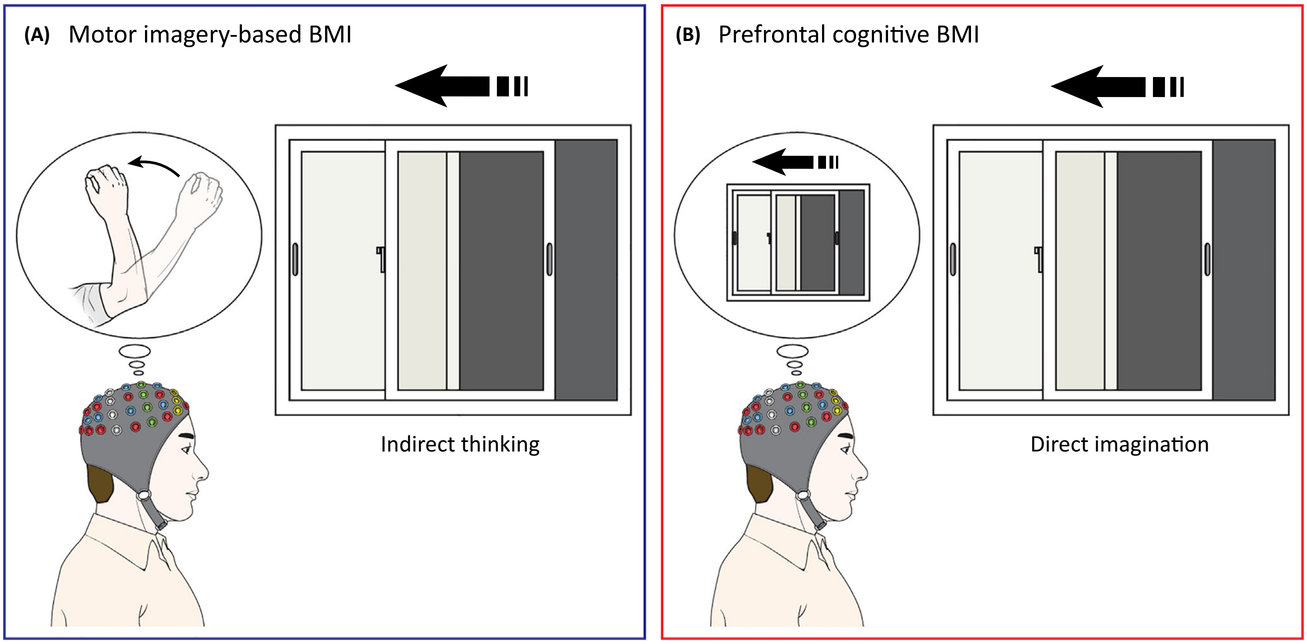
Correlates of Goal-Directed Movement

Typically, BMIs have focused on decoding the kinematics of ongoing movements (via invasive approaches), or on imagining repetitive movements (via non-invasive systems). An alternative is to decode the goal of an upcoming movement. Invasive recordings in humans and nonhuman primates have shown that activity in the parietal cortex enables movement goals to be decoded, including reaching direction and grasping type [15,35]. Early evidence suggests that it is also possible to decode direction and grasping intention using non-invasive techniques [39,84]. Since this approach focuses on decoding high-level intentions, it can be combined with shared-control approaches, where the intelligent prosthesis deals with the details of the execution of the action [33]. Such an approach has been shown to improve performance while reducing the user's cognitive workload [89].

subdivisions implies differently designated functions. For example, the dorsal PFC is associated with generating goals based on recent events, while the ventral PFC is related to generating goals based on sensory contexts [50]. Such topographic and functional subdivisions may also correspond to specific executive functions that could be utilized for cognition-based BMI control. For instance, the DLPFC has roles in motor control and performance monitoring in working memory [49], including implementing programs to achieve an intended goal and monitoring the results of an action to adjust behavior [51]. Thus, decoding DLPFC activity has the potential to become a core cognitive component of BMIs that would exploit information on the monitoring and manipulation of online behavior. The work by Vansteensel and colleagues [41] provides a preliminary example of this type of cognitive BMI.

The role of executive control in working memory, with some functional differences, characterizes the entire lateral PFC [49,52]. By contrast, the anterior PFC enables the online evaluation of a pending task according to the outcomes of an ongoing task. Additionally, the anterior PFC is a crucial component of the executive system, which is involved in decision-making processes [53]. These two areas could provide independent control signals for cognitive BMIs, although this would require the use of invasive techniques (ECoG, LFP, or MUA) or the estimation of intracranial sources from scalp EEG (see Figure 3 and the 'Challenges for Future Cognitive BMIs' section below).

Neuroplasticity is one of the key components of BMI because users should learn to modulate their brainwaves voluntarily via appropriate feedback. Such feedback drives the brain reward system, which can promote the generation of particular neural patterns [1,54]. This is the rationale of BMI-mediated motor neurorehabilitation [55,56]. Similarly, cognitive BCIs exploiting



Trends in Biotechnology

Figure 2. Comparative Overview between Typical Motor-Imagery and Prefrontal Cognitive Brain–Machine Interface (BMI) Paradigms. (A) In motor imagery-based BMIs, the user has to imagine moving a hand to open the window, but this motor imagery of a hand is not directly related to the user's goal of opening the window. (B) In prefrontal cognitive BMIs, when the user intuitively imagines opening the window, the window will be opened. Therefore, indirect thinking is no longer required, and direct imagination of goal-directed intentions will likely be sufficient to control BMI devices.

PFC activity could reinforce targeted patterns in cortical networks, including prefrontal areas. It is noteworthy that the prefrontal area is a critical component of the reward system [57]. Therefore, the approach proposed here can open new avenues in the field of rehabilitation, particularly for patients with PFC-related cognitive disorders. Indeed, since BMI techniques can support neurological treatment as it facilitates neuroplasticity [58,59], including in the prefrontal area [60,61], the cognitive PFC-based BMI approach may contribute to the recovery of impaired prefrontal neural networks. Potential end-users include individuals with autism, Asperger's syndrome, dementia, attention-deficit/hyperactivity disorder (ADHD), and depression. In terms of neural rehabilitation, cognitive BMIs could decode goal-directed intentions from the PFC, and provide a beneficial feedback loop for restoring impaired networks (Figure 3). For example, autism [62] and ADHD [63] are the most frequently observed disorders with prefrontal deficiencies, and neurofeedback treatment for these disorders provides a significant therapeutic effect [64–66]. Therefore, cognitive PFC-based BMI training could be used to promote patterns of prefrontal activity in patients with autism or ADHD that would resemble those of healthy controls. Thus, further studies are needed to evaluate the potential of cognitive BMI techniques to significantly enhance the functioning of prefrontal brain region, and, consequently, contribute to the rehabilitation of patients with cognitive deficits due to prefrontal dysfunctions.

Similarly, cognitive PFC-based BMIs could be used to improve cognitive capabilities in healthy individuals. This point is especially important given our aging society. Experiments in older adults have shown that improvements in cognitive control obtained via video game-based training were correlated with increases of EEG theta activity (4–8 Hz) around the frontal midline brain area [67]. This type of activity is typically observed during mental calculation, concentration, short-term memory, and heightened attention [68]. We hypothesize that BMI systems aimed at actively

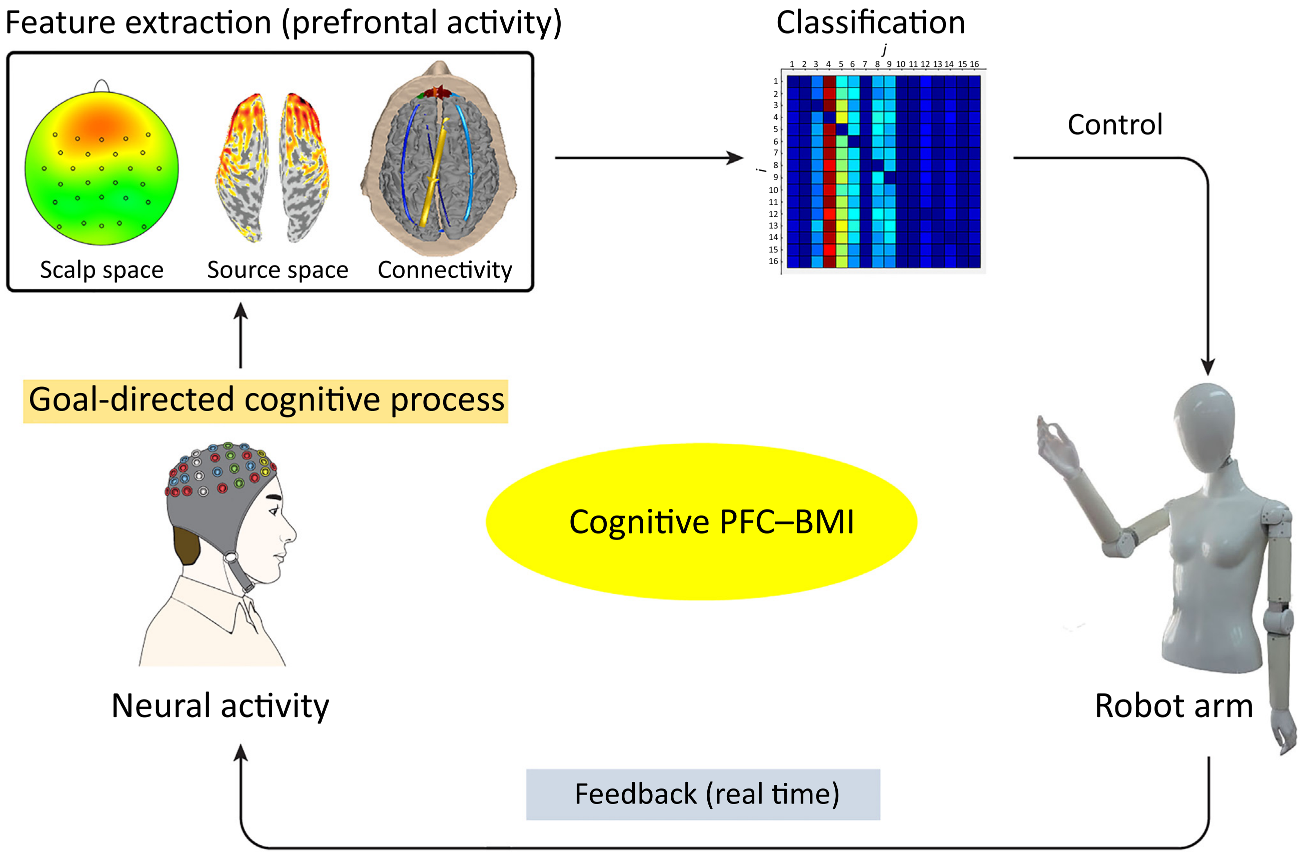


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Figure 3. An Example of a Prefrontal Cognitive Brain–Machine Interface (BMI). Using a prefrontal cognitive BMI system, the estimated prefrontal cortical activity becomes strongly activated when the position of a robot arm is controlled by goal-directed mental processes. Such prefrontal cognitive activity, directly reflecting the goal-directed intention, is used to enhance the ongoing task performance with direct real-time feedback. Through repeated feedback, the cognitive BMI technique can contribute to the rehabilitation (e.g., a beneficial feedback loop for restoring impaired cortical networks) of patients with cognitive deficits owing to prefrontal dysfunctions. The direct imagination of goal-directed intentions can intuitively control BMI devices without goal-irrelevant, indirect thinking. Such frontal cognitive activity can be identified, for instance, according to different spatial patterns in scalp-level electroencephalogram (EEG) activity, cortical-level EEG activity (estimated by source localization of the scalp-level EEG activity), or their causal connectivity.

promoting such PFC patterns may contribute to improvements in cognitive control, potentially boosting the effects obtained through video game-based training. In addition, recent studies have shown that meditation-based cognitive training [69–71] facilitates BMI use. For example, manipulating attention via mindfulness meditation induction improves P300-based BMI performance [69]. Furthermore, participants experiencing mind-body awareness training demonstrated an enhanced ability to control the BMI system, and improved significantly more over time compared with controls [70]. These observations provide insight into the enhancement of cognitive BMI learning and performance by incorporating mind–body awareness training.

Challenges for Future Cognitive BMIs

As discussed, PFC-based cognitive approaches appear to be ideal for generating goal-directed BMI commands. Nevertheless, several challenges must be overcome before such approaches can be used ubiquitously. The first and most critical challenge is to demonstrate the stability and reliability of cognitive BMIs across a range of goal-directed signals. In this respect, it remains to be identified which and how many of such cognitive brain signals can be decoded.

A second but related challenge concerns the necessary spatial resolution for deploying effective cognitive BMIs. Indeed, decoding goal-directed cognitive activity may be problematic because multiple mental processes activate the same areas, which may result in decreased decoding performance. Hence, spatial resolution is a limitation of EEG-based BMIs, especially when decoding signals originate from areas rich in subfunctions, such as the PFC. As discussed, the existence of dissociable PFC subdivisions (i.e., the anterior, dorsolateral, and ventrolateral PFC) supports the diversity of PFC control, but the spatial specificity of these regions has not been precisely mapped. In consequence, the development of signal processing techniques will be essential. Specifically, advanced source-localization methods for non-invasive approaches will be required to extract spatially accurate features that yield effective BMI control signals [72,73]. It is also likely that frequency-specific modulations can be individually observed in the PFC subdivisions, which may help disentangle the spatial specificity problem. In addition, these frequency-specific processes modulate the interactions between different brain areas. For instance, connectivity pattern analysis has been shown to convey information about error-monitoring processes in a BMI paradigm on a single-trial basis [74]. Similarly, cognitive control enhancement in older adults has been shown to correlate with increased long-range theta coherence between frontal and posterior brain areas [67]. Therefore, the use of connectivity-related features in BMIs may help disentangle specific cognitive processes [74–76]. Progress in computing power and parallel computing techniques makes extraction of the source and connectivity features of goal-oriented cognitive processes in real time possible [77].

Concluding Remarks and Future Perspectives

As it has been shown, it is now possible to recognize different goal-directed cognitive signals from the frontal and prefrontal cortices at a variety of levels, including the microscopic (MUA), mesoscopic (LFP), and macroscopic (EEG) levels. Using these different methods will allow us to exploit the individual advantages of each modality and to uncover new cognitive signals, either separately or in combination. As detailed here, the decoding of cognitive correlates of goal-directed tasks may lead to more robust and reliable BMIs. Moreover, since cognitive BMI techniques have the potential to enhance the functioning of prefrontal brain regions, they could contribute to the rehabilitation of patients with cognitive deficits related to prefrontal dysfunctions. Thus, a challenge for the future is to design cognitive BMIs that are appropriate for treating specific prefrontal pathologies (see Outstanding Questions). The assistive and therapeutic applications of prefrontal cognitive BMIs should be explored further with the aim of improving the quality of life of individuals with sensorimotor or cognitive impairments.

Outstanding Questions

Which cognition-related signals from the PFC could be accurately decoded to permit brain–machine interactions?

How important is 'context' for interpreting cognitive signals into BMI goals, and how do we acquire this context?

At a philosophical level, how can 'free will' be guaranteed when a machine may directly decode users' intentions?

What are the best methods for developing stable and reliable cognitive BMIs that can utilize a range of goal-directed signals, thereby allowing users to intuitively convey their intentions?

How can cognitive signals be integrated into the BMI loop to promote intuitive control based on the user's intended goal, independent of the end-actuators and feedback modalities?

Which methods best characterize the correlations of goal-directed behavior in subjects with cognitive deficits?

Which design mechanisms for closed-loop interactions best contribute to the rehabilitation or augmentation of cognitive capabilities?

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