

REVIEW ARTICLE

State-of-the-art non-invasive brain–computer interface for neural rehabilitation: A review

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ABSTRACT

Brain–computer interface (BCI) is a novel communication method between brain and machine. It enables signals from the human brain to influence or control external devices. Currently, much research interest is focused on the BCI-based neural rehabilitation of patients with motor and cognitive diseases. Over the decades, BCI has become an alternative treatment for motor and cognitive rehabilitation. Previous studies demonstrated the usefulness of BCI intervention in restoring motor function and recovery of the damaged brain. Electroencephalogram (EEG)-based BCI intervention could cast light on the mechanisms underlying neuroplasticity during upper limb recovery by providing feedback to the damaged brain. BCI could act as a useful tool to aid patients with daily communication and basic movement in severe motor loss cases like amyotrophic lateral sclerosis (ALS). Furthermore, recent findings have reported the therapeutic efficacy of BCI in people suffering from other diseases with different levels of motor impairment such as spastic cerebral palsy, neuropathic pain, etc. Besides motor functional recovery, BCI also plays its role in improving the behavior of patients with cognitive diseases like attention-deficit/hyperactivity disorder (ADHD). The BCI-based neurofeedback training is focused on either reducing the ratio of theta and beta rhythm, or enabling the patients to regulate their own slow cortical potentials, and both have made progress in increasing attention and alertness. With summary of several clinical studies with strong evidence, we present cutting edge results from the clinical application of BCI in motor and cognitive diseases, including stroke, spinal cord injury, ALS, and ADHD.

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1 Introduction

Brain–computer interface (BCI) provides human beings with an alternative pathway between the brain and external environment. During the past two decades, BCI related research has become extremely active, with articles in this field emerging in quantity [1]. This novel technology has aroused wide interest of scientists, clinical doctors and the public for its multiple application. Presently, people have managed to apply BCI to assist communication [2], provide control [3], restore motor functions [4] and even strengthen brain abilities [5]. Especially, the therapeutic application of BCI is one of the most exciting and prospective aspects. BCI has huge potential in the recovery of motor diseases like stroke, spinal cord injury (SCI) and amyotrophic lateral sclerosis (ALS).

As was reported by the American Heart Association, for patients with complete and chronic motor injuries, the prognosis for recovery is poor [6]. Traditional therapies for those severely paralyzed patients often rely on pharmacology, yet they cannot restore or enhance the neural pathways [6]. BCI intervention, however, may become a promising alternate neurorehabilitative approach. For people with neuromuscular diseases, BCI-controlled prosthetic devices can compensate for their loss of motor abilities, and assist the patients to carry out simple movements [4]. Besides, a growing body of evidence has shown that the presence of BCI reduces neurological deficits and restore the damaged sensorimotor loop [7]. After treatment, patients with stroke [8] and acute SCI [7] showed great functional and neurological recovery. This encouraged researches aimed at developing BCI-based neurorehabilitative programs, and many of them did manage to improve the performance of patients [9–11].

BCI can also serve as an assistive therapy for

children with neurodevelopmental problems, such as autism [12] and attention-deficit/hyperactivity disorder (ADHD) [13]. By reducing the ratio of theta and beta rhythms (theta/beta ratio, TBR) in electroencephalogram (EEG), BCI-based neural feedback training improves participants' focused attention [14, 15]. Research that enables patients to control slow cortical potential also improves their cognitive performance [16].

In the present review, first we explain the principle of BCI and briefly introduce the frontier technologies used in BCI system. Then, we discuss the prevailing clinical application of BCI in neural disease recovery, including motor injury and cognitive disaster. We also clarify some of the basic mechanism of neural rehabilitative therapies. Finally, we discuss some prevalent defects in existing research and the direction of future studies.

2 Principle of BCIs

A standard BCI system comprises five functional modules, namely, brain signal acquisition, signal pre-processing, feature extraction, feature classification, and output devices. Using these modules, BCI systems can decode a user's brain signal and translate it into computer commands for the control of external devices or neural rehabilitation systems.

The signal acquisition module records, amplifies, and digitizes the user's brain signal, which can be, for example, the specified EEG rhythm closely related to motor execution/imagination. Brain signals can be recorded from the central nervous system (CNS) via two main approaches: invasive and non-invasive methods. In addition to motor-induced brain signals, visual and/or muscle-induced signals have also been investigated [1].

Generally, the recorded brain signals (e.g. EEG signals) are contaminated with artifacts or noise, such as electromyography (EMG),

electrooculography (EOG), electrocardiography (ECG) artifacts, and power-line noise. The main purpose of signal pre-processing is to enhance the signal-to-noise ratio (SNR) of the recorded brain signals. According to the artifacts' characteristics, temporal filtering, spectral filtering, and spatial filtering techniques are usually employed to remove artifacts or noise in temporal, spectral, and spatial domains, respectively. For example, power-line noise can be removed by spectral filtering. EOG artifacts, which are caused by blinking and eye movements, generally induce high-amplitude patterns in the low-frequency region. Spatial filtering, which linearly combines multi-channel EEG signals to improve the SNR, can be performed using a data-independent or data-driven approach. The data-independent approach uses the common average reference and a Laplacian filter, and the data-driven approach uses common spatial pattern, canonical correlation analysis, independent component analysis, or principal component analysis [17, 18]. After signal pre-processing, the SNR of the recorded brain signals can be enhanced.

Feature extraction is used to extract features from the brain signals, while those features are representative of the intention. Two widely used features are frequency band power features and temporal features. Frequency band power features are the power of the EEG signals within a specified frequency band (or rhythm), such as alpha, beta, mu, and gamma bands. For example, changes in the mu/beta rhythm over the sensorimotor cortex are an essential feature in motor imagery-based BCIs [19, 20]. Temporal features play an important role in P300-based (or event-related potential) BCIs, in which changes in EEG potentials are time-locked to a given event or stimulus [3].

Feature classification is applied to recognize EEG features that are extracted by the feature extraction module. Over the past few decades, various algorithms have been developed to classify

EEG-related features [17, 21]. The commonly used classifiers are based on linear methods, such as linear discriminant analysis and the support vector machine, as linear methods can perform relatively stable calculations when the labeled data and knowledge about the BCI task are limited [22]. Recently, deep neural networks have also been applied to classifying EEG features in BCI applications [17].

Actions are triggered via output devices, which allow users to act on the real world, regardless of the participation of peripheral nerves and muscles. Actuators include functional electrical stimulation (FES), nerve stimulation, prosthetic devices, and exoskeleton.

FES innervates muscles through electrical stimulation, which also enables proprioceptive feedback to the brain. A robotic prosthesis, such as an avatar arm, works better for patients in acute phases of motor impairment and initiates passive movement. In recent years, hybrid-FES systems consisting of FES and active orthotic components are being more widely used as an effective way to restore everyday manipulation capabilities [23].

In addition to being the intended outcome, movement also provides feedback to the brain, which in turn modifies the process of motor execution to improve speed and accuracy [24, 25]. In the most desirable case, the brain will also modify signal features itself, forming bi-directional adaptation [24].

3 Clinical application of BCI

Several studies have demonstrated the potential of BCI-based functional restoration in patients with different levels of motor and cognitive impairment. The common paradigm of BCI-based functional restoration therapy captures motor intention as signals, then triggers real movement through approaches such as FES and robotic

devices with distinctive features that are tailored according to the nature of the disease.

3.1 BCI in stroke rehabilitation

As the second most common cause of death, stroke involves about 15 million patients per year worldwide [6, 26], while pharmacological therapy is the traditional treatment method to reduce symptoms. Encouragingly, recent studies have shown that BCI is a promising technology for rehabilitating volitional motor capacity in survivors of chronic stroke [27–29]. BCI intervention after stroke can be used for both BCI-assisted rehabilitation and as a decision-making guide for intervention [30]. Application of BCI in stroke treatment aims to restore motor and cognitive abilities, to enhance neuroplasticity during rehabilitation [25].

The clinical efficacy of BCI treatment has been shown in a cohort of patients with chronic stroke through Fugl-Meyer motor assessment [31], proved significant neurophysiological and behavioral improvement in patients with acute stroke after BCI intervention. BCI related targeted neurofeedback (NF) impact the brain structure and function, which could be rapidly detected by magnetic resonance imaging (MRI). The BCI-induced spatial specific brain plasticity promises that therapeutic interventions can be tailored to post-stroke functional deficits [32].

EEG-based motor imagery (MI) BCI systems have also been found to restore motor function. MI can be evoked by motor attempts without real movement, and may thus serve as an adjunct to traditional physical rehabilitation for patients with severe stroke [33]. During motor tasks, EEG records alpha and beta rhythms that present event-related desynchronization/synchronization (ERD/ERS) trends, which provides insights into the mechanisms underlying neuroplasticity in stroke recovery [34]. The protocol of personal

design for BCI rehabilitation is the precise coupling between the brain regions and functions regarding the behavioral, clinical, and neurophysiological changes.

The motor rehabilitation process also provides feedback to the patients' brains, either through proprioception with muscle movement or action observation (Fig. 1). Successful rehabilitation of patients with stroke requires brain activity feedback to be paired with its initial movement intention, thus forming a closed-loop system. BCI-assisted movement enhances the closed-loop circuit by providing valuable information about brain activity and physical responses to CNS. This benefits CNS plasticity and leads to the restoration of normal brain function or a relocation of functional control to undamaged brain areas [30].

While the positive function of proprioceptive feedback in restoring neuroplasticity has been verified, a recent study conducted by Vourvopoulos et al. combined the principles of virtual reality (VR) and BCI as a combination of movement feedback [35]. The authors measured EEG and EMG as signals of the motor intention to drive commands and initiate the movement of a virtual presentation of an avatar arm, while the observation and passive movement process of the visible VR also providing feedback to the patient's brain imagination. The study proposed a useful NF VR-BCI paradigm for efficient motor rehabilitation following stroke, and demonstrated its feasibility as an alternative tool for individuals without proprioceptive feedback pathways. Furthermore, patients with more severe motor impairment achieved a better recovery through EEG-based BCI, while those with active movement benefited more from EMG feedback in a multimodal platform. This finding could inform the future selection of signals in patients with different stage of stroke to indicate more precise information of brain activities. Additionally,

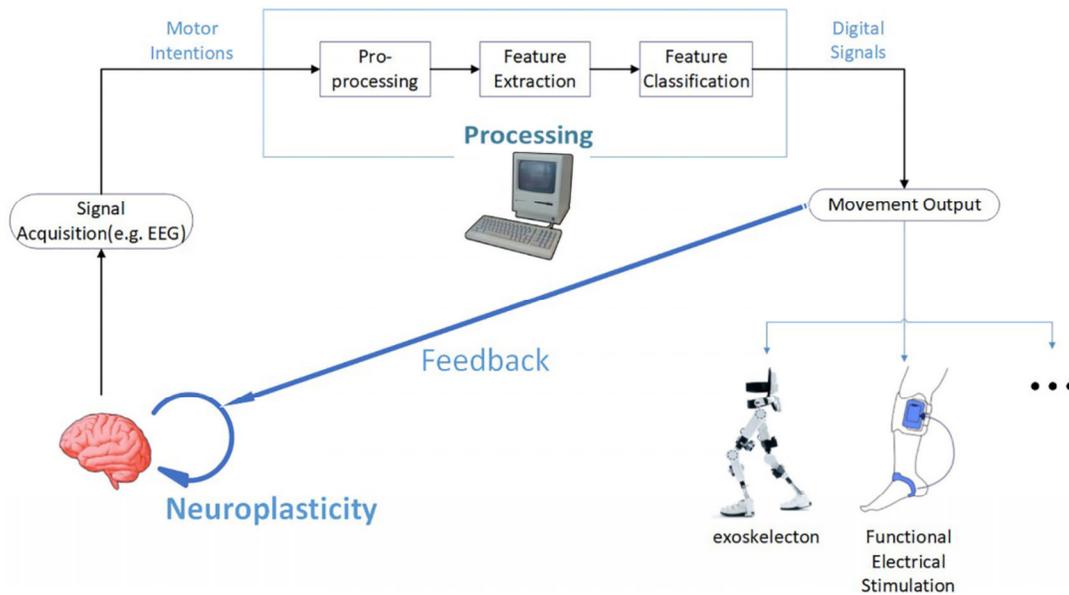


Fig. 1 Motor feedback in BCI-assisted rehabilitation. The basic parts of BCI-assisted rehabilitation include signal input and movement output of the BCI-system to help complete the intended action. In the process, the observation or passive movement could provide feedback to the initial movement intention to the brain which has been proved beneficial to the neurological rehabilitation and modification of the movement signal.

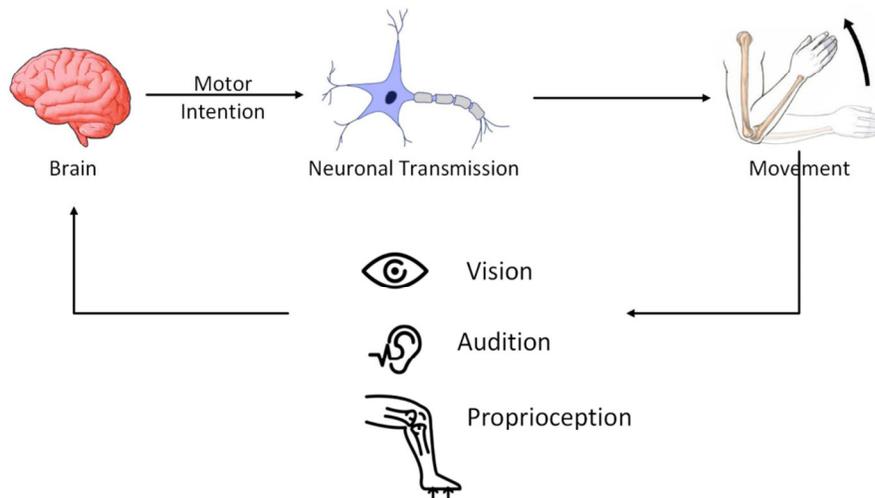


Fig. 2 Neuronal feedback in neurorehabilitation. The process of movement provides visual, auditory, as well as proprioceptive feedback to the brain, serving as signals in modulation and adjustment of the next-step movement. The signals also close the sensorimotor loop, following the principle of neuroplasticity and enhancing the remaining neural pathways, thus promoting neurorehabilitation.

studies on evaluation of brain connectivity indices also demonstrated the therapeutic possibilities of BCI intervention in cognitive rehabilitation after stroke [36].

3.2 BCI in partial motor impairment

For partially paralyzed patients, BCI functions

mainly as alternative trials to restore motor function, whereas for those completely locked-in, BCI interventions focus on communication and environmental control.

Among the majority of patients suffering from partial motor impairment symptoms, upper limb disability is particularly critical because of its high

prevalence and significant effects on patients' daily life [37, 38]. Patients with chronic stroke, SCI, and traumatic brain injury often experience motor impairment of the upper extremities (UE) [39, 40]. Addressing the upper limb disability will help individuals to improve grasp and precise movement abilities, which will facilitate independent living and even a return to work.

The current treatment of upper extremity dysfunction is primarily an implanted BCI-controlled neuroprosthesis, which deciphers neural signals and translates them into outputs such as FES, external prosthetic devices, and a robotic exoskeleton [3, 41–43]. BCI triggers FES-based muscle movement or the replacement of arm function using a robotic prosthetic arm, thus restoring upper limb function. A previous study with sub-analysis reported that a BCI intervention regimen resulted in more improvement and proved effective for the treatment of UE impairment in stroke survivors [44]. Another preliminary study has also demonstrated the therapeutic feasibility of BCI in patients with persistent neuropathic pain [11].

In addition, BCI can be applied in lower limb motor assistance and rehabilitation. Some studies proved the usefulness of exoskeletons for walking assistance, mainly for SCI population [45, 46]. Since 2014, several exoskeletons have been approved by the USA Food and Drug Administration (FDA) for clinical use, including the most studied powered exoskeletons [47]. Compared to traditional physical maneuvers, BCIs can theoretically better enhance the robotic systems because they work in line with natural human movement. They can be used to bypass the lesion and reconnect the brain and lower extremities. Presently, EEG is the primary approach to capture motor intention in human research. Yet, the decoder in BCI system must be able to recognize false alarm, like nodding, to avoid undesired movement [48]. Using intracortical microelectrode

array with invasive device, an exciting animal trial of epidural electrical stimulation (EES) on interfaced leg motor cortex has showed the recovery of their adaptive locomotion after SCI [49].

The advantage of BCI-based rehabilitation is that neurorecovery is correlated with the gain of function, which seems to be a promising approach for future long-term recovery method compared with conventional symptom-only treatment.

A recent longitudinal analysis showed stronger correlations between ERD/ERS in beta rhythms and the time since stroke onset compared with those seen in alpha rhythms. This could be explained by the previous findings that beta activations are more closely related to a closed-loop communication between the sensorimotor cortex and the paralyzed upper limb [50], while alpha rhythms are more closely related to motor learning mechanisms, which indicates the sensorimotor cortex is being activated and rebuilt during the BCI-based treatment. Therefore, EEG-based BCI intervention cast light on the mechanisms underlying neuroplasticity during upper limb recovery; namely, the related findings reinforce the hypothesis that more cortical regions such as frontal temporal and parietal regions, are involved in movement tasks to compensate for severe motor impairment [34].

Driven by the technological advances in multidisciplinary areas such as virtual and augmented reality (VR/AR), robotics, various BCIs, as well as medication, motor rehabilitation is now a fast-growing field. However, BCI-based treatment paradigm for motor impairment still needs to be refined, improved, and personalized in many ways. First, 50% of functional electrical stimulation does not activate the targeted muscle due to damage of the innervating motor neurons. Second, because of the nature of the academic research environment, some motor imaginaries are required to be made rather than volitional

daily movement, making precise signal acquisition impractical for real-life application. Therefore, future research should aim to identify more realistic control commands, and decode more precise and complex movement signals to reassure everyday usage.

3.3 BCI in cases of severe loss of motor function

For patients that are completely locked-in, BCIs allow patients to convey messages and commands to the external world. Preliminary studies have shown the efficacy of BCI as a useful tool to aid patients with ALS in daily communication and basic movement [30, 51–53]. A follow-up study of 42 patients with ALS also demonstrated the feasibility of independent home use of BCI for patients with ALS, providing relief for both caregivers and patients [52].

Furthermore, recent findings have reported the therapeutic efficacy of BCI-FES in children with spastic cerebral palsy. This highlights the clinical possibilities of BCI in provoking contraction of denervated muscles, restoring paralyzed motor function, and treating muscle weakness [51].

There are two major limitations in using a BCI system with locked-in patients. First, the insufficient BCI accuracy, particularly in spelling, means that the basic communicational needs of patients are still not met. Ongoing studies to increase the speed and accuracy of BCI-based communication are conducted [54]. In addition, long-term use of BCI devices may cause side effects such as impaired vision. One way to overcome this limitation could be to use auditory rather than visual stimuli [52].

3.4 BCI in ADHD

Medication and behavioral therapy are the most common treatments for ADHD [55]. In recent years, BCI-based NF therapies have been proposed as a new treatment approach for disorders such

as ADHD. Unlike stimulant treatment, which commonly triggers side effects, NF therapy is associated with relatively few adverse events [56]. Furthermore, a recent analysis demonstrated that BCI-based NF therapy showed longer-term effects than medication [57].

While a previous review refuted the efficacy of NF therapy [58], the better effects could be a result of the small sample sizes and methodological defects. Further randomized controlled trials have revealed a significant effect of neurofeedback training (NFT) on inattention, impulsivity, and hyperactivity, and NFT is therefore considered to result in clinically meaningful improvements [56, 59].

At present, there are two main types of NF protocols, as follows: the reduction of the TBR, and the self-regulation of slow cortical potentials (SCPs).

Some studies have focused on detecting the ratio of theta and beta rhythms for the diagnosis of ADHD. A meta-analysis looked into quantitative EEG studies that evaluated ADHD by the same criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and confirmed that an elevated TBR is a typical trait in ADHD [60]. Nevertheless, a similar change in theta power is found in many other cognitive disorders, and cannot be regarded as pathognomonic of any specific disorder [61]. As such, further research to investigate the combination of EEG techniques and other diagnosis is needed, in order to meet the need of clinical application.

Recent studies have also revealed that NF which aims to reduce the TBR can increase focused attention and improve alertness, although it does not have a specific effect on hyperactivity or impulsivity [14, 15]. Yet, the efficacy and specificity need to be measured by additional larger-scale studies.

Some studies have investigated the ability for NFT to modify patients' abilities to control SCP.

Positive and negative SCP-shifts are related to cortical inhibition and activation, respectively. Most training is focused on practicing and reinforcing the negative polarity concerning neural changes in the brains of patients with ADHD. A preliminary study detected an enhancement of contingent negative variation amplitude in an attention task [10]. Moreover, it has been reported that after 30 sessions of training about SCP self-control, children with ADHD managed to regulate negative slow cortical potentials, and all improvements in behavior, attention and IQ score were still evident at the 6-month follow up [16].

Following this progress, researchers are now looking to develop an independent home-used training program. Some researchers have designed a feasible BCI-based training method for ADHD [9]. In this training program, participants' brainwaves were recorded before and after training to create an individualized EEG pattern. According to the assessment of ADHD rating scale and child behavior checklist, inattentiveness was slightly improved in the intervention group, as expected. Furthermore, the researchers stated that the program is feasible; 24 sessions over an 8-week period was manageable for parents and resulted in a low dropout rate.

NF therapy triggers few adverse effects and little discomfort. It's relatively safe and proved to be effective, and so is a promising potential adjunctive therapy for ADHD. However, NF devices that are easier to use, standardized training programs and uniformed regulations should be developed before BCI-NF therapy is used in clinical practice. Further research should investigate the combination of NF, pharmacology, and behavioral therapy in clinical treatment.

4 Mechanisms of BCI-based neurorehabilitation

Like all other neurorehabilitative methods, the

BCI paradigm concerns two different ways: detouring around breaks in neural pathways and muscles, and directly using brain signals for communication and control; and following the principle of neuroplasticity and enhancing the remaining neural pathways [62].

In this part of the review, we will describe several basic concepts concerning the use of BCI in neurorehabilitation. First, we will explain that neuroplasticity is the internal mechanism underlying functional recovery. Then, we demonstrate how the implementation of motor imagery can promote the recovery of movement disorders. Finally, we will discuss the role of BCI signals in the closure of the sensorimotor loop.

4.1 Neuroplasticity

Neurofeedback is a sort of biofeedback that depends on real-time cortical activity. NF aims to teach patients to regulate brain function, which is reflected in certain EEG features, and can enhance neuroplasticity and restore cognitive abilities. BCI can analyze neural activities and provide real-time feedback, and have therefore been widely employed in NF therapy as a rehabilitation tool for motor injuries [63].

Neuroplasticity is grounded in the concept of Hebbian plasticity, that is, synapses increase their efficiency when they are persistently stimulating the postsynaptic cells. Neuroplasticity includes multiple regenerative processes, such as axonal sprouting of surviving neurons, molecules released by neurons, and the formation of new synapses [64]. It is widely acknowledged that functional impairment results in a reorganization of the central nervous system, and the success of a new therapy is linked to its ability to interact with the new brain architecture after neural injury [65].

BCI-based interventions combined with feedback give rise to a persistent change in cortical connectivity, and are thus applicable in cognitive and motor recovery, such as stroke [66, 67] and SCI

[68]. Especially, robot-assisted rehabilitation serves as a way of neuroplasticity improvement, which is currently the main recovery of stroke [34]. Furthermore, BCI-NF has also been found to normalize functional networks in children with ADHD [5].

4.2 Closed-loop neurostimulator: a compensation for the damaged loop

To date, there are two main protocols for using BCI in neurorehabilitation. One is to elicit neural activity restoration, and the other is to control external devices, such as a neuroprosthesis. These protocols both rely on the dynamical closed-loop system, whereby feedback is essential to respond to the input stimulation and control the output effect [69]. This closed-loop in neural rehabilitation has inspired individualized therapies that adapt to the BCI user's body situation and brain activity.

At present, multiple methods to reestablish the damaged sensorimotor loop have been adopted. Many BCI systems use visual or auditory signals as feedback [70]. Visual elements, including a computer cursor and flickering lights, have been widely used as a feedback signal. However, the high brightness and long training period can cause fatigue and inattention among participants, which thus undermines the performance of the BCI system [71]. Furthermore, these conventional modalities are not suited to patients who are completely paralyzed and can't get their eyes moved, or patients with advanced ALS who may have visual problems.

However, haptic information channels, such as vibrotactile feedback, can overcome such limitations. Unlike visual signals, haptic feedback is simple and doesn't need much attention [72]. Peripheral nerve interfaces can now provide long-term, natural touch sensations, and enable subjects to manipulate objects [73]. Yet, in many current studies, the haptic feedback delay is not

short enough to synchronize with brain activities, which makes it hard to result in long-term neural changes [63]. Further research should investigate the maximum feedback delay that meets the requirement of clinical application.

There are many possible feedback pathways in the application of neuroprostheses [69]. To date, most research interest is focused on implanted devices, especially deep brain stimulation (DBS). DBS uses high-frequency electrical pulses to normalize the neuronal activity of a specific nucleus. It is a widely used therapy to treat movement and psychiatric disorders, such as Parkinson's disease, dystonia, and major depressive disorder. A recent trial developed a closed-loop system with implanted electrodes (both recording and stimulating), whereby the feedback electrical signal was transmitted directly from the robotic effector to the controller [74]. However, neural tissue damage is unavoidable when using invasive electrodes, and can include bleeding, inflammation, physical trauma, and neuron damage [75].

Research into non-invasive recovery therapies that are based on a closed-loop system have also made progress. Using an augmented-reality approach [69], some BCI techniques, such as EEG or fMRI, can acquire cortical signals from the surface or from the scalp, which is safer and more likely to be accepted by users.

5 Conclusion

The preliminary studies presented here demonstrate the therapeutic and clinical potential of BCI-based applications, despite the presence of neutral and negative findings. BCI could serve as an alternative therapy for neurological disorders, with fewer side effects compared with traditional clinical treatment.

We have also summarized some common problems of current existing BCI systems and addressing these questions will expand the clinical

potential of BCIs and guide future research:

First, due to small sample sizes, some studies did not meet the traditional mathematical standard for statistical significance, and some only found weak positive evidence after BCI intervention which were not persuasive enough to demonstrate the clinical efficiency. More studies with larger sample sizes and more diverse patient populations [35] are required to confirm and increase the reliability of previous results.

Second, clinical trials have adopted various experimental designs and included patients with heterogeneous types of motor impairment, which makes it harder to assess the efficiency of BCI interventions [34]. To overcome this limitation, more comprehensive BCI designs that include a more balanced sample of patients with different degrees of impairment are needed through multi-center collaboration [52, 76], which would eliminate irrelevant variables. Moreover, because of ethical or practical obstacles, it is difficult to carry out a blinded experiment. Subsequent trials should increase the level of blinding to eliminate the possibility of confounding variables, for example the placebo effect.

Third, previous data have been analyzed using different scales and standards, making it difficult to perform post hoc analyses [76]. Concerning patient recruitment, strict inclusion and exclusion criteria should be followed. Forthcoming studies are expected to improve the quality through standardization of trials design and measurement to assist their translation into clinical practice.

Finally, the despite positive results from phase I/II trials, the lack of phase III trials has prevented BCI-based therapies from being widely used. Therefore, more work should be done to optimize the BCI system and further confirm its clinical feasibility. There should also be a focus on more personalized BCI systems that are tailored to the patients' clinical and neurophysiological characteristics.

Conflict of interests

The authors declare no conflict of interests in this work.

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