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Research Article

INTERNATIONAL
JOURNAL OF APPLIED BIOLOGY AND
PHARMACEUTICAL TECHNOLOGY
ISSN: 0976-4550

# Methods for Improving Brain-Computer Interface: Using A Brain-Directed Adjuvant and A Second-Generation Artificial Intelligence System to Enhance Information Streaming and Effectiveness of Stimuli

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## Abstract

**Background:** The brain-computer interface (BCI) is gaining much attention to treat neurological disorders and improve brain-dependent functions. Significant achievements over the last decade have focused on engineering and computation technology to enhance the recording of signals and the generation of output stimuli. Nevertheless, many challenges remain for the translation of BCIs to clinical applications.

**Methods:** We review the relevant data on the four significant gaps in enhancing BCI's clinical implementation and effectiveness.

**Results:** The paper describes three methods to bridge the current gaps in the clinical application of BCI. The first is using a brain-directed adjuvant with a high safety profile, which can improve the accuracy of brain signaling, summing of information, and production of stimuli. The second is implementing a second-generation artificial intelligence system that is outcome-oriented for improving data streaming, recording individualized brain-variability patterns into the algorithm, and improving closed-loop learning at the level of the brain and with the target organ. The system overcomes the compensatory mechanisms that underlie the loss of stimuli' effectiveness for ensuring sustainable effects. Finally, we use inherent brain parameters relevant to consciousness and brain function to bridge some of the described gaps.

**Conclusions:** Combined with the currently developed techniques for enhancing effectiveness and ensuring a sustainable response, these methods can potentially improve the clinical outcome of BCI techniques.

**Keywords:** Brain-Computer Interface; Digital health; colchicine; consciousness; brain variability;

**Abbreviations**: BCI: Brain-Computer Interface; AI: artificial intelligence; EEG: electroencephalography; fNIRS: functional near-infrared spectroscopy; EMG: electromyography; EOG: electrooculography; SSVEPs: steady-state visually evoked potentials; SSSEP: steady-state somatosensory evoked potential; MTs: Microtubules; JNK: Jun N-terminal kinase; Con A: concanavalin A; AD: Alzheimer's disease; BSV: Brain signal variability; fMRI: functional magnetic resonance imaging; GAD: generalized anxiety disorder; RSV: Regional signal variability; SMR: sensorimotor rhythm; VR: virtual reality;

## Introduction

Brain-computer interface (BCI) has gained much interest over the last

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**Citation:** Hillel Lehmann, David Arkadir, Yaron Ilan. Methods for Improving Brain-Computer Interface: Using A Brain-Directed Adjuvant and A Second-Generation Artificial Intelligence System to Enhance Information Streaming and Effectiveness of Stimuli. International Journal of Applied Biology and Pharmaceutical Technology. 14 (2023): 42-52.

**Received:** March 29, 2023
**Accepted:** April 04, 2023
**Published:** May 17, 2023

Lehmann H., Int J Appl Biol Pharm 2023
DOI:10.26502/ijabpt.202124

few years. BCI is a communication system of brain signals to control malfunctioning organs or external devices [1]. It enables control of an external output device by interpreting the neural activity. The generation of such systems may be independent of the nervous system, such as in Passive BCI, assisting patients with motor disabilities [2]. Motor BCI comprises electrical recordings from the motor cortex of paralyzed humans. The computer decodes the signals and can drive robotic arms or restore movement in a paralyzed hand by stimulating the muscles in the forearm [3]. Cognitive assessment and training can use BCI. Verbal-motor-free BCI-based tests assessed cognitive domains in patients with Amyotrophic Lateral Sclerosis were developed [2]. Integrating a BCI with the sensory cortex can augment dexterity for improved fine control. BCIs can restore vision in people with acquired blindness and control epileptic seizures [3]. BCI-based cognitive training is part of neurofeedback therapy for neurological developmental disorders, including autism, attention-deficit/hyperactivity disorder, stroke patients, and elderly subjects [2]. Brain's plasticity and Hebbian-based motor recovery use BCI for rewarding cortical activity. These are associated with sensory-motor rhythms using self-guided and assistive modalities [4]. Non-invasive BCIs comprise proprioceptive feedback loops, which include numerous sensory variables. It allows the modulation of brain signals to improve the hand's function. Based on BCI, applications are developed for improving learning, communication, social, memory, attention, visuospatial, creative, collaboration, and emotional skills [5].

In the present paper, we describe several of the gaps in clinical implementation and improving the effectiveness of BCI. We present using brain adjuvants and second-generation artificial intelligence (AI) methods to enhance the signals stream and ensure an improved sustainable response.

## Current gaps in the development and implementation of BCI

BCIs typically consist of three components: a sensor that records brain neural activity; a decoder that processes the signal input by extracting predictive features and classifying the intended movement based on signal features; and an effector, an external device, typically a robotic limb or a screen cursor, that receives instructions from the decoder to execute an order [6]. BCI's clinical application rests on the premise that activity in at least one cortical region associated with motor or sensory functioning is intact. BCI can bypass brain lesions in the cortex or spine by linking cerebral activity to the effector [6]. The first-in-human implanted, wireless, motor neuroprosthesis used an endovascular stent-electrode. The electrode transmitted signals from the motor cortex for numerous command control digital devices in two patients with flaccid upper limb paralysis [7]. Improvement in the development of BCI-based systems occurred due to progress in understanding neural decoders, systems for neural feature extraction, and brain recording modalities [8]. Nevertheless, there remain multiple challenges to the clinical use of BCIs. Improved engineering and computation overcome some of these gaps. However, there are significant challenges in the clinical implementation of these systems. The low reliability of some techniques used today contributes to the end-users' low adaption rate.

Table 1 summarizes some challenges currently faced in implementing BCI in clinical practice, including the technological and computation barriers BCI systems depend on sensors and associated hardware that acquire brain signals. Improvements in this hardware are critical to the future of BCIs. Traditional BCI platforms involve recording brain signals via Electroencephalography (EEG). These systems comprise a rule-based translation algorithm that produces the control commands [1]. Non-invasive procedures based on EEG lack the spatial resolution to record detailed activity at the neuronal circuit level [9]. Signals travel a distance before being acquired by the EEG machine, and the noise and artifacts are causing fundamental problems. EEG requires good performance in different environments and reliability despite the noise generated by devices. Many BCI targets patients surrounded by many electronic pieces of equipment [10].

Wireless recording, machine learning analysis, and real-time temporal resolution can improve EEG-based BCI [11]. Placing electrodes on the cortical surface is less invasive

**Table 1:** Several challenges for implementing BCI in clinical practice

<table>
<tr><td rowspan="2">Hardware / Software</td><td>non-invasive</td><td>a. Low accuracy<br>b. Low reliability<br>c. Isolation of targeted structures<br>d. Lowered accuracy of using non-invasive measures</td></tr>
<tr><td>invasive</td><td>e. Safety – infections, rejection<br>f. Recharged in situ<br>g. Replacement of probes following a failure<br>h. Space limitations<br>i. High cost</td></tr>
<tr><td colspan="2">Decoding</td><td>j. High variability of signal features and continuous change<br>k. Reading and data extraction from recorded data</td></tr>
<tr><td colspan="2">Validation and cost</td><td>l. Low reliability<br>m. Low accuracy of information transfer rate<br>n. Sophisticated<br>o. Small user population<br>p. Delivery of nanomaterials and processing Reading and data extraction from recorded data</td></tr>
<tr><td colspan="2">Ethical</td><td>q. Patient expectations<br>r. Concept of personal identity<br>s. Validity of informed consent</td></tr>
</table>

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DOI:10.26502/ijabpt.202124

but less precise and associated with decreased accuracy [3]. Several challenges include space limitations, replacement of probes following failure, isolation of targeted structures, delivery of nanomaterials, and processing of the recorded data [12]. Functional near-infrared spectroscopy (fNIRS), electromyography (EMG), electrooculography (EOG), and eye tracker combine with EEG [13]. Implementation of multi-sensor data fusion and machine learning-based translation algorithms improves the accuracy of such systems [1]. Artificial intelligence and deep learning algorithms can lead to faster and more accurate sensory input classifications. Neural engineering improved neural recording techniques and clinical translation of neural interfaces.

The electronics used are smaller and faster than neurons. However, challenges of decoding the neural circuits are yet to be overcome [12]. Visual-based BCIs that use P300 or steady-state visually evoked potentials (SSVEPs) improve functionality. The steady-state somatosensory evoked potential (SSSEP) BCIs enhance the visual fatigue that occurs with these BCIs. These are based on selective tactile attention and can overcome motor activity's reduced reliability of motor activity [14]. Invasive BCI systems use implanted electrodes and face a range of complex issues. These systems must be safe and remain intact, functional, and reliable for decades [15]. Long-term safety is of concern as the implant could be associated with infections. These systems must be recharged in situ or have batteries that last for years or decades; they have robust, comfortable, convenient, and discreet external elements that could easily interface with high-performance applications [15].

Motor imagination/movement tasks using functional and reactive tasks combined with cognitive tasks for brain signals increase BCI accuracy [13]. These include using motor imagination with steady-state evoked visual potentials (SSVEP) and motor imagination with P300. SSVEP is most widely combined with P300 to increase the number of commands [13]. Combining more than two modalities is developed for improved brain imaging and prosthesis control. Hybridizing several modalities can augment the number of control commands, improve classification accuracy and reduce the signal detection time. Hybrid BCI systems with multimodal sensory can improve functions [6]. Neurofeedback uses BCI systems to enable the real-time display of subjects' brain activity while performing a task. BCI in this setting allows patients to control their cortical activity. Neurofeedback has improved BCI classification enhancing user control over BCI output [6]. New interface designs may enhance discomfort from daily, long-term use of BCI by ergonomic approaches [16].

High-fidelity connectivity with minor groups of neurons requires the placement of microelectrodes in the cortex [3]. A better understanding of the sensory components is also necessary for improving BCI. A significant challenge for both invasive and non-invasive BCI is decoding the signal. The requirement for months of training, and the marked inter-person differences, make it hard to achieve standardization. Inconsistency of signal features affected by multiple variables, including the users' mental state and circumstances, requires adaptive BCI algorithms and deep learning for proper function [17]. It is unclear why some BCI paradigms or features are effective with some patients and some are not [18]. Establishing systems using BCIs for subjects with disabilities involves validating their value in improving quality of life and cost-effectiveness [19-20].

The validation of BCIs for rehabilitation after strokes or other disorders requires careful comparisons with conventional methods. Current BCIs, with their incomplete abilities, are potentially helpful, mainly for people with very severe disabilities and relatively small populations. Commercial interests have no adequate incentive to produce or promote their widespread dissemination [21]. Ethical issues of using BCI are significant concerns. These include managing patient expectations, the concept of personal identity, and the validity of informed consent [22]. Privacy is a vital issue as the captured neural signals enable access to private data. There are concerns about how BCI data is stored and protected [23]. Current methods for overcoming these gaps focus on improving technology, including computation barriers. Beyond the technological challenges described above, several inherent gaps in the brain function itself remain to improve BCI clinical effectiveness.

**Using brain-targeted adjuvants for improving BCI**

There are multiple engineering and neurological challenges to the clinical application of BCI [12]. Using BCI, targeting brain-relevant mechanisms provides a new venue for improved clinical outcomes. We describe three methods for improving BCI by targeting several brain pathways. Figure 1 presents several gaps that challenge BCI's implementation and improve its efficacy. It shows a schematic presentation of these methods for bridging the current BCI gaps for improving information streaming and the effectiveness of output stimuli.

Microtubules (MTs) are dynamic cytoplasmic tubular polymers that form the cell cytoskeleton [24]. MTs provide the intracellular transport of secretory vesicles, organelles, and intracellular macromolecular assemblies. MTs are involved in cell mitosis and meiosis [25, 26]. MTs are associated with the innate and adaptive arms of the immune system and determine the dynamics of inflammatory cells [27-31]. Polarized CD4 Th1, Th17, CD8 T cells, and NK cells induce MTs destabilization within neurons in multiple sclerosis. Lymphocytes with cytolytic activity drive MTs' axonal destabilization independent of neuronal death [31].

Bidirectional communication between the brain and the

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DOI:10.26502/ijabpt.202124

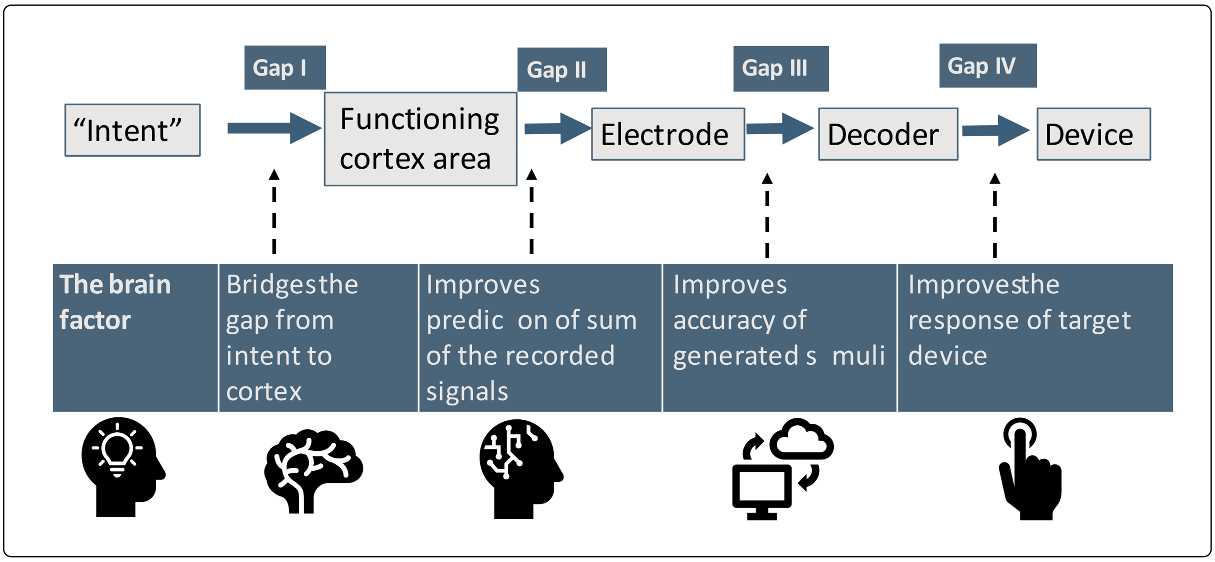


**Figure 1:** Several potential solutions for improved information streaming and effectiveness of stimuli in brain-computer interface (BCI).

intestine occurs in health and disease. Gut-based therapy is a method for affecting systemic systems by generating signals in the intestine and was shown effective in pre-clinical models [32-42]. Preliminary data support the use of this method in humans [33, 36, 43-47]. MTs play a role in gut functions. Jun N-terminal kinase (JNK) is necessary for the elongation of the gut tube and regulates MTs architecture, preserving adhesive contacts between cells in the intestine [48]. Tao-1 destabilizes MTs at the actin-rich cortex, and its loss is associated with the disordered migration of germ cells out of the gut epithelium and subsequent cell death [49].

Methods for altering microglial function by targeting the gut-brain axis carry less toxicity and are easier to control. Targeting the gut MTs using low-dose colchicine exerts a potent anti-inflammatory effect on target organs. Oral administration of non-absorbable low-dose colchicine alleviated immune-mediated hepatitis in mice injected with concanavalin A (Con A). Similarly, it eased the inflammation associated with the metabolic syndrome in the high-fat diet model of type 2 diabetes and fatty liver disease (unpublished). Microglial cells constitute 5-12% of the cells in the brain and are involved in brain homeostasis and its response to triggers [50-52, 53]. Homeostatic dysregulation of the brain's immune system regulated by microglia plays a role in neurodegenerative disorders, including Alzheimer's disease (AD) [54-57]. During disease, the microglia become inflammatory while losing their homeostatic molecular functions [58-62]. In the brain, gut MTs using low-dose colchicine was beneficial in a mouse model of acute neurodegeneration mediated by microglia. The beneficial effect was associated with altering gene expression in genes linked with AD, showing that targeting gut MTs can modulate APOE-regulated genes in microglia in AD (unpublished). This effect may be related to the gut-brain connection by impacting the microbiome [63].

Applying brain-targeted adjuvant to BCI, using non-absorbable low-dose colchicine, which has a high safety profile and targets the gut, can bridge several BCI gaps. The use of a brain adjuvant can improve the intent signals. It may be related to the potential role of MTs in consciousness or other yet-to-be-explored mechanisms [64-66]. The adjuvant can improve the cortex-generated signals and may enhance associations between the relevant brain area with other areas, leading to a better sum of the inputs received from the cortex. At the output stage, adjuvants can improve both the generated stimuli and the closed-loop regulation back to the cortex, thus improving the effectiveness of BCI.

## Implementing second-generation artificial intelligence-based variability for improving and sustaining BCI effectiveness

First-generation AI systems analyze large datasets and predict prognoses. At the same time, these systems aid end-users, patients, and healthcare providers; their overall penetration and everyday use are lower than anticipated [67]. Second-generation systems can improve clinical outcomes and adherence by patients and physicians [67]. These platforms can improve organ function and response to therapies while controlling for the dynamic nature of the host and disease. They overcome the "big data" challenges by implementing an n=1 concept, directing the results toward a single subject providing a method for personalizing the therapy in a clinically meaningful way [67]. Second-generation systems provide a platform for generating clinically significant databases, thus enabling better use of the data generated [67].

Variability characterizes multiple functions in nature and can serve as a method for improving biological systems

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DOI:10.26502/ijabpt.202124

[68-84]. The dynamicity of biological processes determines disease progression, manifestations, and response to stimuli and drugs. Variability characterizes the normal function of many organs, such as the variability in heart rate, gait, breathing, and others [85-88], and is inherent to multiple brain functions [69, 72, 76, 89]. Brain signal variability (BSV) characterizes brain function and reflects the capacity for state transition of neural activities. Prenatal fMRI defines variability patterns of the brain networks and shows the spatial distribution and individual variability in network architecture. Individual variability manifests by decreasing sensorimotor, visual, subcortical, dorsal, and ventral attention networks [90]. Structural brain development covariance may underlie brain variability concerning cognition and disease vulnerability [91]. Genetic variation is associated with altered response to deep brain stimulation in Parkinson's disease, suggesting that variability in brain function is linked to genotypes [92]. The diurnal physiological variability in neuro-metabolite levels suggests a link between chronobiology in brain variability [93].

Patients with a generalized anxiety disorder (GAD) show decreased BSV in widespread regions, including the visual, sensorimotor, frontoparietal, limbic, and thalamus. These systems have decreased BSV associated with an inflexible brain state transfer pattern. A correlation between BSV and trait anxiety score was positive in patients [94]. Differences in cognitive modulation of brain signal variability are associated with subject differences in motor expertise. This process underlies differences in information-processing capacity and information integration during cognitive processing [95]. Regional signal variability (RSV) measures efficiency and modulatory capacity within brain regions and indicates endogenous pain modulatory system responsivity to training following repeated bouts of pain [96]. The second-generation AI system implements personalized variability parameters into treatment algorithms to improve response to chronic interventions in various diseases, including brain disorders [68, 70, 73, 77-82, 97-112]. Implementing second-generation AI in BCI can enhance the accuracy of recording brain inputs. As brain signals are not regular and are dynamic by nature, a system that continuously adapts to changes can improve the accuracy of the information.

The variability in brain networks underlies subject differences in cognition and behaviors [90]. The EEG's sensorimotor rhythms (SMR) used for BCI to rehabilitate motor impairments varies over time and across subjects. The intra- and inter-subject variabilities cause covariate shifts in data distributions that alter the transferability of model parameters among subjects. Machine learning-based methods compensate for inter-and intra-subject variability manifested in EEG-derived feature distributions [113]. Determining the response under a threatening situation showed that both inter-and intra-subject variabilities impacted the performance measured by EEG signals [114].

Second-generation AI includes methods to compensate for inter and intra-subject variabilities [67, 113]. The dynamicity of the system enables it to adapt to constant changes in the host, the disease, the response to intervention, and the environment. As many of these parameters differ between subjects and change over time in the same subject, the system continuously adapts itself to improve the patient's outcome [79, 115]. Variability in brain signals can be quantified and implemented into the second-generation algorithm to improve accuracy. Organ variability is personalized and serves as a basis for subject-tailored platforms, improving information streaming and output stimuli [115]. Second-generation systems can solve the intra-subject and inter-subject variability in the generated signals and the response to stimuli. These systems can improve the response to therapies by implementing signatures of disease-related variabilities into the treatment regimens [68, 70, 73, 77, 80, 82, 98-111]. Implementing a system that controls changes adaptively provides a means for better translation of information into improved personalized stimuli in a dynamic way [115, 116]. The system provides an enhanced platform for a closed loop between brain areas, enabling better summing of the signals between the target organ and the brain.

Examples include systems that follow eye movements that may precede the cortex and quantify and implement into the algorithm eye movement variability [117]. It collects EEG/ECoG data from multiple attempts to quantify personalized variability patterns and add them to cortex-derived data [118, 119]. It quantifies signal variability by adding stimuli to "relevant" and "irrelevant" brain areas and brain autonomic signals, including temperature alterations in different brain areas. It uses intra-brain nano-robots to measure electrical or metabolic activity alteration before cortex-derived signals [120].

Decoy of the effect of stimuli due to compensatory mechanisms and tolerance at different levels of the targets is a significant problem for BCI interventions [79]. Second-generation AI systems overcome these mechanisms, enabling a sustainable long-term response [115]. The use of low-dose colchicine under the control of the second-generation artificial intelligence system can further improve the drug's effectiveness, overcome the loss of response, and reduce side effects [29, 30, 75, 81].

## Implementing inherent brain platforms for overcoming gaps in BCI

Like other complex biological systems, the brain carries information but does not necessarily have perfect structure or symmetry. The irregularity that characterizes some of its pathways provides an opportunity to apply notions of physics to this biological system [69, 72, 76, 83 79, 121]. An alliance between classical and correlative brain function improves BCI.

A direct association mediates correlations between components of complex systems between different elements of this system [122]. Direct contact or the transfer of mediators facilitates the effect [123-125]. Recently a system was developed that correlates between two parts of the immune system without direct interaction or a transfer of mediators between them [126]. The associated states may be present within the system and involve a specific correlation between donors and recipients. Learning and memory capabilities are required for such correlations to occur. A "wave type of memory" means continuous feedback from multiple brain areas, and the target organ or device for transmitting and receiving signals are mandatory for efficient correlations to occur [126, 127].

BCI can benefit from indirect correlations between different brain areas, which can implement various energy transfer types by recording or using signals and producing stimuli that are not measured using current technologies. Other kinds of energies may be involved. Recording signals from multiple brain areas that affect or result from these energies can improve the summing of inputs and outputs at various levels. The technology can expand closed-loop inputs and outputs in the brain and target device by recording "unmeasured responses." Implementing methods based on inherent brain factors can bridge the problematic gap from the intent to the cortex by using consciousness-based mechanisms for improved BCI [128-130]. The effects occur at cellular or subcellular levels. These effects propose that some of the principles of quantum physics may apply to biological systems [128, 129, 131, 132].

Translation of the intention of a human subject to stimulate a rat brain motor area responsible for the tail movement supports a non-natural computer-brain interface to induce an out-of-body effect [133]. Combining BCI with virtual reality (VR) is used to rehabilitate neurological diseases. It involves motor imagery, P300, and steady-state visual-evoked potential. Integrating VR scenes into BCI systems improved the recovery process from nervous system injuries, providing better patient feedback and promoting brain function [134].

The transfer of information between different species' brains using non-invasive methods supports the feasibility of a computer-mediated BCI that connects the neural functions between biological entities. Using these technologies is anticipated to expand the prediction of the sum of the recorded signals and the accuracy of generated stimuli at various system levels. Finally, it improves the brain-controlled target organ or device function. It scales up current BCI methods to enhance their beneficial clinical effects. BCI has become an effective solution for multiple brain and spine disorders. It provides a platform for treating numerous non-neurological diseases by improving brain-target organ regulation. Technological challenges involving engineering and computation are being worked on and continuously improved. However, multiple barriers evolve from the inherent brain function. The suggested venues of using brain adjuvants, second-generation AI in enhancing the stream of information and stimuli, and implementing brain-linked methods for improving brain inputs and outputs to targets, set the basis for improving the clinical effectiveness of BCI.

## Declaration section:

**Ethics approval and consent to participate**: not applicable

**Consent for publication**: Yes

**Availability of data and materials**: Upon request

**Competing interests:** YI is the founder of Oberon Sciences; other authors have nothing to disclose

**Funding:** not applicable

**Authors' contributions:** YI DA and HL wrote the manuscript and approved the final version

**Acknowledgements:** not applicable

Authors' information (optional)

**Disclosure:** YI is the founder of Oberon Sciences

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