

Neuromodulation Based on Brain-computer Interface Technology

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Abstract. Therapeutic brain-computer interface (BCI) is a fast-developing area with considerable potential in improving the life qualities of various patients. Although a complete mechanistic understanding is yet achieved, empirical explorations into neuromodulatory devices, including deep brain stimulation (DBS), transcranial magnetic and electrical stimulation (TMS, TES), and electroencephalography (EEG), have enriched the repertoire for treating many neurologic diseases. Four such diseases discussed are Parkinson's disease (PD), substance use disorder (SUD), epilepsy, and depression. BCI devices alleviate symptoms by modulating neuronal activities, for instance, via directly delivering electrical stimulation, but each disease poses challenges now. Currently, neuromodulation techniques for PD and epilepsy are relatively mature and require few more perfections, while the ones concerning SUD and depression are young and fledgling, but multiple studies have revealed preliminary success and therapeutic potential. This article aims to review four techniques' applications in four common neurologic disorders, including current achievements, associated difficulties, and potential future directions.

Keywords: Neuromodulation, Neuropsychiatric Disease, Deep Brain Stimulation (DBS)

1. Introduction

BCI is a mediating platform realizing direct transmissions between brain electrical signals and external devices without the participation of muscles and peripheral nerves [1]. In recent decades, BCI devices have shown therapeutic promise in neurologic and psychiatric diseases involving aberrant brain activities [2]. BCI-based neuromodulation functions by delivering electrical stimuli to an ensemble of neurons to alter its pathological activity and excitability. BCI devices can be either open-loop or closed-loop (Figure 1). The open-loop neurostimulation means continuous stimulation by delivering a fixed pattern, while closed-loop neurostimulation offers more possibilities by providing a flexible, autonomous feedback system [3]. Future goals of BCI devices should aim at a light, advantageous close-loop system that delivers on-demand stimulation. Many BCI techniques have manifested therapeutic promises in different diseases, alone or in supplements. Extant common neuromodulatory devices encompass DBS, TMS, and TES, while EEG provides a valuable feedback scheme (Figure 2). DBS is highly invasive, while others, including TMS and TES, are non-invasive. Each of these techniques possesses its own merits and drawbacks. Still, preliminary successes of these techniques could grant more thorough investigations to make them more widely adopted.

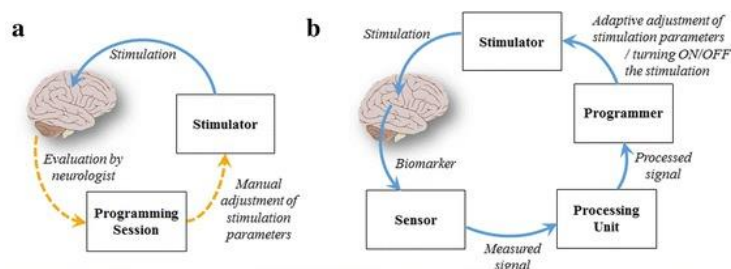


Figure 1. BCI implant neuromodulation overview; (a) Open-loop neurostimulation: The device continuously modulates brain activities, followed by monthly assessment and manual adjustment; (b) Closed-loop neurostimulation: The scheme includes an automated system, coupling the neurostimulator with a sensor that detects a presumed biomarker. It allows automatic adjustment of stimulation parameters and auto-adaptation with the disease progression [3].

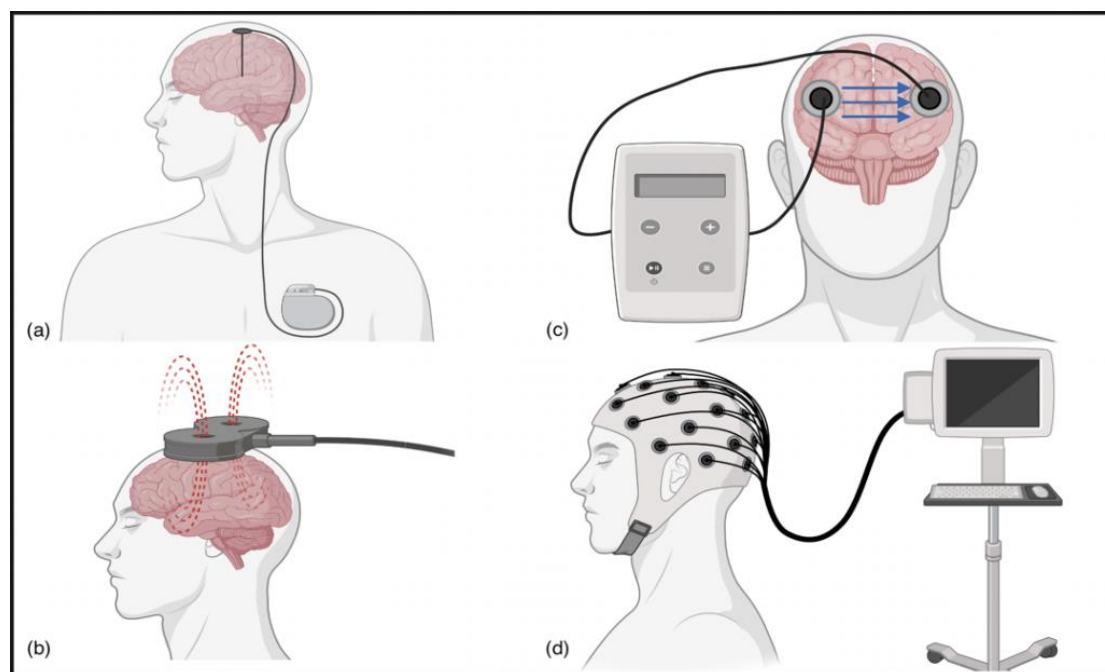


Figure 2. Neuromodulation approaches overview; (a) Invasive DBS. An electrode is surgically inserted into the middle brain for stimulation; (b) Non-invasive TMS; A strong magnetic field generated by coils then induces a neuromodulatory electrical current in the middle brain; (c) Non-invasive TES. A subtle electrical current passes across the cortex to alter neuronal activities; (d) Non-invasive EEG. Multiple electrodes record neural activities and brain waves (Image made with biorender.com).

2. Related works

2.1. Parkinson's disease (PD)

PD is a common neurodegenerative disease, manifested by motor symptoms such as shuffling gait, slow motion (bradykinesia), and hand tremors (dyskinesia) [4, 5]. PD is eventually lethal due to complications. The massive pathological degeneration of dark dopaminergic neurons residing within the pars compacta region of the substantia nigra (SNc) is thought to diminish dopamine levels and result in loss of movement coordination [4]. One non-pharmaceutical approach to alleviate PD is neuromodulating basal ganglia pathways via implantation of deep-brain stimulation (DBS) devices [2, 4]. During neuromodulation, consistent high-frequency stimulation is delivered to the subthalamic nucleus (STN) or internal globus pallidus (GPi) [4], though STN-DBS has recently been reckoned to be superior due to its more pronounced antiakinetic effect and less required energy [6].

DBS utilizes high-frequency stimulation as a reversible lesion mimic to downregulate pathological activities [5, 7, 8]. The silencing effect is via depolarization blockade and the disruption of pathological neural activities [5, 7]. The illustration of the cortico-basal ganglia pathway and STN-DBS neuromodulation is shown in Figure 3. The general scheme contains direct and indirect pathway, which lubricates and suppresses the voluntary movement, respectively (Figure 3a). The constant disruption of the indirect pathway from targeting STN accentuates the excitatory effects of the direct pathway, resulting in higher cortical excitation that raises dopamine levels and relieves PD symptoms (Figure 3b) [7, 8].

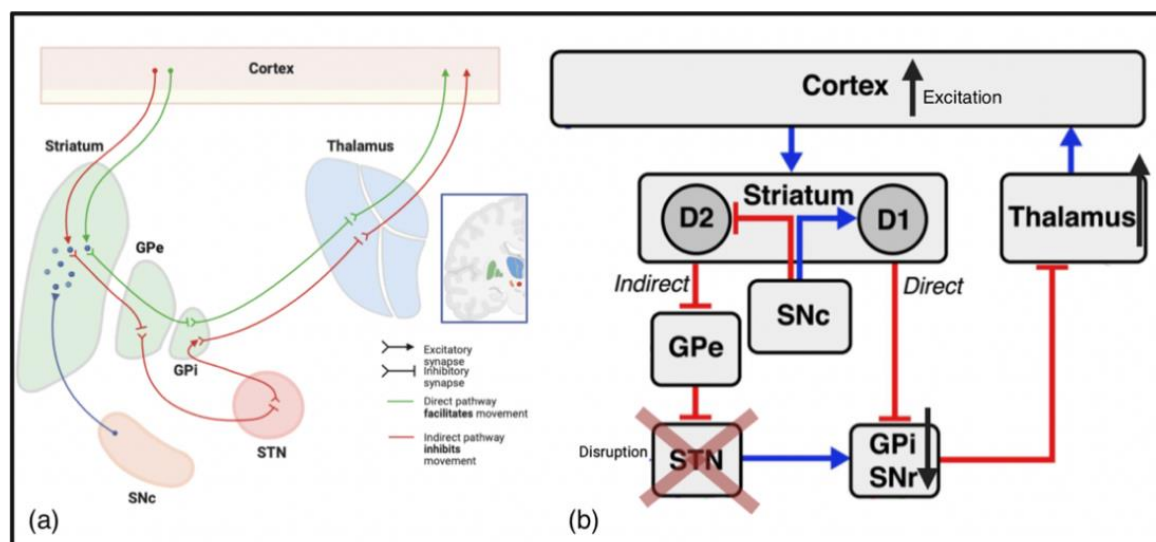


Figure 3. Cortico-basal ganglia pathway and effects of STN-DBS; GPe = external globus pallidus, STN = subthalamic nucleus, GPi = internal globus pallidus, SNr = pars reticulata of substantia nigra, SNc = pars compacta of substantia nigra; (a) Direct (striatum to GPi/SNr) and indirect (striatum reaches additional GPe and STN before to GPi/SNr) pathways. Image made with biorender.com; (b) Effect of STN-DBS in neuromodulation. Red arrows are inhibitory and blue ones are excitatory; Disruptions of STN activities in the indirect pathway leads to cortical excitation as a net effect, which mitigates PD symptoms. Image (b) modified from [7].

Furthermore, amplified pathological beta oscillations (14-30Hz) are observed from STN in PD patients and are associated with symptom severity. Hence, downregulating beta oscillations via DBS is an alternative approach and is proven to ease clinical symptoms, including bradykinesia and general rigidity [2, 7, 9]. From DBS, PD patients can obtain tremendous improvement and more extended life expectancy and quality, as well as social life, with a low risk [5, 8].

The STN-DBS approach mentioned above has substantial merits. STN-DBS involves minimal brain damage and hence is reversible and fault-tolerant, enabling us to examine clinical outcomes with different parameters and reverse when severe side effects occur [4, 8]. Nonetheless, the current DBS technology only achieves limited efficacy. For one, the continuous modulation of a site is more derived from empirical trials than mechanistic understanding, and so far, only 40% of motor enhancement has been achieved. Furthermore, DBS neuromodulation often leads to unwanted complications from stimulating regions for other physiological processes. Incurred side effects can significantly compromise therapy outcomes [7, 9]. Patients will also need to surgically exchange batteries of DBS implants every few years, with inconvenience and the risk of infection [9].

The light, closed-loop DBS implant could be the mainstream of future investigations, in which stimulation is automatically adjusted based on the disease progression and brain state [3, 9].

The latest breakthrough is adaptive DBS (aDBS) which stimulates targets by adjustable frequency only when beta oscillation power surpasses a threshold. aDBS helps to prolong battery longevity and reduce the number of operations [3]. The aDBS studies demonstrated more productivity in curing motor symptoms than the conventional DBS while consuming half less energy [6]. However, many stimulation-induced side effects persist in the aDBS procedure, including speech and gait deterioration [5, 9]. Therefore, the future DBS should emphasize energy efficiency, adaptability, and a more refined target site by propelling closed-loop designs. Augmented energy efficiency can reduce surgical operations and boost convenience, while target refinement and flexible tailoring based on personal brain dynamics are indispensable for minimal side effects and optimal therapy outcomes.

2.2. Substance use disorder (SUD)

SUD, or drug addiction, refers to repeated consumption of addictive substances despite adverse consequences. Drugs could trigger dopamine flooding in the brain, resulting in chronic hyper-

sensitization of the brain's rewarding pathway (mesocorticolimbic circuit). As a result, patients will be over-reactive to drug cues, leading to interminable drug relapse [10]. Currently, many SUD therapy modalities include pharmaceuticals, psychotherapy, and behavior rehabilitation, but relapse is common following the therapy (about 50%-60%), dramatically undermining therapy outcomes [11-14]. Many neurologic stimulation techniques based on open-loop BCI showed promise in suppressing cravings and addiction, including DBS and TMS [11, 12]. Although their mechanisms are far from complete comprehension, empirical therapeutic efficacies revealed by these techniques contribute to SUD alleviation [13].

Deep brain stimulation involves surgical procedures whereby electrodes and pulse generators are inserted into the brain to consistently regulate brain activities via high-frequency disturbances [12, 14]. Studies have indicated improved life quality and reduced relapse in SUD patients following DBS neuromodulation of the nucleus accumbens (NAc) [11, 12]. NAc is preferentially targeted as a critical component in the dopaminergic mesocorticolimbic circuit that generates reward, craving, and motivation [14]. Therefore, NAc-DBS may de-sensitize the mesocorticolimbic system and interfere with craving circuitry, contributing to remission and abstinence [11]. Several studies investigating NAc-DBS modalities in SUD patients show a significant and unanimous reduction in cravings and abuse of alcohol, tobacco (nicotine), cocaine, and opioids [11-14]. Conventional therapy modalities will be subject to a high relapse rate that nullifies the whole therapy, but the neuromodulation based on NAc-DBS offers recovery potential for refractory SUD patients who are not responsive to other treatments. Additionally, remission effects exerted by DBS are long-term, even after the NAc-DBS device is removed [11].

TMS is another non-invasive stimulation technique to treat various neurologic diseases [12]. TMS achieves neuroplasticity changes by inducing depolarization or hyperpolarization of neurons via electromagnetic induction [14], in which electromagnetic coils generate magnetic pulses targeting a brain region, triggering transient electrical current that modulates cortical activities [12]. Modulating the prefrontal cortex can indirectly impact the subcortical limbic system and reward circuitry due to their close associations with the cortex [14]. In several studies, TMS targeting the prefrontal cortex manifests a significantly improved addiction status for alcohol, nicotine, and cocaine [12, 13]. TMS has minor side effects and is surgery free. With low costs and high convenience, TMS is a promising modality for SUD [12].

Transcranial electrical stimulation (TES) can deliver direct, alternate, or haphazard current to control symptoms, while the one usually deployed in SUD is the transcranial direct current stimulation (tDCS). It is a non-invasive modality involving opposite electrodes placed across the scalp to convey a subtle current to a target region. Low-intensity current is thought to modulate neuronal dynamics, including excitability and resting potential, despite unknown mechanisms [12-14]. Clinical studies of tDCS on several aforementioned drug abuses have significantly demonstrated either diminished craving and consumption or prolonged abstinence [12]. However, inconsistent results regarding tDCS in SUD are observed in different studies, mainly due to variable study designs. Furthermore, like TMS, tDCS neuromodulation is subject to poor spatial resolution and thus lack stimulation specificity; tDCS is also restricted to stimulating superficial target, blocking its applications in buried subcortical targets [14]. Generally, tDCS remains effective in treating and palliating SUD, but more large-scale standardized studies and improved targeting precision are necessary.

2.3. Epilepsy

Epilepsy is a frequent and enervating chronic disease afflicting 70 million patients worldwide. It is characterized by intermittent episodes of hypersynchronous activity patterns. Epilepsy often accompanies many other complications, including depression, headaches, and a drastically diminished life quality [15-17]. Although many anti-epilepsy drugs effectively hamper episodic symptoms, one-third of patients are subject to drug-resistant epilepsy and often resort to surgical procedures to remove epileptic foci [16, 17]. However, such patients are often unsuitable to undergo

surgical procedures due to the incapability to identify the initiation region [16]. In light of booming BCI technology, several non-pharmacological neuromodulation options based on BCI have gathered momentum in advancing mitigatory therapies for epilepsy. Those promising therapy modalities incorporate ANT-DBS, TMS, and TES [15].

DBS is a rapidly establishing treatment for epilepsy, recently inspired by its arresting effects on movement disorders [16]. In open-loop DBS, an electrode juxtaposed with a permanent pulse generator is implanted deep within the brain, especially in an extrapolated seizure node of the epileptogenic network. DBS aims to mimic an adjustable and reversible lesion in the node, thereby electrically modulating the network activity and forestalling epilepsy, though the exact mechanism is still elusive [15, 16]. The most targeted region in DBS is the anterior nuclei of the thalamus (ANT) due to its rich interconnectivity with cortex and therefore being significant in seizure spread [15]. In clinical trials, high-frequency neuromodulation of ANT-DBS is found to raise the seizure threshold, diminishing seizure frequency by 40% in human subjects [15]. The hippocampus-DBS also exhibits a considerable decline in seizure severity [16]. However, the current DBS cannot achieve complete control alone; instead, DBS techniques are better supplemented with pharmaceutical and surgical therapies [15]. Future research should seek and define more optimal DBS stimulation parameters.

TMS is a non-invasive technique utilizing induced electrical current to modulate neural activities and alleviate seizure severity. Although its mechanism is not entirely depicted, TMS is reckoned to modify cortical excitability and induce long-term structural network alterations. Several massive studies of TMS neuromodulation in refractory epilepsy patients revealed a significant decline in seizures versus the baseline (>50%), with minor and transient side effects [15, 19]. TMS nevertheless requires further optimization of stimulation parameters and specificity for buried targets. Indeed, recent advances have permitted modulation of rats' hippocampi without stimulating the overlying cortex using temporal interference stimulation, in which interference-induced lower frequencies can target deeply subcortical structures [15].

Although DBS can be successful therapy in drug-resistant epilepsy, chronic and consistent neurostimulation is linked to multiple side effects. Therefore, on-demand electrical stimulation only when necessary became the seeding idea for closed-loop TES, a concept considered crucial in epilepsy which occurs sparsely but with severe symptoms [17]. TES is a less invasive closed-loop stimulation technique whereby an electrical current pass through the cortex to interfere with emerging pathological activities once the device identifies a seizure-triggered pattern [17, 19]. TES could also modulate cortical excitability by subthreshold current [20]. In rat experiments, TES has been proven to successfully decline the duration of spike-and-wave discharge pattern, a hallmark of seizures in human patients [17]; overall, closed-loop TES stimulation leads to a significant >60% decline in episode durations [19]. Improvements obtained by six-week unsupervised closed-loop TES could persist for as long as four months without significant side effects [17]. In contrast to TMS, which requires heavy importable coils, closed-loop TES with ultralight electrode implant and minimal adverse effects is a more prospective approach for long-term epilepsy therapy [19]. Hence, TES manifests tremendous potential for translation to human epilepsy patients in the following years; further preliminary clinical trials and assessments are necessary.

2.4. Depression

Depression is a frequent, severe neurological disorder characterized by continuous stress, significant loss of interest and motivation, and the possibility of suicide, leading to an overall high mortality rate [21]. Generally, pharmaceuticals dominate the antidepressive therapy, whereas DBS began its early-stage expansion to depression treatment in recent years, especially for treatment-resistant patients [22, 23]. An autonomous, closed-loop DBS system for depression could be envisioned in the future. Contrary to the fledgling BCI therapy for depression, a non-invasive BCI named electroencephalography (EEG) has made significant progress in identifying the depression biomarker, an underlying measurable characteristic indicative of pathogenic processes [21]. Besides

its profound applications in diagnostics, EEG could also assist in monitoring and evaluating antidepressive therapy outcomes by providing biomarkers as a golden standard [24].

Deep brain stimulation is reckoned as an experimental modality for depression [23]. DBS is currently under review concerning its applications in depression due to its capability to induce mood changes. Several safe and effective electrode implantation sites have been investigated, such as NAc, ventral striatum, and subgenual anterior cingulate cortex [22], but the best target and optimal stimulation parameters are still undetermined [23]. Due to the device cost and high risks of delicate surgery, DBS is now restricted to the most severe and treatment-refractory depression [22]. Besides, DBS is unsuitable for acute deterioration as it requires months to take effect, and its underlying interactions with antidepressive drugs still await evaluation [22]. Despite being merely a concept, DBS for depression contains much potential due to its high adaptability and reversibility [8, 23]. For instance, with the rapidly evolving DBS technique, a closed-loop DBS device coupling a probe in the amygdala with a stimulation electrode placed in the ventral striatum is foreseeable to regulate depression automatically.

The direct information obtained from EEG is the band power, including amplitude and frequency parameters of alpha to delta bands and the theta band. Each brainwave band could suggest a different corresponding brain state. One approach to extrapolate the biomarker is through classification algorithms and modeling, in which a particular detected band feature yielding high prediction accuracy may be an essential biomarker [21]. Through years of research, multiple reliable biomarkers have been established, one prominent being alpha (8-13Hz) asymmetry [2], which stands for the hemispherical discrepancy of the alpha band at left and right frontal electrodes. In depression patients, high alpha asymmetry refers to a raised alpha band of the left hemisphere, which inhibits the approach behavior and leads to despair. Although recent studies undermine alpha asymmetry as a reliable diagnostic biomarker [21], it still reveals therapeutic applications in a tentative study. Diminishing the alpha discrepancy by raising alpha activity of the right hemisphere demonstrates depression amelioration in a reported pioneering neurofeedback study [2].

Additionally, the band power of gamma and theta brainwaves implies a highly reliable diagnostic precision [21]. The altered sleeping EEG pattern, including elevated REM sleep frequencies and impaired sleeping continuity, could also serve as biomarkers for depression [24]. Nonetheless, the research trial only includes a few sample patients, which may involve high statistical error [21]; more large-scale trials should be conducted for each proposed biomarker. Then, identifying one or multiple universally reliable and indicative biomarkers is still urgent to propel the therapeutic frontier of depression, such as DBS. Lastly, as done in alpha asymmetry, each potential biomarker is worth the trial to empirically discover its contingent therapy, as it may broaden the repertoire of treatments and save more urgent patients.

3. Discussion

Deep brain stimulation has become a successful treatment for multiple neurologic diseases since its invention in the late 1980s, including the ones mentioned above and more [5, 12, 13, 15]. DBS is a well-established and approved modality in PD and epilepsy, while its efficacy in addiction and depression requires more extensive investigation to deserve approval [14]. Compared to TMS and TES/tDCS, DBS can exclusively aim buried subcortical structures with greater resolution, though TMS just revealed such potential [14, 15]. Furthermore, contrary to TMS, which requires heavy coils for modulation, the DBS implant is portable, rendering the concept of closed-loop DBS that gives on-demand stimulation feasible [3, 19]. However, DBS is reckoned to be the most invasive: with surgical implantation, DBS bears high risks and complications, including infections and tissue damage [13, 14]. Besides elucidating the whole mechanism as a goal, further DBS development should promote energy efficiency and closed-loop system design. More compatible biomaterials and operative protocols should also be introduced, aiming to reduce risks and complications.

Both TES and TMS are non-invasive and non-surgical procedures, thus avoiding many operative complications notable in DBS, although moderate complications and discomfort could occur [13]. TMS utilizes coils to generate magnetism-induced current for cortical neuromodulation, and regular TMS sessions can offer minimal invasiveness and maximum convenience [12, 14, 22]. The heavy nature of TMS instruments has primarily determined its session-based therapy and forestalled its potential for closed-loop; TES/tDCS, on the other hand, is more portable and can potentially be encapsulated into an autonomous, closed-loop system in the scalp for chronic symptom control [14, 19]. Both techniques are well-tolerated across patients, but TES is relatively more accessible and cost-efficient [12, 22]. Although both techniques suffer from low stimulating precision absent in DBS, TMS has higher temporal resolution and can potentially modulate deeper structures [12, 14]. The future development of TMS should emphasize coils that focally target deeper structures (higher focality), while TES could specialize in closed-loop design to achieve long-term control [15, 18, 19]. Meantime, EEG may provide on-time feedback scheme in supplements with BCI therapy such as DBS [25]. EEG data may also suggest the pivotal biomarker and potential therapeutic targets in neurologic diseases such as depression, facilitating the diagnostics and BCI therapy [21, 24]. Eventually, DBS, TMS, and TES/tDCS need more mechanistic understanding and empirical clinical data in different diseases to support further development, including optimization of stimulation parameters [14].

4. Conclusion

BCI-based neuromodulating techniques have been introduced and rapidly improved in the last few decades, several prominent techniques including DBS, TMS, TES, and EEG. Since the invention, clinical investigations quickly absorbed them into treatments for various neurologic and psychiatric diseases; they showed palliative effects and recovery potential for many such patients as PD, addiction, epilepsy, and depression. Current techniques are largely based on continuous open-loop stimulation followed by inspection and adjustment, whereas self-adapting closed-loop stimulation could be a future goal and mainstream. For now, each technique has its unique edge and drawback, and each faces many obstacles that require resolution to make the modality more widely adopted. More comprehensive mechanistic insights into neuromodulation techniques could boost their efficacies in the future.

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