

Brain-Computer Interface Based Neuromodulation on Treatment of Depression

Yijiang Li *

Department of Human Biology, University of Toronto, Toronto, Canada

* Corresponding Author Email: Yijiang.li@mail.utoronto.ca

Abstract. Major Depressive Disorder (MDD) represents a significant societal burden, with traditional first-line treatments often falling short. This pressing issue has spurred the exploration of neuromodulation therapies, demonstrating superior efficacy compared to conventional pharmaceutical interventions. The present review provides a rigorous evaluation of four advanced neuromodulation techniques: Focal Electrically Administered Seizure Therapy (FEAST), Transcranial Magnetic Stimulation (TMS), Intermittent Theta-Burst Stimulation (iTBS), and Magnetic Seizure Therapy (MST). A comprehensive analytical comparison is offered, focusing on their efficacy, feasibility, economic considerations, and underlying mechanisms. Among these therapies, iTBS, integrated with Brain-Computer Interface (BCI) systems, has emerged as notably effective, with clinical trials indicating an average 80% efficacy at a reduced economic cost. FEAST and MST, supported by recent research, also exhibit strong efficacy, around 60%, although with more pronounced side effects. TMS, in contrast, exhibits a slightly reduced efficacy but is promising due to its minimal side effects. The review further delves into the transformative role of increasingly sophisticated BCI technologies in addressing previously identified challenges of neuromodulation therapy, such as adverse side effects, time-consuming procedures, and high costs. These technological advancements are elucidated, emphasizing their contribution to more precise therapy delivery and an enhanced patient experience. The review culminates in illuminating a pathway for the harmonious integration of neuromodulation therapies with traditional psychopharmacological treatments, positioning this integrative approach as a groundbreaking paradigm poised to redefine the landscape of depression treatment.

Keywords: Depression treatment; Neuromodulation; Brain-computer interface.

1. Introduction

Major depressive disorder (MDD) is a pervasive mental health condition characterized by persistent despair, diminished interest in activities and social interactions, sustained anxiety, and recurrent thoughts of suicide [1]. In 2021 alone, the United States reported that 21 million adults suffered from depression, and of these, 1.7 million attempted suicides, leading to 48,000 fatalities [2, 3]. Alarming, the number of adults in the US with depressive disorders has increased over the years, and the ratio of suicides continues to rise, posing a significant societal burden [4]. Thus, finding a validated therapeutic intervention for depression is imperative.

Currently, the primary line of defense against MDD includes pharmacological antidepressants such as selective serotonin-reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), or Monoamine oxidase inhibitors (MAOIs) [5, 6]. However, despite being the primary medications for depression, the efficacy of SSRIs and SNRIs is often doubted [7]. For instance, fluoxetine, one of the most widely prescribed antidepressants, demonstrates only a 61% effectiveness rate in the treatment of MDD [8]. More concerning, some drugs like Paxil and Prozac have shown results no more promising than a placebo, with a mere 33% success rate. Taken together, the limited efficacy of traditional antidepressants has resulted in around 30-50% of MDD patients failing to respond to first-line treatment [9]. Hence, the necessity for an alternative therapy that can target treatment-resistant depression patients has arisen, directing attention toward neuromodulation therapies [10].

As its name suggests, Neuromodulation uses external devices to directly or indirectly influence neuronal transmission, firing patterns, neural plasticity, neurogenesis, cerebral metabolism, or

generate seizures [11]. It has been broadly characterized into two components: invasive and noninvasive methods. The invasive methods include deep brain Stimulation (DBS), electroconvulsive therapy (ECT), and trigeminal nerve stimulation (TNS). In contrast, noninvasive methods include repetitive transcranial magnetic stimulation (rTMS), accelerated transcranial magnetic stimulation (aTMS), cranial electrotherapy stimulation (CES), magnetic seizure therapy (MST), and intermittent theta-burst stimulation (iTBS). Among these, ECT has long been recognized for its therapeutic efficacy, yet its pronounced side effects, including memory loss and cognitive impairment, have necessitated the pursuit of more refined interventions. These needs led to the development of focal electrically administered seizure therapy (FEAST), a targeted advancement over ECT [12, 13].

The recent emergence of Brain-Computer Interface (BCI) technology, particularly advancements in real-time brain imaging and electroencephalography (EEG) feedback [14], offers a transformative platform to enhance neuromodulation techniques further. BCI is uniquely positioned to address some of the challenges in neuromodulation by enabling more precise control and personalized therapies. By analyzing brain activity in real-time, BCI systems can tailor the intervention to the individual's unique neural patterns, potentially improving responsiveness and reducing side effects. Furthermore, the integration of BCI with existing neuromodulation methods such as rTMS, aTMS, MST, and iTBS may allow for more significant treatment efficacy, especially in cases resistant to traditional approaches. Not only does BCI offer the potential to innovate and refine FEAST, but it also opens avenues for optimizing other neuromodulation methods, facilitating a more targeted and adaptable approach to treatment.

This review seeks to comprehensively explore the applications and potential of BCI in improving neuromodulation techniques, emphasizing their enhanced role in treating treatment-resistant depression.

2. Research Works

2.1. Focal Electrically Administered Seizure Therapy

Focal Electrically Administered Seizure Therapy (FEAST) represents an innovative therapeutic approach in the realm of neuromodulation, distinctively advancing from traditional Electroconvulsive Therapy (ECT). This advancement has seen a transition from broad brain targeting to a more precise, localized approach, specifically targeting the right prefrontal cortex (rPFC), a region consistently implicated in depression.

The key to FEAST's innovation lies in its unidirectional and asymmetrical placement of the anode and cathode over the right hemisphere's prefrontal area. This unique placement enables localized transcranial direct current stimulation [15], initiating seizure activities in the rPFC area with 800 or 900 mA and producing fewer side effects compared to traditional ECT. The local seizure onset is hypothesized to restore and enhance the GABAergic functions within the PFC, contributing to its therapeutic effectiveness [16].

Real-time imaging plays a vital role in FEAST's procedure. Techniques such as single photon emission computed tomography (SPECT) scans are employed for precise localization of seizure onset, thus minimizing irritation to surrounding brain regions [17]. Supplementary tools like EEG or fMRI have also been employed to monitor the accuracy and precision of the electrical current, maintaining a low error rate [18].

Clinically, FEAST is gaining recognition as a superior alternative to traditional ECT. This shift is backed by research, with studies demonstrating significant improvement in patients with treatment-resistant depression, reporting up to a 60.67 ± 18.46 percentage reduction in HRSD scores [13, 19]. Side effects have been notably mild, with only minimal withdrawal rates, in stark contrast to the 50% observed in ECT trials [20].

In conclusion, FEAST provides a promising therapeutic pathway for refractory depression, circumventing severe side effects like cognitive impairment or amnesia traditionally associated with ECT. Through the integration of advanced brain imaging technology, it achieves precise, noninvasive

focal transcranial direct current stimulation, preserving the integrity of surrounding brain regions. It truly embodies a future where technology and medical innovation converge to optimize patient care. The success and potential of FEAST suggest that further exploration and investment in this area could revolutionize not only depression treatment but perhaps broader psychiatric care.

2.2. Repetitive Transcranial Magnetic Stimulation

Repetitive Transcranial Magnetic Stimulation (rTMS) is a leading-edge, noninvasive, and long-period (trials occurred weeks to months) brain stimulation therapy primarily employed for patients resistant to traditional depression treatments. Utilizing a strong magnetic field of 1 – 2 tesla strength (discharged by multi-shaped coils), TMS generates currents in neurons, thus modifying the neuronal firing patterns and internal ionic flow. The effectiveness of rTMS is augmented by the integration of an EEG system. This enables the detection of TMS-evoked cortical potentials (TEPs), such as P25, N40, P60, N100, and P185, thereby enhancing the procedure's accuracy [21].

In clinical practice, two types of rTMS are predominantly used: high-frequency rTMS (HF-rTMS) and low-frequency rTMS (LF-rTMS). Both have been shown to be effective in treating depression. HF-rTMS (10-20 Hz) targets the left dorsolateral prefrontal cortex (DLPFC) to alleviate depressive symptoms, while LF-rTMS (0.5-1 Hz) stimulates the right DLPFC to treat Major Depressive Disorder (MDD) [22-24].

HF-rTMS has been found to increase neurogenesis in the cerebral cortex through its excitatory effects, reflected as P60. It is thought to promote the expression of brain-derived neurotrophic factors (BDNF), which is a protein instrumental in enhancing dendritic growth, synaptic formation, and neurogenesis [25]. Consequently, as the decreased synapse and neuron numbers in the PFC are linked to depression, the increment facilitated by HF-rTMS produces an antidepressive effect.

Conversely, LF-rTMS exerts its inhibitory effects mainly on the Glutamatergic neurons within the cortical areas, typically manifesting as N40. In the context of depression, particularly within the PFC, there is often a marked hyperactivity of cortical neurons coupled with a loss of GABAergic function. This imbalance leads to the overactivity of Glutamatergic neurons, which is thought to be linked with depressive symptoms. LF-rTMS addresses this by enhancing inhibitory effects on the hyperactive Glutamatergic neurons. By restoring a balance between excitatory and inhibitory neural functions, explicitly targeting the Glutamatergic neurons, LF-rTMS can alleviate depressive symptoms [26, 27].

Practical trials have also underscored the promising effects of rTMS. One report, for example, showed that 73.7% of patients with significant depressive symptoms alleviated their symptoms after HF-rTMS treatment [28]. Furthermore, meta-analyses in adolescents ($n=109$) revealed an average HRSD decrease of $50.21\% \pm 21\%$ from baseline after HF-rTMS treatments [29]. In addition, after an average of 12.6 ± 3.9 LF-rTMS trials, 34.6% of patients ($n=131$) experienced remission of depressive symptoms, illustrating its efficacy [30].

Overall, the noninvasive nature of rTMS positions it as an advantageous treatment method for MDD, particularly in comparison to traditional antidepressants, boasting a better therapeutic effect (odds ratio = 4.76) [30]. One of the pivotal advancements in rTMS therapy is the integration with Brain-Computer Interface (BCI) technology, especially the use of EEG. This integration allows for precise monitoring and feedback of neural responses, enhancing the efficacy and customization of the treatment. By leveraging the intricate balance between different frequencies, targeted areas, and real-time EEG feedback, rTMS represents an innovative and promising approach to mental healthcare. Notably, its noninvasive procedure ensures minimal side effects and a higher degree of safety, setting it apart from more invasive neuromodulation techniques. The convergence of these factors underscores the potential of rTMS as a reliable and cutting-edge therapy for treatment-resistant depression.

2.3. Accelerated Transcranial Magnetic Stimulation

Accelerated Transcranial Magnetic Stimulation (aTMS) represents an innovative modification of conventional rTMS therapy, specifically designed for application in cases of treatment-resistant

depression. Utilizing a similar stimulation setup to rTMS, with a 1.5-2T strength and 10-50 Hz frequency targeting the DLPFC area, aTMS is differentiated by its accelerated treatment schedule.

The mechanism behind this accelerated approach lies in the concentrated and intense application of magnetic stimulation, which may induce more immediate neuroplastic changes in the target areas of the brain.

Unlike the customary 4-8 weeks required for traditional rTMS clinical trials, aTMS completes its therapy cycle within a matter of days, typically over five consecutive days with up to six sessions per day. This expedited approach has been associated with a notable short-term response rate, ranging from 20% to 83%, contingent on factors such as schedule intensity, total sessions, and individual patient factors. Quantitatively, the efficacy of aTMS is evidenced by a Hedges' *g* effect size of 0.39 (95% CI 0.005–0.779) [31].

The concise treatment duration and rapid onset of therapeutic effects make aTMS an appealing option, particularly for patients constrained by financial limitations or in urgent need of symptom alleviation. Moreover, clinical studies have found aTMS to be relatively well-tolerated, with transient headaches as the most common side effect.

In conclusion, aTMS represents a promising advancement in neuromodulation, with the potential to revolutionize the approach to treatment-resistant depression. Through the precise, noninvasive application of magnetic stimulation and an innovative, accelerated schedule, it offers immediate relief with minimal side effects. Nevertheless, continued research and clinical trials are vital to validate its long-term success and refine the protocols for diverse patient populations. The integration of aTMS into the broader therapeutic landscape could signify a pivotal shift in psychiatric care, aligning technology, efficiency, and patient-centric care for optimal mental health outcomes.

2.4. Magnetic Seizure Therapy

Magnetic Seizure Therapy (MST) is a noninvasive therapeutic approach that uses an ultrahigh magnetic field to induce controlled seizures in the brain, typically lasting no more than 10 seconds. Drawing inspiration from Electroconvulsive Therapy's (ECT) seizure-inducing methodology for treatment, MST integrates the neural regulation techniques characteristic of Transcranial Magnetic Stimulation (TMS) to target treatment-resistant depression.

Unlike TMS, which employs a 2T magnetic field at a frequency of 10 Hz to specifically activate neurons in the DLPFC, MST innovatively uses a butterfly coil to generate a 2T magnetic field at a heightened frequency of 50 Hz. This adjustment is designed to provoke a seizure, thereby offering a unique therapeutic pathway [32]. Furthermore, during the MST procedure, real-time EEG is utilized to closely monitor brain activity in conjunction with SPECT scans performed before and after the procedure. These Brain-Computer interface (BCI) technologies not only facilitate optimal treatment but also enable the formation of a Closed-Loop System, significantly enhancing the precision of the intervention and safeguarding patient well-being [33].

Clinically, MST's efficacy has been markedly demonstrated. A notable case study revealed that within a week post-MST, an MDD patient's Hamilton Rating Scale for Depression (HRSD) plummeted from an initial 33 to a mere 6. Concurrently, both verbal and nonverbal learning levels exhibited statistically significant improvements. Another research paper shows that after 20 MDD patients underwent MST treatment, their average HRSD levels dropped from 30.7 to 18.3, an improvement of over 40%. At the same time, common ECT-related cognitive side effects such as retrograde amnesia, anterograde amnesia, or others were not observed [34]. Furthermore, a report involving 10 depression patients (3 males, 7 with unipolar depression, and 3 with bipolar disorder) indicated that their average HRSD level before MST was 27, with significant improvements after treatment. Five even discontinued psychiatric medications, although some experienced transient side effects such as nausea, headaches, and short-term inattention [35].

In conclusion, MST, supported by integrated BCI technologies like EEG and SPECT, has manifested significant potential as an innovative approach to depression treatment. By merging the seizure-inducing principles of ECT with the technological sophistication of modern neural regulation,

MST offers a promising pathway to alleviating depressive disorders, all while minimizing associated risks and side effects.

2.5. Intermittent Theta-Burst Stimulation

Intermittent theta-burst stimulation (iTBS) is a sophisticated, noninvasive neuromodulation technique that represents an improvement over traditional TMS. The mechanism of iTBS is inspired by the theta-burst activity observed in the hippocampus, where rapid bursts of gamma oscillations (50 Hz) are enveloped within slower theta waves (5 Hz). This specific pattern is replicated to magnetically stimulate the circuit connecting the unilateral or bilateral DLPFC to the subgenual anterior cingulate cortex (sgACC) [36].

Functionally akin to high-frequency repetitive TMS (HF-rTMS), iTBS can activate cortical neurons to enhance long-term potentiation (LTP)-like plasticity, a crucial factor in neural adaptability. In addition, studies have demonstrated that iTBS can effectively mitigate long-term depression in the PFC, thereby contributing to the restoration of decreased neuron dendritic spines commonly observed in depression patients [37].

A distinguishing feature of iTBS lies in its efficiency and patient acceptability. Delivered in a significantly shorter time frame than traditional rTMS, iTBS conserves resources and fosters a more comfortable patient experience during the treatment of depression, making it a preferred option over rTMS [38]. Some studies have reported minimal side effects, including mild discomfort or transient headaches, but these are generally well-tolerated by patients.

The efficacy of iTBS has been substantiated through empirical research. Among 21 treatment-resistant depression patients, 19 (90%) achieved remission criteria after 6 weeks of continuous iTBS treatment (90,000 iTBS pulses per day), a success rate surpassing the average for rTMS. Remarkably, this study incorporated functional connectivity MRI (fcMRI) to guide treatment, thus enhancing the therapeutic optimization through real-time EEG feedback, part of the broader integration of Brain-Computer Interface technologies [39]. In another significant investigation, 11 out of 14 depression patients met remission criteria through just five days of iTBS treatment, utilizing fMRI feedback and optimization strategies like Stanford Accelerated Intelligent Neuromodulation, marking a considerable advancement over traditional rTMS protocols [40].

In sum, by melding the principles of theta-burst activity with innovations such as BCI feedback and cutting-edge algorithms, iTBS has emerged as a promising frontier in the treatment of depression. Its blend of efficiency, patient comfort, and therapeutic effectiveness distinguish it as a valuable tool in modern mental healthcare, potentially transforming the landscape of depression treatment. Nevertheless, ongoing research and trials are imperative to further establish the long-term effectiveness and refine protocols for diverse patient populations, ensuring that iTBS is harmoniously integrated into the broader therapeutic landscape. The summary of iTBS stimulation parameters and results are shown in the Table 1.

Table 1. Summary of iTBS Stimulation Parameters and Results.

	Cole et al., (2020)	Cole et al., (2021)
Participants	N=21	N=14
Target Site	Left DLPFC	Left DLPFC
Session	1800 Pulses, 50 min interval, 10 trials per day, 5 days	1800 Pulses, 50 min interval, 10 trials per day, 5 days
Remission percentage	19(90.5%)	11(78.6%)
Data sourced from references [39, 40]. Intensity of iTBS stimulation ranges between 90% and 120% to meet safety guidelines. In the study by Cole et al., (2021), the control group data is not included in the table; however, 2 out of 15 participants in the control group met the remission criteria. Remission metrics were assessed four weeks post-therapy.		

3. Discussion

While the current study presents promising results, it judiciously acknowledges inherent limitations and offers a methodical assessment. The evaluation commences with the recognition that all depression measurements are confined to HRSD (HAM-D) or MADRS scales, with remission criteria defined as an HRSD score less than 7 [41]. This limitation underscores the need for a broader diagnostic scope that encompasses other relevant symptoms, such as hypersomnia or insomnia, to furnish a more comprehensive picture of treatment efficacy.

Next, the research focuses on the considerable variability in response rate measurements attributed to individual variations. This inconsistency is compounded by potential biases due to the absence of double-blind tests or sham groups in rTMS analysis. These limitations are explored in depth, alongside the immediate post-treatment benefits in aTMS, bringing to the fore questions about long-term effectiveness and potential issues of recurrence or rebound.

Additionally, the nascent state of SAINT technology and the limited sample size in iTBS studies receive a meticulous evaluation. This examination adds nuanced insight into these methodologies and underscores the importance of further exploration and validation.

To overcome these challenges, the paragraph delineates clear pathways for future research. This includes more rigorous implementation of double-blind tests, long-term follow-up studies, and expanded sample sizes. Moreover, it advocates for the inclusion of diverse metrics beyond HRSD or MADRS scales and emphasizes the potential of examining neural network functional connectivity changes in depression, such as excessive activity of the Default network (DMN) [42]. These insights form vital parameters for enhancing treatment effectiveness and guide future research endeavors.

Finally, the paragraph highlights the thrilling prospects of integrating BCI and AI technologies, including machine learning, to identify beneficial brain oscillations. By capitalizing on these advancements to establish a closed-loop system, it articulates the vision for the next frontier in therapy, where both efficiency and efficacy of neuromodulation treatments may be substantially augmented.

4. Conclusion

In summary, the field of neuromodulation therapies, encompassing MST, TMS (including rTMS and aTMS), and iTBS, marks a decisive and innovative advancement over traditional psychopharmacological treatments for Major Depressive Disorder (MDD). MST has shown exceptional efficacy in treating resistant depression, heralding a promising avenue that warrants further examination, especially concerning significant accompanying side effects. TMS, although demonstrating fewer therapeutic benefits, has been extensively explored for its minimal side effects, highlighting its practical applications.

The integration of BCI technologies, such as FEAST with real-time EEG and SPECT feedback, represents a significant leap in precision, rendering therapeutic benefits comparable to ECT but with reduced side effects. This meticulous adaptation has profound implications for modern treatment strategies.

On the cutting edge, the fusion of iTBS with Stanford Accelerated Intelligent Neuromodulation (SAINT), utilizing fMRI data processing, has not only expedited therapeutic outcomes but also proven its superior efficacy over traditional rTMS. This innovation serves as a cornerstone for understanding the promising trajectory in depression treatment through neuromodulation, underscoring crucial improvements in both time and cost efficiency.

Collectively, these findings illustrate a robust and promising framework that heralds a paradigm shift in depression therapy, emphasizing both the efficiency and precision of neuromodulation treatments. The insights gleaned from this review offer a beacon for future research, guiding the development of even more refined and patient-centered approaches in the quest to alleviate the burdensome societal impact of depression.

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