Neurostimulation as a treatment for mood disorders in patients: recent findings

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Purpose of review
The use of neurostimulation to treat mood disorders dates back to the 1930s. Recent studies have explored various neurostimulation methods aimed at both restoring a healthy brain and reducing adverse effects in patients. The purpose of this review is to explore the most recent hypotheses and clinical studies investigating the effects of stimulating the brain on mood disorders.

Recent findings
Recent work on brain stimulation and mood disorders has focused mainly on three aspects: enhancing efficacy and safety by developing new approaches and protocols, reducing treatment duration and chances of relapse, and investigating the physiological and pathological mechanisms behind treatment outcomes and possible adverse effects.
This review includes some of the latest studies on both noninvasive techniques, such as transcranial magnetic stimulation, magnetic seizure therapy, transcranial direct current stimulation, transcranial alternating current stimulation, electroconvulsive treatment, and invasive techniques, such as deep brain stimulation and vagus nerve stimulation.

Summary
Brain stimulation is widely used in clinical settings; however, there is a lack of understanding about its neurobiological mechanism. Further studies are needed to understand the neurobiology of brain stimulation and how it can be used to treat mood disorders in their diversity, including comorbidities with other illnesses.

Keywords
bipolar disorder, brain stimulation, major depressive disorder, mood disorders

INTRODUCTION

Mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD) are one of the largest sources of disability worldwide. They are associated with dysfunctions of specific brain networks, including the prefrontal cortex (PFC), the subgenual anterior cingulate cortex (sgACC), the hippocampus, the nucleus accumbens and the amygdala. These areas can be targeted via focal repeated neurostimulation in order to restore physiological brain activity in these regions. Due to the complex neural networks connecting brain areas, stimulation of one part may also affect other parts.

This review covers recent findings from 2021 onwards, on noninvasive brain stimulation methods, including transcranial magnetic stimulation (TMS), magnetic seizure therapy (MST), transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), electroconvulsive therapy (ECT)as well as invasive approaches including deep brain stimulation (DBS) and vagus nerve stimulation (VNS). We have focused mainly on clinical investigations, although some recent preclinical findings describing putative mechanisms are also presented.

NON-INVASIVE APPROACHES

Transcranial magnetic stimulation

In repetitive TMS, brain tissue beneath the skull is targeted by applying a magnetic field which modifies the activity of cortical areas [1]. A survey

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KEY POINTS

- Mood disorders such as depression and bipolar disorder are among the leading causes of disability.
- A variety of noninvasive and invasive brain stimulation techniques have been developed to help patients with mood disorders restore normal brain function while reducing side effects.
- Recent studies have mostly focused on the efficacy and tolerability of brain stimulation, as well as the neural mechanisms behind it.
- Future studies should focus on new physical modalities and protocols to enhance treatment for specific patient populations such as treatment resistant patients.

suggests that this method has a 40–55% response rate (meaning that the mood of patients improved) and a 25–35% remission rate (decrease or disappearance of symptoms) [2]. However, both the identification of the most efficient protocol and the understanding of the biological mechanisms behind it remains a challenge to be met.

Recent studies have addressed the issue of protocol optimization. Classically, a 10 Hz rTMS protocol of 20–30 sessions is used: one session lasts approximately 40 min, targeting the left dorsolateral prefrontal cortex (dlPFC). In 2018, an intermittent theta burst stimulation (iTBS) protocol was approved by the Food and Drug Administration (FDA), based on the assumption that the outcome would remain the same with 3-min sessions of iTBS. iTBS uses three 50 Hz pulses repeated in a 5 Hz intermittent pattern [3]. A study compared the effectiveness of both iTBS and rTMS on the left dlPFC of 60 patients with treatment resistant depression during a 6-month follow-up period, confirming that both were effective [4▪▪]. Another approach is based on a protocol termed ''Dash'' (because faster than the reference one), which was FDA approved in 2016. Ituses the same 10 Hz rTMS parameters, but clinicians adjust inter-trial intervals (ITI) between 11 and 25 s instead of 26 s in the former 10 Hz FDA approved protocol, resulting in shorter sessions. Data gathered from a large group of patients showed that both protocols yielded a similar improvement in symptoms [5].

An important observation from clinical settings is that MDD is highly comorbid with other neuropsychiatric disorders. This contributes to difficulties in treating some patients. In a study aiming at comparing two stimulation protocols in this kind of population, patients suffering from posttraumatic stress disorder (PTSD) with comorbid MDD were treated with either iTBS or rTMS stimulation on the left dlPFC. iTBS (a 50 Hz triplet burst repeated at 5 Hz with 2 s stimulation and 8 s interval for 30 sessions) was not as effective as rTMS (5 Hz, 4 s stimulation and 12 s interval for 30 sessions) when treating these patients in these settings. However, the authors suggest that a greater similarity in clinical outcomes would be reached if more pulses of iTBS were delivered [6]. Another study investigated response rate and neurophysiological biomarkers of 162 patients with MDD comorbid with chronic pain. rTMS was used on the left dlPFC for 30 sessions. In these patients, rTMS was less effective than in a noncomorbid MDD population suggesting multitarget rTMS as a future approach that could be successful in reducing depression symptoms in this specific comorbid condition [7▪▪].

At the neurotransmitter level, MDD has been associated with lower levels of GABA in the medial prefrontal cortex (mPFC) causing hyperactivation of this region. This is prevented by appropriate pharmacological treatment and brain stimulation techniques, such as rTMS on the left dlPFC. Although it is well known that the left dlPFC and mPFC are functionally connected, it is still unclear how this connectivity can lead to elevated levels of GABA in the mPFC (Fig. 1a) [8]. The authors attempted to determine the efficacy of iTBS to treat acute BD using an antimanic drug combined with iTBS in the left dlPFC but found that this method was ineffective [9]. Interestingly, another study pointed out an increase in mPFC GABA levels after left dlPFC iTBS treatment, but this was not associated with improvement in depression symptoms in BD [10]. Thus, a different mechanism could exist in BD.

In conclusion, a careful choice of the neurostimulation parameters is required according to the clinical context. In the case of depression comorbid with other disorders, the brain networks and connections may not function in the same way as in depression, thereby altering the treatment outcome.

Magnetic seizure therapy

MST is another form of rTMS inducing convulsive seizures by continuously stimulating apart of the brain cortex, usually the vertex (the highest point of the head near the middle of the sagittal suture) with high frequencies and strong magnetic pulses (e.g. between 25 and 100 Hz at 100% of stimulator output). It has an antidepressant effect comparable to ECT but with the safety of TMS. This method can stimulate selectively the local cortex without affecting deep brain nuclei. In addition, its cognitive side effects are minimal compared to ECT [11].

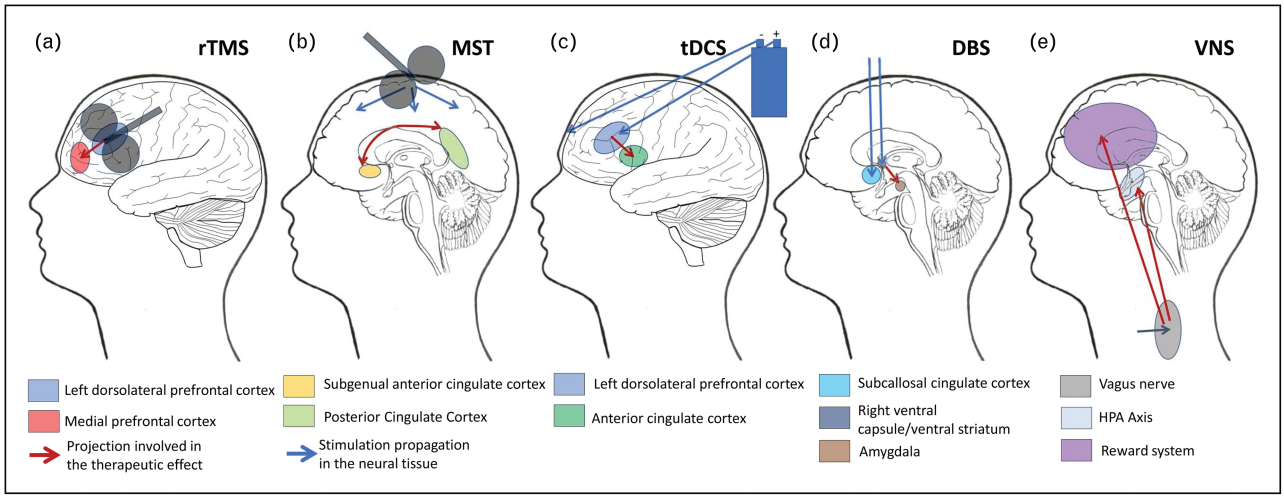

FIGURE 1. Brain stimulation techniques. (a) The stimulation of left dlPFC with TMS (rTMS and iTBS) results in an increased activity in this area and an indirect reduction in the activity of the mPFC. (b) Convulsive seizures caused by MST can reduce the activity of the sgACC and increase functional connectivity between areas, such as sgACC and PCC. (c) tDCS stimulation in dlPFC area indirectly affects the ACC. (d) DBS usually targets SCC and VC/VS regions in depression, and indirectly the amygdala region following VC/VS stimulation. (e) Emotional and reward circuits as well as the HPA axis can also be affected by VNS stimulation. dlPFC, dorsolateral prefrontal cortex; iTBS, intermittent theta burst stimulation; mPFC, medial prefrontal cortex; sgACC, subgenual anterior cingulate cortex; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation.

Recent advances in neuroimaging have provided insights into the underlying mechanisms, but these are still not well understood. A recent study applied MST on the vertex in MDD patients, which resulted in a greater functional connectivity of the sgACC and the posterior cingulate cortex (PCC) (Fig. 1b) [12▪] which was correlated to clinical improvement. These findings support that the therapeutic effect is obtained through neuromodulation of regions connected to the stimulation area, as for rTMS. Another study used electroencephalography (EEG) after bilateral MST treatment on F3 and F4 areas (international 10–20 EEG system) and recorded a change in the resting state and theta connectivity of EEG in the brain [13]. A reduction in theta connectivity can indicate a functional disconnection between brain networks in depression, therefore a change in this connectivity might be a sign of successful treatment [14].

Transcranial direct current stimulation and transcranial alternating current stimulation

In tDCS, low-amplitude current (2 mA maximum) is delivered between electrodes for a short duration (a maximum of 30 min for 20–30 sessions). This modulates the activity of specific brain areas, the anode being typically placed on the left dlPFC and the cathode on the right supra orbital area, thus modulating spontaneous neural activity [15,16]. In recent years, there has been some progress regarding the protocol used and understanding the mechanisms at play. Regarding the protocol, some patients (e.g. older patients) have difficulties in attending facilities where the tDCS is delivered. To address this, a study developed home-based tDCS therapy and showed that it was effective for older adults with MDD after 28 sessions [17].

Regarding neurobiological underpinnings of tDCS, a study using a new protocol based on magnetic resonance imaging (MRI) showed that tDCS does affect the left dlPFC and anterior cingulate cortex (ACC) networks (Fig. 1c) [18].

Another aspect of the pathophysiology of MDD is the altered level of stress hormones due to a dysregulation of the hypothalamic–pituitary–adrenal axis (HPA). In MDD, sensitivity of glucocorticoid receptors is reduced, which increases the concentration of glucocorticoids in the body [19]. A study using a rat model of generalized epilepsy examined how tDCS affected depression and anxiety-like behavior, as well as the influence of the HPA axis on the treatment outcome. tDCS improved anxio-depressive-like behaviors in this rat model, suggesting promising future uses in MDD with comorbid conditions. Interestingly, plasma glucocorticoids decreased after successful treatment [20▪▪].

Another important mechanism to explain the pathophysiology of neuropsychiatric disorders is immune dysregulation, as for BD in which various

inflammatory biomarkers are altered in patients [21]. A recent clinical study suggests that interleukin (IL)-6 may predict tDCS response in BD, while IL-8 may decrease after tDCS treatment [22].

Unlike tDCS, which uses direct current, tACS involves applying alternating currents on the scalp to stimulate the cortex and regulate its excitability. tACS appears to have a significant antidepressant effect when current is applied over the frontal region and both mastoid regions in an 8-week protocol [23]. The left dlPFC plays a key role in positive emotions and it is sometimes affected by disorders that lead to increased alpha oscillations in EEG. According to the study, increased left frontal alpha oscillations are associated with MDD, tACS can reduce these oscillations [24].

Electroconvulsive therapy

ECT has been used in the treatment of psychiatric disorders since the thirties. A systemic seizure caused by ECT is used to treat mood disorders by causing epileptiform discharges in the cortex [25].

ECT is often recommended for severe MDD patients who are at risk of suicide, but there is little data about the effectiveness of ECT for these patients. A cohort study found that ECT treatment was more effective on severe depression than in mild or moderate depression [26]. The quality of life after ECT use is highly variable and is influenced by factors such as marital status and disability. According to a study, better acute responses to ECT can predict improved long-term quality of life in the future [27]. In another cohort study, these sociodemographic factors were even linked to reduced ECT treatment advice [28].

Importantly, the concern about medical complications such as memory loss and death among both professionals and patients has led to the underuse of ECT. Indeed, fear of death is still a major issue for 20% of the public, even though ECT treatment has been shown to decrease suicide risk and serious medical events in a study including both MDD and BD depressive patients [29]. Regarding memory loss, temporary cognitive impairment may occur, such as altered verbal memory delay [30▪▪,31]. This is associated with increased bilateral volume of the dentate gyrus of the hippocampus. There is some evidence from patients with status epilepticus that edema may contribute to hippocampal volume increase [32]. However, a recent MRI study does not support this claim [33].

Electrical field penetration to a specific part of the brain varies depending on its anatomical characteristics, such as skull thickness and brain volume. In one study, various ECT amplitudes (600, 700, and 800 mA) were used and electrical field measurements were conducted based on MRI data. Results showed that 112.5 V/m in the right hippocampus was the optimal electric field to reduce adverse effects of ECT, including cognitive impairment in older adults with MDD [34▪]. In another study, after 1 year of follow-up, it was found that older adults, patients with psychotic depression and those who received lithium as a preventive treatment for MDD had a lower risk of relapse after ECT treatment [35].

In order to prevent relapse, continuation ECT (cECT) can be performed during the6 months following the first treatment, as well as maintenance ECT (mECT) posterior to this 6-month period. As shown in recent findings in a small cohort, patients receiving mECT are less likely to experience a relapse [36]. It has been shown that this method reduces hospitalization in patients with BD and may also stabilize their mood [37▪].

Availability of biomarkers enabling treatment response to be predicted is a crucial step in developing new ECT protocols. In a recent study, functional connectivity in default mode networks and central executive networks have been shown to predict ECT treatment response and outcome [38].

Treatment efficacy can always be improved by seeking innovative approaches. The ultra-brief right unilateral ECT is a new advance with greater focal stimulation. It produces reduced pulse width with fewer cognitive side effects. This method has also been found to be safe and effective in older adults with BD [39▪▪].

INVASIVE APPROACHES

Deep brain stimulation

Since the mid-1990s, deep brain stimulation (DBS) has been used to treat people with psychiatric diseases, using electrodes placed in selected parts of the brain such as the subcallosal cingulate cortex (SCC) in depression [40]. Two approaches co-exist in DBS therapy: open loop (constant, fixed stimulation to a brain region) and closed loop (which triggers the stimulation based on the patient's brain activity only when pathological activity occurs).

In a pilot study with one patient, right ventral capsule/ventral striatum were stimulated with closed loop DBS. Gamma power in the amygdala reflected depression severity in this case; therefore VC/VS was stimulated when a set neurophysiological criterion (gamma power from the amygdala) was reached. This pioneer study suggests that individual electrophysiological characteristics of MDD may serve as biomarkers driving personalized treatment (Fig. 1d) [41]. More studies are needed to

investigate if this specific protocol can be generalized or must be adapted in an individual fashion. In another DBS study with eight patients, SCC stimulation was found to lead to marked reduction in depression symptoms as well as a decrease in the beta power of the SCC, suggesting the latter as a marker for treatment optimization (Fig. 1d) [42▪▪]. For DBS to be successful, it is crucial to choose the correct part of the brain to implant electrodes, the ideal localization according to the situation is still to be identified.

Vagus nerve stimulation

Vagus nerve stimulation (VNS) is invasive and expensive and thus remains uncommon in clinical settings, although it was FDA-approved for depression in 2005. An implanted pulse generator is used in VNS neurostimulation devices, and a lead wire is connected to an electrode cuff encircling the left vagus nerve cervical bundle to induce stimulation [43]. Alternatively, transcutaneous VNS (t-VNS) is a new method to stimulate the vagus nerve noninvasively. Although some studies recommend this device for MDD, there is little information about its side effects and efficacy in patients. In a recent study, t-VNS has been shown to have both good tolerability and usability, and potential antidepressant effects in the short term, but long-term studies are required to confirm this conclusion [44].

The mechanism behind these effects remains to be elucidated. The brain's emotional and reward networks can be affected directly or indirectly by VNS. Furthermore, HPA axis activation by VNS can also provide some anti-inflammatory effects (Fig. 1e) [45].

CONCLUSION

In summary, neurostimulation methods are promising therapeutic avenues for mood disorders, completing pharmacological and psychological options. The recent studies cited here explore new possibilities to improve treatment efficacy and tolerability. They also suggest some neural mechanisms behind stimulation effects. It is important to investigate novel brain stimulation methods applicable to mood disorders to propose new alternatives that might treat these conditions more effectively, especially for comorbid syndromes. In the future, we hope that a more diverse array of physical modalities and protocols for neurostimulation as well as systematic testing in specific patient populations will enable a more differentiated and personalized psychiatry to be established. This effort may provide solutions for populations that are currently resistant to available treatments. Strengthening exchanges between basic, preclinical and clinical research could enhance the development of these new tools and improve understanding of their neurobiology.

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Conflicts of interest

There are no conflicts of interest

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Valiengo L, Maia A, Cotovio G, *et al.* Repetitive transcranial magnetic stimulation for major depressive disorder in older adults: systematic review and meta-analysis. J Gerontol Ser A 2022; 77:851–860.
2. Milev RV, Giacobbe P, Kennedy SH, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can J Psychiatry 2016; 61:561–575.
3. Lee CW, Wu HF, Chu MC, *et al.* Mechanism of intermittent theta-burst stimulation in synaptic pathology in the prefrontal cortex in an antidepressant-resistant depression rat model. Cereb Cortex 2021; 31:575–590.
4. ▪▪ Bulteau S, Laurin A, Pere M, *et al.* Intermittent theta burst stimulation (iTBS) versus 10 Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) to alleviate treatment-resistant unipolar depression: a randomized controlled trial (THETA-DEP). Brain Stimul 2022; 15:870–880.

The purpose of this article was to compare the efficacy of two TMS protocols used in treatment resistant depression, including a 10 Hz rTMS protocol and a shorter duration protocol (iTBS) at 1, 3 and 6 months following successful treatment. They both appear to be effective.

5. Carpenter LL, Aaronson ST, Hutton TM, *et al.* Comparison of clinical outcomes with two transcranial magnetic stimulation treatment protocols for major depressive disorder. Brain Stimul 2021; 14:173–180.
6. Philip NS, Doherty RA, Faucher C, *et al.* Transcranial magnetic stimulation for posttraumatic stress disorder and major depression: comparing commonly used clinical protocols. J Trauma Stress 2022; 35:101–108.
7. ▪▪ Corlier J, Tadayonnejad R, Wilson AC, *et al.* Repetitive transcranial magnetic stimulation treatment of major depressive disorder and comorbid chronic pain: response rates and neurophysiologic biomarkers. Psychol Med 2021; 1–10.

A significant objective of this paper was to evaluate the effect of rTMS therapy on MDD comorbid with chronic pain, as well as differences between genders and some potential biomarkers for success in treating MDD in relatively large groups. It also proposesfuture studies using rTMS in MDD.

8. Dubin MJ, Mao X, Banerjee S, *et al.* Elevated prefrontal cortex GABA in patients with major depressive disorder after TMS treatment measured with proton magnetic resonance spectroscopy. J Psychiatry Neurosci 2016; 41: E37–E45.
9. McGirr A, Vila-Rodriguez F, Cole J, *et al.* Efficacy of active vs sham intermittent theta burst transcranial magnetic stimulation for patients with bipolar depression: a randomized clinical trial. JAMA Netw Open 2021; 4:e210963–e1210963.
10. Diederichs C, DeMayo MM, Cole J, *et al.* Intermittent theta-burst stimulation transcranial magnetic stimulation increases GABA in the medial prefrontal cortex: a preliminary sham-controlled magnetic resonance spectroscopy study in acute bipolar depression. Front Psychiatry 2021; 12:665402.
11. Chen M, Yang X, Liu C, *et al.* Comparative efficacy and cognitive function of magnetic seizure therapy vs. electroconvulsive therapy for major depressive disorder: a systematic review and meta-analysis. Transl Psychiatry 2021; 11:437.
12. ▪ Ge R, Gregory E, Wang J, *et al.* Magnetic seizure therapy is associated with functional and structural brain changes in MDD: therapeutic versus side effect correlates. J Affect Disord 2021; 286:40–48.

The purpose of this article was to examine whether MST had any effect on neural correlates after MDD treatment in 10 participants. The major focus of this research was the sgACC, focal gray matter volume and the hippocampal area.

13. Hill AT, Zomorrodi R, Hadas I, *et al.* Resting-state electroencephalographic functional network alterations in major depressive disorder following magnetic seizure therapy. Prog Neuropsychopharmacol Biol Psychiatry 2021; 108:110082.

14. Fernández-Palleiro P, Rivera-Baltanás T, Rodrigues-Amorim D, *et al.* Brain-waves oscillations as a potential biomarker for major depression disorder risk. Clin EEG Neurosci 2020; 51:3–9.

15. Yamada Y, Sumiyoshi T. Neurobiological mechanisms of transcranial direct current stimulation for psychiatric disorders; neurophysiological, chemical, and anatomical considerations. Front Hum Neurosci 2021; 15:631838.

16. Bennabi D, Haffen E. Transcranial direct current stimulation (tDCS): a promising treatment for major depressive disorder? Brain Sci 2018; 8:1–10.

17. Cappon D, den Boer T, Jordan C, *et al.* Safety and feasibility of tele-supervised home-based transcranial direct current stimulation for major depressive disorder. Front Aging Neurosci 2021; 13:765370.

18. Jog MS, Kim E, Anderson C, *et al.* In-vivo imaging of targeting and modulation of depression-relevant circuitry by transcranial direct current stimulation: a randomized clinical trial. Transl Psychiatry 2021; 11:138.

19. Menke A. Is the HPA axis as target for depression outdated, or is there a new hope? Front Psychiatry 2019; 10:101.

20. ■■ Gouveia FV, Germann J, Oliveira CC, *et al.* Transcranial direct current stimulation reduces anxiety, depression and plasmatic corticosterone in a rat model of atypical generalized epilepsy. Neuroscience 2022; 480:32–41.

This article was a preclinical study investigating the effects of tDCS on depression and anxiety in rat models of epilepsy. This research suggests that corticosterone may contribute to the effects of tDCS.

21. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol Psychiatry 2013; 74:15–25.

22. Goerigk S, Cretaz E, Sampaio-Junior B, *et al.* Effects of tDCS on neuroplasticity and inflammatory biomarkers in bipolar depression: Results from a sham-controlled study. Prog Neuropsychopharmacol Biol Psychiatry 2021; 105:110119.

23. Wang H, Wang K, Xue Q, *et al.* Transcranial alternating current stimulation for treating depression: a randomized controlled trial. Brain 2022; 145:83–91.

24. Riddle J, Alexander ML, Schiller CE, *et al.* Reduction in left frontal alpha oscillations by transcranial alternating current stimulation in major depressive disorder is context dependent in a randomized clinical trial. Biol Psychiatry Cogn Neurosci Neuroimaging 2022; 7:302–311.

25. Li X-K, Qiu H-T. Current progress in neuroimaging research for the treatment of major depression with electroconvulsive therapy. World J Psychiatry 2022; 12:128–139.

26. Rönnqvist I, Nilsson FK, Nordenskjöld A. Electroconvulsive therapy and the risk of suicide in hospitalized patients with major depressive disorder. JAMA Netw Open 2021; 4:e2116589–e12116589.

27. Lex H, Nevers SW, Jensen EL, *et al.* Long-term quality of life in treatment-resistant depression after electroconvulsive therapy. J Affect Disord 2021; 291:135–139.

28. Kaster TS, Blumberger DM, Gomes T, *et al.* Patient-level characteristics and inequitable access to inpatient electroconvulsive therapy for depression: a population-based cross-sectional study. Can J Psychiatry 2021; 66:147–158.

29. Kaster TS, Vigod SN, Gomes T, *et al.* Risk of serious medical events in patients with depression treated with electroconvulsive therapy: a propensity score-matched, retrospective cohort study. Lancet Psychiatry 2021; 8:686–695.

30. ■■ Gbyl K, Støttrup MM, Mitta Raghava J, *et al.* Hippocampal volume and memory impairment after electroconvulsive therapy in patients with depression. Acta Psychiatr Scand 2021; 143:238–252.

The purpose of this article was to explore the relationship between hippocampal subregion volume and cognitive performance after ECT treatment. This study provides a deeper understanding of the mechanisms behind the side effects of ECT.

31. Gbyl K, Rostrup E, Raghava JM, *et al.* Volume of hippocampal subregions and clinical improvement following electroconvulsive therapy in patients with depression. Prog Neuropsychopharmacol Biol Psychiatry 2021; 104: 110048.

32. Lee DJ, Amini M, Hamamura MJ, *et al.* Aquaporin-4-dependent edema clearance following status epilepticus. Epilepsy Res 2012; 98:264–268.

33. Gyger L, Ramponi C, Mall JF, *et al.* Temporal trajectory of brain tissue property changes induced by electroconvulsive therapy. Neuroimage 2021; 232: 117895.

34. ■ Deng Z De, Argyelan M, Miller J, *et al.* Electroconvulsive therapy, electric field, neuroplasticity, and clinical outcomes. Mol Psychiatry 2021; 27: 1676–1682.

The purpose of this article was to identify the optimal ECT field by using MRI data collected on the hippocampus that result in neuroplasticity and reduced cognitive side effects.

35. Jelovac A, Kolshus E, McLoughlin DM. Relapse following bitemporal and high-dose right unilateral electroconvulsive therapy for major depression. Acta Psychiatr Scand 2021; 144:218–229.

36. Ahmadi N, Moss L, Hauser P, *et al.* Clinical outcome of maintenance electroconvulsive therapy in comorbid posttraumatic stress disorder and major depressive disorder. J Psychiatr Res 2018; 105:132–136.

37. ■ Madero S, Anmella G, Sagué-Vilavella M, *et al.* Evaluating maintenance electroconvulsive therapy in bipolar disorders: 3-year mirror-image study. J Affect Disord 2022; 298:58–64.

Througha 3-year retrospective study, this article discusses the importance of maintaining treatment after the initial ECT treatment for BD. The results show that the use of mECT reduced the number of hospitalizations in BD, and to conclude this article recommends that guidelines for the clinicaluse of mECT should be developed.

38. Pang Y, Wei Q, Zhao S, *et al.* Enhanced default mode network functional connectivity links with electroconvulsive therapy response in major depressive disorder. J Affect Disord 2022; 306:47–54.

39. ■■ Parker Schwab P, Dhingra A, Chapman H, *et al.* Ultra-brief right unilateral electroconvulsive therapy for the treatment of late-life bipolar disorder. J Affect Disord 2021; 290:197–201.

The article examined 55 patients who receivedultra-brief right unilateral ECT to determine its efficacy and safety. According to the study, this method is effective and safe for treating BD. This research recommends that future studies should focus on using this method as a maintenance treatment.

40. Döbrössy MD, Ramanathan C, Ashouri Vajari D, *et al.* Neuromodulation in psychiatric disorders: experimental and clinical evidence for reward and motivation network deep brain stimulation: focus on the medial forebrain bundle. Eur J Neurosci 2021; 53:89–113.

41. Scangos KW, Khambhati AN, Daly PM, *et al.* Closed-loop neuromodulation in an individual with treatment-resistant depression. Nat Med 2021; 27: 1696–1700.

42. ■■ Sendi MSE, Waters AC, Tiruvadi V, *et al.* Intraoperative neural signals predict rapid antidepressant effects of deep brain stimulation. Transl Psychiatry 2021; 11:551.

In this article, electrophysiological data were recorded intraoperatively toinvestigate the early antidepressant effect and understand better the mechanism of DBS.

43. Austelle CW, O'Leary GH, Thompson S, *et al.* A comprehensive review of vagus nerve stimulation for depression. Neuromodulation 2022; 25:309–315.

44. Evensen K, Jørgensen MB, Sabers A, Martiny K. Transcutaneous vagal nerve stimulation in treatment-resistant depression: a feasibility study. Neuromodulation 2022; 25:443–449.

45. Liu CH, Yang MH, Zhang GZ, *et al.* Neural networks and the anti-inflammatory effect of transcutaneous auricular vagus nerve stimulation in depression. J Neuroinflammation 2020; 17:54.