Psychotherapy and Psychosomatics

Editorial

Psychother Psychosom
DOI: 10.1159/000542163

Received: July 21, 2024
Accepted: October 17, 2024
Published online: November 14, 2024

Neuromodulations in Psychiatric Disorders: Emerging Lines of Definition

Xiaolei Liu[a, b, c] Hongxing Wang[a, b, d]

[a]Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China; [b]Beijing Psychosomatic Disease Consultation Center, National Center for Neurological Disorders, National Clinical Research Center for Geriatric Diseases, Beijing, China; [c]Department of Neurology, The First Affiliated Hospital of Kunming Medical University, Kunming, China; [d]Beijing Institute for Brain Disorders, Capital Medical University, Beijing, China

Keywords
Classification · Clinimetrics · Neuromodulation · Psychiatric disorders · Staging

Introduction

Psychiatric disorders are characterized by complex and ever-changing clinical features, and from a pathological perspective, they involve multiple abnormal neurotransmitters [1], brain regions, and neural circuits [2–5]. Therapeutic progress has long been challenged by the diagnostic and aetiological heterogeneity of psychiatric disorders [6]. Psychotherapies and pharmacotherapies used alone or in combination have been shown to exert clinical benefits compared with placebo or treatment-as-usual. However, the effectiveness of these treatments remains unsatisfactory [7]. Neuromodulation, such as electrical, magnetic, optical, acoustic, and thermal modalities [8], offers alternatives to pharmacological treatment and psychotherapy and has attracted an increasing amount of attention from peers for the management of psychiatric disorders (Table 1).

Although this burgeoning neuromodulation strategy has developed rapidly in recent years and aims to inhibit, activate, modify, and/or regulate central and peripheral nervous system activities in order to care for patients with many challenging psychiatric conditions [23], the existing classification of neuromodulation fails to clearly address "which, when, and how to choose" a neuromodulation therapy for a specific psychiatric disorder. For instance, electrical stimulation has been applied to treat different psychiatric disorders in clinical settings, such as electroconvulsive therapy (ECT) for schizophrenia [9], deep brain stimulation (DBS) for obsessive-compulsive disorder [24], spinal cord stimulation for chronic pain [25], and transcranial alternating current stimulation (tACS) for chronic insomnia [26] and depressive disorder [13]. Here, we can clearly see that different psychiatric disorders may require corresponding electrical stimulation with varying energy-delivering intensities. Therefore, it is plausible to consider energy as a crucial factor in understanding neuromodulation, at least for electrical stimulation, in various psychiatric disorders.

The use of ECT, DBS, and tACS for treating depressive disorders has been studied. Therefore, in this article, we use electrical stimulation for major depressive disorder (MDD) as an example to illustrate how those neuromodulation techniques can be categorized by the amount of energy, thus facilitating a deeper understanding of the neuromodulation techniques, the disease itself, and the relationships between them. Based on this novel classification, we propose potential strategies, for applying diverse

karger@karger.com
www.karger.com/pps

Correspondence to:
Hongxing Wang, wanghongxing@xwh.ccmu.edu.cn

Table 1. Advantages and disadvantages of the widely applied neuromodulation approaches

Techniques	Advantages	Disadvantages
Electrical		
ECT [9]	A classic brain stimulation method	Side effects, such as fractures, seizures, cognitive deficits
MECT [10]	Nonsurgical stimulation, reducing anticipatory anxiety, and therapeutically more acceptable to patients and families	Cognition disturbance, requires preoperative anesthesia
ECS [11]	Electrodes placed extradurally over the target brain area, currently used to treat refractory depression, pain, movement disorders, and post-stroke rehabilitation	Requires surgery
DBS [11]	Electrodes implanted into specific brain locations provide adjustable stimulation to treat neurological and mental illnesses related to circuit dysfunction, highly focused intervention with typical mm-scale anatomical targets	Requires surgery
TI [12]	Spatial targeting and non-invasive	Intricate operation targeting precise localization
tDCS [13, 14]	Non-invasive brain stimulation methods widely utilized	Low spatial resolution, activation spreads over ≥1 cm, skin lesions similar to burns, mania or hypomania in patients with depression, potential seizure attack in pediatric patients
tACS [13]	Low cost, non-invasive, portability, and potential in-home applications, fueling a proliferation of human trials	Potentially activate excitable peripheral elements between the scalp electrodes
taVNS [15]	Non-invasive neuromodulation therapy modulates brain physiology by electrically stimulating the auricular branch of the vagus nerve. It is currently used to treat depression, as well as other conditions such as epilepsy and stroke	Side effects, including primarily localized reactions (redness, erythema, pain, and irritation), and systemic side effects (dizziness, headaches, and fatigue, among others)
Magnetic		
TMS [16]	Commonly employed non-invasive technique in clinical settings	Activate a relatively limited scope of the brain region, required precision localization
MST [17]	Can induce seizures like ECT with 100 Hz magnetic stimulation	Efficacy needs further confirmation, requires anesthesia
Optical		
tNIRS [18]	Non-invasive, safe, simple to operate, etc.	Excessive photothermal effects may lead to damage to cells and tissues
ILT [19]	Non-invasive stimulation with the potential to treat a wide range of brain conditions	Risk of macular lesions
MIRS [20]	Featuring non-thermal, reversible, and long-range propagation	Not clear
Optogenetic proteins [20]	Highest spatial resolution elucidates brain function through cellular and animal models	Requires genetic modification
Acoustic		
LIPUS [11, 21]	Millimeter-scale spatial resolution, non-invasive and no tissue-damaging heat generation	The effect of relevant parameters is unclear, with significant individual variability
LIFUS [22]	Delivering highly focused ultrasound to specific brain regions with millimeter-level precision, resulting in localized thermal effects	Costly, intricate operation

DBS, deep brain stimulation; ECS, epidural cortical stimulation; ECT, electroconvulsive therapy; ILT, intranasal light therapy; LIFUS, low-intensity focused ultrasound stimulation; LIPUS, low-intensity pulsed ultrasound; MECT, modified electroconvulsive therapy; MIRS, mid-infrared spectroscopy; MST, magnetic seizure therapy; tACS, transcranial alternating current stimulation; taVNS, transcutaneous auricular vagus nerve stimulation; tDCS, transcranial direct current stimulation; TI, temporal interference; TMS, transcranial magnetic stimulation; tNIRS, transcranial near-infrared spectroscopy.

available approaches (i.e., sequential or simultaneous treatment combinations), including various neuromodulations, drugs, and psychotherapies, to address a range of psychiatric disorders in clinical settings.

An Innovative Classification of Neuromodulation

A simple classification of neuromodulation was based on the mediational substance [8] but overlooked to some extent the intrinsic nature of neuromodulation, which encompasses electrical, magnetic, optical, acoustic, and thermal modalities of delivering energy to specific brain areas to achieve the goal of modulating brain function. In addition, this classification neglects various stimulation factors, such as site, frequency, and duration, which strongly affect efficacy across different psychiatric disorders. The mechanism of neuromodulation involves restoring abnormal network activity [4], enhancing neuroplasticity [27], entraining oscillatory activity [28], and disrupting ongoing physiological or pathological oscillations [29] by delivering energy to the brain with personal, spatial and temporal specificity [4]. Essentially, electrical, magnetic, optical, acoustic, and thermal modalities, regardless of the parameters of their stimuli, ultimately act in an energetic manner on the individual's target area. Thus, energy is paramount in the above-mentioned neuromodulations utilized to treat psychiatric disorders. Herein, we propose a further categorization based on the magnitude of energy within the present framework.

A typical example is the application of ECT and modified ECT (MECT) with currents ranging from 800 to 900 mA [30], tACS at 15 mA [13], and tACS at <4 mA [31]. Variations in the intensity of currents among these techniques lead to different clinical effects [32]. ECT and MECT are used as interventions for various refractory psychiatric disorders, producing definite therapeutic effects, albeit with inevitable adverse reactions [9], whereas tACS with a current of 15 mA effectively treats first-episode drug-naïve depressive disorder [13] and chronic primary insomnia [26]. However, tACS at <4 mA has inconsistent clinical outcomes in terms of managing insomnia and depressive disorders [31]. This finding underscores the significance of current intensity as the most crucial parameter closely linked to clinical outcomes. A recent study revealed that extracranial alternating current intensities positively induce intracranial local field potentials (LFPs) [32]. Additionally, findings from rodents (rats) and studies of human cadavers demonstrated that the intracranial electric fields were linearly related to the intensity of the extracranial current and were independent of the electrical stimulation frequency [33]. Therefore, the current intensity directly affects the energy delivered by the electrical stimulation, and higher extracranial alternating currents result in a higher amount of energy being delivered to the brain.

We conducted stereoelectroencephalography recordings to measure LFPs of deep brain tissue while applying different extracranial current intensities of tACS via intracranial electrodes surgically implanted into the brain tissue of patients with drug-resistant epilepsy [32]. Our findings revealed that at low alternating current intensities, there were no statistical differences in LFPs compared with 0 mA, whereas at currents greater than 7 mA, significant differences in LFPs were simultaneously detected in the hippocampus, insula, and amygdala, with increasing alternating current intensities. These results support the classification of non-invasive neuromodulation techniques on the basis of energy levels, particularly for electrical and magnetic stimulation. In light of our findings, we recommend a classification method that considers different media bearing neuromodulatory stimuli, the distinction between invasive and non-invasive approaches, as well as the magnitude of energy delivered, namely, super-high-, high-, and low-intensity techniques (Fig. 1).

Super-High-Intensity Technique (Current >100 mA)

Typically, ECT and MECT [30] utilize currents exceeding 700 mA to induce generalized seizure, by applying stimulation at the whole-brain level, with the aim of rapidly controlling acute psychiatric symptoms. A randomized controlled trial that examined different current intensities of ECT for treating MDD reported that higher amplitudes (700 mA and 800 mA) were more effective for controlling depressive symptoms, whereas a lower amplitude (600 mA) was better for improved cognitive function [30]. Previous research indicates that super-high-intensity currents can penetrate deep brain tissues via the cortex, resulting in a linear relationship between electric fields and hippocampal neuroplasticity, with the latter mediating the interaction between electric fields and the therapeutic effects of antidepressants [34]. Super-high-intensity currents can also modulate functional connectivity within the brain, such as the connectivity between the limbic system and the prefrontal cortex [35], and the functional connectivity of the hippocampus [36]. Additionally, super-high-intensity currents induce neuroplastic changes in synapses (synaptogenesis), neurons

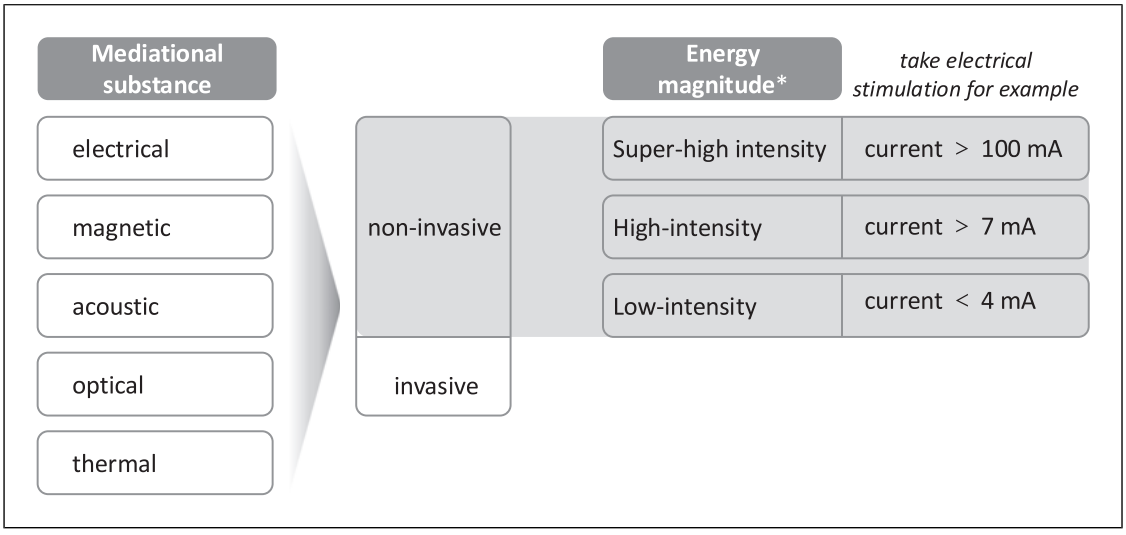

Fig. 1. The recommended classification of neuromodulations based on the energy delivered. *Electrical, magnetic, acoustic, optical, and thermal stimulation can be classified according to varying energy intensities.

(neurogenesis), dendrites (dendritogenesis), the vascular system (angiogenesis), and glial cells and their processes (gliogenesis) [37]. Furthermore, these currents regulate neurotransmitters, including monoaminergic neurotransmitters [38], serotonin [39], and glutamate [40]. ECT has already been recommended for use in severe major depression and other psychiatric disorders, such as bipolar disorder, treatment-resistant schizophrenia, schizoaffective disorder, and neuroleptic malignant syndrome [41]. In summary, ECT is the first choice for severe psychiatric disorders in acute and critical conditions (online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000542163).

High-Intensity Technique (Current >7 mA)

Without inducing a generalized seizure, high-intensity tACS at 15 mA [32] can directly stimulate multiple nuclei, widespread brain regions, and brain networks simultaneously [42], thus generating a synergistic effect across the whole brain. This approach holds potential for a wide range of applications, including the treatment of MDD, treatment-resistant depression (TRD), and chronic insomnia [13, 26, 43, 44]. The brain-wide activation induced by high-intensity tACS could effectively reach deep brain structures, offering a viable approach to modulating or addressing neuropsychiatric disorders linked to the hippocampus, insula, and amygdala [32, 42]. This may explain why high-intensity tACS can rapidly control various symptoms. However, further clinical research is needed to confirm this hypothesis. Therefore, we suggest that high-intensity tACS has the potential to become a primary treatment for psychiatric disorders (online suppl. Fig. S1).

Low-Intensity Technique (Current <4 mA)

Transcranial direct current stimulation (tDCS) [45] and low-intensity tACS [13], with currents below 4 mA, generate approximately 0.5 V/m electric fields in localized brain regions, thereby stimulating the cortex but not directly reaching deep nuclei or only exerting indirect effects on them [46]. tDCS targets the left dorsolateral prefrontal cortex to reduce depression [47]. Low-intensity energy technology has inherent features such as limited energy, claimed linear conduction, a single stimulation target, and localized effects [48]. The operational process is relatively complicated because of the need for precise localization for the stimulation target area. Furthermore, tACS appears to be advantageous because it involves less sensory experience [49] and has fewer known adverse effects [26], leading to an increase in the field of transcranial electrical stimulation.

Transcranial magnetic stimulation (TMS) involves the conversion of electrical energy into a magnetic field, the magnitude of which is proportional to the intensity of the given electrical current, that can pass through the skull without energy loss and precisely stimulate specific areas of the brain cortex associated with conditions such as MDD [50], addiction [51], and obsessive-compulsive disorder [52]. Therefore, we recommend the use of low-intensity TMS to effectively target focal areas of the brain cortex, as this technique exerts therapeutic effects

and offers precision treatment for specific residual symptoms and/or single symptoms (online suppl. Fig. S1). Super-high-intensity TMS, such as magnetic seizure therapy (MST), is used in investigational studies but has not yet gained mature experience [53]. Because of its ability to trigger the seizure process, MST is expected to treat the same refractory mental disorders as ECT [54] but with fewer cognitive side effects than ECT [54]. Therefore, we hypothesized that MST might rival the efficacy of ECT (online suppl. Fig. S1).

The techniques mentioned above have also been shown to have high levels of safety and efficacy among young children and adolescents [55–61]. ECT is applicable for children aged 6–18 years [56], whereas tDCS has been demonstrated to be safe in the same age group within a current range of 0.25 mA–2 mA [57, 60, 61]. The safety of DBS has been established for children aged 7 years and above [58], and TMS has been explored in populations ranging from 3-year-old children to adults up to 84 years of age [59]. Additionally, tACS has been safely used with currents of 1–2 mA in children aged 5–12 years with language disorders [55]. However, these investigations involved relatively small sample sizes, and further research is needed to better define safe parameter ranges for these special populations.

Non-invasive neuromodulation techniques such as electricity, magnetism, sound, light, and heat, in a sense, function by transferring energy to targeted organs, neural tissues, or cells to achieve neuromodulation and functional intervention, allowing these methods can be categorized according to their energy levels. Importantly, the factors affecting the intensity of light and sound differ from those affecting electrical stimulation. For example, in the case of light, energy transfer is governed by the equation $E = h\upsilon = hc/\lambda$ (E, light energy; h, Planck's constant; υ, the frequency of light; c, the speed of light; λ, the wavelength of light). The frequency of light is directly proportional to its energy, meaning that higher-frequency waves carry more energy than lower-frequency waves do [62]. Among visible light, violet has the highest energy, while red has the lowest. As for acoustic energy, its magnitude is related to the intensity of the stimulus and the amplitude of the sound wave [63].

Exploring Potential Approaches of Neuromodulation for Psychiatric Disorders

Psychiatric disorders exhibit a wide range of inter-individual variability in prodromal symptoms, such as unipolar depression, bipolar disorder, and anxiety disorder; furthermore, these disorders encompass diverse types, sequences, and durations of symptoms, thus demonstrating significant heterogeneity [64]. There is also strong intra-individual consistency in the recurrence of prodromal symptoms across subsequent episodes, and residual symptomatology is commonly observed post-treatment [64, 65]. In the longitudinal course, it is also necessary to consider the iatrogenic and psychosocial factors, response to treatment, residual symptomatology, and behavioral toxicity within a comprehensive staging framework [66–68].

Psychiatric disorders are complex, and it is unlikely that a single course of treatment will be sufficient to achieve recovery [69]. Neuromodulation has the potential to serve a dual purpose – priming the brain to maximize homeostatic plasticity during subsequent interventions and then reinforcing those therapeutic effects through consolidation [70]. The sequential model and combined treatments, including neuromodulation, offer opportunities for precision treatment in psychiatric disorders. The sequential model represents an intensive, two-stage approach, which derives from the awareness that a single treatment course may not resolve the intricate disturbances often observed in clinical practice [71]. The rationale of this approach is to use different treatment strategies when they are most likely to make a distinct contribution to patients' well-being and to achieve a more pervasive recovery. In severe or treatment-resistant psychiatric disorders, combined treatment is often required to overcome the limitations of a single therapeutic approach, utilizing various methods such as psychotherapy, pharmacological interventions, and neuromodulation to achieve more effective symptom relief. Clinimetrics [72], as a complement to customary psychiatric taxonomy based on DSM-5 [73], has offered a clinical framework for staging of psychiatric disorders [69, 72, 74]. The best-practice intervention strategies should be administered according to the varying stages of psychiatric disorders characterized by distinct symptoms, dynamic alterations within neurotransmitter systems, or neural circuits.

Potential Sequential Model of Treatments

The sequential model involves the consecutive administration of pre-planned strategies (online suppl. Fig. S2). According to the staging of psychiatric disorders [67], for instance, MDD, in stage 1, characterized by prodromal symptoms, a single utilization of psychotherapy like well-being therapy (WBT) to pursue euthymia may be suitable [3, 75], and high-intensity tACS is another choice for wholly modulating brain activity [32, 42]. In stage 2,

during the acute manifestations of a major depressive episode, high-intensity tACS or antidepressants may relieve patients with moderate to severe symptoms, offering comprehensive and rapid symptom control. In stage 3, when residual symptoms occur, psychotherapy, such as WBT, or low-intensity neuromodulation techniques such as tDCS, low-intensity tACS, and TMS may help alleviate certain residual symptoms and/or particular symptoms by targeting local cortical circuits.

Sequentially integrating psychotherapy after acute-phase pharmacotherapy has been linked to a decreased risk of relapse and recurrence [71], and discontinuing antidepressant medications in MDD patients [69, 76, 77]. Similarly, incorporating the advantages of neuromodulation techniques with varying energy intensities into the sequential treatment model may play a crucial role in alleviating symptoms and reshaping brain function [4, 27–29] at different stages of MDD.

Simultaneously Combined Treatments

There have been clinical explorations of neuromodulation techniques simultaneously combined with other approaches for the treatment of depressive disorders and other psychiatric conditions. Combining ECT with antidepressants, such as imipramine, in TRD patients resulted in improved acute-treatment outcomes compared with ECT alone [78]. In our previous case series study, patients with TRD who received regular antidepressant medication but still exhibited residual symptoms presented significantly reduced depressive symptoms after receiving high-intensity tACS [44]. Studies have explored the combination of tDCS with medication or cognitive-behavioral therapy (CBT) to enhance the antidepressant effect during depressive episodes [79, 80]. A study on individuals with antidepressant-free, moderate to severe, nonpsychotic, unipolar MDD indicated that the synergistic effect of tDCS combined with sertraline was stronger than the effect of tDCS or sertraline alone and was stronger than the effect of sham stimulation and placebo [79]. Moreover, combining CBT with tDCS may yield greater efficacy than CBT alone for the management of moderate MDD [80].

These aforementioned studies offer insights into the complementary effects of combination therapies, supporting our proposal that for severe depression or cases progressing to TRD, super-high-intensity neuromodulation techniques (including ECT, MECT, and MST), high-intensity tACS, or DBS should be considered in combination with antidepressants. Remission and recovery in MDD are one-way streets marked by structural changes in neural architecture and dynamic alterations in gene expression patterns mediated through epigenetic mechanisms [81]. Due to its ability to non-invasively deliver energy to the entire brain, high-intensity tACS may facilitate whole-brain modulation [32, 42], serving as a foundational approach to addressing psychiatric disorders at different stages. According to a patient-centered approach, the assessment and staging of psychiatric disorders should be performed based on clinimetrics and macroanalysis, thus enabling comprehensive and individualized management throughout their longitudinal course. The exploration of both sequential model and simultaneous combined treatments allows the integration of the strengths of various treatment methods, thereby compensating for their weaknesses to enhance clinical efficacy and minimize side effects.

Conclusions

Our proposed classification of electric stimulation may be also extended to cover other neuromodulations, such as magnetic, optical, acoustic, and thermal techniques. In the domain of the clinical application of neuromodulation across different populations and stages, efforts are necessary to explore the optimal parameters, such as intensities, frequencies, and durations, to effectively and safely control symptoms and achieve a more precise management. Additionally, there is a need to investigate the sequential combination of treatment strategies through well-designed clinical studies. These studies are expected to yield robust evidence to support validated and personalized sequential treatments for psychiatric disorders.

Conflict of Interest Statement

The authors have no financial conflicts of interest to declare.

Funding Sources

This work was supported in part by the National Natural Science Foundation of China (82371490, 82160272), the National Key R&D Program of China (2022YFC2503900, 2022YFC2503901), Beijing Health System Leading Talent Grant (2022-02-10), and the "Dengfeng" Talent Training Program of Beijing Hospitals Authority (2024-05-10).

Author Contributions

Dr. Wang conceived, drafted, and critically revised the manuscript. Dr. Liu contributed to the draft manuscript.

References

1 Szabo ST, Gould TD, Manji HK. Neurotransmitters, receptors, signal transduction, and second messengers in psychiatric disorders. In: The American Psychiatric Publishing textbook of psychopharmacology. 3rd ed. New York, NY, US: American Psychoanalytic Association; 2004; p. 3–52.

2 Price JL, Drevets WC. Neural circuits underlying the pathophysiology of mood disorders. Trends Cogn Sci. 2012;16(1):61–71. https://doi.org/10.1016/j.tics.2011.12.011

3 Fava GA. Well-being therapy: current indications and emerging perspectives. Psychother Psychosom. 2016;85(3):136–45. https://doi.org/10.1159/000444114

4 Widge AS, Miller EK. Targeting cognition and networks through neural oscillations: next-generation clinical brain stimulation. JAMA Psychiatry. 2019;76(7):671–2. https://doi.org/10.1001/jamapsychiatry.2019.0740

5 Won SM, Song E, Reeder JT, Rogers JA. Emerging modalities and implantable technologies for neuromodulation. Cell. 2020;181(1):115–35. https://doi.org/10.1016/j.cell.2020.02.054

6 Scangos KW, State MW, Miller AH, Baker JT, Williams LM. New and emerging approaches to treat psychiatric disorders. Nat Med. 2023;29(2):317–33. https://doi.org/10.1038/s41591-022-02197-0

7 Leichsenring F, Steinert C, Rabung S, Ioannidis JPA. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. World Psychiatr. 2022;21(1):133–45. https://doi.org/10.1002/wps.20941

8 Luan S, Williams I, Nikolic K, Constandinou TG. Neuromodulation: present and emerging methods. Front Neuroeng. 2014;7:27. https://doi.org/10.3389/fneng.2014.00027

9 Espinoza RT, Kellner CH. Electroconvulsive therapy. N Engl J Med. 2022;386(7):667–72. https://doi.org/10.1056/NEJMra2034954

10 Lupke K, Warren N, Teodorczuk A, Steele S, Kolur U, Wand A, et al. A systematic review of modified electroconvulsive therapy (ECT) to treat delirium. Acta Psychiatr Scand. 2023;147(5):403–19. https://doi.org/10.1111/acps.13492

11 Wang H. To emphasize the potential of low-intensity pulsed ultrasound in modulating brain. J Neurosci Ment Health. 2018;18(2):77–9. [Chinese]. https://doi.org/10.3969/j.issn.1009-6574.2018.02.001

12 Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk H-J, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell. 2017;169(6):1029–41. e16. https://doi.org/10.1016/j.cell.2017.05.024

13 Wang H, Wang K, Xue Q, Peng M, Yin L, Gu X, et al. Transcranial alternating current stimulation for treating depression: a randomized controlled trial. Brain. 2022;145(1):83–91. https://doi.org/10.1093/brain/awab252

14 Matsumoto H, Ugawa Y. Adverse events of tDCS and tACS: a review. Clin Neurophysiol Pract. 2017;2:19–25. https://doi.org/10.1016/j.cnp.2016.12.003

15 Gerges ANH, Williams EER, Hillier S, Uy J, Hamilton T, Chamberlain S, et al. Clinical application of transcutaneous auricular vagus nerve stimulation: a scoping review. Disabil Rehabil. 2024;16:1–31. https://doi.org/10.1080/09638288.2024.2313123

16 Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med. 2015;58(4):208–13. https://doi.org/10.1016/j.rehab.2015.05.005

17 Deng ZD, Luber B, McClintock SM, Weiner RD, Husain MM, Lisanby SH. Clinical outcomes of magnetic seizure therapy vs electroconvulsive therapy for major depressive episode: a randomized clinical trial. JAMA Psychiatry. 2024;81(3):240–9. https://doi.org/10.1001/jamapsychiatry.2023.4599

18 Zhao C, Li D, Kong Y, Liu H, Hu Y, Niu H, et al. Transcranial photobiomodulation enhances visual working memory capacity in humans. Sci Adv. 2022;8(48):eabq3211. https://doi.org/10.1126/sciadv.abq3211

19 Salehpour F, Gholipour-Khalili S, Farajdokht F, Kamari F, Walski T, Hamblin MR, et al. Therapeutic potential of intranasal photobiomodulation therapy for neurological and neuropsychiatric disorders: a narrative review. Rev Neurosci. 2020;31(3):269–86. https://doi.org/10.1515/revneuro-2019-0063

20 Fan LZ, Kim DK, Jennings JH, Tian H, Wang PY, Ramakrishnan C, et al. All-optical physiology resolves a synaptic basis for behavioral timescale plasticity. Cell. 2023;186(3):543–59.e19. https://doi.org/10.1016/j.cell.2022.12.035

21 Xu M, Wang L, Wu S, Dong Y, Chen X, Wang S, et al. Review on experimental study and clinical application of low-intensity pulsed ultrasound in inflammation. Quant Imaging Med Surg. 2021;11(1):443–62. https://doi.org/10.21037/qims-20-680

22 Mahoney JJ 3rd, Thompson-Lake DGY, Ranjan M, Marton JL, Carpenter JS, Zheng W, et al. Low-intensity focused ultrasound targeting the bilateral nucleus accumbens as a potential treatment for substance use disorder: a first-in-human report. Biol Psychiatry. 2023;94(11):e41–3. https://doi.org/10.1016/j.biopsych.2023.06.031

23 Krames ES, Peckham PH, Rezai A, Aboelsaad F. What is neuromodulation? Neuromodulation. Elsevier; 2009; p. 3–8.

24 Baldermann JC, Schüller T, Kohl S, Voon V, Li N, Hollunder B, et al. Connectomic deep brain stimulation for obsessive-compulsive disorder. Biol Psychiatry. 2021;90(10):678–88. https://doi.org/10.1016/j.biopsych.2021.07.010

25 Song JJ, Popescu A, Bell RL. Present and potential use of spinal cord stimulation to control chronic pain. Pain physician. 2014;17(3):235–46.

26 Wang HX, Wang L, Zhang WR, Xue Q, Peng M, Sun ZC, et al. Effect of transcranial alternating current stimulation for the treatment of chronic insomnia: a randomized, double-blind, parallel-group, placebo-controlled clinical trial. Psychother Psychosom. 2020;89(1):38–47. https://doi.org/10.1159/000504609

27 Wessel MJ, Beanato E, Popa T, Windel F, Vassiliadis P, Menoud P, et al. Noninvasive theta-burst stimulation of the human striatum enhances striatal activity and motor skill learning. Nat Neurosci. 2023;26(11):2005–16. https://doi.org/10.1038/s41593-023-01457-7

28 Violante IR, Alania K, Cassarà AM, Neufeld E, Acerbo E, Carron R, et al. Non-invasive temporal interference electrical stimulation of the human hippocampus. Nat Neurosci. 2023;26(11):1994–2004. https://doi.org/10.1038/s41593-023-01456-8

29 Vassiliadis P, Beanato E, Popa T, Windel F, Morishita T, Neufeld E, et al. Non-invasive stimulation of the human striatum disrupts reinforcement learning of motor skills. Nat Hum Behav. 2024;8(8):1581–98. https://doi.org/10.1038/s41562-024-01901-z

30 Abbott CC, Quinn D, Miller J, Ye E, Iqbal S, Lloyd M, et al. Electroconvulsive therapy pulse amplitude and clinical outcomes. Am J Geriatr Psychiatry. 2021;29(2):166–78. https://doi.org/10.1016/j.jagp.2020.06.008

31 Shekelle PG, Cook IA, Miake-Lye IM, Booth MS, Beroes JM, Mak S. Benefits and harms of cranial electrical stimulation for chronic painful conditions, depression, anxiety, and insomnia: a systematic review. Ann Intern Med. 2018;168(6):414–21. https://doi.org/10.7326/M17-1970

32 Shan Y, Wang H, Yang Y, Wang J, Zhao W, Huang Y, et al. Evidence of a large current of transcranial alternating current stimulation directly to deep brain regions. Mol Psychiatry. 2023;28(12):5402–10. https://doi.org/10.1038/s41380-023-02150-8

33 Liu A, Vöröslakos M, Kronberg G, Henin S, Krause MR, Huang Y, et al. Immediate neurophysiological effects of transcranial electrical stimulation. Nat Commun. 2018;9(1):5092. https://doi.org/10.1038/s41467-018-07233-7

34 Deng ZD, Argyelan M, Miller J, Quinn DK, Lloyd M, Jones TR, et al. Electroconvulsive therapy, electric field, neuroplasticity, and clinical outcomes. Mol Psychiatry. 2022;27(3):1676–82. https://doi.org/10.1038/s41380-021-01380-y

35 Cano M, Cardoner N, Urretavizcaya M, Martinez-Zalacain I, Goldberg X, Via E, et al. Modulation of limbic and prefrontal connectivity by electroconvulsive therapy in treatment-resistant depression: a preliminary study. Brain Stimul. 2016;9(1):65–71. https://doi.org/10.1016/j.brs.2015.08.016
36 Abbott CC, Jones T, Lemke NT, Gallegos P, McClintock SM, Mayer AR, et al. Hippocampal structural and functional changes associated with electroconvulsive therapy response. Transl Psychiatry. 2014;4(11):e483. https://doi.org/10.1038/tp.2014.124
37 Tartt AN, Mariani M, Hen R, Mann JJ, Boldrini M. Electroconvulsive therapy-a shocking inducer of neuroplasticity? Mol Psychiatry. 2024;29(1):35–7. https://doi.org/10.1038/s41380-023-02015-0
38 Landau AM, Chakravarty MM, Clark CM, Zis AP, Doudet DJ. Electroconvulsive therapy alters dopamine signaling in the striatum of nonhuman primates. Neuropsychopharmacology. 2011;36(2):511–8. https://doi.org/10.1038/npp.2010.182
39 Lanzenberger R, Baldinger P, Hahn A, Ungersboeck J, Mitterhauser M, Winkler D, et al. Global decrease of serotonin-1A receptor binding after electroconvulsive therapy in major depression measured by PET. Mol Psychiatry. 2013;18(1):93–100. https://doi.org/10.1038/mp.2012.93
40 Njau S, Joshi SH, Espinoza R, Leaver AM, Vasavada M, Marquina A, et al. Neurochemical correlates of rapid treatment response to electroconvulsive therapy in patients with major depression. J Psychiatry Neurosci. 2017;42(1):6–16. https://doi.org/10.1503/jpn.150177
41 Weiss A, Hussain S, Ng B, Sarma S, Tiller J, Waite S, et al. Royal Australian and New Zealand College of Psychiatrists professional practice guidelines for the administration of electroconvulsive therapy. Aust N Z J Psychiatry. 2019;53(7):609–23. https://doi.org/10.1177/0004867419839139
42 Wang J, Zhao W, Wang H, Leng H, Xue Q, Peng M, et al. Brain-wide activation involved in 15 mA transcranial alternating current stimulation in patients with first-episode major depressive disorder. Gen Psychiatr. 2024;37(2):e101338. https://doi.org/10.1136/gpsych-2023-101338
43 Wang HX, Wang K, Sun ZC, Peng M, Xue Q, Li N, et al. A pilot study of transcranial alternating current stimulation in the treatment of drug-naive adult patients with major depressive disorder. Zhonghua Yixue Zazhi. 2020;100(3):197–201. [Chinese]. https://doi.org/10.3760/cma.j.issn.0376-2491.2020.03.008
44 Zhao W, Wang H, Leng H, Xue Q, Peng M, Jin X, et al. Acute effect of twice-daily 15 mA transcranial alternating current stimulation on treatment-resistant depression: a case series study. Gen Psychiatr. 2023;36(6):e101278. https://doi.org/10.1136/gpsych-2023-101278
45 Ciullo V, Spalletta G, Caltagirone C, Banaj N, Vecchio D, Piras F, et al. Transcranial direct current stimulation and cognition in neuropsychiatric disorders: systematic review of the evidence and future directions. Neuroscientist. 2021;27(3):285–309. https://doi.org/10.1177/1073858420936167
46 Karabanov AN, Saturnino GB, Thielscher A, Siebner HR. Can transcranial electrical stimulation localize brain function? Front Psychol. 2019;10:213. https://doi.org/10.3389/fpsyg.2019.00213
47 Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med. 2012;42(9):1791–800. https://doi.org/10.1017/S0033291711003059
48 Wang HX. Thinking on the classification of non-invasive brain stimulation as neuromodulation technique. Zhonghua Yixue Zazhi. 2024;104(25):2289–95. [Chinese]. https://doi.org/10.3760/cma.j.cn112137-20240112-00095
49 Antal A, Alekseichuk I, Bikson M, Brockmoller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017;128(9):1774–809. https://doi.org/10.1016/j.clinph.2017.06.001
50 Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. Biol Psychiatry. 2014;76(7):517–26. https://doi.org/10.1016/j.biopsych.2014.01.023
51 Hanlon CA, Dowdle LT, Henderson JS. Modulating neural circuits with transcranial magnetic stimulation: implications for addiction treatment development. Pharmacol Rev. 2018;70(3):661–83. https://doi.org/10.1124/pr.116.013649
52 Carmi L, Alyagon U, Barnea-Ygael N, Zohar J, Dar R, Zangen A. Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients. Brain Stimul. 2018;11(1):158–65. https://doi.org/10.1016/j.brs.2017.09.004
53 McCall WV, George MS, Sackeim HA. Magnetic seizure therapy vs electroconvulsive therapy for major depressive episode. JAMA Psychiatry. 2024;81(7):736–7. https://doi.org/10.1001/jamapsychiatry.2024.0692
54 Cycowicz YM, Rowny SB, Luber B, Lisanby SH. Differences in seizure expression between magnetic seizure therapy and electroconvulsive shock. J ECT. 2018;34(2):95–103. https://doi.org/10.1097/YCT.0000000000000470
55 Andrade AC, Magnavita GM, Allegro JVBN, Neto CEBP, Lucena RCS, Fregni F. Feasibility of transcranial direct current stimulation use in children aged 5 to 12 years. J Child Neurol. 2014;29(10):1360–5. https://doi.org/10.1177/0883073813503710
56 Stein ALS, Sacks SM, Roth JR, Habis M, Saltz SB, Chen C. Anesthetic management during electroconvulsive therapy in children: a systematic review of the available literature. Anesth Analg. 2020;130(1):126–40. https://doi.org/10.1213/ANE.0000000000004337
57 Buchanan DM, Bogdanowicz T, Khanna N, Lockman-Dufour G, Robaey P, D'Angiulli A. Systematic review on the safety and tolerability of transcranial direct current stimulation in children and adolescents. Brain Sci. 2021;11(2):212. https://doi.org/10.3390/brainsci11020212
58 Gelineau-Morel R, Kruer MC, Garris JF, Abu Libdeh A, Barbosa DA, Coffman KA, et al. Deep brain stimulation for pediatric dystonia: a review of the literature and suggested programming algorithm. J Child Neurol. 2022;37(10–11):813–24. https://doi.org/10.1177/08830738221115248
59 Alawi M, Lee PF, Deng ZD, Goh YK, Croarkin PE. Modelling the differential effects of age on transcranial magnetic stimulation induced electric fields. J Neural Eng. 2023;20(2):026016. https://doi.org/10.1088/1741-2552/ac9a76
60 Buchanan DM, Amare S, Gaumond G, D'Angiulli A, Robaey P. Safety and tolerability of tDCS across different ages, sexes, diagnoses, and amperages: a randomized double-blind controlled study. J Clin Med. 2023;12(13):4346. https://doi.org/10.3390/jcm12134346
61 Ryan JL, Beal DS, Fehlings DL, Levac DE, Tendera A, Wright FV. Evaluating transcranial direct current stimulation as an adjunct to inpatient physiotherapy in paediatric acquired brain injury: a randomized feasibility trial. Physiother Can. 2023:e20230015. https://doi.org/10.3138/ptc-2023-0015
62 Zhao W, Zhao Y, Wang Q, Liu T, Sun J, Zhang R. Remote light-responsive nanocarriers for controlled drug delivery: advances and perspectives. Small. 2019;15(45):e1903060. https://doi.org/10.1002/smll.201903060
63 Smallcomb M, Khandare S, Vidt ME, Simon JC. Therapeutic ultrasound and shockwave therapy for tendinopathy: a narrative review. Am J Phys Med Rehabil. 2022;101(8):801–7. https://doi.org/10.1097/PHM.0000000000001894
64 Fava GA. Clinical use of staging in psychiatry. Psychother Psychosom. 2024;93(3):143–50. https://doi.org/10.1159/000538526
65 Fava GA, Kellner R. Prodromal symptoms in affective disorders. Am J Psychiatry. 1991;148(7):823–30. https://doi.org/10.1176/ajp.148.7.823
66 Fava GA, Cosci F, Guidi J, Rafanelli C. The deceptive manifestations of treatment resistance in depression: a new look at the problem. Psychother Psychosom. 2020;89(5):265–73. https://doi.org/10.1159/000507227
67 Schnyder U. Longitudinal development of symptoms and staging in psychiatry and clinical psychology: a tribute to giovanni fava. Psychother Psychosom. 2023;92(1):4–8. https://doi.org/10.1159/000527462

68 Deng ZD, Luber B, McClintock SM, Weiner RD, Husain MM, Lisanby SH. Clinical outcomes of magnetic seizure therapy vs electroconvulsive therapy for major depressive episode: a randomized clinical trial. JAMA Psychiatry. 2024;81(3):240–9. https://doi.org/10.1001/jamapsychiatry.2023.4599
69 Fava GA, Rafanelli C, Tomba E. The clinical process in psychiatry: a clinimetric approach. J Clin Psychiatry. 2012;73(2):177–84. https://doi.org/10.4088/JCP.10r06444
70 Ridding MC, Ziemann U. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol. 2010;588(Pt 13):2291–304. https://doi.org/10.1113/jphysiol.2010.190314
71 Guidi J, Fava GA. Sequential combination of pharmacotherapy and psychotherapy in major depressive disorder: a systematic review and meta-analysis. JAMA Psychiatry. 2021;78(3):261–9. https://doi.org/10.1001/jamapsychiatry.2020.3650
72 Fava GA. Forty years of clinimetrics. Psychother Psychosom. 2022;91(1):1–7. https://doi.org/10.1159/000520251
73 American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: American Psychiatric Association; 2013.
74 Carrozzino D, Patierno C, Guidi J, Berrocal Montiel C, Cao J, Charlson ME, et al. Clinimetric criteria for patient-reported outcome measures. Psychother Psychosom. 2021;90(4):222–32. https://doi.org/10.1159/000516599
75 Guidi J, Fava GA. The clinical science of euthymia: a conceptual map. Psychother Psychosom. 2022;91(3):156–67. https://doi.org/10.1159/000524279
76 Fava GA, Tomba E. New modalities of assessment and treatment planning in depression: the sequential approach. CNS Drugs. 2010;24(6):453–65. https://doi.org/10.2165/11531580-000000000-00000
77 Fava GA. Are the same medications that are used in the acute treatment of depression the most suitable for preventing relapse? J Clin Psychopharmacol. 2021;41(6):617–9. https://doi.org/10.1097/JCP.0000000000001468
78 Sackeim HA, Dillingham EM, Prudic J, Cooper T, McCall WV, Rosenquist P, et al. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. Arch Gen Psychiatry. 2009;66(7):729–37. https://doi.org/10.1001/archgenpsychiatry.2009.75
79 Brunoni AR, Valiengo L, Baccaro A, Zanão TA, de Oliveira JF, Goulart A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiatry. 2013;70(4):383–91. https://doi.org/10.1001/2013.jamapsychiatry.32
80 Bajbouj M, Aust S, Spies J, Herrera-Melendez AL, Mayer SV, Peters M, et al. PsychotherapyPlus: augmentation of cognitive behavioral therapy (CBT) with prefrontal transcranial direct current stimulation (tDCS) in major depressive disorder-study design and methodology of a multicenter double-blind randomized placebo-controlled trial. Eur Arch Psychiatry Clin Neurosci. 2018;268(8):797–808. https://doi.org/10.1007/s00406-017-0859-x
81 Fava GA. Discontinuing antidepressant medications. Oxford University Press; 2021.