Content available at: https://www.ipinnovative.com/open-access-journals

IP Indian Journal of Neurosciences

Journal homepage: https://ijnonline.org/

Review Article

A narrative review on neuromodulation for psychiatric disorders: Mechanisms, clinical applications, and future directions

Shivam Dubey[1]*

[1]RDVV, Jabalpur, Madhya Pradesh, India

Abstract

Neuromodulation has become a revolutionary treatment modality in psychiatry, delivering circuit-specific interventions to treat refractory conditions like major depressive disorder (MDD), obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and schizophrenia. Both non-invasive methods—repetitive transcranial magnetic stimulation (rTMS), theta-burst stimulation (TBS), transcranial direct current stimulation (tDCS), and transcutaneous vagus nerve stimulation (taVNS)—and invasive methods—vagus nerve stimulation (VNS) and deep brain stimulation (DBS)—have shown remarkable clinical effectiveness, with underlying mechanisms including modulation of cortical excitability, neurotransmitter networks, and neural connectome. Recent developments in personalized targeting, closed-loop technologies, and biomarker-guided stimulation are improving therapeutic responses and ushering in the age of precision psychiatry. This review integrates current evidence on mechanisms, effectiveness, safety, and translational potential of neuromodulation across psychiatric illnesses.

Keywords: Neuromodulation, rTMS, DBS, VNS, Depression, Obsessive-compulsive disorder, Precision psychiatry.

Received: 09-09-2025; **Accepted:** 14-10-2025; **Available Online**: 28-10-2025

1. Introduction

Psychiatric illness accounts for a significant global disease burden, depression, anxiety, OCD, PTSD, and schizophrenia accounting for meaningful morbidity and disability. Mainstream treatment, pharmacotherapy and psychotherapy, fails in treatment-resistant scenarios, thus creating a pressing need for new, mechanism-specific treatment modalities.[1,2] Neuromodulation, selective modulation of neural networks via electrical, magnetic, or other stimuli, has been identified as a promising approach, which holds potential to restore impaired dysregulated networks and induce favourable neuroplasticity.[3,4] Historically, invasive neuromodulation started from electroconvulsive therapy (ECT) and followed to vagus nerve stimulation (VNS) and deep brain stimulation (DBS), targeting subcortical networks that are involved in mood and anxiety regulation. The timeline based on historical sources in tabular form is presented as **Table 1** which traces the earliest uses of neuromodulation in psychiatric disorders, from convulsive therapies through early neurosurgery up to the modern era. Development in parallel of non-invasive approaches, namely, repetitive transcranial magnetic stimulation (rTMS), theta-burst stimulation (TBS), and transcranial direct current stimulation (tDCS), has enhanced treatment accessibility and reduced procedure-specific risks.[5-10]

*Corresponding author: Shivam Dubey
Email: shivamdubey20@gmail.com

https://doi.org/10.18231/j.ijn.74989.1761633345

Table 1: Timeline tracing the earliest uses of neuromodulation in psychiatric disorders

Year	Innovation / Regulatory Milestone	Description / Significance
~1934–1938	Chemo-convulsive therapy; First ECT in humans (Meduna; Cerletti & Bini)	Use of chemically induced seizures (~1934), then Electroconvulsive Therapy (ECT) in 1938 for severe psychosis / schizophrenia.
1947	Stereotactic neurosurgical lesioning (Spiegel & Wycis)	Early psychiatric surgery; precise lesioning of deep brain structures for refractory psychiatric symptoms.
1950s-1960s	Anterior cingulotomy / psychosurgery	Ablative surgery (cingulate cortex) as means to treat severe psychiatric disorders.
1985	First modern Transcranial Magnetic Stimulation (TMS) device	Non-invasive magnetic stimulation development; foundational work for rTMS.
1998	First Vagus Nerve Stimulation (VNS) implant trial in depression	VNS initially used for epilepsy; in 1998 began trials for treatment-resistant depression.
1999	First DBS for OCD use in internal capsule / ALIC	Early experimental deep brain stimulation in OCD; initial target in anterior limb of the internal capsule.
2005	FDA approves VNS therapy for treatment-resistant depression	First implantable device-based treatment approved for TRD.
2008	FDA clearance of rTMS for major depressive disorder	High-frequency (10 Hz) rTMS over left dorsolateral prefrontal cortex approved.
2009	FDA grants Humanitarian Device Exemption (HDE) for DBS in OCD	Medtronic's "Reclaim" DBS system approved as HDE for severe, treatment-resistant OCD.
2013	Deep TMS (H-coil) approval / regulatory actions	Devices using H-coil (deep TMS) begin receiving regulatory clearance; wider acceptance of TMS variants.
2015	NICE (UK) recommends rTMS for depression	National guidelines in the UK accept rTMS as an option for depression.
2020–2024	Expanded neuromodulation indications, technology enhancements	Studies and regulations broaden rTMS/TBS, optimize targeting; VNS increasingly used; work on biomarkers, closed-loop systems gaining traction.
2023–2025	AI integration, digital phenotyping, modified regulatory approvals	Accelerated/parcel-guided rTMS protocols; closed-loop DBS in research; neuromodulation increasingly considered adjunct in adolescents; focus on precision/neural signature-based targeting.

Current developments focus on circuit-oriented psychiatry, acknowledging that mental illness stems from disordered connectivity between cortical, subcortical, and limbic areas, but not due to localized neurotransmitter imbalances. Therefore, neuromodulation protocols endeavor to remediate maladaptive network functioning, reinstate excitation–inhibition balance, and engender long-term synaptic and structural plasticity.[11-16] Here, we critically discuss existing evidence for non-invasive and invasive neuromodulation in the treatment of psychiatric illness, including mechanisms of action, clinical effectiveness, safety, shortcomings, and new directions in precision and individualized neurostimulation.

2. Mechanisms and Modalities of Neuromodulation

2.1. Neurobiological foundations of neuromodulation: Neuromodulation acts at several levels

2.1.1. Cortical excitability

rTMS, TBS, and tDCS alter cortical excitability through action potential induction or shift in resting membrane potential. Long-term potentiation (LTP) or long-term depression (LTD) type plasticity is induced, as a result, adaptive circuits are fortified and maladaptive hyperactivity is repressed.[17-19]

2.1.2. Neurotransmitter modulation

Both invasive and non-invasive modalities influence neurotransmitter systems. rTMS and DBS enhance glutamatergic transmission, normalize GABAergic inhibitory tone, and modulate dopaminergic reward pathways. VNS activates locus coeruleus–norepinephrine and serotonergic systems, facilitating mood stabilization and cognitive enhancement.[18-20]

2.1.3. Network connectivity

fMRI and electrophysiological research indicate that psychiatric disease encompasses prefrontal-limbic dysconnectivity. Neuromodulation re-establishes synchrony among networks, enhancing top-down regulation of emotion, executive function, and behaviour control. Closed-loop systems also adaptively optimize efficiency in real-time stimulus modulation based on measured network activity.[24-25]

2.1.4. Neuroplasticity and molecular remodelling

Repeated stimulation increases expression of neurotrophic factors, e.g., VEGF and BDNF, induces synaptogenesis, and increases dendritic spine number. Such molecular modifications are responsible for the long-term antidepressive, anxiolytic, and cognitive effects seen clinically.[26-28]

Neuromodulation acts on the rationale that it alters neural circuits, utilizing electrical, magnetic, or chemical manipulations to reorganize pathological patterns of brain activity that cause psychiatric illness. Neural networks that are thought to be involved in mood, cognition, and emotional regulation, and are key targets for modulation, include the prefrontal cortex, limbic system, anterior cingulate cortex, and striatum.[21-23] Circuit dysfunction expresses as distorted neurotransmitter dynamics, synaptic plasticity impairment, and impaired oscillatory synchronization. Neuromodulation aims to re-establish these physiological patterns by promoting long-term potentiation (LTP) or depression (LTD) of synaptic efficacy based on stimulation parameters.[24] On a cellular level, stimulation can alter the firing rate of pyramidal cells, astocyte activation, and glial-neuronal cross-talk.[25] Non-invasive methods, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), cause alterations of resting membrane potentials, increasing cortical excitable and synaptic efficacy.[26] By contrast, invasive modalities, including deep brain stimulation (DBS), focus stimulation of subcortical nuclei (e.g., subgenual cingulate, nucleus accumbens), causing secondary effects on neurotransmitter release, neurotrophic signalling, and metabolic activity.[27,28]

Neuromodulatory interventions have been substantiated in recent neuroimaging and functional and electrophysiological studies utilizing functional MRI, PET, and EEG to reorganize aberrant network connectivity in promoting adaptive plasticity and resilience.[29-30] Pl plasticity resulting from chronic stimulation has been hypothesized to sustain long-term clinical gains after the period of stimulation, marking a shift to self-sustained states of neuroadaptation.[31]

2.2. Non-invasive neuromodulation

2.2.1. Repetitive transcranial magnetic stimulation (rTMS)

rTMS applies magnetic pulses to specific cortical areas. High-frequency left dorsolateral prefrontal cortex (DLPFC) stimulation relieves depressive symptoms, but low-frequency right DLPFC stimulation alters hyperactivity related to OCD and anxiety.[1,5,9] Theta-burst stimulation (TBS) provides fastened protocols of similar efficacy.[10,11]

2.2.2. Transcranial direct current stimulation (tDCS)

tDCS applies weak direct currents to modulate cortical excitability. Despite being mildly effective, tDCS is portable, safe, and additive to cognitive therapy. All recent studies indicate improvement in depression, schizophrenia, and alcohol and drug addiction.[7,8,14]

2.2.3. Transcutaneous auricular vagus nerve stimulation (taVNS)

taVNS non-invasively stimulates the auricular branch of the vagus nerve, modulating subcortical structures involved in mood regulation. Meta-analyses confirm moderate efficacy in depression and anxiety, with minimal adverse effects.[5,12,38]

Non-invasive neuromodulation is an emerging front in psychiatry, being safe, reversible, and feasible as an outpatient treatment. Well-established modalities are repetitive transcranical magnetic stimulation (rTMS), tDCS, transcranial alternating current stimulation (tACS), and focused ultrasound stimulation (FUS).[32] rTMS, which has been approved by the FDA for major depressive disorder and obsessive-compulsive disorder, uses rapidly fluctuating magnetic fields to impose electric currents in cortical tissue, thereby modulating the excitability and connectivity of neurones.[33] High-frequency rTMS (10–20 Hz) increases cortical excitability, while low-frequency rTMS (≤1 Hz) has an inhibitory action.[34] Randomised clinical trials have shown strong evidence of the antidepressive efficacy of high-frequency rTMS, when used to treat the left dorsolateral prefrontal cortex (DLPFC), a likely consequence of a return to normal of hypoactivity in the prefrontal-limbic circuitry.[35]

tDCS, another extensively researched technique, uses weak direct currents transmitted via scalp electrodes to vary cortical excitability without directly causing neuronal firing. Excitability increases under anodal, and it decreases under cathodal.[36] tDCS holds good promise in depression, schizophrenia, and generalized anxiety disorder, particularly when it is used along with cognitive training.[37,38] Novelties like tACS vary oscillatory synchronization within certain bands of frequency, matching deficient neural rhythm in aberrantly instituted anxiety and mood dysregulation.[39] FUS, meanwhile, provides deeper, spatially focused stimulation without craniotomy and holds initial promise for targeting subcortical mood circuits.[40]

2.3. Invasive Neuromodulation

2.3.1. Vagus nerve stimulation (VNS)

VNS devices implanted provide chronic intermittent stimulation to the vagus nerve. Long-term treatment of depression, particularly treatment-resistant depression (TRD), and improvement of cognitive function and quality of life has been demonstrated.[4,12,13,14,44]

2.3.2. Deep brain stimulation (DBS)

DBS targets subcortical nodes such as the subcallosal cingulate (SCC) and ventral capsule/ventral striatum (VC/VS). In refractory OCD, depression, and Tourette's disorder, DBS yields symptom reduction by modulating distributed cortical-subcortical networks. Closed-loop

adaptive DBS represents a frontier for personalized, responsive intervention.[3,15,23,46]

Invasive neuromodulation, even though it requires surgery, provides highly tuneable and precise control over malfunctioning neural networks. Deeply established technologies are deep brain stimulation (DBS), vagus nerve stimulation (VNS), and epidural cortical stimulation (ECS).[41,42] DBS, initially designed for movement disorders, has been used for treatment-resistant depression (TRD), obsessive-compulsive disorder (OCD), and Tourette's syndrome.[43] Electrodes that are implanted in subcortical locations—such as the subcallosal cingulate gyrus or nucleus accumbens—deposit constant current pulses that control activity in networks and synaptic transmission.[44] Long-term studies show continued improvement of symptoms, which can be mediated by long-term plastic reorganization of limbic-prefrontal connections.[45] VNS, which entails left vagal nerve stimulation by an implanted stimulator, impacts central monoaminergic systems and has been shown to have antidepressive effects in TRD and PTSD.[46,47] Neurochemical assays suggest that VNS increases norepinephrine and serotonin turnover and induces hippocampal neurogenesis.[48] Microdirunal electrode implantation over cortical areas, as performed in ECS, provides more localized modulation than DBS. Initial reports indicate that ECS to the DLPFC has the potential to treat depression as a function of enhanced cortical excitation and regional cerebral blood flow.[49] New adaptive stimulation protocols, based on closed-loop feedback, are increasing efficacy and safety in invasively based methods.[50]

3. Comparative Efficacy and Mechanistic Overlaps

Invasive and non-invasive neuromodulation have shared mechanistic templates based on circuit rebalancing, neurotransmitter modulation, and neuroplastic reorganization.[51] Their therapeutic scope and risk profiles, nonetheless, vary. Non-invasive methods provide safer, repeatable, and scalable treatment, which is appropriate for initial-stage or moderate illness, versus invasive modalities for end-stage, treatment-resistant illness.[52] Their meta-analyses indicate that rTMS and DBS have similar effect sizes in TRD, and durability has been noted primarily in DBS, in long-term follow-up.[53] Further, modality combination—with tDCS or TMS, for instance, as an adjunct to pharmacotherapy or as a combination with psychotherapy—has generally been found to provide additive or synergistic effects.[54] The new field of personalized neuromodulation, based on combining neuroimaging-assisted targeting and adaptive algorithm stimulation, strives to provide individualized treatment tailored to individual neurobiological profile.[55] With mechanistic distinctions between the two, shared evidence supports that neuromodulation provides restoration of impaired brain network dynamics, particularly between prefrontal and limbic areas—key areas implicated in the pathology of psychiatry.[56]

4. Clinical Uses of Neuromodulation in Psychiatric Disorders

4.1. Major depressive Disorder (MDD)

1. Major depression (MDD) still constitutes the best studied condition for which to apply neuromodulation. Although there are several classes of antidepressive medications, about 30–40% of patients do not respond satisfactorily and thus become treatment-resistant depression (TRD).[57] Neuromodulation provides a route to re-establish homeostasis of the neurocircuit, specifically along the fronto-limbic circuitry, which regulates affective control, mood, and executive control.[58]
2. Repetitive transcranial magnetic stimulation (rTMS) has achieved international regulatory approval for MDD after large clinical trials and meta-analyses verifying its efficacy and safety.[59,60] High-frequency left dorsolateral prefrontal cortex (DLPFC) rTMS increases cortical excitability and decreases hyperactive limbic structures, such as the amygdala and subgenual cingulate cortex, in a process known as downregulation.[61] Functional imaging studies demonstrate that responders to rTMS have improved prefrontal glucose metabolism and enhanced prefrontal-limbic connectivity after treatment.[62]
3. Transcranial direct current stimulation (tDCS) also demonstrates antidepressant efficacy, but the extent of its impact is lower compared to rTMS.[63] When added to cognitive-behavioural therapy or selective serotonin reuptake inhibitors, tDCS enhances treatment effectiveness by facilitating neuroplastic reorganization.[64] Furthermore, tDCS to fronto-temporal networks has been demonstrated to exert beneficial effects in bipolar depression, indicating its further affective modulation potential.[65]
4. Invasive procedures such as deep brain stimulation (DBS) have been studied in TRD, particularly targeting the subcallosal cingulate (Brodmann area 25), ventral capsule/ventral striatum, and nucleus accumbens.[66] Long-term DBS research has shown sustained remission in 40–60% of TRD patients and the return to normal of the pathologic oscillations of the limbic networks.[67,68] Vagus nerve stimulation (VNS) has also shown sustained antidepressive effects, characteristically emerging after several months of continuous stimulation, signalling accumulating neuroadaptive changes.[69]

Most recent work combining functional MRI-guidance and closed-loop adaptive DBS has improved response rates and has represented a step toward personalized neuromodulation protocols.[70,71] Neuromodulation in general is an effective, mechanism-driven treatment for depression, and particularly for treatment-refractory populations.

4.2. Anxiety disorders and post-traumatic stress disorder (PTSD)

1. Anxiety disorders, including general anxiety disorder (GAD), panic disorder, and PTSD, are a consequence of hyperexcitability of limbic networks, especially amygdala, hippocampus, and anterior cingulate cortex (ACC).[72] Neuromodulation aims to reverse this pathological hyperactivity and reestablish inhibitory-excitatory balance in the fear circuitry.[73]
2. rTMS and tDCS have been promising in anxiety spectrum disorders. High-frequency rTMS to the right DLPFC has decreased hyperarousal and enhanced cognitive flexibility by amygdalo-cortical connectivity modulation.[74] On the other hand, inhibitory low-frequency rTMS over the right DLPFC has been found to have anxiolytic effects by suppressing hyperactive limbic activity.[75] In PTSD, both rTMS and theta-burst stimulation (TBS) to the DLPFC have been found to lead to remarkable decreases in intrusive memories, hypervigilance, and emotional dysregulation.[76,77]
3. tDCS provides a non-invasive adjunctive treatment for anxiety, facilitating extinction learning and increasing emotional resilience when it acts as an adjunct to exposure-based therapies.[78] Randomised controlled trials have demonstrated that left DLPFC anodal tDCS can boost symptoms of anxiety when it increases top-down inhibitory control over the limbic system.[79]
4. Vagus nerve stimulation (VNS) has attracted renewed attention for PTSD and panic disorder, due to its capacity to regulate noradrenergic and serotonergic systems and to lower systemic sympathetic tone.[80] Animal and first-phase human studies suggest that transcutaneous auricular VNS (taVNS)—a non-invasive form—improves fear extinction learning and decreases anxiety-associated physiological reactivity.[81]

New modalities, including transcranial pulsed current stimulation (tPCS) and focused ultrasound (FUS), are being researched for amygdala and insular cortex modulation that are potentially more specific and have fewer side effects.[82] Neuromodulation has great potential in reprogramming aberrant networks of pathologic anxiety through the assistance of neuro-adaptivity and neurometabolic restoration.

4.3. Schizophrenia, obsessive-compulsive disorder (OCD), and alcohol

4.3.1. Schizophrenia

Neuromodulation treatment choices in schizophrenia primarily address cortical dysconnectivity and dopaminergic dysregulation, underlying positive and negative symptoms. rTMS of the left temporoparietal cortex reduces auditory hallucinations by the desynchronization of cortically aberrant oscillations.[83] Meta-analyses report significant hallucination severity reductions with low-frequency rTMS, but effects for cognitive impairment are moderate.[84] tDCS has shown cognitive benefits in schizophrenia, particularly working memory and executive function when incorporated as an adjunct to cognitive remediation.[85] tDCS over the DLPFC may boost glutamatergic neurotransmission and cortical plasticity, and it has a plausible neurophysiological explanation for clinical benefit.[86]

4.3.2. Obsessive-compulsive disorder (OCD)

For OCD, the cortico-striato-thalamo-cortical (CSTC) circuitry constitutes a primary target for treatment. rTMS of the supplementary motor region (SMA) and dorsolateral prefrontal cortex (DLPFC) has been associated with reductions in compulsive behaviour and intrusive thoughts.[87] Deep rTMS utilizing the H-coil system was cleared just recently by the FDA for OCD, as a continuation of trials that demonstrated robust efficacy and durability.[88] Invasive treatment options such as DBS to the anterior limb of the internal capsule (ALIC) or nucleus accumbens have induced durable symptom relief in severe treatment-resistant OCD.[89,90] Neuroimaging demonstrates that DBS normalizes hyperactivity in the orbitofrontal cortex and striatum, confirming its circuital level treatment effectiveness.[91]

4.3.3. Substance use disorders

Neuromodulation has been identified as a novel adjunct in addiction treatment that involves the disruption of maladaptive reward circuitry. rTMS of the DLPFC or medial prefrontal cortex decreases craving and relapse rate in nicotine, alcohol, and cocaine use disorders.[92] Mechanistically, rTMS increases prefrontal inhibitory control of the nucleus accumbens, thus blunting compulsive drug-seeking behaviour.[93] Analogously, tDCS over prefrontal areas has been shown to lower cue-induced craving by enhancing dopamine signalling and controlling impulses.[94] Pilot treatment trials utilizing DBS of the nucleus accumbens have been able to lower relapse rate among patients with refractory substance dependence.[72] These observations suggest the role of neuromodulation in reorganizing pathological reward and motivational networks.

5. Problems and Future Prospects

5.1. Barriers to clinical translation

Despite quick advances in science and technology, there remain a few crucial challenges that slow the widespread clinical application of neuromodulation in psychiatry. Perhaps the greatest challenge among these is inter-individual variability in response to treatment. Neural structure, cortical thickness, skull conductivity, and Reference Network Connectivity vary extensively between patients, creating heterogeneous responses even to standardized protocols.[72,73] Biological variability due to differing skull conductivities and cortical thicknesses are further compounded by variability in stimulation parameters—frequency, intensity, duration, and coil

orientation—that directly impact efficacy.[74] Limited biomarker-guided individualization is yet another barrier. While biomarkers and electrophysiological markers (EEG, fMRI, MEG) have been shown to predict responders, there is no consensus biomarker that can be used as a diagnostic or prognostic biomarker.[75] By consequence, empiric targeting still supersedes accuracy in mapping malfunctioning circuits. This hinders cost-effectiveness and reproducibility.[76]

Regulatory and logistical issues also linger. Prohibitive cost of equipment, trained operator required, and restricted insurance coverage limit access—particularly in low- and middle-income contexts.[77] For invasive techniques like DBS and VNS, the perioperative risks, requirement for maintenance over the long term, and possible hardware-associated adversities (infection, lead movement, depleting battery) are important concerns.[78,79] Moral objections revolve around permanent neural modifications, patient autonomy, and data security in closed-loop schemes.[80] In addition, the variability of the psychiatric disorders themselves makes interpretation difficult. For example, MDD involves several biological subtypes involving dysfunctions of specific circuits; implanting a single locus may not remedy the sub-pathophysiology in every instance.[81] Long-term follow-up data remain scant, and just a minority of studies have extended past a two-year time frame.[82] Taken together, these impediments identify a strong need for standardized, biomarker-guided, and ethically sound frameworks to ease translational contiguity between bench and bed.[83]

Table 2: Major neuromodulation modalities and their psychiatric applications

Modality	Mechanism / Target	Primary Psychiatric Applications	Regulatory Status	Level of Evidence
Electroconvulsive Therapy (ECT)	Electrical induction of generalized seizures; affects limbic and cortical circuits	Major depressive disorder (MDD), bipolar disorder, schizophrenia with catatonia	FDA-approved; gold standard for severe depression	Level I (Meta-analyses & RCTs)
Repetitive Transcranial Magnetic Stimulation (rTMS)	Magnetic induction of cortical currents (DLPFC, ACC)	Treatment-resistant depression, OCD, PTSD	FDA-approved (MDD 2008, OCD 2018)	Level I (Multiple RCTs & systematic reviews)
Theta-Burst Stimulation (TBS)	Patterned rTMS mimicking theta rhythms; short duration, modulates cortical plasticity	Depression, cognitive enhancement, PTSD	FDA-cleared (2019)	Level II (Large RCTs, emerging meta-analyses)
Transcranial Direct Current Stimulation (tDCS)	Weak constant current alters cortical excitability (DLPFC)	Depression, anxiety disorders, schizophrenia (negative symptoms)	Investigational	Level II–III (Moderate evidence, ongoing RCTs)
Deep Brain Stimulation (DBS)	Implanted electrodes targeting subgenual cingulate, nucleus accumbens, ALIC	OCD, depression (experimental), Tourette's	FDA Humanitarian Device Exemption for OCD (2009)	Level II (Controlled trials; limited sample)
Vagus Nerve Stimulation (VNS)	Electrical impulses via cervical vagus nerve to modulate limbic system	Treatment-resistant depression	FDA-approved (2005)	Level II (Long-term cohort and RCT data)
Transcranial Alternating Current Stimulation (tACS)	Oscillatory current entrains neural rhythms	Depression, cognitive modulation	Investigational	Level III (Preliminary clinical studies)
Cranial Electrotherapy Stimulation (CES)	Low-intensity microcurrent across scalp	Anxiety, insomnia, depression	FDA-cleared for anxiety & insomnia	Level III (Mixed evidence)
Focused Ultrasound Neuromodulation (FUS)	Acoustic energy modulates neuronal firing; potential for deep non-invasive targets	Depression, OCD, addiction (experimental)	Investigational	Level IV (Pilot studies, animal/human feasibility)
Closed-Loop / Adaptive Neuromodulation	Real-time feedback systems adjusting stimulation based on neural biomarkers	Severe depression, OCD, PTSD	Experimental (research phase)	Level IV–V (Proof-of-concept & early trials)

5.2. Future outlook and integrative advances

Neuromodulation in psychiatry has a bright future ahead in directions of precision, individualization, and integration. Computational advances in neuroscience, imaging, and engineering are empowering next-generation closed-loop devices that adaptively vary stimulation in real time in response to dynamic neural feedback.[84] Such adaptive models, already proved in initial DBS research in depression and OCD, greatly increase efficacy and lose side effects.[85] (**Table 2**). Connectivity-guided targeting is a breakthrough. Rather than targeting anatomically defined coordinates, stimulation may be directed by individual functional maps derived from resting-state fMRI or diffusion tensor imaging.[86] Clinicians can thus treat disease networks instead of isolated structures, a step in line with the direction of network-based psychiatry. Multimodal integration—integrating neuromodulation with pharmacotherapy, psychotherapy, or digital therapeutics—holds out the potential for synergistic gains. For example, rTMS or tDCS sessions in combination with cognitive-behavioural therapy can hasten neuroplastic reorganization, while concurrent administration with ketamine or SSRIs may increase synaptic reactivity.[87-89]

In a similar manner, taVNS plus mindfulness-based training has been found to optimize autonomic and emotional resilience. New wearable and portable stimulation devices are bringing neuromodulation to daily clinical practice. De miniaturized tDCS headsets, smartphone-controlled taVNS, and home-based rTMS prototypes are making maintenance therapy possible beyond the hospital walls.[90-91] Combination with AI-driven analytics can individualize protocols via machine-learning models that adapt stimulation parameter settings to patient-specific neural and behavioural feedback.[92] Lastly, the ethical boundary of neuromodulation is shifting towards the responsible regulation of neurotechnology. Setting international standards on data safety, algorithmic disclosures, and equal access will be crucial to avoid misuse and provide inclusivity.[93,94] The Approaching decade will shift from fixed, disease-specific stimulation to dynamic, customized, and multi-target neuromodulation systems that reframe therapeutics in psychiatry.[72]

6. Discussion

Neuromodulation is a paradigm-shifting frontier in psychiatric treatment that integrates neurophysiological mechanisms with translational symptom relief by modulation of abnormal brain circuits. The multitude of methods—from non-invasive techniques like repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to invasive techniques like deep brain stimulation (DBS) and vagus nerve stimulation (VNS)—mirrors the timeline of the field itself, with a transition from modulation at the surface level to precision interventions at the circuit level.[1,5,18,55,73] In several psychiatric illnesses, such as major depressive disorder (MDD), obsessive-compulsive disorder (OCD), bipolar depression, and spectrum anxiety disorders, convergent evidence is in support of the neuroregulatory effects of neuromodulation in dysregulated neural activity and functional connectivity.[9,29,54,82,89]

6.1. Fundamental insights

From Neuroplasticity to Network Rebalancing: The treatment mechanisms of neuromodulation centre on synaptic plasticity, neurogenesis, and network rebalancing. rTMS evokes long-term potentiation (LTP) or depression (LTD)-inducing effects, varying cortical excitability and synaptic efficacy.[69,74] tDCS also sets up resting membrane potential and upregulates prefrontal cortical activity, enhancing top-down control of limbic areas involved in mood regulation.[49,74,89] Clinical evidence by neuroimaging proves default mode network (DMN) and salience network (SN) activity normalization with rTMS and tDCS [66,84,85]. This is consistent with electrophysiological evidence indicating increased dorsolateral prefrontal cortex (DLPFC) gamma-band activity, a brain region persistently underactive in depression.[68,74,84]

Invasive methods such as DBS target subcortical structures, including the subcallosal cingulate gyrus (SCG), nucleus accumbens (NAc), and medial forebrain bundle (MFB)—key nodes in affective and reward circuits.[81,84,89] Chronic stimulation modulates downstream limbic-cortical networks, leading to sustained improvements in mood, anhedonia, and cognitive flexibility.[56,71,87,88] Molecular studies have also demonstrated that chronic neuromodulation enhances brain-derived neurotrophic factor (BDNF) signalling and serotonergic plasticity, offering mechanistic parallels with pharmacotherapy but with circuit-level specificity.[83,87]

6.2. Relative efficacy of non-invasive and invasive modalities

The effectiveness of rTMS for treatment-resistant depression is no longer substantiated solely by case reports and open-label studies, but also confirmed by meta-analyses with 25–40% remission rates, specifically with high-frequency protocols at the left DLPFC and with theta-burst protocols.[69,70,74,78] Shorter accelerated iTBS protocols have also condensed treatment length to five days or less without sacrificing effectiveness.[53,70,74] Clinical practice guidelines now support rTMS as a first-line or augmentative therapy for TRD, approved by the Canadian Network for Mood and Anxiety Treatments and the American Psychiatric Association.[69,89] tDCS, though less efficacious, has several logistically favourable features—transportability, cost-effectiveness, and lateral side effect profile.[49,74,80] Augmentative potential with CBT and pharmacotherapy is demonstrated in randomized controlled studies, particularly for mild-to-moderate depression.[62,65] Moreover, tDCS-mediated prefrontal modulation potentially enhances

emotional control and executive function for anxiety and PTSD.[74,86,92]

By contrast, DBS and VNS are reserved for refractory cases in which conventional and non-invasive interventions are ineffective. DBS to SCG and NAc has demonstrated long-term sustained response rates of 40–60% in long-term follow-ups,[60,87,89] although variability across targets is still a problem [84,85,90]. Closed-loop DBS, with adaptive modulation of stimulation based on neural signs of depressive states, is a paradigm-shifting approach.[83,88] Analogously, VNS—both implanted and transcutaneous (taVNS)—has been shown potential in MDD and PTSD based on modulation of vagal afferents that project to the locus coeruleus and amygdala.[42-46,52]

6.3. Safety, ethical, and regulatory considerations

Neuromodulation techniques are relatively safe with adverse effects depending on modalities. rTMS induces transient headache or rare seizures, while tDCS is related to mild irritation on the scalp.[61,69] DBS is associated with surgical adverse events such as infection or haemorrhage or hardware malfunction, although advances in targeted therapy and stereotactic imaging have significantly improved the experience.[56,93] Ethical concerns are with invasiveness, cost, and distributive justice in the provision of fair mental health care, given the socioeconomic disparities.[93,94] Neuroethical controversy also centers on personality change, identity problems, and potential abuse of cognitive enhancement with neuromodulation beyond clinical applications. Interdisciplinary standards involving psychiatrists, ethicists, and neuroengineers are therefore necessary to provide patient autonomy and protection with expanding clinical applications of neuromodulation.[93]

6.4. Clinical translation and response predictors

Even with strong evidence, clinical response prediction is problematic. Baseline neuroimaging reports point to pretherapy connectivity in the subgenual cingulate, amygdala, and fronto-striatal circuits to foretell outcomes.[58,76,90] EEG coherence, cortical thickness, and gene polymorphisms (e.g., BDNF Val66Met) have demonstrated early promise as predictors.[83,90] The combination of machine learning with digital phenotyping permits flexible patient categorization and individually optimized stimulation dosing.[72,94] Furthermore, the conjunction of neuromodulation with psychotherapy or pharmacotherapy can provide synergy. e.g., network plasticity induced by rTMS enhances CBT efficacy by promoting cognitive reappraisal processes.[64,65,85] Correspondingly, the combination of DBS with serotonergic agents increases mood regulation by shared neurochemical means.[83,87]

6.5. New horizons: Closed-loop and AI-integrated neuromodulation

The next decade will see paradigm-shifting innovations in adaptive and AI-guided neuromodulation. Closed-loop DBS devices detect pathological neural oscillation and deliver stimulation in real time with maximum efficacy and minimum power consumption and side effects.[72,88] AI-guided optimisation of stimulation parameters already demonstrated increased target engagement in customised DBS and TMS protocols.[73,93,94] Moreover, neuroimaging-guided connectomic integration permits network-scale instead of region-focused stimulation. This is a conceptual leap from a "where to stimulate" to a "how to modulate" approach, a revolution in psychiatric therapeutics.[59,75,87] Clinical trials with connectomic mapping and patient-specific modelling have the potential to simplify precision psychiatry by matching symptom-specific neural fingerprints with circuit modulation.[53,94,95]

Neuromodulation has reshaped treatment models in psychiatry by targeting disease substrates at the neurocircuit level rather than at symptomatic outcomes. Non-invasive approaches such as rTMS and tDCS are now clinically reasonable, evidence-based options in depression and anxiety, while invasive approaches such as DBS and VNS have life-transforming effects in treatment-resistant patients. The future trajectory of the field toward closed-loop, biomarker-guided, and AI-powered technologies is a trajectory toward genuinely personalized psychiatry. Nevertheless, translational, as well as ethical problems—from mechanism doubt to accessibility inequities—must be surmounted to achieve both safe and equitable deployment.

7. Conclusion

Neuromodulation has progressed from an experimental neuroscientific concept to an established therapeutic pillar in modern psychiatry. The convergence of clinical, neuroimaging, and molecular evidence underscores that psychiatric disorders are fundamentally circuitopathies — dysfunctions of distributed neural networks rather than isolated chemical imbalances. By directly modulating these networks through electrical, magnetic, or ultrasonic means, neuromodulation achieves what pharmacotherapy alone often cannot: restoration of functional connectivity, synaptic balance, and cognitive-emotional integration. Over the past two decades, non-invasive neuromodulation methods—particularly repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)—have matured into first-line or adjunctive treatments for depression, anxiety, and obsessive–compulsive spectrum disorders. Their mechanistic foundations lie in neuroplastic reorganization, long-term potentiation/depression dynamics, and enhanced cortical–limbic regulation. The clinical success of these modalities demonstrates that psychiatric symptomatology can be favourably altered through circuit-level retraining rather than neurochemical alteration alone.

Conversely, invasive neuromodulation approaches such as deep brain stimulation (DBS) and vagus nerve stimulation (VNS) offer hope for treatment-resistant populations who remain refractory to all conventional interventions. By modulating deep limbic and subcortical networks, DBS restores motivational drive and affective stability, while VNS influences brainstem–limbic communication to reduce stress reactivity and depressive symptomatology. The emergence of closed-loop systems, which detect pathological neural signatures and deliver stimulation adaptively, represents a new era of precision psychiatry—one where therapy is guided by the brain's own feedback rather than fixed external parameters.

Despite such advances, many challenges remain. Heterogeneity of psychiatric disorder, both in symptom presentation and neurobiological substrate, defies universal applicability. High-scale, long-term trials must establish predictive response biomarkers, such as EEG and fMRI connectivity profiles, genetic polymorphisms, and digital phenotypes based on wearable neurotechnology. Moreover, assuring ethical governance, patient consent, and distributive access to these interventions is critical as they move from tertiary to mainstream clinical practice. Incorporation of artificial intelligence (AI) into the design, target selection, and monitoring of neuromodulation will probably characterize the coming decade. AI-based algorithms already guide the selection of optimum sites for stimulation, simulate network connectivity, and adjust parameters in real time, based on electrophysiological feedback. These advances foretell a future with intelligent neuromodulation ecosystems—an adaptive, personalized, and minimally interventional system that can learn to respond to unique neural signatures. Along with advances in neuroimaging, connectomics, and biomaterials engineering, neuromodulation is growing into a field where psychiatry converges with computational neuroscience and biomedical engineering. Ultimately, the success of neuromodulation emphasizes a philosophical evolution in psychiatry: mental illness is no longer a chemical imbalance but a dynamic failure of communication at a neural level. Interventions are thus aimed at information flow augmentation, resynchronization of oscillation, and retraining aberrant circuits. This paradigm integrates neuroscientific knowledge with therapeutic potential and holds promise not just for alleviation of symptoms but also functional recovery and cognitive resilience.

Ultimately, then, neuromodulation is at the crossroads of technology and psychiatry—a fast-evolving field with the potential to redefine psychiatry care. As scientific investigation further unravels brain network intricacy, and technological and ethical foundations evolve, the aim of personalized, adaptive, and curative neuromodulation for psychiatric illnesses advances from prospect to certitude. Psychiatric practice in the future will combine AI-guided, multimodal stimulation systems that synchronize neural dynamics with emotional resilience, ushering in the era of precision neuropsychiatry.

8. Source of Funding

None.

9. Conflict of Interest

None.

References

1. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et. al., Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clin Neurophysiol*. 2020;131(2):474-528. https://doi.org/10.1016/j.clinph.2019.11.002. Epub 2020 Jan 1. Erratum in: *Clin Neurophysiol*. 2020;131(5):1168–169. https://doi.org/10.1016/j.clinph.2020.02.003.
2. Scangos KW, Khambhati AN, Daly PM, Makhoul GS, Sugrue LP, Zamanian H, et al. Closed-loop neuromodulation in an individual with treatment-resistant depression. *Nat Med*. 2021;27(10):1696–700. https://doi.org/10.1038/s41591-021-01480-w.
3. Sreeraj VS, Arumugham SS, Venkatasubramanian G. Clinical Practice Guidelines for the Use of Transcranial Direct Current Stimulation in Psychiatry. *Indian J Psychiatry*. 2023;65(2):289–96. https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_496_2.
4. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet.* 2018;391(10131):1683–92. https://doi.org/10.1016/S0140-6736(18)30295-2.
5. Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, et al. Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review with Network Meta-analysis. *JAMA Psychiatry*. 2017;74(2):143–52. https://doi.org/10.1001/jamapsychiatry.2016.3644. Erratum in: *JAMA Psychiatry*. 2017;74(4):424. https://doi.org/10.1001/jamapsychiatry.2017.0062.
6. Jog MV, Wang DJJ, Narr KL. A review of transcranial direct current stimulation (tDCS) for the individualized treatment of depressive symptoms. *Pers Med Psychiatry*. 2019;17-18:17–22. https://doi.org/10.1016/j.pmip.2019.03.001.
7. Agarwal SM, Shivakumar V, Bose A, Subramaniam A, Nawani H, Chhabra H, et al. Transcranial direct current stimulation in schizophrenia. *Clin Psychopharmacol Neurosci*. 2013;11(3):118–25. https://doi.org/10.9758/cpn.2013.11.3.118.
8. Shivakumar V, Dinakaran D, Narayanaswamy JC, Venkatasubramanian G. Non-invasive brain stimulation in obsessive-compulsive disorder. *Indian J Psychiatry*. 2019;61(Suppl 1): S66–S76. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_522_18.
9. Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, et al. Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder. *Biol Psychiatry*. 2016;79(4):266–73. https://doi.org/10.1016/j.biopsych.2015.03.025.
10. Baeken C, Brem AK, Arns M, Brunoni AR, Filipčić I, Ganho-Ávila A, et al. Repetitive transcranial magnetic stimulation treatment for depressive disorders: current knowledge and future directions. *Curr Opin Psychiatry*. 2019;32(5):409–15. https://doi.org/10.1097/YCO.0000000000000533.
11. Mahoney JJ 3rd, Hanlon CA, Marshalek PJ, Rezai AR, Krinke L. Transcranial magnetic stimulation, deep brain stimulation, and other forms of neuromodulation for substance use disorders: Review of modalities and implications for treatment. *J Neurol Sci*. 2020;418:117149. https://doi.org/10.1016/j.jns.2020.117149.

12. Weigand A, Horn A, Caballero R, Cooke D, Stern AP, Taylor SF, et al. Prospective Validation That Subgenual Connectivity Predicts Antidepressant Efficacy of Transcranial Magnetic Stimulation Sites. *Biol Psychiatry*. 2018;84(1):28–37. https://doi.org/10.1016/j.biopsych.2017.10.028.
13. Shinohara R, Aghajanian GK, Abdallah CG. Neurobiology of the Rapid-Acting Antidepressant Effects of Ketamine: Impact and Opportunities. *Biol Psychiatry*. 2021;90(2):85–95. https://doi.org/10.1016/j.biopsych.2020.12.006.
14. Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage*. 2014;85 Pt 3:948-60. https://doi.org/10.1016/j.neuroimage.2013.05.117.
15. Fitzgerald PB, Hoy KE, Elliot D, Susan McQueen RN, Wambeek LE, Daskalakis ZJ. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. *Neuropsychopharmacology*. 2018;43(7):1565–72. https://doi.org/10.1038/s41386-018-0009-9.
16. 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.
17. Mehta S, Downar J, Mulsant BH, Voineskos D, Daskalakis ZJ, et al. Effect of high frequency versus theta-burst repetitive transcranial magnetic stimulation on suicidality in patients with treatment-resistant depression. *Acta Psychiatr Scand*. 2022;145(5):529–38. https://doi.org/10.1111/acps.13412.
18. Smith RC, Boules S, Mattiuz S, Youssef M, Tobe RH, Sershen H, et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: A randomized controlled study. *Schizophr Res*. 2015;168(1-2):260–6. https://doi.org/10.1016/j.schres.2015.06.011.
19. Moffa AH, Brunoni AR, Nikolin S, Loo CK. Transcranial Direct Current Stimulation in Psychiatric Disorders: A Comprehensive Review. *Psychiatr Clin North Am*. 2018;41(3):447–63. https://doi.org/10.1016/j.psc.2018.05.002.
20. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. IM; ELECT-TDCS Investigators. Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression. *N Engl J Med*. 2017;376(26):2523–33. https://doi.org/10.1056/NEJMoa1612999.
21. Lefaucheur JP. Cortical neurostimulation for neuropathic pain: state of the art and perspectives. Pain. 2016;157 Suppl 1:S81–9. https://doi.org/10.1097/j.pain.0000000000000401.
22. George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. *Curr Opin Psychiatry*. 2013;26(1):13–8.https://doi.org/10.1097/YCO.0b013e32835ab46d.
23. Dandekar MP, Fenoy AJ, Carvalho AF, Soares JC, Quevedo J. Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational implications. *Mol Psychiatry.* 2018;23(5):1094–112. https://doi.org/10.1038/mp.2018.2.
24. Crowell AL, Riva-Posse P, Holtzheimer PE, Garlow SJ, Kelley ME, Gross RE, et al. Long-Term Outcomes of Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression. *Am J Psychiatry*. 2019;176(11):949–56. https://doi.org/10.1176/appi.ajp.2019.18121427.
25. Vicheva P, Butler M, Shotbolt P. Deep brain stimulation for obsessive-compulsive disorder: A systematic review of randomised controlled trials. *Neurosci Biobehav Rev*. 2020;109:129–38. https://doi.org/10.1016/j.neubiorev.2020.01.007.
26. Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, et al. A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression. *Biol Psychiatry*. 2015;78(4):240–8. https://doi.org/10.1016/j.biopsych.2014.11.023.
27. Fenoy AJ, Schulz PE, Sanches M, Selvaraj S, Burrows CL, Asir B, et al. Deep brain stimulation of the "medial forebrain bundle": sustained efficacy of antidepressant effect over years. *Mol Psychiatry*. 2022;27(5):2546–53. https://doi.org/10.1038/s41380-022-01504-y.
28. Cirillo P, Gold AK, Nardi AE, Ornelas AC, Nierenberg AA, Camprodon J, et al. Transcranial magnetic stimulation in anxiety and trauma-related disorders: A systematic review and meta-analysis. *Brain Behav*. 2019;9(6):e01284. https://doi.org/10.1002/brb3.1284. Epub 2019 May 7.
29. Edinoff AN, Hegefeld TL, Petersen M, Patterson JC 2nd, Yossi C, Slizewski J, et al. Transcranial Magnetic Stimulation for Post-traumatic stress disorder. *Front Psychiatry*. 2022;13:701348. https://doi.org/10.3389/fpsyt.2022.701348.
30. Philip NS, Barredo J, Aiken E, Larson V, Jones RN, Shea MT, et al. Theta-Burst Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder. Am J Psychiatry. 2019;176(11):939–48. https://doi.org/10.1176/appi.ajp.2019.18101160.
31. Aaronson ST, Sears P, Ruvuna F, Bunker M, Conway CR, Dougherty DD, et al. A 5-Year Observational Study of Patients with Treatment-Resistant Depression Treated with Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. *Am J Psychiatry*. 2017;174(7):640–48. https://doi.org/10.1176/appi.ajp.2017.16010034.
32. Rong P, Liu J, Wang L, Liu R, Fang J, Zhao J, et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study. *J Affect Disord*. 2016;195:172–9. https://doi.org/10.1016/j.jad.2016.02.031.
33. Bremner JD, Gurel NZ, Wittbrodt MT, Shandhi MH, Rapaport MH, Nye JA, et al. Application of Non-invasive Vagal Nerve Stimulation to Stress-Related Psychiatric Disorders. *J Pers Med*. 2020;10(3):119. https://doi.org/10.3390/jpm10030119.
34. Lai J, Liu J, Zhang L, Cao J, Hong Y, Zhang L, et al. Effect of transcutaneous vagus nerve stimulation with electrical stimulation on generalized anxiety disorder: Study protocol for an assessor-participant blinded, randomized sham-controlled trial. *Heliyon*. 2025;11(4):e42469. https://doi.org/10.1016/j.heliyon.2025.e42469.
35. Kaniusas E, Kampusch S, Tittgemeyer M, Panetsos F, Gines RF, Papa M, et al. Current Directions in the Auricular Vagus Nerve Stimulation I - A Physiological Perspective. *Front Neurosci*. 2019;13:854. https://doi.org/10.3389/fnins.2019.00854.
36. Badran BW, Mithoefer OJ, Summer CE, LaBate NT, Glusman CE, Badran AW, et al. Short trains of transcutaneous auricular vagus nerve stimulation (taVNS) have parameter-specific effects on heart rate. *Brain* Stimul. 2018;11(4):699-708. https://doi.org/10.1016/j.brs.2018.04.004.
37. Shiozawa P, Fregni F, Benseñor IM, Lotufo PA, Berlim MT, Daskalakis JZ, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. *Int J Neuropsychopharmacol*. 2014;17(9):1443–52. https://doi.org/10.1017/S1461145714000418. Epub 2014 Apr 8. Erratum in: *Int J Neuropsychopharmacol*. 2014;17(9):1539.
38. Osińska A, Rynkiewicz A, Binder M, Komendziński T, Borowicz A, Leszczyński A. Non-invasive Vagus Nerve Stimulation in Treatment of Disorders of Consciousness - Longitudinal Case Study. *Front Neurosci*. 2022;16:834507. https://doi.org/10.3389/fnins.2022.834507.
39. Kishi T, Ikuta T, Sakuma K, Hatano M, Matsuda Y, Wilkening J, et al. Theta burst stimulation for depression: a systematic review and network and pairwise meta-analysis. *Mol Psychiatry*. 2024;29(12):3893–9. https://doi.org/10.1038/s41380-024-02630-5.
40. Ranjan M, Mahoney JJ 3rd, Rezai AR. Neurosurgical neuromodulation therapy for psychiatric disorders. *Neurotherapeutics*. 2024;21(3):e00366. https://doi.org/10.1016/j.neurot.2024.e00366.
41. Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, et al. Deep brain stimulation: current challenges and future directions. Nat Rev Neurol. 2019;15(3):148–60. https://doi.org/10.1038/s41582-018-0128-2.
42. Little S, Pogosyan A, Neal S, Zavala B, Zrinzo L, Hariz M, et al. Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol*. 2013;74(3):449–57. https://doi.org/10.1002/ana.23951.

43. Dunlop BW, Rajendra JK, Craighead WE, Kelley ME, McGrath CL, Choi KS, et al. Functional Connectivity of the Subcallosal Cingulate Cortex and Differential Outcomes to Treatment with Cognitive-Behavioural Therapy or Antidepressant Medication for Major Depressive Disorder. *Am J Psychiatry*. 2017;174(6):533–45. https://doi.org/10.1176/appi.ajp.2016.16050518. Epub 2017 Mar 24. Erratum in: *Am J Psychiatry*. 2017;174(6):604. https://doi.org/10.1176/appi.ajp.2017.1746correction3.
44. Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *Lancet Psychiatry*. 2017;4(11):839–49. https://doi.org/10.1016/S2215-0366(17)30371-1.
45. Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol*. 2021;132(1):269-306. https://doi.org/10.1016/j.clinph.2020.10.003.
46. Manenti R, Cotelli MS, Cobelli C, Gobbi E, Brambilla M, Rusich D, et al. Transcranial direct current stimulation combined with cognitive training for the treatment of Parkinson Disease: A randomized, placebo-controlled study. *Brain Stimul*. 2018;11(6):1251–62. https://doi.org/10.1016/j.brs.2018.07.046.
47. Li CT, Cheng CM, Chen MH, Juan CH, Tu PC, Bai YM, et al. Antidepressant Efficacy of Prolonged Intermittent Theta Burst Stimulation Monotherapy for Recurrent Depression and Comparison of Methods for Coil Positioning: A Randomized, Double-Blind, Sham-Controlled Study. *Biol Psychiatry*. 2020;87(5):443–50. https://doi.org/10.1016/j.biopsych.2019.07.031.
48. Goldsworthy MR, Hordacre B. Dose dependency of transcranial direct current stimulation: implications for neuroplasticity induction in health and disease. *J Physiol*. 2017;595(11):3265–6. https://doi.org/10.1113/JP274089.
49. Tulay EE, Metin B, Tarhan N, Arıkan MK. Multimodal Neuroimaging: Basic Concepts and Classification of Neuropsychiatric Diseases. *Clin EEG Neurosci*. 2019;50(1):20–33. https://doi.org/10.1177/1550059418782093.
50. Downar J, Geraci J, Salomons TV, Dunlop K, Wheeler S, McAndrews MP, et al. Anhedonia and reward-circuit connectivity distinguish non-responders from responders to dorsomedial prefrontal repetitive transcranial magnetic stimulation in major depression. *Biol Psychiatry*. 2014;76(3):176–85. https://doi.org/10.1016/j.biopsych.2013.10.026.
51. Fidalgo TM, Morales-Quezada JL, Muzy GS, Chiavetta NM, Mendonca ME, Santana MV, et al. Biological markers in noninvasive brain stimulation trials in major depressive disorder: a systematic review. *J ECT*. 2014;30(1):47–61. https://doi.org/10.1097/YCT.0b013e31828b34d8.
52. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, C et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol*. 2017;128(1):56–92. https://doi.org/10.1016/j.clinph.2016.10.087.
53. Chu HT, Cheng CM, Liang CS, Chang WH, Juan CH, Huang YZ, et al. Efficacy and tolerability of theta-burst stimulation for major depression: A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;106:110168. https://doi.org/10.1016/j.pnpbp.2020.110168.
54. Coenen VA, Sajonz B, Reisert M, Bostroem J, Bewernick B, Urbach H, et al. Tractography-assisted deep brain stimulation of the superolateral branch of the medial forebrain bundle (slMFB DBS) in major depression. *Neuroimage Clin*. 2018;20:580–93. https://doi.org/10.1016/j.nicl.2018.08.020.
55. Scangos KW, Makhoul GS, Sugrue LP, Chang EF, Krystal AD. State-dependent responses to intracranial brain stimulation in a patient with depression. *Nat Med*. 2021;27(2):229–31. https://doi.org/10.1038/s41591-020-01175-8. Epub 2021 Jan 18. Erratum in: Nat Med. 2022;28(10):2218. https://doi.org/10.1038/s41591-022-01950-9.
56. Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Kolivakis TT, et al. A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. J Neurosurg. 2012;116(2):315–22. https://doi.org/10.3171/2011.10.JNS102122.
57. Tortella G, Casati R, Aparicio LV, Mantovani A, Senço N, D'Urso G, et al. Transcranial direct current stimulation in psychiatric disorders. *World J Psychiatry*. 2015;5(1):88-102. https://doi.org/10.5498/wjp.v5.i1.88.
58. Baeken C, Lefaucheur JP, Van Schuerbeek P. The impact of accelerated high frequency rTMS on brain neurochemicals in treatment-resistant depression: Insights from 1H MR spectroscopy. *Clin Neurophysiol*. 2017;128(9):1664–72. https://doi.org/10.1016/j.clinph.2017.06.243.
59. Fitzgerald PB, Hoy KE, Herring SE, Clinton AM, Downey G, Daskalakis ZJ. Pilot study of the clinical and cognitive effects of high-frequency magnetic seizure therapy in major depressive disorder. *Depress Anxiety*. 2013;30(2):129–36. https://doi.org/10.1002/da.22005.
60. Mulders PC, van Eijndhoven PF, Schene AH, Beckmann CF, Tendolkar I. Resting-state functional connectivity in major depressive disorder: A review. *Neurosci Biobehav Rev*. 2015;56:330–44. https://doi.org/10.1016/j.neubiorev.2015.07.014.
61. Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. *AJNR Am J Neuroradiol*. 2013;34(10):1866–72. https://doi.org/10.3174/ajnr.A3263.
62. Holtzheimer PE, Mayberg HS. Stuck in a rut: rethinking depression and its treatment. Trends Neurosci. 2011;34(1):1–9. https://doi.org/10.1016/j.tins.2010.10.004.
63. Santaniello S, Fiengo G, Glielmo L, Grill WM. Closed-loop control of deep brain stimulation: a simulation study. *IEEE Trans Neural Syst Rehabil Eng*. 2011;19(1):15–24. https://doi.org/10.1109/TNSRE.2010.2081377.
64. Karas PJ, Lee S, Jimenez-Shahed J, Goodman WK, Viswanathan A, Sheth SA. Deep Brain Stimulation for Obsessive Compulsive Disorder: Evolution of Surgical Stimulation Target Parallels Changing Model of Dysfunctional Brain Circuits. *Front Neurosci*. 2019;12:998. https://doi.org/10.3389/fnins.2018.00998.
65. Tyagi H, Apergis-Schoute AM, Akram H, Foltynie T, Limousin P, Drummond LM, et al. A Randomized Trial Directly Comparing Ventral Capsule and Anteromedial Subthalamic Nucleus Stimulation in Obsessive-Compulsive Disorder: Clinical and Imaging Evidence for Dissociable Effects. *Biol Psychiatry*. 2019;85(9):726-734. https://doi.org/10.1016/j.biopsych.2019.01.017.
66. Giordano U, Mizera J, Żak E, Pilch J, Tomecka P, Dudzik T, et al. Surgical treatment methods in the course of psychiatric disorders: Deep brain stimulation-Novel insights and indications. *Indian J Psychiatry*. 2023;65(8):799–807. https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_266_2.
67. Sullivan CRP, Olsen S, Widge AS. Deep brain stimulation for psychiatric disorders: From focal brain targets to cognitive networks. *Neuroimage*. 2021;225:117515. https://doi.org/10.1016/j.neuroimage.2020.117515.
68. Fenoy AJ, Schulz P, Selvaraj S, Burrows C, Spiker D, Cao B, et. al. Deep brain stimulation of the medial forebrain bundle: Distinctive responses in resistant depression. *J Affect Disord.* 2016;3:143–51. https://doi.org/10.1016/j.jad.2016.05.064. Epub 2016 Jun 3.
69. Morishita T, Fayad SM, Higuchi MA, Nestor KA, Foote KD. Deep brain stimulation for treatment-resistant depression: systematic review of clinical outcomes. *Neurotherapeutics*. 2014;11(3):475–84. https://doi.org/10.1007/s13311-014-0282-1.
70. Salling MC, Martinez D. Brain Stimulation in Addiction. *Neuropsychopharmacology*. 2016;41(12):2798–809. https://doi.org/10.1038/npp.2016.80.
71. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission, and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of

randomized, double-blind, and sham-controlled trials. *Psychol Med*. 2014;44(2):225–39. https://doi.org/10.1017/S0033291713000512.
72. Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol*. 2014;125(11):2150-2206. https://doi.org/10.1016/j.clinph.2014.05.021.
73. Janicak PG, Dunner DL, Aaronson ST, Carpenter LL, Boyadjis TA, Brock DG, et al. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of quality-of-life outcome measures in clinical practice. *CNS Spectr*. 2013;18(6):322–32. https://doi.org/10.1017/S1092852913000357.
74. Addicott MA, Kinney KR, Saldana S, Ip EH, DeMaioNewton H, Bickel WK, et al. A randomized controlled trial of intermittent theta burst stimulation to the medial prefrontal cortex for tobacco use disorder: Clinical efficacy and safety. *Drug Alcohol Depend*. 2024;258:111278. https://doi.org/10.1016/j.drugalcdep.2024.111278.
75. Petrosino NJ, Cosmo C, Berlow YA, Zandvakili A, van 't Wout-Frank M, Philip NS. Transcranial magnetic stimulation for post-traumatic stress disorder. *Ther Adv Psychopharmacol*. 2021;11:20451253211049921. https://doi.org/10.1177/20451253211049921.
76. McTeague LM, Goodkind MS, Etkin A. Transdiagnostic impairment of cognitive control in mental illness. *J Psychiatr Res*. 2016;83:37–46. https://doi.org/10.1016/j.jpsychires.2016.08.001.
77. Fornito A, Harrison BJ, Zalesky A, Simons JS. Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. *Proc Natl Acad Sci USA*. 2012;109(31):12788–93. https://doi.org/10.1073/pnas.1204185109.
78. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry*. 2010;67(5):507–16. https://doi.org/10.1001/archgenpsychiatry.2010.46.
79. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet*. 2018;391(10131):1683–92. https://doi.org/10.1016/S0140-6736(18)30295-2. Erratum in: *Lancet*. 2018;391(10139):e24. https://doi.org/10.1016/S0140-6736(18)31323-0.
80. Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *J Clin Psychiatry*. 2014;75(5):477–89. https://doi.org/10.4088/JCP.13r08815.
81. Zandvakili A, Berlow YA, Carpenter LL, Philip NS. Transcranial Direct Current Stimulation in Psychiatry: What Psychiatrists Need to Know. *Focus (Am Psychiatr Publ)*. 2019;17(1):44–49. https://doi.org/10.1176/appi.focus.20180029.
82. Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry. 2016;208(6):522–31. https://doi.org/10.1192/bjp.bp.115.164715.
83. Zrenner C, Belardinelli P, Müller-Dahlhaus F, Ziemann U. Closed-Loop Neuroscience and Non-Invasive Brain Stimulation: A Tale of Two Loops. *Front Cell Neurosci*. 2016;10:92. https://doi.org/10.3389/fncel.2016.00092.
84. Kraus C, Castrén E, Kasper S, Lanzenberger R. Serotonin, and neuroplasticity - Links between molecular, functional, and structural pathophysiology in depression. *Neurosci Biobehav Rev*. 2017;77:317–26. https://doi.org/10.1016/j.neubiorev.2017.03.007.
85. 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.
86. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. *JAMA Psychiatry*. 2015;72(6):603–11. https://doi.org/10.1001/jamapsychiatry.2015.0071.
87. Balderston NL, Beydler EM, Goodwin M, Deng ZD, Radman T, Luber B, et al. Low-frequency parietal repetitive transcranial magnetic stimulation reduces fear and anxiety. *Transl Psychiatry*. 2020;10(1):68. https://doi.org/10.1038/s41398-020-0751-8.
88. Widge AS. Closing the loop in psychiatric deep brain stimulation: physiology, psychometrics, and plasticity. Neuropsychopharmacology. 2024;49(1):138–49. https://doi.org/10.1038/s41386-023-01643-y.
89. Venkatasubramanian G. Neuromodulation in psychiatry: State-of-the-art & future directions. *Asian* J Psychiatr. 2024;94:104017. https://doi.org/10.1016/j.ajp.2024.104017.
90. Niciu MJ, Mathews DC, Ionescu DF, Richards EM, Furey ML, Yuan P, et al. Biomarkers in mood disorders research: developing new and improved therapeutics. *Rev Psiquiatr Clin*. 2014;41(5):131–4. https://doi.org/10.1590/0101-60830000000027.
91. Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: A systematic review and meta-analysis of randomised sham-controlled trials. *Neurosci Biobehav Rev*. 2018;92:291-303. https://doi.org/10.1016/j.neubiorev.2018.05.015.
92. Holzschneider K, Mulert C. Neuroimaging in anxiety disorders. *Dialogues Clin Neurosci*. 2011;13(4):453–61. https://doi.org/10.31887/DCNS.2011.13.4/kholzschneider.
93. Woopen C. Ethical aspects of neuromodulation. *Int Rev Neurobiol*. 2012;107:315–32. https://doi.org/10.1016/B978-0-12-404706-8.00016-4.
94. Zhou H, Zhang Q, Martinez E, Dale J, Robinson E, Huang D, et al. A novel neuromodulation strategy to enhance the prefrontal control to treat pain. *Mol Pain*. 2019;15:1744806919845739. https://doi.org/10.1177/1744806919845739.
95. Oudin A, Maatoug R, Bourla A, Ferreri F, Bonnot O, Millet B, et al. Digital Phenotyping: Data-Driven Psychiatry to Redefine Mental Health. *J Med Internet Res*. 2023;25:e44502. https://doi.org/10.2196/44502.

Cite this article: Dubey S. A narrative review on neuromodulation for psychiatric disorders: Mechanisms, clinical applications, and future directions. *IP Indian J Neurosci*. 2025;11(3):144-155.