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Neurostimulation in the treatment of psychiatric disorders: Underlying mechanisms and critical analysis of circuit-based interventions

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Neurostimulation of targeted brain regions has emerged as a novel therapeutic approach to induce remission in patients with various psychiatric disorders. This strategy encompasses several modalities, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), and transcranial focused ultrasound neurostimulation (tFUS), all of which aim to modulate dysfunctional neural circuits and restore activity toward physiological ranges. While the clinical efficacy of these techniques is increasingly documented, the mechanisms underlying their effects—beyond immediate changes in regional excitability—remain incompletely understood. Further, neurostimulation represents not only a technical advance, but also a conceptual shift in psychiatry, moving from interventions aimed at modulating neurotransmission or cognition toward circuit-based models of mental illness. This review surveys the current literature to clarify the mechanisms of action of neurostimulation across multiple levels of biological integration, ranging from large-scale neural circuits to cellular and subcellular processes. Subsequently, it explores innovative targets and emerging modalities that expand the scope of circuit-based interventions beyond traditional approaches. Finally, it engages in a critical epistemological reflection, addressing the conceptual challenges that accompany the translation of circuit-based models from neuroscience to clinical psychiatry.

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INTRODUCTION

Psychiatric disorders, including schizophrenia, bipolar disorder (BD), obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and post-traumatic stress disorder (PTSD), are disabling conditions that profoundly affect emotional, cognitive, and social functioning. The mainstay of treatment relies on chronic pharmacotherapy and sometimes psychotherapies. However, these interventions remain markedly inadequate. Many patients experience only partial symptom relief with pharmacotherapies, while a substantial proportion exhibit treatment non-response or resistance. For example, over one-third of patients with MDD or schizophrenia do not experience significant improvement [1, 2]. Side effects further compromise adherence, long-term outcomes, and use in vulnerable populations (e.g. pregnant women). Psychotherapies, despite their low relapse rate, are also limited by cost, poor accessibility, and cultural barriers. These shortcomings highlight the pressing need for innovative, mechanism-based therapeutic approaches. In this context, repeated neurostimulation has gained increasing attention as a promising alternative or adjunct to conventional therapies.

Several neurostimulation modalities have demonstrated therapeutic potential across various psychiatric conditions. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a non-invasive alternative, with substantial evidence supporting its efficacy in MDD, schizophrenia, OCD and PTSD, though protocols are still not fully standardized [3–6]. Transcranial direct current stimulation (tDCS) has reproducible benefits in treating MDD and negative symptoms of schizophrenia as an adjunct, though clinical outcomes remain variable [7–9]. At a more invasive level, vagus nerve stimulation (VNS) and deep brain stimulation (DBS) have been explored for TRD and refractory OCD [10–12]. While DBS has produced robust effects in certain patients, its application remains limited by surgical risks and scalability constraints associated with individualized target optimization [13]. Theta burst stimulation (TBS), a patterned form of TMS that can also be applied to other modalities, offers shorter session durations and enhanced efficacy [14]. More recently, transcranial focused ultrasound neurostimulation (tFUS) has emerged as a novel, non-invasive technique capable of modulating deep brain structures with high spatial precision [15].

Collectively, these modalities reflect a paradigm shift toward circuit-based therapeutic strategies that directly modulate dysfunctional neural networks underlying symptomatology, potentially overcoming many limitations of pharmacological and psychotherapeutic approaches. This idea comes from advances in biological psychiatry showing that these disorders are associated with abnormal activity in specific neural networks: these dysfunctions could be restored by neurostimulation, thus treating the disease. Despite the growing clinical evidence supporting the efficacy of these neurostimulation modalities, the

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mechanisms underlying their therapeutic effects remain only partially understood.

The objective of this review is to provide a critical examination of the emerging concept of circuit-based interventions in psychiatry. Beyond summarizing current evidence on efficacy and mechanisms, this work aims to evaluate the challenges that accompany this paradigm shift by adopting a critical and integrative perspective. We will limit the scope to focused approaches, thus excluding electroconvulsive therapy and VNS. Accordingly, we begin by examining the brain abnormalities in psychiatric conditions at the system/network level and how these abnormalities are targeted by focused neurostimulation, modifying activity in the targeted regions as well as in projecting areas. We continue by focusing on acute neurophysiological mechanisms and then progress to cellular and molecular changes after chronic neurostimulation, exploring how transient effects are maintained over time through neuroplasticity. Subsequently, we explore innovative strategies that expand the scope of circuit-based interventions beyond traditional cortical and subcortical regions. Finally, we engage in a critical epistemological reflection, addressing the conceptual and methodological challenges that accompany the translation of circuit-based models from neuroscience to clinical psychiatry. Through this multi-level and critical approach, the review seeks to clarify both the promise and the inherent limitations of circuit-based interventions as a transformative framework for treating psychiatric disorders.

Mechanisms at a network/system level

In recent decades, accumulating evidence from neuroimaging studies has supported the idea that the pathogenesis of psychiatric disorders is underlain by cerebral morphological and functional alterations [16–19]. This idea is based on 3 key claims: a) Psychiatric disorders are defined by disturbances in cognition, motivation and emotion, emerging from abnormalities across multiple, interconnected brain regions; b) Therapies that counteract these abnormalities—such as repeated neurostimulation targeting the specific brain area involved in the abnormalities—can lead to a resolution of symptomatology;c) Recovery in patients is accompanied by a normalization of brain function and structure, not only in the targeted region but also across the broader neural network associated with the disorder. Here, we will detail the observations on which these claims rely. A summary of the key findings can be found in Table 1 and supplementary Table 1.

Brain abnormalities in psychiatric conditions. Psychiatric conditions share core dysfunctions, e.g., emotional dysregulation, impaired executive functions and anhedonia; they can therefore be described along a continuum. This aligns with the RDoC (Research Domain Criteria) and the Hierarchical Taxonomy of Psychopathology (HiTOP) frameworks, both describing how psychopathology can be conceptualized in a dimensional framework [20, 21]. While the RDoC is aimed at discovering biological mechanisms and biomarkers, the HiTOP model is rather built on symptom clustering, clinical applications and relevance. Consistent with these models, neuroimaging studies have identified cross-disorder alterations in both brain morphology and function. For instance, MDD, OCD, BD, and schizophrenia all exhibit structural abnormalities in a set of interconnected areas, including grey matter loss in the dorsomedial PFC, the hippocampus, the rostral and dorsal anterior cingulate cortex (ACC), the thalamus, the amygdala, and the insula [22] (Fig. 1a). Moreover, MDD, BD, anxiety disorders, and schizophrenia share overlapping patterns of hypoactivation in the left PFC, right insula, right ventrolateral PFC, and right intraparietal sulcus, together with hyperactivation in the mid-cingulate and pre-supplementary motor area (SMA) [22] (Fig. 1b). Other studies focused on activation patterns during specific tasks. For example, MDD, schizophrenic or BD patients show altered ventral striatum (VS) activation when processing rewards [23–25]. In addition, disorder-specific neural abnormalities have also been described, e.g., functional and connectivity abnormalities of the superior temporal gyrus in schizophrenia, or reduced volume of the orbitofrontal cortex, decreased volume and increased activity of the lateral habenula in MDD [26–29]. Connectivity patterns can also be altered between single brain regions: for example, altered functional connectivity between the VS/ventral capsule (VC) region and PFC/limbic areas has been shown in OCD and in BD, increased connectivity has been found between the VS and the default mode network (DMN) in schizophrenia and altered structural connectivity of the medial forebrain bundle (MFB) has been reported in MDD [30–34]. These brain regions are highly interconnected and interact within large-scale functional canonical networks supporting cognitive and emotional processes. These include the DMN, anchored in the medial PFC (including the subgenual ACC: sgACC) and posterior parietal cortex (PPC), which is involved in self-referential mental activity; the salience network, anchored in the dorsal ACC and anterior insula, which detects and filters salient stimuli; and the central executive network, anchored in the dorsolateral PFC (dlPFC) and PPC, supporting working memory and attention. Aberrant engagement of these networks has been linked to various forms of psychopathology [35]. Overall, dysfunctions within any of these individual regions or abnormal connectivity between them can disrupt large-scale network dynamics, ultimately contributing to the emergence and maintenance of psychiatric symptoms.

Effectiveness of repeated/continuous neurostimulation of targeted regions (Fig. 1c). Whatever the methodology used (TMS, tDCS, DBS, tFUS), neurostimulation consists in repeatedly (TMS, tDCS, tFUS) or continuously (DBS) targeting a brain region in psychiatric patients to restore normal cerebral functioning. Except for DBS and tFUS, which can selectively reach deep subcortical regions without affecting superficial cortex, neurostimulation predominantly targets cortical areas implicated in each disorder. Which evidence has been found?

The cortical brain region most targeted by non-invasive stimulation techniques (rTMS and tDCS) is the dlPFC. In the context of rTMS, various stimulation strategies have been explored, including high (10 Hz) and low-frequency (1 HZ) protocols (HF and LF, respectively) and TBS (50 Hz pulses, packaged into bursts at 5 Hz) [30]. HF stimulation of the left dlPFC has consistently demonstrated efficacy in MDD and TRD [31, 32]. Other approaches, e.g., LF right dlPFC stimulation, bilateral dlPFC stimulation (combining HF on one side and LF contralaterally) and TBS of dlPFC have also shown beneficial effects in MDD [33, 34, 36, 37]. Further, HF rTMS or TBS-TMS of the dlPFC are beneficial for negative symptoms of schizophrenia [38–40]. For positive symptoms of schizophrenia, TBS-TMS of the PFC has demonstrated therapeutic effects [41]. Moreover, LF of the right dlPFC is effective in PTSD, while bilateral dlPFC stimulation is effective in OCD [42–46]. Finally, tDCS studies targeting the dlPFC have reported that anodal (starting from the positive electrode) stimulation of the left dlPFC alleviates depressive symptoms [47–49]. Taken together, these findings indicate that dlPFC stimulation exerts transdiagnostic therapeutic effects, even if the efficacy across disorders appears to depend on stimulation parameters, e.g., lateralization (left, right, bilateral) and protocol type (HF, LF, TBS), suggesting that the underlying neural abnormalities only partially overlap. Less evidence exists for other cortical targets. For example, left temporoparietal cortex (TPC), targeted via LF rTMS or via cathodal tDCS is effective in alleviating schizophrenic symptomatology and LF-rTMS as well as anodal tDCS of the SMA is effective in the treatment of OCD [30].

Other strategies, e.g., DBS and tFUS, allow targeting dysfunctional deeply located subcortical circuits. Regarding DBS, most studies showing efficiency in patients with MDD and TRD have

Table 1. Summary of neuropsychiatric conditions and clinical evidence for effects of various neurostimulation techniques.

Disorder	Target region	Parameters	Clinical evidence		Preclinical evidence	Rate
			Data	Summary		
MDD / TRD	**Technique: Transcranial Magnetic Stimulation (TMS / iTBS / Deep TMS)**					
	L-dlPFC	**HF rTMS** (10–20 Hz)	**Study**: 1 MA (N = 30) [31].	→ **Reduction of MDD severity (dose-response)**, *FDA-cleared for TRD (NeuroStar)*	**Model**: *chronic stress model (CUS), in rats* [205–207].→ **rTMS reverses depression-like phenotype**	★★★
	L-dlPFC	**iTBS** (50 Hz triplets at 5 Hz)	**Studies**: 2 MAs (N = 5, 10) [36, 37].	→ **Non-inferior to HF rTMS with shorter sessions,** *FDA-cleared (MagVenture)*		★★★
	L-dlPFC/ACC, fMRI-guided)	**Accelerated iTBS**	**Study**: 1 RCT (n = 29) [208]	→ **High remission rates with guided protocol, rapid onset,** *FDA-cleared (Magnus SNT)*		★★★
	BL-mPFC/dlPFC	**Deep TMS** coil 18 Hz	**Study**: 1 RCT (n = 212) [209]	→ **Effective in TRD,** *FDA-cleared for MDD (BrainsWay)*		★★★
	R-dlPFC	**LF rTMS** (1 Hz)	**Study**: 1 MA (N = 12) [33]	→ **Non-inferior to HF L-dlPFC, alternative protocol for TRD**		★★
	Technique: Transcranial Direct Current Stimulation (tDCS)					
	Anode L-dlPFC / cathode R-dlPFC	**tDCS** (2 mA)	**Studies**: 2 MAs (N = 7, 9) [48, 49], 2 RCTs (n = 120, 245) [47, 210].	→ **Moderate efficacy in MDD**		★★
	Technique: Deep Brain Stimulation (DBS)					
	sgACC	**HF DBS** chronic	**Studies**: 1 RCT (n = 90) [61], 3 open-labels (n = 6, 20, 28) [50, 53, 60].	⚠ ***Moderate response in severe TRD, but pivotal RCT failed***	**Models**: *CUS rats (IL stimulation as sgACC homologue)* [130, 137, 139] → **Reverses anxiety- and depression-like phenotype**	★
	slMFB	**HF DBS** chronic	**Studies**: 2 open-labels (n = 7, 8) [51, 211].	→ Preliminary rapid (days) response targeting reward circuitry		★★
	NAcc / VC-VS	**HF DBS** chronic	**Study**: 1 MA (N = 7) [62] + 1 RCT (n = 29). [212]	⚠ ***Pivotal RCT failed, Limited efficacy in anhedonia-driven TRD***		★
	LHb	**HF DBS** chronic	**Study**: 1 open-label (n = 7) [213].	→ Preliminary response in TRD but high attrition		★
	Technique: Transcranial Focused Ultrasound (tFUS)					
	ILC	**tFUS** (500 kHz 400 kPa)	—	—	**Model**: *UCMS mice* [59] → **Reverses depression-like phenotype** > to SSRI)	**P**
Schizo-phrenia	**Technique: Transcranial Magnetic Stimulation (rTMS)**					
	L-dlPFC	**HF rTMS**	**Studies**: 3 MAs (N = 57, 17, 14) [214–216]	→ **Moderate efficacy on negative symptoms**, no effect on positive symptoms or cognition	**Model**: *MIA (poly I:C) rats*. [217]. ⚠ *No reversal, slight cognitive effect*	★★★
	L-TPJ	**LF rTMS**	**Studies:** 2 MAs (N = 19, 11) [218, 219].	→ **Moderate efficacy for AVH reduction**		★★
	Technique: Transcranial Direct Current Stimulation (tDCS)					
	Anode L-dlPFC / cathode L-TPJ	**tDCS** (2 mA)	**Studies**: 1 MA (N = 10) [220], 1 RCT (n = 100) [9].	→ **Effective on AH and negative symptoms, especially with intensive protocols**	**Models**: *MIA (poly I:C) rats* [221] → **Prevented positive symptoms** (not negative)	★★

Table 1. continued

Disorder	Target region	Parameters	Clinical evidence		Preclinical evidence	Rate
			Data	Summary		
OCD	**Technique: Transcranial Magnetic Stimulation (rTMS / Deep TMS)**					
	BL-dlPFC preSMA mPFC/ ACC	**HF rTMS / Deep TMS**	**Studies**: 5 MAs (N = 10, 25, 18, 21, 24) [5, 45, 46, 222, 223] + 1 RCT (n = 99, Deep TMS) [224].	→ **Efficacy across multiple targets (dlPFC, preSMA),** *Deep TMS H7 FDA-cleared for OCD (BrainsWay)*	—	★★★
	preSMA / SMA	**LF rTMS** (1 Hz)	**Studies**: 3 MAs (N = 10, 18, 21) [45, 46, 222]	→ **Inhibitory rTMS over SMA significantly reduces Y-BOCS**		★★
	Technique: Transcranial Direct Current Stimulation (tDCS)					
	preSMA / SMA / OFC	**tDCS** (2 mA)	**Studies**: 3 MAs (N = 3, 8, 6) [223, 225, 226]	⚠ ***No active-vs-sham superiority across 3 MAs***	—	★
	Technique: Deep Brain Stimulation (DBS)					
	ALIC VC-VS NAcc BNST STN ITP	**HF DBS** chronic	**Study**: 1 MA (N = 31) [227].	→ **Effective in severe refractory OCD across multiple targets,** *FDA-Humanitarian Device Exemption (Medtronic Reclaim)*	**Model**: *SAPAP3 KO mice* [228] → **Reverses OCD-like behaviours**	★★★
PTSD	**Technique: Transcranial Magnetic Stimulation (rTMS)**					
	R-dlPFC	**HF rTMS / LF rTMS**	**Studies**: 4 MAs (N = 3, 11, 8, 15) [229–232].	→ **Robust replicated efficacy on PTSD**, HF favored over LF.	**Model**: *single-prolonged stress (SPS) rats* [233] → **Prevents anxiety**	★★
	Technique: Transcranial Direct Current Stimulation (tDCS) + Virtual Reality (VR)					
	vmPFC	**tDCS** (2 mA, anodal)	**Study**: 1 RCT (n = 54, tDCS+VR vs sham+VR). [234].	→ Preliminary positive evidence	—	★
	Technique: Transcranial Focused Ultrasound (tFUS)					
	ILC	**tFUS**	—	—	**Model**: *fear-conditioned rats* [235] → **extinction ↑**	**P**
Bipolar disorder	**Technique: Transcranial Magnetic Stimulation (rTMS / iTBS / Deep TMS)**					
	L-dlPFC / R-dlPFC	**HF rTMS, iTBS, Deep TMS**	**Studies**: 4 MAs (N = 14, 11, 12, 56) [236–239] + 1 RCT (n = 50, Deep TMS) [240].	→ **Efficacy in BD-Dep**, mania subgroup inconclusive, *FDA breakthrough device designation (NeuroStar) for BD-Dep).*	—	★★★
	Technique: Deep Brain Stimulation (DBS)					
	sgACC	**HF DBS** chronic	**Study**: 2 open-labels (n = 17, 28) [53, 241].	→ **moderate efficacy in BP-II as in TRD**	—	★

Scoring legend. ★★★ Robust clinical evidence (multiple converging RCTs and/or meta-analyses, established or regulatory-approved indication). ★★ Moderate clinical evidence (replicated RCTs or consistent meta-analytic findings). ★ Limited or preliminary clinical evidence (single trials, small samples, open-label or variable outcomes). **P** Predominantly preclinical evidence, not yet established in humans for this disorder × target × stimulation combination. ⚠ flags critical caveats (e.g. pivotal RCT failed, limited efficacy in specific subpopulation).

ACC Anterior cingulate cortex, *AH* auditory hallucinations, *ALIC* anterior limb of the internal capsule, *AVH* auditory verbal hallucinations, *BD* bipolar disorder, *BD-Dep* depressive phase of bipolar depression, *BL* bilateral, *BNST* bed nucleus of the stria terminalis, *BP-II* bipolar disorder type II, *CUS* chronic unpredictable stress (rodent model), *DBS* deep brain stimulation, *Deep TMS* deep transcranial magnetic stimulation (H-coil family), *dlPFC* dorsolateral prefrontal cortex, *FDA* U.S. Food and Drug Administration, *fMRI* functional magnetic resonance imaging, *HF* high frequency, *ILC* infralimbic cortex (rodent homologue of human vmPFC / sgACC), *iTBS* intermittent theta-burst stimulation, *ITP* inferior thalamic peduncle, *L-dlPFC / R-dlPFC* left / right dorsolateral prefrontal cortex, *LF* low frequency, *LHb* lateral habenula, *MA* meta-analysis, *MDD* major depressive disorder, *MIA* maternal immune activation, *mPFC* medial prefrontal cortex, *NAcc* nucleus accumbens, *OCD* obsessive-compulsive disorder, *OFC* orbitofrontal cortex, *preSMA* pre-supplementary motor area, *PTSD* post-traumatic stress disorder, *RCT* randomized controlled trial, *rTMS* repetitive transcranial magnetic stimulation, *sgACC* subgenual anterior cingulate cortex (Brodmann area 25), *sham* inactive comparator (placebo stimulation), *slMFB* supero-lateral branch of the medial forebrain bundle, *SMA* supplementary motor area, *SPS* single prolonged stress (rodent model of PTSD), *SSRI* selective serotonin reuptake inhibitor, *STN* subthalamic nucleus, *tDCS* transcranial direct current stimulation, *tFUS* transcranial focused ultrasound, *TMS* transcranial magnetic stimulation, *TPJ* temporo-parietal junction, *TRD* treatment-resistant depression, *UCMS* unpredictable chronic mild stress (rodent model), *VC-VS* ventral capsule / ventral striatum (combined target), *vmPFC* ventromedial prefrontal cortex, *VR* virtual reality.

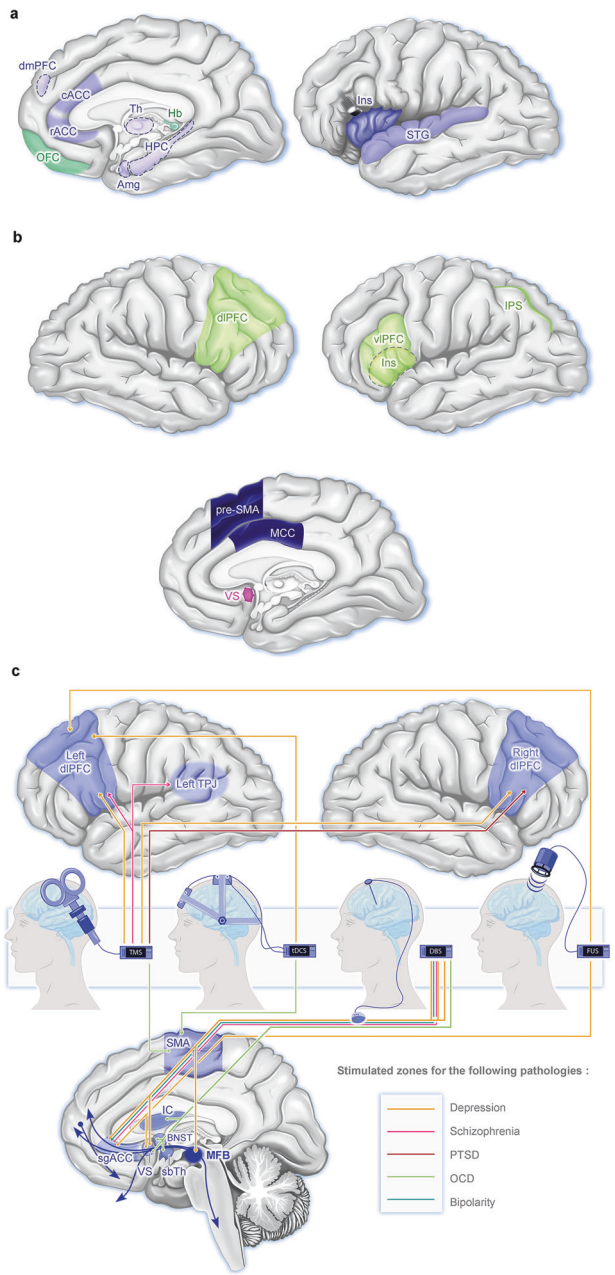

Fig. 1 Brain alterations in psychiatric disorders and cerebral targets of neurostimulation. a Structural abnormalities present across various psychiatric disorders (purple) or specifically observed in specific disorders such as MDD (green); (**b**) Changes in activity across various disorders. In green, areas showing hypoactivation at rest, in midnight blue regions showing hyperactivation at rest; in pink, area showing hypoactivation in specific situations ; (**c**) Brain targets of various neurostimulation modalities in specific psychiatric disorders. dmPFC dorsomedial prefrontal cortex, dlPFC dorsolateral prefrontal cortex, vlPFC ventrolateral prefrontal cortex, TPJ temporoparietal junction, OFC orbitofrontal cortex, MCC mid cingulate cortex, dACC dorsal cingulate cortex, rACC rostral anterior cingulate cortex, sgACC subgenual anterior cingulate cortex, Ins insula, STG superior temporal gyrus, Tha thalamus, dmTh dorsomedial thalamus, Hb habenula, HPC hippocampus, Amg amygdala, VS ventral striatum, BNST bed nucleus of stria terminalis, MFB medial forebrain bundle, TMS transcranial magnetic stimulation, tDCS transcranial direct current stimulation, DBS deep brain stimulation, tFUS focused ultrasound stimulation.

focused on targetssuch as the sgACC, the VC/VS, and the MFB [13, 50, 51]. Similar neural structures have been explored in OCD, where stimulation sites have included the ventral anterior limb of the internal capsule, the VS, the bed nucleus of the stria terminalis and the subthalamic nucleus [52]. Fewer studies have investigated DBS in BD, most targeting the sgACC as in MDD [53]. In schizophrenia, DBS research remains limited, though preliminary studies have targeted the sgACC and VS to modulate dysfunctional limbic circuitry [54, 55]. Regarding tFUS, studies mainly included MDD and TRD patients or animal models of MDD. In patients, severity of the symptoms is reduced when targeting the left dlPFC or the VC/VS while in animal models targeting the functional equivalent of sgACC is effective [56–59].

Focused neurostimulation modifies not only the activity within the targeted area but also within interconnected brain networks (Fig. 2). As psychiatric disorders are increasingly understood as disturbances of large-scale interconnected brain regions rather than dysfunctions of isolated regions, one can ask: how can focal neurostimulation induce remission in globally dysregulated systems? One prevailing hypothesis is that repeated/continuous neurostimulation of a node within a network can affect activity in interconnected regions, thereby restoring normal connectivity and function across distributed circuits [50]. In this frame, neurostimulation acts as a network-level modulator, rather than a purely local intervention. This is supported by evidence from structural and functional neuroimaging. For instance, DBS of the sgACC in TRD has been shown to normalize hyperconnectivity between the sgACC and limbic regions (amygdala, hypothalamus), while strengthening connectivity with PFC regions [50]. Similarly, functional MRI (fMRI) and PET studies have demonstrated that chronic sgACC or VC/VS stimulation results in widespread metabolic and connectivity changes encompassing the mPFC, orbitofrontal, and thalamic regions, correlating with clinical improvement [60–62]. Comparable effects have been observed in non-invasive stimulation approaches. For example, resting-state fMRI studies show that TMS targeting the left dlPFC in MDD modulates connectivity with the sgACC [63, 64]. Regions with the strongest anticorrelation between the stimulation site and the sgACC are associated with the greatest clinical benefit, highlighting the importance of network connectivity in determining treatment efficacy [65].

Collectively, neuroimaging evidence thus supports the view that focal neurostimulation induces distributed network reorganization through modulation of structural and functional connectivity, restoring balanced communication among cortical and subcortical regions. Thus, while the stimulation is anatomically localized, its therapeutic action is fundamentally network-mediated, consistent with the circuit-based framework of psychiatry. However, alternative explanations could be proposed as well. For example, it could be that, in the diseased brain, new function induced by the neurostimulation has appeared that might help cope with the cognitive dysfunction. Therefore, the focused neurostimulation might, by altering the dysfunctional circuit, decrease the resulting symptoms.

Neurophysiological mechanisms

Neurostimulation techniques modify neuro-synaptic components at various levels–from acute functional processes to neuroplastic stabilization, likely occurring in a progressive and feedforward manner (Fig. 3). The gradual attainment of activation thresholds across hierarchical functional levels translates intracellular processes to synaptic, trans-synaptic, neuroplastic, and eventually circuit and network level changes. Here, we analyse acute neurophysiological effects, i.e., at the level of single neurons and of population of neurons. Table 2 provides a summary of these mechanisms across different modalities.

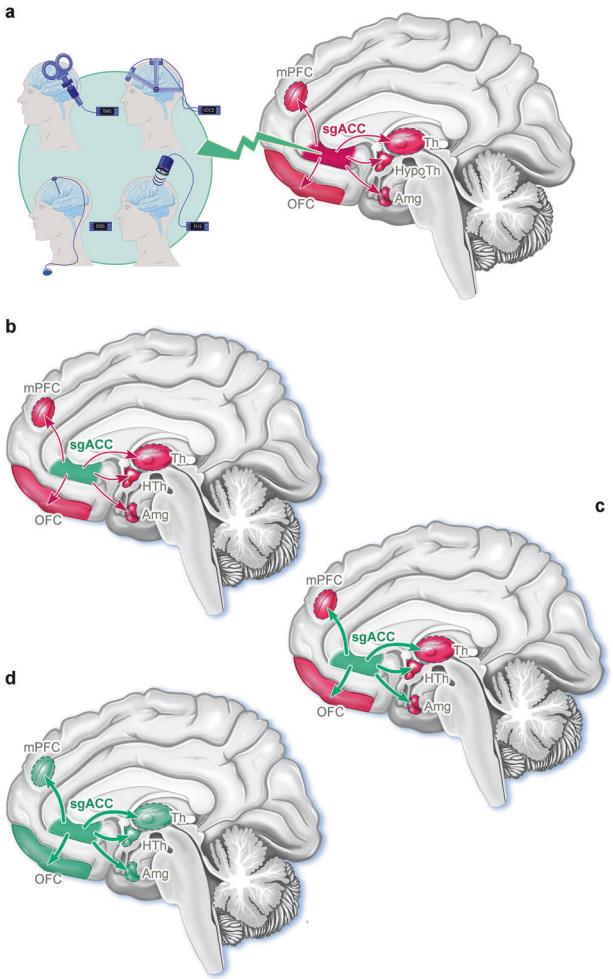

Fig. 2 Mechanisms underlying therapeutic effects of repeated focused neurostimulation: network level. a Circuit of interconnected brain areas that are dysfunctional in a given disorder; (**b**) The sgACC is targeted in a focused way by different neurostimulation methods to treat the disorder, (**c**) Projections of the sgACC are recruited, (**d**) The function of the brain areas to which the sgACC is projecting turn back to a physiological function, inducing alleviation of symptoms. mPFC: medial prefrontal cortex, OFC: orbitofrontal cortex, sgACC: subgenual anterior cingulate cortex, Th: thalamus, HTh: hypothalamus, Amg: amygdala.

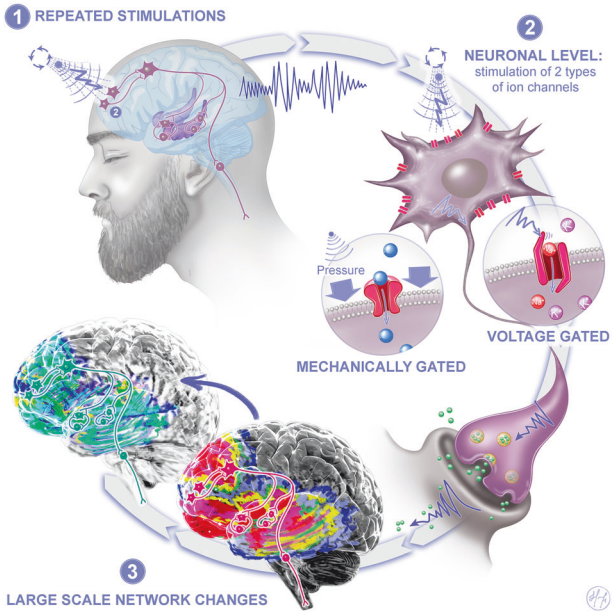

Fig. 3 Acute and chronic effects of neurostimulation across different organizational levels. 1 Repeated delivery of input stimuli - electrical current, magnetic fields or ultrasound - modifies the activity of neuronal ensembles embedded within a complex circuit, which could extend to distal subcortical regions of the brain. This would lead to defined changes in oscillatory activity [electroencephalographic(EEG) or local field potential (LFP) detection]. **2** At the microscopic level, these scaled changes are due to interventions in the somatodendritic activity of neurons: rTMS through electromagnetic induction, FUS through activation of pressure-sensitive and mechanically gated ion channels and tDCS through the activation of voltage-gated ion channels. Downstream and at the level of the synapse, the resultant electrochemical changes translate to alterations in the exocytosis of neurotransmitters across different synaptic regions within the affected macro-circuits. **3** These molecular and cell circuit events are magnified in frequency, timing and power by repeated neurostimulations paving way to neuroplasticity-conducive changes simultaneously occurring across different regions of the brain. Altogether, this can ultimately lead to stable large-scale changes in network activity; and in the disordered brain, the stable recovery of normal or close-to-normal brain-wide activational responses and stress adaptation.

Acute/short-term effects of direct electrical stimulation. To understand network-level effects, it is essential to examine how neural interfaces generate signals at intracellular and synaptic levels. The exact mechanisms in this transduction process are not completely understood, especially in how energy fields percolate through the anisotropic features of neural tissue and how this affects physiological changes.

Early DBS mechanism studies revealed challenges due to the heterogeneous composition of neural tissues, leading to the hypothesis of stimulation-induced reversible functional lesioning [66, 67]. As demonstrated in animal studies, attenuation of neuronal firing can result from depolarization blockade, inactivation of voltage-gated sodium channels or indirect effects on calcium dynamics in glia and neurons [68–70]. Moreover, the simultaneous stimulation of excitatory and inhibitory neurons contributes to mutual cancellation of effects and to functional inactivation [71, 72]. While some of these molecular mechanisms have been observed with newer, non-invasive modalities, such as on calcium mobilization in glia and neurons, there are specific ones that are not, partly due to differences in signal strength and other features, as discussed later [73]. For example, tDCS does not seem to achieve abovefiring thresholds to induce depolarization blockade but rather modifies below-firing membrane potentials that affects cell excitability [73] (see next sections).

Nonetheless, for all electrical stimulations, quantifying inputs can be complex due to separable stimulation effects on somatodendrites and fibers. Indeed, this decoupling could be an emergent phenomenon earlier observed with DBS if it yields to axonal firing occurring asynchronously with somatodendritic activation [51]. More precise determination of the net effect of neurostimulation should take into account the resistive properties of overlying layers, the cytoarchitecture of the target (gray matter and myelinated or unmyelinated axons) and its neurochemical anatomy (e.g. glutamatergic vs. GABAergic), the orientation of target structures relative to the stimulus-input, hodological connectivity of the target and its functional network (central nodes vs. edges), and the immediate microenvironment of the input-interface (e.g. glial composition) [74]. Recognizing the relative sensitivity of axonal fibers to stimulation and the need to narrow down variables, the focus shifted toward targeting white matter pathways.

The hypothesized principle underlying direct electrical modulation of axons can be articulated as the interaction between

Table 2. Summary of neurophysiological and neuroplastic mechanisms of focused neurostimulation modalities in treating psychiatric disorders.

Neurostimulation technique		Invasive?	Stimulation characteristics			Cellular effects			Circuit-level effects		
			Physical principle	Depth/ focality	Key parameters	Primary cellular targets	Mechanism of action	Neuroplastic effects	Oscillatory/ network effects	Target sites	Target pathologies
DBS		Yes	Direct electrical stimulation	Highly localized and focused; reaches deep subcortical regions [13, 50–55]	2–5 mA; orientation-selective electrodes; electrode polarity [75–79]	Somatodendrites, axon fibers, white matter pathways, nodes of Ranvier [75–79]	Depolarization blockade, sodium channel inactivation, asynchronous activation [66–72]	Chronic stimulation increases hippocampal neurogenesis and synaptic proteins (BDNF, CREB), facilitating long-term potentiation (LTP) and synaptic remodelling [128–131, 135, 137, 139]	Normalizes hyperconnectivity; enhances mood-related oscillatory rhythms; reduces beta oscillations in OCD [50, 60–62, 114]	sgACC, VC/VS, MFB, internal capsule, STN [13, 50–55]	TRD, refractory OCD, BD, schizophrenia [13, 50–55]
tDCS		No	Direct electrical stimulation	Diffuse electric fields across multilayered tissue; lower focality/selectivity [79, 80]	1–4 mA; anodal/ cathodal polarity [80]	Somatodendrites and axon fibers broadly affected [79, 80]	Sub-threshold modulation of membrane potentials and neuronal excitability [79, 80]	Increases BDNF/TrkB signaling for synaptogenesis. Strongly recruits metaplasticity; pairs effectively with immersive behavioral/ VR therapies to stabilize structural rewiring; induces LTP-like plasticity in the hippocampus [135, 150, 151, 163, 175–179]	Reduces alpha and beta oscillations; can synchronize oscillations to therapeutic frequencies [106, 107]	left dlPFC, left TPC, SMA [30, 47–49]	MDD, schizophrenia, OCD [7–9, 30]
TMS	rTMS	No	Electromagnetic induction	Primarily cortical (~4 cm depth); affects gray and white matter [81, 83, 84]	HF (10 Hz), LF (1 Hz), lateralized or bilateral protocols [30–34, 36–46]	Gray and white matter neurons, myelinated axons [81, 83, 84];	Trans-synaptic activation, intracellular calcium signalling, depolarization blockade [81, 83, 84]	Enhances cell proliferation and immature neuron markers (DCX); increases synapsin and PSD-95 expression [123, 124]; Single-session effects on hippocampal neurogenesis remain inconsistent [125]; Rescues stress-induced dendritic spine loss in IT neurons [146, 147]; Increased PFC dendritic arborization and spinal density [157, 158]; Potentiates excitatory synpases on CA1 neurons [149]	Modulates theta/ gamma oscillations; increases gamma power; alters sgACC connectivity [63–65, 108–110, 160]	dlPFC, PL, TPC, SMA [30–34, 36–46, 146, 147]	MDD, TRD, schizophrenia, OCD, PTSD [30–34, 36–46]
	TBS	No	Electromagnetic induction using patterned theta bursts	Improved focality and shorter sessions relative to conventional rTMS [14, 31, 92, 93, 95, 96]	50 Hz pulses delivered in 5 Hz bursts; continuous vs intermittent paradigms [14, 31, 92, 93, 95, 96]	Gray and white matter neurons, myelinated axons [81, 83, 84, 92, 93, 95, 96] IT neurons in the dmPFC and PL [146, 147]	Theta-patterned stimulation facilitates synaptic plasticity and oscillatory entrainment [81, 83, 84, 92, 93, 95, 96]		Enhances theta and gamma entrainment; continuous paradigms inhibitory, intermittent paradigms excitatory [92, 93, 95, 96]		
tFUS		No	Mechanical/ acoustic induction	Deep brain stimulation with high spatial precision (~1 × 1.5 mm focal point) [85, 87, 88]	Low intensity (<3 W/cm^2), 200–650 kHz, 10 Hz–3 kHz pulse repetition frequency [85]	Deep cortical and subcortical neurons; mechanosensitive ion channels (TRPP1/2, TRPC1, Piezo1) [86–88]	Membrane tension activates mechanosensitive calcium-permeable ion channels, driving burst firing [86–88]	Calcium-dependent pathways drive the expression of plasticity-related growth factors [142]; activation of synaptogenic kinases such as CamK and Akt [143]; potential metaplastic effects where inhibitory priming boosts later facilitatory responses [164, 165]	Selectively modulates oscillatory activity in targeted regions [111]	Left dlPFC, VC/ VS, sgACC homologues [56–59]	MDD, TRD [56–59]

BD Bipolar disorder, *BDNF* brain-derived neurotrophic factor, *CREB* cAMP response element-binding protein, *DBS* deep brain stimulation, *DCX* doublecortin, *dlPFC* dorsolateral prefrontal cortex, *HF* high frequency, *IT* intratelencephalic, *LF* low frequency, *LTP* long-term potentiation, *MDD* major depressive disorder, *MFB* medial forebrain bundle, *OCD* obsessive-compulsive disorder, *PL* pre-limbic cortex, *PSD-95* postsynaptic density protein 95, *PTSD* post-traumatic stress disorder, *rTMS* repetitive transcranial magnetic stimulation, *sgACC* subgenual anterior cingulate cortex, *SMA* supplementary motor area, *STN* subthalamic nucleus, *TBS* theta burst stimulation, *tDCS* transcranial direct current stimulation, *tFUS* transcranial focused ultrasound, *TMS* transcranial magnetic stimulation, *TPC* temporoparietal cortex, *TRD* treatment-resistant depression, *TrkB* tropomyosin receptor kinase B, *TRPC1* transient receptor potential canonical 1, *TRPP1/2* transient receptor potential polycystic 1/2, *VC/VS* ventral capsule / ventral striatum, *VR* virtual reality.

stimulus-input and transmembrane ionic flow, particularly at the nodes of Ranvier, where a high concentration of voltage-gated and leak channels is present. This interaction exemplifies a fundamental mechanism in signal propagation. A cathode deployed at the input interface likely leads to cationic accumulation, resulting in action potential generation, whereas an anode causes hyperpolarization [75, 76]. The local effects of electrical stimulation have been shown to largely depend on the orientation of the electrode lead relative to the axonal fibers, motivating advances in orientation-selective electrode designs [77, 78].

Other relevant input-interface parameters include amplitude and pulse width, which are moderated by the resistive properties of overlying layers. While DBS and tDCS typically use similar current ranges (2–5 mA for DBS, 1–4 mA for tDCS) [79, 80], tDCS results in lower charge densities reaching the target due to impedance from the scalp and surrounding tissues. At similar frequencies, anodal tDCS delivers low charge densities and electric field strengths, which, while sub-threshold for direct action potential excitation, can gradually alter membrane potentials and increase excitability [80]. The weak and diffuse electric fields of tDCS propagating across larger multi-layered areas contrast sharply with DBS-generated localized and focused input. Because of this, the acute effects of tDCS depart from the traditional mechanisms of DBS. Specifically, cathodal tDCS hyperpolarizes membranes while anodal-type depolarizes them without altering tonic firing, decreasing and increasing excitability, respectively [10, 58, 73, 80]. Unlike DBS, tDCS has lower selectivity between somatodendrites and axon fibers, making it harder to achieve precise stimulation effects [80].

Acute/short-term effects of non-electrical stimulation. Non-invasive modalities, e.g., TMS and tFUS employ the principles of electromagnetic and mechanical induction, respectively [81, 82]. Conventional TMS coils generate magnetic pulses that predominantly penetrate only the superficial layers, reaching cortical depths of ~ 4 cm [83]. The efficacy of electrical induction decreases with depth yet remains capable of affecting gray and white matter. The presence of myelinated axons facilitates trans-synaptic activation. This is largely due to their orthogonal orientation relative to the magnetic field. This recapitulates interface-fiber orientation effects demonstrated in DBS. Another molecular effect shared with DBS, but not with tDCS, is the capacity of TMS to achieve depolarization blockade and inactivation states [84].

tFUS induction likewise depends on defined stimulus-input parameters [83]. Indeed, non-thermogenic, low intensity (<3 W/cm^2), low fundamental frequency (200–650 kHz), and low pulse repetition frequency (10 Hz to 3 kHz) have been identified as the goldilocks zone for therapeutic effects. Relative to TMS, low-intensity and high-frequency tFUS can target deeper brain structures with fine precision. This is achieved by the convergence of multiple ultrasound beams into a steerable focal point as small as a 1×1.5 mm area [85]. The build-up of acoustic energy induces membrane tension that activates mechanosensitive, calcium-permeable ion channels, including the polycystin transient receptor potential-1 and -2 (TRPP1/2), the transient receptor potential canonical-1 (TRPC1) and Piezo1. The ensuing excitatory response results in increased inward calcium conductance, without the need for cavitation, temperature changes, structural deformation or altered synaptic transmission. This effect is further amplified by subsequent activation of calcium-activated and voltage-gated channels, which altogether can drive burst firing [86].

As another non-invasive technique, tFUS offers advantages in spatial resolution and deeper brain stimulation. tFUS signals undergo attenuation up to 80% before reaching cortical targets [87, 88]. However, several methodologies and adjustments have been proposed to mitigate this, including the deployment of hemispherical phased-array transducers, real-time guidance via CT/MRI imaging, and the application of scalp-cooling techniques [89–91]. Additionally, the effects of pulsing patterns for both TMS and tFUS have been investigated.

Recent efforts have determined that mimicking the brain's natural theta rhythm (4–8 Hz; e.g. 3 pulses at 50 Hz, repeated at intervals of 200 ms) using theta burst FUS and TBS-TMS enhances potency and amplitude of effects [92, 93], as well as, improves focality of stimulation targeting [94]. Another parameter of interest is the continuity of patterned stimulation. It has been shown that continuous stimulation or a single burst train typically 20–40 seconds long has an inhibitory effect on cortical excitability. On the other hand, intermittent stimulation, consisting of repeated 2-second sequences every 10 seconds, is excitatory [95, 96]. The precise mechanisms underlying these effects are under investigation.

Acute effects on oscillatory brain rhythm. Single-unit and ensemble activity integrate into population activity within circuits. This, in turn, contributes to the generation of brain wave oscillations through broader inter-circuit communication. The synchronization of population activity serves as a timing framework for the modulation of cognitive-emotional processes. Aberrant alterations of oscillatory patterns across frequency bands often signify network-level dysfunction. A prominent observation across a spectrum of psychiatric disorders is a general shift toward decreased oscillatory rhythm in slow-wave (delta and theta) and fast-wave activity (gamma) [97–103], though paradoxical cases have also been shown, e.g., increased alpha and beta activity [100]. These involve a shared array of brain regions, predominantly the PFC (particularly the right hemisphere), cingulate gyrus, thalamus, insula, hippocampus, amygdala, and basal ganglia. While such overlaps are apparent, distinctive patterns of laterality (e.g., alpha asymmetry in schizophrenia compared to MDD) and differences in functional connectivity (coherence) across specific frequency bands (e.g., beta and gamma power disparities between schizophrenia and BD) could also serve to differentiate psychiatric conditions [104, 105].

Localized subcellular effects of neurostimulation can rapidly influence the synchronization and frequency of neural oscillations, thereby altering overall brain activity. For example, tDCS has been shown to reduce alpha and beta wave activity in targeted cortical regions [106]. Elevated activity has been linked with negative thinking and rumination, while attenuations with improved mood and anxiolysis [107]. Similarly, rTMS modulates theta and gamma oscillations, potentially leading to enhanced cognitive-affective processing [108]. In MDD, DBS and rTMS enhance the amplitude of specific oscillatory rhythms associated with mood regulation, particularly within the PFC and associated limbic structures. For instance, rTMS targeting the dlPFC has been correlated with increased gamma oscillations [108], which promote synaptic plasticity and positively influence mood [109, 110]. Synchronization and coherence within the gamma band correlate with increased cognitive processing. They reflect the precise timing of neuronal activity, which facilitates spike-timing-dependent plasticity [109]. Likewise, tFUS has shown to selectively modulate oscillatory activity in targeted brain regions [111], a potentially useful approach for rebalancing dysfunctional circuits frequently observed in MDD.

In the context of psychiatric pathology, the modulation of neural oscillations through various neurostimulation interventions can regulate dysfunction within the associated neural networks. For instance, anodal tDCS can efficiently synchronize brain oscillations to desired frequencies, which may help alleviate excessive theta activity commonly observed in anxiety/depressive episodes [112, 113]. In OCD, DBS has been associated with reductions in beta oscillations [114, 115].

The effects of neurostimulation on oscillatory rhythm is not just mirroring local neurophysiological activity. They may also predict

the spatiotemporal trajectory of stable neuroplastic changes following repeated stimulation, reflecting network-level connectivity associated with therapeutic benefit. Oscillations create spatiotemporal windows of heightened responsivity. The synchronization of these windows lead to more efficient communication between involved distinct regions. As oscillatory patterns stabilize, information integration across neural networks is enhanced, indicating a more robust functional state. These effects, especially on theta and gamma, are crucial in facilitating the conditions necessary for spike timing-dependent plasticity and long-term potentiation (LTP) [116]. As ensembles of presynaptic and postsynaptic neurons are coincidentally activated within optimal phases of these oscillations, the probability of Hebbian plasticity is heightened [117, 118]. The capacity of neurostimulation techniques to achieve rapid and precise modifications in oscillatory patterns therefore presents great potential in developing effective network-level interventions to enhance therapeutic outcomes. Repeated neurostimulation will likely induce persistent modifications in frequency, power, coherence, and phase synchronization of brain waves across different regions.

Neurostimulation-induced changes in brain oscillations are likely not only correlational with pro-growth plasticity but causally linked in a bidirectional manner. While causal demonstrations remain sparse, some studies have pointed out areas where they can indicate causal linkages. As an example, brainwave frequency bands can be entrained to rTMS signal input synchronized with their oscillations. Locking into this dramatically increases the encoding of new information, modifies neural excitability and promotes plasticity [119].

Finally, it is worth raising a caveat regarding heterogenous oscillatory rhythm responses to neurostimulation and inconsistent outcomes, yielding maladaptive plasticity under certain conditions. This may well implicate individual differences partly attributed to baseline psychobiological and emotional states that could impact subsequent responses to plasticity-inducing stimulation protocols. These metaplasticity influences will be discussed in more detail in the next section.

NEUROPLASTICITY-RELATED MECHANISMS AT CELLULAR AND MOLECULAR LEVELS: CHRONIC EFFECT OF NEUROSTIMULATION

The network-level effects of repeated stimulation are accompanied by cellular and molecular adaptations that may contribute to these functional changes, including neural progenitor proliferation, neurogenesis, and synaptic and structural plasticity.

Cellular level: Adult hippocampal neurogenesis

Adult neurogenesis refers to the proliferation of neural stem cells and their subsequent differentiation into neurons during adulthood. This occurs primarily in the subventricular and subgranular zone of the hippocampal dentate gyrus (DG). Some pharmacotherapies such as antidepressants increase both hippocampal cell proliferation and neurogenesis. Experimental suppression of adult-born neurons blocks their therapeutic effects [120–123]. This raises the question: does neurostimulation also increase adult-born hippocampal neurons?

Preclinical evidence suggests rTMS enhances DG cell proliferation and immature neuron marker expression (e.g., DCX) [124] though neurogenic effects vary by protocol. For instance, one study found that a single session of rTMS or TBS-TMS did *not* significantly alter markers of cell proliferation in adult mouse hippocampus [125] while in another study, a particular form of rTMS elicited changes in behavior but not in hippocampal neurogenesis [126]. Furthermore, in most studies, the rTMS protocol used was not focal, thus, not reflecting clinical conditions. Furthermore, these pieces of evidence are only correlational, and not causal: to our knowledge, no study investigated whether suppression of adult neurogenesis prevented the therapeutic effects of rTMS.

DBS effects on adult neurogenesis are region- and protocol-dependent. In rodents, continuous dorsal DG DBS increased hippocampal BrdU-labelled cells [127] while an acute anterior thalamic DBS enhanced DG neurogenesis and reversed corticosterone-induced reductions [128]. In addition, DBS of the thalamic reticular nucleus produced antidepressant-like behavioral effects accompanied an increase in hippocampal immature neurons [129]. In stressed animals, continuous DBS of the ventromedial PFC induced anxiolytic and antidepressant effects and boosted hippocampal neurogenesis [130]. Interestingly, the anxiolytic effects seem linked to the therapeutic effects, as suppression of neurogenesis by injection of the antimitotic drug temozolomide prevented the anxiolytic but not antidepressant effects [130]. Finally, when targeting the nucleus accumbens in a high-anxiety mouse strain, continuous DBS produced anxiolytic and antidepressant effects, suggesting sustained stimulation is needed to influence neurogenic and behavioral outcomes [130]. Interestingly, most of these effects on hippocampal neurogenesis appear only after chronic continuous, but not after acute DBS, coinciding with therapeutic effects [131]. These findings apply to pathologies treatable with antidepressants, such as MDD or PTSD and have not been explored in other diseases such as schizophrenia.

Subcellular level: Synaptogenesis

Chronic conventional treatments, e.g. by antidepressants, mobilize multiple molecular signalling pathways from diverse upstream precursors crucial to therapeutic structural changes [132–134]. PFC-tDCS increases BDNF and BDNF-TrkB signalling [135]. This promotes survival, neuronal growth, and repair. Anodal tDCS that enhances the frequency and synchronization of neural oscillations could improve the timing of synaptic activity and support structural rescue [136]. Meanwhile, continuous DBS augments the expression of synaptic proteins, including BDNF and cAMP response element-binding protein (CREB) facilitates LTP and synaptic remodelling, enhancing connectivity and ameliorating the dysfunctional circuitry commonly observed in OCD and MDD [137–139]. rTMS increases expression of synapse-associated proteins (e.g. synapsin and postsynaptic density protein-95) critical for maintaining synaptic stability and function [140]. The synaptogenic effects of dlPFC-rTMS is mediated by enhanced activation of glutamate and dopamine pathways [141]. Hippocampal tFUS also promotes synaptogenesis through calcium-dependent mechanisms [142]. Quantitative proteomic analysis after tFUS determined the involvement of CaMK and phosphatidyl inositol-3 kinase (PI3K)/serine threonine kinase (Akt) and phospholipase C (PLC)-γ pathways [143].

Intracellular cascades may be variably activated by different modalities, the general inducible requirements may likely be shared across modalities. Investigations into rapid antidepressant mechanisms, e.g., those by ketamine [144], proposed possible common pathways converging onto the mechanistic target of rapamycin complex-1 (mTORC1) [132]. mTORC1 regulates proteogenesis, structural restoration and plasticity by modulating translational regulators, e.g. ribosomal S6 kinases, eukaryotic initiation factor 4E, and eukaryotic elongation factor 2. mTORC1 modulation has been seen with antidepressants, anxiolytics and antipsychotics [132, 145]. Based on the progression of functional and structural plasticity and antidepressant onset in pre-clinical studies, mTORC1-mediated structural changes are hypothesized to precede the therapeutic effects of neurostimulation [133]. Some protocols, notably an accelerated-intermittent form of TBS, have shown a fairly rapid therapeutic progression [146, 147], and could be tested in the future.

Regarding synaptic plasticity effects, acute or short-term neurostimulation has reliably induced LTP, likely by reproducing

relevant temporal tetanic patterns (e.g., with homotypic or non-associative LTP), spatial convergence (e.g., with heterotypic or associative LTP) and timing dynamics (spike-timing-dependent plasticity) of repeated /sustained neuro-electrochemical stimulation [148]. In NMDA receptor (NMDAR)-dependent plasticity, the induced depolarization pattern within the circuit would clear magnesium from the pore and allow calcium influx to form calcium-calmodulin complexes, subsequently activating kinases (e.g., CaMKII and mTOR) to modulate ion channel conductance, AMPA receptor membrane insertion, and gene expression [134]. Low-frequency neurostimulation can induce long-term depression (LTD). Therapeutic effects may depend on the circuit location of synaptic weakening, potentially restoring excitatory-inhibitory homeostasis [148].

Animal neurostimulation studies have demonstrated LTP/LTD-like postsynaptic potential modulation ex vivo and in vivo by rTMS [149], tDCS [150, 151] and FUS [143]. In humans, anodal tDCS (1–3 mA for 10–15 min) of the human occipital or motor cortex potentiates visually evoked EEG potentials [152] or single-pulse TMS-elicited motor evoked potential [153]. While not limbic recordings, they may serve as proxies for LTP.

Whereas synaptic plasticity can be verified in vivo through electrophysiology in animals or TMS-EEG measurements in both humans and animals, structural plasticity in vivo is indirectly inferred from brain imaging (e.g. fMRI studies and 3D tractography) [134]. With imaging in MDD patients, left dlPFC HD-tDCS resulted in significant gray matter increases in limbic regions functionally connected with the stimulation target and associated with mood improvements [154]. Likewise, dlPFC-rTMS produced structural changes in cortical and subcortical regions [155, 156].

Larger timescales with repeated neurostimulation recruits both synaptic and circuit plasticity potentially through mTORC1-mediated synaptogenesis and spinogenesis. In mice, the antidepressant-like effects of low- (1 Hz, 72 sec x 75 stimuli) [157] and high- frequency (15 Hz, 5 sec x 75 stimuli per train, progressively increasing) [158] TMS for 5 days had antidepressant-like effects. These effects were associated with increased hippocampal granule cell dendritic arborization and PFC spine density at local input and output regions [157]. This suggests transsynaptic/ downstream propagation outside the stimulation target. For instance, PFC-tDCS in mice produced immediate activational effects in raphe serotonergic neurons [159]. These percolations could translate to broad recalibration, affecting the overall functional network configuration, and significantly impacting therapeutic symptom resolution. Indeed, large-scale structural network changes correlated with functional connectivity and therapeutic response [160], e.g. with 1-Hz rTMS in TRD patients [147]. In mice, various techniques demonstrated that prelimbic-TBS activated a fronto-insular network, which was necessary and sufficient for its therapeutic effect.

As with other treatments, causal linkages between synaptic structural plasticity changes and symptom resolution may be addressed by adopting interventional protocols within short spatiotemporal resolution scales. Recently, a fast-acting TBS protocol showed rapid reversal of chronic stress/corticosterone-induced behavioural deficits in mice, an effect mediated by long-range intratelencephalic (IT) neurons of the dmPFC [146, 147]. De novo spinogenesis and neuritogenesis strengthen circuit connectivity, possibly adjusting the functional configuration of the network. Indeed, confocal imaging confirmed augmentations in dendritic spine density and restoration of stress-induced losses [146].

On the other hand, the use of multi-photon microscopy can better improve the spatiotemporal resolution of observed synapto-/spinogenesis in live animals that can be imaged repeatedly. Currently, this can only be carried out in animal studies because of the invasive nature of the procedure [133]. In lieu of this, human PET imaging with contrast agents for synapse-associated proteins, e.g., synaptic vesicle glycoprotein 2 A (SV2A) could be used in the future to assess the ability of neurostimulation to reverse disease-induced synaptic loss with better spatiotemporal resolution [133, 161, 162].

Beyond neuroplastic effects, repeated neurostimulation can also induce metaplasticity by altering the thresholds for subsequent plasticity induction, as supported by cellular and molecular evidence from rTMS and tDCS studies [163]. For example, priming the motor cortex with inhibitory TMS or FUS results in subsequent excitatory protocol that yields a much stronger facilitatory response than it would alone [164, 165]. Moreover, stacking rTMS sessions with very short (minutes) intervals leads to suppression or abrogation of the LTP-inducing effects of a subsequent protocol, such as continuous TBS [165]. Metaplasticity is also shaped by baseline excitability (likely, emotional states) partly explaining inter-subject variability in LTP and LTD [164–166]. Such phenomena have informed clinical optimization to accrue cumulative, therapeutic synaptic adaptations and generate stimulation periods of heightened plasticity and emotional recovery [165].

Through metaplastic effects, combining neurostimulation with a behavioural or psychotherapeutic modality leads to greater symptom improvement [167–169]. This supports the idea that repeated neurostimulation promotes synaptic activity that is refined by behaviour- and disorder-specific rehabilitation, with circuit-specific engagement guiding neuronal rewiring within relevant networks [170–172].

With repeated non-invasive neurostimulation, e.g., anodal PFC-tDCS and rTMS, an enhancement of gamma oscillations, linked to increased cognitive functioning and flexibility was found. rTMS administered to schizophrenics has been shown to normalize impaired gamma rhythms [173]. Likewise, high-definition (HD)-tDCS has demonstrated increased alpha and beta oscillations, improving synchronicity in the PFC. The sustained effects on these frequency bands have been linked to enhanced neuroplasticity, restoring normal network activity [95, 174]. It is not surprising that combined tDCS and immersive therapy (e.g., virtual reality [VR] or cognitive-emotional training) further promotes neuroplastic stabilization [175–177]. Metaplasticity likely contributes to this stabilization, promoted by immersive, emotionally conducive and sensorimotor-rich states or excitability. For instance, VR exposure therapy safely simulates traumatic events and phobias with precise control, and when combined with targeted neurostimulation, can potentiate or accelerate plasticity and metaplasticity [178, 179]. See Table 2 for a detailed overview of these neuroplastic mechanisms.

Innovation and neurostimulation of the future

Innovations in neurostimulation technology show promise in enhancing therapeutic efficacy and broadening applications in clinical practice. We highlight here five key areas: (a) real-time imaging and mapping, (b) refinement of spatiotemporal target resolution, (c) multi-modal neurostimulation therapy development, (d) miniaturization of less invasive techniques, and (e) closed-loop systems (Fig. 4). Overall, given the low spatiotemporal target resolution and focality of rTMS and the depth-dependent input decline observed with tFUS, newer non-invasive techniques would move towards the development of high-yield and high-focality modalities (Table 1). Although mostly still in the proof-of-concept stage, many of these innovations are expected to progress rapidly (see Table 3 for summary).

Real-time imaging and mapping. Integration of real-time neuroimaging techniques, e.g., MRI, diffusion-weighted imaging (DWI) and EEG, with neurostimulation methodologies will enable more precise targeting based on individualized anatomical and functional neuroimaging data [180]. This considers individual differences in morphological and electrophysiological characteristics and enhances patient-specificity of stimulation and intervention

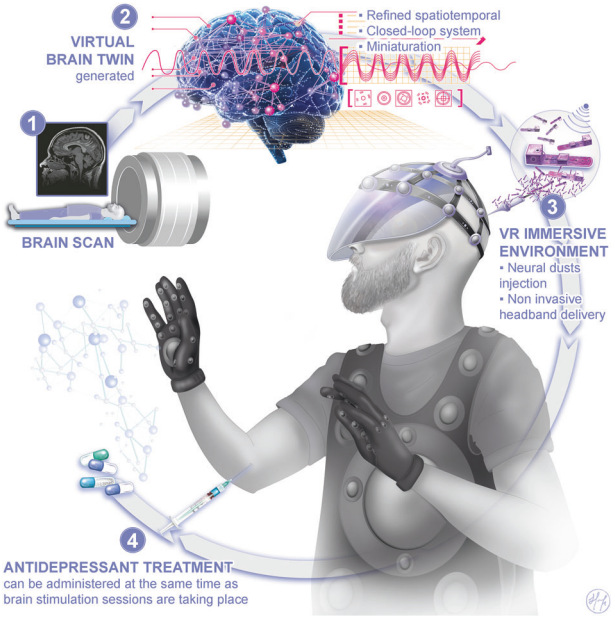

Fig. 4 Future innovations in the therapeutic neurostimulation. 1 Advancements in brain scan technology (e.g., with MRI) and computational neurology allow for the extrapolation of high-precision calculation of input resistance and trajectory. **2** Brain scans can generate a personalized virtual brain twin used to track the spread of activation within the individual's actual brain in real time. Combined with other innovations optimizing spatiotemporal resolution in target trajectory [e.g., high-definition tDCS (HD-tDCS)], facilitating immediate sensing and correction of stimulation intensities (closed-loop system) and optimizing miniaturization for non-obstructive input delivery, further refinements in controlling for the spread of activation within discrete regions of the brain can be better achieved. **3** Cognitive and behavioural remediation can be accelerated by combining non-obstructive and miniaturized closed-loop innovations (e.g., neural dusts) or non-invasive modality inventions (e.g., headbands). **4** Cognitive and behavioural improvements can also be achieved by combining the aforementioned innovations with other established treatment modalities, e.g., antidepressant drug treatments, psychotherapy or behavioural modification procedure.

configurations. Numerous human psychiatric clinical studies have highlighted personalizing non-invasive stimulation, such as rTMS, with neuroimaging and EEG [181]. Accessorizing neuroimaging with computational models is a step further in personalized neurostimulation that can construct *"virtual or digital twins"* of an individual's brain [182, 183]. This data-driven pilot (proof-of-principle) framework aims to identify optimal trajectories and targets while selecting stimulation parameters that are well-suited for the individual. Personalized data derived from these methods can be integrated into a remote exchange network involving neurostimulation devices, digital health applications, and cloud-based platforms. This integration would facilitate continuous remote patient monitoring and data collection, fostering active patient engagement in their own treatment processes. This integrative approach has been tested for DBS, using pathway-activation models, which combines patient-specific DWI data with biophysical simulations to predict axonal pathways activated by the generated electric field [184, 185].

Methodological and conceptual refinement of spatiotemporal target resolution. Innovations in non-invasive neurostimulation modalities aim to refine focal targeting (see Table 1). An advancement here is the development of HD-tDCS [186, 187]. This involves the use of an array of smaller electrodes following a concentric configuration, e.g., a 4×1 ring, wherein a single active electrode is surrounded by multiple return electrodes to constrain the current. This has been shown to provide a more focal neurostimulation than conventional tDCS, and is being explored for therapeutic applications, e.g., in MDD [7] and schizophrenia [188, 189]. At an experimental stage, a similar multi-electrode montage has been applied to deliver multiple temporally interfering high-frequency electric fields (TIF) [190]. This is based on the premise that neurons are unable to follow high-frequency oscillating fields, which pass inertly through the superficial layers. The collision of the fields would produce a prominent envelope modulated at the difference frequency, where neurons are stimulated. This allows safe and selective targeting of deep structures, e.g., the hippocampus and the striatum. The principle was initially tested on rodent motor responses but could be further developed to enhance clinical translatability. Indeed, a recent study by Zhang et al. [191] submitted TIF to resting-state fMRI testing on healthy adults, pre- vs. post-stimulation. They ascertained that TIF mimics the network-disrupting effects of high-frequency DBS, modulating the activity of the nucleus accumbens and the reward circuit in a parameter-specific manner, indicating a strong potential for clinical application. Similar motivations in refining tDCS focality have led Bambico and co-workers [192] to conceive an innovative approach that combines a dual tDCS electrode montage with excitability priming drugs, e.g., SK-type potassium channel antagonists. Placement coordinates of two anode-cathode supra-cranial assemblies would allow colliding fields to superimpose within the target region containing the specific cell types targeted by the priming drugs. While still in development, this combination approach would potentially allow for the non-invasive stimulation of specific cell types within a confined region [192]. The abovementioned innovations have mainly been explored using animal (rodent) models as proof of concept. On the other hand, HD-tDCS has additionally been subjected to small-scale clinical investigations and trials and still awaits broad regulatory approval [193].

Multi-modal neurostimulation therapies. Across psychiatric therapies, synergistic application of biological ("bottom-up") approaches and psycho-behavioural interventions ("top-down") facilitates rapid symptom remission [194]. The underlying motivation is the notion that biological and somatic approaches would effectively stimulate neuroplastic growth and repair. This would include combining neurostimulation with pharmacotherapy, e.g., antidepressant drug treatment. On the other hand, adjunctive psychotherapy, behavioural interventions or task-specific immersive environments, e.g., VR games, can serve to provide the psychological and behavioural matrix or context that will guide rewiring towards and within specific neural networks through adaptive coding [195]. Indeed, combined rTMS and cognitive-behavioral therapies showed augmentative effects on clinical outcomes [196], and increased response and remission rates in MDD patients when compared to single modalities [197]. Along these same lines, combining tDCS with VR exposure reported marked reductions in PTSD symptom severity [176]. Unlike direct modifications of neurostimulation hardware, this adjuvantization with pharmaco- or psycho-behavioural therapies has had long-established precedence with replete human clinical data, suggesting both tolerability/safety and efficacy [194–197].

Miniaturization and unobtrusive approaches. These strategies have not gone beyond proof-of-concept studies and proposals. An increasing trend toward smaller and more portable, less obtrusive devices has since invigorated the field. These devices could better facilitate multi-modal neurostimulation therapies, when users would need to engage in rehabilitative tasks and psycho-behavioural interventions. Wireless nanometer- to millimeter-sized nerve sensors and stimulators called neural dusts are recent experimental developments in nanotechnology that hold

Table 3. Summary of emerging innovations in neurostimulation techniques and technologies for psychiatric disorders.

Innovation Category	Technique / Innovation	Translational Stage	Evidence / Mechanism Mentioned in Text
Real-time imaging & mapping	MRI/DWI/EEG-guided neurostimulation	Clinically investigated	Enables precise targeting based on individualized anatomical and functional neuroimaging data [180]; personalizes rTMS [181].
	Digital twin / computational brain models	Proof-of-principle	Data-driven pilot framework to construct virtual brains, identifying optimal trajectories, targets, and stimulation parameters [182, 183].
	DBS pathway-activation models	Clinically tested	Combines patient-specific DWI data with biophysical simulations to predict axonal pathways activated by the electric field [184, 185].
Refinement of spatiotemporal target resolution	High-Definition tDCS (HD-tDCS)	Small-scale clinical investigations	Uses concentric arrays (e.g., 4×1 ring) to constrain current for more focal stimulation; explored in MDD and schizophrenia [7, 187–189, 193].
	Temporally interfering electric fields (TIF)	Experimental / Preclinical (fMRI tested)	Field collision produces an envelope at the difference frequency to safely target deep structures; mimics network-disrupting effects of high-frequency DBS [190, 191]
	Dual tDCS montage + excitability-priming drugs	In development / Proof-of-concept	Combines colliding fields with SK-type potassium channel antagonists for cell-type-specific stimulation within a confined region [192]
Multi-modal neurostimulation therapies	rTMS + Cognitive-Behavioral Therapies (CBT)	Clinically investigated	Augmentative effects on clinical outcomes; increased response and remission rates in MDD patients compared to single modalities [197]
	tDCS + virtual reality (VR) exposure	Clinically investigated	Combined therapy yielded marked reductions in PTSD symptom severity [176]
	Combined biological & psycho-behavioural interventions	Clinically established	Synergistic "bottom-up" (somatic/pharmacotherapy) and "top-down" (psychotherapy/VR) approaches guide adaptive rewiring within specific neural networks [194, 195]
Miniaturization & unobtrusive approaches	Neural dusts (wireless nano/millimeter-sized stimulators)	Preclinically tested / Proof-of-concept	Tested as peripheral interventions; proposed brain delivery via intracerebral needle injections to minimize invasive surgical risks [198, 199].
Closed-loop systems	AI/ML-assisted closed-loop stimulation	Proof-of-principle	Delivers and adapts stimulation in response to real-time physiological signals rather than relying on predetermined schedules [200–202].
	Neural dust-integrated closed-loop systems	Proof-of-principle	Utilizes integrated sensors (motes) to optimize biomarker monitoring and allow for immediate adjustments of stimulation parameters in real time [198, 199]

AI Artificial intelligence, *CBT* cognitive-behavioral therapies, *DBS* deep brain stimulation, *DWI* diffusion-weighted imaging, *EEG* electroencephalography, *fMRI* functional magnetic resonance imaging, *HD-tDCS* high-definition transcranial direct current stimulation, *MDD* major depressive disorder, *ML* machine learning, *MRI* magnetic resonance imaging, *PTSD* post-traumatic stress disorder, *rTMS* repetitive transcranial magnetic stimulation, *SK* small conductance calcium-activated potassium (channel), *tDCS* transcranial direct current stimulation, *TIF* temporally interfering electric fields, *VR* Virtual reality.

promise for future clinical use [198, 199]. While being preclinically tested as peripheral interventions, their brain delivery may require intracerebral needle injections. This approach could preclude major surgical procedures and minimize the risks associated with invasive techniques.

Closed-loop systems. Closed-loop systems are likewise at the proof-of-principle phase. Their sophistication is predicated on controlled stimulation delivery in response to real-time physiological signals from the brain and body [200–202]. In contrast to open-loop systems, which provide stimulation on a predetermined schedule, closed-loop systems incorporate sensors to continuously monitor brain or nerve activity, process the data, and respond according to the individual's immediate physiological state. This feedback mechanism enhances treatment precision and personalization, potentially resulting in more effective therapeutic outcomes. The rapid advancements in artificial intelligence and machine learning technologies further augment the feasibility of closed-loop systems. Moreover, the sensor systems integrated in neural dusts (motes) also highlight the prospect of closed-loop systems in nanotechnologies. These technologies facilitate the optimization of monitoring protocols for brain and body biomarkers, allowing for immediate adjustments of stimulation parameters in real time. Such dynamic and adaptive approaches not only enhance the efficiency of neurostimulation therapies but also align treatment modalities more closely with individual's changing needs, ultimately improving patient outcomes.

CONCEPTUAL LIMITS OF THE NEUROSTIMULATION PROCESS IN PSYCHIATRY

The efficacy of repeated neurostimulation in treating psychiatric disorders is often interpreted through an overly reductionist lens, along following chain of reasoning: a) psychiatric disorders are linked to functional and structural abnormalities in specific neural circuits; b) restoring "normal" activity within these networks through circuit-based interventions alleviates symptoms; c) because circuit activity emerges from the activity of constituent cells and molecules, d) psychiatric disorders can ultimately be

explained and cured entirely through these molecular, cellular and circuit-level restorations. Each step in this reasoning, however, warrants scrutiny. The relationships between circuit dysfunctions, cellular mechanisms, and clinical symptoms are far more complex than this linear framework suggests.

First, neuroimaging findings are often interpreted as if psychiatric pathologies could be fully explained by brain dysfunction alone, which is overly simplistic. While in some cases the brain alterations detected through neuroimaging may contribute directly to specific symptoms, in other cases these neural patterns may reflect compensatory mechanisms, or even incidental, non-causal correlates accompanying the disorder without playing any causal role. A concrete example comes from studies of MDD: reduced activity in the dlPFC is sometimes assumed to be a primary driver of depressive symptoms, e.g., reduced cognitive flexibility/anticipatory pleasure and increased ruminations. Yet in many patients, evidence suggests that this reduced activity may not be the root cause. Instead, it could be a downstream consequence of broader dysregulation in affective and motivational systems, or a compensatory neural adaptation to chronic stress [203]. Treating this correlation as inherently causal can misguide therapeutic interventions—a strategy focusing solely on boosting dlPFC activity might temporally alleviate the apparent symptoms without addressing the underlying dysfunction. This could lead to only short-term improvement, followed by a relapse of the original symptoms or the emergence of new ones. This has indeed been observed in depression following traumatic brain injury: a meta-analysis showed that in this condition, rTMS was effective immediately after the treatment (effect size of 1.03) but the effect size was reduced (0.39) after a 1-month follow-up and was no more significant at this time point [204]. However, this should be considered with caution as only 3 studies did the follow-up after one month. where effects dissipated after a 1-month follow-up [204]. Furthermore, as many brain alterations are non-specific, occurring trans-diagnostically, they cannot be interpreted as the unique causal mechanism of any single disorder. A critical step for neurostimulation is therefore to distinguish between causal, compensatory and incidental neural changes. This distinction is essential for developing interventions that target mechanisms genuinely responsible for symptoms, rather than merely modulating non-specific correlates of a disorder.

Second, evidence increasingly demonstrates that combining repeated neurostimulation with complementary therapeutic approaches, e.g., psychotherapy produce superior clinical outcomes compared to psychotherapy alone [168, 169]. For example, rTMS combined with psychological interventions improves overall symptom severity beyond the gains achieved by psychological interventions alone [196], suggesting that neurostimulation may function less as a direct elicitor of remission and more as a facilitator of therapeutic outcome. By modulating key brain circuits, techniques like rTMS could "prime" the brain to become more responsive to psychological interventions for instance, by transiently enhancing cognitive control, emotional regulation, or the capacity for therapeutic engagement. The precise neurocognitive mechanisms enabling this facilitation remains a critical area for further research. These findings underscore a limitation of a strictly circuit-based explanatory framework and highlight the necessity of moving beyond a logic of simple neural causation to adopt an integrated, multi-level perspective on therapeutic action. Within this framework, neurostimulation is reconceptualized not as a standalone curative agent, but as a potentiating component within a broader biopsychosocial process. It may create a permissive neural state conducive to change, often insufficient for sustained remission without the current psychological work that addresses the meaning, learning and behavioural patterns central to the disorder.

Third, while it is true that behavioural properties are grounded in the activity of neural circuits, and that these circuits are themselves depending on cellular and molecular mechanisms, it is a conceptual error to assume a complete reduction of one level to another one. Translating between levels is not a lossless process; something essential, the organizing logic of the phenomena itself, is somehow abstracted away. Each level of analysis (behavioral, circuit-based, cellular, molecular) is characterized by its own unique principles, emergent dynamics, and causal constraints. These high-order regularities, while dependent on their substrate, are not exhaustively explainable by it. It therefore seems that the grammar of behaviour (may it be functional or dysfunctional to the individual) cannot be fully translated into a lexicon of synaptic potentials, molecular reactions, just as the logical of a circuit cannot be reduced to a summation of its biochemical parts without losing the very properties- such as information processing or functional resilience – that define it as a circuit and in fine as a brain function.

CONCLUSION

Synthesizing the literature on the mechanisms of different neurostimulation techniques through a transnosographic framework allowed us to demonstrate that they converge on shared brain circuits and neurobiological mechanisms.

Together, these considerations highlight the limits of a purely brain-centric account of psychiatric disorders and point toward a more integrative, embodied framework. Neural alterations observed in neuroimaging cannot be assumed to reflect causal mechanisms, nor can they be understood in isolation from the experiential and environmental contexts in which they arise. Likewise, the enhanced efficacy of combined neurostimulation and psychotherapy suggests that changing brain circuits alone is rarely sufficient; meaningful therapeutic change emerges through interactions between neural modulation, bodily states, subjective experience, and engagement with the world. Finally, acknowledging that each explanatory level—from molecular processes to circuits, cognition, and lived bodily experience—has its own emergent properties underscores that psychiatric conditions are not reducible to any single layer. An embodied perspective thus encourages treatments that target not only neural systems but also the sensorimotor, affective, and relational dimensions through which individuals inhabit their bodies and environments, offering a more comprehensive and clinically grounded understanding of mental disorder.

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