

Neuromodulation techniques in obsessive-compulsive disorder: Current state of the art

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Obsessive-compulsive disorder (OCD) is a chronic neuropsychiatric condition often resistant to conventional treatments such as cognitive behavioral therapy and pharmacotherapy. For treatment-refractory cases, neuromodulation techniques offer promising alternatives. This review provides an overview of recent advances in three major neuromodulation strategies: transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS). DBS has demonstrated robust efficacy across several brain targets, though clinical outcomes are influenced by interindividual variability in fiber anatomy, lead positioning, correct parameter adjustments, and symptomatology. Recent efforts focus on connectivity-based targeting, patient-specific imaging, and the development of closed-loop systems guided by electrophysiological and neuroimaging biomarkers. rTMS, a noninvasive neuromodulation technique, shows therapeutic potential but lacks consensus on optimal parameters and cortical targets, despite FDA approval of certain stimulation protocols. tDCS, while the most accessible modality, presents inconclusive evidence due to small sample sizes and heterogeneity in electrode montages. Overall, these neuromodulation techniques are rapidly evolving and hold considerable promise, but further high-quality studies are needed to standardize stimulation protocols, validate reliable biomarkers and tailor interventions to individual patient profiles. Personalized neuromodulation may represent the future of therapeutic strategies in OCD.

Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition characterized by persistent, intrusive thoughts and dysfunctional, repetitive, and ritualized behaviors (1). It typically manifests in childhood or adolescence and is frequently accompanied by comorbid anxiety and depressive symptoms (2, 3). The lifetime prevalence of OCD in the general population is approximately 2%–3% and symptoms are commonly managed with cognitive behavioral therapy and pharmacotherapy (3–5). Although serotonin reuptake inhibitors are first-line treatments with demonstrated efficacy in OCD, up to 40%–60% of patients exhibit an inadequate response (6).

For these cases, neuromodulation techniques such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS) represent potential alternatives. These techniques may modulate the orbitofronto-striato-pallido-thalamic circuitry, encompassing the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (mPFC), and thalamus, that is dysfunctional in OCD (7, 8).

The aim of this invited review is to provide a summary of recent advances in these three major neuromodulation techniques and their effectiveness in treating patients with OCD.

Transcranial direct current stimulation

tDCS is a noninvasive brain stimulation procedure that may alleviate OCD symptoms by delivering low-intensity electrical current to specific brain areas via two scalp electrodes: an anode (excitatory) and a cathode (inhibitory) (9).

tDCS offers advantages over other neurostimulation approaches, including portability and relatively low cost, supporting the feasibility of home-based use (10, 11).

Anodal or cathodal tDCS modulates cortical excitability by depolarizing or hyperpolarizing neuronal resting membrane potentials, respectively, influencing synaptic transmission (9) and regional cerebral blood flow (12). In OCD, hyperactivity of cortico-striato-thalamo-cortical circuits, including the caudate nucleus, the OFC, the anterior cingulate cortex (ACC) (13) and the subthalamic nucleus (STN) (14, 15), has been implicated in symptomatology. Through cortical neuromodulation, tDCS may attenuate this hyperactivity, contributing to symptom improvement.

Synaptic plasticity—particularly long-term potentiation (LTP) and long-term depression—is central to learning and memory and its dysregulation has been associated with OCD (16, 17). The rationale for tDCS in OCD involves LTP-like mechanisms thought to modulate dysfunctional circuits (18, 19).

However, findings from meta-analyses evaluating tDCS in OCD remain inconclusive, due to small sample sizes, clinical heterogeneity of OCD and methodological inconsistencies, including unstandardized stimulation protocols and lack of neuronavigation (20).

Ibrahim *et al.*, in their systematic review, reviewed randomized controlled trials (RCTs) involving 147 patients with OCD and found no significant difference between active and sham tDCS; surprisingly, sham tDCS was associated with greater symptom reduction, questioning the clinical value of tDCS for OCD (21).

Similarly, Pinto *et al.* reported no significant differences between active and sham stimulation (22). However, montages placing the primary electrode over the pre-supplementary motor area (pre-SMA) and an extracephalic reference generated stronger electric fields in OCD-relevant brain regions (22). These findings align with prior evidence showing that cathodal pre-SMA stimulation reduced symptoms, likely by downregulating pathological hyperactivity in this area (23).

Potential symptom reduction with tDCS without increased adverse effects was also observed in one study; however, the small sample sizes and methodological variability limit interpretability, underscoring the need for further high-quality trials (24).

Regarding stimulation targets, Silva *et al.* found modest improvements with SMA (25), whereas Fineberg *et al.* proposed the OFC as a potentially more effective target (26).

Given the limited evidence regarding the efficacy of tDCS in OCD, largely attributable to the considerable heterogeneity of stimulation protocols, which has led to divergent results across clinical trials (20), tDCS is not yet employed in clinical practice for the treatment of OCD. At this stage of evidence, reflection on the optimal protocol and target remains





premature from a clinical standpoint. Future studies should focus on standardizing stimulation parameters, including electrode placement, as well as session duration and frequency, in order to generate more robust findings and clarify whether this neuromodulation technique is truly effective in this disorder. The favorable feasibility and tolerability profile of tDCS makes it a promising technique for further investigation; although it cannot yet be recommended for routine clinical use, patient inclusion in clinical trials may be encouraged.

tDCS is generally safe, with adverse effects typically mild and transient. In a retrospective analysis of 171 subjects undergoing 2005 tDCS sessions, the most common adverse events were burning sensations (16.2%), skin redness (12.3%), and scalp pain (10.1%), followed by itching (6.7%) and tingling (6.3%), all rated as mild and transient, further supporting the overall safety of tDCS in clinical psychiatric settings (27).

Repetitive transcranial magnetic stimulation

rTMS is a noninvasive neuromodulation technique that alters brain activity using a magnetic coil generating a field through the scalp (28). Brain activity changes with stimulation frequency: low-frequency (≤ 1 Hz) is generally inhibitory, whereas high-frequency (≥ 5 Hz) is typically excitatory (29).

The therapeutic effect of rTMS in OCD is presumed to involve modulation of dysfunctional cortico-striato-thalamo-cortical circuits, aiming to normalize hyperactive areas like the OFC and SMA through inhibitory protocols or enhance hypoactive areas via excitatory stimulation, thus restoring network functional balance (30).

In 2018, the FDA approved rTMS for resistant OCD using a high-frequency deep stimulation protocol targeting the prefrontal cortex (PFC) and ACC (31, 32). In this pivotal multicenter RCT involving 100 participants, significantly more patients responded to active treatment (45.2%) compared to sham (17.8%), with response defined as a $\geq 30\%$ reduction in Yale-Brown obsessive compulsive scale (Y-BOCS) scores (32). Interestingly, although high-frequency stimulation is typically excitatory, its application to the hyperactive mPFC/ACC did not appear to further worsen hyperactivity.

Beyond the mPFC/ACC, alternative targets have been investigated: bilateral and right DLPFC (34–36), as well as left DLPFC, SMA and OFC (34, 37, 38).

Despite numerous meta-analyses, consensus is lacking regarding optimal rTMS parameters for OCD, including frequency, target site, and duration (33). As summarized in Table 1, clinical outcomes vary considerably across stimulation targets and protocols. In practical terms, bilateral DLPFC and SMA protocols appear to yield the largest and most consistent improvements, whereas mPFC/ACC and OFC stimulations show more variable or time-limited effects, suggesting that clinicians should prioritize dorsolateral and motor network targets when selecting rTMS strategies for OCD (Table 1).

Liang *et al.* demonstrated the efficacy of low-frequency stimulation (LF-rTMS) over the SMA and DLPFC, while high-frequency rTMS (HF-rTMS) of the mPFC/ACC, despite being FDA-approved, did not show significant benefit (34). Conversely, Perera *et al.* found bilateral DLPFC stimulation, both LF or HF, more efficacious than other protocols (35).

Subsequent meta-analyses confirmed comparable efficacy across several protocols, including bilateral HF-rTMS of the DLPFC, bilateral LF-rTMS of the pre-SMA, right DLPFC LF-rTMS, and bilateral mPFC/ACC stimulation with both HF and LF frequencies (33, 36, 39). The OFC has also emerged as a potential target. LF-rTMS applied to the left OFC for 3 weeks led to significantly improved Y-BOCS scores at weeks 3 and 10 compared to control (40).

Regarding treatment duration, extending sessions beyond 4 weeks has not consistently added benefit (33). Other meta-analyses indicate that 10–20 sessions may suffice for therapeutic effect, with no clear gain from longer protocols (41, 42).

In terms of stimulation type, although theta burst stimulation (TBS) is time-efficient and theoretically potent, current clinical evidence does not support its efficacy in OCD. Harika-Germaneau *et al.* applied continuous TBS, an inhibitory protocol, over the SMA, but found no significant

improvement relative to sham, possibly due to the low number of pulses (600) and subtherapeutic intensity (70% resting motor threshold [RMT]) relative to effective rTMS studies (43). Liu *et al.* delivered intermittent TBS, an excitatory protocol, to the DLPFC and compared it to 1 Hz rTMS over the SMA; again, no significant difference emerged. The authors noted limitations such as nonindividualized targeting and low session count (44). Furthermore, interindividual variability in neuroplastic response, potentially influenced by genetic factors such as the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism, may partly explain outcome heterogeneity, as proposed by Harika-Germaneau *et al.* and mechanistically supported in Chung *et al.* (2016), who demonstrated that BDNF genotype influences the direction and magnitude of TBS-induced plasticity (45).

On the other hand, the commonly held dichotomy of HF as excitatory and LF as inhibitory does not consistently predict changes in the activity of the targeted brain region. HF-rTMS may instead work by disrupting maladaptive circuit activity (31), as seen in other neuropsychiatric disorders, such as epilepsy (46). This variability underscores the complexity of brain dynamics, with outcomes influenced by baseline excitability, individual differences and circuit state during stimulation.

Furthermore, the accelerated rTMS protocol, involving multiple HF stimulation sessions per day over a condensed period (e.g., 5 days), aims for faster and stronger clinical effects. The Stanford SAINT protocol, which applies ten sessions of intermittent TBS daily, guided by individualized functional magnetic resonance imaging targeting, has demonstrated rapid efficacy in treatment-resistant depression (47). To date, no accelerated rTMS protocols with comparable intensity, frequency or proven efficacy have been established for OCD. This may reflect inconsistent TBS outcomes in OCD, potentially due to subtherapeutic stimulation parameters and lack of individualized targeting.

Due to difficulties in predicting clinical outcomes based solely on stimulation frequency or target region, there is increasing support for personalizing rTMS protocols based on individual neurophysiological profiles. rTMS may benefit from personalized target selection and stimulation parameters (48, 49).

The level of evidence supporting the efficacy of rTMS in OCD is moderate to high, making it a viable clinical option for treatment-refractory cases before considering more invasive techniques, namely DBS, particularly when balancing the risks and benefits of each intervention (50).

rTMS is generally safe and well-tolerated. The most serious adverse effect, seizure, is rare and usually associated with HF stimulation or predisposing neurological conditions (51). More commonly, side effects are mild and transient, including scalp discomfort, tension-type headaches, tingling or auditory sensitivity from the clicking noise, all usually resolving without the need to discontinue treatment (51).

Deep brain stimulation

DBS has supplanted ablative neurosurgical procedures and is indicated for patients with treatment-resistant OCD (52). The technique entails the implantation of electrodes in a specific deep brain target, connected to a pulse generator that delivers electrical stimulation (52). In 2009, the FDA granted DBS for OCD a Humanitarian Device Exemption.

The most common targets for OCD are: the anterior limb of the internal capsule, (ALIC), ventral capsule/ventral striatum (VC/VS), nucleus accumbens (NAC)—noting that these three regions often refer to anatomically overlapping regions, caudate nucleus and the bed nucleus of the stria terminalis (BNST) (53), a component of the extended amygdala that is heavily interconnected with the ventral striatum and involved in anxiety and compulsive behavior regulation. These structures constitute components of cognitive-affective circuits involved in reward processing, motivational regulation and compulsive behavior (53).

Clinical trials have demonstrated the efficacy of DBS targeting these structures. In 2010, Denys *et al.* conducted an RCT of ALIC-NAC stimulation, achieving full response in 9 of 16 patients with a mean reduction of 46% in Y-BOCS scores (54). Subsequently, Luyten *et al.* carried out a double-blind crossover study in 17 patients implanted with a single electrode per hemisphere targeting the ALIC-BNST region. Although

**Table 1.** Summary of rTMS targets, protocols, and clinical outcomes in OCD treatment

Target	Stimulation Type	Outcome	Study	Study Type
Bilateral DLPFC ^a	LF ^b - or HF ^c -rTMS	Both significantly superior to sham; larger effect size than other protocols (left DLPFC, right DLPFC, SMA ^d , OFC ^e or mPFC ^f) with Hedge's g of 1.04	Perera <i>et al.</i> , 2021	Meta-analysis (26 RCTs ^g)
	HF-rTMS	Superior to sham; DLPFC and mPFC/ACC protocols more likely to be among the highest-ranked interventions	Vinod <i>et al.</i> , 2024	Meta-analysis (33 RCTs)
	HF-rTMS	More efficacious than sham with Hedge's g of 0.90; similar efficacy to LF-rTMS of right DLPFC and LF-rTMS of bilateral pre-SMA	Fitzsimmons <i>et al.</i> , 2022	Meta-analysis (21 RCTs)
Right DLPFC	LF-rTMS	Superior to sham	Vinod <i>et al.</i> , 2024	Meta-analysis (33 RCTs)
	LF-rTMS	More efficacious than sham with Hedge's g of 1.03; similar efficacy to HF-rTMS of bilateral DLPFC and LF-rTMS of bilateral pre-SMA	Fitzsimmons <i>et al.</i> , 2022	Meta-analysis (21 RCTs)
Left DLPFC	LF-rTMS	More efficacious than sham; Y-BOCS weighted mean difference of 6.34 compared to sham; might be the most effective intervention among all rTMS strategies for OCD treatment	Liang <i>et al.</i> , 2021	Meta-analysis (22 RCTs)
	HF-rTMS	More efficacious than sham; Y-BOCS weighted mean difference of 3.77 compared to sham	Liang <i>et al.</i> , 2021	Meta-analysis (22 RCTs)
Bilateral mPFC/ACC ^h	HF-dTMS	More efficacious than sham; reduction of 6 points in Y-BOCS in the active group vs 3.3 points in the sham group	Carmi <i>et al.</i> , 2019	RCT (99 subjects)
	HF or LF-rTMS	Superior to sham; DLPFC and mPFC/ACC protocols more likely to be among the highest-ranked interventions	Vinod <i>et al.</i> , 2024	Meta-analysis (33 RCTs)
mPFC/ACC	HF-rTMS	Not more efficacious than sham, despite FDA approval	Liang <i>et al.</i> , 2021	Meta-analysis (22 RCTs)
Bilateral pre-SMA	LF-rTMS	More efficacious than sham with Hedge's g of 0.56; similar efficacy to LF-rTMS of right DLPFC and HF-rTMS of bilateral DLPFC	Fitzsimmons <i>et al.</i> , 2022	Meta-analysis (21 RCTs)
Bilateral SMA SMA	LF-rTMS	Superior to sham	Vinod <i>et al.</i> , 2024	Meta-analysis (33 RCTs)
	LF-rTMS	More efficacious than sham; Y-BOCS weighted mean difference of 4.33 compared to sham	Liang <i>et al.</i> , 2021	Meta-analysis (22 RCTs)
	LF-rTMS	More efficacious than rTMS over DLPFC or OFC with Hedge's g of 1.68 for SMA and 0.97 for LF-rTMS	Rehn <i>et al.</i> , 2018	Meta-analysis (18 RCTs)
OFC	LF-rTMS	More efficacious than sham with Hedge's g of 1.37 for SMA and OFC and 0.8 for LF-rTMS	Berlim <i>et al.</i> , 2013	Meta-analysis (10 RCTs)
	LF-rTMS	Not more efficacious than sham	Liang <i>et al.</i> , 2021	Meta-analysis (22 RCTs)
	LF-rTMS	Significant but time-limited improvement compared to sham; Y-BOCS reduction of $\geq 25\%$ for 50% of the subjects and $\geq 35\%$ for 25% of the subjects	Ruffini <i>et al.</i> , 2009	RCT (23 subjects)
	LF-rTMS	More efficacious than sham with Hedge's g of 1.37 for SMA and OFC and 0.8 for LF-rTMS	Berlim <i>et al.</i> , 2013	Meta-analysis (10 RCTs)

Hedge's g values were recoded so that positive values indicate superiority of active treatment over sham.

^aDLPFC: dorsolateral prefrontal cortex.

^bLF: low frequency.

^cHF: high frequency.

^dSMA: supplementary motor area.

^eOFC: orbitofrontal cortex.

^fmPFC: medial prefrontal cortex

^gRCT: randomized controlled trial.

^hACC: anterior cingulate cortex.

the electrode trajectory allowed anatomical coverage of both areas, stimulation was delivered either to ALIC or to BNST depending on the activated contact. The study reported a 53% response rate and a 37% median improvement during the blinded phase; during the open-label phase, 67% of patients were full responders, with a 58% median reduction in

Y-BOCS scores. Notably, patients with active contacts in BNST showed significantly greater improvement than those stimulated in ALIC (55). More recently, Mosley *et al.* replicated these results in a randomized, double-blind, sham-controlled trial involving 9 patients using ALIC-BNST stimulation, finding a statistically significant difference from sham ($p = 0.025$),



Table 2. Summary table has been adapted from Raviv *et al.* (2020), integrating data from RCTs and high-quality case series investigating various DBS targets for treatment-resistant OCD. Evidence levels and GRADE categories reflect the quality and strength of the findings across studies. Anatomical overlap and variability in target nomenclature are noted where relevant

Target	Main Findings	Level of Evidence	GRADE	Notes
BNST ^a /ALIC ^b	Significantly reduced OCD ^c , anxiety and depressive symptoms; improved global functioning. Long-term safety up to 14 years.	II	High	One electrode can anatomically cover both targets; clinical effects differ by contact site.
STN ^d	Reduced Y-BOCS by ~41%; increased positive emotional ratings; improved global functioning. Effects on depression/anxiety variable.	I–III	High-Moderate	Potential for motor/limbic symptom targeting; cognitive flexibility may improve.
NAC ^e	Median 50% symptom reduction in responders. Often overlaps with caudate/VC/VS ^f regions.	II–III	High-Moderate	Target for reward-related symptoms, but anatomical boundaries often overlap with VC/VS.
Caudate nucleus	35% to 60% Y-BOCS reduction in small studies; improvements associated with decreased caudate hyperactivity.	III	Low	Targeted in small series; often combined with NAC stimulation.
VC/VS	Reduced Y-BOCS and improved functioning. Effects similar to STN in some trials.	II–III	Moderate-Low	Overlaps with ALIC and NAC; inconsistent nomenclature across studies.
ITP ^g	~50% Y-BOCS decrease; promising but limited evidence.	III	Moderate-Low	Uncommon target; potential role in emotion regulation.
Gpi ^h	Dramatic improvement in vocal tics and OCD in all 4 patients in small series.	III	Moderate	Rarely used; explored for overlap between OCD and Tourette.

^aBNST: bed nucleus of the stria terminalis.

^bALIC: anterior limb of the internal capsule.

^cOCD: obsessive-compulsive disorder.

^dSTN: subthalamic nucleus.

^eNAC: nucleus accumbens.

^fVC/VS: ventral capsule/ventral striatum

^gITP: inferior thalamic peduncle.

^hGpi: globus pallidus internus

along with a 50% mean Y-BOCS reduction and 78% response rate during the open phase (56). Provenza *et al.* further confirmed these effects in an open-label phase followed by cognitive behavioral therapy and a double-blind withdrawal: all 5 participants responded fully with a 55% mean Y-BOCS reduction; symptoms recurred upon DBS cessation and remitted upon reactivation, affirming the causal role of stimulation (57) (Table 2).

The STN is a well-established DBS target in treatment-refractory OCD, with reported Y-BOCS reductions from 33 to 21.8 with a 67% response rate in one study (15) and from 28 (sham) to 19 with 75% response in another study (14), using $\geq 35\%$ Y-BOCS reduction as the response criterion (Table 2).

Other investigated targets include the anteromedial globus pallidus internus (amGPI), currently a DBS target for Tourette syndrome with encouraging findings for OCD symptoms (58), the inferior thalamic peduncle (53), the lateral habenula, the superolateral medial forebrain bundle (59) and the zona incerta (60). However, for these targets, evidence is still limited and further studies are needed to evaluate the efficacy in treating OCD (Table 2).

It is increasingly recognized that DBS targets overlap anatomically and stimulation effects may depend on activated tissue volume (53). These targets are embedded in interrelated networks governing behavior, dysfunction of which may underlie OCD symptoms (61). Tractography and connectivity analysis have been proposed to define optimal DBS pathways (62), though no consensus exists on a specific white matter tract. Proposed white matter targets include the medial forebrain bundle (63), the fronto-thalamic tract (64) and the hyperdirect pathway between the PFC and the STN (65).

Given substantial interindividual variability in fiber anatomy, advanced patient-specific imaging is imperative (66). Symptom dimensions, such as checking or contamination, appear to activate distinct prefrontal regions (67). Barcia *et al.* found that optimal stimulation contacts exhibited stronger connectivity with prefrontal areas activated by symptom provocation (68). On the other hand, Tyagi *et al.* observed that STN-DBS preferentially improved cognitive symptoms whereas VC/VS-DBS alleviated depressive features (15). Finally, Li *et al.* proposed a common therapeutic pathway originating in the ALIC, connecting to the dorsal ACC and ventrolateral PFC and culminating in the anteromedial STN, potentially underlying core OCD symptom relief, with additional pathways necessary for specific symptom clusters (65).

Although normative connectomes derived from healthy populations facilitate network mapping, they fail to capture individual anatomical variability or disease-driven alterations (69). For instance, the distinct tracts traversing the ALIC link the PFC to the thalamus, ventral tegmental area and STN (70, 71) and display considerable individual anatomical variability (66, 70), possibly explaining heterogeneous ALIC-DBS outcomes and reinforcing the need for patient-specific imaging before defining stimulation targets (69, 72). Nonetheless, normative maps remain useful when individual data is unavailable (62).

Recent work has challenged the concept of fixed anatomical “target,” proposing instead that DBS acts by modulating a common functional network engaged across multiple stimulation sites. In a large connectomic analysis, Li *et al.* demonstrated that effective stimulation sites, regardless of anatomical location, converged on a unified network encompassing the ACC, precuneus, mPFC, and insula. This shift from a “valid target” to a “valid network” paradigm suggests that optimal outcomes may

Neuromodulation approaches for treatment-resistant OCD

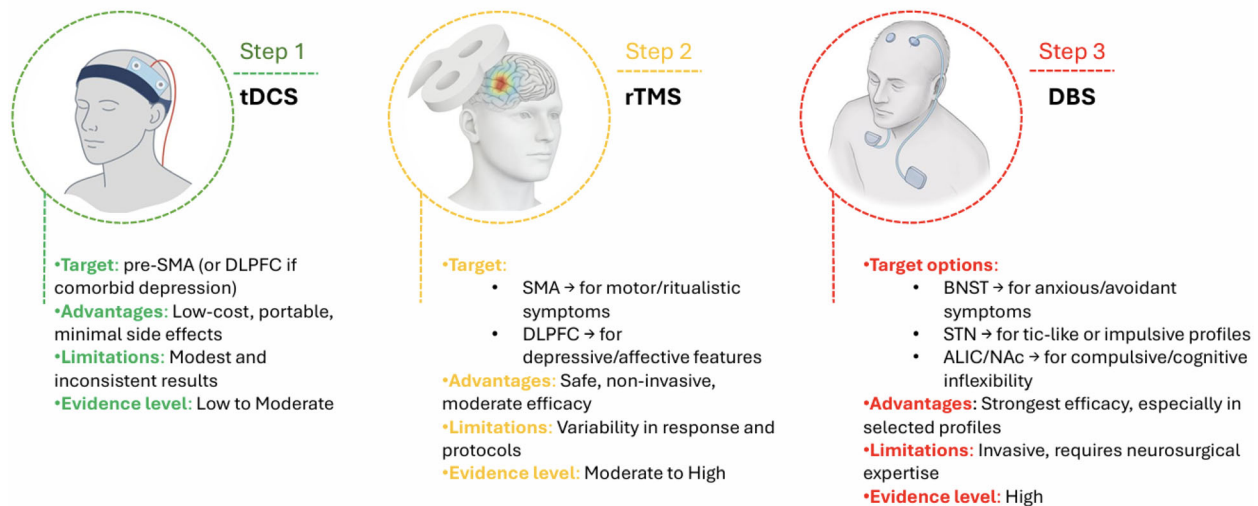


Figure 1. Pre-SMA: Pre-Supplementary Motor Area; DLPFC: Dorsolateral Prefrontal Cortex; SMA: Supplementary Motor Area; BNST: Bed Nucleus of the Stria Terminalis; STN: Subthalamic Nucleus; ALIC: Anterior Limb of the Internal Capsule; NAc: Nucleus Accumbens. This figure outlines a proposed sequential algorithm for neuromodulatory interventions in treatment-resistant obsessive-compulsive disorder. Rather than being organized strictly by evidence level, this framework prioritizes a gradient of clinical feasibility and invasiveness, moving from the least to the most invasive approaches.

depend more on the connectivity profile of the stimulated region than on its anatomical label (73).

Biomarker-guided personalization of DBS is an emerging framework with predictive potential (74). A significant challenge in OCD is the temporal dissociation between electrophysiological changes and clinical response, unlike Parkinson's disease, for example, where real-time suppression of STN beta activity correlates with symptom relief (75). Psychiatric DBS typically requires months for symptom amelioration during parameter optimization (52, 76).

In OCD, electrophysiological biomarkers like local field potentials (LFPs) remain unclear. Theta and delta frequency bands are most studied but lack consistent clinical correlation (77). A case report suggested that identifying the contact with the highest beta activity peak could optimize clinical outcomes for DBS in the VC/VS (78). Provenza *et al.* observed a negative correlation between delta power and symptom severity (57) and Nho *et al.* associated low-frequency intracranial electroencephalogram (EEG) signals (<15 Hz) with obsessive thought episodes (79).

There is also interest in STN functioning in OCD, driven by prior Parkinson's disease research. Investigations in STN functioning have revealed burst-like LFP patterns in both groups (80); theta activity during emotional stimuli correlated with OCD severity (81); increased STN oscillations during symptomatic states and reduced gamma/beta activity in the right ventral STN have been reported (82) and Fridgeirsson *et al.* described individualized LFP signatures within the NAc, ventral ALIC and globus pallidus externus (83).

Emerging evidence suggests that STN DBS may exert disease-modifying effects through modulation of BDNF signaling, potentially supporting neuroplasticity and functional restoration. Although primarily studied in Parkinson's disease, these mechanisms may inform understanding of STN-related circuit modulation in OCD, guide therapeutic strategies and provide a line of investigation to account, at least partially, for the heterogeneity of clinical outcomes despite identical stimulation targets (84).

Furthermore, intraoperative observations of smiling and facial expression changes elicited by VC/VS stimulation have been linked to favorable outcomes and may guide electrode placement (85, 86).

A recent preclinical investigation utilizing a closed-loop optogenetic approach in Sapap3-knockout mice—a validated OCD model—demonstrated that real-time detection of low-frequency delta signals in the OFC triggered activation of striatal parvalbumin-positive interneurons,

effectively interrupting compulsive grooming (87). This result provides a potential mechanistic foundation for closed-loop DBS in human OCD.

In conclusion, biomarkers are crucial for optimizing neuromodulation and implementing closed-loop DBS (52, 65).

Closed-loop neurostimulation systems offer a novel approach by continuously adjusting stimulation parameters based on real-time biomarker feedback (88). Contrary to traditional open-loop systems with fixed settings, closed-loop models cater to the fluctuating nature of neuropsychiatric disorders by using electrophysiological or neurochemical indicators to tailor therapy automatically (88).

The efficacy of such systems depends on identifying robust neuropsychiatric biomarkers. EEG and LFPs monitoring enable real-time assessment of brain activity and evaluation of stimulation effects, guiding postimplantation parameter tuning (89). However, no biomarker has yet been definitively linked to changes in mood (89). Indeed, adapting DBS parameters in response to symptom fluctuation may improve outcomes and reduce side effects with lower energy consumption (89). Closed-loop DBS has been shown to monitor LFPs in real time and modify stimulation to further reduce obsessive thoughts and compulsive behaviors while mitigating acute mood-related side effects, including hypomania (90).

Nonetheless, implementing closed-loop DBS entails significant challenges, including ensuring biomarker specificity to accurately reflect clinical state, employing rigorous signal filtering to prevent erroneous adjustments and achieving high temporal resolution to promptly adjust stimulation in response to neural dynamics (88).

DBS is associated with adverse effects in approximately 4.8%–7.7% of cases (91). The most serious complication is intraoperative hemorrhage, although it occurs in less than 1% of procedures. Electrode misplacement and intracranial infections are more common and are among the leading causes of device removal. Postoperative seizures are rare and typically linked to edema around the electrode. Stimulation-induced side effects most notably hypomania, typically resolve with parameter adjustment, although weight gain, insomnia, memory impairment, and anxiety have also been reported (92, 93). Other concerns relate to suicidality; the relationship between DBS and increased suicidality remains debated and may reflect the baseline severity of illness or unmet expectations (94, 95).

In contrast to movement disorders treated with DBS, neuropsychiatric illnesses treated with DBS lack immediate symptomatic improvement,



making it much more complicated and time-consuming to reach optimal parameters. Indeed, improvements in OCD symptoms and anxiety may take weeks, several months, or even years to be achieved, whereas Parkinsonian rigidity or tremor resolves in a few seconds or minutes in front of the examiner programming the DBS.

In clinical practice, given that DBS is an invasive procedure, it is reserved for cases of treatment-refractory OCD (50). Nevertheless, the current evidence regarding its efficacy is the most consistent and robust when compared with the other two techniques.

Conclusion

Neuromodulation techniques such as tDCS, rTMS, and DBS hold significant promise, particularly for patients with treatment-refractory OCD. DBS, although more invasive, has demonstrated clinical efficacy in reducing OCD symptoms across various brain targets. Nevertheless, clinical responses remain heterogeneous, largely due to anatomical variability and differences in symptom dimensions. Moving forward, the field will likely be shaped by advances in personalized neuromodulation. Critical priorities include the development of robust electrophysiological biomarkers, individualized tractography to optimize target selection and the implementation of adaptive closed-loop stimulation systems capable of dynamically tailoring treatment. In contrast, while rTMS and tDCS offer less invasive alternatives, they face certain limitations. rTMS lacks consensus regarding optimal stimulation parameters and target regions and the efficacy of tDCS in OCD remains a subject of debate due to methodological shortcomings and variability in electrode montages. In summary, these neuromodulation strategies are advancing rapidly, but further high-quality research is required to optimize protocols. Ultimately, harmonization of trial design, coupled with biomarker-guided and patient-specific approaches, will be essential to personalize neuromodulation and to maximize the therapeutic potential of these techniques in OCD.

Author contributions

KSL and CV conducted the conceptualization, data curation, investigation, methodology, resources, visualization, writing – original draft and writing – review and editing. KSL also conducted the project administration and supervision. LM conducted the conceptualization, methodology, validation, writing – original draft and writing – review and editing. JFA, JE, JFB, JB, PV, EMM, BPM, PV, and AVG conducted the conceptualization, methodology and writing – review and editing.

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