REVIEW

Transcranial magnetic stimulation in the treatment of obsessive–compulsive disorder: current perspectives

Ana Lusicic[1]
Koen RJ Schruers[2]
Stefano Pallanti[3,4]
David J Castle[5,6]

[1]PACE Clinic, Orygen Youth Health, Melbourne, VIC, Australia; [2]Research Institute for Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands; [3]Institute of Neurosciences, Florence, Italy; [4]Stanford University, Palo Alto, CA, USA; [5]St Vincent's Hospital, [6]University of Melbourne, Melbourne, VIC, Australia

Correspondence: Ana Lusicic
PACE Clinic, Orygen Youth Health, 35 Poplar Road, Parkville, Melbourne, VIC 3052, Australia
Email ana.lusicic@mh.org.au

Abstract: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neurostimulation technique receiving increasing attention in the treatment of different psychiatric disorders. Evidence for rTMS use in obsessive–compulsive disorder (OCD) is accumulating and informing further developments in the neurostimulation field, the latest being deep transcranial magnetic stimulation (dTMS). dTMS allows direct stimulation of deeper subcortical structures and larger brain volume than conventional rTMS. Underlying neurobiological mechanisms related to transcranial magnetic stimulation are still under evaluation, but appear to offer a novel "third" way of addressing symptoms via localized electrical stimulation compared to pharmacotherapy and psychotherapy approaches. This systematic review focuses on the effects of rTMS and dTMS stimulation on different brain targets in OCD. Brain areas included are the dorsolateral prefrontal cortex, supplementary motor area, orbitofrontal cortex/medial prefrontal cortex, and anterior cingulate cortex (ACC). Improved understanding of the therapeutic effects of rTMS in OCD will support fine-tuning of the method and help determine how we can best optimize the approach via rTMS or dTMS to achieve clinically relevant results.

Keywords: repetitive transcranial magnetic stimulation, rTMS, deep TMS, obsessive–compulsive disorder, OCD, noninvasive neurostimulation

Introduction

Obsessive–compulsive disorder (OCD), characterized by intrusive obsessive and repetitive compulsive symptoms as per DSM5 and ICD10 diagnostic criteria,[1,2] is known for its chronic, waxing, and waning course and detrimental effect on quality of life.[3] At 1.6%–2.3%, lifetime prevalence is consistent across cultures.[4,5] Although there is an initial male predominance in childhood and adolescence, by early adulthood gender distribution is almost equal.[6] Many patients experience delay in recognition and treatment,[7] with high rates of patients failing to achieve full symptomatic remission despite therapy.[8,9]

Worldwide, OCD treatment guidelines[10–12] indicate the effectiveness of both pharmacological and psychological treatments. Consistent first-line recommendations include serotonin-reuptake inhibitors (SRIs), including selective SRIs (SSRIs) or clomipramine, and exposure/response prevention cognitive behavioral therapy strategies. Many (40%–60%) patients do not show clinically meaningful response to an SRI, with only a third showing response after switching to another SRI.[13,14] Other treatment strategies include augmentation with antipsychotics and use of adjunctive treatments, such as exercise, motivational interviewing,[10,12,15] and cognitive therapy or acceptance and commitment therapy.[10] However, many patients remain symptomatic and impaired.

Therefore, other strategies, notably ones that directly impact OCD neurocircuitry, are of longstanding interest.

The neurobiology of OCD is well established, and an understanding of neurocircuitry can help inform treatments, notably brain stimulation and lesion approaches. Neurobiological models of OCD describe alterations in cortico-striato-thalamo-cortical (CSTC) circuits responsible for affective, cognitive, and motor functions. More recently, other brain regions, such as the limbic and parietal cortices, have also been implicated.[16]

Historically, Alexander et al[17] described five parallel basal ganglia–thalamocortical circuits, comprising specific areas of the cerebral cortex linked with the striatum, pallidum, substantia nigra, and thalamus. Subsequently, it was shown that CSTC loops were interconnected and not as segregated as previously considered.[16–19] "Net activity" of CSTC circuitry is thought to be modulated by the interplay between "direct" and "indirect" pathways connecting the cortex and subcortical structures. The "direct pathway" is thought to be driven by glutamate and γ-aminobutyric acid-neurotransmitter interplay among the cortex, striatum, and globus pallidus, resulting in disinhibition of the thalamus and excitation of the cortex. The "indirect pathway", with its γ-aminobutyric acid-inhibitory projections from the striatum to the globus pallidus externa and subthalamic nucleus, excites the globus pallidus interna and inhibits the thalamic input to the cortex. CTSC loops implicated in OCD include the components outlined in the following sections.

Motor circuit/sensorimotor circuit

This connects the sensorimotor and motor cortices, including the supplementary motor area (SMA) with putamen. Putamen projects to the globus pallidus interna and externa and caudal substantia nigra. The internal pallidal segment in turn projects to the ventrolateral thalamic nucleus and finally back to the sensorimotor cortex. Functional alteration of the loop might be responsible for interfering with suppression of "internally triggered intrusive and repetitive movements and thoughts".[20]

Dorsal cognitive circuit/dorsolateral prefrontal circuit

This projects from the dorsal prefrontal region (dorsolateral prefrontal cortex [dlPFC], including the dorsal anterior cingulate cortex [ACC])[21] to the dorsolateral caudate nucleus, which is further connected to dorsomedial parts of the globus pallidus and rostral substantia nigra. Functionally, the dlPFC is linked to executive cognitive functions, including adjustment of cognitive and behavioral programs.[18,19] Deficits

in this circuits might be linked to increased attention to obsessive thoughts.[22]

Ventral cognitive circuit

This is formed by projections from the anterolateral orbitofrontal cortex (OFC) to the ventromedial caudate nucleus, which in turn innervates the dorsomedial part of the internal pallidum and rostromedial substantia nigra. Lesions to the lateral OFC appear to interfere with the ability to make appropriate shifts in behavioral sets and may be relevant for ritualized behavioral responses.[16,17] Hyperactivity of the lateral OFC in this context may mediate obsessions.[16] It has been suggested that excessive activity in the direct pathway of the OFC–ACC loop "traps obsessive thoughts".[23]

Affective anterior cingulate circuit

This connects the ventromedial prefrontal cortex (PFC), medial OFC, and ventral ACC[24] with the ventral striatum, the nucleus accumbens, and further the ventral pallidum and substantia nigra. It closes the loop by projection to the thalamus and back to the ACC and ventromedial PFC. It appears to be relevant for processing affective and reward information. In OCD, its hyperactivity is linked to altered monitoring of behavior and impairment in modifying behavioral responses.

Historically, neurosurgery was considered the last treatment option for OCD after pharmacological and psychological strategies had been exhausted. Targets have included the cingulate gyrus and anterior limb of the internal capsule, as well as tracts that connect the cortex to thalamic nuclei. Such interventions have shown variable levels of effectiveness, with variable long-term success.[11] Also, such interventions are irreversible. More recently, there has been interest in noninvasive neuromodulation, including repetitive transcranial magnetic stimulation (rTMS), transcranial direct-current stimulation, and more recently deep transcranial magnetic stimulation (dTMS). rTMS uses a low-intensity magnetic field applied to the scalp surface via specially designed coils to induce neurophysiological changes in the cortex and subcortical areas. Stimulation protocols include low-frequency (LF) rTMS (<5 Hz), inducing decreased neuronal activity in the cortex,[25] or high-frequency (HF) rTMS (>5 Hz), considered to increase the cortical activity via facilitation of synaptic efficiency.[26] dTMS uses specifically designed coils to reach deeper subcortical structures while generating a localized magnetic field.

Published systematic reviews and meta-analyses[27–31] have focused on the overall effectiveness of neurostimulation

in OCD, with mixed conclusions. Such reviews have not explored the neurobiological rationale of modulation of different brain targets that subsume neurobiological mechanisms driving obsessive, compulsive, and anxiety symptoms in OCD. Extant systematic reviews and meta-analysis of neuromodulation in OCD have not fully explored the heterogeneity of treatment parameters. Therefore, this systematic review analyzes randomized controlled trials (RCTs) of rTMS and dTMS stimulation over different brain targets in OCD and using different stimulation parameters. Targeted brain areas included in the review are the dlPFC, SMA, OFC/medial PFC (mPFC), and ACC, all of which have been implicated in OCD.

Materials and methods
Search strategy

Separate searches for randomized sham-controlled trials and systematic reviews (including meta-analyses) were conducted using the PubMed/Medline, Ovid SP, and PsycInfo databases for the period from January 1980 to October 2017, accompanied by a manual search for additional references from identified publications (Figure 1). Search terms were as follows: transcranial magnetic stimulation or transcranial magnetic stimulation (TMS) + obsessive compulsive disorder or OCD. Inclusion criteria for this systematic review were

sham-controlled trials in humans using active rTMS, θ-burst rTMS, or dTMS versus Sham TMS, double-blind or single-blind randomized trials, and English language articles. We excluded nonrandomized trials, case series, case reports, and uncontrolled trials. Seven systematic reviews and meta-analyses were identified using the same keywords with systematic reviews and/or a meta-analysis filter.

rTMS of dlPFC

The dlPFC emerged as a target for OCD treatment after converging evidence accrued via neuroimaging research, noting its relevance in the pathophysiology of CSTC networks, specifically of the dorsal cortical (cognitive/associative) loop. Functionally, the "dorsal cognitive loop" is known to be involved in executive functions of planning and working memory and implementation of control via attention during execution of tasks.[19,32,33] The dlPFC has also been shown to be relevant for retaining and manipulating spatial information[34] and integration of emotional and cognitive processing.[16,19] Involvement of the dorsal cognitive loop in OCD is underpinned by neuroimaging findings involving structural, resting-state, symptom provocation, and cognitive task paradigms and studies exploring functional changes associated with treatment. One proposition in understanding

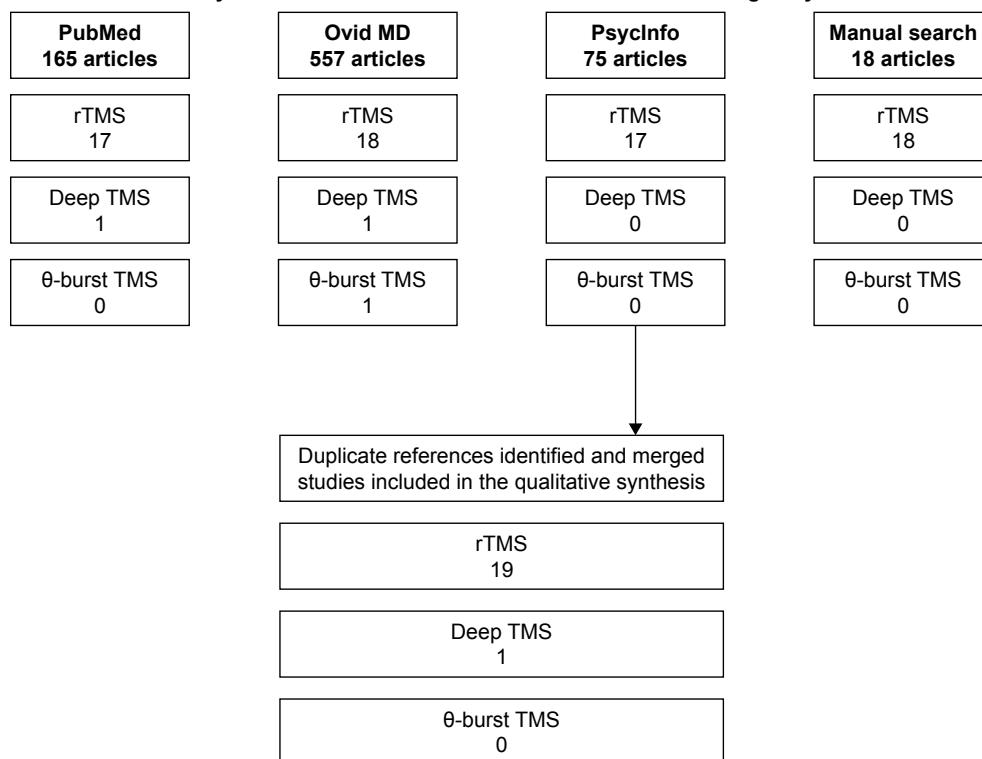**Records identified by database search + full text articles assessed for eligibility:**

PubMed 165 articles	Ovid MD 557 articles	PsycInfo 75 articles	Manual search 18 articles
rTMS 17	rTMS 18	rTMS 17	rTMS 18
Deep TMS 1	Deep TMS 1	Deep TMS 0	Deep TMS 0
θ-burst TMS 0	θ-burst TMS 1	θ-burst TMS 0	θ-burst TMS 0

Duplicate references identified and merged studies included in the qualitative synthesis

rTMS 19
Deep TMS 1
θ-burst TMS 0

Figure 1 Search strategy.
Abbreviations: rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation.

the deficits of the dorsal cognitive loop in OCD is dominance of the indirect over direct cortical pathway.[19,35] The superficial position of the dlPFC, easily accessible to magnetic stimulation, made it an appealing target in the treatment of OCD, especially as it was already shown to be an effective target in the treatment of depression. Greenberg et al[36] were the first to study the effects of rTMS on the PFC. A single 20-minute session of 20 Hz rTMS applied over the prefrontal area in 12 OCD patients was associated with a decrease in compulsive symptoms during as well as 30 minutes ($P \leq 0.01$) and 8 hours after ($P < 0.02$) right PFC stimulation. Left PFC stimulation ($P = 0.05$) did not show this effect.

Studies using LF (1 Hz) rTMS over the right dlPFC
Several studies have studied LF stimulation over the right dlPFC. Alonso et al[37] examined the effects of LF vs sham stimulation over the right dlPFC in a double-blind RCT with 18 unmedicated and medicated OCD subjects. The right dlPFC, inclusive of Brodmann areas (BAs) 6, 8, 10, 44, and 45, was stimulated using a circular coil with 1 Hz frequency three times a week for 6 weeks. Baseline mean Yale–Brown Obsessive–Compulsive Scale (YBOCS) scores were in the moderate–severe range. There were no statistically significant effects of active treatment compared to sham treatment on YBOCS ($P = 0.81$) or Hamilton Depression Rating Scale (HDRS) scores ($P = 0.95$) at 10 weeks. The authors raised type II error as a potential explanation for the negative findings. Inclusion of treatment-resistant (TR) patients, heterogeneity in medication status, unclear duration of illness, and active sham coil might have contributed to negative results. Importantly, use of a circular coil has previously been shown to have limited convergence of neurostimuli.[38] In an RCT of 27 TR OCD patients, Seo et al[39] employed 1 Hz 20-minute train stimulations of the right DLPFC with a figure-eight coil over 3 weeks. The sham protocol was identical, apart from the use of an inactive coil. There was a highly significant difference between two groups after 3 weeks on YBOCS score ($P = 0.008$). However, no significant difference was found in the number of responders to treatment (reduction in YBOCS scores $\geq 25\%$) between groups ($P = 0.148$). Between-group effects were significant for the HDRS ($P = 0.009$) at week 2 and Clinical Global Impression – severity (CGI-S) scale scores at week 3 ($P = 0.008$). The authors did not address whether the improved YBOCS scores could have been secondary to improved mood. Other limitations included the small sample, lack of double blinding, and potential variability between sessions in precise mapping of targets (Table 1).

In a separate study, Elbeh et al[40] examined the effects of 1 Hz, 10 Hz, or sham treatment applied to the right dlPFC in 45 OCD patients with a mean duration of illness of 19.2 ± 11.5 months. Stimulation was applied over 10 sessions, with a follow-up of 3 months. Sham-stimulation parameters were identical to the 10 Hz group, but the coil was set at 90° to the scalp. There was a statistically significant difference between the 1 Hz rTMS group and the sham group on YBOCS scores at 2 weeks and 3 months ($P = 0.001$), but no significant difference on YBOCS scores for the 10 Hz group vs the sham group at 2 weeks ($P = 0.08$) or 3 months ($P = 0.098$). The group receiving 1 Hz frequency showed a statistically significant reduction in YBOCS scores compared to the 10 Hz group ($P = 0.019$) after 3 months. The study showed good response to 1 Hz stimulation in young, non-TR OCD patients with short mean duration of illness compared to the 10 Hz and sham groups. Interestingly, Hamilton Anxiety Rating Scale (HARS) scores reduced significantly in the 1 Hz group in comparison with the 10 Hz and sham treatment, but were not addressed as potentially relevant to the decrease in YBOCS scores (Table 1).

Studies using HF (≥ 5 Hz) rTMS over the right dlPFC
The effects of 10 Hz rTMS over the right dlPFC were further tested in a 6-week double-blind RCT, followed by a 6-week open-label phase in 27 TR OCD patients with baseline YBOCS scores in the severe–extreme range.[41] There were no significant differences between groups after 6 weeks of initial treatment ($P = 0.710$). Between-group differences on HDRS ($P = 0.637$) and HARS ($P = 0.539$) scores were not significant either. The additional 6 weeks of open-label active rTMS in 10 patients from the sham group significantly reduced YBOCS scores by week 8 ($P = 0.023$), with a rebound thereafter. There were no clinical responders in the active group (defined as $\geq 30\%$ improvement in YBOCS with "much improved/very much improved" CGI scores). Long duration and severity of illness might have contributed to the modest effects of treatment (Table 1).

Studies using LF (1 Hz) rTMS over the left dlPFC
In a double-blind RCT study with 33 TR OCD patients, 1 Hz or sham stimulation was applied over the left dlPFC for 2 weeks.[42] Active and sham stimulation was positioned at 90° over the same area with the same stimulation parameters as the active coil. There were no statistically significant differences between active and sham treatments at 2 and 4 weeks poststimulation. There was a significant difference between baseline YBOCS scores in the active (YBOCS 29.82 ± 5.8)

Table I rTMS over the right dlPFC

Low frequency (1 Hz)

Study	Study design	Baseline scores and definition of response	rTMS protocol parameters and baseline scores	Results	Duration of follow up and results	Limitations
Alonso et al[37]	18 patients medicated and unmedicated; 13 TR patients; RCT; mean age 35.2±12.1 years	Baseline YBOCS, active 24.0±5.3, sham group 25.6±6.1; response, global reduction in YBOCS ≥40%	18 sessions/3 × week/6 weeks; 20-minute sessions; 110% RMT; circular coil; neuronavigation; sham coil; 1 Hz at 20 RMT; time parameters same	NS difference between groups (P=0.081) at 10 weeks	10 weeks	Small sample, inclusion of TR subjects, medication synergy; use of circular coil
Seo et al[39]	27 TR patients; RCT; mean age 34.5±9.8 years active, 36.3±12.5 years sham; duration of illness 9.8–11.7±9.5 years	Baseline scores not reported; response, reduction in YBOCS scores ≥25%	15 sessions; 5 × week; 20-minute sessions; 1,200 pulses/day; 100% RMT; figure-eight coil; manual targeting	At 3 weeks, significant improvement in active vs sham YBOCS (P=0.008); NS difference on the responder rate in the active vs sham groups (P=0.148)	3 weeks	Small sample, lack of double-blinding, potential variable localization of targets due to manual targeting, HDRS scores not factored in, in the final results
Elbeh et al[40]	45 patients (3 groups of 15); double-blinded, randomized trial; mean duration of illness 19.2±11.5 months	1 Hz (baseline), YBOCS 26.7±6.5; 10 Hz, YBOCS 25.3±4.7; sham group, YBOCS 24.9±5.7; response rates not reported	2 weeks; 10 sessions; 1 Hz, 4 trains ×500 pulses/day, 40-second intertrain interval; 10 Hz: 10 trains ×200 pulses, 20-second intertrain interval, 100% RMT; sham rTMS, protocol identical to 10 Hz group, apart from position of coil; figure-eight coil	2 weeks, significant reduction in 1 Hz YBOCS (P=0.001)	3 months, significant reduction in 1 Hz vs sham (P=0.001); reduction in YBOCS between 1 Hz vs 10 Hz (P=0.019)	Heterogeneity of sample symptom dimension not explored. Small sample, unclear medication status

High frequency (10 Hz)

Study	Study design	Baseline scores and definition of response	rTMS protocol parameters and baseline scores	Results	Duration of follow up and results	Limitations
Mansur et al[41]	27 patients (13 active rTMS, 14 sham); 6-week double-blind RCT + 6-week open-label trial in 10 patients; duration of illness 15.6–26.2 years	Baseline YBOCS, active 30±3, sham 29±4.9; response, YBOCS ≥30% reduction + "much or very much improved" CGI	Initial 6 weeks, 30 sessions, 40 trains; 5-second trains + 25-second intertrain interval, 60,000 pulses; 110% RMT; figure-eight coil; manual targeting; sham, deactivated coil	No significant difference after 6 weeks of initial treatment between groups (P=0.71)	Additional 6-week open-label trial for 10 patients from the previous sham group; week 8, YBOCS, P=0.023; effect lost after week 8	Small sample, imprecision linked to manual targeting, severity and long duration of illness
Elbeh et al[40]	45 patients, 3 groups of 15 patients; double-blind, randomized trial; mean duration of illness 19.2±11.5 months	1 Hz baseline YBOCS 26.7±6.5; 10 Hz YBOCS 25.3±4.7; sham group YBOCS 24.9±5.7; response rates not reported	2 weeks; 10 sessions; 1 Hz, four trains, 500 pulses/day; 40-second intertrain interval; 10 Hz, 10 trains, 200 pulses/day; 20-second intertrain interval, 100% RMT; sham rTMS, protocol identical to the 10 Hz group, apart from the position of coil; figure-eight coil	2 weeks, significant reduction YBOCS 1 Hz (P=0.001)	3 months, significant reduction in 1 Hz vs sham (P=0.001); reduction in YBOCS scores in 1 Hz vs 10 Hz (P=0.019)	Heterogeneity of sample symptom dimension not explored, small sample, unclear current medication status

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; CGI, Clinical Global Impression; dlPFC, dorsolateral prefrontal cortex; YBOCS, Yale–Brown Obsessive–Compulsive Scale; RMT, resting motor threshold; NS, nonsignificant; RCT, randomized controlled trial; HDRS, Hamilton Depression Rating Scale; TR, treatment-resistant.

and sham (YBOCS 23.42±4.9) groups, which was taken into account in a final comparison between groups (Table 2).

High-frequency (≥5 Hz) rTMS over the left dlPFC

In 2007, Sachdev et al compared 10 Hz rTMS to sham rTMS over the left dlPFC in 18 TR OCD patients.[43] Stimulation was applied over 10 sessions using a figure-eight coil, with an open extension to 20 sessions. The same parameters were used for the sham coil, positioned at 1 m from the scalp. The mean duration of illness for both groups was approximately 12 years, with mean ages 29.5±9.9 years in the active and 35.8±8.2 years in the sham group. There was no significant difference between groups on YBOCS scores at 2 or 4 weeks (P=0.76, P=0.24) of treatment, even after correcting for Montgomery–Åsberg Depression Rating Scale (MADRS) scores, which improved after 4 weeks (P=0.041). The study included a small sample of OCD patients with mild depressive disorder (Table 2).

rTMS over bilateral dlPFC

Using HF α-rTMS over bilateral dlPFC

Ma et al[44] used an innovative approach to stimulate the dlPFC using individualized rTMS frequency based on individually measured electroencephalography (EEG) α-frequency. They compared α-guided rTMS at 8–12 Hz frequencies with sham stimulation over 10 days in 46 medicated OCD patients: α-rTMS sessions were 20 minutes long, delivered by a circular coil, using manual mapping of bilateral dlPFC. A sham coil was inactive, but with the same positioning as the active coil. Frequency of α-rTMS was determined by average individual intrinsic α-EEG frequency, resulting in delivery of 648–872 pulses per treatment. At week 2, the α-rTMS group showed significant reductions in YBOCS scores compared to the sham group (P<0.01) and remained statistically significant at 1 week posttreatment for obsession (P=0.016), but not for compulsion subscores (P=0.144). HARS scores showed significant reduction after 2 weeks of treatment (P<0.01) and at 1 week follow-up (P<0.01), but HDRS scores showed no significant changes between active and sham groups (P≥0.05). So far, this is the only published study to use individualized rTMS frequency and replication, and this would be interesting in a larger OCD group (Table 3).

Studies using HF rTMS for bilateral dlPFC stimulation

Haghighi et al[45] and Jahangard et al[46] analyzed 20 Hz rTMS applied sequentially over the left and right dlPFC in TR OCD patients. Both studies used a randomized single-blind crossover design to compare active rTMS to sham stimulation over 4 weeks. Both studies reported significant improvements in YBOCS scores in active versus sham groups. Limitations of both studies included single-blind design and lack

Table 2 LF and HF rTMS over the left dlPFC

Study	Study design	Baseline scores and definition of response	rTMS protocol parameters and baseline scores	Results	Duration of follow up and results	Limitations
Low-frequency (1 Hz) rTMS over the left dlPFC						
Prasko et al[42]	30 TR OCD patients; RCT; active vs sham; age 28.9–33.4 years, mean duration of illness ~15 years	YBOCS, active 29.82±5.8, sham 23.42±4.9; response definition NA	2 weeks, 30-minute sessions, 1,800 pulses/ session; 110% RMT; sham stimulation, same parameters at 90° over the left dlPFC; figure-eight coil; manual targeting	2 weeks; NS difference between groups	4 weeks, NS effects on YBOCS, CGI-S, HARS between groups	Small sample, baseline difference on YBOCS scores between active and sham groups, manual targeting of left dlPFC, active sham coil
High-frequency (>5 Hz) rTMS over the left dlPFC						
Sachdev et al[43]	18 TR OCD patients; 2-week RCT + 2-week open-label study; mean age, active 29.5±9.9 years, sham 35.8±8.2 years; duration of illness, active 12.6±7.5 years, sham 12.3±5.4 years	Baseline YBOCS, active 25.8±5.7, sham 23.9±9.9; clinically significant improvement definition, reduction in YBOCS ≥40%	10 sessions/2 weeks–20 sessions/4 weeks; each session 30 trains ×5 seconds + 25-second intertrain interval; 110% RMT; manual targeting	NS at 2 weeks (P=0.76)	NS at 4 weeks (P=0.24); clinically significant improvement in 6 patients	Small sample, TR illness in chronic OCD patients

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; dlPFC, dorsolateral prefrontal cortex; TR, treatment-resistant; OCD, obsessive–compulsive disorder; RCT, randomized controlled trial; YBOCS, Yale–Brown Obsessive–Compulsive Scale; NA, not applicable; RMT, resting motor threshold; NS, nonsignificant; CGI-S, Clinical Global Impression – severity; HARS, Hamilton Anxiety Rating Scale.

Table 3 Stimulation of bilateral dlPFC

Study	Study design	Baseline scores and definition of response	rTMS protocol parameters	Results	Duration of follow up and results	Limitations
HF α-guided rTMS						
Ma et al[44]	46 patients in active and control groups; RCT; age, active 27.12±8.97 years, sham 29.86±9.42 years; duration of illness, active 11.40±5.65 years, sham 12.48±5.34 years	YBOCS, active 25.4±6.2, control 23.4±5.7; definition of response, CGI 1 to ≥2, <35% YBOCS, remission, YBOCS <16	2 weeks; 20-minute sessions; 4-second train + 56-second intertrain interval/minute; circular coil; manual targeting; inactive sham coil; same protocol	At 2 weeks, reduction in total YBOCS and obsessive scores, active vs sham ($P=0.001$); response to treatment, active vs sham ($P<0.01$)	At 3 weeks, group difference in YBOCS ($P<0.05$); response to treatment, active vs sham ($P<0.05$)	Use of circular coil, manual targeting
HF (>5 Hz) rTMS of bilateral dlPFC						
Haghighi et al[45]	21 TR OCD patients; single-blind crossover RCT; mean age 35.8 years; unknown duration of illness	First active rTMS group YBOCS 30.40±6.54; first sham rTMS YBOCS 30.09±8.08; definition of response, Pallanti and Quercioli[14]	20 Hz; 2 weeks active + 2 weeks sham rTMS; stimulation of left then right dlPFC with same parameters; 750 pulses; 25 trains with 1.5 seconds duration intertrain interval; 100% RMT; figure-eight coil; manual targeting; coil 45°–90° to the skull	2-week improvement in YBOCS for active, but not sham ($P<0.001$)	At 4 weeks, full and partial responses to treatment, active vs sham ($P=0.002/P=0.003$)	Small sample, single-blind study design, unknown duration of illness
Jahangard et al[46]	10 patients; single-blind RCT crossover design; mean age 33.1 years; unknown duration of illness	Baseline YBOCS, active group 31±2.25, sham group 31±2.25	20 Hz; 2 weeks active + 2 weeks sham rTMS; stimulation of left then right dlPFC with same parameters: 750 pulses; 25-second train + 1.5-second intertrain interval; 100% RMT; figure-eight coil; manual targeting; coil 45°–90° to the skull	At 2 weeks, decrease in YBOCS for active-then-sham group ($P<0.01$) + improvement in cognitive performances	At 4 weeks, sham-then-active group had significant decrease in YBOCS ($P<0.01$)	Small sample; single-blind study design; unknown duration of illness; active sham coil
Low-frequency (1 Hz) sequential rTMS over dlPFC and SMA						
Kang et al[47]	21 TR OCD patients; RCT; active vs sham; age, active 28.60±12.66 years, sham 26.20±10.52 years; duration of illness, active 8.17±3.81 years, sham 9.46±9.41 years	Baseline YBOCS, active 26.50±5.64, sham 26.30±4.06	10 days; 1 Hz for 10 minutes on right dlPFC, 1,200 stimuli/day 110% RMT + 1 Hz for 10 minutes on SMA; 1,200 stimuli/day; 100% RMT; figure-eight coil; 45° coil-tilt method	4 weeks; NS difference between groups; YBOCS $P=0.92$; NS difference for depression (MADRS, $P=0.67$) or anxiety (HARS, $P=0.84$) scales	4 weeks	Active sham conditions, small sample, TR OCD patients

Abbreviations: dlPFC, dorsolateral prefrontal cortex; CGI, Clinical Global Impression; rTMS, repetitive transcranial magnetic stimulation; HF, high-frequency; RCT, randomized controlled trial; YBOCS, Yale–Brown Obsessive–Compulsive Scale; TR, treatment-resistant; OCD, obsessive–compulsive disorder; RMT, resting motor threshold; SMA, supplementary motor area; NS, nonsignificant; MADRS, Montgomery–Åsberg Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale.

of monitoring for anxiety and depression symptoms, which can potentially moderate the intensity of OCD symptoms (Table 3).

Studies using LF sequential rTMS over the right dlPFC and SMA

In an RCT with 20 TR OCD patients, Kang et al[47] assessed sham or 1 Hz stimulation over the right dlPFC at 110% resting motor threshold (RMT) for 10 minutes, followed by 10 minutes of SMA stimulation with 1 Hz at 100% RMT, over a period of 10 days. Sham stimulation was applied using a coil-tilt method, positioned at 45° toward the scalp. Duration of OCD in both patient groups was 8.17±3.81–9.46±9.41 years. There was a significant effect of time on YBOCS scores in each group (P=0.009), but no significant difference between groups (P=0.92). There was no difference between groups on depression (MADRS) or anxiety (HARS) scores. Limitations included small groups and potential effects of sham stimulation (Table 3).

In summary, stimulation of exclusively right or left dlPFC has not shown consistent data on the effectiveness of either HF or LF stimulation in OCD. Differences in methodology of reviewed studies including illness heterogeneity, stage of illness, and medication status, which have impacted the outcomes. More consistent data are accumulating on HF rTMS of the bilateral dlPFC,[45,46] and an innovative α-rTMS protocol over the bilateral dlPFC offers a promising way of individualizing HF stimulation of dlPFC and calls for replication.[44]

Interestingly, positive findings on LF stimulation over the right dlPFC[39,40] were associated with a reduction in depressive and anxiety scores, an effect previously shown in LF rTMS stimulation over the right dlPFC in depression. Neurobiologically, there is insufficient understanding of deficits in the dorsal cognitive loop in OCD to guide the targeting of this circuitry in treatment. Identifying specific OCD symptom dimensions that respond to dlPFC stimulation and any comorbidities (eg, depression) that may be more likely to respond to stimulation over the dlPFC could inform future use of rTMS in OCD patients.

rTMS over the SMA

rTMS stimulation over the pre-SMA and SMA in OCD patients was first explored by Mantovani et al.[48] The pre-SMA (BA32/BA8) and SMA (BA 6) form a part of the sensorimotor CSTC circuit, together with the motor (M1) and premotor cortices. These cortical regions project topographically to the putamen, which in turn projects by direct (via globus

pallidus interna) and indirect (via globus pallidus externa) pathways via basal ganglia to the thalamus and cortex, forming a sensorimotor CSTC loop.[17,18,49]

Research has delineated that rostral "associative" and caudal "sensorimotor" components of the sensorimotor cortex serve different functions in the process of planning and executing motor movements.[50,51] The rostral, associative part of the sensorimotor cortex, including the pre-SMA, rostral cingulate motor area, and rostral premotor areas, are thought to be involved in sequence generation and motor learning, and have close connections with other PFC regions.[50] Caudal components, including the SMA, motor cortex, caudal cingulate motor area, and premotor areas, are considered responsible for movement execution.[18] The SMA is thought to be involved in internal generation of movement and construction of motor sequences with its direct projections to M1, spinal cord, and striatum.[50] The pre-SMA subsumes the resolution of competing motor plans[52] by mechanisms of updating and implementing competing response plans.[53] Functional alteration of the sensorimotor loop in OCD might be responsible for interfering with suppression of "internally triggered intrusive and repetitive movements and thoughts".[20]

There is a paucity of neuroimaging data on sensorimotor areas in OCD. Most of the evidence for abnormalities in the sensorimotor CTSC loop in OCD is underpinned by structural and functional neuroimaging studies focusing on different target areas or using different symptom-provocation/neurocognitive paradigms.[54–59] Findings of high motor excitability, structural deficits, and hyperactivity of the pre-SMA/SMA region in functional studies informed the use of inhibitory frequencies in rTMS stimulation of the SMA (Table 4).

Mantovani et al[60] revisited the effects of 1 Hz rTMS over the SMA in 2010, following neuroimaging/spectroscopy findings of hyperactivity in premotor areas (including the SMA) and the dorsal ACC in OCD.[61] In a 4-week double-blind study followed by a 4-week open-label trial, 18 patients were initially randomly assigned to active rTMS or sham rTMS. In the open-label trial, nonresponders to sham rTMS and responders to active or sham rTMS were offered additional active rTMS for 4 weeks. Groups were followed every 2 weeks for 3 months with YBOCS and YBOCS self-reports as primary outcome measures. YBOCS results at baseline, week 2 (P=0.294), and week 4 (P=0.153) were not statistically significant between groups, but scores on YBOCS self-report scale (P=0.031) and CGI-S for the active group (P=0.044) improved after 4 weeks of treatment. The group who received 8 weeks of active rTMS had a statistically

Table 4 LF rTMS over the SMA

Study	Study design	Baseline scores and definition of response	rTMS-protocol parameters	Results	Duration of follow up and results	Limitations
Mantovani et al[60]	21 patients, (9 active rTMS, 9 sham rTMS); 4-week RCT and 4-week open-label; age, active 39.7±8.6 years, sham, 39.4±10.2 years; duration of illness, active 22.4±13.8 years, sham 22.1±7.3 years	YBOCS, active 26±5.4, sham 26.7±5.5; response definition, patients with 25% YBOCS reduction at the end of phase I	8 weeks; 1 Hz; SMA; figure-eight coil; mapping via international 10–20 EEG system; phase I, active vs sham rTMS 4 weeks, 5 days/week; 20-minute train/session; 1,200 pulses/day; 100% RMT; phase 2, 4-week open-label rTMS to nonresponders to sham and responders and nonresponders to active rTMS in phase I	NS response rate between active and sham groups at week 2 and week 4 ($P=0.294$, $P=0.153$); at 4 weeks, active vs sham YBOCS NS; active vs sham YBOCS SR $P=0.031$	8 weeks; phase 2; control vs active, significant effect of time on YBOCS ($P=0.000$); sham vs active, NS YBOCS change; at 3 months, six responders to active rTMS showed a 51% decrease from baseline YBOCS	Small sample, "imperfect" sham system, potential synergistic effect with medication
Gomes et al[62]	22 patients; double-blind RCT; active rTMS 12, sham rTMS 10; mean age, active 35.5±7.5 years + duration of illness 17±8 years; sham, age 37.5±16 years; duration of illness 19.5±12 years	Active YBOCS 36.4±3.2, sham YBOCS 31.8±3.5; responders, patients with 25% YBOCS reduction	2 weeks; 1 Hz; 5 days a week; 20-minute trains; 1,200 pulses/day; figure-eight coil; 100% RMT; bilateral pre-SMA localized via international 10–20 EEG system	Week 2, significant reduction in YBOCS between active and sham ($P=0.0076$); response rate, active vs sham $P<0.001$	14 weeks; YBOCS active vs sham $P<0.0001$; response rate, active vs sham $P<0.001$	Small sample, limitations in sham design, synergy with medications, manual navigation system
Arumugham et al[63]	34 treatment-refractory OCD patients; active vs sham rTMS; RCT; baseline demographic data not reported	Baseline data not reported; definition of response NA	3 weeks, 18 days; 1 Hz; 1,200 pulses/day; pre-SMA; process of targeting NA; coil description NA	Week 3, NS difference between active and sham rTMS ($P=0.972$)	12 weeks – results NA	Description of sham rTMS NA, stimulation protocol and duration of pulse intervals NA
Hawken et al[64]	22 patients; multicenter double-blind RCT; age, active 33±11 years, sham 34±14 years; duration of illness, center B vs center T, $P=0.037$	Center B, YBOCS 28±5; center T, YBOCS 28±4; responders, YBOCS reduction >25%	6 weeks; 1 Hz; 5 days a week for 4 weeks, then 3 days a week for 1 week and 2 days a week for 1 week 20-minute sessions (5-minute trains and 2-minute intertrain intervals); figure-eight coil; 110% RMT; bilateral SMA localized via international 10–20 EEG system; active tilted coil 90° from the skull; 110% RMT	Significant effect; after 5 weeks (25 treatments), YBOCS active vs sham $P=0.023$	8 weeks; significant effect; 2 weeks after last treatment, YBOCS active vs sham $P=0.044$	Small sample, potential blinding issue with sham treatment due to imperfect sham design, multicenter design with significant difference in the duration of illness between sites
Pelissolo et al[65]	36 patients with YBOCS >15, >2 years of illness and 8 weeks of nonresponse to two SSRIs; 75% with comorbid MDD; age 41.5±10.7 years; duration of illness, active 19.8±12.8 years, sham 24±10.9 years	YBOCS, active 30.2±4.2, sham 28.6±4.6; unclear definition of responders	4 weeks; 1 Hz; 26-minute sessions; 4/5-minute trains with 2-minute rest; 1,500 pulses/day; figure-eight coil; 100% RMT; bilateral pre-SMA; T, MRI neuronavigation; sham rTMS, Magstim sham coil	NS differences between active and sham at week 4	NS difference over 12 weeks	Comorbidity with depressive symptoms

Abbreviations: LF, low-frequency; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; RCT, randomized controlled trial; YBOCS, Yale–Brown Obsessive–Compulsive Scale; EEG, electroencephalography; RMT, resting motor threshold; NS, nonsignificant; SR, self-report; OCD, obsessive–compulsive disorder; NA, not available; SSRIs, selective serotonin-reuptake inhibitors; MDD, major depressive disorder; MRI, magnetic resonance imaging.

significant decrease in YBOCS (*P*=0.000), while the sham rTMS group did not achieve statistically significant improvement in OCD symptoms when assigned to 4 weeks of active treatment, although they showed a significant improvement in general anxiety symptoms (HARS, *P*=0.033). Right-hemisphere MT and right–left symmetry improved after active rTMS, but no significant change was observed in groups receiving sham rTMS. The authors suggested that it remained unclear whether baseline hyperactivation of motor and premotor areas was a primary alteration or a compensatory state reflecting neuronal deficit in another part of CTSC neurocircuitry.

In a 2-week, double-blind RCT, Gomes et al[62] applied 1 Hz rTMS over the bilateral pre-SMA in 22 OCD patients, measuring YBOCS scores after active vs sham treatment. After 2 weeks of treatment, patients in the active group showed a significant reduction in YBOCS scores by 15.3±2.4 points compared to 5.3±2.6 points in the sham group (*P*=0.0001). Reduction in YBOCS scores persisted for 14 weeks posttreatment in the active rTMS group. Initial improvement in anxiety scores on HARS, statistically significant for both groups, did not persist at 14 weeks, and there was no change in depression HDRS scores at the 2nd or 14th week for either group. Small samples, sham rTMS design, manual targeting of the pre-SMA region, and possible synergy with pharmacological treatment present methodological limitations of this study. In an RCT with 34 TR OCD patients, Arumugham et al[63] applied 1 Hz rTMS or sham treatment over the bilateral pre-SMA for 3 weeks. There was no difference between groups on YBOCS scores (*P*=0.972) after 3 weeks of treatment. Lack of baseline demographic data and baseline YBOCS and no description of the sham protocol allow limited interpretation of the findings.

In a 6-week, multicenter placebo RCT, Hawken et al[64] examined 1 Hz rTMS in 22 TR OCD patients. The protocol consisted of daily rTMS in 20-minute sessions 5 days a week for the initial 4 weeks, reduced to 3 days a week in the fifth week, and twice a week in the sixth week of treatment. The bilateral SMA was stimulated after manual targeting via the international 10–20 EEG system. After 25 treatments, the group receiving active rTMS showed significant reduction in YBOCS scores (*P*=0.023), and 80% of participants experienced a clinical response (YBOCS reduction >25%). Reduction in YBOCS scores in the active group persisted for 2 weeks posttreatment (*P*=0.044). The active rTMS group also showed a significant reduction in depression scores measured by HDRS (*P*=0.021) without influencing YBOCS results. Limitations of the study included a small sample,

significant difference in the duration of illness between groups (*P*=0.037), lack of end-of-treatment follow-up for one center, and imperfect sham design. Pelissolo et al[65] conducted an RCT of 1 Hz rTMS over the pre-SMA in 36 TR OCD patients over 4 weeks. At the end of week 4, there was no difference between responders (*P*=0.63) and completers (*P*=0.47). It is worth noting that 75% of subjects had comorbid major depressive disorder (DSM-IV-TR), and there was no difference in depression scores measured by MADRS between groups after treatment. The authors proposed that having a severely TR sample with comorbid depression might explain the negative results (Table 4).

In summary, it appears that the majority of studies using the inhibitory 1 Hz rTMS over the bilateral pre-SMA/SMA have shown positive but short-term effects on reducing obsessive and compulsive symptoms. Generalizing study findings are restricted by small samples and a great deal of heterogeneity in severity of OCD symptoms, duration of illness, study designs, and methodology. Most importantly, stimulation protocols differed between studies in the duration of trains and intertrain intervals, the total number of pulses in a session, duration of treatment, and the delivery at different RMT thresholds. All these parameters influence the direction of stimulation and the duration of the effect. Although ideal stimulation parameters are so far unknown, studies using protocols consisting of 20-minute trains with 1,200 pulses/day and at least 2 weeks' treatment seem to have resulted in positive outcomes on YBOCS scores.

rTMS of the OFC

Situated at a ventral bottom portion of the frontal lobes, the OFC forms a cortical part of the "ventral cognitive circuit" and is closely linked to the "affective CSTC circuit".[19,66] Lesions to the OFC interfere with appropriate decision-making and response selection and impair adaptive response selection.[17] OCD symptomatology is thought to arise as a result of excessive activity in parts of the ventral cognitive circuit, with the inability to resolve intrusive obsessions, and interrupt urges and anxiety that lead to repetitive compulsive behaviors.[16,23] Table 5 summarizes the studies of rTMS in OCD targeting the OFC (Table 5).

Ruffini et al[67] stimulated the OFC with active or sham rTMS in 23 TR OCD patients on medication, 5 days a week, for three consecutive weeks. Active stimulation was performed using a figure-of-eight-shaped 70 mm coil positioned over the left OFC (localized via international EEG system at Fp1). There was a significant reduction in YBOCS scores between the active and sham groups (*P*<0.04), with significant

Table 5 LF rTMS stimulation of OFC

Study	Study design	Baseline scores and definition of response	rTMS protocol parameters	Results	Duration of follow up and results	Limitations
Ruffini et al[67]	23 TR OCD patients; active vs sham; baseline YBOCS scores >30 in both groups; age NA; duration of illness NA	Baseline YBOCS scores >30 in both groups; response definition not stated	15 days/15 sessions; 10-minute sessions; 1 Hz; left OFC; figure-eight coil; manual targeting; 80% RMT; sham coil, inactive rTMS coil placed perpendicularly to the left OFC	15 days; active vs sham $P<0.04$	3 months; significant difference until week 10 ($P<0.06$)	
Nauczyciel et al[68]	19 TR OCD patients; RCT crossover design; on–off 39 (24–56); off–on 40 (24–56)	On–off YBOCS 32 (15–36); off–on 32 (16–36); level of response not measured	10 sessions/2 × day in the first week; 1 Hz; 120% RMT; 1,200 pulses/session; right OFC; D8-80 butterfly double-cone coil; sham coil placebo	YBOCS active vs sham $P=0.07$	35 days; active vs sham YBOCS $P=0.94$	Small sample, design prone to unblinding

Abbreviations: LF, low-frequency; rTMS, repetitive transcranial magnetic stimulation; OFC, orbitofrontal cortex; TR, treatment-resistant; OCD, obsessive–compulsive disorder; YBOCS, Yale–Brown Obsessive–Compulsive Scale; NA, not available; RMT, resting motor threshold; RCT, randomized controlled trial.

difference between active and sham stimulation measured at 10 weeks post-rTMS ($P<0.02$). However, the effect was lost at a 10-week follow-up ($P<0.06$). There was no significant decrease in depression or anxiety scores between the groups. In terms of response, 15 of 16 patients receiving active rTMS had a >35% reduction in YBOCS scores. The small sample, stimulation at 80% RMT, lack of precise localization of the target, and lack of supporting neuroimaging data ensuring OFC were indeed targeted and accessible to rTMS call for replication of the study. In a randomized double-blind cross-over trial, Nauczyciel et al[68] employed active vs sham rTMS targeted to the right OFC in 19 TR OCD patients with DB-80 coil. Ten patients underwent resting-state positron emission tomography scans: one after active stimulation sequence and one after sham stimulation. YBOCS scores decreased after 1 week in the active ($P<0.01$) and sham groups ($P=0.02$), with a trend toward a greater decrease in scores after active compared to sham stimulation ($P=0.07$). Differences in YBOCS scores between groups dissipated at 35 days. There were no changes in MADRS scores over time. Positron emission tomography scan findings of the 10 patients after the active stimulation showed significant decreases in metabolism in the right frontal lobe (BA9), middle gyrus (BA10), orbital gyrus (BA47, BA11), left ACC (BA25), left frontal lobe (BA11), and left putamen. There were no brain regions with increased metabolism under active stimulation conditions. Decreased YBOCS scores correlated with a decrease in the metabolic activity of the right OFC (BA47).

dTMS

The development of dTMS in OCD emerged after the observed effectiveness of deep brain stimulation on subcortical structures in OCD patients, in addition to exploring noninvasive methods of stimulating deep brain structures.[69] Double-cone and H coils have been developed to reach and stimulate deeper subcortical structures.[70] dTMS targets of interest in OCD have been the mPFC and ACC, consistently implicated in OCD CSTC neurocircuitry by neuroimaging findings and observations of improvement in OCD symptoms after anterior cingulotomy or anterior capsulotomy.[71] So far there have been two published RCTs on the use of dTMS in OCD. Carmi et al observed the effects on OCD symptoms after stimulating the mPFC and ACC,[72] while Nauczyciel et al examined the effects of targeting OFC[68] (Table 6).

In a double-blind controlled study, Carmi et al[72] used dTMS H7-coil or sham treatment over 5 weeks in 41 OCD patients on SRIs. The majority of patients had OCD for >10 years and were in the 25- to 40-year age group. Patients were randomized to 20 Hz, 1 Hz, or sham treatment, and target areas were the mPFC and ACC. The group receiving 20 Hz dTMS improved significantly in YBOCS scores compared to the 1 Hz and placebo groups (28% vs 6% reduction, $t_{93}=-2.29$; $P=0.0243$). YBOCS scores recorded over the following 3 months remained stable. The H7 coil used by Carmi et al is designed to reach the mPFC and ACC. A D8-80 butterfly double-cone coil had been used previously with a positive effect over the right OFC.[68] Pairing dTMS stimulation with functional neuroimaging tools would improve the reliability of reaching intended targets and offer the possibility of correlating neuroimaging findings with any potential clinical effects. Concurrent stimulation of superficial cortical areas with dTMS devices might contribute to treatment effects (Table 6).

Table 6 HF and LF stimulation via dTMS

Study	Study design	Baseline scores and definition of response	rTMS protocol parameters and baseline scores	Results	Duration of follow up and results	Limitations
Carmi et al[72]	Double-blind, controlled trial; 41 OCD patients; sham 20 Hz, active 1 Hz; + simultaneous with symptom provocation; age 28±3.1 years, 35±3.5 years, 36±2.1 years	Baseline YBOCS 25–28	5 weeks; 1 Hz/20 Hz; targeting mPFC, including ACC; LF, 1 Hz, 110% RMT, 900 pulses; HF, 20 Hz, 100% RMT, 50 2-second trains (2,000 pulses); H7 coil; sham coil NA	At 5 weeks, 20 Hz dTMS vs 1 Hz dTMS P=0.0243	At 3 months, stability in improvements measured by YBOCS	Accessibility of specific coil for general use; particular stimulation protocol linked with symptom provocation

Abbreviations: HF, high-frequency; LF, low-frequency; dTMS, deep transcranial magnetic stimulation; OCD, obsessive–compulsive disorder; YBOCS, Yale–Brown Obsessive–Compulsive Scale; rTMS, repetitive TMS; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; RMT, resting motor threshold; NA, not available.

Discussion

Electrical activity in the brain has been a source of interest for over two centuries, with electrophysiology emerging as a "pre-eminent method for the localization of brain functions".[73] In recent years, the field of affective neuroscience has become richer, with the availability of sophisticated neuroimaging and new neurostimulation techniques that are able to detect, monitor, and correlate neural changes with affective, cognitive, and behavioral processes. Recognition that neural networks are interconnected and communicate at different levels has facilitated a better understanding of the neurobiological concepts related to psychiatric disorders. However, consistent treatment outcomes of complex psychiatric conditions, such as OCD, have been elusive. rTMS offers a treatment approach with a mechanism of action that can directly impact obsessive and compulsive symptom circuitry.

Stimulation of different brain areas, such as the dlPFC, SMA, OFC, and ACC, has so far elicited encouraging but mixed results, making it a potential add-on treatment strategy, though in need of refinement. A small number of studies suggest that HF stimulation of the right dlPFC,[41,74] sequential HF stimulation of the bilateral dlPFC,[45,46] and novel α-guided rTMS using HF ranges[44] may result in short-term improvement in OCD symptoms. This is in line with a recent meta-analysis[30] reporting on the effectiveness of HF stimulation over the bilateral dlPFC – right dlPFC and left dlPFC – in improving OCD symptoms; however, previous systematic reviews and meta-analyses concluded that rTMS over the dlPFC was not more effective than sham stimulation.[27,28,75–78]

Outcomes have been more consistent for rTMS over the bilateral SMA, with significant beneficial effects noted as early as 4 weeks and lasting for up to 14 weeks.[60,62] Interestingly, methodological heterogeneity comprising different inhibitory stimulation protocols, different OCD subtypes,

and concomitant medication did not affect the findings in any profound way. One possible explanation could be that inhibitory rTMS over the SMA has a larger effect due to "stronger" connectivity with striatal regions compared to the dlPFC in OCD patients. Therefore, inhibition of the SMA might lead to short-term "normalization" of the SMA CTSC and interconnected regions, and subsequently help patients deal better with intrusive thoughts, impulses, and compulsions.[78]

Two studies using LF inhibitory stimulation over the OFC yielded temporary but statistically significant positive results for OCD symptoms compared to sham stimulation in TR OCD patients.[67,68] This is consistent with the findings of OFC hyperactivity in OCD.[79] Previous studies have highlighted the promising acute therapeutic response of rTMS applied to OFC.[28,30,76] In terms of dTMS, studies targeting the ACC and mPFC have shown positive effects on OCD symptoms using double-cone and H7 coil under different stimulation parameters and protocols.[68,72] Stimulation via dTMS devices reaches varying brain surface areas and depths.[70] Positive effects of dTMS could be conceptualized as a sum of all stimulated cortical and subcortical regions at the time of stimulation. Therefore, dTMS could likely surpass the rTMS limitations of cortical superficial stimulation by the extent of effect on subcortical circuits. However, the number of trials using dTMS is limited, and more research is required.

The interpretation and generalizability of findings from rTMS research in OCD is challenged by a number of design and methodological differences across studies. For example, there is a wide between-study variability in such patient characteristics as age of OCD onset, severity, OCD subtype, and of illness (months to years), treatment status, and stimulation protocols. Age of onset and duration of illness might impact the degree of response to rTMS, as both these factors have been associated with comorbidities and treatment resistance.[80] Severe versus mild–moderate illness might

additionally influence the extent of therapeutic rTMS effects, as shown in depression, where the severity of depression has been shown to predict the remission rates with rTMS, such that people with mild and moderate symptoms appeared to respond better to the treatment.[81]

A further challenge for the field is identifying which brain areas are responsible for mediating different OCD symptom dimensions. Such an understanding could inform which targets are most likely to be responsive to rTMS at an individual patient level. Further consideration also needs to be given to precise stimulation parameters. For example, Zhou et al[30] showed that stimulation at 100% RMT was more effective than stimulation at other intensities across a number of studies. Variability in sham protocols between studies has been shown to impact treatment effect sizes, depending on the use of active or inactive coil.[30] The underlying mechanisms are unclear, especially considering a generally low placebo effect in severe OCD.[82]

Meta-analyses[27–31] of TMS in OCD have attempted to aggregate data from a number of different studies. Though relevant in generating information on promising targets and stimulation parameters, combined effect results have limitations in enhancing our understanding of clinical predictors (age, duration of OCD, baseline medication) and stimulation-relevant factors (eg, target, frequency range, and stimulation frequency) that are potentially associated with positive treatment outcomes. In addition, it is not yet clear whether there are significant differences in efficacy between targets. The modest number of studies and clinical heterogeneity among studies calls for careful interpretation. Apart from the effect of rTMS on the SMA (use of only LF stimulation on SMA), which yields a moderate effect size, results from other meta-analyses combining HF and LF parameters and different stimulation duration, as well as different sham conditions, are not specific enough to guide clinical practice.

The majority of rTMS studies in OCD have been conducted in TR OCD patients as an augmentation strategy to standard pharmacological treatment. There is a lack of studies comparing other augmentation strategies with rTMS as an add-on treatment in this subgroup of patients.[83] There is a need to address the design and methodological heterogeneity of rTMS studies, including the difference in stimulation protocols, the underlying variability in pharmacological treatment, and the heterogeneity of OCD subtypes, which might have obscured the true therapeutic effect of rTMS. Addressing these issues will help clarify to what extent rTMS is clinically comparable with other augmentation strategies and thus valuable in the OCD treatment armamentarium.

Larger studies will also provide more statistical power to detect meaningful effects of treatment.

In conclusion, as a new neurostimulation technique, rTMS shows promise as part of a toolbox of current psychiatric treatment options for OCD. Its noninvasiveness with good tolerability and side-effect profile make it an appealing treatment consideration. Underlying neurobiological mechanisms related to TMS are still under evaluation, but appear to offer a novel "third" way of addressing symptoms via localized electrical stimulation compared to pharmacotherapy and psychotherapy approaches. Recent studies have considered rTMS as an adjunct treatment in TR patients with long duration of illness. In future, apart from managing design and methodology issues encountered in previous studies, it will be of interest to address rTMS as an augmentation strategy earlier in the course of treatment and consider parallel stimulation of a few cortical regions. Also, rTMS could be evaluated as an option in medication-naïve patients who cannot tolerate pharmacological treatment and have limited benefits from psychotherapy approaches. Advances in targeted brain stimulation via development of dTMS H coils paired with functional neuroimaging are offering a step further in understanding and management of OCD. However, it is yet to be determined how we can best optimize the approach via rTMS or dTMS to achieve clinically relevant results.

Disclosure

The authors report no conflicts of interest in this work.

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