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REVIEW ARTICLE

Transcranial magnetic stimulation of the medial prefrontal cortex for psychiatric disorders: a systematic review

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Objective: The medial prefrontal cortex (mPFC) is a highly connected cortical region that acts as a hub in major large-scale brain networks. Its dysfunction is associated with a number of psychiatric disorders, such as schizophrenia, autism, depression, substance use disorder (SUD), obsessive-compulsive disorder (OCD), and anxiety disorders. Repetitive transcranial magnetic stimulation (rTMS) studies targeting the mPFC indicate that it may be a useful therapeutic resource in psychiatry due to its selective modulation of this area and connected regions.
Methods: This review examines six mPFC rTMS trials selected from 697 initial search results. We discuss the main results, technical and methodological details, safety, tolerability, and localization strategies.
Results: Six different protocols were identified, including inhibitory (1 Hz) and excitatory (5, 10, and 20 Hz) frequencies applied therapeutically to patient populations diagnosed with major depressive disorder, OCD, autistic spectrum disorder, SUD, specific phobia, and post-traumatic stress disorder (PTSD). In the OCD and acrophobia trials, rTMS significantly reduced symptoms compared to placebo.
Conclusion: These protocols were considered safe and add interesting new evidence to the growing body of mPFC rTMS literature. However, the small number and low methodological quality of the studies indicate the need for further research.

Keywords: Prefrontal cortex; medial prefrontal cortex; noninvasive transcranial stimulation; transcranial magnetic stimulation; depression; PTSD; autism spectrum disorder; substance-related disorders; phobic disorders

Introduction

The medial prefrontal cortex (mPFC) is a heteromodal association area that includes several cortical regions located along the midline of the PFC.[1-3] While there is some terminological ambiguity and a lack of precise anatomical delimitation regarding the mPFC, it is generally defined as posteriorly bordering the secondary motor areas, anteriorly extending to the frontopolar cortex and ventrally to include parts of the anterior cingulate cortex (ACC), especially its more dorsal portions.[4-6] The mPFC receives association fibers from sensory cortical areas and medial temporal lobe structures, especially the hippocampus and subiculum, as well as projections from the subcortical structures, such as the amygdala.[3,7-9] It also connects with the nucleus accumbens (NAcc), the posterior cingulate cortex, the insula, and the hypothalamus.[3,4,6,7,10-13] Recently, the mPFC has been considered of central importance for the pathophysiological understanding of mental disorders.[13-17]

Functionally, the mPFC has been associated with many different neuropsychological processes commonly affected by psychiatric disorders, such as social cognition,[18-21] self-referential thinking,[22-26] emotion regulation,[27-29] behavioral reinforcement,[6,10,30,31] implicit associative learning,[32-34] decision making,[35-39] and episodic memory consolidation and retrieval.[8,9,39]

Indeed, neuroimaging and lesion studies have identified the mPFC as one of the main structures involved in psychiatric disorders, including schizophrenia,[17,40-43] autistic spectrum disorder (ASD),[44-46] substance use disorder (SUD),[12,30,31,47,48] major depressive disorder (MDD),[49-51] obsessive-compulsive disorder (OCD),[52-54] and anxiety disorders, such as specific phobia[55,56] and post-traumatic stress disorder (PTSD).[57-59] In a comparison between neuroimaging studies of various neurological and psychiatric disorders, mental illnesses were more strongly related to mPFC abnormalities.[60] Functional neuroimaging of multiple categories of psychiatric disorders have also shown that the mPFC is of transdiagnostic importance, suggesting that mPFC abnormalities may be a common neural substrate for these conditions.[61]

The associations between the mPFC and different types of mental illness and neuropsychological processes

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probably stem from its high connectivity and hub function, since it integrates large-scale brain networks, namely the default-mode network (DMN) and the salience network (SN).[17,62-64] These two networks, which are associated with emotion, behavior, and the Self, have been identified as central to the pathophysiology of psychiatric disorders, together with the central executive network (CEN), which involves the dorsolateral PFC (dlPFC) and the parietal regions, which are related to cognitive control and working memory.[14,17,65,66] Importantly, they seem to influence one another, and functional connectivity data suggest that a mPFC node is a major mediator of this interaction.[51,67,68]

The SN consists of brain regions usually associated with emotion regulation and reward/motivation.[13,62,69] This network is anchored in two subsystems that share a mPFC connection: one based on corticolimbic and fronto-insular connections and noradrenergic amygdala activity, and another based on the frontostriatal circuitry of the dopaminergic reward/motivation system. The DMN is a resting-state brain network that is deactivated during task-related behaviors, essentially becoming silent when external attention is required, although its components do not always follow this pattern.[70-73] Anatomically, the DMN mainly consists of midline brain regions, such as the mPFC, the posterior cingulate cortex, the precuneus and the medial temporal lobe. Together, they form a system that involves different aspects of self-related mental processes, which is activated during mental simulation tasks, such as perspective taking or imagining scenes.[70] DMN and SN abnormalities have been linked to psychiatric disorders such as SUD, MDD, ASD, and schizophrenia.[16,43,70]

Transcranial magnetic stimulation of the medial prefrontal cortex

Recent advances in the pathophysiology of psychiatric disorders have brought attention to the mPFC as a promising target for therapeutic intervention, particularly transcranial magnetic stimulation (TMS). Due to its ability to modify brain function in an anatomically selective manner, TMS has been proposed as tool for modulating mPFC activity.[14,15,66,74] Interest in the mPFC represents a shift in TMS research, which, over the past decades has been focused on the dlPFC, a region more directly involved in CEN-related functions.[14]

TMS is achieved through magnetic pulses generated by a coil that receives electrical current at a controlled frequency. The magnetic field can influence electrical activity in conductive media, such as the cerebral cortex, through electromagnetic induction.[75] The coil is positioned over predetermined points on the scalp, targeting specific cortical areas at a depth of 4-5 cm, which causes depolarization.[76] When magnetic pulse sequences are applied over a period of time, long-lasting effects in cortical plasticity can be achieved.[77,78] In this case, the technique is called repetitive TMS (rTMS) and, depending on the frequency of the stimulation, may result in an excitatory (high frequency protocols, usually greater than 5 Hz) or an inhibitory (low frequency protocols, usually 1 Hz or less) effect, although this is disputed.[79,80] The geometry of the coil is another relevant factor, since it determines the shape of the magnetic field and, therefore, the depth and focality of stimulation. There is a trade-off between these two characteristics: more depth results in less focus, and vice-versa.[81] In psychiatry, rTMS targeting the dlPFC is a well-established treatment for MDD,[82] the therapeutic effect of which might be due to DMN and CEN modulation.[83,84]

The mPFC is readily accessible to TMS, particularly its more dorsal and rostral portions.[14,66,85] Some TMS coil designs that generate greater depth of magnetic field can allegedly reach ventral mPFC structures and the ACC, and are usually considered deep TMS (dTMS) techniques.[86] Nonetheless, the more usual coils, such as figure-of-eight and circular models, may also modulate deeper regions that are connected to the stimulation site, as has been confirmed by meta-analytic data from functional neuroimaging studies.[87] Considering the high connectivity of the mPFC, this rings particularly true, and mPFC TMS studies with functional neuroimaging readings have reported modulated brain activity in cortical and subcortical regions, including the dlPFC, ACC, NAcc, hippocampus, dorsal striatum, and thalamus.[31,88-91]

Moreover, mPFC TMS studies with healthy subjects have successfully modulated behavioral outcomes related to psychiatric morbidity, such as social cognition,[92-97] the processing of self-referential information,[98,99] fear conditioning,[100] avoidance behavior,[101] pain processing,[102-104] delayed discounting,[105] semantic processing,[106] and memory consolidation.[107]

Some preliminary clinical evidence has been published regarding mPFC rTMS as a treatment for psychiatric disorders: case reports, open-label studies, and chart reviews have demonstrated favorable results in populations with MDD,[89,91,108,109] OCD,[90] SUD,[85,110] and eating disorders,[111] reporting good tolerability and feasibility. This has led to the inclusion of mPFC rTMS as a third line alternative for refractory MDD treatment in an influential Canadian guideline for the treatment of mood disorders.[74]

Thus, mPFC rTMS seems to have a clinical impact on many different psychiatric disorders, possibly due to the high connectivity and hub function of this region and its involvement in the SN and the DMN. Nevertheless, a preliminary search of the literature revealed no existing reviews of clinical trials investigating mPFC rTMS in the area of psychiatry. Therefore, this review systematically searched the literature for randomized, controlled clinical trials on mPFC rTMS in populations diagnosed with psychiatric disorders.

Methods

The included studies were randomized, controlled trials (RCT) with clinical outcome measures in populations diagnosed with psychiatric disorders that included a clear description of the mPFC rTMS protocol, including coil types and stimulation parameters. The review protocol was registered in PROSPERO (CRD42018096525). The objectives included reviewing the main results, technical, and methodological details, safety, tolerability, and localization strategies of mPFC rTMS protocols. In May 2018, we searched Medline, PsycINFO, and Scopus using

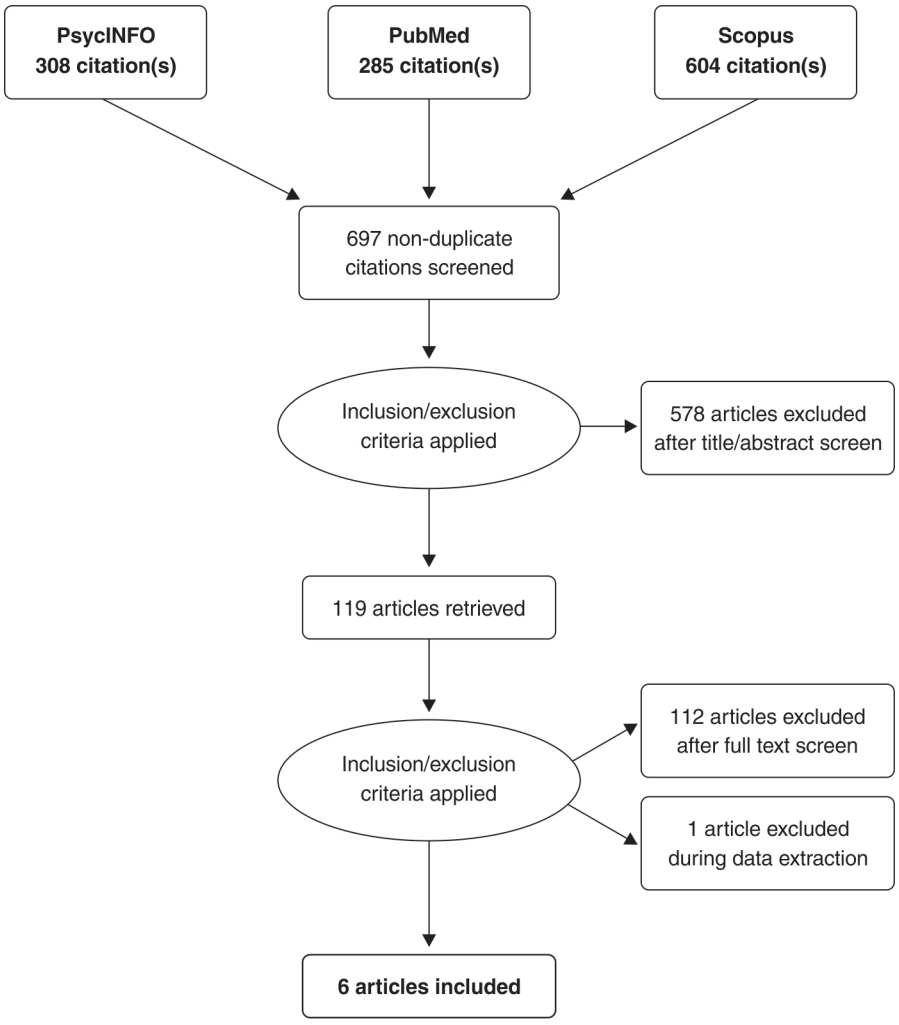

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) selection process flowchart.

the following string: ((''*medial* prefrontal'' OR ''medio* prefrontal'' OR ''cingulate'' OR ''*ACC'' OR DMPFC OR VMPFC) AND (''transcranial magnetic stimulation'' OR rTMS OR TMS)). No filters or date and language restrictions were applied. This resulted in a total of 697 articles after excluding duplicates (Figure 1). Study selection was performed independently by two authors (RCM and LV). Exclusion criteria included: not being an original research study (257 articles), not involving mPFC stimulation (195 articles), involving healthy subjects (59 articles), animal studies (16 articles), not involving TMS (121 articles), no clinical outcome (seven articles), no psychiatric disorder (11 articles), and not being a RCT (25 articles). Metanalysis was not performed due to high heterogeneity of selected studies.

Results and discussion

Overview of selected studies

An overview of the main characteristics of the selected studies can be viewed in Table 1. The six selected trials included a total of 211 individuals, of which 98 received active mPFC rTMS. The stimulation frequencies were 1, 5, 10, and 20 Hz. The results of the Cochrane Quality Assessment Tool may be viewed in Figure 2.

Five studies were dTMS trials with H1,[113,114,116] H7,[112] or double-cone[117] coil models. H1 coils are composed of 14 strips of 7-12 cm long wire encased in a helmet. These configurations produce a summation of the electric field from several coil elements that carry current in the same direction, resulting in a deeper reach for the magnetic pulse.[118,119] They are specifically produced for dTMS, and the H7 coil is a more recent version of this model, created with mPFC rTMS in mind. It is hoped that such a coil can stimulate regions such as the NAcc, ACC, and insula. Direct activation of these areas by dTMS may have different therapeutic properties than stimulation with more conventional coil designs.[86,118,119]

The double-cone coil consists of two large circular coils forming an obtuse angle. At the expense of focus, this type of coil is useful for reaching deeper brain structures of interest, such as the representation of the lower limbs in the primary motor cortex, which is located within the interhemispheric fissure. In particular, such coils may

Table 1 Main characteristics of the selected studies

Article	Participants	Intervention	Outcomes	Notes
Carmi[112]	41 OCD patients, 38 completers, 38 reported.	H7 coil, 20 Hz (50,000 total pulses), or 1 Hz (22,500 total pulses), 100-110% RMT. 4 cm anterior to the hot spot.	20 Hz significantly better than sham at completion and 1 week follow up.	Un-blinding and removal of 1 Hz group prior to study completion.
Ceccanti[113]	18 male patients with alcohol use disorder, three completers, 18 reported.	H-coil, 20 Hz (15,000 total pulses), 120% RMT. 5 cm anterior to the hot spot.	Reduced alcohol intake up to 3 months in active group after completion.	No intergroup difference in clinical outcomes, but significant reduction of prolactinemia and cortisolemia.
Enticott[114]	30 high-functioning autistic adults, 19 completers, 18 reported.	H-coil, 5 Hz (15,000 total pulses), 100% RMT. 7 cm anterior to the hot spot.	Social relations improved in active group.	Significant differences only in subscales, full clinical measures scores unaffected.
Herrmann[115]	47 acrophobic patients, 44 completers, 39 reported.	Round coil, 10 Hz (3,120 total pulses), 100% RMT. Reference point 10% of nasion-inion distance.	Acrophobic symptoms improved in active group.	Results were not sustained at 3 months follow up.
Isserles[116]	30 PTSD patients, 25 completers, 26 reported.	H-coil, 20 Hz (20,160 total pulses), 120% RMT.3 cm above nasion.	Improvement in rTMS + traumatic exposure group for up to 2 months follow up.	No intergroup difference with control or rTMS + no exposure groups. Exposure procedure not measured for effectiveness.
Kreuzer[117]	45 patients with moderate/severe depression, 40 completers, 40 reported.	Double cone (mPFC) or figure-of-eight (dlPFC), 10 Hz (30,000 total pulses), 110% RMT. 1.5 cm anterior to one-third of nasion-inion distance (mPFC stimulation site).	mPFC group responded better than dlPFC group by the end of treatment sessions.	Significant difference in mPFC vs. dlPFC group. Neither group differed from sham.

dlPFC = dorsolateral prefrontal cortex; mPFC = medial prefrontal cortex; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress disorder; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation.

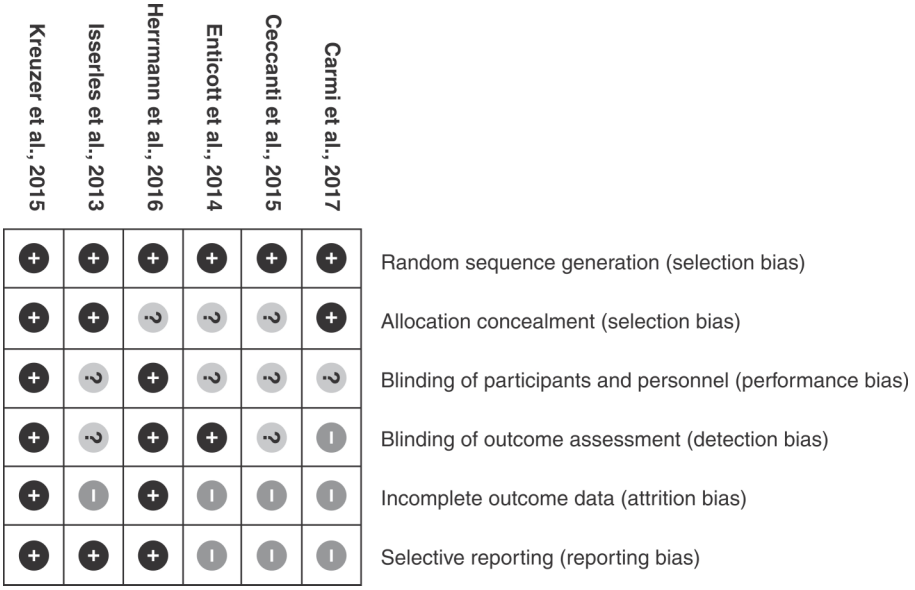

Figure 2 Cochrane Quality Assessment Tool results.

enable stimulation of limbic cortical regions, such as the ACC.[120]

One study used a round coil,[121] a model not used for dTMS, to stimulate a wide region of superficial cerebral tissue (for instance, inducing bilateral effects when placed over the vertex).[120]

All studies positioned the coil on different points along the midline of the scalp. This positioning promoted bilateral

stimulation, allowing the magnetic field to modulate the medial portion of both hemispheres simultaneously. Three protocols used a fixed distance from the motor hot spot to establish coil position (4,[112] 5,[113] 7 cm[114] anterior to the hot spot). The remainder chose to use the nasion-inion measure to establish the stimulation point (10% of nasion-inion distance[115] and 1.5 cm anterior to 30% of the distance[117]). Although Isserles et al.[116] did not report the exact site of coil positioning, in posterior publications, they described the stimulation point as being 3 cm above the nasion.[116,122] The Kreuzer et al.[116] trial also had a left dlPFC group, with the figure-of-eight coil being positioned 5 cm anterior to the left motor hot spot in sagittal direction.

Safety and tolerability

Although few studies provided detailed tolerability data, overall, the procedure was reported to have good tolerability and safety profiles. Nonetheless, headache and local discomfort were frequent complaints (over 50% of participants in one study[117]). There were 33 drop-outs among the studies, with 15 coming from sham stimulation groups. One study reported a participant who could not tolerate the proposed stimulation intensity (20 Hz dTMS at 120% motor threshold) and was allowed to complete the protocol at a lower intensity, being excluded from the final analysis.[116] This same trial reported a self-limited generalized tonic-clonic seizure that ceased without treatment.[116] Although rare, self-limited seizures are a possible complication of TMS and are considered the most severe side effect.[123]

Sham stimulation

The four studies that used H1 or H7 coils used a sham stimulation method provided by manufacturer (Brainsway, Israel).[112-114,116] In this case, sham stimulation involved a helmet containing the same coils used in real stimulation, which produced sounds similar to those heard in active rTMS but did not generate relevant electrical activity. Patient and researcher blinding was accomplished through the use of a randomly assigned card that automatically set the stimulator to real or sham mode, thereby eliminating the need to handle the stimulator equipment. The studies that chose double-cone and round coil used a placebo coil, which also produced acoustic artifacts similar to real stimulation, but with no significant magnetic fields. In this case, the equipment had to be handled by the research team.

Major depressive disorder

Kreuzer et al.[117] (n=45) evaluated mPFC rTMS with a double cone coil for MDD, delivering 30,000 total pulses at 10 Hz. This was the only trial with a low risk of bias for each item in the quality assessment tool. The double cone mPFC rTMS group was compared to sham treatment and traditional left dlPFC rTMS with a figure-of-eight coil. After 15 sessions, which were performed over a 3-week period, there was a significant time effect for the primary outcome, reduction of depressive symptoms according to the 21-item Hamilton Depression Rating Scale. There was a trend toward greater MDD severity in the mPFC group, and post-hoc *t*-tests with baseline corrected values showed a significant difference between double cone and figure-of-eight coils at the end of treatment ($p = 0.014$), although there were no significant effects when comparing either of the active rTMS groups with placebo ($p = 0.216$; $p = 0.270$). Furthermore, the double cone coil's superiority over the figure-of-eight was lost after 12 weeks of follow up.

Structural and functional neuroimaging evidence indicates that midline PFC structures are intimately involved in MDD, especially the ACC and the mPFC related to the DMN.[43,49,51,83,124-126] Open-label and chart review studies have found favorable results and good tolerability for mPFC rTMS treatment in MDD, including a good cognitive safety profile, which sets it apart from brain stimulation treatments such as electroconvulsive therapy.[127] Pre-/post-comparisons of functional magnetic resonance imaging (fMRI) readings in MDD patients reveal that mPFC rTMS, even when regular (non-deep) coils are used, may modulate activity in structures such as the amygdala, ventral striatum/NAcc, temporal pole, anterior insula, and left dlPFC, i.e. it mainly affects structures in the SN and DMN.[66,89] Some studies have also suggested that certain fMRI patterns may be predictive of a mPFC rTMS response in MDD.[91]

In the reviewed study, the results of mPFC rTMS were not significantly different from placebo for MDD treatment. Nevertheless, the reduction in depressive symptomatology between pre- and post-intervention and the significant difference between the double cone and figure-of-eight coil types, in addition to the other above-mentioned evidence, make mPFC rTMS a clinically interesting subject for MDD treatment research.

Anxiety disorders

While being clinically distinct syndromes, PTSD and specific phobia share many characteristics, especially the importance of fear learning and memory consolidation mechanisms in the development of both disorders.[56,57,100,128] Thus, Herrmann et al.[115,121] and Isserles et al.[116] will be discussed in the same section. Herrmann et al.[121] RCT (n=39) assessed the efficacy of 10 Hz rTMS in accelerating extinction learning in a group of patients with a specific phobia of heights (acrophobia). The rTMS protocol and coil positioning were based on previously reported data, including validating the reference point (Fpz) by near-infrared spectroscopy imaging.[100] Stimulation took place immediately before a virtual reality exposure therapy session, and was performed twice over a 2-week period. In the real rTMS group, both the anxiety ($p = < 0.05$) and avoidance subscales ($p = < 0.05$) of the main outcome measure (Acrophobia Questionnaire) were significantly reduced compared to sham treatment. Although this effect was detected at the first follow-up assessment 1 week after the therapy sessions, further improvement was noted at the 3-month follow up, with mean scores of 36.3 ± 18.7 in the anxiety subscale

(sham = 43.2±19.4) and 27.7±5.2 in the avoidance subscale (sham = 30.0±6.2).

Isserles et al.,[116] whose sample included 30 PTSD patients, compared 12 sessions of 20 Hz dTMS with or without script-driven imagery of a traumatic experience prior to the beginning of the session. The control group received sham stimulation combined with the trauma exposure procedure. The Clinician Administered PTSD Scale (CAPS-II) score was the main study outcome. There was a significant pre-/post-treatment reduction in CAPS-II score in the exposure/real stimulation group (p = 0.0003). The reduction was not significant in comparison to the other two groups (no exposure/real stimulation, and exposure/sham stimulation). When the outcome was treated as dichotomous, using a 50% or greater reduction in CAPS-II score as the response criteria, 44% of patients in the exposure/real stimulation group, 12.5% of the no exposure/real stimulation group and 0% of the exposure/sham stimulation qualified as responders. Ten patients crossed over to the exposure/real stimulation group in an open phase of the study, and achieved a mean reduction of 14 points in CAPS-II score, which was significant in a pre-/post-comparison (p = 0.0096). Both the original exposure/real stimulation group and the crossover group retained the clinical response at the 2-month follow up.

The neurocircuitry of anxiety disorders mainly involves the mPFC, ACC, hippocampus, and amygdala (Jin & Maren,[9] Zubieta et al.,[57] Coutinho et al.,[129] Giustino & Maren[130]). The prefrontal component of this circuit projects a large amount of fibers onto the hypothalamus, thereby exerting an influence over the hypophysis and, thus, over the adrenal glands and the regulation of systemic stress response.[7,27,131] These mechanisms, accessed by mPFC rTMS, are pivotal for fear conditioning, the development of pathological anxiety, and the formation of trauma related memories.[100,132] Furthermore, modulation of memory reconsolidation by prefrontal-hippocampal circuits is one of the putative mechanisms of action for the clinical effect verified in the reviewed trials, since both used symptom provocation techniques prior to rTMS sessions, which may be interpreted as a method of memory recall followed by an reconsolidation-modifying intervention.[34,133-135]

Guhn et al.[100] investigated the modulation of conditioned fear extinction with mPFC rTMS in 88 healthy volunteers. A 10 Hz protocol successfully increased extinction learning and diminished extinction recall of conditioned fear acquired by aversive auditory stimuli. In particular, the extinction learning phase was associated with significant changes in physiological measures. Memory consolidation has also been targeted by TMS studies,[133] and mPFC TMS in particular was tested by Berkers et al.[107] in 59 healthy individuals, who found that this form of TMS can modulate memory consolidation, reducing the formation of false memories in a Deese-Roediger-McDermott paradigm.

Taking all this evidence as a whole, it would seem that mPFC rTMS has clinical potential as a treatment for anxiety disorders and as an intervention capable of modulating memory reconsolidation for therapeutic purposes. While the clinical results were only slightly positive and not statistically significant for PTSD treatment, the methodologically sound RCT for acrophobia revealed a significant response rate for mPFC rTMS plus exposure therapy for this specific phobia, thereby encouraging future research in this area.

Autistic spectrum disorder

A trial (n=28) by Enticott et al.[114] tested the efficacy of 10 sessions of 5 Hz dTMS over the mPFC for symptom reduction in high-functioning ASD patients. The main outcome measure was the Ritvo Autism-Asperger Diagnostic Scale. Although there was no statistically significant difference in intergroup measures of the full score, there was a significant pre-/post-TMS symptom reduction in the social relatedness subscale (p = 0.004), which remained significant at the 1-month follow up (p = 0.001). There was also a significant reduction in the Interpersonal Reactivity Index score, which broadly measures self-oriented anxiety, comparing the pre-treatment scores with the follow-up measure (p = 0.004). These results are in line with previous evidence from a case report by the same author.[136]

mPFC dysfunction plays an important role in the neurobiology of ASD.[137,138] For example, fetal mPFC is an important nexus for a subset of ASD risk genes, and there is evidence for aberrant mPFC activity and connectivity in both human and animal studies, some of which specifically associate mPFC dysfunction with social cognition impairment in ASD.[137-139] In fact, the mPFC has been considered one of the main components of the ''social brain,'' and evidence from functional neuroimaging meta-analysis indicates that its more dorsal and rostral portions are more directly involved in the processes that contribute to our social behavior, such as theory of mind,[4,5,18] a function associated with the DMN.[140,141]

Part of the evidence that causally links the mPFC with social cognition comes from the TMS literature. TMS studies have shown that mPFC stimulation can modulate several aspects of social cognition, such as facial emotion recognition,[95,142] group perception,[96,97,143] theory of mind,[144,145] empathy,[92,146] and the integration of different modalities of social impressions.[143]

The reviewed trial demonstrates that while some improvement occurred in social functioning, the clinical use of rTMS for ASD did not differ from placebo. Nonetheless, additional evidence from neuroimaging and TMS research adds biological plausibility to the idea that mPFC modulation could contribute to ASD treatment. This, together with very low efficacy rates for traditional therapeutics, make mPFC rTMS an interesting future alternative for ASD patients.

Substance use disorder

In a clinical trial by Ceccanti et al.,[113] which had an initial sample of 18 patients with alcohol use disorder, 10 sessions of 20 Hz mPFC stimulation were performed after exposure to a visual and olfactory stimulus (a glass of the participant's favorite alcoholic drink). After the TMS sessions, follow-up measures were recorded monthly for 6 months and included serum cortisol and prolactin assays.

There was a high dropout rate during the follow-up period, with only two patients in the active TMS group completing all proposed measures. Nonetheless, there was a significant time vs. condition reduction in daily alcohol intake until the 3-month follow up ($p = 0.046$), when statistical significance was lost. The two patients that remained until the 6-month follow up completely ceased alcohol consumption. There was also a significant pre-/post-difference in maximum alcohol intake for the active group ($p = 0.013$), as well as craving score reductions ($p = 0.025$). Significant reductions in prolactinemia ($p = 0.019$) and cortisolemia ($p = 0.018$) were observed in the active rTMS groups compared to controls.

The mPFC plays a prominent role in reward mechanisms and is one of the main cortical regions that participate in the SN.[10,13,16] Structurally, the mPFC has extensive dopaminergic input that extends from the ventral tegmental area and the ventral striatum via the medial forebrain bundle, accounting for the larger part of the cortical destination of these fibers, which are a main component of the SN.[13,147] The development of SUD is related to changes in dopaminergic transmission, increased activity of SN regions, including the mPFC, insula and NAcc, and impairment of dlPFC activity, which is more strongly related to the CEN.[12,47,65,148,149] The use of provocative stimuli prior do rTMS make this intervention a potential modulator of memory reconsolidation, an approach that has been proposed for SUD treatment.[133]

Some non-RCT studies have successfully used mPFC rTMS to modulate addiction-related outcomes, especially craving in patients with cocaine[85,110] and tobacco use disorder,[150] as well as drug self-administration in cocaine use disorder[151] and delayed discounting in healthy subjects.[105] A study by Hanlon et al.[85] with cocaine users also used fMRI to measure NAcc activity, finding a dose-dependent reduction of blood-oxygen-level dependent signal secondary to left mPFC inhibitory rTMS.

The reviewed study presented a high risk of bias and there were no significant differences between groups, although two patients became abstinent after the 6-month follow up. Nonetheless, the biological measures indicated that mPFC rTMS modulated dopaminergic pathways and cortisol release. Given the limited efficacy of traditional treatments for SUD, it would be interesting to conduct bigger and better studies to clarify the real potential of TMS in this area.

Obsessive-compulsive disorder

Carmi et al.[112] compared the efficacy of 25 sessions of 20 Hz (2,000 pulses per session), 1 Hz (900 pulses per session), or sham dTMS in reducing Yale-Brown Obsessive Compulsive Scale (YBOCS) scores in 41 OCD patients. Stimulation sessions were performed after a planned provocation of OCD symptoms. Due to the slow recruitment rate, limited resources and a trend demonstrating a lack of clinical benefit (the study was unblinded prior to completion), the 1 Hz group was discontinued and further recruitment was directed to the other two groups. The authors chose to omit the 1 Hz group measures from the final analysis. Compared to sham, 20 Hz dTMS resulted in a significantly greater reduction of YBOCS score beginning at the fourth week of treatment ($p = 0.001$). Considering a 30% reduction in YBOCS score as a response, 43.75% of the 20 Hz and 7.14% of the sham group were responders at 5 weeks of treatment ($p < 0.05$). A one-week follow-up visit revealed that the response rate had been maintained, but was no longer significant at the 1-month follow up. As a secondary measure, electroencephalography data collected during a Stroop task revealed higher theta activity in response to a mistake following treatment in the 20 Hz group compared to sham ($p = 0.01$).

Human and animal studies suggest that abnormalities in frontal-subcortical circuitry may be central to OCD pathophysiology.[52,152] When spontaneously active or after provocation, OCD symptoms are associated with higher activity of the OFC, the dorsal ACC, and the thamalus.[153] OCD patients have gray matter reductions and lower white matter integrity in the ACC, with gray matter increases in the thalamus and ventral striatum/NAcc. Data from fMRI demonstrate abnormal hyperconnectivity between cortical regions that are part of the mPFC or that maintain a high connectivity pattern with mPFC structures and the ventral striatum/NAcc.[90]

In an open-label mPFC rTMS trial with fMRI measures, Dunlop et al.[90] demonstrated a significant reduction in OCD symptoms and found a significantly different fMRI pattern in the responder group, with increased mPFC connectivity with the bilateral somatosensory cortex and the left precuneus and decreased mPFC connectivity with the bilateral caudate, midbrain, thalamus, superior frontal gyrus, and right hippocampus. Apart from suggesting that mPFC rTMS has positive results in OCD treatment, these findings reaffirm the importance of the mPFC in OCD pathophysiology and the possible use of functional mPFC readings as a biomarker in this population.

Despite methodological difficulties and risk of bias, this study indicates that mPFC rTMS may be a valid therapeutic modality for OCD, with statistically significant symptom reduction compared to placebo. This is in line with additional evidence from non-RCT. Nonetheless, there were important methodological flaws in this RCT, and more studies are needed to confirm these results and establish the appropriate rTMS parameters.

Conclusion

There were significant differences between mPFC rTMS treatment and placebo in OCD and acrophobia patients. The results for SUD, ASD, MDD, and PTSD were also favorable, although they were only significant in within-group analysis. While most reviewed trials used dTMS coil models, results differed from placebo in a study that used a non-deep TMS coil, which suggests that the mPFC may be effectively modulated by more superficial forms of rTMS. Studies not formally included in this review also indicate that mPFC activity is amenable to rTMS, and that this technique may be of therapeutic value in psychiatric disorders. This technique's potential to modulate large-scale brain networks such as the SN and the DMN, which are prominently involved in the

pathophysiology of several psychiatric disorders, lends biological plausibility to the above-mentioned effects.

It seems that mPFC rTMS has a good safety profile, although there was one report of a tonic-clonic seizure with 20 Hz dTMS at an intensity of 120% of the resting motor threshold.[116] Another patient could not tolerate the proposed intensity (20 Hz at 120% RMT).[116] This would seem to indicate that lower intensities and/or lower frequencies might be safer and more tolerable.

The main limitation of the evidence was the high risk of bias in the majority of studies, with only one study being free of methodological issues according to the quality assessment tool. The reviewed protocols followed different midline scalp reference points for stimulation and only one study guided coil positioning by previously reported neuroimaging data.[121] Therefore, it is likely that different divisions of the mPFC were stimulated in each study, which is relevant since the mPFC involves functional diversity and different connectivity patterns over its antero-posterior axis.[4-6] In addition, the use of different coil types results in different field geometry and stimulation depths,[81] which could extend stimulation to neighboring cortical regions and produce clinical effects not necessarily related to mPFC function.

Despite the growing interest in mPFC rTMS research, only a relatively small and very heterogeneous group of studies have resulted so far, and they have only begun to gather evidence regarding the technique's safety and efficacy as a treatment for psychiatric disorders. This represents a shift in interest from traditional dlPFC rTMS research and opens new neuroscientific and clinical possibilities, since it may differentially access major large-scale brain networks, particularly the SN and DMN. However, more studies with better methodology are needed to confirm the preliminary clinical findings about mPFC rTMS, providing appropriate comparability and reproducibility for the data and allowing quantitative analysis to be performed.

Disclosure

The authors report no conflicts of interest.

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