Curr Psychiatry Rep (2015) 17: 36
DOI 10.1007/s11920-015-0571-3

Transcranial Cortical Stimulation in the Treatment of Obsessive-Compulsive Disorders: Efficacy Studies

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Published online: 1 April 2015

Abstract Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are non-invasive brain stimulation methods that became widely used as therapeutic tools during the past two decades especially in cases of depression and schizophrenia. Low frequency rTMS and cathodal effect of tDCS inhibits cortical functioning while high frequency and anodal effect of tDCS have the opposite effect. Prolonged and repetitive application of either methods leads to changes in excitability of the human cortex that outlast the period of stimulation. Both rTMS and tDCS induce functional changes in the brain-modulating neural activity at cortical level. This paper reviews rTMS and tDCS effects in clinical trials for obsessive-compulsive disorder (OCD). Low frequency rTMS, particularly targeting the supplementary motor area and the orbital frontal cortex, seems to be the most promising in terms of therapeutic efficacy while older studies targeting the prefrontal dorsal cortex were not as successful. tDCS clearly needs to be investigated in large scale and sufficiently powered randomized control studies. From a general point of view, these non-invasive techniques hold promise as novel therapeutic tools for OCD patients.

Keywords Obsessive-compulsive disorder · tDCS · rTMS · Stimulation

This article is part of the Topical Collection on *Anxiety Disorders*

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Introduction

The lifetime prevalence of obsessive-compulsive disorders (OCD) is estimated to be around 3 % in the general population. Selective serotonin reuptake inhibitors (SSRIs) are considered to be the primary treatment strategy of OCD beside psychotherapy. Unfortunately, current medications, augmentation strategies, and behavioral therapies fail to provide adequate benefits in many cases. A notable percentage of patients (40 to 60 %) do not show satisfactory response to the standard treatments, some of them experiencing a chronically deteriorating course, leading to dramatic interpersonal and occupational impairments [1]. Brain imaging studies performed over the past 20 years have generated new knowledge about specific brain areas involved in psychiatric diseases, including OCD, leading researchers to investigate whether brain stimulation might be a potential treatment for these disorders. Deep brain stimulation (DBS) techniques show promising results for severe and highly resistant OCD [2], but they cannot be applied to a large number of patients for safety reasons.

In recent years, non-invasive neuromodulatory techniques have been increasingly studied as potential adjunct or alternative therapies for a wide range of neurological and psychiatric conditions including pain disorder, depression, and stroke rehabilitation [3–5]. Two transcranial cortical stimulation methods are currently used: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Both of them are remarkable new tools for investigating brain function and have shown fast modification of neural function underneath the coil and in connected brain regions [6, 7]. rTMS and tDCS are non-invasive techniques that deliver low intensities of electromagnetic fields through the scalp resulting in alterations of synaptic connections. Both of them have shown efficacy in treating depression [5, 8] and schizophrenia [9, 10]. Since 2000, several studies also assessed therapeutic effects of transcranial stimulations in OCD patients. In

this article, we review the research studies that have investigated rTMS or tDCS as a putative treatment for OCD examining the efficacy of these brain stimulation technologies. For this purpose, we searched the MEDLINE for relevant trials including randomized controlled studies and open label trials published to date. We used a combination of the following terms: "obsessive compulsive disorder," "OCD," "tDCS," "rTMS," and "stimulation".

Transcranial Magnetic Stimulation

The principle of brain stimulation using rTMS is based on Faraday's law of inducing a time varying magnetic field generated by a current pulse through a coil placed over the scalp. This magnetic field crosses the skull painlessly and unimpeded resulting in depolarization of cortical neurons. The rapid change of the magnetic field induces a current flow in the underlying brain tissue, reaching sub-cortical neural circuitry through a trans-synaptic mechanism [11]. It is now well established that stimulation frequency produces different effect on cortical areas: low frequency rTMS (LF-rTMS) (1 Hz or less) has an inhibitory effect while high frequency rTMS (HF-rTMS) (>5 Hz) has an excitatory effect [12, 13].

In fact, several neuroimaging studies have confirmed the activation of underlying brain areas after TMS over the motor cortex or over the prefrontal cortex [14]. Speer et al. [13] found increased blood flow (measured with H^2O positron emission tomography) after 10 Hz rTMS over the left DLPFC, whereas 1Hz stimulation decreased blood flow.

Transcranial devices can deliver either single pulse, paired pulses, or repeated pulses at frequencies up to 50 Hz. Single pulse and paired pulses are useful for neurophysiological studies that help understand the pathophysiology of psychiatric illnesses. However, for therapeutic applications, it is necessary to create a long-lasting effect of the depolarized neurons [12, 15]. For this purpose, application of repetitive TMS (rTMS) is needed.

Since the late nineties, several randomized controlled studies using rTMS demonstrated strong therapeutic effect especially in depression and schizophrenia. Regarding OCD and considering the knowledge of the putative neural network underlying OCD disorders, rTMS has been applied as a therapeutic tool over several cortical brain targets. These studies will be reviewed below.

Transcranial Direct Current Stimulation

Direct current stimulation was studied in the 1960s to induce modifications of cortical excitability in animal models [16]. It was later probed as a therapeutic tool, mainly for depression. However, due to conflicting results, it was not implemented in clinical routine practices [17, 18]. More recently, new stimulation protocols were developed based on functional effects in healthy subjects with reliable modulation of motor cortex excitability attracting an increasing number of researchers in adopting tDCS as a therapeutic and research tool for neurological and psychiatric conditions [17, 19]. Transcranial direct current stimulation (tDCS) involves delivering a weak direct current (1–2 mA) through two large electrodes fixed on the scalp for a certain amount of minutes (1 to 30). Specific brain regions can be targeted via specific electrode placement. tDCS modulates the excitability of the human brain cortex depending on the current polarity, duration, or strength and is able to induce after-effect excitability changes [20, 21]. Since the effects of tDCS are polarity specific, by assessing spontaneous discharge rate or the amplitude of evoked potentials, mechanisms of action at neuronal membrane level have been proposed: a cathodal stimulation hyperpolarizes neurons whereas anodal stimulation depolarizes them [15–17].

Current Knowledge on the Pathophysiology of OCD

The neurobiology and etiology of OCD are not completely understood, however, a growing body of evidence suggests that the illness is associated with dysfunctions in the orbitofronto-striato-pallido-thalamic circuits [22]. Some components of this pathway are subcortical and deep areas (basal ganglia, ventral striatum), which are the targets of DBS techniques, but other are more superficial and accessible to transcranial modulations. Indeed, recent neurophysiological and neuroimaging studies demonstrated that dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal cortices (MPFC), anterior cingulate gyrus, and supplementary motor area (SMA) functioning are altered in OCD [23–25]. Neurophysiological studies also showed that some cortical areas are hyperactive in OCD in particular the SMA, that has extensive connections and plays a central role in response control [26, 27], the orbitofrontal cortex and the DLPFC [28] while enhanced precentral somatosensory evoked potentials and a tonic high level of cortical excitability of motor and related areas were found [29]. These cortical areas might be interesting rTMS and tDCS targets for the treatment of OCD given their mechanism of action using low frequency rTMS or cathodal effect to modulate their activity.

Early rTMS Studies in OCD

The first trial using rTMS to treat OCD was published in 1997 [30]. Twelve patients were randomized to receive, on separate days, a single session of active rTMS (20 Hz during two seconds per minute for 20 min, 80 % of the MT) applied to

the right dorsolateral prefrontal cortex (DLPFC), left DLPFC, and mid occipital site (control group). Right DLPFC treatment significantly reduced patient-rated compulsion but not obsessions during 8 h with a modest effect on mood lasting 30 min after the session. Since then, several other trials have been published targeting the DLPFC trying to corroborate Greenberg's results [31–35]. Conflicting results were found especially in randomized sham-controlled studies (RCT) with no difference between active and sham groups using high frequency rTMS regardless of depressive symptoms [31, 33–35].

The results of the latest double blind sham controlled study over the right DLPFC assessing the efficacy of HF-rTMS (10 Hz, 110 % of the MT, 200 pulses per session during 6 weeks with 6 weeks of follow up) in 30 treatment-resistant OCD patients also provided non-conclusive results. The primary outcome measure was a positive response (30 % improvement in Y-BOCS score) but no significant differences between active and sham groups. The authors concluded that in treating resistant OCD, active rTMS over the right DLPFC does not appear to be superior to sham rTMS, raising the issue of a probable placebo effect [36]. Table 1 summarizes RCT studies of rTMS over the DLPC for the treatment of OCD. A total of five RCT [31, 33–35] that included 141 patients found no significant differences between groups. These results suggest that HF-rTMS stimulation of the DLPFC does not seem to be the appropriate target area to alleviate obsessive-compulsive disorder symptoms. Even though significant improvement was found in some studies [31, 34–36], no differences were found between active and sham stimulation.

Recent Interventions (SMA and OFC)

The available data from RCT studies have produced non-conclusive or negative results on the efficacy of rTMS over the DLPFC, leading researchers to investigate other cortical targets (SMA and OFC). Early studies targeting the SMA, a region found to be hyperactive in OCD, were initially conducted by Montovani et al. [37, 38••]. Based on pathophysiology and neuroimaging findings, they hypothesized that the inhibition of the SMA could be effective in treating OCD. They carried out an open trial of 10 patients with OCD and Tourette's syndrome using LF-rTMS (1 Hz, 100 %MT, 10 days). A progressive reduction in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score was found after 2 weeks of treatment [37]. The subsequent trial conducted by Montovani et al. [38••] was the first randomized sham-

Table 1 RCT of repetitive transcranial magnetic stimulation over the DLPFC for the treatment of obsessive-compulsive disorder

Author	Design	N (A/S)	Target	Parameters	Results
Alonso [31]	Double blind randomized Sham controlled	18 (10/8)	RDLPFC	1 Hz, 110 % MT 20 mn 18 sessions Circular coil	No significant improvement between active and sham groups on Y-BOCS scores
Sachdev [32]	Single blind Non-Sham controlled Active rTMS	12 (6/6)	RDLPFC LDLPFC	10 Hz, 110 % MT 10 sessions Figure 8 coil	Reduction in Y-BOCS scores no significant difference between the two groups
Prasko [34]	Double blind, randomized Sham controlled	33 (18/12)	LDLPFC	1 Hz, 110 % MT 10 sessions Figure 8 coil Sham: coil angled 90°	Reduction in Y-BOCS scores No significant difference between active and sham groups at the end of the treatment
Sachdev [33]	Double blind, randomized Sham controlled study Followed by open-label phase	18 (10/8)	LDLPFC	10 Hz, 110 % MT 10 sessions Figure 8 coil	Negative results: no significant difference between active and sham groups at the end of the sham-controlled phase
Sarkhel [35]	Randomized single-blind Sham-controlled	42 (21/21)	RDLPFC	10 Hz, 110 % MT 10 sessions, figure 8 coil Sham: coil angled 45°	No significant improvement in either groups Effect over time for HDRS and HARS
Mansur [36]	Randomized double-blind Sham controlled study for 6 week followed by a 6 weeks open phase	30 (15/15)	RDLPFC	10 Hz, 110 % MT 30 sessions, figure 8 coil Sham: deactivated coil	No significant difference in Y-BOCS scores between active and sham groups at 6 weeks and 12 weeks
Xiaoyang [60•]	Double-blind Sham-controlled study Alpha-EEG rTMS	46 (25/21) 25 α-rTMS 21 sham	Bilaterally DLPFC	α-EEG frequency 80 % MT, 10 sessions 9 cm circular coil	Significant difference between α-rTMS frequency and sham groups on obsessions but not compulsions

HARS Hamilton Anxiety Rating Scale, *HDRS* Hamilton Depression Rating Scale, *LDLPFC* left DLPFC, *MT* motor threshold, *N (A/S)* number of patients (active/sham), *OFC* orbito-frontal cortex, *RCT* randomized controlled studies, *RDLPFC* right dorsolateral prefrontal cortex, *SMA* supplementary motor area, *Y-BOCS* Yale-Brown obsessive compulsive scale

controlled study of SMA stimulation in the treatment of OCD patients. After four weeks of treatment using low frequency parameters (1 HZ, 100%MT, 1200 stimuli per day), patients receiving active treatment showed a mean reduction of 25 % in the Y-BOCS versus 12 % in the sham group with a response rate of 67 % for active and 22 % for sham rTMS.

A double blind sham-controlled study investigated the possible therapeutic effects and safety of sequentially combined LF-rTMS to the right DLPFC (1 Hz, 110 % of the MT) and the SMA (1 Hz, 100 % of the MT) in 20 patients with refractory OCD. In this study, treatments were applied during 2 weeks and patients were rated using Y-BOCS, the Montgomery-Asberg Depression Rating Scale (MADRS), and the Hamilton Anxiety Rating Scale (HARS) after 1 and 2 weeks of stimulation and 2 weeks after the final session. Y-BOCS, MADRS, and HARS severity scores were significantly reduced at treatment endpoint (2 weeks) and at two weeks post-treatment but without any statistically significant differences between the groups. The lack of efficacy in this study might be explained by a partial real stimulation effect in the sham-treatment group because sham treatment was applied with the coil angled at 45° from the scalp over the same area as the active group. It is thus not possible to completely exclude a partial magnetic field effects in the cortical area [39].

In 2011, Kumar and Chadda [1] used rTMS as an add-on treatment in twelve subjects with treatment-resistant OCD in a non-controlled design. Mean scores on Y-BOCS after 10 session of LF-rTMS decreased between baseline (mean scores 26.17) and the end of the treatment (mean scores 17.17) showing a significant improvement.

Gomes et al. [40••], also using low frequencies, randomized 22 patients to receive active (N=12) or sham rTMS (N=10) over the pre-SMA area (bilaterally) during 2 weeks. Patients were rated before treatment, immediately after treatment and 3 months thereafter. After 3 months, the response rate was 41 % with active and 10 % with sham treatment. Patients receiving active rTMS showed, on average, a 35 % reduction on the Y-BOCS as compared with a 6.2 % reduction in those receiving sham treatment.

More recently, Montovani et al. [41] assessed the efficacy of LF-rTMS (1 Hz, 100 % of the MT, 1200 pulses per day during 4 weeks) stimulation of the SMA bilaterally in 18 patients with OCD. After 4 weeks of treatment, clinical response rate (defined as Y-BOCS reduction of 25 % or more) was 67 % in the active and 22 % in the sham rTMS with an average reduction of 25 % in Y-BOCS scores in the active group versus 12 % in the sham group. The difference remained significant after controlling for baseline depressive scores. Clinical improvement in the active rTMS group was correlated with a normalization of the hemispheric asymmetry and an increase of the right MT.

Another recently conducted RCT in patients with severe and refractory OCD treated with 4-weeks rTMS on the SMA found no significant differences between rTMS and sham stimulation (Pelissolo et al., in preparation).

The other region of interest in the field of TMS in the treatment of OCD is the OFC. This region plays a major role in the pathophysiology of OCD since obsessions and compulsions seem to be mediated by functional hyperactivity of the orbito-frontal cortex either bilaterally [42] or restricted to the left side [43, 44]. Ruffini and colleagues [45] conducted the only study on rTMS over the left OFC in drug-resistant OCD patients supposing that stimulating this cortical area could be OCD specific. In a sham-controlled study, patients were randomly administered real (n=16) or sham (n=7) LF-rTMS during three consecutive weeks (1 Hz, 80 % of the MT). A significant reduction of Y-BOCS scores comparing active versus sham treatment was found at 3 weeks and at 10 weeks after the end of the rTMS with loss of significance after 12 weeks. Anxiety and depression symptoms were reduced but with no significant differences between the two groups. This study suggests that low frequency rTMS of the OFC may only temporarily improve obsessive-compulsive symptoms.

Table 2 summarizes the RCT of rTMS over the SMA and OFC for the treatment of OCD. The results from RCT over these two cortical areas are promising, showing a statistically significant effect in favor of active compared to sham low frequency rTMS.

tDCS in the Treatment of OCD

The use of tDCS protocols in the treatment of depression and schizophrenia resulted in significant benefits in treating depression symptoms [8] as well as auditory hallucinations [46]. It is noteworthy that clinical improvements in those studies were correlated with increased excitability of the left DLPFC using anodal tDCS in depression and a reduction of cortical excitability of the left temporo-parietal cortex in schizophrenia using cathodal tDCS. These promising results did not however generate more enthusiasm among researchers studying OCD, and it is surprising to note that only a single case was reported in the literature [47•]. In this case, the effect of tDCS and rTMS on obsessive and compulsive symptoms and resting state brain activity was assessed. tDCS and rTMS had no effect on obsessive and compulsive symptoms but improved depression and anxiety. Functional neuro-imaging found an interhemispheric asymmetry, which was restored after tDCS but not rTMS treatment, thus raising the question whether tDCS is more effective than rTMS in restoring interhemispheric imbalance.

Discussion

Clinical findings from trials using rTMS or tDCS show promising results. For TMS use, the overall results show that HF-

Table 2 RCT of repetitive transcranial magnetic stimulation over the SMA and OFC for the treatment of obsessive-compulsive disorder

Author	Design	N (A/S)	Target	Parameters	Results
Montovani [38••]	Randomized Sham-controlled		Bilaterally	10 sessions Figure 8 coil	In active versus sham groups in Y-BOCS scores
Montovani [41]	Double-blind randomized	18 (9/9)	SMA	1 Hz, 100 % MT, 20 sessions	25 % reduction on Y-BOCS in active group versus 12 % in sham group.
	Sham-controlled With study of cortical excitability		Bilaterally CSP, SICI ICF, RMT	Figure 8 coil	Normalization of inter-hemispheric asymmetry. Increased right SICI correlated with Y-BOCS scores change
Kang [39]	Double-blind randomized	20 (10/10)	RDLPFC	1 Hz, 110 % MT, 10 sessions, figure 8 coil	No significant improvement of OCD in both groups
	Sham-controlled		Followed by bilaterally SMA at 45°	Sham: coil angled	
Gomes [40••]	Double-blind randomized	22 (12/10)	Pre-SMA	1 Hz, 100 % MT, 10 sessions	At 14 weeks: response rate active (41 %) versus sham (10 %)
	Sham-controlled 2 weeks treatment 3-month follow-up		Bilaterally	Figure 8 coil Sham coil	Y-BOCS scores reduction 35 % versus 6.2 %
Ruffini [45]	Single-blind randomized	23 (16/7)	Left-OFC	1 Hz, 80 % MT, 15 sessions	Significant reductions of Y-BOCS scores in active versus sham at 3 weeks and 10 weeks post-treatment
	Sham-controlled			Figure 8 coil	

CSP cortical silent period, *ICF* intra-cortical facilitation, *N (A/S)* number of patients (active/sham), *OFC* orbito-frontal cortex, *RCT* randomized controlled studies, *RDLPFC* right dorsolateral prefrontal cortex, *RMT* resting motor threshold, *SICI* short-interval cortical inhibition, *SMA* supplementary motor area, *Y-BOCS* Yale-Brown obsessive compulsive scale

rTMS over the DLPFC does not seem to be an effective option for the treatment of OCD. Even if the reductions of Y-BOCS scores are significant, no differences were found with sham stimulation [31, 33–35]. Conversely, stimulation of SMA and OFC using LF-rTMS provides statistically significant superiority of active compared to sham stimulation in several studies [41, 38••, 39, 40••]. Early meta-analysis [48–50] concluded that there were insufficient data from RCT to recommend rTMS as a therapeutic tool in the treatment of OCD. A likely explanation of these conclusions is the lack of statistical power among the RCT [51].

Adding recent studies published from RCT, Berlim and his colleagues [52•] conducted an updated systematic review and meta-analysis on this topic. The overall results demonstrated that RCT on LF-rTMS yielded statistically significant improvement in Y-BOCS scores and only a trend toward improvements in HDRS/MADRS scores while in contrast RCT on HF-rTMS did not result in significant overall improvement in Y-BOCS, HDRS/MADRS, or HADRS. Concerning the site of stimulation, subgroups analysis indicated that HF-rTMS applied over the DLPFC did not appear to be more effective than sham rTMS. However, LF-rTMS targeting the SMA and OFC seem to be the most promising for treating OCD-related symptoms.

The efficacy of LF-rTMS on OC symptoms might be explained by the inhibitory effect of low frequencies on hyperactive orbitofronto-striatal circuits that seem to underlie deficient inhibition of irrelevant information and response control in OCD [26, 51, 52•, 53, 54].

Results from cortical excitability studies found that 1-Hz rTMS to the pre-SMA area increased inhibition in primary motor cortex as measured by resting motor threshold (RMT) and short interval cortical inhibition (SICI). On the other hand, interhemispheric asymmetry found prior to treatment, was normalized over the course of trial, which is correlated with clinical improvement [41, 55]. The SMA area is related to motor planning and response-inhibition [56, 57] and is also connected with several regions widely implicated in cognitive and emotional processes [58]. The hypothesis is that inhibiting areas such as pre-SMA or OFC may alleviate OCD related-symptoms by modulating hyperactivity of cortico-striato-thalamo-cortical circuitry [41]. In other words, LF-rTMS induced normalization of SMA/OFC activity could have enhanced the ability of patients with OCD to inhibit intrusive thoughts, impulses and repetitive motor responses [38••, 39, 40••, 41–45].

Major considerations still remain to outline the optimum protocol for OCD especially for DLPFC stimulation. Further

studies should investigate new ways of enhancing the effect of rTMS on OCD with clinically relevant stimulation parameters. Recently, novel stimulation paradigms have been designed such as alpha-electroencephalogram (α-EEG) guided rTMS or theta-burst stimulation. Low intensity of theta-burst rTMS at 50 Hz showed a more consistent and longer lasting effect in a case of OCD with concomitant depression [59].

Xiaoyang [60•] performed an α-EEG guided rTMS randomizing 46 OCD patients to receive active *versus* sham stimulation during 2 weeks, adjusting the frequency to the α frequency, which was found to be abnormal in left and right frontal regions and temporal lobes. Bilateral stimulation of frontal regions significantly improved obsessions but not compulsions raising the issue of a differential effect of stimulation parameters. A differential effect on compulsions was found as well using HF-rTMS over the right DLPFC [30]. The majority of the studies targeting DLPFC used 10 Hz frequency with negative results [32, 33, 35, 36]. Thus, Greenberg's [30] and Xiaoyang [60•] studies are of clinical relevance suggesting that a differential effect on specific symptoms would probably be obtained when considering different stimulation parameters. The treatment status and placebo effect of sham stimulation are other major issues to be considered. It is important to note that most of the studies recruited treatment resistant OCD patients [32, 34–37]. Refractoriness could be a confounding factor limiting the effectiveness of this technique. However, rTMS is difficult to apply as a first line treatment because drugs and psychotherapy are simpler therapeutic strategies.

On the other hand, as the improvement of symptoms is often noted during sham conditions, it would be interesting to investigate neural alteration caused by sham rTMS stimulation. Since a considerable number of studies titled the coil to an angle of 45 or 90° [31, 34–37, 38••, 39, 40••, 41–46, 47•, 48–51, 52•, 53–59, 60•, 61], it cannot be guaranteed that no cortical stimulation, albeit minimal, occurs. A real sham coil should be used in order to control sham effect.

As for tDCS, very few data are available making it difficult to draw clear conclusions. However, because tDCS has been shown to have an impact on functional cortico-subcortical networks including cortico-striatal and cortico-thalamic loops involved in the pathophysiology of OCD [62], this technique holds great promise as a novel tool in the treatment of OCD. There is also an emerging literature on the priming effect of tDCS on TMS which suggest that tDCS may modulate neurons in a way that makes them more or less sensitive to subsequent TMS. Preconditioning the motor cortex with tDCS (1 mA, 10 min) enhances subsequent effects of rTMS (1 or 5 Hz) within the same stimulation session [63, 64].

Conclusion

This paper reviews the clinical trials conducted so far in the treatment of OCD using rTMS and tDCS. In general, the results are promising even though further research is still needed. Both rTMS and tDCS induce functional changes in the brain and modulate neural activity at cortical levels. LF-rTMS (particularly targeting the SMA and OFC) seems to be the most promising in terms of therapeutic efficacy while tDCS clearly needs larger scale and sufficiently powered RCT to better understand its therapeutic role.

Compliance with Ethics Guidelines

Conflict of Interest Ghassen Saba, Albert Moukheiber, and Antoine Pelissolo declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kumar N, Chadda RK. Augmentation effect of repetitive transcranial magnetic stimulation over the supplementary motor cortex in the treatment of refractory patients with obsessive-compulsive disorders. Indian J Psychiatry. 2011;53(4):340–2.
2. Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med. 2008;359(20):2121–34.
3. Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain. 2005;128(3):490–9.
4. Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain. 2006;122(1–2):197–209.
5. Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol. 2008;11(2):249–54.
6. George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatry. 2013;26(1):13–8.
7. Antal A, Nitsche MA, Paulus W. Transcranial direct current stimulation and the visual cortex. Brain Res Bull. 2006;68(6):459–63.
8. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 2006;8(2):203–4.
9. Hoffman RE, Gueorguieva R, Hawkins KA, Varanko M, Boutros NN, Wu YT, et al. Temporoparietal transcranial magnetic

stimulation for auditory hallucinations: safety, efficacy and moderators in a fifty patient sample. Biol Psychiatry. 2005;58(2):97–104.
10. Aleman A, Sommer IE, Kahn RS. Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. J Clin Psychiatry. 2007;68(3):416–21.
11. Hallet M. Transcranial magnetic stimulation and the human brain. Nature. 2000;406(6792):147–50.
12. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study of modulation of human cortical excitability with transcranial magnetic stimulation. J Clin Neurophysiol. 1998;15(4):333–43.
13. Speer AM, Benson BE, Kimbrell TK, Wassermann EM, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on mood in depressed patients: relationship to baseline cerebral activity on PET. J Affect Disord. 2009;115(3):386–94.
14. Siebner HR, Takano B, Peinemann A, Schwaiger M, Conrad B, Drzezga A. Continuous transcranial magnetic stimulation during positron emission tomography: a suitable tool for imaging regional excitability of the human cortex. Neurimage. 2001;14(4):883–90.
15. Priori A, Hallet M, Rothwell JC. Repetitive transcranial magnetic stimulation or trancranial direct current stimulation ? Brain Stim. 2009;2(4):241–5.
16. Bindam L, Lippold O, Redfearn JWT. The action of brief polarizing currents on the cerebral cortex of the rat during current flow and in the production of long lasting after-effects. J Physiol. 1964;172:369–82.
17. Nitsche MA, Nitsche M, Klein C, Tergau F, Rothwell J, Paulus W. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol. 2003;114(4):600–4.
18. Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A. Treatment of depression with transcranial direct current stimulation (tDCS): a review. Exp Neurol. 2009;219(1):14–9.
19. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art. Brain Stim. 2008;1(3):206–23.
20. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(3):633–9.
21. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57(10):1899–901.
22. Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. Br J Psychiatry Suppl. 1998;(35):26–37
23. Del Casale A, Kotzalidis GD, Rapinesi C, Serata D, Ambrosi E, Simonetti A, et al. Functional neuroimaging in obsessive-compulsive disorders. Neuropsychobiology. 2011;64(2):61–85.
24. Fineberg NA, Chamberlain SR, Hollander E, Boulougouris V, Robbins TW. Translational approaches to obsessive-compulsive disorders: from animal models to clinical treatment. Br J Pharmacol. 2011;164(4):1044–61.
25. Milad MR, Rauch SL. Obsessive-compulsive disorders: beyond segregated cortico-striatal pathways. Trends Cogn Sci. 2012;16(1):43–51.
26. van den Heuvel OA, Veltman DJ, Groenewegen HJ, Cath DC, van Balkom AJ, van Hartskamp J, et al. Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. Arch Gen Psychiatry. 2005;62(3):301–9.
27. Chamberlain SR, Fineberg NA, Blackwell AD, Robbins TW, Sahakian BJ. Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. Am J Psychiatry. 2006;163(7):1282–4.
28. Whiteside SP, Port JD, Abramowitz JS. A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. Psychiatry Res. 2004;132(1):69–79.
29. Rossi S, Bartalini S, Ulivelli M, Montovani A, Di Muro A, Goracci A, et al. Hypofunctioning of sensory gating mechanisms in patients with obsessive-compulsive disorder. Biol Psychiatry. 2005;57(1):16–20.
30. Greenberg BD, George M, Martin J, Benjamin J, Schleapfer TE, Altemus M, et al. Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. Am J Psychiatry. 1997;154(6):867–9.
31. Alonso P, Pujol J, Cardoner N, Benlloch L, Deus J, Menchon JM, et al. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a double blind placebo-controlled study. Am J Psychiatry. 2001;158(7):1143–5.
32. Sachdev PS, McBride R, Loo CK, Mitchell PB, Malhi GS, Croker VM. Right versus left prefrontal transcranial magnetic stimulation for obsessive-compulsive disorder: a preliminary investigation. J Clin Psychiatry. 2001;62(12):981–4.
33. Sachdev PS, Loo C, Mitchell PB, McFarquhar TF, Malhi GS. Repetitive transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder: a double blind controlled investigation. Psychol Med. 2007;37(11):1645–9.
34. Prasko J, Paskova B, Zalesky R, Novak T, Kopecek M, Bares M, et al. The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive-compulsive disorder. A randomized, double blind; sham controlled study. Neuro Endocrinol Lett. 2006;27(3):327–32.
35. Sarkhel S, Sinha VK, Praharaj SK. Adjunctive high-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) was not effective in obsessive-compulsive disorder but improved secondary depression. J Anxiety Disord. 2010;24(5):535–9.
36. Mansur CG, Myczkowki ML, de Barros CS, Sartorelli Mdo C, Bellini BB, Dias AM, et al. Placebo effect after prefrontal magnetic stimulation in the treatment of resistant obsessive-compulsive disorder: a randomized controlled trial. Int J Neuropsychopharmacol. 2011;14(10):1389–97.
37. Montovani A, Lisanby SH, Pieraccini F, Ulivelli M, Castrogiovanni P, Rossi S. Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) and Tourette's syndrome (TS). Int J Neuropsychopharmacol. 2006;9(1):95–100.
38.•• Montovani A, Simpson HB, Fallon BA, Rossi S, Lisanby SH. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant of obsessive-compulsive disorder. Int J Neuropsychopharmacol. 2010;13(2):217–27. *This first randomized trial of SMA stimulation in the treatment of resistant OCD showed a 67% response rates in the rTMS group versus 22% in the sham group*.
39. Kang JI, Kim CH, Namkoong K, Lee C, Kim SJ. A randomized controlled study of sequentially applied repetitive transcranial magnetic stimulation in obsessive-compulsive disorder. J Clin Psychiatry. 2009;70(12):1645–51.
40.•• Gomes PVO, Brasil-Neto JP, Allam N, de Souza ER. A randomized, double blind trial of repetitive transcranial magnetic stimulation in obsessive-compulsive disorder with three months follow-up. J Neuropsychiatry Clin Neurosci. 2012;24(4):437–43. *At 14 weeks, patients receiving active rTMS on pre-SMA area showed, on average, a 35% reduction on the Y-BOCS, as compared with a 6.2% reduction in those receiving sham treatment*.
41. Montovani A, Rossi S, Bassi BD, Simpson HB, Fallon BA, Lisanby SH. Modulation of motor cortex excitability in obsessive-compulsive disorders: an exploratory study on the relations of neurophysiology measures with clinical outcome. Psychiatry Res. 2013;210(3):1026–32.
42. Alptekin K, Degirmenci B, Kivircik B, Durak H, Yemez B, Derebek E, et al. Tc-99 m HMPAO brain perfusion SPECT in drug-free obsessive-compulsive patients without depression. Psychiatry Res. 2001;107(1):51–6.

43. Baxter LR Jr, Schwartz JM, Mazziotta JC, Phelps ME, Pahl JJ, Guze BH, Fairbanks L. Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. Am J Psychiatry. 198;145(12):1560–1563.
44. Swedo SE, Pietrini P, Leonard HL, Schapiro MB, Rettew DC, Goldberger EL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. Arch Gen Psychiatry. 1992;49(9):690–4.
45. Ruffini C, Locatelli M, Luca A, Benedetti F, Insacco C, Smeraldi E. Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation. Prim Care Comp J Clin Psychiatry. 2009;11(5):226–30.
46. Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny MF, et al. Examining transcranial direct current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatry. 2012;169(7):719–24.
47.• Volpato C, Piccione F, Cavinato M, Duzzi D, Schiff S, Foscolo L, et al. Modulation of affective symptoms and resting state activity by brain stimulation in a treatment-resistant case of obsessive-compulsive disorder. Neurocase. 2013;19(4):360–70. *tDCS seemed to be more effective than rTMS in restoring interhemispheric imbalance and improving anxiety and depression in OCD.*
48. Burt T, Lisanby SH, Sackheim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol. 2002;5(1):73–103.
49. Martin JL, Barbaboj MJ, Perez V, Sacristan M. Transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder. Cochrane Database Syst Rev. 2003;3:CD003387.
50. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment method to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010;71(7):873–84.
51. Maxwell SE, Kelly K, Rausch JR. Sample size planning for statistical power and accuracy in parameter estimation. Ann Rev Psychol. 2008;59:537–63.
52.• Berlim MT, Neufeld NH, Van den Eynde F. Repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder: an exploratory meta-analysis of randomized and sham-controlled trials. J Psychiatr Res. 2013;47(8):999–1006. *Low Frequency rTMS and protocols targeting the orbitofrontal cortex or the supplementary motor area seemed to be the most promising.*
53. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev. 2008;32(3):525–49.
54. Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ. The neuropsychology of obsessive-compulsive disorder: the importance of failure in cognitive and behavioural inhibition as candidate phenotype markers. Neurosci Biobehav Rev. 2005;29(3):399–419.
55. Montovani A, Leckman JF, Grantz H, King AL, Sporn AL, Lisanby SH. Repetitive transcranial magnetic stimulation of the supplementary motor area in the treatment of Tourette syndrome: report of two cases. Clin Neurophysiol. 2007;118(10):2314–5.
56. Mostosfsky SH, Simmonds DJ. Response inhibition and response selection: two sides of the same coin. J Cogn Neurosci. 2008;20(5):751–61.
57. Picard N, Strick PL. Activation of the supplementary motor area (SMA) during performance of visually guided movements. Cereb Cortex. 2003;13(9):977–86.
58. Oliveri M, Babiloni C, Filippi MM, Caltagirone C, Babiloni F, Cicinelli P, et al. Influence of the supplementary motor area on primary motor cortex excitability during movements triggered by neutral or emotionally unpleasant visual cues. Exp Brain Res. 2003;149(2):214–21.
59. Wu CC, Tsai CH, Lu MK, Chen CM, Shen WC, Su KP. Theta-burst repetitive transcranial magnetic stimulation for treatment resistant obsessive-compulsive disorder with concomitant depression. J Clin Psychiatry. 2010;71(4):504–6.
60.• Xiaoyang M, Yueqin H, Liwei L, Yi J. A randomized double blind controlled trial of α electroencephalogram-guided transcranial magnetic stimulation for obsessive-compulsive disorder. Chin Med J (Engl). 2014;127(4):601–6. *This first EEG-guided study suggested that bilateral stimulation of frontal regions significantly improved obsessions but not compulsions, raising the issue of a differential effect of stimulation parameter.*
61. Jaafari N, Rachid F, Rotge JY, Polosan M, El-Hage W, Belin D, et al. Safety and efficacy of repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder: a review. World J Biol Psychiatry. 2012;13(3):164–77.
62. Polonia R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp. 2012;33(10):2499–508.
63. Lang N, Siebner HR, Ernst D, Nitsche MA, Paulus W, Lemon RN, et al. Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid rate transcranial magnetic stimulation and controls the direction of the after-effects. Biol Psychiatry. 2004;56(9):634–9.
64. Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, et al. Preconditioning of low frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence of homeostatic plasticity in the human motor cortex. J Neurosci. 2004;24(13):3379–85.