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EXPERT REVIEWS

Transcranial direct current stimulation in obsessive–compulsive disorder: emerging clinical evidence and considerations for optimal montage of electrodes

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Background: Neuromodulation techniques for obsessive–compulsive disorder (OCD) treatment have expanded with greater understanding of the brain circuits involved. Transcranial direct current stimulation (tDCS) might be a potential new treatment for OCD, although the optimal montage is unclear. Objective: To perform a systematic review on meta-analyses of repetitive transcranianal magnetic stimulation (rTMS) and deep brain stimulation (DBS) trials for OCD, aiming to identify brain stimulation targets for future tDCS trials and to support the empirical evidence with computer head modeling analysis. Methods: Systematic reviews of rTMS and DBS trials on OCD in Pubmed/MEDLINE were searched. For the tDCS computational analysis, we employed head models with the goal of optimally targeting current delivery to structures of interest. Results: Only three references matched our eligibility criteria. We simulated four different electrodes montages and analyzed current direction and intensity. Conclusion: Although DBS, rTMS and tDCS are not directly comparable and our theoretical model, based on DBS and rTMS targets, needs empirical validation, we found that the tDCS montage with the cathode over the pre-supplementary motor area and extra-cephalic anode seems to activate most of the areas related to OCD.

KEYWORDS: computer-based modeling • non-invasive brain stimulation • obsessive–compulsive disorder • repetitive transcranial magnetic stimulation • transcranial direct current stimulation

Obsessive–compulsive disorder (OCD) is a neuropsychiatric disorder with a 2% lifetime prevalence [1,2]. Commonly, OCD symptoms begin during childhood and have a chronic course, causing severe impairments in interpersonal and occupational functioning [3–5]. It is estimated that in 2015, OCD is going to be the sixth most incapacitating neuropsychiatric disorder [6]. This is expected because the illness affects not only the individual, but also the quality of life of family and caregivers [3,7]. In addition, pharmacotherapy is only effective in 40–60% patients [8], and cognitive-behavior therapy, although effective for OCD patients [8], is not readily available for most of them. Although deep brain stimulation (DBS) and repetitive transcranial magnetic stimulation (rTMS) are also not easily available, transcranial direct current stimulation (tDCS) might constitute an accessible treatment in the future due to its advantages regarding cost, low side-effect profile and portability. Overall, 30% of OCD patients are refractory to any conventional first or second line treatment [9]. Taken together the increasing prevalence of OCD and its devastating effects on the quality

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of life of patients, when they fail to respond to conventional interventions, it highlights the need for developing new approaches to treatment-resistant OCD.

Several non-pharmacological approaches for treating OCD have been developed over the past decades, based on the increased understanding of the neural circuits involved in its pathophysiology. Although many aspects of the etiology and pathophysiology of OCD still remain unclear, growing evidence suggests that this illness is associated with dysfunctions in the fronto-striato-pallido-thalamic circuitry including the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), medial prefrontal cortices such as the supplementary motor area (SMA), the anterior cingulate gyrus and the basal ganglia [10–12]. Two non-pharmacological techniques have been developed recently based on such evidences: DBS and rTMS, the former arises as a potential treatment for refractory OCD [13]. The intervention consists in the implant of stereotactic electrodes connected to an implantable electrical stimulator, capable of inducing reversible changes on the functionality of specific brain circuits [13]. DBS does not simply create functional lesions through a depolarization blockage of those neural circuits close to the electrodes, but also activates neural circuitry in the brain to modulate activation patterns [14–16]. rTMS is an alternative non-invasive technique that modulates cortical and subcortical activity through electric currents induced by a magnetic coil positioned over the head [17]. Low and high frequencies of the rTMS pulses result in decreased and increased neural excitability and brain activity, respectively [17]. It has been hypothesized that the inhibitory effect of low-frequency rTMS may be useful in treating those OCD symptoms that are caused by hypermetabolic medial prefrontal brain regions. Although promising, both techniques are limited by their relatively high-cost, mixed findings (for rTMS) [18] and invasiveness (for DBS), to justify the development of other non-pharmacological strategies.

In this context, tDCS is a new non-pharmacological treatment showing promising results in several neuropsychiatric disorders [19]. The tDCS directly applies a weak, constant current to the scalp that flows from the anode to the cathode with a fraction of the current entering the brain. Depending on polarity, these currents increase or decrease cortical excitability [20] by producing low-intensity electric field (<1 V/m) [21] in the brain. This leads to small changes (<1 mV) [22] in the neuron's membrane potential, thus influencing the frequency of spiking and modifying the net cortical excitability [23]. Nonetheless, the effects of tDCS on neuronal function are more complex [24], and might depend on the nature of ongoing activity [25] and pharmacotherapy [26–29]. Clinically, tDCS has important advantages over other non-pharmacological therapies, such as low cost, ease of use, portability, safety and tolerability [30,31]. For all these reasons, tDCS has gained increased interest in clinical psychiatry over the past decade, showing promising results in the treatment of major depression [28] and schizophrenia [29].

With regard to OCD, one case report described the use of tDCS using anodal tDCS over the left DLPFC, with inconclusive findings regarding efficacy [30]. [D'Urso G, Mantovani A, Pers. Comm.] submitted the report of a cross-over case study of anodal versus cathodal tDCS over the pre-SMA, describing that the cathodal application was significantly superior to anodal tDCS in reducing OCD symptoms. Thus, the key questions are which brain area should be targeted and what the optimal stimulation parameters are. For instance, in a recent rTMS meta-analysis [12], the authors could only conclude that 'non-DLPFC' areas should be used, considering the promising results with SMA and OFC rTMS, and that low (vs high) frequency rTMS would lead to greater improvements in OCD. Nonetheless, the translation between rTMS and tDCS parameters is not straightforward – critically, tDCS does not induce action potentials [20,31] and can induce neuromodulatory effects that are, in fact, very distinct than those induced by rTMS. In this context, simulated predictions of electric flow models might be useful for designing tDCS trials, as they aid in predicting current flow in brain regions critically involved in OCD pathophysiology.

Therefore, our aim is to review previous studies of DBS and rTMS in order to identify the parameters of those studies associated with clinical efficacy. Based on the findings, we then used high-resolution MRI-derived head model to select electrode montages that optimize stimulation intensity on the brain areas of interest. The significance of this overall approach lies in the combination of clinical outcomes with computer models to investigate the most relevant brain network and the mechanisms of action of tDCS in OCD and to prospectively design novel sham-controlled tDCS trials in OCD.

Methods

Search strategy

According to our study aim, we looked for rTMS and DBS meta-analyses (including pooled analyses) for OCD. We searched for articles published from the first date available to May 2014 in Pubmed/MEDLINE, using the following keywords: 'deep brain stimulation' OR 'brain stimulation' OR 'electric stimulation' OR 'transcranial magnetic stimulation' AND 'obsessive compulsive disorder'. Only articles in English were selected. We also performed bibliography screening of the selected articles and personal communication to identify possible articles from other sources.

The approach to look for a meta-analytic synthesis of current evidence instead of individual clinical trials was chosen because our goal was to assess the summary evidence of efficacy and, based on that, to identify potential brain targets associated with better clinical response. Thus, we identified articles summarizing the evidence found in clinical studies, prioritizing a comprehensive review of these findings.

Study selection

We searched for meta-analyses and pooled analyses evaluating clinical studies of patients meeting the OCD criteria according to Diagnostic and Statistical Manual of Mental Disorders IV-repetition time (TR) [32] or International Classification of

Diseases [33], who underwent a treatment with DBS or rTMS. OCD severity and treatment outcome were evaluated with a standardized scale, the Yale–Brown Obsessive Compulsive Scale (Y-BOCS). All manuscripts were written in English.

Computational modeling

We used computational resources to theoretically predict the behavior of electric current in the brain. A computational model contains numerous variables that characterize the system being studied. To study this particular phenomenon, we created finite element models of tDCS for OCD from two sources, referred as individual head and standard head. One is the MRI scan of a healthy adult male (referred as individual head in the sequel). The T1-weighted images were collected using a gradient echo sequence on a 3T Trio scanner (Siemens, Erlangen, Germany), with echo time (TE) = 2.3 ms, TR = 1900 ms, 280 × 320 matrix scan with 208 sagittal slices. The second source is the MNI-152 head (non-linear 6th generation, [34], referred as standard head in the sequel), generated by averaging the MRI scans of 152 subjects at the Montreal Neurological Institute (Montreal, Quebec, Canada). Both the individual and standard heads have an isotropic resolution of 1 mm^3.

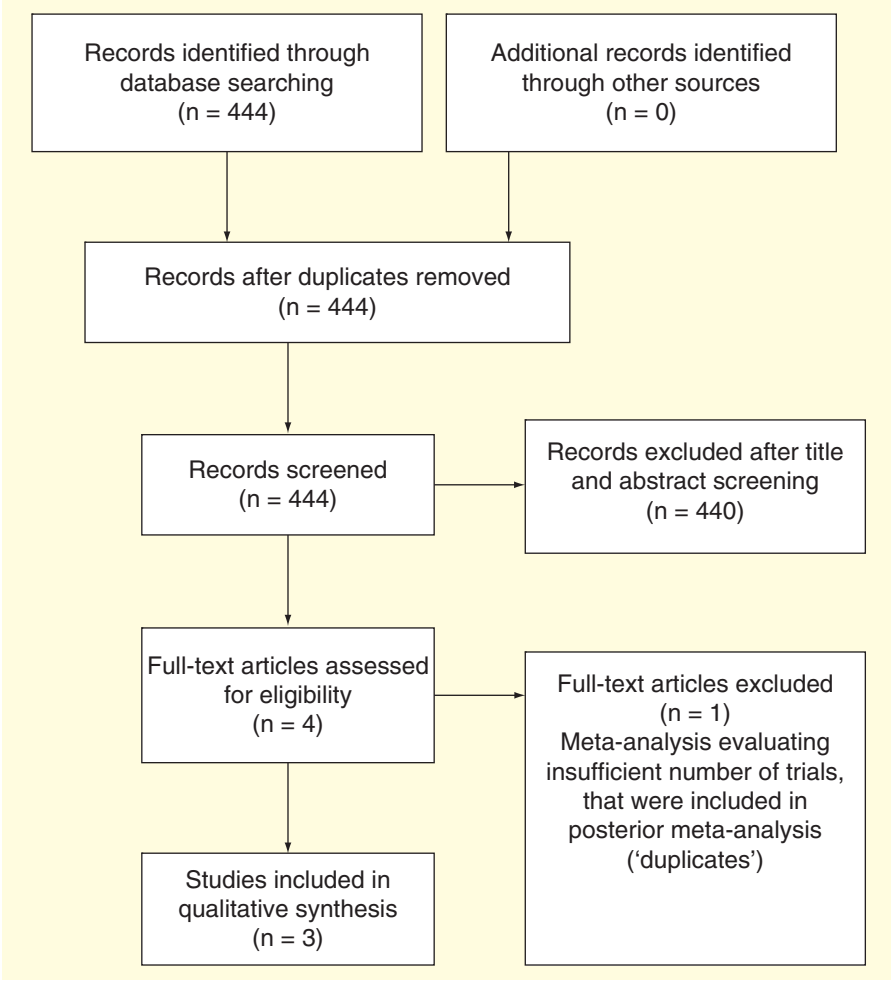

Figure 1. Flow chart or assessed studies in our review, according to PRISMA guidelines.

The models were built following previously described protocols [35]. Briefly, the MRI was automatically segmented into six tissue types in Statistical Parametric Mapping 8 (SPM8; Welcome Trust Centre for Neuroimaging, London, UK). Subsequently, an automated routine was used to correct segmentation errors. Remaining errors in anatomical details were manually corrected in ScanIP (v4.2, Simpleware Ltd, Exeter, UK). High-definition electrodes (12 mm diameter) were placed automatically using a script in Matlab (R2010b; MathWorks, Natick, MA, USA), and then the finite element model for all tissues and placed electrodes was generated in ScanIP (+ScanFE module). Abaqus (v6.9; SIMULIA, Providence, RI, USA) was used then to solve the finite element models under the field equation (Laplace, $-\dot{s}(\sigma V) = 0$). The boundary conditions were set to: insulated on the skin surface, grounded on the cathode surface and 1 A/m^2 inward current density on the anode surface. This was done for all possible bipolar electrode configurations. Based on the solutions, an optimization algorithm [3] was then applied to generate the optimal electrode montage such that the electric field intensity at the brain area of interest is maximized. The present algorithm differed from [36] in that we aimed to maximize intensity on target bilaterally, that is, maximizing magnitude squared of the electric field summed over the two equivalent areas on left and right hemispheres.

Results

Overview

Using the keywords defined above, we retrieved 444 articles from the Pubmed/MEDLINE. Of the selected articles, 441 were excluded because of the following: incompatible study design or the study was focused on other disease or intervention (440 studies) and duplicate data (1 study). (Figure 1) ilustrates the procedure of study selection.

Deep brain stimulation

The search retrieved two DBS studies. Nangunoori *et al.* (2013) performed a pooled analysis based on the statement that there are scarce DBS randomized clinical trials, and intended to gather a larger number of subjects reported individually or in case series [37]. Kisely *et al.* (2014) chose to perform a meta-analysis of sham-controlled randomized clinical trials [50]. Therefore, while the first review included a larger number of studies, the second evaluated studies with a more consistent design.

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The first DBS study included in our review is the pooled analysis performed by Nangunoori *et al.* (2013) that evaluated the efficacy of DBS in OCD, major depressive disorder and Tourette syndrome (TS) [37]. To perform the analysis, the authors included all clinical study articles in MEDLINE that reported pre-operative and post-operative Y-BOCS scores for each individual patient. Due to the investigational nature of studies involving DBS, they chose to include case reports, as long as the aforementioned criteria were met [37].

Among the disorders evaluated, they found the most robust DBS treatment response for TS, another OCD spectrum disorder. This fact may stem from the experience of targeting nuclei such as the globus pallidus internus for movement disorders. In fact, TS can be conceptualized as a movement disorder with psychiatric manifestations. According to the pooled analysis, the effect of DBS was most pronounced in TS than OCD or major depression subjects, and it is likely that a number of them achieved remission (though a definition for this was not given in the literature included). As the disorder presents an early onset and a range of severity, the inclusion criteria for these patients must be strict [38].

As the length of each study was not uniform, when the study had multiple endpoints, the longest follow-up available was used. For OCD, seven case reports and three clinical studies were included. The pooled analysis demonstrated that DBS is an effective treatment option for OCD, although the between-study heterogeneity was significantly high ($p < 0.0001$) [37]. Several DBS brain targets were described in the analyzed studies, such as the Anterior Limb of the Internal Capsule (ALIC), the Ventral Capsule and Ventral Striatum (VC/VS), the Nucleus Accumbens (Nacc) and the Subthalamic Nucleus (STN). As presented below, the authors concluded that all DBS targets are effective for OCD and a larger number of subjects in the pooled analysis performed VC/VS stimulation. As the studies were notably limited by several methodological aspects, it was not possible to conclude which target seems to be the most promising one.

The ALIC was one of the first target areas for DBS that was selected based on neurosurgery studies in OCD. Anderson and Ahmed (2003) reported one case of bilateral ALIC stimulation with complete remission [39]. In a subsequent study, Abelson *et al.* (2005) reported a case series of four patients. Although two patients were responders, one of the four did not show any response to the treatment [40]. Baker *et al.* (2007) reported a successful case of ALIC DBS stimulation, but the electrodes were implanted in an area of the ALIC that is also at the level of the ventral striatum [41]. Another study failed to show a robust response to ALIC stimulation [42]. Chang *et al.* (2010) reported a case with no response at all [42].

The VC/VS target area was also investigated, which showed more consistent results. Aouizerate *et al.* (2004, 2009) studied DBS stimulation on VC in one case and VS in two other cases. They all showed remission of OCD symptoms [43,44]. Greenberg *et al.* (2010) reported the results of four centers, and found that 16 of 26 patients were full responders (35% Y-BOCS reduction) and 10 of them were full remitters [45].

The Nacc, which lies within the VS, was also investigated. Franzini *et al.* (2010) reported two cases of implanted Nacc DBS. One patient was a full responder, while the other one presented a 33% Y-BOCS reduction [46]. Huff *et al.* (2010) published a study of 10 patients who received Nacc DBS, in which only 1 showed full response (35% Y-BOCS reduction) and 4 patients showed a partial response (25% Y-BOCS reduction) [47]. This review did not include the Nacc DBS trial of Denys *et al.* that evaluated 16 patients [48].

Finally, the STN was investigated by Mallet *et al.* (2008) who performed bilateral DBS in 16 OCD patients. This region was chosen based on previous findings of patients with Parkinson's disease that also reported amelioration of OCD symptoms. In this study, six patients achieved an improvement of at least 25% in their symptoms [49].

Kisely *et al.* (2014) performed a meta-analysis to evaluate DBS effects on major depressive disorder, anorexia and OCD [50]. Due to the inclusion and exclusion criteria for the clinical trials, they only evaluated five OCD trials [40,48,49,51,52]. Some of these trials [40,49] were also included in the previous pooled analysis [40], although the studies differed in the different eligibility criteria used in these systematic reviews. This meta-analysis included the studies of Goodman *et al.* (2010) [51]and Nuttin *et al.* (2003) [52]that performed the intervention in the anterior limb of the anterior capsule, and found that high treatment responses were reported in both studies [51,52], while Denys *et al.* (2010) stimulated Nacc, with 9 of 16 patients meeting the response criteria [48]. This meta-analysis also concluded that DBS may show promise for treatment-resistant OCD, but there are still insufficient randomized controlled data for other psychiatric conditions. The study did not identify any preferential DBS target [50]. On the other hand, independently on the specific stimulation site, it seems that DBS may modulate cortico-subcortical circuits connecting OFC, medial prefrontal cortex, striatum and thalamus, which are central to the pathophysiology of OCD [13].

Transcranial magnetic stimulation

The third study included in our review is the meta-analysis of Berlim *et al.* (2013) [12], which evaluated rTMS efficacy in 10 randomized, sham-controlled clinical trials, gathering 282 subjects [53–62]. The authors searched the literature using several databases and performed an exploratory random-effects meta-analysis with the main outcome measures being pre–post changes in Y-BOCS scores, response to treatment and overall dropout rates at the study end.

Although the included randomized clinical trials had relatively small samples and were heterogeneous in terms of demographic/clinical variables and stimulation parameters, limiting the ability to conclusively synthesize the literature, it was possible to conclude that low-frequency rTMS (particularly targeting the SMA or the OFC) seems to be the most promising approach in terms of potential efficacy [12].

This was the first meta-analysis assessing the efficacy and acceptability of rTMS for OCD. The findings showed that active rTMS significantly reduced overall OCD symptoms and OCD-related anxiety and depression. Furthermore, active and sham rTMS groups did not differ in terms of depression scores at baseline or dropout rates at the study end, although baseline Y-BOCS scores for the active rTMS group were significantly higher [12].

The rTMS was an effective intervention, with 35 and 13% of patients showing response to active and sham, respectively (odds ratio [OR] = 3.39; p = 0.002), and low-frequency (inhibitory) rTMS was superior to high-frequency (excitatory) stimulation. The authors concluded that non-DLPFC targets are more promising than DLPFC stimulation, considering the positive results obtained by rTMS over the OFC and pre-SMA [12].

Although the meta-analysis was not powered to detect differences between non-DLPFC areas, it is worth noting that the study by Mantovani *et al.* [55] that stimulated the pre-SMA reported the most promising results. Two more sham-controlled studies were recently published on rTMS to the pre-SMA in OCD and the findings showed active rTMS to be significantly superior to sham in reducing symptoms [58,63]. In fact, the SMA has been targeted with rTMS as a result of the role that the region plays in conveying information from limbic to cognitive and motor circuits [64]. Conversely, OFC was targeted starting from the consolidated neuroimaging finding of an involvement of this area in OCD pathophysiology [65].

Optimal electrode montages

In summary, ALIC, VC/VS, STN and Nacc were the targets investigated in the DBS studies, with the largest studies targeting the VS/VC areas. For rTMS, SMA and OFC seem to be the most promising targets. Based on these findings, we searched for montages that achieved maximal stimulation intensity for each of the following targets: VS, ventral putamen, OFC and SMA. For this optimization, we used a new model of electric conductance in the head (based on the MNI-152 standard) and searched for electrodes' locations that achieve the largest intensity at a desired bilateral target, irrespective of the intensities achieved at other locations.

Different montages produced different field intensities and direction in the cortex and subcortical structures (Figure 2). Generally, stimulation with both electrodes placed on the head produced more intense electric fields in the prefrontal areas (Figure 2C–2E), while cathodal stimulation with an extra-cephalic anode stimulated more specifically the structures involved in OCD circuits, such as anterior cingulate cortex and anterior basal ganglia (Figure 2A). Since we optimized for intensity and not focality, we obtained broadly distributed electric current flow reaching several brain structures. Figure 2A shows cathodal stimulation over pre-SMA, with the anode positioned in an extra-cephalic region. The electric current reaches the largest number of structures of interest, including the medial prefrontal cortex (i.e., SMA, OCF, anterior cingulate cortex [ACC]), the DLPFC and basal ganglia. This model provided the most desirable pattern of stimulation with regards to OCD pathophysiology. To confirm that this distribution of activity is not specific to the standard head model, we computed current distribution with this same montage for an individual subject (Figure 2B). The intensities are smaller (due to increased shunting on the scalp and CSF for this subject), but the overall distributions are comparable.

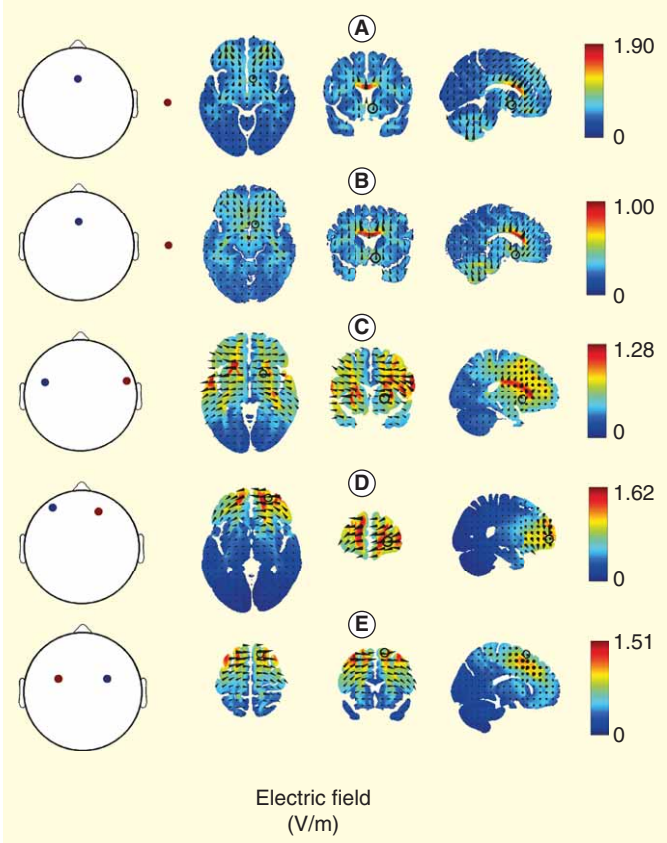

Figure 2. Estimated current flow for various transcranial direct current stimulation electrode configurations. These montages were optimized to achieve maximal stimulation intensities on the following bilateral targets (numbers indicate MNI coordinates): **(A, B)** inferior ventral striatum (±9, 9, −8); **(C)** ventral putamen (±20, 12, −3); **(D)** orbitofrontal cortex (±24, 58, −1); **(E)** supplementary motor area (±15, 17, 61). **(B)** The result from an individual head model using the inferior ventral striatum as the target. First column indicates locations of anode (dark red) and cathode (dark blue). For case **(A)** and **(B)**, the anode is extra-cephalic. Stimulation here was 2 mA through small, 'high-density' electrodes. Axial, coronal and sagittal slices pass through the target (cyan circle). Color indicates intensity of electric field relative to the maximum value (same value for each row, shown above the slices).

The following montages place both electrodes on the head. Figure 2C shows a montage that optimally targets DLPFC. Although stimulating this cortical area is not our main goal, this configuration allowed current flow to stimulate subcortical regions as well, with high intensity in ventral putamen. Figure 2D shows optimal stimulation for OFC and Figure 2E shows

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it in SMA. Although these montages produced an intense current flow in the prefrontal cortex, the stimulation effect was observed to be not as strong as in other structures of interest.

Discussion

In the context of OCD pathophysiology, evidence supports the hypothesis that obsessive–compulsive symptoms are related with alterations in the cortico-striato-thalamo-cortical circuits [10]. It has been speculated that hyperactivation of prefrontal–thalamic circuits and the lack of inhibition of the cortico-striato-thalamo-cortical pathways are implicated in OCD pathophysiology [11]. The cortico-striato-thalamo-cortical circuits convey information flow from cortical and limbic regions to modulate several processes, including motivation, attention and motor function [66,67]. According to this rationale, key structures would include the DLPFC, OFC, ACC and striatum (specifically the caudate) [68]. The evidence deriving from the clinical efficacy of inhibitory rTMS and tDCS and from neurophysiological measures of altered motor cortex excitability in OCD [69], which normalized after low-frequency (1 Hz) rTMS to the pre-SMA, suggests that the pre-motor/motor system is also abnormally hyperactive in OCD, and that there is a pathophysiological link between such hyperexcitability and OCD symptoms [69].

Electrical versus magnetic stimulation

Presently, there are different hypotheses to explain the therapeutic mechanism(s) of DBS. Depolarization blockade [70], synaptic inhibition [71], synaptic depression [72] and stimulation-induced disruption of pathological network activity [73] are among them.

Functional neuroimaging studies with DBS have shown changes in regional cerebral blood flow in the circuitry implicated in OCD. Rauch *et al.* (2006) found that acute high-frequency DBS of the VC/VS significantly increased regional cerebral blood flow within the OFC, anterior cingulate cortex, striatum, globus pallidus and thalamus, compared with control conditions [74], whereas a decrease of prefrontal metabolic activity, especially in the subgenual anterior cingulate, was observed by Van Laere *et al.* (2006) after chronic anterior capsular stimulation [75]. A high-frequency, bilateral DBS at the STN decreased prefrontal cortex metabolism in refractory OCD patients [76]. In 2013, Figee *et al.* found that DBS of the NAcc normalized NAcc activity and excessive frontostriatal connectivity [77]. Lastly, Suetens *et al.* have shown that DBS at the bed nucleus of the stria terminalis decreased regional cerebral blood flow in the anterior cingulate and the prefrontal and orbitofrontal cortices [78]. There are only a few neuroimaging studies that investigate metabolic changes after rTMS in OCD. Nauczyciel *et al.* (2014) found that low-frequency rTMS over the right OFC in OCD patients was related to a bilateral decrease in the metabolism of this region [79]. Thus, taking the results from neuroimaging studies, it seems that both DBS and rTMS, directly or indirectly, have similar effects on networks encompassing cortical-striatum-thalamic circuits. To the best of our knowledge, there is no neuroimaging data available for tDCS in OCD.

Furthermore, although magnetic stimulation can be used for stimulating peripheral nerves with a mechanism of activation similar to an electrical stimulation, when it is applied to the cerebral cortex, some features emerge that distinguish it from the transcranial electrical stimulation [80]. Lastly, repetitive transcranial stimulation exerts a lasting effect on brain function even after the stimulation has ceased [80]. Even though conventional TMS can directly activate only cortical neurons, it may also affect brain regions at some distance from the stimulation site, most likely through trans-synaptic connections [81–84].

Regarding the adverse events, both techniques might present risks, although DBS is more invasive and associated with severe events. DBS adverse events might be related to the surgical procedure or are secondary to stimulation; most of them are transient and related to the stimulation, including hypomania, anxiety, paresthesias, dyskinesias, impulsivity, facial asymmetry, dysarthria, dysphagia and walking difficulties [48,49]. Reported side effects for rTMS include headache, scalp discomfort, facial twitching, tearfulness, local erythema and drowsiness, and are more often associated with high-frequency rTMS than with low-frequency rTMS [85].

In this study, we reviewed DBS and rTMS studies on OCD, aiming to provide a rationale for electrode placement in tDCS studies. Although the evidence is limited for both DBS and rTMS studies, we identified that cortical stimulation of the SMA and OFC were associated with better results, whereas the ALIC, VC/VS, STN and Nacc subcortical regions were investigated in most DBS studies. Based on these findings, we performed several computer-based models to predict brain current flow in these structures. The aim of the intervention is to perform an inhibitory stimulation in prefrontal and subcortical structures such as the anterior basal ganglia. Although there is an important overlap between electric flow across different tDCS montages, the computer models suggest that the tDCS montage using the cathode over the pre-SMA and anode over an extra-cephalic region, which provides greater electric flow over the inferior ventral striatum, stimulates the largest number of structures of interest, including the medial prefrontal cortex (i.e., SMA, OFC, ACC), the DLPFC and basal ganglia [65]. Therefore, we selected this model as the most promising montage for OCD.

Limitations

Some study limitations should be underscored. First, regarding our review, the number of included studies is small, presenting mixed findings and limited by methodological concerns. Second, we intended to extrapolate findings from other brain stimulation techniques to build a computational model for a tDCS intervention, although the interventions might not be comparable in every matter, as they are also associated with distinct neurophysiological effects. There is still little standardization in the application of these neuromodulatory techniques and

selecting an ideal brain target is controversial, especially regarding DBS intervention.

In addition, OCD is a complex, heterogeneous condition, with clinical subtypes and high comorbidity rates; therefore, although the meta-analyses and pooled analysis pointed out the efficacy of specific brain targets' stimulation, these findings might not be replicable to all OCD patients. In this regard, Gentil *et al.* (2014) found hoarding symptom to be a predictor of poor response to neurosurgical intervention in OCD [86].

Finally, our tDCS computer modeling is evidently theoretical and like any other model, it benefits from ongoing experimental validation and refinement. However, the computational modeling parameters applied in this study have been confirmed through neurophysiology [87] and imaging [88] studies and, moreover, they have been used to guide and explain a series of neurophysiological and clinical trials [89]. The models themselves are based on undisputed physics (Ohm's law) and benefit form state-of-the-art precision in segmentation and workflow that preserves resolution through the entire modeling process. Moreover, the models are used here to make general predictions on current flow that should be robust to parameterization.

Expert commentary

tDCS is a relatively novel non-pharmacological intervention that has been increasingly investigated in the treatment of mental disorders. tDCS has important advantages over other brain stimulation interventions, such as ease of use, portability, low cost and a low profile of adverse effects. In this study, we aimed to identify possible brain targets for the treatment of OCD using tDCS intervention. As this is a novel approach and there is a lack of evidence at the present moment, we searched other neuromodulatory techniques employed in OCD, such as DBS and rTMS. The most promising results regarding rTMS intervention were low-frequency stimulation in SMA and OFC [12].

In general DBS stimulation studies reported greater treatment response rates than rTMS; however, in most of the DBS studies evaluated, factors such as lack of standardization in the intervention parameters and small sample size raised difficulties in the comparison of the efficacy of each brain target. Although the most effective DBS target remains inconclusive, it seems that a larger number of subjects underwent DBS in VS/VC and showed significant treatment responses [37,50].

Based on these findings and on tDCS simulation models, computational models were performed to simulate electrodes montages targeting OCD brain regions. The montage using cathode over the pre-SMA and anode over an extra-cephalic location appears to be the most promising to be explored in further OCD trials, as it modulates several brain areas related to OCD pathophysiology, including the inferior ventral striatum.

Five-year view

Computational models of brain current flow are already being increasingly used to understand and optimize tDCS clinical trials. In 5 years, irrespective of whether these computational models will become more readily accessible to clinical researchers (perhaps through open-source or web-based software), these tools will be broadly used in the design of tDCS trials. In addition, given the results presented in this study, we expect that tDCS will be increasingly used and tested for the treatment of OCD.

Financial and competing interests disclosure

M Bikson has patents as an inventor of a transcranial direct current stimulation device and owns equity in Soterix Medical. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Key issues

- Over the last decades, non-pharmacological techniques for obsessive–compulsive disorder (OCD) treatment, such as repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS), have expanded our understanding of the brain circuits involved in this disorder.
- However, mixed findings from rTMS and invasiveness of DBS highlight the need for the development of alternative non-invasive approaches.
- Transcranial direct current stimulation (tDCS) is a relatively novel non-pharmacological intervention that has been increasingly investigated in the treatment of mental disorders and it has important advantages over other brain stimulation interventions.
- In this context, tDCS might be a potential new treatment for OCD, although the optimal tDCS montage is unclear.
- A search in the Pubmed/MEDLINE was conducted for systematic reviews with quantitative analyses of rTMS and DBS trials for OCD.
- For the tDCS computational analysis, we employed both individualized and standard head models, with the goal of optimally targeting current delivery to the structures of interest.
- Electrodes montages aimed current flow to reach both rTMS superficial and DBS deeper targets.
- The montage with the cathode over the pre-supplementary motor area and the anode in an extra-cephalic placement seems to best activate most of the areas related to OCD, in particular, the anterior region of the basal ganglia.

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