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Efficacy of pre-supplementary motor area transcranial direct current stimulation for treatment resistant obsessive compulsive disorder: A randomized, double blinded, sham controlled trial

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ABSTRACT

Background: A significant proportion of obsessive compulsive disorder (OCD) patients do not respond to specific serotonin reuptake inhibitors (SSRIs). There is a need to evaluate novel treatment options for OCD.

Objective: In this double blinded, randomized, sham controlled study, we investigated the efficacy of add-on transcranial direct current stimulation (tDCS) in reducing the symptoms in SSRI-resistant OCD patients by employing anodal pre-supplementary motor area (pre-SMA) stimulation.

Method: Twenty-five patients with DSM-IV OCD having persistent symptoms despite adequate and stable treatment with at least one SSRI were randomly allocated to receive 20 min of verum (active) 2-mA tDCS or sham stimulation twice daily on 5 consecutive days [anode over Pre-SMA; cathode over right supra-orbital area]. Response to treatment was defined as at least 35% reduction in the Yale-Brown Obsessive-Compulsive Scale (YBOCS) total score along with a Clinical Global Impression – Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved).

Results: The response rate was significantly greater in the verum tDCS(4 out of 12) compared to sham-tDCS (0 out of 13) [Fisher's exact test, $p = 0.04$]. Repeated measures analysis of variance with tDCS type (verum vs. sham) as between subjects factor showed that there was a significant tDCS-type X time-point interaction with significantly greater reduction of YBOCS total score [$F\ (1,22) = 4.95, p = 0.04$, partial-$\eta^2 = 0.18$] in verum-tDCS group.

Conclusions: The results of this RCT suggest that tDCS may be effective in treating SSRI-resistant OCD. Future studies should examine the efficacy in larger samples of OCD and explore other potential target regions using randomized sham-controlled designs, in addition to examining the sustainability of the beneficial effects.

Trial registration: Clinical Trials Registry India (http://ctri.nic.in/Clinicaltrials/login.php): Registration Number- CTRI/2016/04/006837).

Introduction

Obsessive compulsive disorder (OCD) is a chronic and disabling condition which affects about 1–2% of the general population. Selective serotonin reuptake inhibitors (SSRI) and cognitive behaviour therapy (CBT) are the first-line treatments for OCD [1]. Treatment guidelines of OCD indicate the utility of selective serotonin reuptake inhibitors (SSRI) and cognitive behaviour therapy (CBT) as the

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main treatment strategies [2–4]. However, a sizeable proportion of patients does not respond or only partially respond to the conventional treatment options resulting in severe distress and functional disability. The issue of treatment resistance is common in OCD [1]. When multiple treatment options such as SSRI, CBT and other augmentation strategies such as antipsychotics are ineffective, the patients are considered for treatment with invasive strategies such as deep brain stimulation.

Converging evidence suggests the role of cortico-striato-thalamo-cortical (CSTC) circuits in the neurobiological basis of OCD [5]. Neuroimaging studies have indicated the involvement of prefrontal cortical regions in the pathophysiology of OCD. Structural and functional alterations in the regions sub-serving the CSTC circuits explain the neurobiological aberrations associated with the disorder [6].

Non-invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are being tested for their efficacy in treatment resistant OCD. The tDCS, a non-invasive, relatively inexpensive and safe brain stimulation technique is gaining interest in various neuro-psychiatric disorders such as schizophrenia [7]. It involves application of weak intensity direct current (2 mA) to the scalp through electrodes, resulting in polarity dependent neuromodulation of the brain regions [8]. At this point of time, tDCS has not been considered as a treatment option for OCD according to the treatment guidelines presumably due to the fact that the evidence for its efficacy is weak.

Various cortical components of the CSTC circuitry such as orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC) and pre-supplementary motor area (pre-SMA) have been subjected to examination in OCD using non-invasive brain stimulation [9,10]. However, as reviewed recently by Brunelin et al., it is evident that the electrode placements and protocols used have varied widely [11]. Our group reported the first successful application of tDCS in OCD in two patients with treatment resistant symptoms using anodal pre-SMA stimulation [12]. Pre-SMA appears to have an important role in the neurobiology of OCD. This is a critical region involved in mediating important cognitive functions such as response inhibition [13–15]. Subsequently, Mondino et al. reported reduction of symptoms in a treatment resistant OCD patient using cathodal OFC stimulation (cathode: left OFC; anode contralateral occipital area) [16]. An open label study involving 8 OCD patients, reported benefit of tDCS application with cathode over the left OFC and the anode over the right cerebellum [17]. More recently, a small RCT with 12 participants with cross-over design without sham control recently reported benefit of using cathodal pre-SMA stimulation in OCD(anode over bilateral pre-SMA in the midline, cathode on the right deltoid and vice versa on cross over) [18]. Najafi et al. examined the efficacy of tDCS (anode leads over left parietal, temporal, and occipital areas; cathode over right supra-orbital area) in a relatively larger sample in an open label fashion and found it to be useful in treating treatment resistant patients [19]. Taken together, these studies indicate the preliminary evidence for the potential utility of tDCS in OCD.

Given its superficial location, pre-SMA forms an attractive target for therapeutic neuromodulation by brain stimulation [9]. Error-monitoring and response inhibition, critical cognitive functions linked to the OCD symptoms, are sub-served by the pre-SMA in addition to cingulate cortex [14,20]. Lack of pre-SMA inhibition on the striatal function [21] with resultant striatal hyperactivity is hypothesised to underlie OCD pathogenesis [22]. In OCD, pre-SMA activation has been correlated with better response inhibition function and reduction in symptom severity [15]. We previously reported improvement in OCD symptom severity using anodal stimulation of pre-SMA [12]. Studies in healthy volunteers have also shown improved response inhibition following anodal pre-SMA stimulation improved response inhibition [20,23]. Recently it has been suggested that mild depolarisation of neuronal membranes through anodal tDCS could make the neurons better receptive to both excitatory and inhibitory inputs [24]. Thus, modulating the pre-SMA activity using anodal tDCS might have beneficial effects.

In this study, we examined the efficacy of anodal (activating) pre-SMA tDCS using a randomized double-blinded, sham-controlled design in treatment resistant OCD patients. We hypothesised that verum (active) tDCS group will have significantly greater number of “responders” compared to the sham-tDCS group. We also hypothesised that there will be significant improvement in the OCD symptom severity among the verum-tDCS compared to sham-tDCS. Additionally, we conducted an exploratory open-label extension (OLE) phase in consenting participants who reported inadequate improvement at the end of RCT phase.

Method

Sample

We recruited 25 right-handed DSM-IV OCD patients (age range, 18–45 years), attending the specialty OCD clinic of the National Institute of Mental Health and Neurosciences (NIMHANS),Bengaluru, India (November 2015 and April 2017). The NIMHANS institute ethics committee approved the research protocol for ethical aspects. The study was conducted in accordance with the Declaration of Helsinki and its latest amendments. All patients gave written informed consent to participate in the study after the study procedure was explained to them. The research protocol was registered in Clinical Trials Registry India (http://ctri.nic.in/Clinicaltrials/login.php;Registration Number:CTRI/2016/04/006837).

Assessments

The first author administered the Mini International Neuropsychiatric Interview (MINI-5.0.0) [25] to confirm DSM-IV diagnosis of OCD. An experienced consultant psychiatrist of the OCD clinic (JCN/YCJR) reconfirmed the diagnosis of OCD. Right-handedness was ascertained by the Edinburgh Handedness Inventory [26]. All the patients were further assessed using the Yale-Brown Obsessive Compulsive Scale (YBOCS) which includes the checklist, severity rating scale and item-11 for assessment of insight [27], the Clinical Global Impression severity (CGI-S) and improvement (CGI-I) subscales, the Hamilton depression rating scale–(HDRS) [28] and the Hamilton Rating Scale for Anxiety– (HARS) [29].

Inclusion and exclusion criteria

The patients needed to have clinically significant OCD symptoms (YBOCS $\geq$ 16) despite adequate treatment with at least one SSRI for a minimum period of three months to be recruited for the study. All the psychotropic medications had to be at stable doses for at least 3 months to be eligible for recruitment. No changes in the medications and their dosages were allowed throughout the study period. Exclusion criteria included concurrent cognitive behaviour therapy (CBT), lifetime presence of substance dependence, psychosis, bipolar disorder and neurological diseases, psychiatric emergency (such as active suicidal ideation, recent emergency department visits and recent history of severe aggression),

uncontrolled medical condition, pregnancy/post-partum status and contraindication for tDCS (e.g.local lesion, metal in head).

Outcome measures

The primary outcome measure was "response" to treatment. Those patients achieving at least 35% reduction in the YBOCS total score along with a CGI-I score of 1 (very much improved) or 2 (improved) were categorized as "responders" [30]. The change in severity rating scores on the YBOCS, the HDRS and the HARS were secondary outcome measures. The first author, blind to the group status (verum/sham) of the patient administered the primary outcome measures, the YBOCS and the CGI, which was verified independently by the second author (inter-rater reliability: intra-class co-efficient = 0.96). Clinical assessments were done prior to the first tDCS session of the RCT phase (baseline), immediately after the last session of the RCT phase (reassessment-1) and when applicable, immediately after the last session of OLE phase (reassessment-2).

Study design

The study design had two phases (Figure-1): a double-blinded, randomized, parallel-arm, sham-controlled (RCT phase) and an OLE phase [31,32]. A computer-generated list of randomization sequence generated by a researcher (GV) not involved in administration of tDCS/rating scales was utilised for randomized allocation into the two groups in the RCT phase (1:1 ratio, blocks of 4). In order to ensure allocation concealment, tDCS was administered using "study mode" in which a five-digit numerical code unique to each patient was fed into the device which resulted in either sham or verum (active) stimulation. In this manner, tDCS administrators, patients and the rater (SG) were blinded to tDCS stimulation type (verum or sham). Importantly, the allocation concealment was maintained till the overall study completion.

The RCT phase lasted for 5 days and the patients were re-assessed after 5 days of twice-daily (10 sessions) tDCS administration. If there was no response during the RCT phase, the patient was given the option to enter the 2nd phase of the study. In the, OLE phase, irrespective of the type of tDCS (i.e. verum or sham) received during the RCT phase, patients received verum-tDCS for additional 5 days of twice-daily sessions. The flow of participants in each phase is shown in figure-2.

tDCS procedure

tDCS was administered using a standard equipment (Neuroconn DC Stimulator Plus, http://www.neuroconn.de/dc-stimulator_plus_en/) with established stringent safety measures by the study investigators (SG, AB, HC, NH, SB). Two conductive siliconized rubber electrodes inserted inside 0.9% saline soaked sponge pockets (7×5 cm^2) referenced as anode and cathode were used for delivering stimulation. The electrodes were positioned as per 10–20 international electrode placement system. The anodal stimulation site (left Pre-SMA) was localized with midpoint of inner edge of electrode (35-cm^2) placed over Fz [33]; cathode was placed over the right supra-orbital area. These electrodes were held in position by non-conducting rubber straps affixed around the head.

A constant current of 2 mA was delivered for 20 min with additional ramp-up and ramp-down phase of 20 s each at the beginning and end of the session respectively during the verum-tDCS condition. In contrast, for the sham stimulation, tDCS was administered at 2 mA strength for the first 40 s (this resulted in a brief period of skin sensations similar to that of verum stimulation) followed by only a brief and small current pulse every 550 ms (110-μA over 15 ms with peak current lasting for 3 ms). The sham stimulation parameters of our study ensured effective blinding [34]. The tolerability of tDCS as well skin sensations to tDCS were assessed after each session using a structured questionnaire [35]. Irrespective of verum or sham stimulation, all the patients report tingling/itching sensation with the onset of stimulation. The information regarding sensations on the scalp where electrodes were placed was inferred based on the side effect questionnaire mentioned previously.

During the tDCS session, patients were instructed to relax and stay awake with eyes open. In both phases (RCT & OLE), twice-daily sessions separated by at least 3 h were scheduled during morning (between 9 a.m. and 10 a.m.) and afternoon hours (between 12pm and 1pm).

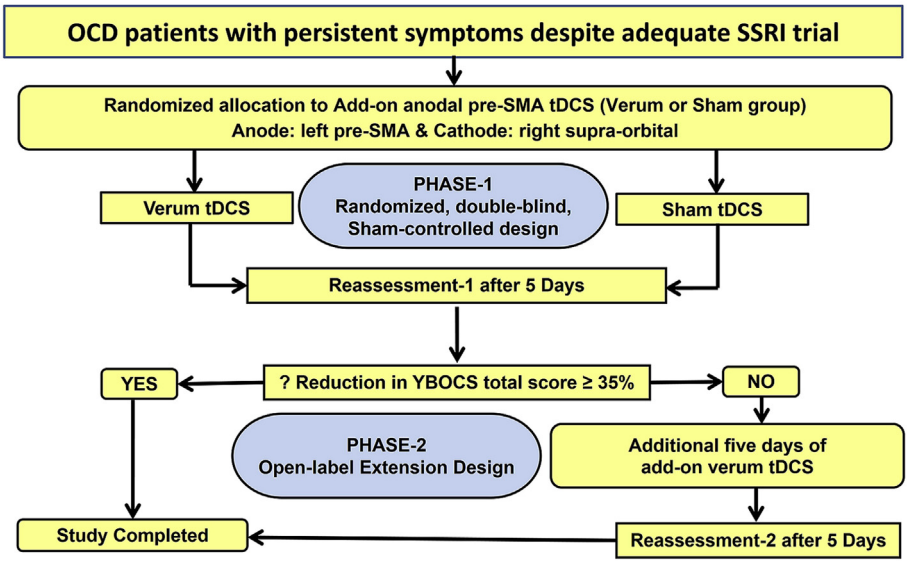

Fig. 1. The study design depicting the phases of the trial.

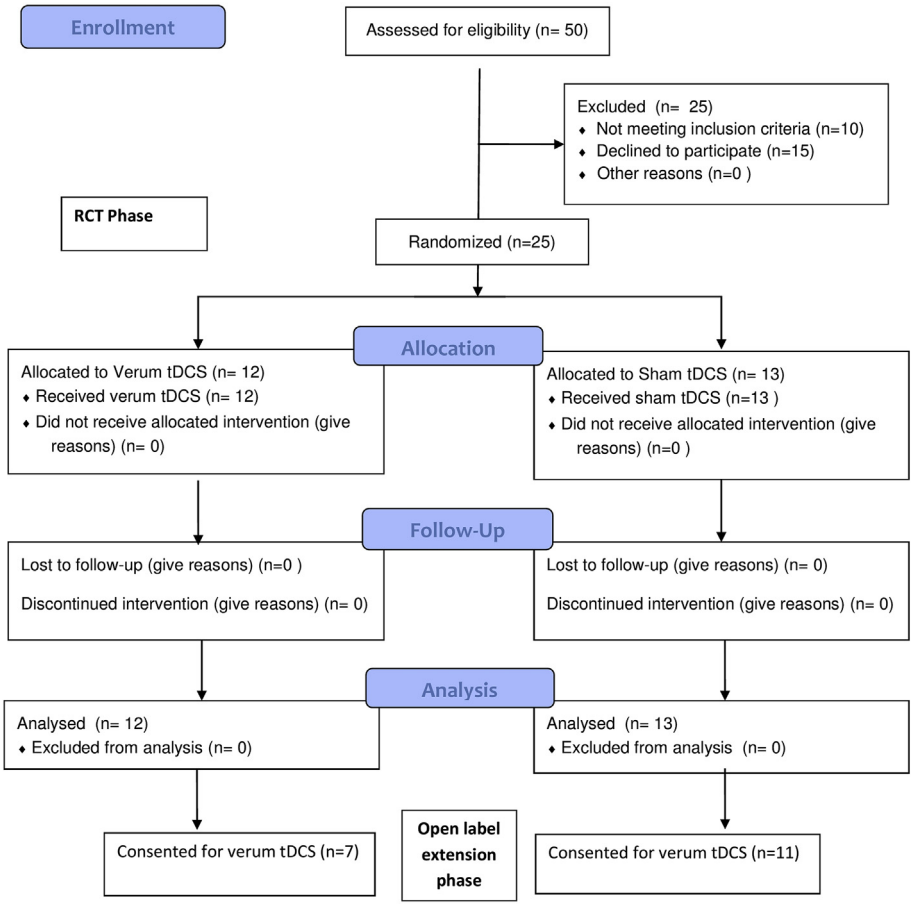

Fig. 2. The CONSORT flowchart with the number of participants in each phase.

Statistical analyses

We used Statistical Package for Social Sciences software version 22.0 (IBMSPSS Statistics for Windows, Armonk, NY: IBM Corp). Since there are no previous sham-controlled studies on the topic, we used the following method to calculate sample size. Based on a predicted medium effect size ($f = 0.25$), for repeated measures analysis of variance design (RM-ANOVA) it was estimated that a sample size of atleast 24 subjects (12 in each arm for an allocation ratio of 1:1 for the primary objective of YBOCS change) was be required to detect a two-tailed significant difference of $\alpha = 0.05$ with an estimated 90% power [36]. The correlation among the repeated measures was considered as 0.75 based on our own observations from an unpublished open label pilot data. Data was examined for normality in distribution using the Shapiro-Wilk test; accordingly, appropriate statistical tests were used. Response rate between the groups was compared using chi square test. To examine for tDCS-type X time-point interaction repeated measures analysis of variance (RMANOVA) was performed with type of tDCS(Verum-vs.-Sham) as between-subjects factor and YBOCS score as the primary outcome variable. Age of the participants was included as a covariate in the RMANOVA analysis in view of significant difference in age between the groups. Similar method was employed to examine the effect on HARS and HDRS.

To examine the difference in the percentage reduction in YBOCS total score between RCT phase and OLE phase in true and sham groups separately, paired *t*-test was employed. Finally, the degree of insight (YBOCS item 11) change between the time points in each group was ascertained using the Wilcoxon signed rank test. Figure depicting the YBOCS change during RCT phase was generated using RStudio (version-0.99.902) (https://www.rstudio.com/) interface for R (version 3.3.1) (https://www.r-project.org/).

Results

Comparative profile of patient characteristics

All the 25 patients completed the phase 1 (RCT phase) [verum arm ($n = 12$) and sham-tDCS arm ($n = 13$)]. Baseline comparison of the two groups (verum versus sham) as shown in Table 1 revealed that the sham-tDCS group exclusively comprised of males (verum vs. sham, male: female = 8:4 vs. 13:0) and the groups also differed with respect to age.

The principal OCD symptoms were as follows: fear of contamination and washing ($n = 7$, 28%), pathological doubts and checking ($n = 1$,4%), forbidden thoughts of sexual or aggressive content ($n = 8$,32%), need for symmetry ($n = 1$,4%) and miscellaneous obsessions and compulsions ($n = 8$,32%). Comorbidity rates in the sample were low: major depressive disorder ($n = 1$) (lifetime), generalised anxiety disorder (current) ($n = 2$) and body dysmorphic disorder (current) ($n = 1$). The groups did not differ based on the number of comorbidities ($p = 0.60$). The patients were on the following SSRIs: fluoxetine ($n = 7$), sertraline ($n = 3$), escitalopram ($n = 7$), clomipramine ($n = 6$), fluvoxamine ($n = 2$). Augmentation with antipsychotics was present in 5 patients: risperidone ($n = 3$) and aripiprazole ($n = 2$). Six patients were on clonazepam in addition to SSRIs.

Table 1
Comparative baseline demographic and clinical profile of study participants in verum (active) (n = 12) and sham (n = 13) groups.

	Verum tDCS (n = 12)	Sham tDCS (n = 13)	Test statistics (t/χ^2/Fisher's exact/U)	P-value
Age [Mean (SD)]	30.83 (5.87)	25.92 (5.15)	2.22	0.04
Sex (Male:Female	8:4	13:0		0.04[c]
Years of education [Mean (SD)]	13.16 (1.89)	13.61 (2.29)	0.53	0.60
Occupation (Employed:unemployed)	6:6	9:4	0.96[b]	0.43
No Failed trials of SSRIs [Mean (SD)]	1.66 (0.77)	2.00 (1.08)	66[a]	0.48
Duration of illness, years [Mean (SD)]	9.91 (6.54)	8.23 (3.70)	0.78	0.44
Baseline YBOCS obsession [Mean (SD)]	13.41 (1.97)	14.23 (2.48)	0.90	0.38
Baseline YBOCS compulsions Mean (SD)	13.07 (2.98)	12.50 (3.58)	74[a]	0.83
Baseline YBOCS Total [Mean (SD)]	25.83 (4.88)	27.31 (5.23)	0.72	0.48
Baseline Insight score (YBOCS item 11)	1.58 (0.668)	1.46 (0.967)	72[a]	0.73
Baseline CGI-S	4.91 (0.792)	5.07 (0.862)	71.5[a]	0.70
Baseline HDRS	7.08 (4.67)	7.00 (3.34)	0.05	0.96
Baseline HAM-A	8.75 (5.17)	9.00 (4.26)	0.13	0.90

[a] Mann-Whitney *U* test.
[b] Chi square test.
[c] Fisher's exact test.

Overall, in both the phases, tDCS sessions were well tolerated by all patients. There were no drop-outs due to adverse effects.

RCT phase

Four out of 12 patients in the verum-tDCS responded compared to none in the sham-tDCS [4/12 vs. 0/13; Fisher's exact test p = 0.04; number needed to treat (NNT) = 3] (Fig. 3). The baseline and post-RCT phase YBOCS total scores were 25.83 (4.88) and 20.42 (6.91) in the verum group and 27.31 (5.23) and 24.08 (5.50) in sham group. At the end of the RCT phase, the percentage of reduction in YBOCS obsession, compulsion and total scores in verum group was 17.75(21.64), 27.68(30.24) and 22.06 (24.33) respectively compared to sham group - 12.27(9.69), 12.3(11.16) and 12.04 (6.26) respectively. RMANOVA showed that there was a significant tDCS-type X time interaction with significantly greater reduction of YBOCS compulsion score [F (1,22) = 5.46, p = 0.03, partial-η^2 = 0.20] and total score [F (1,22) = 4.95, p = 0.04,partial-η^2 = 0.18] in the verum-tDCS group as compared to the sham group after controlling for age (Figure-3). We controlled for age because of a significant interaction effect of age with the YBOCS total score (F = 5.29, p = 0.032).

A significant improvement in the insight scores was observed for the verum-tDCS group (p = 0.01), but not for the sham group. However, there was no significant tDCS-type X time-point interaction on the reduction of anxiety rating based on HARS score [F (1,22) = 1.46; p = 0.24; partial-η^2 = 0.06] or depressive symptom rating based on HDRS score [F (1,22) = 1.54,p = 0.23; partial-η^2 = 0.07]. Inclusion of gender into the above models resulted in lack of significant findings in RMANOVA design.

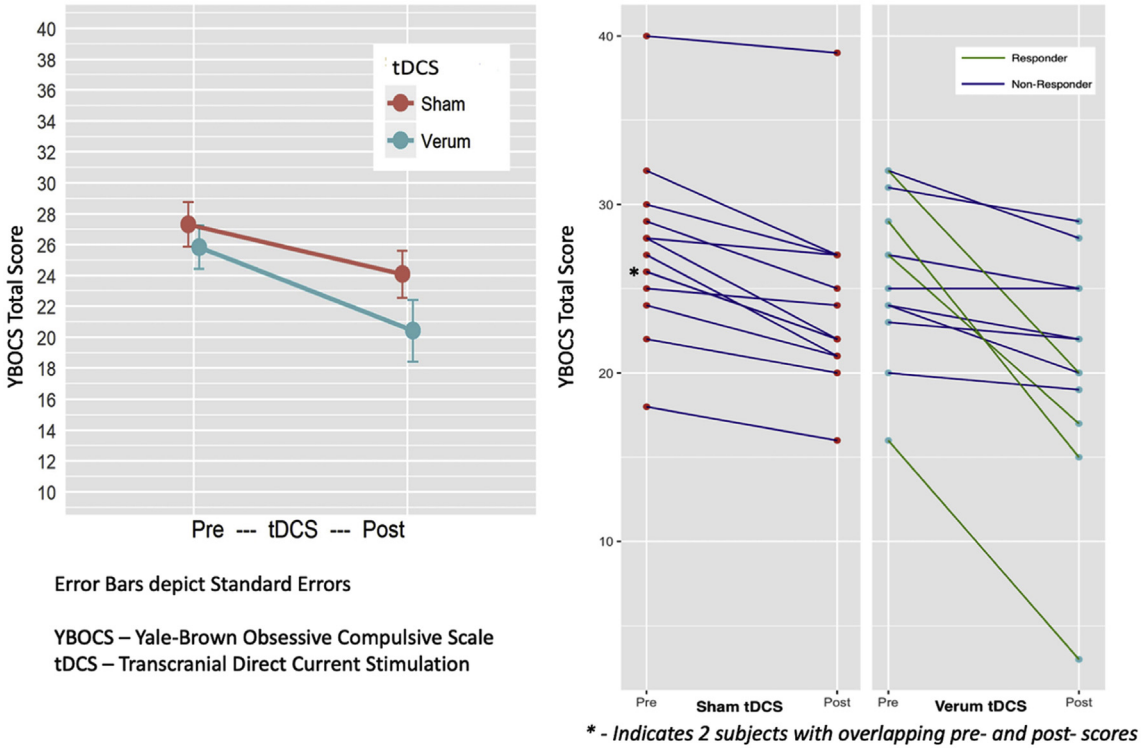

Fig. 3. Comparison of change in OCD symptom severity between verum (active) and sham groups.

Open-label extension (OLE) phase

Out of the 13 participants who received sham stimulation in the RCT phase, 11 participants entered the OLE. However, for these subjects, we did not observe significant difference in the percentage reduction of YBOCS total score between the RCT phase [11.7% (6.8%)] and OLE [8.4% (8.1%)] phase ($t = 1.05$; $p = 0.32$) and none of these subjects became responders. Among the participants who received verum stimulation in the RCT phase, 7 participants entered the OLE phase because they had not shown response. However, at the end of OLE phase, There was a significant difference in the percentage reduction of YBOCS total score between the RCT phase [7.75% (5.50%)] and OLE phase [15.29% (8.68%)]($t = 2.67$; $p = 0.04$) for these participants. However, none of these subjects attained "responder" status.

Discussion

To the best of our knowledge, this is the first report of a sham-controlled double blind RCT of add-on tDCS for SSRI resistant OCD. As we hypothesised, there was a significant beneficial effect of verum-tDCS on pre-SMA. The fact that none in the sham group showed response underscores the impact of verum stimulation. The results are consistent with our previous report of good response in 2 SSRI-resistant patients to anodal pre-SMA tDCS [12]. Importantly, all the subjects had persistent symptoms despite adequate treatment with atleast one SSRI and most of them had a history of failure of response with two SSRIs. Response to tDCS in such a sample might indicate the potential of add-on tDCS in treatment resistant OCD. In addition, among those participants who received verum-tDCS and subsequently entered the OLE phase, there was a further significant reduction in YBOCS score upon receiving additional verum-tDCS sessions.

Pre-SMA is an important cortical region implicated in OCD and it is thought to mediate error monitoring and response inhibition along with other brain regions such as cingulum [14,20]. Dysfunction of these cognitive processes has been implicated as a mechanism underlying intrusive ideas and ritualistic behaviors seen in OCD [37]. Pre-SMA along with the basal ganglia structures such as putamen is considered to play a pivotal role in habit formation and this understanding remains critical in conceptualising and treating compulsivity [13,14,38]. Lack of pre-SMA inhibition on the striatal function could result in hyperactivity of striatum [21]. In healthy individuals, anodal tDCS on pre-SMA resulted in improvement in response inhibition as evidenced through reduction of stop-signal reaction time (SSRT) [20]. In the context of OCD, these benefits might translate into improvement in severity of symptoms as observed in this study.

We also observed a significant improvement in insight with verum tDCS. Pre-SMA has been considered to be critical for self-awareness and control over voluntary behaviour [39]. Frontal cognitive deficits may be associated with poorer insight in OCD [40] as in schizophrenia, where prefrontal anodal stimulation improved insight [41]. Improvement in the illness severity might have as well resulted in improvement in insight, considering the association of insight with severity of illness [42]. Patients who did not respond to verum stimulation in RCT phase had further reduction in YBOCS scores from additional verum-tDCS in the OLE phase which indicates that some patients may perhaps benefit with greater number of tDCS sessions. It is known that the effects of tDCS on cortical excitability are based on subthreshold neuronal membrane polarization and that prolonged stimulation results in greater neuroplastic effects [8]. In the absence of sufficient number of studies, there is no consensus regarding the optimal number of tDCS sessions to be used for OCD. It is possible that greater number of tDCS sessions might culminate in greater therapeutic benefits. However, none of the subjects who received sham stimulation in the RCT phase improved with verum tDCS in the OLE phase. It is difficult to explain this negative finding in the cross-over design. It is possible that only a subset of OCD patients may benefit from tDCS and in a study with a relatively smaller sample size, such tDCS-responsive patients may not have been represented proportionately in both arms. It is well-known that OCD is heterogeneous not only with respect to clinical phenotype [43] but also with respect to treatment response [44]. Therefore, larger RCTs may identify as to who benefits most from tDCS. Lack of serious adverse effects and drop-outs due to intolerance is consistent with the safety profile of tDCS [45].

The specificity of the anodal stimulation on pre-SMA needs to be evaluated and discussed carefully. Although previous studies reported utility of cathodal pre-SMA stimulation over anodal stimulation [18,46], smaller number of participants, absence of sham group and lack of blinding makes it difficult to draw definitive conclusions. Mantovani et al. found low frequency (inhibitory) rTMS over SMA to be useful which is contradictory to our stimulation protocol [47,48]. At present, it may be difficult to clearly state the mechanism through which anodal stimulation would have helped in our study. Recently, anodal tDCS has been postulated to make the neurons better receptive to both excitatory and inhibitory inputs by adaptively altering the brain alterations [24]. It is possible that anodal pre-SMA stimulation improves response inhibition and thereby improves OCD [11]. The pre-SMA plays a crucial role along with right inferior frontal gyrus (IFG) in mediating response inhibition [13,14]. These findings suggest that activating pre-SMA might have beneficial effects. However, one also needs to keep in mind that a recent meta-analysis has demonstrated similar efficacy for both high and low frequency rTMS (i.e., excitatory and inhibitory stimulation) [49].

The main strengths of this study are the sham-controlled design and the patients being on stable dose of medications for at least 3 months without concomitant CBT. There are certain limitations. Even though our sample size is comparable with the previous tDCS RCTs in psychiatrically ill population [7], examining larger sample of patients would have been ideal. However, feasibility of recruiting SSRI resistant OCD patients stabilized on medications is indeed a challenge. The solution to this problem could be to conduct multi-site studies to evaluate larger study samples. The fact that none of the subjects in the sham arm became responders needs to be interpreted with caution. We believe that this effect might mostly be driven by the relatively small sample size. However, analysis using continuous measures with repeated measures ANOVA complements the finding shown using a dichotomous outcome. A larger RCT might throw light on this aspect. The marginal additional improvement noticed at the end of OLE phase among the verum group patients could be due to placebo effect. The further reduction in total YBOCS score observed in the OLE phase is not greater than the reduction observed in the sham group.

The positioning of cathode on the right supra-orbital region was conceived as method of employing it as an "inert" reference electrode. However, it is also possible to ascribe the improvement to cathodal effect on right OFC. However, in order to specifically examine the efficacy of stimulation of pre-SMA, optimised stimulation using high definition tDCS might be useful. In addition, it was found that gender plays a significant role in mediating response. Such sex-specific tDCS effects are getting recognised recently [50].

Another potential limitation is the absence of follow-up assessment beyond the study period. It is unclear about the sustainability of tDCS effects in OCD. OCD is a heterogeneous disorder with multiple symptom dimensions [43]. The sample size of this study would be insufficient to examine the effect of various

symptom dimensions on the clinical benefit with tDCS. Apart from these, it is also important to mention that focality of stimulation using conventional tDCS could be considered inferior to its recent advancement – high definition tDCS. In summary, using a randomized, double-blind, sham-controlled design, we have demonstrated the efficacy and safety of anodal pre-SMA stimulation in OCD. Future efforts can incorporate functional activation data to implement MRI-guided stimulation apart from including computational modeling for optimised stimulation protocol. Such approaches are critical in disorders such as OCD with neurobiological heterogeneity. Availability of more focal methods such as high-definition tDCS technique has potential to evolve as personalised neuromodulatory strategy [51].Future studies should examine larger samples of OCD and examine other potential target regions using randomized sham controlled designs, in addition to examining the sustainability of the beneficial effects.

Conflicts of interest

None to disclose.

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Previous presentation

The pilot findings of this work was presented by the first author as oral presentation at the World Psychiatric Association World Congress (8–12 October 2017) held at Berlin, Germany; The final results were presented at Society of Biological Psychiatry annual meeting (10–12 May 2018) held at New York, USA.

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