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Feasibility, acceptability and practicality of transcranial stimulation in obsessive compulsive symptoms (FEATSOCS): A randomised controlled crossover trial

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a non-invasive form of neurostimulation with potential for development as a self-administered intervention. It has shown promise as a safe and effective treatment for obsessive compulsive disorder (OCD) in a small number of studies. The two most favourable stimulation targets appear to be the left orbitofrontal cortex (L-OFC) and the supplementary motor area (SMA). We report the first study to test these targets head-to-head within a randomised sham-controlled trial. Our aim was to inform the design of future clinical research studies, by focussing on the acceptability and safety of the intervention, feasibility of recruitment, adherence to and tolerability of tDCS, and the size of any treatment-effect.

Methods: FEATSOCS was a randomised, double-blind, sham-controlled, cross-over, multicentre study. Twenty adults with DSM-5-defined OCD were randomised to treatment, comprising three courses of clinic-based tDCS (SMA, L-OFC, Sham), randomly allocated and delivered in counterbalanced order. Each course comprised four 20-min 2 mA stimulations, delivered over two consecutive days, separated by a 'washout' period of at least four weeks. Assessments were carried out by raters who were blind to stimulation-type. Clinical outcomes were assessed before, during, and up to four weeks after stimulation. Patient representatives with lived experience of OCD were actively involved at all stages.

Results: Clinicians showed willingness to recruit participants and recruitment to target was achieved. Adherence to treatment and study interventions was generally good, with only two dropouts. There were no serious adverse events, and adverse effects which did occur were transient and mostly mild in intensity. Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores were numerically improved from baseline to 24 h after the final stimulation across all intervention groups but tended to worsen thereafter. The greatest effect size was seen in the L-OFC arm, (Cohen's d = −0.5 [95% CI −1.2 to 0.2] versus Sham), suggesting this stimulation site should be pursued in further studies. Additional significant sham referenced improvements in secondary outcomes occurred in the L-OFC arm, and to a lesser extent with SMA stimulation.

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Conclusions: tDCS was acceptable, practicable to apply, well-tolerated and appears a promising potential treatment for OCD. The L-OFC represents the most promising target based on clinical changes, though the effects on OCD symptoms were not statistically significant compared to sham. SMA stimulation showed lesser signs of promise. Further investigation of tDCS in OCD is warranted, to determine the optimal stimulation protocol (current, frequency, duration), longer-term effectiveness and brain-based mechanisms of effect. If efficacy is substantiated, consideration of home-based approaches represents a rational next step.
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1. Introduction

Obsessive Compulsive Disorder (OCD) is one of the most common, costly and burdensome psychiatric disorders and constitutes a leading global cause of functional disability and impairment in social, occupational and health-related quality of life (HR-QOL) [1,2]. OCD typically emerges in childhood or adolescence and follows a prolonged fluctuating course [3]. All population groups are approximately equally affected, regardless of gender or culture [4]. Existing evidence-based treatments, principally involving cognitive behaviour therapy (CBT) with exposure and response prevention (ERP), or pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI), often produce disappointing outcomes: approximately 40% patients do not respond and 50% require further treatment [5,6]. Chronic OCD is associated with substantial psychiatric and somatic comorbidity and in severe cases can lead to suicidal behaviour, long-term hospitalisation and residential care [5,7–11]. Development of new treatments to improve health outcomes for individuals with OCD is a well-established research priority [12,13].

Brain-imaging findings implicate aberrant cortico-striatal neurocircuitry in the underlying pathology of OCD, so representing a potential treatment target [14–17]. Ablative neurosurgery or deep brain (invasive) stimulation (DBS) of tracts or nodes within this circuitry [18] is sometimes found to improve OCD, possibly by enhancing information-processing functions [5,15,19]. However, ablative surgery and DBS are highly specialised, costly and burdensome procedures associated with significant risk and tolerability problems, rendering them inappropriate for all but the most severely ill, treatment-refractory patients [15].

Non-invasive neurostimulation, targeting superficial cortical nodes within cortico-striatal circuitry, is a safer and more acceptable alternative, with potential for scaling up and applying to a larger patient population, earlier in the course of illness. If found to be effective, this could have significant implications for improving patient outcomes, as delayed treatment is known to prolong illness and reduce therapeutic gains [20–22].

Repetitive transcranial magnetic stimulation (rTMS) is the form of neuromodulation studied most in OCD. Evidence from randomised controlled trials (RCTs) and meta-analyses supports its efficacy and has identified the orbitofrontal cortex (OFC) and supplementary motor area (SMA) as promising targets [23,24]. Deep TMS is a form of rTMS that can theoretically modulate deeper subcortical structures. Deep TMS targeting the anterior cingulate cortex has been found to be effective for OCD in 2 sham-controlled trials [25,26] and has been granted FDA approval. However, the constituent studies varied markedly in quality, and generally recruited small samples of patients [27]. In August 2020, the UK National Institute of Health and Care Excellence (NICE) stipulated that rTMS should only be used in the context of research in patients with OCD [28]. rTMS is also relatively costly, involves specialist technical equipment and staff, and cannot be delivered in patients' homes.

Transcranial direct current stimulation (tDCS) is an alternative method for delivering non-invasive neurostimulation to cortico-striatal neurocircuitry. It involves applying a low-amplitude (1-3 mA) electric current to the brain via electrodes placed on the scalp. Anodal tDCS is thought to enhance cortical excitability, whereas cathodal tDCS may have an inhibitory effect [29]. Compared with rTMS, tDCS tends to electrically modulate a more diffuse and superficial brain area, but it could represent a preferable option for patients with common mental disorders such as OCD, as it is cheaper, portable, simple and safe to use [30]. Application of tDCS was associated with minimal risk in numerous studies when applied within standard parameters: there have been no recorded serious adverse events; common adverse effects such as reddening of the skin are mild and short-lived; and reasonable efforts at assessment have determined there is no evidence of substantive damage to brain structure or function [31,32]. Systematic reviews and meta-analyses indicate adequate safety, tolerability and potential efficacy for tDCS in depression and other psychiatric disorders including OCD [29,33–41]. In 2015, NICE reported that the evidence relating to the use of tDCS for depression raised no major safety concerns and encouraged further research into this form of intervention [42].

Research into tDCS for OCD, however, remains at an early stage. Small uncontrolled studies and case reports mainly describe its effects in patients with treatment-resistant conditions [43]. Encouraging findings have supported its safety in this patient-group, and hint at possible efficacy for protocols targeting the OFC, SMA and some other regions (such as dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, and cerebellum) [29,35–38,44–50]. However, as with rTMS, the studies show significant heterogeneity, with methodological differences in sample selection criteria, concomitant treatment and stimulation protocols [27,29,38,45].

As the response to standard treatments (CBT, SSRI) is often partial, there is increasing interest in investigating the augmenting effect of tDCS. A randomised, double-blind sham-controlled trial assessed the safety and efficacy of tDCS (24 stimulation session, anode over the L-DLPFC, cathode over the R-OFC) as an adjunctive therapy in fluoxetine-treated patients with moderate-severe OCD ($n = 60$) [50]. This study found no statistical differences between experimental (fluoxetine + active tDCS) and control group (fluoxetine+ sham tDCS). tDCS was generally well tolerated and no major adverse events were reported [50]. The effect of tDCS as an adjunct to non-pharmacological treatments such as ERP has not yet been rigorously tested in double blind, sham controlled clinical trials [51].

The first RCT in OCD ($n = 21$ patients with treatment-resistant conditions) applied cathodal tDCS over the L-OFC, with the anode placed over the right cerebellum, and found active tDCS significantly decreased obsessive-compulsive symptoms immediately after 10 tDCS sessions ($F(1,19) = 5.26$, $p = 0.03$), but the effect was no longer present at one-month follow-up or the 12-week study endpoint [48]. Another RCT ($n = 24$ patients with treatment-resistant OCD) demonstrated efficacy for a protocol involving anodal tDCS administered over the bilateral pre-SMA, with the cathode placed over the right supra-orbital region. The response rate was significantly greater in the active tDCS compared to sham-tDCS arm after 10 tDCS sessions [Fisher's exact test, $p = 0.04$] [52]. The largest RCT ($n = 43$ patients with treatment-resistant OCD) investigated cathodal tDCS over the SMA, with the anode positioned over the left deltoid muscle [49]. After 20 tDCS sessions, at the 12-week study endpoint, active tDCS produced a significant improvement in obsessive-compulsive symptoms compared to sham, with mean (SD) Y-BOCS score changes from baseline of 6.68 (5.83) and 2.84 (6.3) points respectively (Cohen's d: 0.62 (0.06–1.18), $p = 0.03$). The treatment in both arms was well tolerated, however, only four patients in the active tDCS group and one patient in the sham group achieved a clinical response and there were no significant concomitant improvements in

either depression or anxiety [49].

Based on these findings and on emerging theoretical and computational models, some have suggested that cathodal tDCS with an extracephalic montage for the anode may be the best protocol for treating patients with OCD [30,45].

In summary, tDCS research in OCD is in its infancy, and evidence about its therapeutic potential is limited. Preliminary findings suggest tDCS may be effective in OCD, and the most promising brain areas for electrode application appear to be the L-OFC and pre-SMA/SMA [29,30,35–38,40,48,49,52]. However, there is much uncertainty about the optimal stimulation target, montage, frequency, magnitude and duration of effect, acceptability, tolerability and practicality of tDCS in clinical settings, as well as its mechanisms of action and interactions with existing treatment, and thus further studies are warranted [30,35–37,53]. As existing data are inadequate to support a full-scale trial, FEATSOCS was undertaken to address key research questions and knowledge gaps, so enabling the design of a subsequent definitive study.

2. Material and methods

2.1. Design

We conducted a double-blind, randomised, sham-controlled, multicentre cross-over feasibility trial in adults with OCD. The trial took place in Hertfordshire and Southampton from 23/07/2019 to 31/07/2021 and overlapped with a period when the UK was substantially affected by the COVID-19 pandemic. Patients identified as potentially eligible were screened and, if eligible, provided consent prior to randomisation.

A detailed description of the study design and protocol is reported elsewhere [54]. A summary of the key aspects of the methodology is given below. Briefly, patients who were randomised received 3 rounds of treatment, each delivered over 2 days, with 28 days of washout between rounds. In each round, patients received tDCS of one target (OFC, SMA), or sham in one of six random orders (see Fig. 1, Supplementary Materials).

2.2. Aims and objectives

The main aim of this pilot study was to inform the development of a definitive efficacy study. The objectives of this feasibility study were to assess the following:

- Feasibility of recruitment and willingness of clinicians to recruit participants
- Acceptability, tolerability, and adherence to tDCS and study assessments
- Safety of the intervention
- Practicality of applying tDCS in the clinical setting
- Effect of tDCS on OCD symptoms in order to estimate the likely effect size of a future trial.

2.3. Participants

Patients were eligible if they: (a) were aged 18 years or older[1]; (b) had DSM-5-defined OCD determined by a research psychiatrist using the Mini International Neuropsychiatric Interview version 7.0.2 for DSM-5 [55,56]; (c) duration of symptoms >1 year (from medical history); and (d) had a baseline score on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [57] of 20 or more, representing at least moderate severity OCD. Participants taking ongoing psychotropic medication (SSRI, tricyclic antidepressant, antipsychotic, benzodiazepine) were eligible, provided that the dosage was kept stable for a sustained period before randomisation ($\geq$ 6 weeks) and remained so throughout the study.

Patients were excluded if they: (a) were receiving CBT during or within 6 weeks of the start of the intervention; (b) had a clinical history of schizophrenia, psychotic symptoms, bipolar disorder, Tourette syndrome (tic disorders not amounting to Tourette syndrome were not excluded), organic mental disorder, psychosurgery, personality disorder of borderline or histrionic type; (c) had alcohol or substance use disorders within the past 12 months; (d) had another DSM-5 disorder that was considered the primary focus of treatment; or (e) had severe depression, defined by a Montgomery-Åsberg Depression Rating Scale (MÅDRS) [58] score > 30 at baseline.

2.4. Recruitment

Recruitment took place at two outpatient centres (Hertfordshire and Southampton). Patients were identified for screening from OCD clinics, primary healthcare services (e.g., Improved Access to Psychological Therapies (IAPT) services), charity/support networks, adverts/promotional material, and Trust databases. Participant information was provided to those potentially interested in learning more about the study. Patients provided consent to be screened for the study. Then a medically trained member of the research team with clinical experience of working with patients with OCD and their comorbidities assessed eligibility according to the above criteria and took a brief medical history. Some screening and follow-up assessments were performed via telephone to mitigate COVID-19 risks.

Eligible participants provided consent to study enrolment and randomisation separately. The clinician had authorised access to an online randomisation programme, accessed remotely via a specific password-protected internet site [59].

2.5. Intervention

Enrolled patients were allocated to receive one of six tDCS treatment patterns (involving L-OFC, SMA and Sham stimulation) allocated using simple, counterbalanced randomisation (see Fig. 1, Supplementary Materials). Each round comprised four sessions of 20-min stimulations to the same target (or sham), delivered over two consecutive days (two rounds per day), separated by at least a four-week washout period. Based on long-term study data, albeit limited, which seems to indicate that the clinical effect of acute stimulation is not sustained once stimulation ceases [48], we expected four weeks to be long enough for any residual clinical effects of tDCS to disappear.

Stimulation took place in a quiet clinical room, with the patient awake in a comfortable chair. The clinicians responsible for the montage were instructed regarding the target site (L-OFC or SMA) or to provide sham stimulation by the external randomisation allocation. Electrodes were placed using the International 10–20 System [60]. The active electrode was placed over either the SMA (cathodal, Fz point) or L-OFC (cathodal, FP1 point) and attached to the scalp using a personalised sterile head net tubular bandage [60]. The inactive (reference) electrode (anode) was placed over the right deltoid muscle using an elastic band. Settings on the tDCS stimulator, marked with “1” and “2” codes known to the clinician responsible for the tDCS montage and delivery, were preselected for active or Sham stimulation [61]. Individual personalised sponge electrodes, soaked in saline solution and standard electroencephalogram gel to ensure optimal electrical conduction, were used.

In each round of active treatment, a 2 mA current was delivered for 20 min, twice on Day 1 (0 h and 4 h) and twice on Day 2 (at the same time points). Sham stimulation used the same methodology apart from the current setting on the stimulator which included a very brief initial period of current “ramp up”, enabling the initial cutaneous sensations associated with stimulation, whilst the current then remained off for the

[1] An upper age limit (65 years) was included in the original protocol, but was subsequently removed, as it was felt clinically relevant to provide an opportunity for tDCS to be tested in older people with OCD.

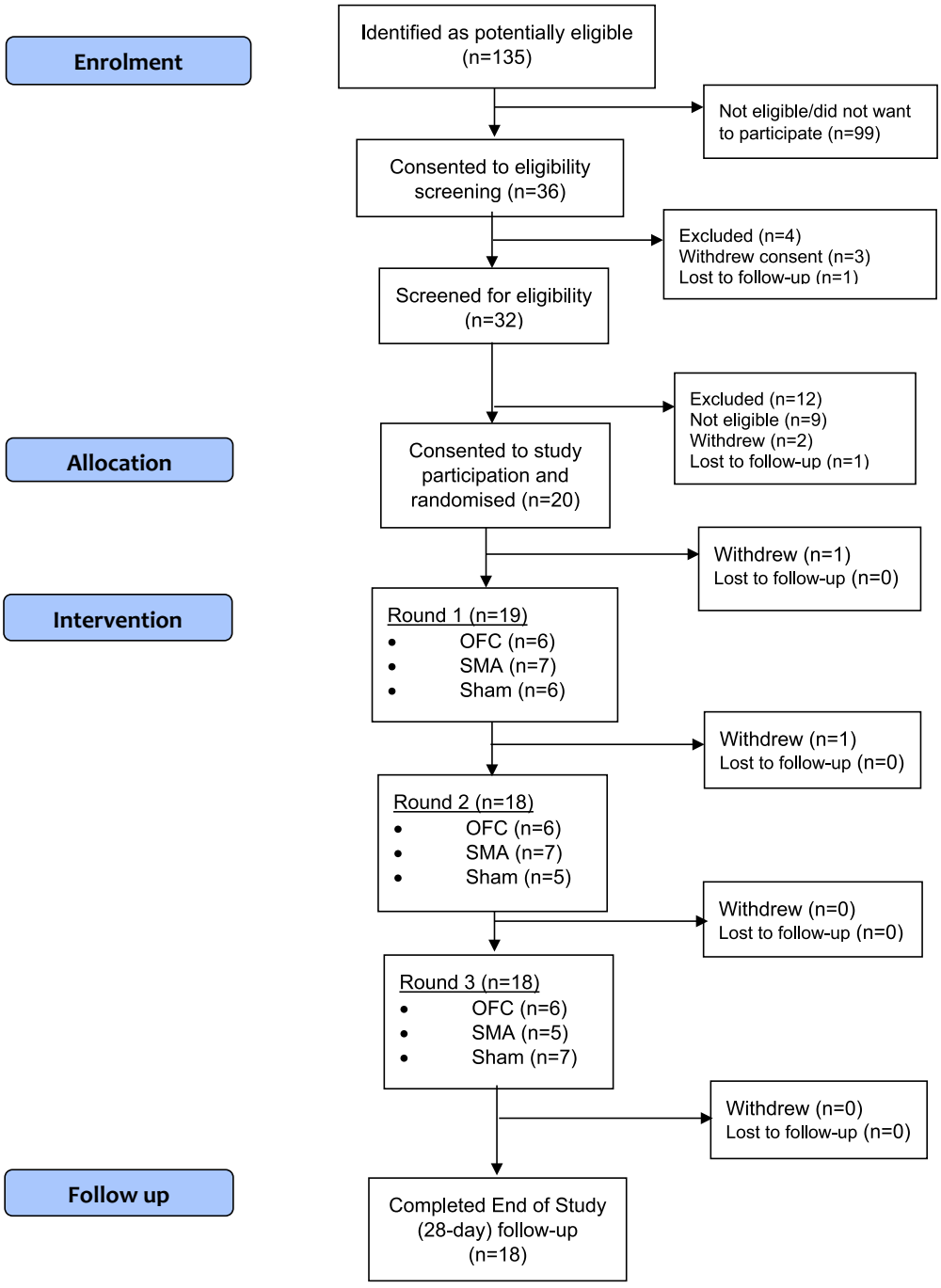

Fig. 1. Participant flow through the study.

rest of the session. The stimulation protocol followed expert safety recommendations [32] and a clinician was available out-of-hours on call for patients after the stimulation day in case of arising clinical concerns.

Participants were blinded to Sham or active stimulation, but not to stimulation site. The outcome assessments were performed by trained researchers who were fully blinded to site and active/sham stimulation. Unblinding was possible if deemed appropriate, e.g., in the case of an adverse event. No unblinding took place.

2.6. Assessments

The following assessments were used to gather baseline data:

- Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [57]
- Yale-Brown Obsessive Compulsive Challenge Scale (Y-BOCS Challenge) [62] which is designed for researchers or patients to evaluate short-lived changes in symptom severity using a visual analogue scale (see Supplementary materials)
- Montgomery-Åsberg Depression Rating Scale (MÅDRS) [63]
- Sheehan Disability Scale (SDS) [64]
- Clinical Global Impression Severity CGI—S) and Improvement (CGI—I) Scales [65]
- Barratt Impulsiveness Scale (BIS) [66]

Participants were assessed in person before each stimulation (baseline), and at 1, 2 and 4 h after each stimulation, over each two-day treatment round. Participants then received follow-up telephone assessments at 24 h, and 7, 14, and 28 days following the final tDCS

stimulation of each treatment round (following round 1 and 2, the 28th day acted as the baseline for the next treatment round).

Adverse events (AEs) were recorded at all visits, at each time point listed above except baseline on day 1 of each round (i.e., a total of 49 AE reporting opportunities per participant over the course of the study), using a questionnaire developed by Brunoni et al. [67] specifically for tDCS: this asks patients to rate 10 common AEs plus any others experienced, each on a scale of 1 (absent) to 4 (severe) and whether they were related to the treatment on a scale of 1 (unrelated) to 5 (definitely related). AEs listed as present but with missing 'relatedness' scores were assumed to be unrelated to the treatment conditions.

An optional semi-structured interview (see Table 1, Supplementary Materials) was conducted by a research assistant during the final follow-up (28 days) using a topic guide informed by existing literature and consultation with Patient Public Involvement (PPI) representatives. The interview explored impressions, benefits, problems, satisfaction, suggested improvements to the study, and participants' opinions about tDCS home use.[2]

A series of neurocognitive tests of behavioural inhibition, cooperation, and habit-learning were also performed during stimulation days: these will be reported separately, along with data from the BIS.

2.7. Data analysis

All statistical analyses were conducted using Stata/IC 15.1. Feasibility of recruitment was evaluated by the number of patients identified, screened, and randomised to the study as well as reasons for refusal to take part. The willingness of clinicians to recruit participants was evaluated by recording the number of patients referred by study site. The acceptability of tDCS was assessed via the ascertainment ratio, calculated as the number of patients randomised in relation to those potentially eligible for screening (target >10%), and the numbers of patients citing tDCS as the reason for refusal (target <20%) [52].

AEs rated as scoring ≥ 3/4 on the questionnaire [67] were considered severe. Acceptability, tolerability and adherence to tDCS and study assessments was quantified as the number of completed, shortened and missed sessions, assessments or responses, and the number of related AEs reported. Reasons for refusal to complete, or missed, treatment sessions were also recorded. Acceptability, tolerability, and practicality of applying tDCS in a clinical setting were also assessed via the optional end of study semi-structured interview exploring participants' experiences (see 2.6 and Table 1, Supplementary Materials).

The effect of tDCS on OCD symptoms was evaluated by comparing mean Y-BOCS, MADRS, CGI—S, and SDS scores across each of the three treatment rounds over the course of the study, evaluated as differences between treatment targets (OFC, SMA vs Sham), with the aim of providing an indication of the likely effect size for each active stimulation round. As the effect on OCD was expected to be short-lived, we chose the Y-BOCS rating occurring 24 h after the final stimulation of each treatment round (day 3) as the rating of maximum interest. A lower limit of the effect size of >0.1 was chosen a priori to indicate a positive signal to proceed to a definitive trial [52]. A period of 28 days between treatment rounds was deemed a suitable length of wash-out period such that effects from one stimulation site were unlikely to be present by the next treatment round. The small sample size and nature of the study (three treatment arms) meant that we did not have the statistical power to assess for any carry-over effect, so analyses assumed no such effect.

Additional analyses were performed, adjusting for baseline Y-BOCS scores. As the number of participants recruited was small, the study was not expected to have the power to evaluate with certainty the superiority of either stimulation target in terms of improving clinical symptoms, but we anticipated that it might provide an indication for favouring one target over the other (see 2.2).

Where possible, group differences were adjusted for participant age, gender and baseline Y-BOCS scores as fixed effects, with participant and time (measured in days) as random effects, through mixed modelling. The Y-BOCS Challenge scores were evaluated more frequently (hourly) to model symptom-change over time. Change over time was evaluated separately for the L-OFC and SMA targets, identifying the time-point at which the Y-BOCS Challenge was no longer different from pre-stimulation levels.

Table 1
Baseline Demographic and Clinical Characteristics of those entering the first treatment round.

Characteristic	N	
Age (years), mean (sd)	19	45 (16.6)
Male, N (%)	19	10 (52.6%)
Y-BOCS, mean (sd)	19	24.1 (5.2)
Y-BOCS Challenge, mean (sd)	19	12.5 (6.0)
MADRS, mean (sd)	19	17.2 (8.5)
SDS, mean (sd)	19	15.0 (7.2)
CGI-S, mean (sd)	19	4.0 (0.97)
Current medication, N (%)	19	15 (79.0%)
Symptom duration (years), mean (SD)	19	31.1 (19.7)

Note: sd: Standard Deviation, Y-BOCS: Yale-Brown Obsessive Compulsive Scale, MADRS: Montgomery-Åsberg Depression Rating Scale, SDS: Sheehan Disability Scale, CGI—S: Clinical Global Impressions Severity Scale.

[2] The inclusion of this question was an amendment to the original approved topic guide document.

2.8. Ethics committee approval

Cambridgeshire and Hertfordshire Research Ethics Committee approval was granted on 27th March 2019 (REC ref.: 19/EE/0046) and the study received Health Research Authority (HRA) approval to begin on 29th March 2019. This study was co-sponsored by the University of Hertfordshire and Hertfordshire Partnership Foundation NHS Trust.

3. Results

3.1. Feasibility of recruitment and willingness of clinicians to recruit participants

Fig. 1 shows the flow of participants through the study. A total of 135 patients were identified as being potentially eligible. Most participants were identified via clinicians (n = 106; 79%) and others were self-referrals via advertisement (n = 29; 21%).

The most common reasons for declining to take part included childcare duties, work commitments, personal circumstances, did not feel sufficiently symptomatic or in need of OCD support, or difficulty in commuting to the study site. Also reported, but not commonly, were patients being too unwell or unstable to take part, not being keen on the intervention or electrodes on the head, wanting to try alternative treatments (e.g., medication), and concern that study assessments would induce stress.

Of those identified as potentially eligible, 36 patients consented to eligibility screening. Prior to screening, three withdrew consent and one was lost to follow-up. Following screening, nine patients were excluded (other primary diagnosis n = 3, MADRS>30 n = 2, Y-BOCS≤20 n = 1, other n = 3), two declined to participate, and one was lost to follow up. Twenty participants were therefore randomised, 14 (70%) at the HPFT centre and 6 (30%) at Southampton (Ascertainment Ratio = 15% (20/135) – thus meeting our a priori target), although one randomised participant withdrew before the first treatment round. Participants entering treatment had a mean age of 45 (+/− 16.6) years, 10 were male and 9 female. Fifteen participants (79%) were taking stable doses of medication (13 SSRI +/− adjunctive psychotropic medication, 2 venlafaxine, 2 other medication). Table 1 shows the baseline characteristics

of participants in more detail.

3.2. Acceptability, tolerability and adherence to tDCS and study assessments

One of the 19 patients entering treatment withdrew after round 1, due to COVID-19-related anxiety, and another was unable to attend the second day of round 2 due to unconnected ill-health, but stimulation sessions were otherwise fully attended (overall ≥ 70% of treatment sessions were completed).

Of the 18 participants who completed the study, 12 completed the extra semi-structured interview at day 28 (see Table 1, Supplementary Materials).

3.3. Safety

No Serious Adverse Events (SAEs) were reported and there were no reports of patients contacting clinicians out-of-hours to raise concerns about possible AEs.

Table 2 shows the number of patients reporting AEs[3] (including severe AEs) across the whole study. Overall AEs were not common, reported on 6.3% of times when patients were asked. A total of 258 (41.8% of the total AEs reported) were judged to be unrelated to stimulation, the other 359 (58.2%) judged to be adverse device events (≥2 out of 5 on the 'related' aspect of the Brunoni scale). Severe AEs (≥3 on the Brunoni scale) were very infrequently reported (0.9% of time patients were asked): 38 (43.7%) of these were unrelated, and 49 (56.3%) were judged to be adverse device events.

AEs were recorded frequently throughout each treatment round, with an additional report on day 28 for round 3. This gave patients many opportunities to report AEs: 294 for OFC, 301 for SMA and 295 for Sham; a total of 890. Considering this high frequency of assessment over the course of the study, the number of reported AEs, including severe AEs, was small. Across all treatment rounds, sleepiness (18% of all possible reports), trouble concentrating (13%) and headaches (12%) were the most commonly reported AEs (Table 2). Acute mood change was reported on 33 occasions (3.7%), and 12 of these instances (1.3%) were severe: however, on an additional 24 occasions an acutely improved mood was noted, judged to be beneficial, and so these reports were excluded from the AE figures.

Reported AEs were numerically more common for OFC stimulation (243 AEs were listed [7.5% of possible reports] compared to 195 [5.9%] SMA and 179 [5.5%] Sham), noting that the 11 named AEs listed in the Brunoni scale, mean that AEs could have been reported 9790 times across all 890 reporting opportunities, i.e., a maximum of approximately 3200 for each treatment arm. However, there was no discernable difference in reports of severe AEs across the 3 treatment rounds (OFC 25 [0.8% of all possible reports], SMA 36 [1.1%], Sham 26 [0.8%]). The AEs reported as most common during active stimulation were tingling (4.2%), skin redness (5.6%) and burning sensation (2.4%), but the vast majority of reports were mild. On all occasions reported, the AEs spontaneously resolved, and none required any form of clinical intervention.

3.4. Practicality of applying tDCS in a clinical setting

The inconvenience of long periods spent in the clinic (around 8 h per day), lack of comfortable seating, limited access to food and drink, and boredom, were cited by some participants as disincentives to participating in the trial. Interest in home based tDCS as an alternative to clinic based tDCS was reported by some participants (see Table 1; Supplementary Materials).

When asked if participating had any benefit for their wellbeing, all participants responded positively. Three participants said that the distraction of attending the trial centre helped with their OCD symptoms. In particular, participants frequently commented that they felt comfortable and relaxed, both during and after the stimulation days.

3.5. The effect of tDCS on OCD symptoms

3.5.1. Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

The mean and standard deviation of the reported Y-BOCS scores by treatment round and time point are described in Tables 3 and Fig. 2.

The primary focus, in terms of efficacy, involved an analysis of Y-BOCS scores on Day 3 i.e., 24 h following the final stimulation of each two-day round of stimulation. Although there was no formal assessment for carry-over effects from one stimulation to the next, graphical representation of the mean YBOCS trajectory of each treatment combination (A-F) (available in supplementary materials) demonstrates that the effect of treatment generally did not exceed three days, where the interval between rounds was 28 days.

Table 3 shows Y-BOCS scores over time for all treatment rounds; Compared with baseline, mean within-round improvement in the Y-BOCS score at Day 3 was numerically greater for the OFC target than the SMA or sham (−3.7 Sham, −3.9 SMA, and − 6.6 for OFC). Moreover, the OFC target had a larger effect (−2.9, 95% CI -6.8 - 1.0, d = 0.5) on Y-BOCS than SMA (−0.2, 95% CI -3.6 - 3.1, d = 0.0) when compared with sham stimulation.

3.5.2. Yale-Brown Obsessive Compulsive Scale Challenge (Y-BOCS Challenge)

Table 4 and Fig. 3 show the Y-BOCS Challenge scores, which were completed on 12 occasions over the 2 days of each treatment round, and also at 7, 14 and 28 days after the final stimulation of each round. For each time point and treatment round, the statistical difference compared to baseline on the first day is reported. A mixed model was used across all time points, with adjustment for baseline time and baseline Y-BOCS challenge score.

On each stimulation day, Y-BOCS Challenge scores decreased when compared to baseline scores, across all treatment rounds. OFC stimulation showed a more consistent within-round decrease in Y-BOCS Challenge scores over time than both the SMA and the OFC ($p < 0.01$ at all but one time point). Symptom reduction following OFC stimulation was also sustained for longer, with a significant reduction compared with baseline at the last evaluation of the second day ($p < 0.01$) following OFC but not SMA or sham stimulation. However, by Day 3 the Y-BOCS challenge scores were not significantly different from baseline in any treatment round (we note that this is not the case for the full Y-BOCS assessment for the OFC).

3.5.3. Montgomery-Åsberg Depression Rating Scale (MADRS)

Mean MADRS scores are reported in Table 5 and Fig. 4. There was an initial significant within-round improvement from baseline in mean total MADRS across all three treatment rounds, which returned to near baseline values by Day 28. The effect of stimulation of the OFC target was sustained for longer than the effect of stimulation of the SMA. Stimulation of the OFC demonstrated a consistent advantage over Sham in terms of reduction in MADRS scores for 7 days (−3.8, 95% CI -7.7, 0.0) compared with the SMA which was only sustained for 3 days (−4.7, 95% CI -8.6, −0.7).

[3] On reflection, the method by which AEs were recorded was not ideal. Each patient was asked each time they completed a follow-up assessment (52 times) whether they were experiencing an AE (52 × 19 = 988 total AE recordings). As these recordings were frequently spaced apart by only one or two hours, the same AE (e.g., headache, tiredness) may have been reported on multiple occasions. The number and proportion of reported AEs are therefore likely to be an overestimate of the true number of events experienced by patients.

Table 2
Total and Severe (3+) Reported Adverse Events (AEs) by Treatment Condition.

	Total		OFC		SMA		Sham	
	All	Severe	All	Severe	All	Severe	All	Severe
AE by Type (Brunoni)								
Headache	107 (12.0%)	18 (2.0%)	31 (10.5%)	4 (1.4%)	41 (13.6%)	9 (3.0%)	35 (11.9%)	5 (1.7%)
Neck pain	24 (2.7%)	1 (0.1%)	12 (4.1%)	1 (0.3%)	8 (2.7%)	0 (0.0%)	4 (1.4%)	0 (0.0%)
Scalp pain	9 (1.0%)	0 (0.0%)	4 (1.4%)	0 (0.0%)	5 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tingling	37 (4.2%)	5 (0.6%)	15 (5.1%)	1 (0.3%)	16 (5.3%)	4 (1.3%)	6 (2.0%)	0 (0.0%)
Itching	7 (0.8%)	1 (0.1%)	1 (0.3%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	5 (1.7%)	1 (0.3%)
Burning Sensation	21 (2.4%)	1 (0.1%)	12 (4.1%)	1 (0.3%)	8 (2.7%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Skin redness	50 (5.6%)	3 (0.3%)	34 (11.6%)	1 (0.3%)	14 (4.7%)	2 (0.7%)	2 (0.7%)	0 (0.0%)
Sleepiness	165 (18.5%)	28 (3.1%)	52 (17.7%)	9 (3.1%)	53 (17.6%)	10 (3.3%)	60 (20.3%)	9 (3.1%)
Trouble concentrating	116 (13.0%)	15 (1.7%)	46 (15.6%)	4 (1.4%)	29 (9.6%)	6 (2.0%)	41 (13.9%)	5 (1.7%)
Acute mood change	33 (3.7%)	12 (1.3%)	8 (2.7%)	2 (0.7%)	10 (3.3%)	4 (1.3%)	15 (5.1%)	6 (2.0%)
Others	48 (5.4%)	3 (0.3%)	28 (9.5%)	2 (0.7%)	10 (3.3%)	1 (0.3%)	10 (3.4%)	0 (0.0%)
Total AEs	617 (6.3%)	87 (0.9%)	243 (7.5%)	25 (0.8%)	195 (5.9%)	36 (1.1%)	179 (5.5%)	26 (0.8%)
Unrelated AE	258	38	60	6	112	19	86	13
Adverse Device Effects	359	49	183	19	84	17	92	13

Note: AEs were recorded multiple times throughout each treatment round, with an additional collection on day 28 for round 3, giving a total of 890 possible reporting timepoints (OFC 294, SMA 301, Sham 295). As there are 11 possible types of AE at each report, there was potential for $890 \times 11 = 9790$ total AE reports. We record the total number of reports, rather than the total number of events. As each event (e.g., a headache) may have been reported on several ocasions, the number of reported events are therefore described as a percentage of the number of reporting opportunities.
OFC: orbitofrontal cortex, SMA: supplementary motor area, AE: Adverse Event.
'Severe' based on scores of 3 or more on a 4-point scale and Adverse Device Effects are those rated 2 or more on a 5-point scale, both according to Brunoni scale. Conditions listed as present but with related scores missing were assumed to be unrelated to the treatment.

Table 3
Observed Y-BOCS scores over time (including adjusted difference at Day 3).

	Y-BOCS; Mean (SD)			OFC-Sham		SMA-Sham	
	OFC	SMA	Sham	Mean (95% CI)	d (95% CI)	Mean (95% CI)	d (95% CI)
Baseline	24.5 (3.6)	23.3 (7.0)	22.9 (5.6)				
Day 2	19.1 (7.8)	20.5 (5.7)	20.8 (6.9)				
Day 3 (24 h)	17.9 (7.5)	19.4 (7.3)	19.2 (7.9)	-1.2 (−3.6,1.2)	−0.2 (−0.8,0.5)	0.2 (−1.6,2.7)	0.0 (−0.6,0.7)
Difference (compared with baseline)	−6.6 (6.5)	−3.9 (5.1)	−3.7 (4.8)	−2.9 (−6.8, 1.0)	−0.5 (−1.2, 0.2)	−0.2 (−3.6, 3.1)	0.0 (−0.7, 0.6)
Day 7	21.3 (6.2)	21.5 (6.0)	19.9 (7.3)				
Day 14	21.1 (6.0)	20.5 (6.4)	21.4 (6.0)				
Day 28	22.0 (6.3)	21.6 (5.3)	22.8 (5.8)				

Y-BOCS: Yale-Brown Obsessive Compulsive Scale, OFC: orbitofrontal cortex, SMA: supplementary motor area.

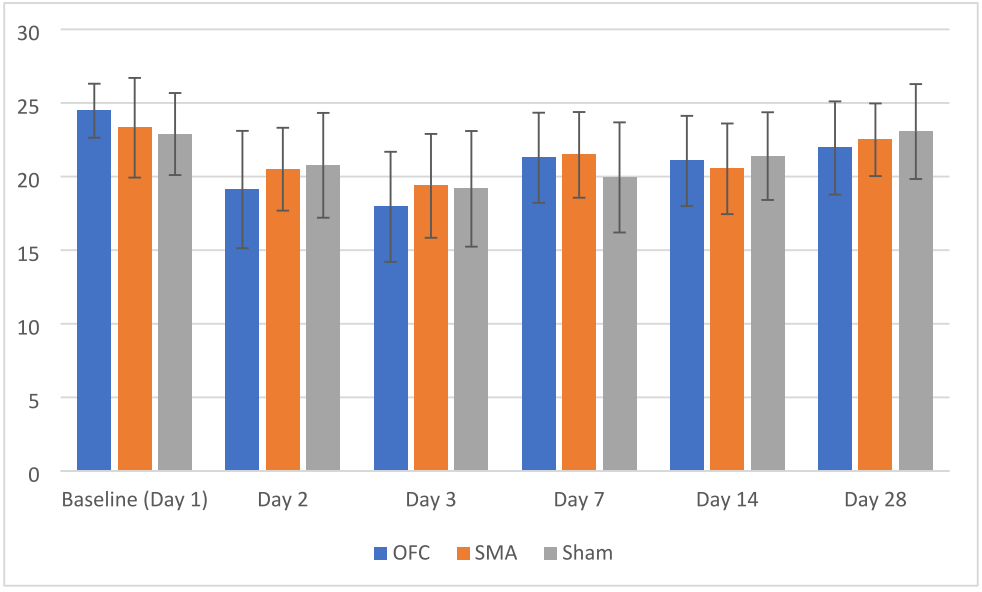

Fig. 2. Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) Mean Score (95% Confidence Interval error bars) by Treatment Arm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Y-BOCS Challenge Scores over time for each treatment round by treatment target.

		Study Arm, mean (SD)		
		OFC	SMA	Sham
Day 1	Baseline	13.1 (6.9)	11.4 (6.6)	12.5 (6.2)
	1 h	8.6** (5.3)	9.2* (6.9)	8.7** (5.7)
	2 h	7.2** (5.8)	9.5 (6.1)	10.6 (6.5)
	4 h	7.8** (6.8)	9.1* (6.3)	8.4** (5.9)
	1 h	7.8** (5.9)	7.9** (5.9)	8.2** (4.8)
	2 h	6.3** (6.0)	7.5* (6.5)	8.2** (6.0)
	4 h	9.4** (6.4)	9.1* (6.1)	8.3** (6.4)
Day 2	Baseline	11.2 (6.7)	13.2 (5.5)	13.0 (6.7)
	1 h	8.5** (6.4)	9.5* (6.8)	8.5** (5.6)
	2 h	7.9** (6.4)	9.1* (6.3)	8.1** (4.9)
	4 h	10.1 (6.8)	10.8 (7.1)	9.9 (7.7)
	1 h	7.6** (5.0)	9.2* (6.9)	9.7* (7.5)
	2 h	7.8** (5.8)	8.6* (5.8)	9.8 (6.6)
	4 h	8.6** (5.5)	10.6 (6.6)	10.2 (7.1)
Day 3 (24 h)		11.4 (8.0)	11.8 (6.2)	11.3 (7.0)
Day 7		12.7 (8.2)	12.8 (6.4)	12.3 (5.7)
Day 14		12.4 (7.8)	12.0 (6.8)	12.6 (5.6)
Day 28		12.3 (6.6)	12.0 (6.6)	12.8 (7.7)

Note: Differences from baseline on each day are identified as *p < 0.05, **p < 0.01 (paired t-tests).
Y-BOCS Challenge: Yale-Brown Obsessive Compulsive Challenge Scale, OFC: orbitofrontal cortex, SMA: supplementary motor area. The 28-day score is the baseline for the subsequent treatment round, apart from the last round.

3.5.4. Sheehan Disability Scale (SDS) and Clinical Global Impression Severity (CGI—S) and Improvement Scales (CGI—I)

SDS scores (Table 6) decreased in all treatment rounds, but with less variation than in Y-BOCS and MADRS values. Changes in SDS score with OFC, SMA and Sham were broadly similar, with Day 28 scores slightly lower than those at Baseline (OFC 13.7 [SD 5.8] to 12.7 [SD 6.8]; SMA 13.8 [SD 7.5] to 12.7 [SD 5.9]; Sham 13.7, [SD 7.4] to 11.9 [SD 7.2]).

The CGI-S (Table 6) improved marginally by day 2 and was sustained to day 14. The improvement for the OFC and SMA targets at day 3 was similar (0.23 and 0.22, respectively). The CGI-I reported improvement across all arms which was sustained to Day 28.

4. Discussion

FEATSOCS is the first study to test the two most promising tDCS approaches for OCD (cathodal stimulation of L-OFC and SMA) head-to-head in a sham-controlled RCT. The cross-over design allowed within-patient comparisons for each treatment. This design was more efficient in resources than a similar sized, parallel group trial in which each subject is exposed to only one treatment. The 2-day rounds of tDCS were spaced a minimum of four weeks apart to avoid any potential carry-over effects, which we observed, and to allow for the duration of effect to be evaluated. Prior studies had indicated that this procedure is tolerated

Table 5
MADRS Mean Scores by Treatment Target.

	MADRS; Mean (sd)			Difference (95% CI) adjusted	
	OFC	SMA	Sham	OFC-Sham	SMA-Sham
Baseline	16.1 (9.0)	16.0 (8.5)	15.7 (7.7)		
Day 3 (24 h)	9.7** (8.2)	11.3** (6.8)	11.0** (8.7)	−5.8 (−9.7, −1.9)#	−4.7 (−8.6, −0.7) #
Day 7	11.4* (8.2)	13.7 (7.3)	12.4* (7.6)	−3.9 (−7.8, 0.0) #	−2.8 (−6.7, 1.1)
Day 14	12.7* (9.0)	12.4* (7.9)	12.2 (8.3)	−3.8 (−7.7, 0.0)	−2.7 (−6.6,1.2)
Day 28	13.5 (8.7)	13.5 (7.8)	15.1 (7.6)	−2.2 (−6.1, 1.7)	−1.0 (−4.9, 2.9)

Note: Differences from Baseline are identified as *p < 0.05, **p < 0.01 (paired t-tests). Differences between groups identified as #p < 0.05. Difference adjusted for baseline characteristics (age and baseline MADRS). SD: standard deviation, MADRS: Montgomery-Åsberg Depression Rating Scale, SDS: Sheehan Disability Scale, OFC: orbitofrontal cortex, SMA: supplementary motor area.

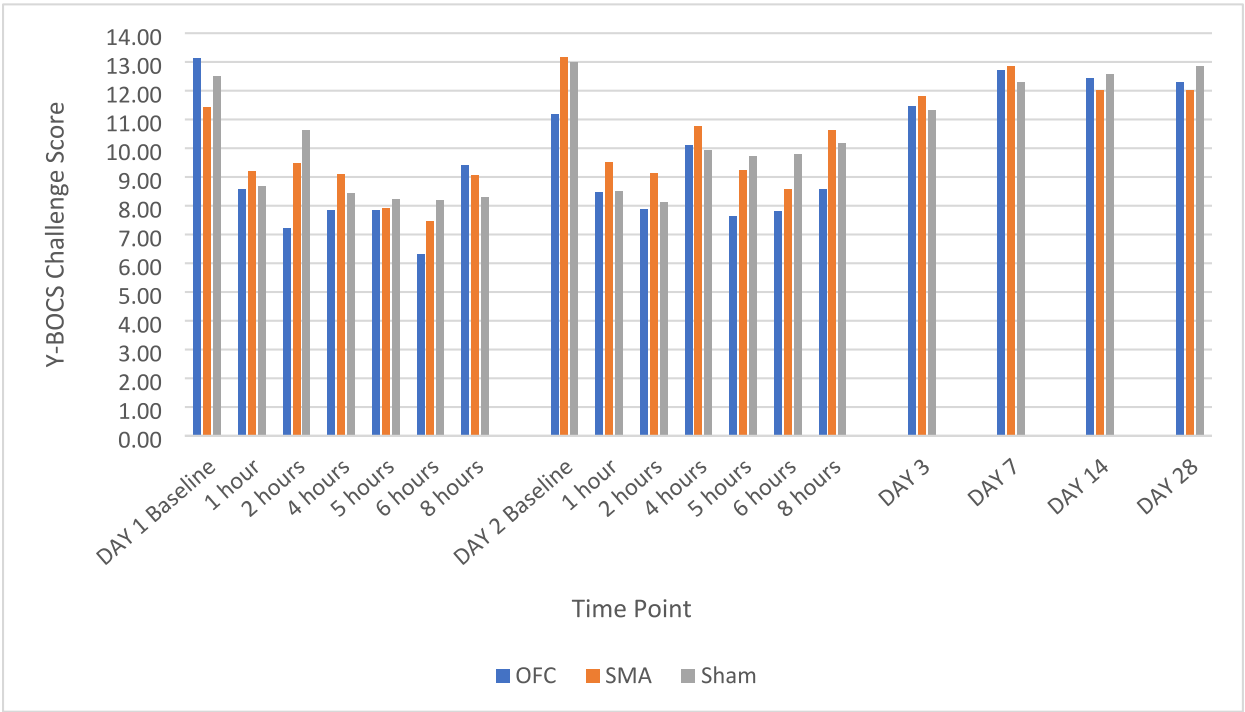

Fig. 3. Y-BOCS Challenge Scores over time for each treatment round by treatment target. Y-BOCS Challenge: Yale-Brown Obsessive Compulsive Challenge Scale, OFC: orbitofrontal cortex, SMA: supplementary motor area. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

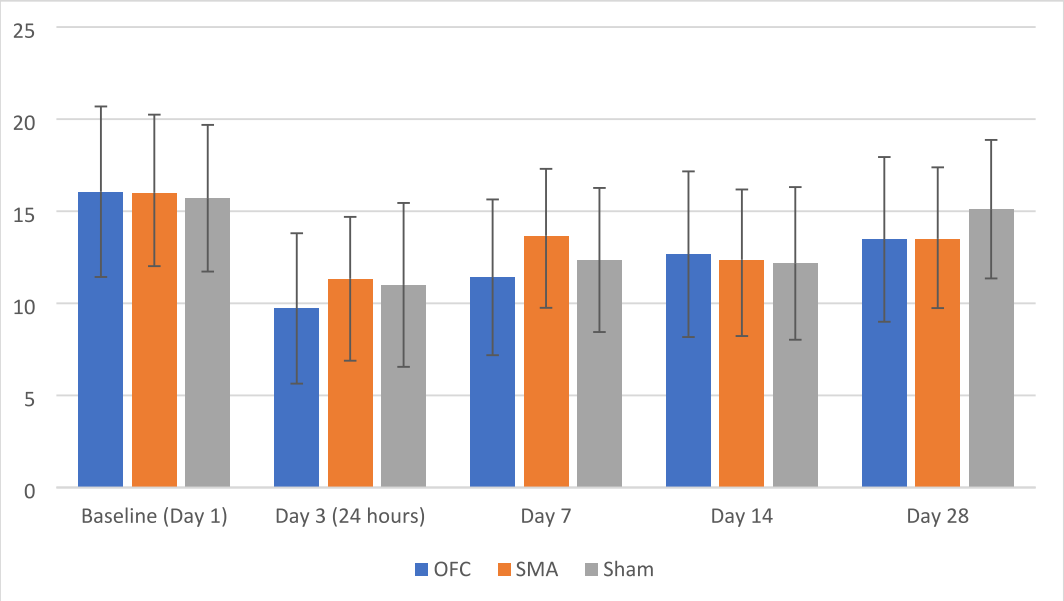

Fig. 4. Montgomery and Åsberg Depression Rating scale (MADRS) Mean Score (95% Confidence Interval error bars) by Treatment Arm.

Table 6
Sheehan Disability Scale and Clinical Global Impression Scale Scores by Treatment Target.

SDS; Mean (SD)			
	OFC	SMA	Sham
Baseline	13.7 (5.8)	13.8 (7.5)	13.7 (7.4)
Day 3 (24 h)	10.4 (7.2)	12.2 (7.3)	10.4 (8.1)
Day 7	10.6 (7.0)	12.5 (7.0)	9.6 (7.0)
Day 14	11.4 (7.0)	10.9 (8.1)	13.2 (7.7)
Day 28	12.7 (6.8)	12.7 (5.9)	11.9 (7.2)
CGI-S; Mean (SD)			
	OFC	SMA	Sham
Baseline	4.06 (0.73)	3.95(1.03)	4.00 (0.97)
Day 2	3.89 (0.68)	4.00 (0.84)	3.89 (0.90)
Day 3 (24 h)	3.83 (0.79)	3.89 (0.76)	3.78 (1.00)
Day 7	3.89 (0.76)	3.84 (0.83)	3.83 (0.86)
Day 14	3.89 (0.68)	3.79 (0.79)	3.88 (0.99)
Day 28	4.33 (0.82)	3.60 (0.55)	3.57 (0.79)
CGI-I; Mean (SD)			
	OFC	SMA	Sham
Day 2	3.28 (0.75)	3.72 (0.83)	3.67 (0.69)
Day 3 (24 h)	3.72 (1.07)	3.67 (0.84)	3.39 (0.98)
Day 7	3.72 (0.75)	3.89 (1.08)	3.72 (0.83)
Day 14	4.00 (0.77)	3.79 (0.54)	3.76 (0.90)
Day 28	4.00 (0.00)	4.00 (0.71)	3.57 (1.27)

Note: SDS: Sheehan Disability Scale. CGI—S: Clinical Global Impression Severity Scale, OFC: orbitofrontal cortex, SMA: supplementary motor area, CGI—I: Clinical Global Impression Scale for Improvement.

well by participants with mental disorders, with reliability of sham procedures [31–33,36,37,61,68].

Our findings indicate that a progression to a subsequent study is merited. The principal findings are that patients were willing to engage in the treatment (few refused to participate in the study for reasons related to neurostimulation per se), and that tDCS is an acceptable and safe treatment for use by patients with OCD (study adherence was excellent, premature discontinuations were few and the adverse event profile was benign). In line with research recommendations in the field [69], we systematically assessed and recorded, using standardised tools, reports of AEs and discontinuation rates and reasons, to evaluate the safety and tolerability of tDCS among OCD patients who are known to be sensitive and risk-averse. Ratings for AEs took place at each rating point, including at hourly intervals during stimulation. There were no serious adverse effects and although AEs of varying severity were reported over the course of the study, particularly headaches, drowsiness and trouble concentrating (experienced by patients during both active and sham stimulations equally), there was little difference in frequency or intensity of reported AEs between active and sham interventions. Furthermore, most AEs were judged as mild in severity, all were short-lived, and none required any form of medical intervention. Finally, no study discontinuations were related to AEs, suggesting active tDCS is well tolerated in this patient group.

Most participants were recruited via clinicians (79%), and the ascertainment ratio was approximately 15%, indicating that recruitment to a definitive multi-centre national study is feasible. Moreover, the study protocol was conducted in a clinical setting, during a global pandemic, with only one participant missing one planned stimulation session, and premature withdrawals ($n = 2$) were few, indicating adequate adherence to and tolerability of tDCS and study assessments.

Comments about participating in the study and about the intervention itself, in terms of acceptability and tolerability, were strongly positive and reflective of the sense of purpose that taking part provided. Participants generally felt comfortable and relaxed during the study, although they found the two-day commitment in clinic onerous. Although there is lack of agreement on the optimal tDCS protocol for OCD, most definitive tDCS studies deliver of the order of 20 tDCS sessions. Therefore, other treatment options, including single daily sessions delivered over a more prolonged period of several week (e.g. [49]), merit consideration. Interest in home based tDCS as an alternative to clinic based tDCS was reported by some participants (see Table 1; Supplementary Materials). Thus, a transition to home-based use of tDCS could be explored in future research to reduce participant burden and to encourage self-management of OCD.

Taking the Y-BOCS at 24 h after the final stimulation of each treatment round (labelled as Day 3) as the key metric, there was an immediate effect on OCD symptoms of moderate size in the L-OFC target ($d = -0.5$, 95% CI -1.2 to 0.2, $p = 0.063$), which, though not statistically significant, nevertheless exceeded our a priori threshold ($d > 0.1$) to proceed to a definitive trial. In contrast, the effect of SMA stimulation did not numerically differentiate from sham. A similar pattern of differential responses was seen in other relevant clinical outcomes following OFC stimulation, including the Y-BOCCS measuring short lived changes in obsessive-compulsive symptoms and the MADRS, producing short-lived but significant improvements in core depressive

symptoms. In contrast, the positive effects of SMA stimulation on secondary outcomes were more subtle and short-lived. The L-OFC therefore constitutes the more promising stimulation target in terms of OCD symptom change for confirmation in future tDCS studies.

However, considering that the mechanism of effect of tDCS at the SMA is likely to be different from that at the OFC, the course of stimulation and follow-up in our study was very short, and other studies have shown a delayed response for tDCS [70,71], including one other study of cathodal SMA stimulation showing a statistical separation from sham on the Y-BOCS only at the week 12 assessment [49], we may infer that SMA stimulation may also qualify for further study, and that longer stimulation and follow up periods are likely to be required for this cortical target.

The finding of acute improvement in obsessive-compulsive symptoms together with depressed mood is reminiscent of the almost immediate improvement in Y-BOCS and MADRS seen following deep brain stimulation (DBS) of the ventral capsule/ventral striatum in highly treatment-resistant patients with OCD [72]. Indeed, perioperative brain imaging in that study suggested that VC/VS DBS modulates electrical activity within the affective cortico-striatal loop, extending to the OFC and anterior cingulate cortex. Our findings therefore hint that tDCS of the L-OFC may produce these clinical improvements by stimulating the same or similar affective cortico-striatal circuitry, via non-invasive targeting of a cortical node within this circuit.

The mechanism mediating the effects of tDCS are not well understood but may involve changes in neurocognitive processing (measurable via standardised tasks), functional connectivity (measurable via resting state fMRI), regional cerebral blood blow (measurable via PET), γ-amino-butyric acid/glutamine ratio (measurable using magnetic resonance spectroscopy) or changes in alpha, beta, gamma synchronisation (measurable using EEG, MEG) [73–76]. Future studies assessing parameters such as these may shed further light on the mechanisms of effect of tDCS, and act as a step toward personalising clinical care.

The effect of L-OFC stimulation was relatively short-lived and was not evident on the Y-BOCS beyond Day 3 (24 h post stimulation). Nevertheless, it should be noted that the effect of tDCS on depressive symptoms measured through the MADRS was more sustained compared to the effect on obsessive-compulsive symptoms (Y-BOCS) and was present up to day 14. This finding may be expected, as clinical improvement in obsessive-compulsive symptomatology is more difficult to achieve compared with improvement in depressive symptoms.

These findings suggest that treatments may need to be delivered at least daily or even more frequently to derive maximal sustained benefit. tDCS research in other psychiatric conditions such as depression and schizophrenia also suggests that enhanced stimulation protocols (e.g., higher frequency, more sessions) and use of maintenance sessions may improve clinical outcomes and duration of effects [77,78], although the optimal frequency and duration of stimulation have not been established. Further research directed at these questions is warranted as they will have major implications for clinical service delivery, for example, consideration of self-managed, home-based stimulation, to reduce participant-burden and strengthen self-management approaches for this chronic debilitating disorder.

Study limitations include the relatively small sample size, which meant the study was not powered to detect a statistical difference between interventions, short course of stimulation, reliance on ‘standard’ tDCS rather than the use of high definition tDCS to ‘sharpen the focus’ of stimulation, and inability to use MRI mapping for personalising electrode placement. Hence, the analysis is primarily descriptive in nature. Our semi-structured interview assessing acceptability factors was optional, and completed by only two thirds of the study sample. Nevertheless, FEATSOCS complements and extends the published and ongoing efficacy studies in the field by employing a blinded tDCS stimulation protocol that allowed direct comparisons to be made across two different stimulation targets in a study sample with well-defined characteristics, generalisable to other treatment-seeking patients with OCD.

To strengthen the veracity of the sham control, we did not allow any discussion between the blinded rater, the participants and the research clinician administering the intervention, who was not blinded. In addition, the sham setting included a very brief initial period of current “ramp up”, enabling the initial cutaneous sensations associated with stimulation, whilst the current then remained off for the rest of the session. However, we did not encourage patients to guess whether they were taking active or sham treatment, as we considered that this could increase the risk of the blind being broken. Therefore, we do not have subjective report data to confirm how effective the blinding actually was. Nevertheless, as it has previously been shown that blinding integrity of tDCS is mainly associated with efficacy rather than blinding failure [61], and as between-arm differences in clinical improvements were small [59], we can be reasonably confident that the observed clinical effects were not unduly affected by blinding failures.

Our study sample had stable illness mainly of mild-moderate severity and of long duration (mean duration of symptoms around 30 years). Although they were not specifically selected as a treatment resistant group, the majority (79%) was receiving treatment with medication, which was kept stable throughout the study. Research to date suggests multiple classes of medications may impact tDCS effects, although the exact mechanisms of interaction remain unclear [73]. Hence further sub-group analysis and mechanistic studies are encouraged aiming at better identifying responders' characteristics and possible predictors of response.

5. Conclusion

Our principal findings are that tDCS is safe and acceptable for use by patients with OCD. Obsessive-compulsive symptoms and mood were improved across all intervention groups until 24 h after the final stimulation. Though OCD symptom-changes were not statistically significant the greatest effect was seen in the L-OFC arm, suggesting this represents the most promising stimulation target. Our findings indicate that progression to a definitive trial, ideally including translational measures to detect the underpinning brain-based mechanisms, is warranted.

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Declaration of Competing Interest

Prof. Naomi Fineberg reports in the past 3 years she has held research or networking grants from the UK NIHR, COST Action, Orchard; accepted travel and/or hospitality expenses from the BAP, ECNP, RCPsych, CINP, International Forum of Mood and Anxiety Disorders, World Psychiatric Association; received payment from Elsevier for editorial duties and the Mental Health Academy for lecturing. Previously, she has accepted paid speaking engagements in various industry supported symposia and recruited patients for various industry-sponsored studies in the field of OCD treatment. She leads an NHS treatment service for OCD. She holds Board membership for various registered charities linked to OCD. She gives expert advice on psychopharmacology to the UK MHRA. She has participated in a WHO working group focussing on diagnosis and classification of obsessive compulsive or related disorders for the ICD-11.

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Pellegrini have no competing interests to declare.

Prof. Trevor W Robbins provides consultancy for Cambridge Cognition and receives royalties for CANTAB. He offers consultancy for Arcadia, Takeda, Cassava, Greenfield Bioventures. He has received research grants from Shionogi and GlaxoSmithKline. He has received Editorial Honoraria from Springer, Nature and Elsevier.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2023.152371.

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