

tDCS for Inhibitory Control Deficits: A Test in OCD. Alternate title (Consent Form):
Transcranial Direct Current Stimulation Augmented Exposure and Response Prevention
for Obsessive-Compulsive Disorder

NCT02329587

II. DESCRIPTION OF STUDY

A. Specific Aims

The long-term goal of this research program is to leverage a well-developed body of literature on the neural basis of response control to develop more effective treatment approaches for patients with deficits in behavioral inhibition. The overall objective of this project, which is the first step toward this long-term goal, is to evaluate feasibility, acceptability, and preliminary efficacy of transcranial direct current stimulation (tDCS) over right inferior frontal gyrus (rIFG) as an adjunct to exposure and response prevention (ERP) for obsessive-compulsive disorder (OCD) patients. The rationale for this proposal is that effectively enhancing inhibitory control in OCD patients may allow them to better engage in ERP, resulting in improved treatment outcomes. The objectives will be achieved by pursuing these specific aims:

Aim 1: Establish feasibility and acceptability of research procedures and clinical intervention.

Hypothesis: Patients with OCD will tolerate this combined ERP + tDCS treatment and will find it acceptable, as determined by rates of retention, treatment completion, and patient report.

Aim 2: Gather evidence on preliminary efficacy of tDCS over rIFG as an adjunct to ERP for OCD.

Hypothesis: Patients in the group receiving ERP + active tDCS will show greater reduction in symptom severity over 10 sessions of the combined treatment than those receiving ERP + sham tDCS.

Aim 3: Characterize the relationship between measures of inhibitory control and outcome of the combined intervention.

Hypotheses: a) Response inhibition, as measured by the stop signal task (SST), will improve more after ERP plus active vs sham tDCS; b) Improvement in OCD severity will correspond to improved inhibitory control on the SST; and c) Patients receiving ERP plus active tDCS will report less difficulty inhibiting compulsions during ERP exercises than those receiving ERP plus sham tDCS.

B. Background

Deficient inhibitory control is a hallmark of many types of psychopathology, including attention deficit hyperactivity disorder, substance abuse and dependence, and obsessive-compulsive and related disorders. As of yet, there are no established interventions broadly targeting deficits in inhibitory control. Addressing inhibitory control deficits is now a tractable problem. The neurocircuitry underlying behavioral inhibition is becoming increasingly well understood while, simultaneously, non-invasive methods of modulating brain functioning, such as transcranial direct current stimulation (tDCS) are seeing a resurgence in both clinical and research settings. The time is right to begin leveraging findings in neuroscience to develop a neurocircuit-based method to address disorders of inhibitory control.

Obsessive-compulsive disorder (OCD) patients are one group with well-established deficits in behavioral inhibition. The ritualistic compulsions which characterize this disorder clearly indicate difficulty with inhibitory control. In inhibition paradigms, OCD patients consistently perform worse than healthy individuals on tasks requiring inhibition of a prepotent response (e.g., stop-signal task, go/no-go task). A recent study by Gillan et al. also found that patients with OCD continue responding in a way they have learned will avoid punishment despite explicit knowledge that punishment is no longer possible.

Paradoxically (given these deficits), successful inhibitory control is also an essential component of the first-line psychosocial treatment for OCD – exposure and response prevention (ERP). During ERP, patients face situations which trigger irrational fear or discomfort (i.e., exposure), while simultaneously inhibiting their compulsions (i.e., response prevention). ERP is effective at reducing symptom severity for many patients who complete a full course of the treatment; however, few patients are “cured” of their symptoms following ERP and many patients are unwilling or unable to complete a full course of this challenging treatment. Although this is the best known treatment, it is, unfortunately, far from perfect in its outcomes.

Enhancing inhibitory control via non-invasive neurostimulation may improve the efficacy and efficiency of ERP for OCD. The right inferior frontal gyrus (rIFG) is a particularly promising target for such an approach. This region is a key node in neurocircuitry underlying inhibition of a prepotent response. The location of rIFG makes it easily accessible to tDCS, a type of non-invasive neurostimulation delivering a weak electrical current (1-2 mA) via two electrodes placed on the scalp. Neurostimulation via tDCS modulates neuronal excitability by changing membrane potentials and can enhance behavioral plasticity. In healthy individuals, tDCS over rIFG improves inhibitory control of a prepotent response during the SST, a well-established response inhibition paradigm. Such effects have been seen after a single tDCS session, and when stimulation over rIFG was delivered during a course of inhibition training sessions over four days. We propose to extend this approach by coupling tDCS and behavioral training, i.e., ERP, to inhibit compulsive behaviors in OCD.

C. Experimental Method

1. Brief Description of Subjects

For the TIES (Therapy Integrating Exposure and Stimulation) study we will recruit 32 patients with a primary diagnosis of OCD, aged 18-65, with clinically significant OCD symptoms (Y-BOCS total score of ≥ 16). Participants will be naïve to tDCS and will never have completed a minimally adequate trial of ERP (see human subjects section below for additional inclusion/exclusion criteria).

2. Study Design

For this study we will recruit 32 patients with a primary diagnosis of OCD. Each participant will undergo an assessment which will include a structured clinical interview, brief assessments of depression, anxiety, OCD symptoms, and medication and treatment history. Participants will be randomized to one of two combination interventions: Exposure and response prevention (ERP) plus active transcranial direct current stimulation (tDCS) over right inferior frontal gyrus (rIFG) or ERP plus sham tDCS over rIFG. Each group will complete 1 session of psychoeducation and treatment planning, followed by 10 90-minute sessions of their assigned combination intervention. Participants will also complete a post-treatment and one month follow-up assessment.

3. Specific Procedures or Treatments

Screening. Interested individuals will be screened via brief telephone interviews and those meeting entry criteria will be invited to participate. After providing informed consent to trained study personnel, patients will complete a thorough screening interview which will include the following measures: the Structured Clinical Interview for DSM-IV (SCID-IV) will be used to verify a DSM-IV diagnosis of OCD, as well as to assess for comorbid Axis I diagnoses which constitute exclusion from the study (see “Participants”). We will supplement the SCID by asking a few additional questions as part of the semi-structured interview to assess new specifiers added to the DSM-5 OCD diagnosis (e.g., tic-related OCD and absent insight) ; a modified version of the OCD Database,⁴¹ a semi-

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structured clinical interview, will be used to gather information about demographic and clinical features of OCD and assess medication and treatment history; the Hoarding Rating Scale will be used to assess any hoarding symptoms endorsed on the Y-BOCS-SC; the Yale-Brown Obsessive Compulsive Scale -- Symptom Checklist (Y-BOCS-SC), a 58-item checklist, will be used to assess presence/absence of specific current and past OCD symptoms^{43, 44}; the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) will be used to assess OCD symptom severity^{43, 44}; the Beck Depression Inventory-II (BDI-II)⁴⁵ will be used to assess depressive symptoms, including suicidality; the Cognitive-Behavioral Treatment History Form (Abramowitz, 2006), will be used to assess whether a patient has had an adequate course of CBT for OCD.

Table 1. Schedule of Assessments

| Assessment | Scr | BL | Psychoed/ Planning | Sn1 | Sn2 | Sn3 | Sn4 | Sn5 | Sn6 | Sn7 | Sn8 | Sn9 | Sn10 | PT | 1M |
|-----------------------|-----|----|-----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|----|----|
| SCID-IV | X | X | | | | | | | | | | | | | |
| OCD Database | X | | | | | | | | | | | | | | |
| Med. History | X | | | | | | | | | | | | | | |
| Hoarding Rating Scale | X | | | | | | | | | | | | | | |
| Y-BOCS-SC | X | | | | | | | | | | | | | | |
| Y-BOCS | X | X | | X | | X | | X | | X | | X | | X | X |
| BDI | X | X | | X | | X | | X | | X | | X | | X | X |
| BAI | | X | | X | | X | | X | | X | | X | | X | X |
| PEAS | | | | X | X | X | X | X | X | X | X | X | X | | |
| SST | | X | | | | | | | | | | | | X | X |
| CSQ-8 | | | | | | | | | | | | | | X | X |
| Inhibition VAS | | | | X | X | X | X | X | X | X | X | X | X | | |
| SAFTEE-SI | | X | | X | | X | | X | | X | | X | | X | X |
| FMPS | | X | | | | | | | | | | | | X | X |
| POPS | | X | | | | | | | | | | | | X | X |
| OBQ | | X | | | | | | | | | | | | X | X |
| IUS | | X | | | | | | | | | | | | X | X |
| OC-TCDQ | | X | | | | | | | | | | | | X | X |

Scr=screen, BL= baseline, Sn=Session, PT=Post-treatment, 1M=1month follow-up

Monitoring Assessments.

To monitor for symptom change, short assessments will be given at baseline, and approximate weekly (see Table 1) during treatment (for clinical symptoms monitoring), post-treatment, and 1-month after treatment, using the Y-BOCS^{43, 44}; BDI-II⁴⁵ (see "Screening," above); and the Beck Anxiety Inventory (BAI),⁴⁶ to assess general anxiety symptoms. The

Patient Ex/RP Adherence Scale (PEAS)⁴⁷ will be used at each ERP session to assess adherence to ERP homework, since adherence relates to treatment outcome.⁴⁸ Patients will also complete the 8-item Client Satisfaction Questionnaire (CSQ-8)⁴⁹ at post-treatment and 1-month follow-up to assess satisfaction with the intervention. A modified version of the Systematic Assessment for Treatment Emergent Events-Specific Inquiry (SAFTEE-SI) will be administered assess for emergent side-effects. This is a self-report measure which inquires about the presence and severity of 55 of the most commonly reported side effects in clinical trials, as well as how much reported side effects bother patients or interfere with daily activities. The SAFTEE-SI will be administered at baseline, at sessions 1, 3, 5, 7, and 9, at post-treatment, and at 1 month follow-up. At each administration, the evaluator or therapist will note items rated more bothersome than during the previous administration. The therapist or evaluator will inquire further about each such item, including asking for a description of the side effect, when it occurs, how much it interfered, and what the participant attributes the symptom to. The therapist or evaluator will also inquire in an open-ended fashion about any other adverse effects experienced which are not listed on the SAFTEE-SI and will document the nature and tolerability of any additional side-effects reported. For any item rated "severe," or if the participant reports that side effects are interfering with daily activities "markedly," the therapist or evaluator will notify Dr. [Name] MD (PI) (or covering physician) immediately and Dr. [Name] (or covering physician) will provide further evaluation as medically necessary. Any item rated as "moderate" or

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"moderately" interfering will be reported to Dr. [Name] by the therapist or evaluator within 24 hours. All other reported side-effects endorsed on the SAFTEE-SI will be discussed with Dr. [Name] during weekly meetings of study staff. Additionally, the following self-report measures will be given at baseline, post-treatment, and 1-month follow-up: the Frost Multidimensional Perfectionism Scale (FMPS), to assess dimensions of perfectionism; the Pathological Obsessive-Compulsive Personality Scale (POPS), to assess current Obsessive Compulsive Personality Disorder; the Obsessional Beliefs Questionnaire (OBQ), to assess dysfunctional beliefs typical of OCD patients; the Intolerance of Uncertainty Scale (IUS), to assess reactions to uncertainty, ambiguous situations, and the future; and the Obsessive-Compulsive Trait Core Dimensions Questionnaire (OC-TCDQ), a measure of harm avoidance and incompleteness. Finally, at the post-treatment assessment, we will use a questionnaire to probe the integrity of the blind.

Measures of Inhibitory Control. Stop-signal task (SST). We will evaluate the impact of active vs sham tDCS plus ERP on a laboratory measure of inhibitory control (Aim 3). Participants will be tested using the SST⁵⁰ at baseline, post-treatment, and 1 month post-treatment. During the SST, participants will see images of either a right- or left-pointing arrow on a computer screen. They develop a prepotent response (based on instruction) to press a button with their right or left index finger, congruent with the direction of the arrow. On a small percent of trials, participants will hear a beep, indicating they should try to stop themselves from pressing the button. The primary outcome variable used to assess inhibitory control is stop-signal reaction time (SSRT), which is the estimated time it takes to inhibit the prepotent response. ***Visual Analog Scale (VAS).*** To evaluate the impact of active vs sham tDCS plus ERP on participants' clinical state, we will use a self-report, asking them to rate their ability to resist engaging compulsive behavior during the ERP exercises. Immediately after each ERP exercise, they will rate their experience on a standard VAS, a face-valid assessment of inhibitory control in the clinical context.

tDCS procedures. tDCS delivers brain stimulation noninvasively. While cellular and molecular mechanisms of tDCS are still under investigation, it is known to modulate the excitability of underlying cortex.^{53, 54} During tDCS, the low amplitude current (typically 1-2 mA) is delivered via two scalp electrodes.⁵⁴ This low-level current passes from the positive electrode, or anode, to the negative electrode, or cathode. When current passes from anode to cathode, it simultaneously enhances excitability of the cortex by the anode and decreases excitability near the cathode.^{53, 54} If tDCS is delivered for a sufficient duration (e.g., >10 min,) these excitability changes have been found to persist for up to 1 hour.^{55, 56} There is strong indication that long-lasting changes in excitability can be induced with repeated stimulation, giving tDCS the potential for use as a therapeutic tool.⁵⁷ The tDCS device is battery-powered and is adjustable in both intensity and duration of stimulation delivered.

While tDCS was first used more than a century ago, it has recently seen a marked resurgence of interest in basic and systems neuroscience,⁵⁴ and in neurotherapeutics research.⁵⁸ A recent review of clinical research with tDCS⁴⁰ noted that "tDCS has been tested in thousands of subjects world-wide with no evidence of toxic effects to date." The most common side effects include mild local sensations at the electrode sites, including tingling or itching, and moderate fatigue, and headache.^{40, 59} In general, these effects have paralleled those of sham stimulation. In research experience totaling 567 tDCS sessions, no participants requested tDCS be stopped or required any medical intervention

during or after stimulation.⁵⁹ Notably, adverse effects did not differ between healthy individuals and patients.⁵⁹ Additional safety information is detailed in Human Subjects.

In the present study, each participant will undergo 10 separate 20-minute sessions of either active or sham tDCS in a between-subjects design. Each session of tDCS will be immediately followed by a behavioral intervention (see “Behavioral Intervention” section below). Active tDCS intensity will be 1.5 mA. The anode and cathode are each contained in a 5x5cm rectangular sponge (25 cm²). Electrode placements will follow Jacobson et al.¹⁹: the anode will be over rIFG, defined as the intersection between T4-Fz and F8-Cz in the EEG 10-20 system and the cathode over the left eyebrow (over IOFC). Small marks may be placed on the scalp with a washable, non-toxic marker to aid in the correct placement of the electrodes. tDCS will be delivered via two saline-soaked surface sponge electrodes and a battery-driven, constant current stimulator (NeuroConn DC-Stimulator Plus). For those randomized to sham tDCS, electrodes will be placed in the same locations as for active tDCS. To simulate the sensation of active tDCS, stimulation will be ramped up and back down over a 30-second period at the beginning of sham tDCS. This “ramp up/ramp down” sham approach has been found to be an effective sham condition in previous studies using tDCS at 1-2mA.⁶⁰⁻⁶² Immediately following the 20-minute tDCS period participants will undergo the following behavioral intervention:

Behavioral Intervention: Exposure and Response Prevention (ERP) is a specific type of CBT that has been shown to be effective at reducing symptom severity in OCD. ERP involves individuals placing themselves in anxiety-provoking situations (exposure) and inhibiting their compulsions (response prevention). Compulsive behaviors usually serve as an attempt to reduce distress. By refraining from compulsions, participants gain corrective information that the feared situation is not dangerous. ERP typically proceeds in a graded manner, as it will here, beginning with exposure to more manageable situations and progressing to more difficult situations as treatment continues. The behavioral intervention here includes 11 sessions in total: one 90-minute session including psychoeducation and treatment planning followed by 10 ERP sessions lasting approximately 90-min each. These 11 sessions will be delivered twice-weekly over a 5.5 week period. All intervention sessions must be completed within a maximum of seven weeks. Between sessions, self-directed ERP will be assigned as homework. During each of the 10 ERP sessions, tDCS will be delivered for 20 min immediately prior to the ERP exercise. We selected a 10-session ERP intervention (plus 1 session of psychoeducation and treatment planning) in an attempt to balance feasibility with allowing sufficient sessions to evaluate treatment effects. While 10 sessions is shorter than most manualized ERP protocols, ERP interventions of similar length, session frequency, session content, and design have often been used to evaluate the efficacy of augmentation of ERP with pharmacotherapy including D-cycloserine (Kushner et al., 2007; Storch et al., 2010; Wilhelm et al., 2008). All sessions will be audio recorded using digital voice recorders in order to assess for treatment fidelity. As stated below, 15% of sessions will be reviewed to ensure adherence to the treatment protocol. In order to obtain an unbiased assessment of therapist fidelity to the intervention, participants will not be allowed to opt out of session recording. (Handling of digital audio recordings to protect against loss of confidentiality and privacy is outlined below under III. Human Subjects.)

Assessment Training and Monitoring of Treatment Integrity. Assessments will be completed by a trained, supervised, advanced (i.e., BA or higher) evaluator who will be kept blind to participant's group assignment. The evaluator will initially be trained to an inter-rater reliability of ≥ 0.80 . Assessments will be audio recorded and will be checked periodically to minimize rater drift. To

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ensure fidelity to the intervention and consistency between therapists, study therapists will undergo training in this approach including directed readings and regular supervision of on-going cases. Treatment sessions will be audio recorded and a randomly selected 15% of sessions will be reviewed to ensure adherence to the treatment protocol.

Participant Withdrawal. Participants may be withdrawn from the study for any of the following reasons: 1) A significantly deteriorating clinical course, such as the emergence of active suicidal ideation or a need for hospitalization, 2) Significant adverse reaction to tDCS, assessed using a modified version of the Systematic Assessment for Treatment Emergent Events (SAFTEE), 3) Serious physical illness, 4) Missing two consecutive study visits, 5) Initiation or reinstitution of other treatment (psychosocial treatment with proven efficacy, psychotropic medication changes) during the acute treatment phase, 6) Investigators' decision that withdrawal from the study is in the participant's best interest, 7) Participant's decision to withdraw. Reasons for withdrawal will be documented, participants will be referred for appropriate treatment, and we will make every attempt to conduct scheduled follow-ups with those who withdraw. The current study will employ several measures to minimize attrition, including frequent contact with participants for the duration of the study and compensation for participants' time for post-treatment and follow-up assessment visits.

4. Data Analysis

Original Data Analysis Plan:

Preliminary and Primary Data Analyses. As the proposed study is a small-sample pilot study, our primary focus will be on examining feasibility, acceptability, and direction of effects. Additionally, all randomized participants will be used in an intent-to-treat analysis. We will use chi-square and t-tests to evaluate any differences between the two conditions at baseline on demographic and other relevant variables, such as initial symptom severity, comorbid depression, or patient adherence to ERP homework. If significant differences exist, we will covary for these variables in our analyses (though we do not anticipate significant group differences at baseline, as urn randomization tends to result in balanced samples.)

Aim 1: Establish feasibility and acceptability of research procedures and clinical intervention.

Hypothesis: Patients with OCD will tolerate this combined ERP + tDCS treatment and will find it acceptable, as determined by rates of retention, treatment completion, and patient report. For Aim 1, we will chi-square or t-test to compare treatment conditions on rates of retention, session attendance, homework and treatment completion, and patient satisfaction on the CSQ-8.

Aim 2: Gather evidence on preliminary efficacy of tDCS over rIFG as an adjunct to ERP for OCD.

Hypothesis: Patients in the group receiving ERP + active tDCS will show greater reduction in symptom severity over 10 sessions of the combined treatment than those receiving ERP + sham tDCS. For Aim 2, we will use repeated-measures ANOVA with a between-group factor (condition) to evaluate differences in Y-BOCS severity between groups across assessment timepoints. Since this is a small pilot study (N=32), we will also examine group means and direction of effects across all timepoints, not relying solely on statistical approaches which may be underpowered to detect a significant effect.

Aim 3: Characterize the relationship between measures of inhibitory control and outcome of the combined intervention. Hypotheses: a) Response inhibition, as measured by the SST, will improve more after ERP plus active vs sham tDCS; b) Improvement in OCD severity will correspond to improved inhibitory control on the SST; and c) Patients receiving ERP plus active tDCS will report less difficulty inhibiting compulsions during ERP exercises than those receiving ERP plus sham tDCS. To test our hypotheses for Aim 3, we will: a) use independent measures t-tests to compare change in SSRT from pre- to post-treatment between conditions, and from pre-treatment to follow-up; b) compute a correlation between percent change in Y-BOCS score and percent change in SSRT from baseline to post-treatment, and from baseline to 1-month follow-up, c) use an independent measures t-test to compare self-reported mean difficulty inhibiting compulsions (VAS) during ERP across stimulation conditions.

Revised Data Analysis Plan:

Preliminary and Primary Data Analyses. Given that this study resulted in a smaller than anticipated final sample size, we created a revised analysis plan, appropriate for the smaller sample. Consistent with the original plan for this pilot study, our primary focus will be on examining feasibility, acceptability, and direction of effects. Additionally, all randomized participants will be used in an intent-to-treat analysis. Analyses will focus on descriptive statistics (e.g., means or proportions) with between-group effect sizes calculated, as appropriate.

Aim 1: Establish feasibility and acceptability of research procedures and clinical intervention.

Hypothesis: Patients with OCD will tolerate this combined ERP + tDCS treatment and will find it acceptable, as determined by rates of retention, treatment completion, and patient report. Our primary feasibility outcome of interest is rates of session completion. Our primary acceptability outcome is patient-reported client satisfaction.

Aim 2: Gather evidence on preliminary efficacy of tDCS over rIFG as an adjunct to ERP for OCD.

Hypothesis: Patients in the group receiving ERP + active tDCS will show greater reduction in symptom severity over 10 sessions of the combined treatment than those receiving ERP + sham tDCS. For Aim 2, we will examine group means on the Y-BOCS and direction of effects at post-treatment, and 1-month follow-up, not relying on statistical approaches which will be underpowered to detect an effect. The Y-BOCS is our primary clinical outcome.

Aim 3: Characterize the relationship between measures of inhibitory control and outcome of the combined intervention. Hypotheses: a) Response inhibition, as measured by the SST, will improve more after ERP plus active vs sham tDCS; b) Improvement in OCD severity will correspond to improved inhibitory control on the SST; and c) Patients receiving ERP plus active tDCS will report less difficulty inhibiting compulsions during ERP exercises than those receiving ERP plus sham tDCS. We regard aim 3 and related hypotheses to be largely exploratory. To investigate our hypotheses for Aim 3, we will: a) calculate mean change in SSRT from pre- to post-treatment, and from pre-treatment to follow-up for both conditions, and between groups effect size; b) compute a correlation between percent change in Y-BOCS score and percent change in SSRT from baseline to post-treatment, and from baseline to 1-month follow-up, c) calculate self-reported mean difficulty inhibiting compulsions (VAS) during ERP and direction of effects across stimulation conditions.

D. Material Inducements

Compensation for participation in assessments will be offered as part of this study. No compensation will be offered for participation in ERP sessions. Participants will receive a payment of \$25 for completing the screening assessment. Participants will participate in a total of 8 additional assessments during the study (baseline, sessions 1, 3, 5, 7, 9, post-treatment, and 1 month follow-up); they will receive payment for completion of each of these assessments (\$30 for the baseline assessment, \$10 for each mid-treatment assessment, \$40 for the baseline assessment, and \$40 for the post-treatment assessment) for maximum compensation of \$185 for completing the screening and all assessments. Participants will have the option to receive payment by check in the mail or Stop & Shop gift card after each assessment.

E. Training of Research Personnel

All research personnel will be trained to properly administer the study instruments by the Co-PIs. All research staff will have completed research ethics training—including data management and procedures for maintaining data confidentiality and safety—before being allowed to work on the project. Postdoctoral therapists training in ERP will include assigned readings, listening to training sessions, role play, and weekly supervision. Therapists will also be trained in tDCS prior to administering stimulation in this protocol. A physician with advanced training in neuromodulation techniques (Dr. [Name] or another qualified research physician) will oversee all tDCS administration and will be immediately available for management of emergent events. Prior to administering tDCS in this protocol, all research clinicians will be required to undergo training and demonstrate competence in the safe delivery of tDCS. There are multiple components of training for a research clinician to be qualified for administering tDCS:

- (1) The PI [Initials] will provide initial didactic training to introduce concepts critical to tDCS. Reading materials and lecture format will be used to teach the basic electrophysiology principles that underlie the mechanism of tDCS for modulating neuronal activity. Visual aids will be used to convey anatomical guidelines used for identifying targets for electrode placement. Theoretical considerations for choice of stimulation targets, electrode size and montage, and stimulation parameters will be reviewed (though these factors will not vary in the current study). Training will include methods for identifying and managing potential side effects from the tDCS procedure, and review of procedures for managing a patient found to have significant clinical deterioration that could put him or others at risk for harm.
- (2) Research staff will observe each of the following activities with a minimum of 3 participants: a) administration of a safety screening questionnaire and interviewing prospective study participants to assess possible contraindications to the method; b) administration of tDCS following standard methods; c) “debriefing” of participants immediately following the tDCS and evaluation of any treatment-emergent adverse effects.
- (3) Research staff will have ample opportunity to practice the various steps of setting up/administering tDCS and conducting pre/post treatment clinical evaluations, on non-patient volunteers. Practice will include role play session for administering the modified SAFTEE instrument

as part of routine safety assessment, role-play of scenarios in which the PI or another physician should be summoned to further address adverse events related to the study protocol.

(4) Research staff will demonstrate competency in all aspects of relevant subject assessment and in administration of the entire tDCS procedure on a minimum of 2 participants, under direct observation by the PI [Initials]. Competence in specific aspects of the procedure comprising best practice standards for tDCS will be documented in line with [Name] Hospital policy.

(5) Subject feedback will be solicited to further aid training and refine the skills of research staff delivering tDCS in this protocol.

III. HUMAN SUBJECTS

A. Subject Population (include number; gender; age; diagnosis; inpatient vs. outpatient; physical health; inclusion/exclusion criteria; rationale for use of special groups)

For this study we will recruit 32 outpatients with a primary diagnosis of OCD: *Inclusion criteria are as follows:* (1) current DSM-5 OCD diagnosis and current Y-BOCS total score of ≥ 16 , (2) 18-65 years of age; (3) ability to speak, read, write, and understand English sufficiently well to complete study procedures and provide informed consent; (4) no use of psychiatric medications or stable psychiatric medication use for a minimum of 6 week prior to study entry. Psychiatric medications will be limited to the following: serotonin reuptake inhibitors (SRI; including clomipramine), combination antidepressants (including bupropion and SNRIs), buspirone, benzodiazepines, stimulants and/or antipsychotics (with the exception of aripiprazole); (5) naive to tDCS; *Exclusion criteria include:* (1) active substance use disorder; (2) lifetime diagnosis of psychotic or bipolar mood disorder; (3) previous minimally adequate trial of ERP (at least 16 sessions including both therapist and self-directed exposure and response prevention), (4) therapy outside the study protocol which has evidence for efficacy with OCD during the study intervention period, (5) active suicidal or homicidal ideation; (6) organic brain disease or injury; (7) any health problems that would interfere with study participation, including contraindications to tDCS (e.g., skin condition, mental implant in skull), (8) Women who are pregnant or breastfeeding. All women participants of child-bearing age are required to have a negative pregnancy test prior to treatment, and must use medically acceptable birth control during study participation. Medically acceptable birth control includes: established oral, injected, implanted, or vaginal ring hormonal contraception, an intrauterine device (IUD), two barrier contraception methods (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), or having a vasectomized partner, (10) use of anticonvulsant medications (including depakote, gabapentin, tegretol, dilantin, lamictal) and/or glutamate-acting agents (including n-acetylcysteine, riluzole, amantadine, memantine).

B. Recruitment and Consent Procedures

Participants will be primarily recruited from the [Name] Hospital OCD Clinic which serves over 300 active patients and has averaged 120 new OCD patient evaluations annually for 20 years. Past study recruitment efforts through this clinic have been very successful. Any recruitment materials developed for the web, or other advertisements for potential participants, will be submitted to the IRB for approval prior to postings.

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Participants who appear to meet criteria for participation will be approached by study staff, provided with a brief verbal description of the study, and invited to participate. An initial assessment session will be scheduled. During the initial session, potential participants will again be provided with a description of the study and if they remain interested, study staff will obtain written informed consent. Participants will be given the opportunity to ask any questions they may have, and they will receive a copy of the informed consent document including contact information, should any questions or concerns arise at a later time.

C. Potential Risks

There are relatively few risks involved in the proposed study. Potential risks to all subjects include: (1) Coercion. Subjects may feel coerced to participate, (2) Breach of confidentiality or loss of privacy. In the course of this study we will collect sensitive information which, if released, may cause shame, embarrassment, or distress; (3) Distress due to assessment procedures. During the assessments we will ask participants about their thoughts, feelings, behaviors, and symptoms. It is possible that asking participants about this information may increase distress or discomfort. (4) Risks due to tDCS. There is some inherent risk with tDCS, mainly risk of skin irritation and, as in a small number of case reports, local skin burns where the electrodes are attached. Such cases have typically been seen only after repeated daily stimulation to the same region (Palm, 2008), or after unintentional abrasion of the skin with alcohol swabs prior to stimulation (Loo, 2011). Though a possible risk, skin burns are rare. In a recent review of clinical research with tDCS, Brunoni and colleagues (2011) noted that “tDCS has been tested in thousands of subjects world-wide with no evidence of toxic effects to date.” In addition, we are aware of reports of a small percentage of patients developing temporary hypomania during the course of a daily tDCS protocol for depression targeting the dorsolateral prefrontal cortex. It is unclear whether this is a risk for tDCS targeting rIFG or with the electrode montage used in this study. The most common side effects include mild local sensations at the electrode sites, including tingling or itching, and moderate fatigue, and headache (Brunoni, 2011; Poreisz, 2007). In general, these effects have paralleled those of sham stimulation. In research experience totaling 567 tDCS sessions, no participants requested tDCS be stopped or required any medical intervention during or after stimulation. Notably, adverse effects did not differ between healthy individuals and patients (Poreisz, 2007). Safety testing of tDCS has found high tolerability and no reports of discomfort by participants when stimulating for 20 minutes at either 1 or 2mA for 20 minutes (Iyer, 2005). (5) Distress due to treatment procedures. Treatment of OCD with ERP involves patients facing situations which make them anxious, both directly and in their imaginations.

D. Protection of the Subject (include measures to minimize potential risks and to ensure confidentiality)

D.1. Measures to minimize potential risks

The following procedures will be followed to minimize risks to all participants: (1) To minimize risk of coercion, standard procedures will be followed in obtaining written informed consent. The voluntary nature of participation will be emphasized. Risks and benefits of participation will be explained, along with the rights of the participant, including the right to withdraw from the study at any time. Additionally, participants will be informed that should they choose to withdraw from the study, this will in no way affect care they receive at [Name] Hospital or their right to participate in

future research studies. (2) To minimize the risk of distress arising from the assessment procedure, study staff that has been adequately trained in the assessment battery will complete all assessments, and [the PIs] will supervise all assessors. (3) To minimize risks due to tDCS, all participants will be carefully screened prior to tDCS for contraindications to tDCS. Moreover, we will obtain a release to gather information from participants' current medical providers for screening purposes and ongoing clinical record keeping. All tDCS will be administered by a trained member of the research staff under the supervision of a credentialed physician (Dr. [Name] or covering physician). Use of an electrically isolated power source (i.e., battery-powered DC stimulation device) also protects against delivery of more intense currents than intended. Participants will be closely observed for signs of skin burns, discomfort, or other stress. Participants will be closely monitored to ensuring the electrode sponges stay moist with saline in order to help prevent burns by improving electrode-to-skin contact. Participants will have the option of discontinuing the study at any time and will be explicitly instructed to inform the experimenters immediately if they experience any discomfort. The experimenter will inform the supervising physician about any participant who has significant skin discomfort or a skin lesion after current delivery. If there is any doubt about the mental or physical status of an individual after testing, the PI or other supervising physician will evaluate the participants and make a recommendation for follow-up care, if required. Telephone or in-person follow-up will be arranged as needed and will not be considered a protocol deviation. Adverse effects will be monitored regularly using the SAFTEE-SI. This measure includes symptoms of hypomania, including feeling hyper, unable to sit still, changes in appetite, and sleep disturbance, as well as a number of frequently reported side effects in clinical trials. Any participant judged on clinical grounds to have suffered adverse effects will thus be evaluated and treated as necessary and withdrawn from the study, if necessary. For each SAFTEE item, participants are asked to report how bothersome each symptom on the form has been for him/her in the past week, with response options "None," "Mild," "Moderate," or "Severe." Additionally, a single item inquires about how much all reported side-effects have bothered the participant or interfered with daily activities (response options: "No side effects," "Mildly," "Moderately," or "Markedly"). The SAFTEE-SI will be administered at baseline, once per week during the 5.5 week protocol, at post-treatment, and at 1 month follow-up. At each administration, the evaluator will note items rated more bothersome than during the previous administration and will inquire further about each such item. The therapist or evaluator will also inquire in an open-ended fashion about any other adverse effects experienced which are not listed on the SAFTEE-SI and will document the nature and tolerability of any additional side-effects reported. For any item rated "severe," or if the participant reports that side effects are interfering with daily activities "markedly," the therapist or evaluator will notify Dr. [Name] MD (PI) (or covering physician) immediately. Dr. [Name] (or covering physician) will provide further evaluation as medically necessary and we will take appropriate safety measures such as study withdrawal and/or referral to higher level of clinical care, if necessary. Any item rated as "moderate" or "moderately" interfering will be reported to Dr. [Name] by the therapist or evaluator within 24 hours. All other reported side-effects endorsed on the SAFTEE-SI will be discussed with Dr. [Name] during weekly meetings of study staff. Follow-up or further evaluation will occur as medically necessary. (4) To minimize the risk of distress due to treatment procedures, we have selected a treatment which has been shown to be efficacious in reducing OCD symptoms. While this treatment involves clients placing themselves in situations which provoke anxiety, this is necessary and effective for clinical improvement and generally represents no more distress than in experienced in daily living for these individuals. Participants will be informed that they will be encouraged to

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tolerate the discomfort during the sessions but that they can stop the exercises at any time. In the case of a participant who experiences extreme distress, clinical judgment and consultation will be used to determine whether the participant should be discontinued from the study. Participants who experience a significant worsening of symptoms during the study will be discontinued and referred for alternative treatment.

To minimize risk of clinical deterioration, we have excluded participants from entry into the study who have active suicidal or homicidal ideation. At baseline, participants will be provided with a set of emergency contact numbers, including phone numbers for local mental health care providers ([Hospital Names]). One of the PIs or a covering clinician will also be available at all times to study participants in the event of a clinical emergency. All participants will be given oral and written information on how to reach the PIs in the case of such an emergency; participants will be told to contact research personnel by telephone or pager for any significant worsening of symptoms or adverse events, and may be seen for an additional evaluation, which will not be considered a protocol violation. We will assess suicide risk at baseline and every week using item 9 on the BDI-II to screen for suicidal ideation. Any presence (BDI-II item 9 > 0) or increase in suicidal ideation will result in a clinical assessment for suicide risk by the clinician and clinically appropriate steps will be taken (e.g., creating a plan for safety or higher level of clinical care, if necessary). We will monitor clinical symptoms weekly using the BDI, BAI, and Y-BOCS. In the event that a participant experiences significant symptom worsening (i.e., 25% increase of pre-randomization Y-BOCS), he or she will be more thoroughly evaluated and we will take appropriate safety measures such as study withdrawal or a higher level of clinical care, if necessary. Participants will be offered referrals to alternative treatment at study discontinuation.

D.2. Measures to ensure confidentiality

(2) To protect against breaches of confidentiality, all information collected from participants will be handled by staff trained in the responsible conduct of research who have passed ethics training via the CITI Course for the Protection of Human Subjects or the NIH Human Participants Protection Education for Research Teams training. Audio recordings of sessions will be immediately uploaded onto a secure research server and deleted from the audio recording device – these recordings will be identified by code number only. All study forms and data will be identified only by code numbers, and will be stored in locked file cabinets or on secure research servers. Identifying information (contact information, name, consent documents) will be separated from the research data and be stored separately in a different locked file cabinet. REDCap (Research Electronic Data Capture) will be used for data collection, entry and management. REDCap, maintained by [Hospital] Data Center, is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). All data collected and entered into REDCap will be identified only by patient ID; No PHI will be stored in REDCap. All other computerized data, including digital audio files of assessments and treatment sessions, will be stored on a secure drive, password-protected, and will be accessible only to research staff. These files will be transferred to the secure drive immediately following assessments and treatment sessions and deleted from the digital recording device. Digital audio files will be labeled only with subject ID number. Digital audio files will be erased at the end of

this study. No personal participant information will be presented in any publication or presentations resulting from this research.

D.3. Data safety monitoring plan

Procedures to protect participant confidentiality are described above (section D.2.). [The PIs] will be responsible for supervision of data entry and management and training of study personnel. Hard copy data will be stored in a filing cabinet in one of the PI's locked offices. Digital audio files will be stored on a secure server, and labeled only with participant unique identification code. In order to maintain anonymity in computer data files participants will be only listed with their unique identification code. The PI's will monitor procedures for assuring participant privacy and confidentiality, and the quality and integrity of data collected. Corrective action will be taken as needed. Should any adverse events arise, the PI's will be responsible for completing an Adverse Events Form and reporting Serious Adverse Events to the [Hospital Name] IRB within 24 hours of having received notice of the event. The PI will gather any information needed to investigate the event and to determine subsequent action. Any subsequent action will be documented and reported to the [Hospital Name] IRB.

This study has also appointed a data safety monitoring board (DSMB). Members of the DSMB include [Name] (who will serve as DSMB Chair), [Name], and [Name]. Dr. [Name], of [Affiliation], has expertise in behavior therapy for OCD and statistics. Dr. [Name], of the [Affiliation], has expertise in OCD, neuromodulation, and clinical trials. Dr. [Name] has expertise in clinical bioethics, with a focus on neuroethics. This board convenes twice per year (unless more frequent meetings are deemed necessary) and is responsible for reviewing the research protocol and plans for data and safety monitoring, evaluating the progress of the trial, and inquiring for further information as necessary to accomplish their mission, and maintaining confidentiality during all phases of the trial including the monitoring, preparation of interim results, review and response to monitoring recommendation. As they deem necessary, the members of the DSMB will evaluate whether the presence of side effects or adverse consequences are significant enough to warrant amendment, suspension, or early termination of the study and will independently make recommendations to the PI to continue, to amend or to terminate the trial.

E. Potential Benefits

The assessments included in this study are not intended to be diagnostic in nature and therefore will not be of any direct benefit to participants. Participants in the OCD group may receive benefit from receiving a treatment which has previously been shown to be efficacious in reducing OCD symptoms; however, response to treatment cannot be guaranteed.

F. Risk-Benefit Ratio

Knowledge gained from this study has the potential to inform further development of improved treatment approaches for OCD, and future development of neurostimulation-based treatments for disorders of inhibitory control. Given the chronic and impairing nature of OCD and other disorders of inhibitory control, high patient burden, and high number of individuals who respond less than optimally to available treatments, the benefit of this knowledge clearly outweighs potential risks involved.

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