

**PARTNERS HUMAN RESEARCH COMMITTEE
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tDCS modulation of neurocognitive processes underlying pediatric OCD

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I. SPECIFIC AIMS

In this study, we aim to understand the role of transcranial direct current stimulation (tDCS) in modulating aberrant neurocognitive processes implicated in pediatric patients with obsessive compulsive disorder (OCD). We propose two arms of the study that will investigate fear extinction learning and inhibitory control in one arm (A), and goal orientated versus habit-based behavior and inhibitory control in the other (B). All subjects will undergo three study conditions: two with active tDCS to each of two different brain targets and one under sham tDCS. The order of stimulation (sham or active tDCS) will be randomized.

The NIMH Research Domain Criteria (RDoC) were established in 2009 as a matrix to help guide research on mental disorders “based on dimensions of neurobiology and observable behavior” rather than reliance on symptom presentation.¹ Three constructs have particular relevance in OCD, namely ‘acute threat (fear)’ within the ‘Negative Valence System’ domain; ‘habit’ within the ‘Positive Valence System’ domain; and ‘response selection and inhibition’ within the ‘Cognitive Systems’ domain. We have chosen to focus on these areas as subcomponents contributing to the symptomatology seen in OCD in terms of fear conditioning/extinction, the balance between goal orientated versus habit-based behaviors, and response inhibition.

Arm A- fear extinction learning and inhibitory control

Each visit in arm A will be conducted over two consecutive days, with approximately one week between tDCS sessions. On day 1 of arm A, each subject will complete an inhibitory control task and then be conditioned to associate a geometric colored shape with a fearful stimulus (an aversive image and sound, the unconditioned stimulus) and then have this association extinguished. During extinction, they will receive tDCS stimulation and then repeat the inhibitory control task. They will then return the next day for an extinction recall task to test the dependent variable of most interest for translation to a clinical effect- reducing the extent a patient experiences fear to a stimulus following completion of fear exposure therapy. Subjects will be randomized to receive one of each of the three stimulation schedules on day 1 of the three separate visits, which comprise two different targets of active stimulation and one sham session. Subjects will have electroencephalography (EEG), electrocardiogram (ECG) and skin conductance response (SCR) recordings monitored throughout the testing paradigms as behavioral biomarker assays.

Arm B- goal orientated versus habit-based behavior and inhibitory control

Each of three visits in arm B will take place over one day, with approximately one day to one week between tDCS sessions. Each subject will complete an inhibitory control task, then a computer task to measure their response to rewards in different situations as a measure of goal-orientated versus habit-based learning. They will then receive tDCS stimulation and repeat the neurocognitive tasks above immediately following this. Subjects will be randomized to receive one of each of the three stimulation schedules over the three days, which comprise two different targets of active stimulation and one sham session. Electroencephalography (EEG) recordings will be monitored throughout each session.

Primary Aim 1- To determine the cognitive effects of tDCS to the pre-SMA and vLPFC in youth with OCD.

Hypothesis 1A- active tDCS rather than sham stimulation will show greater levels of inhibitory control after tDCS, and anodal vLPFC will be equivalent to cathodal pre-SMA.

Hypothesis 1B- active tDCS rather than sham stimulation will show reduced extinction recall of an extinguished conditioned stimulus task after tDCS, and anodal vLPFC will be superior to cathodal pre-SMA.

Hypothesis 1C- active tDCS rather than sham stimulation will show greater levels of goal-oriented behavior to a reward task after tDCS, and anodal vLPFC will be superior to cathodal pre-SMA.

Primary Aim 2- To determine the physiological effects of tDCS to the pre-SMA and vLPFC in youth with OCD

Hypothesis 2A- active tDCS rather than sham stimulation will show greater decrease of N200 and increase in P300 electroencephalogram (EEG) event related potentials (ERPs) amplitudes during tasks measuring inhibitory control, and anodal vLPFC will be equivalent to cathodal pre-SMA.

Hypothesis 2B- active tDCS rather than sham stimulation will show greater P50 suppression electroencephalogram (EEG) event related potentials (ERPs) amplitudes during the fear extinction task, and anodal vLPFC will be equivalent to cathodal pre-SMA.

Hypothesis 2C (exploratory)- given the paucity of existing neurophysiological evidence supporting goal-oriented versus habit-based behavior, exploratory analyses will investigate ERPs and oscillatory processes (e.g., spectrograms) changing with tDCS compared to sham and correlating with changes in behavioral outcomes across interventions.

Exploratory Aim 1- To determine if there is a correlation between the inhibitory control scores, extent of goal orientated versus habit-based behavior, and extent of fear extinction recall within subjects both before and after tDCS, and if these vary depending between the two active targets and sham stimulation conditions.

II. BACKGROUND AND SIGNIFICANCE

OCD

Obsessive-compulsive disorder (OCD) among children and adolescents has a prevalence of approximately 1-2%^{2,3}. OCD is a significant public health problem, causes impairment in academic, social and family functioning, and left untreated is frequently unremitting into adulthood.⁴⁻⁶ Currently, two treatment modalities have demonstrated efficacy among pediatric OCD patients, namely pharmacotherapy with serotonin reuptake inhibitors (SRIs) and cognitive-behavioral therapy (CBT) with exposure and response prevention (E/RP; see⁷ for a meta-analytic review). However, between 61-79% of youth receiving CBT or SRI monotherapy and 46% of those receiving combined treatment

remain symptomatic,⁸ there's a shortage of trained CBT providers and pharmacological interventions involving serotonergic medications are efficacious but rarely produce remission,⁸ may be accompanied by side effects,^{9,10} and may not be an acceptable intervention to some parents.¹¹

Therefore, the search continues for more effective and better tolerated treatments. The expanding field of neuromodulation by non-invasive brain stimulation is a promising avenue in the treatment of a number of psychiatric disorders,¹² including OCD,¹³ that deserves further exploration. Because childhood onset of OCD (before adolescence) appears to have a different gender ratio, genetic loading, co-morbidity profile, treatment response and distribution of obsession/compulsive types to adult onset OCD it may represent a developmental subtype of this disorder.¹⁴ For this reason, it is imperative that studies into OCD are also conducted directly with pediatric samples, rather than relying solely on the extrapolation of findings from adults.

Increasing evidence is emerging about several putative neurocognitive 'endophenotypes' of OCD-heritable, state independent, specific neurocognitive abnormalities seen more often in patients with OCD and their unaffected first degree relatives in comparison to the general population.¹⁵ Research has indicated that these may include response inhibition, planning, decision making, action monitoring and cognitive flexibility and modulation of these neurocognitive areas could potentially lead to downstream improvements in illness symptomatology. However, most of the studies in this area have focused on adults, and a review by Aziz Marzuki and colleagues¹⁶ suggests that these endophenotypes may not overlap with the findings from research of childhood onset OCD.

Fear conditioning and extinction

Although a host of factors contribute to the maintenance of functionally impairing obsessions and compulsions seen in OCD, fear conditioning and extinction learning are regarded as important components in the cognitive behavioral model of the etiology and treatment of this and other anxiety disorders.

Fear conditioning occurs when an emotionally neutral 'conditioned' stimulus (CS) is repeatedly paired with an aversive 'unconditioned' stimulus (UCS) such as an unpleasant noise or sound so that the CS eventually leads to a conditioned response (CR) in and of itself. In the context of OCD, for patients with contamination obsessional fears, the CS might be a door handle that is thought to be a source of pathogens that could lead to a serious illness (US) with the CS alone eventually leading to a CR of fear. The CR can be measured by psychophysiological changes such as electrodermal activity by skin conductance response (SCR), heart rate (HR), respiratory rate, and subjective self-reports of fear.

Fear extinction occurs when repeated exposure to the CS does not lead to the feared outcome (touching the handle does not lead to illness) so that a new association of 'CS- no UCS' is made which competes with the original association of 'CS-US'.¹⁷ Engagement in safety behaviors (i.e. avoiding touching door handles in the example above), prevents this learning from happening however so the association persists, which explains the rationale for the use of E/RP in CBT treatment. Extinction recall is the process of an inhibitory learning response to the past 'CS-US' association that has now been updated to 'CS-no US' that is retained over time¹⁸ and is usually experimentally assessed one to seven days following extinction learning.¹⁹

In differential tasks of fear conditioning, two or more CS are present with some being paired with an US (CS+) and others never paired with an US (CS-), representing a ‘safe’ stimulus. In a large meta-analysis by Duits and colleagues,²⁰ adults with anxiety disorders generally show a similar fear response to the CS+ as healthy controls but an increased response to the CS- in the conditioning phase. They also show increased fear responses to the CS+ during extinction, indicating delayed/reduced fear extinction. Milad and colleagues²¹ focused on OCD in their study and found impairments in extinction recall in comparison to healthy adults.

In the review by McGuire and colleagues¹⁹ of threat acquisition and extinction in youth with anxiety disorders, they concluded that although acquisition of fear was largely comparable with healthy controls, subjects with anxiety disorders tended to have deficits in extinction learning and that this was due to deficiencies in inhibitory learning. Similar findings were also seen in studies that focused specifically on youth with OCD^{22–24} and these deficits in extinction learning may translate to deficits in inhibitory learning following E/RP therapy and theoretically account for some of the variability in response rates to CBT. Understanding more about these deficits in extinction learning and inhibition of previously learned ‘CS-US’ associations will hopefully allow tailoring of the most appropriate treatment modalities for young patients with OCD to allow for new ‘CS-no US’ associations to dominate and reduce burden of symptoms.

Several tasks to assess fear conditioning, extinction and recall have been adapted for use in children, including the use of neutral faces²⁵ or geometric shape of different colors²⁶ as the CS (either CS+ or CS-) and the US being a fearful face (with or without a paired simultaneous scream) or an aversive bell noise.

Goal orientated verses habit-based learning

Habits can be defined as repetitive cognitive or motor behaviors that are triggered by a certain stimulus and can be carried out largely without conscious effort once initiated and therefore efficient in familiar situations. They are the opposite of goal directed behaviors that predominate when new behavior is being learnt and are strategically responsive to changes in the environment to achieve specific goals. A computational model of this concept is that two rules act in parallel during trial and error instrumental learning to learn action preferences. This posits that goal-directed choices arise from ‘model based’ ‘action-outcome’ associations that are adaptable to changes in circumstances, whereas habit-based choices are driven by a ‘model-free’ system from ‘stimulus-response’ learnt associations.^{27–30}

Although the classic view has been that obsessions lead to compulsive behaviors to ‘neutralize’ the distress, an alternative view gaining traction is that deficiencies in goal-directed behavior lead to an over-reliance on habitual action, leading to compulsions.³¹ Obsessions and subjective anxiety are thought to arise as a cognitive conceptualization of these compulsive urges, in the face of cognitive dissonance of their ego-dystonic nature.^{32,33}

Studies in adults with OCD show that performance on tasks that incorporate ‘outcome devaluation’³⁴ is less adaptable to changes in motivational cues. For example, if a stimulus was taught to lead to a reward on a computerized task but then this prompt was later changed to no longer lead to the reward (devalued), patients with OCD would be less able to refrain from the ‘habit’ of reacting to the original outcome cue and shift their behavior to a new reward stimulus.^{32,35} This can be seen as a proxy for a

bias towards habit-based behavior rather than goal-orientated actions, depending on the changing environment.

Developmentally, younger children tend to use mainly habitually learnt behaviors more than goal directed behaviors, which develop with the maturation of the prefrontal-hippocampal-striatal circuit that integrates state, behavior and outcome information to direct goal orientated action.³⁶ Although this construct has been investigated in pediatric populations with a diagnosis of autism spectrum disorder (ASD)³⁷ and healthy controls,³⁶ we are not aware of any studies looking specifically at goal orientated verses habit-based behavior in pediatric OCD.

However, work being done on decision making as a potential OCD endophenotype suggests that children with this condition tend to face difficulties when there is uncertainty in a task and focus more on internally generated signals, less on external cues and are slower at learning the patterns/rules of an experimental task.³⁸

Inhibitory control

At the symptomatic level, the inability to inhibit intrusive thoughts/obsessions and carry out compulsions are hallmarks of OCD. Deficits in inhibitory control may help explain and understand the mechanisms behind impaired extinction recall in patients with fear based psychiatric disorders, as well as the transdiagnostic concept of compulsivity, also seen in eating disorder and addiction for example.³⁹

Response inhibition can be divided into motor response inhibition whereby a pre-potent/automatic motor action is suppressed/restrained or cancelled;⁴⁰ and interference control which relates to the ability to ignore competing non-relevant stimuli.⁴¹ There are a variety of neurocognitive tests that assess these aspects of inhibitory control, including the Go/No Go (GNG) task⁴² that measures action restraint, Stop Signal Task (SST)⁴³ that measures action cancellation and the Stroop⁴⁴, Flanker⁴⁵ and Simon⁴⁶ tasks that measure interference control. It has been suggested that of all three types of test, action cancellation has the highest inhibitory load as an action that has already started to commence has to be stopped.⁴⁷

Markers of deficient inhibitory control in adult patients with OCD (and their first degree relatives as a potential endophenotype for this condition) have been extensively evidenced, including delayed motor and interference inhibition on neurocognitive tests.^{48,49} Studies focusing on pediatric OCD populations have also shown decreased response inhibition in versions of the SST⁵⁰ and GNG,⁵¹ although other trials have not demonstrated any OCD specific inhibitory control deficits on these tasks,⁵²⁻⁵⁶ suggesting potential divergence between pediatric and adult patients with OCD and the need for age-specific research in this area.

Electroencephalography event related potentials

There are also electroencephalography (EEG) event related potentials (ERPs) that are associated with motor response inhibition. In the go/no-go task, an increase in frontal-midline negativity is seen around 200ms after the onset of the stimulus (N200) and then a positive response in the frontal-midline/midline-parietal region approximately 300ms after the stimulus (P300). Together these are known as the N2/P3 complex.^{57,58} Klimesch⁵⁹ also found that the P100 visual ERP (a positive inflection on EEG seen approximately 100ms after a visual stimulus and associated with the extra-striate cortex) was

associated with visual inhibitory control in his 2011 experiment. Subtle differences have been noted in these ERP signatures that can be differentiated from healthy controls and conditions where inhibitory control comes into play.⁶⁰

Luque and colleagues⁶¹ also demonstrated separate spatiotemporal markers of brain activity during a learning reinforcement task looking at goal orientated versus habit-based behaviors in humans. The stimulus-locked P100 ERP component was associated with a bias towards habit behaviors and that the P3b (from 550-700ms) was sensitive to more goal-orientated learning.

Signature ERPs of decreased auditory P50 (a positive inflection approximately 50ms after an auditory stimulus) suppression in response to fear extinction have also been observed.⁶²

Neuromodulation: an overview of transcranial direct current stimulation (tDCS)

Noninvasive brain stimulation encompasses a group of clinical and research tools which enable physicians and researchers to modulate brain and behavior safely and reversibly with minimal risks. The two most common methods employed are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), the latter being simpler, cheaper, safer, portable and can be used as a home treatment, all factors that highlight its potential public health impact and utility for younger patients.

In tDCS, electrodes are applied on the scalp to transmit direct current at low current amplitudes.⁶³ At the synaptic level, the current causes changes in the transmembrane potential thus affecting the probability of synaptic firing⁶⁴. At a neurotransmitter level, the current affects the balance between excitation and inhibition through GABA and glutamate concentrations. Anodal stimulation increases the chance of firing by depolarizing the membrane (excitatory) whereas cathodal stimulation decreases this probability by hyperpolarizing the membrane (inhibitory). Such neuromodulation is complex however, as anodal stimulation to an inhibitory circuit will have downstream inhibitory effects, while cathodal stimulation decreases downstream inhibition so that the primary function of brain targets is important to consider.

tDCS has already been applied to adults with a range of neuropsychiatric illnesses with promising results on improving symptoms, including major depressive disorder and OCD- see the 2018 review by Brunelin and colleagues for details.¹³ A review of a total of 567 patients and controls undergoing tDCS using recommended parameters revealed that mild tingling at the site of stimulation was the most common side effect, with less likely occurrences of headache (11.8%) and nausea (2.9%) post-stimulation⁶⁵. Multisession tDCS given serially over weeks to months is already being used as an off-label treatment for a number of conditions in several countries including the US, Iran, Germany, Italy, Brazil and France.⁶⁶ The effects of a single session of tDCS however are transient and reversible, with cognitive or behavioral changes lasting between 30 and 60 minutes.

Efficacy and tolerability in children

tDCS has also been used in research and treatment of several conditions in children including attention deficit hyperactivity disorder (ADHD),^{67,68} epilepsy,^{69,70} ASD⁷¹ and psychosis.⁷²

Krishnan and colleagues concluded that tDCS is a safe modality for the use in children from their 2015 systematic review of 15 studies where no serious adverse events were recorded and the main side effects

were transient skin changes (e.g. itching, tingling and burning sensations), none of which required medical attention.⁷³

Tissue structure of the skull and extra axial cerebrospinal fluid (CSF) volumes changes with age, with possible implications on electrical conductivity from stimulating the scalp. There are also age dependent changes in grey and white matter that may affect tDCS effects in youth. In terms of considering whether the dosage of stimulation needs to be adjusted for age because of these factors, the consensus from review of the literature and MRI modelling⁷⁴ is that a dose up to 2mA for 30 minutes is well tolerated in children and not unsafe.⁷⁵

Neurocircuitry of OCD

The symptoms of OCD have been traditionally hypothesized to be due to a dysfunction in cortico–striato–thalamo–cortical (CSTC) circuitry; including the dorsolateral prefrontal cortex (dlPFC), medial prefrontal cortex (supplementary motor area [SMA], and anterior cingulate cortex [ACC]), orbitofrontal cortex (OFC) and basal ganglia.⁷⁶ Structural MRI studies consistently highlight abnormalities in the OFC, ACC and striatum, with the largest multisite structural MRI study to date showing increased grey matter in the ventral striatum and decreased grey matter in the OFC.⁷⁷ However more recent research employing fMRI techniques has refined this theory to also emphasize the importance of the distinct roles of the lateral and medial areas of the OFC, and the specific contribution of the dorsal ACC (dACC), as well as the role of amygdalo-cortical circuits in fear expression and regulation.⁷⁸

Originally thought to comprise of five separate circuits between the basal ganglia, thalamus and cortex, more recent thinking points towards interconnected loops between the cortex and subcortical structures, governed by overall net activity from the ‘direct pathway’ glutamatergic excitation or the inhibitory Gamma aminobutyric acid (GABA) connections of the ‘indirect pathway’. The CSTC loops thought to be most relevant for OCD include the motor/sensorimotor circuit, dorsal cognitive/dorsolateral prefrontal cortex, ventral cognitive circuit and affective anterior cingulate circuit elaborated below:⁷⁹

- Motor/sensorimotor circuit- cortical areas include the pre-SMA, SMA, motor and pre-motor cortex connections to the basal ganglia. Functional changes in this loop are thought to interfere with the suppression of “internally triggered repetitive movements and thoughts”⁸⁰
- Dorsal cognitive/dorsolateral prefrontal circuit- includes projections from the dlPFC and dACC to the basal ganglia and deficits are hypothesized to lead to increased attention to obsessive thoughts.⁸¹
- Ventral cognitive circuit- this involves projections from the lateral OFC (lOFC) to subcortical structures and is thought to be implicated in ritualized behavioral responses and increased activity here may lead to a limitation in appropriately shifting behavior sets when needed.^{76,78} Hyperactivity in the lOFC is correlated with OCD symptom provocation^{82,83} and may mediate obsessions.
- Affective anterior cingulate circuit- cortical areas include the medial OFC (mOFC), ventral ACC (vACC) and ventromedial prefrontal cortex (vmPFC) looping with subcortical structures and it appears to have a role in affective and reward information processing. Hyperactivity in OCD is again linked to impaired appropriate modification of behavioral responses.

Fear extinction

Deficiencies in the mOFC and adjacent vmPFC appear to have particular roles in fear conditioning and extinction, limiting extinction recall.⁸⁴⁻⁸⁶ Etkin and colleagues⁸⁷ used the peak voxel plots from 73 published and unpublished studies on fear conditioning and found that brain activation showed clustering around the supplementary motor area (SMA) and pre-SMA as well as the dACC, rather than an even distribution through the ACC and mPFC. The dACC is significantly reduced in grey matter volume in subjects with OCD⁸⁸ and correlates with galvanic skin responses of fear learning.⁸⁹

Inhibitory control

The dACC is also implicated in inhibitory control via its possible role in monitoring error signaling-becoming activated in tasks of inhibitory control.⁹⁰ Activation in the ACC as well as right OFC (rOFC) has been shown to inversely correlate with OCD symptom severity on a go/no go task of inhibitory control.⁹¹ The right inferior frontal gyrus (rIFG) has also consistently been identified as an important area for inhibitory control, with reduced grey matter volumes predictive of prolonged SST in fMRI studies in adults^{92,93} and decreased activity seen in children/adolescents with OCD compared to healthy controls on the SST.^{94,95} Another cortical region that appears to have a role is hyperactivity in the pre-SMA which correlated with increased SST reaction time in both OCD patients and their siblings.⁹⁶ The ventrolateral prefrontal cortex (vlPFC), also known as the inferior frontal cortex (IFC), has also been consistently associated with response inhibition, from human lesion mapping studies.⁹⁷

In an fMRI study of adolescent males with OCD, Woolley and colleagues⁹⁴ showed under-activation in several areas of the cortico-striatal-thalamo circuit whilst completing a ‘stop task’ of inhibiting an already initiated motor response; including bilateral OFC, right thalamus and basal ganglia. Correlations have also been noted between impaired performance on tasks of inhibitory control in patients with OCD/their unaffected first-degree relatives and structural brain changes including reduced grey matter in the OFC and rIFC, and increased grey matter volume in the cingulate cortex, striatum and parietal cortex.⁹²

Goal orientated verses habit-based learning

There is a clear difference in the neural substrates of the goal directed and the habit-based stimulus-response system,⁹⁸ as demonstrated from research into lesions and optogenetics in rodent models and structural/functional imaging in human subjects as reported by Gillan and colleagues in 2016.⁹⁹ In this article, they conclude that overall, the most important regions appear to be the mOFC and caudate nucleus¹⁰⁰ for goal directed behavior and the putamen for the gradual reinforcement of stimulus-response habit behaviors over time. Sjoerds and colleagues¹⁰¹ indeed found reduced brain activity in the areas of the vmPFC/mOFC and increased activation of the posterior putamen in their neuroimaging study of alcohol dependent subjects who demonstrated an over-reliance on habit based learning.

Neuromodulation of OCD

Several researchers have attempted to improve OCD symptoms using tDCS to modulate the circuitry outlined above and believed to be involved in this condition, as reviewed by Brunelin and colleagues in 2018.¹³ They identified 12 studies in adults that targeted either the dlPFC, OFC or pre-SMA in eight case reports, three open label studies and one randomized controlled trial (RCT) by d’Urso and colleagues¹⁰² with two active arms but no sham control condition. Overall, promising results were seen by a reduction in YBOCS score that persisted several months later in two trials.^{103,104} The review concluded that an optimal montage of targets was unclear, although Senço and colleagues¹⁰⁵ suggested

cathodal placement over the pre-SMA and an extra-cephalic anode in their computer head modelling study, as used by d'Urso and colleagues above.¹⁰² However Gowda and colleagues¹⁰⁶ found that anodal stimulation of the pre-SMA (with the cathode over the right supra-orbital area) led to a significant improvement in OCD symptoms in their recent randomized sham controlled double blind tDCS trial in adults.

Although there have been no studies to date on the use of tDCS in children with OCD, Pedapati and colleagues¹⁰⁷ did use repetitive TMS (rTMS) in an fMRI guided sham controlled trial in this population, and suggested that inhibition of over activity seen in the rIFG may be a good target to ameliorate symptoms.

Neuromodulation of inhibitory control

In their 2016 review of non-invasive brain stimulation and modulation of inhibitory control in adults, Brevet-Aeby and colleagues noted that the two main structures that have been studied in TMS/tDCS are the dlPFC and rIFG. From the 11 studies looking at tDCS, they concluded that anodal stimulation of the rIFG seemed to improve inhibitory control whereas cathodal stimulation of the right dlPFC appeared to worsen it.¹⁰⁸ Breitling and colleagues also concluded that anodal tDCS stimulation of the rIFG could improve inhibitory control in adolescents with ADHD.¹⁰⁹

There have also been studies using tDCS in children/adolescents to modulate inhibitory control, although mainly in those with a diagnosis of ADHD. Soltaninejad and colleagues⁶⁸ found that 15 minutes of 1.5mA cathodal stimulation over the left dlPFC in adolescents with ADHD increased their accuracy during the pre-potent inhibitory stage of the Go/No-Go task, in comparison to sham stimulation. A similar result was seen in the experiment by Nejati and colleagues¹¹⁰ of improved inhibitory control in children with ADHD and cathodal stimulation of the left dlPFC.

Neuromodulation of fear extinction/recall

Although there have not been any studies investigating tDCS and fear extinction/ recall in children, there have been trials looking at this in adults. Herrmann and colleagues¹¹¹ conducted a review in 2019 of two studies that used rTMS and five using tDCS to modulate fear extinction. Overall, they concluded that the results were promising for both modalities. However, only rTMS to the mPFC has thus far been translated into a successful therapeutic trial for reduction of fear, in this instance in patients with acrophobia.¹¹²

In terms of the tDCS studies, van't Wout and colleagues¹¹³ used a within-subject design with habituation, conditioning and extinction taking place on day one with two different CS+ and extinction recall occurring the day after. Informed by computer modelling to reach the vmPFC, they placed the anode at the AF3 EEG electrode placement position and the cathode on the contralateral left mastoid. They used either sham or active tDCS before and during the extinction phase of one CS+ and either sham or active (depending on the first condition) to the same areas before and during the extinction of a second CS+. They found that subjects who received real stimulation during the first block of extinction had significantly less of a fear response during the later trials of a second block of extinction compared to those who received sham stimulation in the first block and active tDCS in the second. This therefore highlights the importance of timing of tDCS and raised the suggestion that brief anxiolytic effects of active tDCS could have impacted the second block of extinction during sham tDCS. Of note,

they did not see any effect of tDCS on extinction recall on day two, when any possible aftereffects of tDCS should have dissipated.

Abend and colleagues¹¹⁴ applied either AC, DC or sham transcranial electrical stimulation (tES) to the vmPFC (FPz and Oz on the EEG 10:20-system) in adults over a three day experiment of conditioning on day one, tDCS on day two during fear extinction, and extinction recall on day three. They found that active stimulation influenced brain activity more than sham, but that unfortunately this led to potentiation of the fear response to CS+ with AC stimulation and a generalization of fear to the CS- with DC stimulation.

Van't Wout and colleagues¹¹⁵ published a later report in which patients completed fear conditioning and extinction on day one, with extinction recall tested on day two. The tDCS anode was again applied to AF3 and the cathode applied to the contralateral left mastoid either during or after the extinction phase on day one. There was no difference seen between the two groups in terms of extinction at the end of day one, but on day two, there was less of a response to the CS+ in patients who had received tDCS after extinction on day one, rather than during the task.

Dittert and colleagues¹¹⁶ later targeted the vmPFC (F7 and F8 on the EEG 10:20-system) with either right or left anodal or sham stimulation and found a significant augmentation of fear extinction with real stimulation, as a quicker loss of CS+/CS- discrimination and decreased reaction to the CS+. There were mixed results for whether left or right vmPFC anodal stimulation was the preferred target. Of note however, they also found an increase in reaction to CS- stimuli with real versus sham stimulation, again cautioning a possible effect of fear generalization with real tDCS.

Abend and van't Wout¹¹⁷ provided a commentary on this study highlighting the need for separation of conditioning and extinction recall over different days, to increase ecological validity and allow for the consolidation of the fear memory. Otherwise, they argue that perhaps memory consolidation is being modulated rather than fear extinction by tDCS. They also raise the point that extinction recall is in fact the dependent variable of most interest in translation to a clinical effect, in terms of the aim of reducing the extent a patient experiences fear to a stimulus following the completion of fear exposure therapy.

Ganho-Ávila and colleagues¹¹⁸ conducted a study in 2019 where they argued that as the vmPFC cannot be directly accessed by tDCS, other more accessible cortical areas of the fear network with connectivity to this region should be targeted instead. They chose to stimulate the right dlPFC as previous fMRI studies demonstrated inhibition of the amygdala during fear extinction learning via projections from this area via the vmPFC, leading to a downregulation of fear responses. They placed the tDCS cathode at F4 on the EEG 10:20 system and the anode at the contralateral left deltoid, in active and sham parallel trials.

Their study design consisted of habituation and fear conditioning on day one, either real or sham tDCS before extinction the next day, and then on day three (one to three months later) subjects received un-signalized reinstatement of the US followed by presentation of the CS+/CS- as a measure of extinction recall. Self-report, SCR and an approach avoidance task (AAT) indicated that there were no immediate effects at the extinction phase of tDCS but that there was an increased long-term negative effect on SCR at the reinstatement/re-extinction phase for participants who had received real versus sham tDCS. However, significant difference seen on the AAT for those who had had real tDCS showing increased

‘safety recognition’ of the CS- compared to sham. There was no effect seen on the time window between session two and three. They concluded that although there was no direct effect of tDCS on CS+ learning, perhaps it aids fear extinction by increasing the discrimination between CS+ and CS- and limiting generalization, a transdiagnostic feature of anxiety disorders. Anxiety generalization is a notoriously difficult area to treat with currently available psychological and pharmacological treatments and perhaps represents a potential niche for tDCS to join these therapies.

Neuromodulation of goal orientated/ habit-based behavior

To our knowledge, there are no studies looking at tDCS and neuromodulation of goal orientated verses habit-based behavior, although investigations have been conducted on this experimental paradigm using TMS. Bogdanov and colleagues¹¹⁹ used neuro-navigated theta burst stimulation (TBS) to either inhibit or excite the inferolateral prefrontal cortex (ilPFC) and found that inhibition led to a decrease in the ability to adapt their behavior to changing task demands (goal orientated behavior), compared to sham or excitatory stimulation of the ilPFC which showed no significant difference to an unstimulated control group.

III. SUBJECT SELECTION

The subjects will be youth diagnosed with OCD, as per DSM-5 criteria. They will be recruited from the Child Psychiatry Program and the Pediatric OCD clinic at Massachusetts General Hospital (MGH), and we will also allow referrals from other clinics in the Boston area. A total of 18 male and female subjects will be recruited for each arm of the study, 36 in total. We aim to enroll 25 patients for each arm (total 50) in anticipation of a 20-30% rate of subjects who do not meet inclusion criteria after screening⁵ or drop out during the study. Participating in one arm of the study does not preclude the participant from enrolling in the second but they will be re-consented. Along with consideration of tolerability and acceptability of the study tasks and procedures in younger subjects, evidence also suggests that children under the age of ten years may show poor discrimination to conditioned stimuli;¹²⁰. Therefore, only subjects between the age of 10-17 will be recruited. Because advancing age is known to produce maturational differences in the neurobiology of fear conditioning and extinction, it is important to conduct research directly on child populations so that accurate conclusions can be drawn that contribute more useful translation to clinical practice for younger patients.¹²¹

Inclusion Criteria

Only youth who meet OCD diagnostic criteria (assessed via all available information and confirmed by the caseness panel) with 100% consensus will be included.

- a) Outpatient youth between the ages 10-17 years
- b) OCD must be determined to be the primary or co-primary diagnosis using the KSADS-PL/KSADS-COMP based on all available information.
- c) Child has a full-scale IQ $\geq$ 85 as assessed on the Wechsler Abbreviated Scale of Intelligence[®] Second Edition (WASI[®]-II)¹²² (within 90% CI). NOTE: To decrease participant burden, the WASI[®]-II will only be conducted in cases of suspected intellectual disability after meeting with the PI.
- d) English speaking.

Exclusion Criteria

- a) Receiving concurrent psychotherapy for subject’s OCD (except maintenance). Subject’s receiving pre-established concurrent psychotherapy for at least 2 weeks regarding other psychological issues

are eligible for enrollment.

- b) New Treatments: Initiation of an antidepressant within 2 weeks before study enrollment or an antipsychotic 2 weeks before study enrollment. No new alternative medications, nutritional or therapeutic diets within 2 weeks of study enrollment.
- c) Established Treatment changes: Any change in established psychotropic medication (e.g., antidepressants, anxiolytics, stimulant, alpha agonist, antipsychotic) within 2 weeks before study enrollment. Alternative medications must be stable for 2 weeks prior to baseline. Any medications must remain stable during treatment; consistent with the NIH-funded Child Anxiety Multimodal Study (CAMS) trial,⁸² downward adjustments due to side effects may be acceptable and will be discussed with Dr. Geller and the community psychiatrist.
- d) Current clinically significant suicidality or individuals who have engaged in suicidal behaviors within 6 months will be excluded and referred for appropriate clinical care.
- e) DSM-V conduct disorder, autism spectrum disorder (ASD), bipolar affective disorder, schizophrenia or schizoaffective disorders
- f) Weight less than 22.5kg
- g) Contraindication to tDCS: history or epilepsy, metallic implants in the head and neck, brain stimulators, vagus nerve stimulators, VP shunt, pacemakers.
- h) Any active substance dependence.
- i) Pregnant or nursing females as the effects of tDCS on pregnancy are unknown.
- j) Presence of a significant and/or unstable medical illness that might lead to hospitalization during the study.

Exclusionary criteria for the use of EMLA exist for

- a) Individuals with pre-existing methemoglobinemia, glucose-6-phosphate deficiencies.
- b) Individuals who have allergic contact dermatitis to lidocaine, and/or prilocaine.

Patients who do not meet stable dose criteria, as specified in the exclusion criteria will not be included in the study. At no point, will patients be withdrawn from medication as a means of meeting inclusion criteria.

IV. SUBJECT ENROLLMENT

Patients will be recruited from Dr Geller's private practice and MGH, specifically from the Pediatric Psychiatry OCD and Tic Disorders Program, an institution nationally known for its work in pediatric OCD, and the MGH OCD Program's Volunteer Research Registry, which includes patients who have already agreed to be contacted about research studies in the program. This site has a catchment area with a population in the millions, patient numbers of many hundreds, a wide network of referring community psychologists and psychiatrists who screen >10 pediatric OCD patients a month without advertising. An informational letter will also be sent to local medical clinics and schools, providing study information to pediatricians, mental health clinicians, and school guidance counselors in the greater Boston area who can help identify potential participants. We have successfully met enrollment targets for past grants in child and adult OCD. Experience shows that ~50% of our subject pool would not qualify for this study and of those that qualify, ~50% would not be interested in participating. Given that we see ~120 new patients per year, ~60 would be eligible to participate of which we estimate ~50% would be interested in participating (N=30/year). Procedures will be in place to ensure that the risk of patients and their parents feeling obliged to participate are minimized and they will be assured that their decision to participate or not will have no impact on their child's medical care.

Patients of the Pediatric Psychiatry OCD and Tic Disorders Program will be recruited in the following manner. Patients of this Program indicate on their intake form whether they agree to be contacted about future research studies and also indicate whether they would like to opt-in or opt-out of encrypted email. Patients who have agreed to be contacted about research will be emailed (via Send Seure if they chose to opt-in or via regular email if they chose to opt-out) a recruitment letter signed by the PI of this study and the Director of the Program. This email may be followed up by a phone call from the study coordinators. Patients who indicate that they are interested in learning more may be emailed the study consent forms (parent/guardian informed consent form and child assent form), as this is a convenient way of passing along detailed information about the study in lay terms.

We will also employ the Research Patient Database Registry (RPDR) to identify potential participants. We will contact potential participants via Patient Gateway who have not opted-out of receiving invitations. We will use the required MGB Research Invitation template and will indicate in the invitation that we may follow-up with potential participants via a phone call.

Recruitment and Informed Consent.

A multi-gate recruitment procedure will be used, like that used in the Pediatric OCD Treatment Studies^{8,123} to ensure that symptoms are in the clinical range before commencing the study (see Figure 1). Gate A is a 20-minute semi-scripted telephone screen to elicit preliminary inclusion/exclusion information and to provide additional information to the caller. Gate B assessment determines "caseness" (formal presentation of the informed consent agreement, diagnostic assessment, and WASI®-II and pregnancy test if applicable; ~1-2 hours). Gate C is a baseline assessment and randomization on the same day as Gate B (visit 0) but after a break as needed, if the subject is deemed eligible (~1.5 hours).

Gate	Time (approximately)	Aim	Tasks
A	20 minutes	Elicit preliminary inclusion/exclusion information	Semi-scripted phone screen
B	1 hour	Determine "caseness"	Diagnostic assessment, pregnancy test and WASI-II if applicable. Informed consent/assent agreement.
C	0.5 hours	Baseline assessment and randomization	Symptomatic questionnaires

Figure 1- multi-gate recruitment procedure

Informed consent/ child assent will be obtained from children and their parents or legal guardians prior to the performance of any protocol procedures by the PI. The informed consent document will be used to explain in simple terms the risks and benefits of study participation to the subject. The nature of the study will be fully explained to the subject by the PI, co-investigators or specially trained research coordinators. The subject will be encouraged to ask questions pertaining to their participation in the study and the subject may take as much time as they feel necessary to consider his/her participation in the study as well as consult with family members or their physicians. Participation in this study is voluntary and the subjects may withdraw from the study at any time.

The informed consent/assent document will also ask to for approval to collect images and/or video of the subject wearing the tDCS cap with electrodes for teaching and educational purposes in accredited scientific and teaching hospital forums only; no public disclosure of images/videos will be permitted. The permitted photographs/videos we collect during the subject's participation will be kept for 5 years after the conclusion of the study and will then be destroyed. The permitted photographs/videos we collect during the subject's participation will not become part of their medical record. The subject's decision to allow or prohibit the collection of photographs/videos will not interfere with their study participation.

Written consent will be obtained from both parents or legal guardian(s) using the PHRC approved Consent Form, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. Assent will be obtained from each child 10-17 years of age who, in the opinion of the Investigator, is capable of providing assent based on their age, maturity, and psychological state and will be documented for subjects 14 through 17 years of age in writing using the PHRC-approved Consent Form, and in writing on the Assent Form for subjects 10 through 13 years of age. When assent is not obtained, the Investigator will document their rationale in the research records.

In light of the COVID-19 pandemic, informed consent and assent will be obtained virtually over Healthcare Secure Zoom by the PI (Dr Geller) to limit in-person contact. Families will be sent a private survey link to access the informed consent/assent form in REDCap. The survey link will contain a blank PDF upload of the informed consent/assent form, as well as an attached PDF for download. Families will have the opportunity to follow along with Dr. Geller in reviewing the document.

REDCap survey options, including checkboxes designating "Yes" or "No", as well as signature lines in which families can sign off with their computer mouse, will allow the study to obtain and document informed consent and assent. When the family has no further questions and have documented consent/assent appropriately, Dr. Geller will receive authorization in REDCap to acknowledge he obtained consent by signing his name, as well as inputting his encrypted Partners username and password.

Study staff will import the signed informed consent/assent into REDCap eDC and the electronic study regulatory binder and email the participant and family copies of their signed informed consent/assent.

The research team will carefully protect confidentiality of participants' research information. Researchers will be carefully trained about the importance of confidentiality and required to undergo HIPAA training. In addition, all paper-generated data will be stored in double-locked files in Dr. Geller's laboratory at Simches Research Center, Charles River Plaza, 185 Cambridge St, Boston, MA 02114. and all computer-generated data and participant photographs/videos will be maintained in password-limited hard drive files or stored in Partner's encrypted electronic data-entry database, 'REDCap', on a secure server at Massachusetts General Hospital. Participant names (or any other identifying information) will not be kept on the study measures themselves. Instead, code numbers will be used on the actual data gathering tools. Participants will be told that they can discontinue participation at any time or refuse to answer any study questions without adverse consequence.

V. STUDY PROCEDURES

To accomplish our specified aims, we propose to recruit 36 patients, 18 for each arm. After providing study information and obtaining IRB approved informed consent, participants will undergo a psychiatric assessment to determine eligibility for inclusion and exclusion criteria. Half of the subjects will be tested on

fear extinction and inhibitory control paradigms and the other half will undergo tests of goal orientated versus habit-based behavior and inhibitory control. The following scales will be utilized during the initial evaluation and at other points in the study as shown in Table 1 and 2. Taking part in one arm of the study does not exclude the participant from taking part in the other arm. Each subject will undergo 3 experimental visits (corresponding to 3 tDCS conditions) consisting of either one or two days each and tested on the same tasks for each experimental visit, as demonstrated in Tables 1 and 2 and detailed further in Figures 5 and 6 below. In light of the COVID-19 pandemic, the whole of Visit 0 and the questionnaire completion component of Visit 3 will now be conducted virtually via a secure video call, in order to minimize in-person visit time.

Questionnaires:

Clinician-Rated Measures.

*The Schedule for Affective Disorders and Schizophrenia for School-Age Children--Present and Lifetime Version (KSADS-PL)*¹²⁴ is a clinician-administered diagnostic interview for DSM-V childhood disorders. This will be administered at baseline to both parents and children, and clinical judgment used to determine diagnoses based upon combined reports. To allow for increased social distancing during the COVID-19 pandemic, in some circumstances the web-based computerized version (KSADS-COMP) will be used instead of the KSADS-PL.¹²⁵

*The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)*¹²⁶ is a clinician-administered interview with the parent and child of OCD symptoms and severity.

Clinical Global Impression-Severity (CGI-S). The CGI-S¹²⁷ is a widely used 7-point clinician rating of clinical severity.

Children's Depression Rating Scale-Revised (CDRS-R). The CDRS-R¹²⁸ is a semi-structured child interview to assess depression severity.

Family Accommodation Scale- Interviewer Rated (FAS-IR). The FAS-IR¹²⁹ assesses family accommodation of the child's OCD symptoms.

Wechsler Abbreviated Scale of Intelligence® Second Edition (WASI®-II). The WASI®-II¹²² assesses IQ and will only be conducted in cases of suspected intellectual disability after meeting with the PI.

Parent and Child Measures.

Child Obsessive Compulsive Impact Scale- Revised: Child Rating (COIS-RC) and Parent Rating (COIS-RP). The COIS-R⁵ are 56-item, child- or parent-report measures, (COIS-RC/COIS-RP), which assess OCD-related impairment.

Pediatric Quality of Life Inventory (PedsQL). The PedsQL¹³⁰ consists of parallel child and parent proxy measures of children's quality of life.

Screen for Child Anxiety Related Emotional Disorders (SCARED) The SCARED¹³¹ is a psychometrically sound 41 item self-report questionnaire that assesses five symptom factor domains of panic/somatic anxiety, generalized anxiety, separation anxiety, social phobia, and school phobia.

Real/sham tDCS questionnaire, to assess the extent of blinding, parents and children will be asked to

comment on whether they think they received real or sham stimulation after each session

Parent-rated measures.

ADHD Rating Scale-IV: Home Version (ADHD-RS). The ADHD IV RS¹³² is an 18-item parent-report measure designed to identify the frequency of each ADHD diagnostic symptom based on the subscales of inattention and hyperactivity-impulsivity.

Youth-Rated Measures.

Obsessive-Compulsive Inventory-Child Version (OCI-CV). The OCI-CV¹³³ is a 21-item self-report measure designed to assess varied OCD symptom dimensions.

Self-rating scale, adapted from the version developed by Abend and colleagues¹¹⁴ Participants will be shown the CS+ and CS- (on paper) and asked to indicate how afraid they are when they see each shape on a Likert scale from 1-10 (1 = not afraid, 10 = extremely afraid).

*tDCS adverse effects questionnaire*¹³⁴ asks about the presence of common side effects from a list and the extent to which the participant feels they are related to tDCS.

EMLA Cream Safety Question is asked to any participant who opts for its use to ensure no pre-existing allergies, diagnoses, or sensitivities exist that are known to have a negative and/or harmful reaction with the application of EMLA.

*Edinburgh Handedness Inventory-Short Form*¹⁵⁸ is a 4-item self-report measure used to assess preference to use one hand more than the other (handedness).

Computer tasks:

The following computer-based cognitive tasks will be used as outcomes to measure neurocognitive function.

Assessment of Fear Extinction

A computer-administered fear conditioning paradigm will be conducted where children learn to associate an aversive unconditioned stimulus (US) with a paired conditioned stimulus (CS+) but not an unpaired conditioned stimulus (CS-).²⁵ The methodology associated with this paradigm has been shown to be ecologically-valid and well-tolerated by anxious youth, while avoiding the safety and ethical issues related to more aversive unconditioned stimuli (e.g. electric shocks).¹³⁵ At the onset of the task, which takes place at a computer terminal in a private room, youngsters will be told: "You will see pictures of two shapes on the screen. Please watch the pictures while they are on the computer screen. While you are watching the pictures, you will see a mildly unpleasant picture of a person and an unpleasant sound". Youth will then be told they may discontinue the study procedures at any point if they desire by simply telling the investigator or informing their parent.

In the first phase (habituation), children are presented with neutral CSs of two geometric shapes that are different in shape and color and each is shown four times, totaling eight presentations, similar to the stimuli used by Orr and colleagues.¹³⁶ These CSs are presented for 8 seconds at a time, with an inter-stimulus interval in the range of 20-26 seconds. In the next phase (acquisition), youth view these same two shapes for a total of 2x10 trials; one stimulus (CS+) is paired with a moderately aversive unconditioned stimulus (UCS), i.e., a female screaming face and a loud but brief 60-95 dB scream.

Each CS+ presentation will be immediately followed by the UCS while the other stimulus (CS-) will not be paired with the UCS on any of the 10 trials. The UCS will remain for a duration of 3 seconds. The decibel level of the scream noise will be determined for each individual participant as to be “highly annoying;” intensity will range from 60-95dB.

In the third phase (extinction), 2x10 presentations of each shape will be presented without the UCS. Prior to, and following, extinction subjects will indicate on a 10-point Likert-type scale the degree to which they felt afraid of the CS+ and CS-. Skin conductance, ECG and EEG will be continuously recorded throughout the procedure and response scores will be calculated for the CS+, CS- and UCS. In the fourth phase, extinction recall will be tested the next day, where the shapes will be re-presented 10 times each without the UCS (see Figure 2 below). These four phases will be repeated for each of the three tDCS visits with different shapes and colors used to differentiate the CS+ and CS-.

Stimuli will be presented using SuperLab (Cedrus Corporation) software and data will be recorded with AcqKnowledge (BIOPAC® Systems Inc.) software. The script will be analyzed with MATLAB (MathWorks®) post-experimentally.

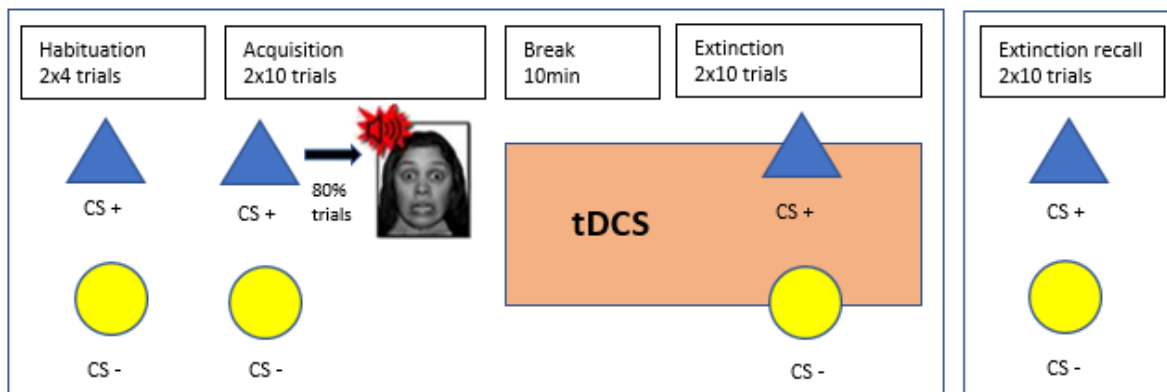


Figure 2- Graphical representation of the fear extinction experimental component over two days

Inhibitory control tasks

*Stop Signal Task:*⁴³ This task measures the ability to inhibit a response. The participant pushes a key on the keyboard when a ‘go’ signal appears for example a right facing arrow but in 25% of cases, this is followed by a ‘stop’ signal where they must inhibit this action (see Figure 3 below). The outcome of inhibitory control is measured by the stop signal reaction time (SSRT), calculated by subtracting the stop signal delay (SSD) from the go signal response time (RT), and with the use of a tracking algorithm can measure the time taken to inhibit an already initiated motor response to press the corresponding key. Longer SSRTs are associated with a subject needing longer to suppress pre-potent motor responses and are therefore seen a marker of decreased inhibitory control. We will compare the change in this time for each subject before and after each tDCS stimulation episode.

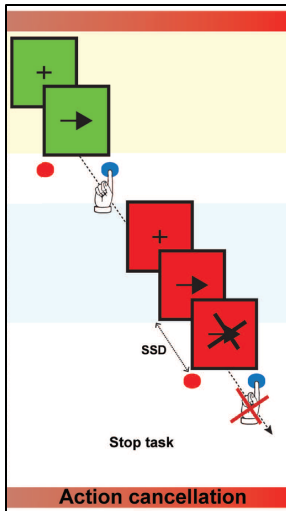


Figure 3- Stop Signal Task from van Velzen and colleagues.⁴⁷ SSD= Stop Signal Delay, the time between the go stimulus presentation and the stop signal.

Goal orientated verses habit-based behavior

The sequential spaceship task was developed by Decker and colleagues³⁶ to investigate the balance of goal orientated as opposed to habit-based behavior in children. It was adapted from a sequential learning task developed by Daw and colleagues,¹³⁷ which has also been used longitudinally with adults.¹³⁸

The task begins with an automated tutorial written in MATLAB and using Psychophysics toolbox extensions^{139–141} to convey a back story of the scenario and key concepts, i.e. probabilistic rewards and transitions, in child friendly terminology. Participants verbally assert that they understand before the task of collecting ‘space treasure’ begins. At the first stage, children chose between two different colored spaceships that each travel to one of two planets more than the other, i.e., the blue spaceship has a 70% chance of travelling to the red alien planet (common transition) and 30% chance of arriving at the purple alien planet (rare transition), whereas the opposite is true for the green spaceship (see Figure 4a). At the second stage, participants choose between two different aliens on the planet they have ‘landed on’ and there is a slowly drifting probability (between 0.2-0.8) of obtaining a reward or nothing (an empty circle), designed to encourage exploration to maximize the chance of obtaining a reward. Subjects are given 3 seconds to make a choice at each step, with 1 second of an animation, 1 second of reward feedback and a 1 second interval between trials. Overall, there are 200 trials in two blocks after a practice task, separated by breaks. Subjects will be informed that they will earn a bonus of \$5 per task depending on how much treasure they find, which is repeated twice at each of the three visits.

Figure 4b shows bar-chart idealized representations of purely model free/ habit-based, and model based/goal orientated behavior. In more habit-based learners on the left-hand chart, they tend to make the choice at the first stage that led to a reward in the last trial (stimulus-response), irrespective of how common or rare the transition type is (the model). Purely model based/ goal-orientated subjects adapt to the model of probabilities and demonstrate action-outcome learning.

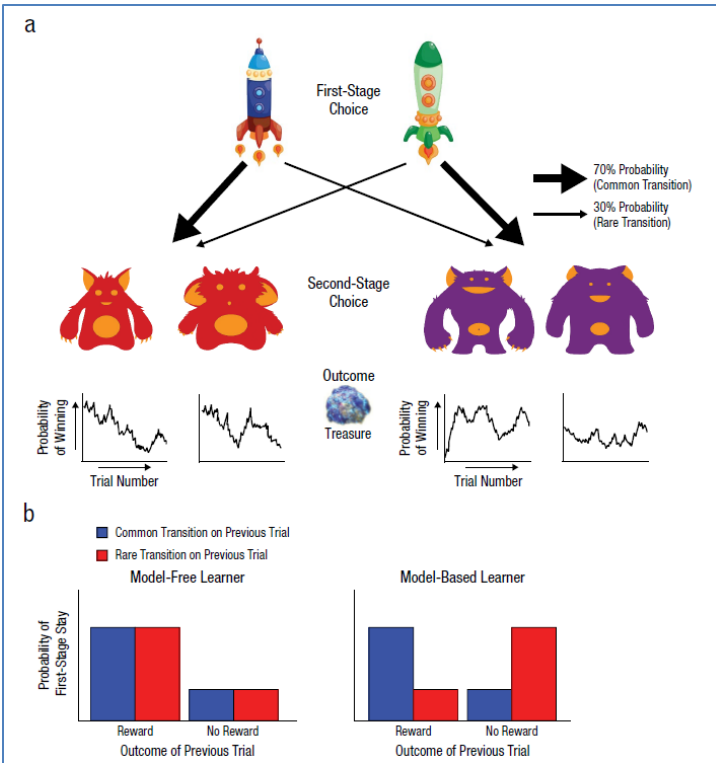


Figure 4- a) Sequential spaceship task,³⁶ b) idealized model-free and model-based behavior

Biological measures

Skin Conductance Response (SCR)

This will provide one of the primary dependent measures of fear conditioning and will be recorded continuously during the fear conditioning components of arm A. This will two conductive-gel-coated BIOPAC® EL504 disposable adhesive electrodes placed 10mm apart on the hypothenar eminence of the participant's non-dominant hand, in a similar method to that used by Pace-Scott and colleagues.¹⁴² Measurements will be made using BIOPAC® Systems Inc. (Goleta, CA) MP150 system, AcqKnowledge software and a BIOPAC® GSR100C Electrodermal Activity Amplifier.

Electrocardiogram (ECG)

Used as another primary dependent measure of fear conditioning, in terms of measuring variations in HR acceleration (HRA) shortly after (1-4 seconds) an aversive stimulus as a marker for increased sympathetic nervous system activation. ECG leads will be placed on the subject via two EL503 Ag/AgCl 11-mm disposable electrodes stuck below the left eighth rib and under the right clavicle. These will be attached to a BIOPAC® Systems Inc. (Goleta, CA) four-channel MP36R data acquisition system with a built-in ECG100C amplifier, using AcqKnowledge software.

Pregnancy test

A urine pregnancy test will be performed when deemed relevant.

Electroencephalography (EEG)

Electrodes will be placed according to the international 10:20 system, with measurements taken throughout the study in order to identify ERPs.¹⁴³

tDCS stimulation

Within each arm, a total of 18 subjects will be randomized to either sham or active stimulation during the extinction phase of session 1 and have the intervention switched for session 2. If subjects did not receive sham stimulation for session 2, then they will receive sham stimulation for session 3. Overall, subjects will receive sham stimulation for one session and active stimulation for two sessions. Subjects will be presented with the SST and a self-report rating scale of fear before and after sham/active stimulation, as well as a tDCS side effects questionnaire afterwards. The average testing time is expected to be 20-40 minutes both pre, and post tDCS.

For the two active tDCS sessions, one will target the right vLPFC (F8) with +2mA excitatory anodal stimulation (with the -2mA cathodal reference electrode placed at Fpz) and the other active session will target the pre-SMA (Fz) with -2mA cathodal inhibitory stimulation (with four +0.5mA anodal reference electrodes placed at F3, F4, P3 and P4). The sessions will last 30 minutes in each case and at 2mA. The current will be applied by a battery-driven tDCS stimulator (Starstim, manufactured by Neuroelectronics Barcelona) connected to specifically designed tDCS electrodes, which are applied to pre-determined targets on the head surface using electrophysiological conductive gel for improved contact and impedance.

For the sham condition, the electrodes will be placed at the same positions, but the current will be applied only for a 15 second ramp up phase at the beginning, 5 seconds of stimulation and a 30 second ramp down phase and end of the 30-minute sham-stimulation period, to simulate the potential experience of local tingling sensation that real stimulation produces but without sustained effect on cortical activity. This sham protocol is standard, validated and programmed in our system. Stimulation may also be administered with simultaneous electroencephalography (EEG) to record neurophysiological correlates of the neurocognitive function modulation, an electrode placed at Pz will be used for EEG recordings only.

tDCS will be administered by trained technicians, under the supervision of Dr. Camprodon. These selected technicians have followed an internal training and certification process under the supervision of the chief of the MGH TMS clinical service, Dr. Camprodon, who is one of the co-investigators of this study. These procedures have been approved by the department's quality and safety committee. The training involves not only theoretical principles and practical hands-on use of these forms of noninvasive neuromodulation, but a thorough understanding of possible risks, how to identify them and how to activate the laboratory and/or clinic's safety plan in case they occur. After this training, technicians and clinicians alike need to take an exam and have a period of observation until they can demonstrate proficiency in the use of TMS and tDCS. Experiments in the Laboratory for Neuropsychiatry and Neuromodulation follow the same high standards and criteria used in the MGH TMS clinical service, which is part of the same clinical and research program directed by Dr. Camprodon. These noninvasive neuromodulation modalities are considered low risk and it is standard in clinics and laboratories nation-wide that well-trained non-MDs apply the stimulation, just like MRI technicians run the MRI scans and radiologists are not present during the procedure.

Rater Training. All symptom-oriented assessments will be conducted by highly trained doctoral level blinded raters. Precautions taken to maintain the IE blind include subjects and their families being reminded before each assessment to not disclose treatment-identifying information to the IE.

Procedures	Visit 0	Visit 1 (Day 1)	Visit 1 (Day 2)	Visit 2 (Day 1)	Visit 2 (Day 2)	Visit 3 (Day 1)	Visit 3 (Day 2)
KSADS-PL/KSADS-COMP	X						
CY-BOCS; CDRS-R; COIS-RC; COIS-RP PedsQL; SCARED; OCI-CV; CGI-S; FAS-IR, ADHD IV RS	X						X
tDCS		X		X		X	
tDCS adverse effects questionnaire		X		X		X	
Real/sham tDCS questionnaire		X		X		X	
EMLA cream questionnaire (if applicable)		X		X		X	
Stop Signal Task		X		X		X	
Fear Habituation, Acquisition and Extinction		X		X		X	
Extinction Recall			X		X		X
Self report of fear, SCR and ECG		X	X	X	X	X	X
EEG		X	X	X	X	X	X
Pregnancy Test (if applicable)		X					
WASI-II® (if applicable)		X					
Edinburgh Handedness Inventory-Short Form		X					

Table 1. Study Visit and Assessment Schedule for the fear extinction/ inhibitory control arm (A)

	Visit 1, 2 or 3, Day 1							Visit 1,2 or 3, Day 2 (next day)		
Stop Signal Task	X						X			
Fear Extinction Paradigm		Habituation		Acquisition		Extinction			Extinction recall	
SCR, ECG		X	X	X	X	X		X	X	X
Self-report fear			X		X		X	X		X
tDCS						30min sham/ real				
tDCS adverse effects questionnaire							X			

Real/sham tDCS questionnaire							X			
EMLA cream questionnaire (if applicable)	X									
EEG	X	X	X	X	X	X	X	X	X	X
Time										

Figure 5- Detail of one study visit over approximately two days in the fear extinction/ inhibitory control arm (A)

Procedures	Visit 0	Visit 1	Visit 2	Visit 3
KSADS-PL/KSADS-COMP	X			
CY-BOCS, CDRS-R; COIS-RC; COIS-RP; PedsQL; SCARED; OCI-CV; CGI-S; FAR-IR, ADHD IV RS	X			X
Stop Signal Task		X	X	X
Sequential Spaceship Task		X	X	X
tDCS		X	X	X
EEG		X	X	X
tDCS adverse effects questionnaire		X	X	X
Real/sham tDCS questionnaire		X	X	X
EMLA cream questionnaire (if applicable)		X	X	X
Pregnancy Test (if applicable)		X		
WASI®-II (if applicable)		X		
Edinburgh Handedness Inventory-Short Form		X		

Table 2. Study Visit and Assessment Schedule for the goal orientated verses habit-based behavior/inhibitory control arm (B)

	Visit 1, 2 or 3				
Stop Signal Task	X			X	
Sequential Spaceship Task		X			X
tDCS			30min real/ sham		
tDCS adverse effects questionnaire				X	
Real/sham tDCS questionnaire				X	
EMLA cream questionnaire (if applicable)	X				
EEG	X	X	X	X	X
Time					

Figure 6- Detail of one study visit over approximately one day in the goal-orientated verses habit-based behavior/ inhibitory control arm (B)

VI. STATISTICAL ANALYSIS

For the stop-signal task, the outcome of inhibitory control is measured by the stop signal reaction time (SSRT), calculated by subtracting the stop signal delay (SSD) from the go signal response time (RT). We will compare the change in this time for each subject before and after each tDCS stimulation episode.

The Sequential Spaceship task will be analyzed for the degree of model based/goal-orientated behavior versus model free/ habit-based behavior. Questionnaires administered at the beginning of the first study visit will be clinical measures that are included as regressors in our models.

The fear extinction task will measure the difference in SCR, ECG and self-rated fear scores between habituation, conditioning and extinction/extinction recall stages of the experiment. Using the same method as Orr and colleagues,¹³⁶ the SCR score will be calculated for each CS presentation by subtracting the average SC level during the 2 second interval just before CS presentation from the peak SC level during the 8 seconds of CS display. Similarly, a SC unconditioned response score (UCR) will be calculated by subtracting the average SC level during the last 2 seconds of the CS interval from the peak SC level during the 5 seconds following onset of the UCS. ECGs will be recorded at 2000 Hz and HRA will be calculated by subtracting the mean HR for the 1 second before the aversive stimulus from the mean HR 1-4 seconds following it.¹⁴⁴ To reduce heteroscedasticity, SCR and HRA scores will be square root transformed and if the original figure is a negative value, then the negative sign will be retained by calculating the square root of its absolute value.¹³⁶

We will be using a three treatment by three period cross-over design with two orthogonal Latin squares¹⁴⁵ to maintain treatment balance over all six treatment sequences: ABC, BCA, CAB, ACB, BAC, CBA; where A is active tDCS target 1, B is active tDCS target 2 and C is sham tDCS. Subjects and researchers conducting the study/analyzing the data will be blinded to this ordering.

Statistical analysis will be done by repeated measures ANOVA, using a fully unstructured co-variance matrix to correctly account for the within subject correlation of repeated measures. The model will include main effects of treatment and period. Will we also test for a period by treatment interaction but expect to be able to remove it from the model by allowing a sufficient washout period of at least 24 hours between tDCS stimulation episodes.

As this is a pilot study using novel methods, that to our knowledge have never been studied in this patient population before, sample size considerations are based on ensuring adequate precision of our primary outcome data rather than null hypothesis significance testing. For pilot studies, Julious¹⁴⁶ recommends that a sample size of at least 12 subjects is acceptable for pilot studies to balance feasibility and obtaining reasonable precision of estimated means. He showed that the large gains in precision, as measured by the half-width of the 95% confidence interval, begins to diminish at around a sample size of 12 subjects. Considering both the feasibility of recruiting subjects and the six-sequence design, we aim for a sample size of 18 subjects to allow three subjects for each of the six treatment sequences. With this sample size the half-width of the 95% confidence interval around the mean treatment effect will be on the order of 0.50 standard deviations of the within patient treatment difference. Based on prior studies, we expect up to 25% of subjects might start but not complete the study. Therefore, we expect we may need to recruit 24 patients for each of the two study arms, although completing one arm would not exclude a participant from joining the other after being re-consented.

We have been grateful for the advice of biostatisticians through Harvard Catalyst in assisting with the design of the study and will also consult the MGH Biostatistics Center Core in the data analysis and interpretation phase of the study.

VII. RISKS AND DISCOMFORTS

Risks Associated with Transcranial Direct Current Stimulation (tDCS):

tDCS is an investigational device that does not pose a significant risk to participants. The safety of this technique has been studied and summarized by different research groups around the world, especially in recent years.¹³⁴ The method has a history dating back to the time of Ancient Greece¹⁴⁷ and in a review conducted in 2016 of over 700 studies, no reports of serious adverse events or irreversible injury were found in conventional protocols of tDCS in humans, across more than 30,000 sessions and 1000 subjects.¹⁴⁸ In a comprehensive review of studies published from 1998 to 2008, it was concluded: “Extensive animal and human evidence and theoretical knowledge indicate that the currently used tDCS protocols are safe.”¹⁴⁹

Reviews focusing specifically on pediatric populations and have also concluded that tDCS is generally safe and effective in children.^{73–75} And although there are no studies on tDCS for pediatric OCD subjects, there has been a review attesting to the safety and tolerability of this modality in adults with the condition.¹³

Accordingly, we will strictly follow standard methodology for tDCS application and stimulation parameters that have been used in previous research studies. We will also exclude participants with unstable medical conditions, or any illness that may increase the risk of stimulation, for example epilepsy. Furthermore, subjects should have no metallic implants. All these elements will be considered in this study and are included in the informed consent. tDCS appears to be less hazardous than other forms of brain stimulation, even other noninvasive modalities such as transcranial magnetic stimulation (TMS).

The protocol to be used will apply stimulation levels that fall within safety standards established by studies investigating neural tissue damage, as well as numerous studies applying tDCS to human participants. Human studies that reported safety outcomes have included patient populations and stimulation schemes of up to 6 weeks of daily stimulation.¹⁵⁰ No major adverse effects were reported using these parameters. Most importantly, the subjects will only be receiving two short-lived active stimulation sessions during each arm of the study, which will lead to transient after-effects lasting 30–90 minutes.

Side Effects:

The most common side effects associated with tDCS according to the most recent data available^{73,134,149,150} are:

1. Sensations reported by subjects under the electrode (these sensations can sometimes, though rarely, continue throughout the stimulation time and for a brief period following completion of the tDCS but usually resolve shortly after the initiation of tDCS): mild tingling, light itching, slight burning, discomfort or mild pain.
2. Effects reported that occur only during tDCS: visual sensation during switching on and off the stimulation. Other effects that can occur both during and after tDCS include: moderate

fatigue, skin redness, headache and difficulties in concentration.

Rare side effects:

1. Nausea
2. Nervousness
3. Shock-like sensation at the initiation of tDCS

Subjects will be offered the use of the topical anesthetic EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) to decrease sensation on the area of the scalp that will undergo stimulation only.¹⁵¹ EMLA will be applied only to intact skin, and areas where the skin is not intact (e.g. skin irritation, wound skin) or inflamed will be avoided, including areas around and near the eyes. Prior to the administration of EMLA Cream, participants will be asked about any skin allergies and informed about possible side effects that may be expected from the cream. Local side effects include blanching and erythema, but this preparation is widely accepted as safe and well tolerated in children over three months of age.¹⁵²

We do not anticipate any clinically significant adverse events in the application of EMLA over multiple days in the event of back-to-back sessions. If a subject opts for the use of EMLA, this will be used per their preference and desire upon each individual session, regardless of sham or active tDCS as it is a double blinded study.

Changes in the activity of the prefrontal region have the potential to induce acute changes in mood. Hypomania has been reported in a few patients receiving tDCS for bipolar disorder^{153,154} and depression¹⁵⁵ but not, to our knowledge, in patients not suffering from mood disorders. To minimize risk of exacerbating a comorbid mental health condition, individuals with moderate to severe symptoms of a poorly controlled comorbid condition will be excluded. It is important to note that many of the side effects listed above have been also reported in association with sham tDCS, even with similar rates.^{156,157}

Although there are no reports suggesting increased risk for tDCS during pregnancy, pregnant females are excluded from this study due to insufficient knowledge of the effects of the strong magnetic fields on the fetus. Potential subjects who are female and of childbearing age will be asked about their pregnancy status, sexual activity, whether pregnancy is being sought, and use of contraception. Study staff will record her responses to these questions. If the potential subject cannot rule out the possibility of pregnancy, or if her answers to these questions suggest pregnancy is possible, a pregnancy test will be conducted prior to study enrollment.

Risks from questionnaires, rating scales and computer tasks

One potential risk of participating in this project includes discomfort associated with the psychiatric evaluation, neurocognitive computer tasks and administration of rating scales – either due to the discussion of subjectively difficult topics, or due to the length of time required for the interviews, tasks and questionnaires. In efforts to minimize subject burden, we only chose measures that were central to study questions and did not overlap considerably with other study measures. Regarding potential discomfort, our experience indicates that most people welcome the opportunity to discuss their experiences with a trained clinician; and any information shared by the subject will be kept confidential. We recognize that child participants must complete several measures that were chosen to assess a range of constructs that we believe may be impacted by the intervention or help understand (i.e., moderate) treatment outcome. We have done our best to minimize subject burden while assessing relevant

constructs and maintaining the internal validity of the study.

Specifically for the fear extinction task, the methodology associated with this paradigm has been shown to be ecologically-valid and well-tolerated by anxious youth, while avoiding the safety and ethical issues related to more aversive unconditioned stimuli (e.g., electric shocks).²⁴ Youth will be told they may discontinue the study procedures at any point if they desire by simply telling the investigator or informing their parent. The decibel level of the loud, shrieking noise will be calibrated to each individual participant, ranging from 60-95dB to ensure that the sound is tolerable at each individual's level and not overly aversive. Study staff will also monitor the extent of discomfort from the self-rated scales of fear and SCR recordings to ensure that participants are not overly fearful during the experiments.

Breaks will be given as much as possible to decrease boredom and physical/psychological discomfort. We will also compensate families \$100 for each study visit they attend (\$100 per visit for arm a and \$90 plus \$10 bonus per visit for arm b), amounting to \$300 total if they attend all sessions of the study arm. We will also provide vouchers to families for parking when needed.

VIII. CONFIDENTIALITY

All research-related records initiated by a subject's participation in this study that reveal the subject's identity will remain confidential except as may be required by law. Data obtained from this study will not identify the subjects individually. Subjects will be assigned code-names and ID numbers. Data obtained from our studies may be published. Original research-related records may be reviewed by the Partners Human Research Committee, and regulatory authorities, to verify clinical trial procedures and/or data. Information may be held and processed on a computer. Access to these computerized records will be password protected and restricted to study staff. Subjects will only be contacted regarding future studies if they indicate that they are interested in being contacted by initialing in the specific section of the consent form. Healthcare Secure Zoom will be used for all virtual visits, as per Partners HealthCare recommendations.

IX. POTENTIAL BENEFITS

Participants will not receive any direct benefit from this study. It is possible that after real tDCS executive function may improve, but this would only be transient and last for 30-90 minutes at most. This is not a therapeutic clinical trial, but a translational cognitive neuroscience study. Information derived from this research could reveal benefits from tDCS in this patient population, leading to future treatment-oriented clinical trials. Families will also be compensated with \$100 for each of the study visits they attend, amounting to \$300 total if they attend all sessions of the study arm (\$100 per visit for arm a, and \$90 plus \$10 bonus per visit for arm b), as well as parking vouchers when needed.

X. MONITORING AND QUALITY ASSURANCE

The principal investigator will oversee the collection, maintenance, and analysis of all data. He will also be responsible for ensuring that all adverse events are reported according to the Partners Human Research Committee Adverse Event Reporting Guidelines-

<https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Reporting-Unanticipated-Problems-including-Adverse-Events.pdf>.

The principal investigator acknowledges a possible and/or probable discovery of undiagnosed ADHD in participants during one's screening assessment with the inclusion of the ADHD Rating Scale. In the event of a diagnosis arising, the investigator will make a diagnostic assessment using expert clinical judgement regarding the presence of ADHD. The DSM 5 will be used as guidelines.

Any adverse events experienced by a subject will be communicated to the principal investigator and conveyed to the Partner's IRB. The principal investigator will review the completeness and accuracy of informed consent after each patient. The performance data will be automatically recorded on the computer workstation to ensure accuracy. Access to this digital data will require a password.

Every effort will be made to maintain patient confidentiality. We will use a coded ID numbers consisting of sequential numbers and a combination of letters on all results acquired and stored. The only name identification can be found on the consent form and other forms the subject has filled out. Partners consent forms will be stored electronically in the Partners encrypted electronic data-entry database 'REDCap' on a secure server at Massachusetts General Hospital, and any paper versions in a designated locked cabinet. No identifying information will be used in any publications or presentations that emerge from this data.

Any experimental data will be passed on only to the principal investigator, co-investigators, and to study staff. Information derived from this study will be made available to the MGH IRB. The information collected in our study will be used only for research purposes. Computer-based data and hardcopies will be made available only to the research team, e.g., stored on password-protected computers or in locked file cabinets. We will use only the minimum amount of information necessary for our study. Data will not be part of a patient's chart, as this information is investigational only, and not diagnostic. All researchers are trained in methods to protect confidentiality

All adverse events and unanticipated problems involving risks to subjects or others will be reported to the HRC in accordance with HRC adverse event and unanticipated problems reporting guidelines.

If patients respond positively to questions regarding suicidality in the screening questionnaires, a licensed study clinician will be notified, and a safety evaluation will be performed. If clinically indicated or if psychiatric symptoms worsen, the participant will be referred to the MGH Acute Psychiatry Service. In severe cases, as determined by the licensed study clinician, we will contact security, call 911, and transport the participant to MGH via ambulance.

XI. REFERENCES

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