1) Protocol Title

Title: The Effects of Transcranial Direct Current Stimulation on the Neuronal Mechanisms of Cognitive Control in Schizophrenia
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2) Objectives

The purpose of this study is to better understand the neural correlates of cognitive control (CC) deficits in schizophrenia and determine how these mechanisms can be modulated by transcranial direct current stimulation (tDCS). CC is a critical neurocognitive process that is required for flexible, directed thought and action based on goals and intentions. Identifying and developing paradigms to improve CC is therefore a mental health priority. Current theories of CC postulate that recruitment of the dorsolateral prefrontal cortex (DLPFC) is essential for this process by maintaining high-level information that it can then use to orchestrate patterns of activation in other brain networks to support optimal performance. tDCS is a safe, noninvasive method of modulating regional brain excitability via brief (15-20 m) application of a weak (1-2 mA) current. The goal of the proposed experiments is to combine tDCS with functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) to test the hypotheses that 1) acute tDCS over the DLPFC can improve performance during a CC task (the dot pattern expectancy (DPX) variant of the AX-CPT) in schizophrenia, and 2) acute tDCS over the DLPFC can increase recruitment of the DLPFC during the DPX. Sham stimulation over the DLPFC and acute stimulation over the somatomotor cortex (SMC) will also be performed as control conditions. Effects of tDCS on brain functional connectivity (during CC as well as during the resting state) will also be examined, as well as effects on an episodic memory task. EEG recordings will be incorporated into this study in order to better understand the physiological mechanisms associated with cognitive function, as well as with non-invasive stimulation The current study will be the first to use fMRI to examine the effects of tDCS on the neuronal mechanisms of CC in schizophrenia, and has potentially important implications for therapeutic development for this treatment refractory yet disabling aspect of the illness.

This study is solely intended as basic research in order to understand brain function in healthy individuals and brain function in patients with schizophrenia. <u>This study is not intended to diagnose, cure, or treat schizophrenia or any other disease.</u>

3) Background

Cognitive deficits in schizophrenia are not only the single greatest determinant of functional disability in the illness (Green, 1996) but also the least well-treated symptom. To that end, increased understanding of the neurobiology of cognitive symptoms of schizophrenia as well as developing new treatments for these symptoms remains a priority for neuropsychiatric research. Of these symptoms, CC is one of the most readily measured, consistently observed, and translational deficits in the illness. Indeed, for these and other reasons the 2007 CNTRICS meeting recommended CC be emphasized for treatment development (Carter et al., 2012). Unfortunately, as yet no FDA-approved treatment exists to improve CC in schizophrenia.

CC is a critical neurocognitive process that is required for flexible, directed thought and action based on goals and intentions, allowing us to direct behavior from the "top down" rather than automatically and reflexively from the surrounding environment. CC helps us override prepotent responses, select amongst competing stimuli, control our emotions, perform multiple tasks at the same time, and accomplish long-term goals in the face of adversity. Longitudinal studies demonstrate that "grit" and "conscientiousness," personality traits closely related to CC, are significant predictors of career success and future income (Duckworth et al., 2007; Sutin et al., 2009). Indeed, CC influences a myriad of cognitive functions such as attention, sensory perception, learning and memory, processing speed, and reasoning/problem solving. As may be expected, performance impairment during CC is a significant predictor of functional outcome in schizophrenia (Chang et al., 2014; Sheffield et al., 2014).

Based on this evidence, it follows that developing treatments for CC deficits in schizophrenia is expected to markedly improve functional outcomes and quality of life in the disease, alleviating the suffering of millions. The overall hypothesis tested here is that transcranical direct current stimulation (tDCS) will improve performance and restore normal recruitment of brain networks during a CC task in schizophrenia patients.

Neuronal Mechanisms of CC. The neurobiology of human CC has received considerable focus since the advent of fMRI. Two brain networks are believed to be essential for CC. One network, called the frontal-parietal network (FPN), consists of the dorsolateral prefrontal cortex (DLPFC) and dorsal parietal cortex. This network (especially the DLPFC hub) is thought to store neuronal representations of task goals in order to bias attention and responses in order to facilitate the achievement of those goals (Cocchi et al., 2013; Dosenbach et al., 2008; Dosenbach et al., 2007). The second network, the cingulo-opercular network (CON), includes the anterior cingulate and insula. This network is involved in trial-by-trial control and performance monitoring during cognitive tasks. Through its connectivity to other networks including the FPN, the CON may then use this information in order to help maintain goal-representations, adjust strategies, and maximize task performance (Cocchi et al., 2013; Dosenbach et al., 2008; Dosenbach et al., 2007).

Disrupted CC Mechanisms in Schizophrenia. In his early descriptions of schizophrenia (or "Dementia Praecox") Kraepelin referred to the mind of a schizophrenia patient as like "an orchestra without a conductor" (Kraepelin, 1919), strongly suggestive of a loss of CC. Subsequent behavioral studies of executive function reinforced his suppositions (Cameron, 1939; Rappaport et al., 1945/1946; Vigotsky, 1934), but it has only been since the advent of fMRI that researchers have been able to noninvasively understand the neuronal mechanisms that underlie loss of CC in schizophrenia.

Consequently, abnormal neuronal response during CC has become one of the most widely replicated neuroimaging findings in schizophrenia. The most consistent result in patients is reduced response (relative to healthy controls) during CC in the DLPFC (Lesh et al., 2011; Lesh et al., 2013; Perlstein et al., 2003; Poppe et al., 2016; Ragland et al., 2015; Snitz et al., 2005; Yoon et al., 2008a; Yoon et al., 2008b) (Figure 1). Hypoactivation of the parietal cortex and anterior

cingulate (ACC) has also been observed (Poppe et al., 2016; Snitz et al., 2005). Consistent with these findings, a meta-analysis of 41 neuroimaging studies of executive function in schizophrenia reported reduced activation of the DLPFC, ACC, and parietal cortex, and thalamus in patients (Minzenberg et al., 2009). Adding to these findings, a study in first-episode patients found reduced functional connectivity of a frontoparietal network consisting of the DLPFC and inferior parietal cortex during CC (Yoon et al., 2008a).

Reduced DLPFC activation has also been observed during CC in unaffected first-degree relatives of schizophrenia patients (Becker et al., 2008) and persons at high risk for psychosis (Colibazzi et al., 2016). Interestingly, the relative inability to recruit the DLPFC during CC also may predict conversion to psychosis in at-risk individuals (Colibazzi et al., 2016). In regards to drug effects, our lab has observed improved performance and increased recruitment of the DLPFC during the AX-CPT task in patients treated with atypical antipsychotics, although PFC function and CC performance were not restored to healthy levels (Lesh et al., 2015). These results suggest that 1) disrupted CC in schizophrenia is associated with DLPFC and frontoparietal circuit dysfunction, and 2) a manipulation that effectively targets this system may improve CC in the illness.

Transcranial Direct Current Stimulation. Ideally, a treatment for cognitive symptoms of schizophrenia should be able to precisely target the underlying dysfunctional neuronal systems while minimizing financial cost and side effects. Transcranial direct current stimulation (tDCS) is a promising technique that offers these advantages and therefore has recently gained considerable attention for the treatment of schizophrenia as well as many other psychiatric and neurological diseases (Aparicio et al., 2016; Bikson et al., 2016; Cho and Hallett, 2016; Elsner et al., 2016a, b; Gschwind and Seeck, 2016; Hsu et al., 2015; Kekic et al., 2016; Naro et al., 2016; Palm et al., 2014; Sauvaget et al., 2015; Zaghi et al., 2009).

In tDCS, saline-soaked electrodes are temporary affixed to the scalp and connected to a battery-powered current generator. A weak (1-2 mA) constant current is then briefly applied (e.g. 20 minute) to stimulate the targeted brain area (e.g. the DLPFC). To control for placebo effects, studies may utilize a sham stimulation protocol that consists of very brief constant stimulation (e.g. 1 minute). Subjects usually cannot discern the difference between the sham and experimental stimulation protocols due to habituation (Poreisz et al., 2007).

The primary effect of tDCS is to alter neuronal excitability by increasing the neuronal membrane potential but not inducing action potentials (Fertonani and Miniussi, 2016). Notably, tDCS effects persist beyond the stimulation period, perhaps due to persistent enhancement of glutamate receptor signaling in a mechanism conceptually akin to long-term potentiation (Liebetanz et al., 2002). The neurocognitive effects of tDCS are enhanced if stimulation occurs concurrently with a task that engages the neuronal systems to be targeted (e.g. a working memory task during DLPFC stimulation). This is thought to be due to tDCS primarily affecting neurons close to the discharge threshold (i.e. "active" neurons) (Fertonani and Miniussi, 2016).

tDCS is generally agreed to be safe and well-tolerated (Bikson et al., 2016). Indeed, a recent meta-analysis of tDCS clinical trials did not find a single severe

adverse event across 33,200 sessions (Bikson et al., 2016). The most common side effect is skin erythema that resolves soon after stimulation (Guarienti et al., 2015). No evidence exists that suggests tDCS may cause tissue damage or another irreversible form of brain injury (Bikson et al., 2016). The likelihood of inducing seizures is also low due to the fact that tDCS current strengths are almost always administered at least an order of magnitude lower than that required to induce epileptiform activity, even during gamma oscillations (Bikson et al., 2016; Bikson et al., 2004).

Effects of tDCS in Schizophrenia. The great majority of tDCS studies in schizophrenia have targeted the DLPFC. Most studies have observed reduced positive and/or negative symptoms, with no studies reporting severe adverse events (reviewed by Kekic et al., 2016). To date, however, few studies have examined the effects of tDCS on cognition in schizophrenia. A 2014 study by Hoy et al. observed improved working memory in patients after a single 20 minute, 2 mA session of tDCS over the left DLPFC (Hoy et al., 2014). This effect was later shown to be associated with increased gamma synchrony in the region (Hoy et al., 2015). Rassovsky et al. reported improved performance on a social cognition task after bilateral DLPFC stimulation (Rassovsky et al., 2015), and Reinhart and colleagues have observed enhanced task learning and adaptive control after stimulation of the medial PFC in schizophrenia (Reinhart et al., 2015a, b). The most comprehensive neurocognitive study to date was conducted by Smith et al., who reported increased overall score on the MATRICS Consensus Cognitive Battery after 2 mA DLPFC stimulation (Smith et al., 2015). The effect was driven by improvement in working memory and attention-vigilance (Smith et al., 2015).

The fact that evidence is limited for pro-cognitive effects of tDCS in schizophrenia is likely because the technique has been underutilized from a cognitive perspective. Few tDCS (or any other noninvasive stimulation) studies in schizophrenia have included cognitive processes as primary outcome measures (Hasan et al., 2016). As a result, studies may be 1) underpowered to detect group differences, and/or 2) do not examine cognitive domains relevant to the brain area being targeted (Fertonani and Miniussi, 2016). The fact that many previous studies have demonstrated pro-cognitive effects of tDCS in other patient and control populations suggests that tDCS may also ameliorate cognitive dysfunction in schizophrenia (reviewed by Dedoncker et al., 2016).

To sum up, we plan to explore how tDCS affects brain response during CC in schizophrenia. We will conduct a series of experiments using active or sham tDCS and measure the effects on brain response (measured by fMRI) on CC in both patients with schizophrenia and healthy control subjects. This project will help us understand basic questions about the role of brain response in CC and if tDCS may be purposed to improve CC in schizophrenia.

4) Inclusion and Exclusion Criteria

Healthy subjects and patients with schizophrenia between the ages of 18-35 will be recruited for this study. Participants will be carefully screened and will be excluded if they do not adhere to our criteria.

- Participants must be able to sufficiently speak and understand English so as to be able to understand and complete cognitive tasks.
- All subjects must have the ability to give valid informed consent.

- No children under the age of 18 will be recruited.

No pregnant women will be recruited. Although there is no known significant risk associated with study procedures for pregnant participants, they will be excluded as an extra precautionary measure.
No prisoners will be included.

EEG

- Hairstyles that hinder the placement of electrodes

MRI and tDCS

Exclusion criteria include:

- Pacemakers
- Implanted electrical (brain and spinal) stimulators
- Implanted defribrillator
- Metallic implants
- Skin damage or skin conditions such as eczema at the sites where electrodes will be placed
- Subjects with dreadlocks or other hairstyles hindering the placement of tDCS electrodes will also be excluded.
- Cranial pathologies
- Head trauma
- Epilepsy
- Mental retardation
- Encephalitis or history of encephalitis
- Any known history of neurological disorders (including epilepsy, ALS, MS, stroke, cerebral palsy, any DSM-5 axis I psychiatric disorder (for healthy control subjects), autism)
- Uncorrected vision problems that would hinder cognitive testing (this also pertains to subjects with color blindness in tasks where discriminating colored objects/items is necessary for successful performance).
- Pregnant women: There is no known risk of MR brain scanning of a pregnant woman to the developing fetus for scanning at 4T or less, and no known mechanism of potential risk under normal operating procedures. Nonetheless, the possibility that risks may be discovered in the future cannot be completely ruled out. Therefore, as a general precaution, pregnant women will be excluded. If subjects are unsure if they are pregnant and still wish to participate, a pregnancy test will be provided. In keeping with human subjects protocols currently used by other MRI research groups at UC Davis, each female participant will be asked if there is a possibility that she could be pregnant. These measures also apply to brain stimulation research. There is no known significant risk associated with noninvasive stimulation procedures in pregnancy. Excluding pregnant women is simply as an extra precautionary measure.

Other than nicotine, no subjects reporting substance dependence in the past six months and no substance abuse in the past month will be recruited.

The tDCS and MRI pre-screening forms are included in the IRB application.

For studies of patients with schizophrenia:
Our inclusion criteria will be:

- Diagnosis of schizophrenia, schizophreniform or schizoaffective disorder;
- No medication changes in the prior month;
- No medication changes anticipated in the upcoming month;
- Stable outpatient or partial hospital status;
- Normal IQ (>70; IQ will be measured by administering the Wechsler Abbreviated Scale of Intelligence (WASI) test).
- Must not be currently taking the antipsychotic clozapine

In addition, all exclusion criteria listed above for healthy controls also apply to recruitment of patients (except for being diagnosed with schizophrenia, schizophreniform or schizoaffective disorder;).

5) Study Timelines

This study will enroll approximately 250 patients with schizophrenia and 50 demographically (age/gender) matched control subjects. Depending on the success of our methods, the overall study is projected to last up to 5 years. An individual subject's participation will generally consist of six visits (a screening/questionnaire/interview visit, three stimulation visits with fMRI or EEG and two non-stimulation visits with fMRI or EEG).

In addition to a clinical/screening visit, this study will incorporate a crossover design consisting of 5-10 sessions separated by at least 24-48 hours.
For these sessions, the tDCS protocol (sham with task, DLPFC with task, sham without task, DLPFC without task, or SMC stimulation) may be followed by fMRI or EEG. Up to 4 tDCS sessions (2 sham, 2 stim) may be conducted without fMRI or EEG afterwards. The order of sessions (sham with task, DLPFC with task, sham without task, DLPFC without task,or SMC stimulation) will be randomized and counterbalanced for each group (patients and controls).

The estimated study completion date is March 1, 2022, with all subjects expected to be enrolled by March 1, 2021, and all primary analyses complete by March 1, 2022.

6) Study Endpoints

Participation for each subject is considered complete following participation in all of the tDCS conditions and sessions (sham with task, DLPFC with task, sham without task, DLPFC without task, and SMC stimulation) for an experiment. Although we do not anticipate any safety concerns, studies may be terminated prior to completion in the case of any skin irritations, lesions or other adverse reactions to stimulation. Subjects may also choose to withdraw at any point during the study.

7) Procedures Involved

Recruitment Methods. Healthy young adult participants will be recruited by ads and word of mouth from the UC Davis community; ads will be placed in the Department of Psychology, Center for Neuroscience, or UCDMC as well as around the community (grocery stores, churches, community centers, coffee shops, etc). These flyers are included in the IRB application. Ads will also be placed on our lab web page. Additional subjects will be recruited through the Sona system paid

participation website. Studies of volunteers who are directly supervised by the investigator(s) or who are the investigator's students will be avoided. Students who choose to participate will be freely chosen.

Patients with schizophrenia will be recruited from two primary sources: 1) UCDMC EDAPT (Early Diagnosis and Preventative Treatment of Psychotic Illness) clinic 2) present and former participants in studies conducted in the Translational Cognitive and Affective Neuroscience Laboratory directed by Dr. Cameron Carter. The two protocols we will recruit from are the "Understanding Early Psychosis" (Protocol # 226043-1) and "Cognitive Neuroscience Task Reliability & Clinical Application Consortium" (Protocol # 219516-2). Only subjects who have consented to be contacted for future studies will be recruited from these two protocols. Participation of potential schizophrenic subjects from EDAPT will be attained through direct communication to patients by personnel at the EDAPT clinic. The EDAPT clinic is staffed by Faculty and staff within the Department of Psychiatry at UC Davis. Upon entry to the EDAPT clinic, patients are told that EDAPT is a research clinic and that they are welcome to take part in research activities if they are interested, but that participation is voluntary and that whether or not they participate in this or any other study will not affect their care at UCDMC. Recruitment will take place at potential subjects' initial entry into the EDAPT clinic as well as during later clinical visits. Subjects will be given a recruitment letter explaining the study to take home and review. We have included a screening form to be used by study personnel to screen potential participants to see if they qualify. We have also created a patient flyer that can be posted in EDAPT clinic so that the potential subjects may contact us if they are interested. Subjects from other studies who have consented to be contacted about other studies will be called to see if they are interested in participating and screened. The phone script, recruitment letter, and patient flyer are included in this IRB submission.

Pre-screening forms would be used on the basis of exclusion and inclusion. When prospective subjects contact the lab, the experimental procedures and scheduling requirements will be explained, and a brief phone/e-mail screening questionnaire will be administered to determine eligibility. For phone screening, we will continue screening only after obtaining their consent. For e-mail screening, we will send them the pre-screening form only after receiving their e-mail confirmation. They can skip any questions they don't want to answer and they can stop at any time. These documents are included in our IRB application.

The items in the pre-screening forms aim to identify any contraindications to the participant's participation in the study with regards to safety and comfort (see Risks below). It also aims to verify whether participants are neurologically healthy, screening out participants with any history of neurological or psychiatric (for healthy controls) problems, such as epilepsy, head trauma, mental retardation, and neurological disorders. For the MRI study, additional questions ask whether participants are taking any medication that can make them drowsy. The proposed experiments require that the participant be alert throughout the duration of the study. This question is intended to screen out participants who may fall asleep in the scanner. Finally, the questionnaire will also be used to determine whether participants can participate in experiments involving vision (i.e., do they have

normal visual acuity and color vision?). The pre- screening and consent forms are included in the IRB application.

The pre-screening forms will be kept strictly confidential and will remain on password- protected computers or password encrypted lab web space. Health information in the pre- screening form is used only for recruitment purposes. It will not be reused for other purposes or disclosed to another person or entity. A code that carries no personal identifiable information will be used to label pre-screening forms. Keys to identities will be kept separately from experimental records, and pre-screening consents will be stored separately from the pre- screening forms. Only individuals on the Research Personnel List will have access to the system.

No identifiers, used for recruitment purposes, will be disclosed to a third party except as required by law or for authorized oversight of the research project.

General Procedure . Overall, during testing sessions subjects will first undergo the tDCS protocol assigned to that session (sham with task, DLPFC with task, sham without task, DLPFC without task, and SMC stimulation) immediately followed by MRI scanning, or EEG recording. MRI scanning will consist of (in order): prescanning procedures (e.g. high order shim, anatomical (T1) scan), a CC task (the Dot-Probe Expectancy (DPX) task), an episodic memory task (The Relational and Item-Specific Encoding (RISE) task) and a 10 minute resting state scan.

Prior to the start of each experiment, the participant will be properly consented and fill out a demographic form. This demographic form may be a paper version or a Google form. We will record subject number, gender, age, racial background, and ethnic background on the form. Completion of the form is entirely optional and subjects can choose not to answer any of the questions on the form. The subject number is a code that carries no personal identifiable information. Only researchers on the Research Personnel list have access to the answers stored on the Google Drive. All demographic forms will be stored in locked file cabinets in lab space. Only researchers on the Research Personnel list have access to the file cabinets.

Subjects without previously confirmed diagnoses of schizophrenia or schizoaffective disorder will then undergo the Structured Clinical Interview for DSM-V (SCID), and a complete psychiatric history will be taken.

Subjects will then undergo diagnostic (clinical) interviews if no current clinical ratings/information are available (ratings < 1 month old are considered current). These rating scales will include the Brief Psychiatric Rating Scale (24 item), the Scale of the Assessment of Positive Symptoms, the Scale for the Assessment of Negative Symptoms, and may also include the following (see attached packets for actual questionnaires):

The Global Functioning Scales
The Global Functioning Scale: Social (GFS: Social; Auther et al., 2006) and Global Functioning Scale: Role (GFS: Role; Niendam et al., 2006a) provide ratings of functioning in social and role domains, respectively, on two separate 10-point Likert scales, which are scored independently of symptom severity.

Psychosocial Treatment Survey
The psychosocial treatment questionnaires evaluates social adjustment of subjects.

Medication Summary
This survey provides a comprehensive assessment of medication history.

Family History of Mental Illness
This survey provides a comprehensive history of mental illness.

Modified Mini-Mental Status Exam
This survey provides a brief assessment of acute mental status.

Calgary Depression Scale
The Calgary Depression Scale is a valid and reliable interview-based 9-item scale for measuring risk factors for suicide in schizophrenia, and at present is the only scale that is valid for assessing depression in schizophrenia. Items are rated on a 4-point scale, assessing symptoms of depression such as self-deprecation, guilt, hopelessness and suicidal thoughts.

Columbia-Suicide Severity Rating Scale (C-SSRS)
The Columbia-Suicide Severity Rating Scale (C-SSRS) is an interview-based scale to assess suicide risk that assesses the content and intensity of suicidal thoughts, and suicidal and self-injurious behaviors, and also allows the investigator to characterize the nature and severity of past suicidal acts. This scale is rapidly emerging as the standard for suicide risk assessment and has been informally recommended by a committee of the American Federation for Suicide Prevention.

Strauss-Carpenter Outcome Scale (SCOS)
The Strauss-Carpenter Outcome Scale (SCOS, Strauss & Carpenter, 1972) contains 4 items assessing duration and frequency of hospitalizations, social contacts with individuals outside of the family, useful employment or participation in school, and severity of symptoms

Young Mania Rating Scale (YMRS)
The YMRS is a valid and reliable measure of symptoms related to mania. Eleven items are rated on a 0-to-4 scale, assessing symptoms such as elevated mood, increased motor activity, changes in sleep, and pressured speech.

Premorbid Assessment Scale (PAS)
The PAS is a widely used unconstructed instrument to retrospectively assess premorbid adjustment. It contains a 28 item rating scale that measures social isolation, peer relationships, functioning outside the family and school performance, as well as social-sexual aspects of life starting at age 15. As a supplement the PAS includes a section of 9 general items relating to educational and job achievement, work and school performance immediately preceding the onset of psychosis, the highest level of independence achieved from family, the highest level of social personal adjustment, and the degree of interest in life and energy level.

Fagerstrom Nicotine Dependence and Smoking History Questionnaire
The Fagerstrom test for nicotine dependence (Heatherton, et al., 1991) is a self-report questionnaire that can be completed in less than five minutes. Participants are asked to answer questions related to frequency and history of nicotine use as well as assessing current symptoms of dependence.

Self-Report Measures:
The Barratt Impulsivity Scale 11th version
The Barratt Impulsivity Scale 11th version is a questionnaire that assesses various forms of impulsive thinking and behavior. 30 items are rated on a 4-point scale by subjects, and assess non-planning, attentional and behavioral impulsivity with items such as "I plan tasks carefully" and "I do things quickly without thinking." This is one of the most widely-used scales in the study of impulsive behavior, across a range of clinical and non-clinical populations.

Cannabis Use Problems Identification Test (CUPIT)
The 16-item CUPIT (Bashford, 2007) was developed as a screening tool to capture signs of dependence, abuse and risk for dependence/abuse of cannabis in adolescents and young adults. Individuals answer questions about their amount of cannabis use and related difficulties. In addition to the CUPIT, an additional 7 questions re: cannabis dependence (the CANNEX) will be asked that are based on information gathered re: cannabis use in the SCID.

Drug Use Screening Inventory
The DUSI (Tarter & Kirisci, 1997) is a self-report measure of 10 domains of substance use, psychological functioning, and social functioning. We are using the substance abuse section (labeled DUSI-SU-Self Report) of this measure only to assess participant's use of various substances and alcohol. Questions examine amount of use over the lifetime and recently (past 6 months, past month) and its impact on functioning.

Barkley ADHD Scales (Childhood/Current Symptoms Scale-Self Report)
The Barkley ADHD Scales assess severity of self-reported current and childhood ADHD symptoms, including inattention, hyperactivity and oppositional behaviors. Individuals rate the severity of symptoms or impact on functioning on a 4-point Likert scale from "never or rarely" to "very often".

Wender Utah Scale
The Wender Utah Rating Scale can be used to assess adults for Attention Deficit Hyperactivity Disorder with a subset of 25 questions associated with that diagnosis.

Participant Health and Treatment History:
Parents or caregivers will be asked to provide information on the participant's developmental, medical, school, family, substance use and treatment history. If a parent or caregiver is not available, adult participants will be asked to complete this form.

Beck Anxiety Inventory (BAI)
The BAI is a 21-item self-report assessing the cognitive and physical symptoms associated with anxiety. Participants rate how much each item bothered them in the past month on a 4 point scale: 0 = Not at all; 1 = Mildly but it didn't bother me much; 2 = Moderately – it wasn't pleasant; and 3 = Severely – it bothered me a lot.

Rejection Sensitivity Questionnaire (RSQ):
Participants may be asked to complete the Rejection Sensitivity Questionnaire-Personal (RSQ-Personal) (Downey & Feldman, 1996). This measure asks participants to assess how anxious or angry they would feel and what they would expect to happen in various hypothetical social situations.

Affective Reactivity Scale (ARI) – Self Report
The ARI contains s six items related to feelings/behaviors specific for irritability and one question assessing impairment due to irritability ('overall, irritability causes him/her (or ''me'' by self-report) problems'). Each item has a three-level response category: 'not true', 'somewhat true', 'certainly true' – scored as '0', '1', '2', respectively, giving a range of possible scores of 0–12. The total score is the sum of the first six items. The impairment item is not counted in the total score.

Positive Urgency Measure (PUM)
The PUM is a 14-item self report scale that examines an individual's ability to control their thoughts and emotions during elevated mood states. Individuals rate their agreement with the items on a 4 point scale (1= Agree Strongly, 2 = Agree, 3 = Disagree, 4 = Disagree Strongly).

Buss-Perry Aggression Questionnaire (BP-S)
The BP-S is a 29 item self report survey that examines personality traits associated with 4 dimensions of aggression: physical aggression, verbal aggression, anger and hostility. Participants rank certain statements along a 5 point continuum from "extremely uncharacteristic of me" to "extremely characteristic of me." The scores are normalized on a scale of 0 to 1, with 1 being the highest level of aggression.

Reactive-Proactive Questionnaire (RPQ)
This 22 item self report examines both reactive and proactive motivations behind aggressive behavior, including verbal and physical aggression. Participants rate the frequency that they have demonstrated certain behaviors on a scale: 0=Never; 1= Sometimes; 2 = Often.

Levenson's Self-Report Psychopathy Scale (LSRPS)
This 26-item self report for ages 18 and older examines personality characteristics associated with psychopathy. Participants rate their agreement with the items on a 5 point likert scale from "strongly disagree" to "strongly agree."

During the first session the subject will be given instructions for the cognitive tasks to be completed at later sessions, and some time to practice the tasks. These tasks will involve looking at a computer screen where different types of stimuli will be presented. These will be figures, symbols, numbers, letters, words or sentences. The subject will be asked to respond to these by pressing a button, reading aloud

what you see on screen or generating your own verbal responses, or picking from among a group of answers on the screen.

The participant will also fill out a standard MRI screening questionnaire he or she can be safely included in the study. If the researcher is using electronic consent forms, the subject will be asked to use the mouse or sign pad to place their electronic signature, and we will email an electronic copy of the signed consent. Then, they will be explained all of the experimental procedures by the experimenter. Because it is not clear whether tDCS has any reliable effects on CC or brain activity, we may adjust tDCS stimulation parameters during the study. More specifically, tDCS may vary with the type of current (direct current or sham stimulation), magnitude of current (up to 2 mA), time of stimulation (up to 20 minute) and stimulation sites. The difference between sham and direct current stimulation is that sham stimulation only persists for the first minute of stimulation (after which it is removed) whereas direct current stimulation will last up to 20 minute. Only sites designated by the Starstim cap will be used. The Starstim cap only has standard electrode sites from the 10-20 system. Note that, although different stimulation parameters may be utilized, these differences will not affect the safety or tolerability of the procedure.

Subjects will undergo sham and direct current stimulation on separate visits separated by at least 24-48 hours. Subjects will be blinded to their condition on each visit. During the first visit, we will inform the subjects the number of visits and all the stimulation conditions they will be doing for the specific experiments. However, they will not know which visit is for which condition (the active tDCS or sham conditions) and we will give the same instructions for every visit. The order of the active versus sham conditions will be fully counterbalanced across subjects. Many participants can feel the onset of the stimulation (which leads to a brief tingling or itching sensation), but people cannot generally feel the continued stimulation beyond one minute. By beginning the active and sham stimulation conditions with a period of stimulation, we can ensure that participants will not know if they are receiving either type of active or sham stimulation.

We will use tDCS to stimulate specifically the DLPFC or SMC, and we will concurrently measure the effects of the stimulation on CC by means of behavioral measurements of accuracy and reaction time. These may be combined with fMRI or EEG after some of the stimulation sessions to measure brain response during a CC task as well as the resting state. The fMRI and EEG measurements are noninvasive. The CC paradigm we will use is described below.

Prior to the start of an experiment, the experimenter will explain all of the experimental procedures to the participants, and the participants will read and sign consent forms if they agree to participate. To familiarize subjects with test procedures, prior to tDCS stimulation subjects will complete a short practice session on the DPX task on a computer screen outside of the MRI scanner. Subjects unfamiliar with MRI scanning procedures may also participate in a mock scanning session (mock scanner that visually resembles the actual MRI scanner) prior to tDCS.

For fMRI sessions, subjects will perform the DPX and RISE tasks while lying supine in the MRI scanner. For EEG sessions, subjects will be seated in a

comfortable chair in front of a computer screen. Participants will be presented with visual (e.g., a picture of an object) stimuli. Participants will be asked to make responses to the series of visual stimuli using a numbered pad or keyboard. To constrain learning strategies, participants may be asked to make a simple perceptual or semantic judgment about each stimulus. See below for further details regarding the DPX and RISE tasks. At the end of the session, participants will be debriefed and they will remain in the laboratory in a relaxed state until mood and mental state return to baseline. More details about the experimental design are highlighted below.

Following the completion of each experiment, participants will be fully debriefed on the goals and hypotheses of the experiment and be given the opportunity to provide feedback regarding their experiences and strategies that they used in the study. Below is a table summarizing the possible stimulation parameters that may be used in the proposed experiments:

<table>
<tr><th>Stimulation sites</th><th>Number of stimulation electrodes</th><th>Stimulation electrodes</th><th>Current parameters</th></tr>
<tr><td>SPONSTIM-8
8 cm^2 sponge electrode</td><td rowspan="3">Any electrode sites from the standard 10-20 EEG system</td><td rowspan="2">Up to 39</td><td rowspan="3">The first 30 -60s: up to 2 mA
Active stimulation: continue to receive up to 2.0 mA stimulation
Sham stimulation : reduce to 0.0-0.1 mA for remainder of the session
Time: Up to 20 minutes</td></tr>
<tr><td>SPONSTIM-25
25 cm^2 sponge electrode</td></tr>
<tr><td>PISTIM
Pi cm^2 Ag/AgCl electrodes</td><td>PISTIM
Pi cm^2 Ag/AgCl electrodes</td></tr>
</table>

MRI. For MRI scans, a brief phone/e-mail pre-screening form will be administered when prospective participants contact the lab (see Recruitment Methods). The items in the form aim to identify any contraindications to the subject's participation in the study with regard to their safety and comfort. This pre- screening form is applied only during initial subject contact to determine eligibility.
During the scan, the participant will lay supine on the MRI table, with an RF coil placed over his/her head, and will be put into the center of the magnet. This protocol does not involve any contrast agents, drugs, or other invasive procedures, and uses established MRI sequences. Typical scan parameters are as follows: (Precise pulse sequence settings may be changed to test specific hypotheses.)

- For echo planar imaging (EPI) scans during the DPX: gradient recalled echo, voxel size 3.75 x 3.75 x 4.55 mm, slice gap=0 mm, TR=2 sec, TE=29 ms, FA=75 degrees, matrix=64x64, FOV=240x240 mm, images per slice=150-200;
- For echo planar imaging (EPI) scans during the resting state: gradient recalled echo, voxel size 3.75 x 3.75 mm^2, slice gap=0.5 mm, TR=2 sec, TE=32 ms, FA=70 degrees, matrix=64x64, FOV=240x240 mm, images per slice=180-300;
- For high resolution anatomical scans: fast spin echo, slice thickness=3.4 mm, gap=0 mm, TR=3.1sec, TE=36 and 136 ms, echo train=8, matrix= 256x256, FOV=240x240 mm.

All MRI studies will be performed on a 3T Siemens Skyra (at the MRI Facility for Integrative Neurosciences at the UC Davis Center for Neuroscience) or 3T Siemens Time Trio (at the IRC) scanner with a 32-channel phased array head coil. T1, T2, and proton-density weighted structural MRI scans will be obtained. In additional to these structural scans, images sensitive to BOLD contrast may be acquired with an echoplanar imaging sequence. We will carefully monitor subject motion, employing scrubbing techniques (Power et al., 2014) and, when necessary, excluding data from participants with excessive motion. In the scanner, visual stimuli may be presented on a magnet-compatible monitor placed behind the scanner, which participants will view via a mirror. Any responses by the subject will be made with 2 custom-built 5-button fiber- optic response devices. We anticipate that the total time to prepare a participant, run structural scans, and complete any EPI scanning will be approximately 90-120 minutes, which includes initial setup time, the anatomical scans, any functional scans, and rest time between the scans. Data processing is done after the session is finished.

Note that the MRI pictures of subjects' brains are for research purposes. The MRI data are not meant to evaluate subjects' health, as they would be if they were part of a clinical (non-research) visit to the doctor or hospital. The pictures will not receive any routine clinical review by specifically trained physicians (radiologists) who interpret MRI scans. This means that all abnormalities may not necessarily be noticed. However, if in the routine administration of the MRI pictures, the research staff notices any possible abnormalities, they will notify Cameron Carter, M.D. If Dr. Carter deems it appropriate, he will discuss these possible problems with the subject, and will help to obtain a more complete review of the MRI scans by a trained physician who can determine if any clinical health condition is present. If the physician thinks that there may be a clinical problem, we will provide the subject with a copy of the MRI picture to take to the physician of their choosing. If they prefer, we can send the pictures electronically, but there is a small risk that someone else could view electronically sent files.

EEG Recording:

The participant's electroencephalogram (EEG or "brain waves") will be recorded using conventional methods that we have used in a number of our other protocols. We will use the Starstim device (Neuroelectrics), while they perform a cognitive task and/or remain at a resting state. Electrodes (metallic disks with wires attached) are used to sample the electrical signals of the brain at the scalp.

During EEG recording, the participant sits comfortably in a chair in a sound-attenuating, electrically shielded room (dimensions: 10'x 8' with a ceiling height of 8') while viewing visual stimuli or listening to auditory stimuli. Electrodes and caps are sterilized between uses and dried completely prior to next use. Application materials are discarded after every use and new materials are utilized for each participant.

StarStim system:

The electrodes used for EEG recording with the StarStim device will be the "EEG Only" or "Stimulation and EEG" electrodes listed below. The electrodes are worn in an elastic cap that is commercially available from Neuroelectrics. The scalp is

cleansed (alcohol may be used) and prepared using a non-toxic electrically conductive gel (except in the case of dry electrodes- see below) that is placed between the electrode surface and the scalp. Standard EEG recording equipment protects the participant from any hazard of electrical shock using isolated grounding procedures. In addition to electrodes in the cap, external STICKTRODES may be placed on the mastoid bones (for references), or above/below/to the side of the eyes in order to measure eye blink and movement artifacts.

StarStim Electrodes:

STIMULATION ONLY ELECTRODES		STIMULATION AND EEG	EEG ONLY ELECTRODES
			
SPONSTIM-8 8 cm² Sponge Electrode **Code:** NE026b	**SPONSTIM-25** 25 cm² Sponge Electrode **Code:** NE026a	**PISTIM** Pi cm² Ag/AgCl Electrodee **Code:** NE024	**DRYTRODE** Dry EEG Electrode for the Scalp **Code:** NE023
▪ 8 cm² Sponge for stimulation with conductive rubber core electrode. ▪ This electrode is used for stimulation only (EEG measurements are poor). ▪ To use, it must be wetted before with about 5 ml of saline solution. ▪ Similar to SPONSTIM-25 but more focal. ▪ See the current safety chart for recommended maximal currents.	▪ 25 cm² Sponge for stimulation with conductive rubber core electrode. ▪ This electrode is used for stimulation only (EEG measurements are poor). ▪ To use, it must be wetted before with about 5 ml of saline solution. ▪ See the current safety chart for recommended maximal currents	▪ Pi cm2 (i.e., ϖ=3.14.. cm2) Ag/AgCl gel-based stimulation electrode with rear-fill aperture for gel supply. ▪ This Ag/AgCl electrode can be used for both stimulation or EEG. ▪ Its small area provides for more focal stimulation protocols. ▪ It must be used with conductive gel. ▪ See the current safety chart for recommended maximal currents.	▪ Dry EEG electrode. ▪ This is a scalp EEG electrode requiring no gel and designed for easy hair penetration. ▪ Use of gel on the tips is optional

EEG ONLY ELECTRODES		
		
FORETRODE Dry EEG Electrode for the forehead **Code:** NE021	**GELTRODE** Gel EEG Electrode **Code:** NE022	**STICKTRODE** Adhesive EEG and DRL/CMS electrode **Code:** NE025
▪ Frontal dry EEG electrode, suitable for bare-skin scalp areas free of hair (e.g., the frontal area). ▪ Use of gel on the tip is optional	▪ Wet EEG electrodes with rear-fill aperture for gel supply. ▪ Requires use of conductive gel	▪ Self-adhesive EEG electrode suitable for both DRL/CMS referencing on bare skin (e.g., mastoid) and for application in bare skin areas (e.g., for EOG under eye).

DPX Task. The DPX task has been utilized previously by our lab, including in an fMRI study (Lopez-Garcia et al., 2016).

The DPX is a more challenging (less susceptible to ceiling effects) variant of the AX-Continuous Performance Task (CPT), in which the letter (A, B, X, Y) cues found in the AX-CPT are replaced by Braille stimuli. Subjects are asked to respond (button press) to a target probe ("A") after it follows a target cue ("X"), but not otherwise ("AY", "BX", or "BY" trials) (Figure 1) . AX targets occur with high frequency (69%), setting up the tendency to make the target response to the X probe. An intact goal-maintenance system of CC influences performance on this task by decreasing BX errors (processing the absence of context associated with the prepotent response) and increasing AY errors (processing the presence of context associated with the prepotent response). The goal maintenance aspect of CC, therefore, is measured by the difference between AY and BX errors. Previous work from our lab has shown deficits in this aspect of the task in schizophrenia (Henderson et al., 2012).

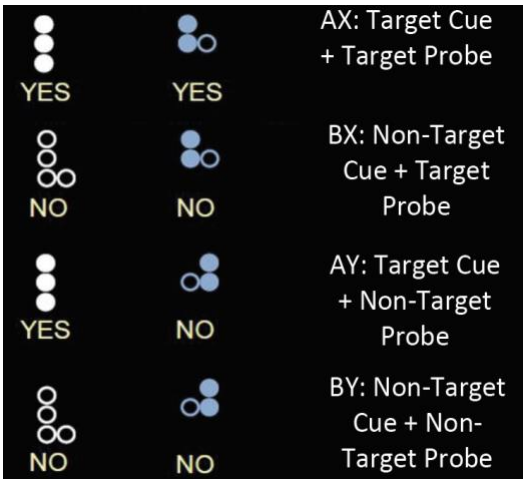

Figure 1. The DPX task. Subjects button press in response to the target cue followed by the target probe (AX trial) but not the other cue/probe combinations. CC is measured by the difference between AY and BX percent correct.

RISE Task. The RISE tests an individual's recognition memory for a list of visual objects. Objects are presented during two learning conditions. During item-specific encoding, the subject will see an object and decide whether it is living or non-living. During relational encoding they view two objects and decide whether one can fit inside the other. They are then presented with a longer list of items, including the items that they just studied as well as new items, and are asked to judge whether the item is old or new, and provide a 3-point confidence judgment. The task ends with an associative recognition task, where the subject is presented with the original pairs of items that were studied during the relational encoding condition along with re-arranged pairs of items which combine items that were studied during different encoding trials, and the subject is asked to decide if the item pair is the same as the pair that they originally studied, of if the pair has been re-arranged. The RISE takes approximately 20 minutes to administer.

tDCS. We will use the Starstim device (Neuroelectrics) prior to having subjects complete the DPX, RISE, and resting state fMRI scans. Electrodes (metallic disks with wires attached) are used to stimulate the brain at the scalp. During stimulation, the participant sits comfortably in a chair in a sound-attenuating, electrically shielded room (dimensions: 10'x 8' with a ceiling height of 8') while performing a working memory task (n-back, see below) to engage the DLPFC. Electrodes and caps are sterilized between uses and dried completely prior to next use. Application materials are discarded after every use and new materials are utilized for each participant.

StarStim system. The electrodes used with the StarStim device will be or "Stimulation Only" or "Stimulation and EEG" electrodes listed above. The

electrodes are worn in an elastic cap that is commercially available from Neuroelectrics. The scalp is cleansed (alcohol may be used) and prepared using a non-toxic electrically conductive gel (except in the case of dry electrodes- see below) that is placed between the electrode surface and the scalp. Standard StarStim equipment protects the participant from any hazard of electrical shock using isolated grounding procedures.

tDCS/Sham Stimulation Session Procedure

Mood and Mental State Assessment (5 minutes). A 1-page questionnaire (see attached) will be administered. This brief mood and mental state questionnaire will serve as a baseline for the subject's mood and mental state.

tDCS preparation (~10 minutes). Prior to electrode placement, the skin at the electrode sites will be inspected to ensure that it is free of abrasions or irritation. The area will then be gently cleaned with rubbing alcohol, but not abraded.

"Stimulation Only" or "Stimulation and EEG" electrodes may be used (see electrode chart above). Note, for ease of these experiments, the "Stimulation Only" electrodes will be used in most cases. For these electrodes, sponge electrodes will be moistened (with saline), prior to placement on the subject's scalp. Alternatively, "Stimulation and EEG" electrodes (PISTIM) will be applied using conductive electrode gel. See chart above for electrode sizes and specification. Up to 8 electrodes may be used at any given time (in addition to external/reference electrodes. See above). Only scalp electrode sites designated on the Starstim cap will be used. The cap only uses standard electrode sites from the 10-20 system.

tDCS stimulation (~25 minutes). During this phase, participants will first receive a few minutes of training on the DPX task and complete a brief practice session. Subjects will also be familiarized with the working memory task (see below). After practice, stimulation (or sham stimulation) will begin.

Following the practice session, subjects will undergo sham with task, DLPFC with task, sham without task, DLPFC without task, or SMC active stimulation. The order of the conditions will be fully counterbalanced across subjects. This experiment involves five tDCS visits, and may include tDCS at any of the designated scalp electrode sites in the Starstim cap. Each stimulation visit will be separated by at least 24-48 hours.

Subjects will receive up to 20 minutes of tDCS stimulation or sham, in addition to a few seconds of ramp up and ramp down time at the beginning and end of each session, using the Starstim device. All subjects will receive up to 2.0 mA for the first 30-60 s of stimulation. Current strength will be ramped down, and then reduced to 0.0-0.1 mA in subjects receiving sham stimulation for the remainder of the session. The active stimulation subjects will continue to receive up to 2.0 mA stimulation. Many participants can feel the onset of the stimulation (which leads to a brief tingling or itching sensation), but people cannot generally feel the continued stimulation beyond one minute. By beginning both the active and sham stimulation conditions with a period of stimulation, we can ensure that participants will not

know if they are receiving active or sham stimulation. The sham conditions serve as an important control, which is similar in procedure and results in similar initial sensations, but does not provide a significant level of stimulation. The SMC stimulation condition is another important, "active" control that controls for the effect of stimulation at a location other than the DLPFC area of interest for which tDCS is hypothesized to have effects on CC.

A sensation questionnaire will be administered at 3 separate time points during stimulation, starting at approximately 5 minutes after the beginning of stimulation, and then approximately every 10 minutes during stimulation. In this assessment, subjects will be asked to report the level of sensation arising from the stimulation on a 10 point scale, with 1 meaning no sensation and 10 meaning mild pain. Stimulation will be terminated immediately if the reported sensation level is 7 or higher at any assessment. Participants—who will be in constant communication with an experimenter—will also be instructed to inform the experimenter if pain is experienced at any other time, which will lead to immediate termination of stimulation. Additionally, the experimenter will monitor the electrodes to ensure that they do not dry out or otherwise cause discomfort.

No-Task Sessions: While subjects are undergoing sham without task or direct current stimulation without task they will rest quietly while seated at a computer desk. The experimenter will be available to chat with the participants and administer the sensation questionnaires as described above. The purpose of the No-Task sessions is to be able to compare the effects of sham/stimulation without task to sham/stimulation with a concurrent task, as previous work has suggested that there may be a benefit to completing a concurrent task during tDCS (see below).

Concurrent Visuospatial N -Back Working Memory Task: While subjects are undergoing sham or direct current stimulation they will concurrently perform a simple “n-back” (three-back) working memory task. This is because tDCS effects on tasks that engage the prefrontal cortex (e.g. the DPX) are enhanced if the stimulation occurs at the same time as either the same task or another task that also engages the prefrontal cortex (i.e. “state-dependent” effects) (Tremblay et al., 2014).

In the three-back task, subjects will be asked to remember the location of an object presented three objects previously on a computer screen. To register a match, a key on a keypad, keyboard, or mouse will be pressed. No response is required for non-targets.

Wash up: The stimulating electrodes will be removed, cleaned, and disinfected according to the manufacturers instructions. As the electrodes are removed, the experimenter will inspect the skin at and near the electrode sites for redness, irritation, or damage and note if present.

For sessions that include fMRI scans, scanning will begin immediately following wash-up and will last up to 1 hour (Stimulation will only last for 20 minutes). See above for specific imaging procedures.

Mood Assessment (30-90 minutes):

After imaging is complete, participants will undergo a relaxation period (~30 minutes) during which the electrodes will be removed and the participants will relax (by sitting quietly or watching a video). Subjects will then take the mood and mental state questionnaire again to make sure that they have no lingering effects of the stimulation. In the unlikely case that a subject still has any lingering effects, the subject will relax for an additional 15 minutes, and then repeat the mood/mental state assessment. This will be repeated until the participant returns to baseline. There are no known reports of lingering effects of tDCS after 90 minutes, so we anticipate that the relaxation period will be complete within 90 minutes in all participants. We will also perform a 48-hour follow-up call or email to ensure that subjects have not experienced any additional adverse effects.

Compensation. Subjects will be compensated $25 for completing the questionnaires and clinical interview, $25 for each tDCS session that does not include fMRI or EEG afterwards, $75 for each tDCS session that is followed by fMRI or EEG, and given a $50 bonus for completing all sessions of a given modality (EEG or fMRI).

8) Data and/or Specimen Management and Confidentiality

The Biomedical Informatics Program of the UC Davis Clinical and Translational Science Center will be used as a central location for data management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Biomedical Informatics Program. The iterative development and testing process results in a well-planned data collection strategy for individual studies. The REDCap system provides secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. These systems offer easy data manipulation with audit trails for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus) REDCap servers are housed in a local data center at UC Davis Health System and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines. REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (www.project-redcap.org).

Access to REDCap is limited to research personnel who are on the IRB-approved study personnel list. Some study questionnaires may be administered electronically through REDCap Survey, a secure web application for building and managing online surveys for research. Additionally, data that is not easily stored in REDCap (i.e. raw MRI data and some behavioral testing files) will be stored de-identified on password-protected servers at the Imaging Research Center that are protected by an institutional firewall or in locked filing cabinets.

Under no circumstances will individually identifiable data be released to anyone without the written consent of the subject, and study results will be reported as group findings only. Behavioral and imaging data will be labeled with a code that carries no personal identifiable information; keys to identities will be kept separately from experimental records on a secure computer, and consent forms with subjects' names will be stored separately in a secure filing cabinet. Only individuals on the IRB personnel list will have access to the system.

9) Data and/or Specimen Banking

Select data from this study may be submitted to the National Institute of Mental Health Data Archive (NDA). NDA is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share de-identified information with each other. The data repository is accessible only to qualified investigators. All subject data will be de-identified (subject names will not be used) and each subject will have a separate identifier called a Global Unique Identifier (GUID) to remove any possibility that "the identities of the subjects cannot be readily ascertained or otherwise associated with the data by the repository staff or secondary data users." (45 CFR, 46.102). The GUID is a universal subject ID that allows researchers to share data specific to a study participant without exposing personally identifiable information. The following information will be collected and entered into the study database to generate a GUID: First name, Last name, Middle name (if applicable), Month of birth, Day of birth, Year of birth, Physical sex at birth, and Name of city/municipality of birth. Once GUID is generated, all personal information will be deleted from the study database.

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

N/A this study does not involve more than minimal risk to subjects.

11) Withdrawal of Subjects

There may be circumstances in which some participants miss sessions or show unexpected adverse effects (e.g. severe allergic reactions to tDCS). In these cases, the study may be terminated for those subjects. In this case, subjects will be informed that the study is being terminated, and they will be paid in a pro-rated manner for the time in which that participated. If a subject decides that they do not wish to continue with the study for any reason they will be paid in a prorated manner. Additionally, if during the study timelines a subject no longer meets our inclusion and exclusion criteria the study will be terminated. The subject will be paid in a prorated manner for their time.

12) Risks to Subjects

Because the protocol involves multiple methods, we separately list potential risks associated with each method below.

Magnetic Resonance Imaging

An MRI scan is a painless radiology technique, which has the advantage of avoiding x- ray radiation exposure. There are no known side effects of an MRI scan. Typical fMRI pulse sequences without any contrast agents will be used in an FDA- approved scanner. As the scanner produces a loud noise during the

scanning procedure, participants will be required to wear earplugs as protection against hearing damage. Pre-screening for metal, pacemakers and other risk factors will be pre-screened prior to the study. No subjects with these contraindications will be allowed to participate in MRI scans.

EEG Recording

Potential risks are minimal. Standard, commercially purchased equipment is used for recording the EEG (Starstim). The equipment uses isolated ground procedures to minimize the possibilities of electrical shock to the participants, and all current safety guidelines are met (e.g., recessed electrode leads to prevent accidental contact of electrodes with sources of electric current). Sterilization procedures conform to published guidelines for protection of participants from transfer of viral or bacterial agents via electrodes. Briefly, the electrode caps and any loose- lead electrodes are washed using detergent and warm water, then rinsed thoroughly and towel-dried. Caps are then rinsed thoroughly, and hung to dry.

Use of tDCS Equipment (e.g. Electrodes)
Potential risks are minimal. Standard, commercially purchased equipment is used for stimulation (Starstim). The equipment uses isolated ground procedures to minimize the possibilities of electrical shock to the participants, and all current safety guidelines are met (e.g., recessed electrode leads to prevent accidental contact of electrodes with sources of electric current). Sterilization procedures conform to published guidelines for protection of participants from transfer of viral or bacterial agents via electrodes. Briefly, the electrode caps and any loose- lead electrodes are washed using detergent and warm water, then rinsed thoroughly and towel-dried. Caps are then rinsed thoroughly, and hung to dry.

Brain Stimulation
Uncommon Risks:

- Sensations ranging from tingling to itching
- Physical discomfort, including (but not limited to) pain or burning at the electrode site and/or headache.
- Skin irritation, redness or itching.

Very Rare Risks:

- Tissue discomfort, redness, or damage at the electrode site.
- Allergic skin reactions
- Changes in mood
- Seizure

tDCS involves very minimal risks to subjects. Several investigators have examined the safety aspects associated with tDCS. For example, Iyer et al. (2005) applied 1 and 2 mA and sham stimulation to the left prefrontal cortex for 20 minutes in 103 subjects, while clinical electroencephalography (EEG) was recorded in 9 of the subjects. Subjects were encouraged to report any discomfort or subjective sensations while undergoing stimulation. These researchers observed no aversive EEG abnormalities resulting from DC stimulation, and no subjects asked to stop the study or reported any significant discomfort. Differences in mood between

sham and stimulation were assessed using the Visual Analog Mood Scale (VAMS) that measures subjective reports of anger, anxiety, confusion, energy, fright, happiness, sadness, tension, and tiredness. The investigators found no measurable effects of stimulation on subjects' VAMS scores. Based on their findings, they concluded that limited exposure to direct current stimulation between 1 and 2 mA is a safe procedure in healthy subjects.

In another study conducted by Gandiga et al. (2006) tDCS and sham were compared in healthy volunteers and chronic stroke victims. Discomfort was measured using a 10-point scale, where 1 represented no discomfort and 10 represented extreme discomfort and pain. These researchers report transient and mild discomfort of sensations (1-2 on the 10 point scale) that were not significant between sham and stimulation conditions, or between healthy volunteers and stroke victims. Most subjects from both groups only reported a slight tingling sensation associated with both stimulation and sham conditions. These investigators concluded that tDCS can be successfully used in neurorehabilitative and cognitive neuroscience settings, and is safe for both stroke victims and healthy volunteers.

Poreisz et al. (2007) reported on their extensive experience (567 sessions) with tDCS to multiple brain regions in healthy subjects and patients. None of the subjects asked for a session to be terminated or required any medical assistance. 102 of their subjects completed a questionnaire inquiring about potential adverse effects. Subjects included healthy subjects (75.5%), migraineuers (8.8%), post-stroke patients (5.9%) and patients with tinnitus (9.8%). A mild tingling sensation was the most common symptom, occurring in 71% of subjects; the mean rating of the tingling was 1.74 ± .84 on a 1-5 scale. Moderate fatigue was noted in 35% of subjects during the stimulation; the mean rating was 2.17 ±1.11. Itching under the electrode was reported by 30%; the mean rating was 1.6 ±.72.

Clark et al. (2012) have assessed safety during 30 minutes of tDCS (ranging from 0.1 to 2.0 mA) tDCS. We have been consulting with Dr. Clark, and have based many of our experimental parameters on his work. The following is a statement from Dr. Clark: “(as of 2010) we only found two subjects who developed a rash out of the 83 tested using tDCS, and one of these was in the low-current sham control group (likely an allergic reaction to the electrode holder). We have tested an additional 120+ subjects in our ongoing study, roughly half using the 2.0 mA current for 30 minutes. Of these, only one subject asked to be removed for excessive sensation, but he was in a car accident earlier that day and was still emotionally upset. Not one subject has reported phosphenes (visual disturbances) resulting from tDCS.” Overall, sensations were minimal. Most commonly, subjects reported tingling or itching as the dominant sensations, with no serious adverse side effects.

Additionally, tDCS has demonstrated safety at UC Davis. Using similar stimulation parameters that we propose, Emily Kappenman, research personnel in Dr. Luck’s lab at UC Davis is currently acquiring data using tDCS. She submitted the following statement regarding their experiments:

“Using IRB Protocol #2550573-3, we have used the approved tDCS procedure in PI Dr. Luck’s laboratory in 164 subjects (approximately half in the sham condition

and half in the stimulation condition). Of the 164 subjects we have tested, only 1 person has requested to discontinue the procedure, citing excessing itching. During the stimulation/sham, sensations reported across subjects included: a tingling sensation at the electrode location, arm aching at the cathode electrode location, a prickling sensation that felt like small needles, weird taste in mouth, and itching at the electrode site. In all of these cases, the reported pain level on a scale from 1 (no pain) to 10 (extreme pain) never exceeded a value of 7. At the end of the procedure, self-report measures showed no adverse effects on mood or attention, no dizziness, persisting pain or discomfort, or confusion at the end of the procedure compared with the reported measures before the session."

Furthermore, a review by Nitsche et al. (2008) presented the behavioral, cognitive and side effects of tDCS in over 90 studies that had been conducted between 1998-2008. In summary, these reports have indicated that tDCS is a noninvasive procedure with strong promise for improving learning and memory across a wide population. The majority of tDCS studies that were reviewed reported no side effects. Approximately one third of these studies reported mild itching or tingling under the electrodes as the most severe and common side effect. Of more than 90 studies, less than 10 of these papers indicated that subjects experienced headache, and in most cases only one participant reported headache in those studies.

In our collaborator Dr. Ranganath's laboratory, using Protocol #468198-3, a tDCS experiment was completed in 21 individuals. No adverse events have occurred during this experiment. Sensations reported across subjects included an itching or tingling sensation at the electrode location, a prickling sensation that felt like small needles, or mild heat sensations at the electrode site. In all of these cases, the reported pain level on a scale from 1 (no pain) to 10 (extreme pain) never exceeded a value of 6. The median self reported pain value was a 2. At the end of the procedure, self-report measures showed no adverse effects on mood at the end of the procedure compared with the reported measures before the session.

Since the Nitsche review in 2008, the field of tDCS has quickly expanded, and to date a PubMed search of "transcranial direct current stimulation" results in 2705 published articles. In these studies there have been almost no reported seizures, loss of consciousness or persistent neurologic signs or symptoms. Therefore, the evidence to date suggests that the main risk associated with tDCS is a mild burning/tingling sensation. After approximately 10 years of experience and hundreds of publications with the technique, there have only very rarely been reports of serious adverse effects in subjects who have participated, including those studies involving multiple sessions (a rare case report was recently published by Ekici (2015) that described a seizure in a boy diagnosed with spastic tetraparesis induced after 3 consecutive days of direct stimulation to the motor cortex). The likelihood of inducing seizures is low due to the fact that tDCS current strengths are almost always administered at least an order of magnitude lower than that required to induce epileptiform activity, even during gamma oscillations (Bikson et al., 2016; Bikson et al., 2004). For example, our colleagues, Lauren Richmond and Ingrid Olson at the University of Pennsylvania, reported that 10 sessions of tDCS (with 2 weeks of 5 sessions over consecutive days) did not result in any serious adverse effects, and the repeated exposure to stimulation did not

result in an increased incidence of adverse effects when compared to shorter-term studies (Richmond et al., 2013).

Given that itching, tingling, and burning tend to be the most likely adverse effects associated with noninvasive stimulation studies, protocols have been outlined to help minimize the risk of skin damage or burning. In a paper by Loo et al. (2011) they outlined a protocol to address the potential risk of skin burns during tDCS experiments. They suggested that skin burns are attributed to drying out of electrodes and/or uneven skin abrasion. In order to prevent skin burns they suggested incorporating a few simple steps, including screening subjects for any skin conditions, inspecting skin at stimulation site for cuts, rash, etc. prior to placing electrodes, cleaning but not abrading skin prior to electrode placement, disinfecting electrodes, dampening sponges with saline when using single-use sponge electrodes (and monitoring them so that they do not dry out), periodically questioning subjects about sensations at the electrode site, stopping stimulation or adjusting electrodes if the subject reports discomfort, and inspecting skin for redness or damage following stimulation. In order to minimize skin burning in our experiments, we have incorporated these steps into our protocol (see 11. Procedures). Loo et al. (2011) reported that, by following these procedures, they were able to conduct over 2000 experiments without the incidence of any skin burns. This is the most extensive report on 2 mA stimulation. In addition, they reported that skin burns are usually preceded by pain. By asking the subjects to report any instance of pain, as well as periodic sensation questionnaires, the occurrence of skin burns can be minimized.

Noninvasive stimulation techniques such as tDCS have also been used safely to study cognitive function in several patient populations, including Parkinson's Disease (Boggio et al., 2006), stroke (Jo et al., 2009), Alzheimer's Disease (Boggio et al., 2009), and schizophrenia (reviewed by Kekic et al., 2016). Most relevant to this protocol, Brunelin et al. (2012) conducted a pilot study to explore the safety and efficacy in refractory schizophrenia. In this experiment patients received 2 mA of current for 20 minutes twice a day with a 3-hour interval, across 5 consecutive days. Patients improved on measures of symptoms, particularly in auditory hallucinations. No adverse events occurred. Patients only described a transient mild tingling or a slight itching sensation associated with the onset of stimulation. Additionally, the tolerability of tDCS in childhood-onset schizophrenia has been assessed (Mattai et al., 2011). In this study, patients received 2 mA or sham stimulation in 20-minute sessions, across 10 sessions (over 2 weeks). tDCS was well tolerated in all subjects, and no serious adverse events were reported. Again, the most common effect reported was tingling and itching, and a few reports of mild fatigue.

The great majority of tDCS studies in schizophrenia have targeted the DLPFC. Most studies have observed reduced positive and/or negative symptoms, with no studies reporting severe adverse events (reviewed by Kekic et al., 2016). These studies involve a range of patients, including patients with childhood-onset schizophrenia, catatonic schizophrenia, and treatment-resistant schizophrenia. There have been no reports of serious adverse effects, and no reports of seizures in any of these patient studies.

Finally, the risk of excitotoxic damage is not applicable to tDCS. Stimulation levels of 1 or 2 mA do not directly induce firing in cells that are not spontaneously active. Instead, it has been shown in animals that tDCS increases spontaneous neuronal firing rates only to a moderate degree and did not reach the threshold for excitotoxicity (Bindman et al., 1964). At 1 or 2 mA, it has been shown that tDCS does not increase levels of serum neurone-specific enolase (Nitsche et al., 2003; Nitsche and Paulus, 2001) a sensitive marker of neuronal damage (Steinhoff et al., 1999). In rats, only at doses 100 times higher than those used in humans was neural pathology evident. Whereas 800 mA is used in humans for electroconvulsive shock therapy (ECT), which is intended to induce seizures, we only intend to use a maximum of 2 mA. Therefore, it is highly unlikely that this dose will produce seizures in a non-epileptic population. Furthermore, we would like to re-emphasize that non-invasive stimulation techniques such as tDCS and tACS are not at all similar to ECT, and therefore, the risks are quite different. In addition, tDCS is also quite different from, and considered less invasive than, other stimulation techniques such as transcranial magnetic stimulation (TMS). The risks associated with tDCS and tACS have been shown to be minimal.

Some additional potential risks have been identified, and although these events rarely (if ever) occur, every precaution will be made to prevent these risks. These risks include tissue damage, changes in mood, and electrical shock.

Plan For Minimizing Risk To Subjects :
Normal patient handling procedures are followed to eliminate risks. The subjects will be able to communicate with the investigators at all times. The subject's emotional state and mood will be assessed before and after stimulation; and physical sensation will also be monitored with a questionnaire administered before, during, and after the stimulation procedure (see above for details). The subject can ask to stop the experiment at any time for any reason. Likewise, the experimenter may stop the experiment at any time if the subject reports experiencing any pain or discomfort. When stopping the stimulation, the current will be gradually ramped down using the safe stop mode in order to avoid any unpleasantness or painfulness associated with abruptly aborting stimulation. It is also important to note that individuals may respond differently across tDCS conditions. Therefore, we will monitor all participants closely even when they have completed previous visits with no adverse effects. In the unlikely event that a subject experiences serious side effects or injury due to the experiment, the experimenter will call 911, and these details will be immediately communicated to the IRB. We have identified the following potential risks associated with tDCS and address them in turn:

I. Skin Damage or Irritation: Nitsche et al. (2003) suggest that there may be a slight risk of skin damage or irritation resulting from tDCS stimulation. With the exception of Iyer et al. (2005) who reported transient redness at the stimulating electrode site in two men who had recently shaved their heads, we have encountered no reports of skin damage or irritation in any of the tDCS literature. The possibility of skin damage resulting from electrode heat has also been tested using stimulation parameters comparable to those outlined in this protocol. None of these results have indicated skin damage due to electrode heat. Furthermore, we will be using saline-soaked electrodes, or we will use electrode paste, for our study, which minimizes the possibility of chemical reactions at the electrode-skin

interface and resultant skin damage. The scalps of each subject will be visually inspected immediately before stimulation. Any identified irritation or evidence of recent shaving of the head will postpone or terminate that subject's participation in the study. Subjects will also be asked to remove any jewelry that may come into contact with the electrodes. Subjects will be encouraged at the beginning of the tDCS procedure to report any pain or discomfort that they may encounter throughout the procedure. Any such reports, or evidence of redness or irritation of the scalp, will result in the immediate termination of stimulation. Additionally, subjects will be screened for latex allergies to prevent allergic reactions to the electrodes. If allergic reactions are noted at any time, stimulation will be ceased, and electrodes will be removed. Overall, these methods for prevention of skin damage follow the suggestions of Loo et al. (2011, see above).

To avoid burning the patient, there is a recommended limit of 0.1 mA/cm^2 for DC current applications (per the device manual). For example, using electrodes with a surface area of 35 cm^2 with a current of 1 mA applies a current density of 0.02857 mA/cm^2. It is possible that subjects may experience pain at lower levels of current, and therefore, we will closely monitor subjects' responses on the questionnaires. To avoid permanent injury of tissue, current density should not be higher than 25 mA/cm^2 at any given electrode site. This limit is far above the limit for thermal effects of the current density. Note that the maximum current in this protocol is 2 mA, and the surface area of the Starstim PISTIM electrodes is 3.14 cm^2. Other Starstim stimulating electrode options include the SPONSTIM electrodes in either 8 cm^2 or 25 cm^2. Thus, the maximal current density used in this protocol will range from 0.080 - 0.64 mA/cm^2. Therefore, the maximum current density will always be set below the recommended limit to avoid any skin burning or damage.

II. Tissue Damage and Discomfort : To minimize any possible tissue damage we have subjects fill out a tDCS sensation questionnaire form throughout the tDCS procedure. This questionnaire allows us to monitor what the subjects are physically feeling at the electrode sites. This will be given at the following time points: 1 minute after start of tDCS, 5 minutes after start of tDCS, and 20 minutes after tDCS. If at any time the subject reports a sensation level of 7 on a 10-point scale, we immediately discontinue the experiment. We will also administer a subjective mood questionnaire before and following experimentation. Any significant changes in answers provided following the experiment will result in further assessment every 15 minutes until subjects return to near baseline state. (also see above "Skin damage or irritation" for further details).

III. Pain: At very strong, focal current density can result in pain. We will be using large electrodes and passing weak electrical current. As previously stated, with protocols similar to ours, most subjects report only mild, transient tingling at the stimulation site. Any subject report of pain resulting from tDCS will result in immediate termination of stimulation.

IV. Alterations in Mood or Affect: There is evidence that tDCS can result in changes in mood and concentration. While no studies have reported negative affect resulting from DC stimulation, several studies have reported improved mood after tDCS. It should be noted that, in these studies, stimulation was applied for significantly longer durations. Studies designed to investigate the safety aspects of non-invasive brain stimulation have reported no significant changes in mood as

measured with the VAMS (Visual Analog Mood Scales) and no significant changes in measures of fatigue when comparing stimulation to sham. Therefore, we do not anticipate any changes in mood or affect resulting from our study. To further ensure that subjects are not experiencing alterations in mood or mental state that could potentially debilitate them, we will administer a subjective mood questionnaire before and following experimentation. Any significant changes in answers provided following the experiment will result in further assessment every 15 minutes until subjects return to near baseline state.

V. Electrical Shock: As with any contact between persons and electrical apparatuses, there is a slight possibility of electrical shock. To our knowledge, no studies have reported any incidents of significant electrical shock resulting from DC stimulation, and we do not anticipate this event occurring in our experiment. To help ensure the prevention of electrical shock, we will avoid conducting experiments near potential liquid spills. Further, we will ensure that subjects are not in contact with any potential conductors other than those specified in the experimental design. This measure greatly reduces the likelihood that electrical shock will result from short-circuiting or inadequate insulation. In the very unlikely event that the subject experiences a shocking sensation, the current will be first be ramped down, turned off, and then the electrodes will be removed.

There is the possibility of an electrostatic discharge by touching the patient (for example the patient's head) or the DC-STIMULATOR PLUS. Having an electrostatic discharge while electrodes are attached to a subject may cause a discharge current to flow through the electrodes leading to a shock sensation similar to that experienced in everyday life. Such currents are not dangerous but they are unpleasant. As such, we will avoid touching the patient during stimulation.

The output circuit of the constant current source of the DC-STIMULATOR PLUS is equipped with an electrical fuse that limits the current to 5 mA. Therefore, in any faulty condition and during normal operation, current will be ramped down and then turned off.

There is a potential of a strong stimulus to be delivered if the electrodes are disconnected while current is flowing. Therefore, electrodes will not be disconnected while current is flowing. Instead, current will be ramped down until it is off completely before electrodes will be removed.

VI. Avoiding Electrode Placements Outside the Head: For safety reasons, we will never use bipolar stimulation on any other part of the body apart from the head. Although not reported in any tDCS studies, it is plausible that bipolar stimulation setups could potentially harm the heart if electrodes are set up in a manner that would pass current across the heart. Similarly, we will avoid electrode setups that could lead to the stimulation of the brain stem and cerebellum (vagus nerve). Care will always be taken during electrode placement to ensure that areas outside the head are not stimulated.

VII. Contraindications for Subjects with Electrical Support Systems: Stimulation from tDCS may interfere with pacemakers or implanted brain stimulators. Accordingly, subjects will be carefully screened for pacemakers or

brain stimulators prior to the initiation of the study. Subjects with pacemakers or brain stimulators will not be allowed to participate.

VIII. Availability of PIs: With the above safeguards in place, the tDCS stimulation procedures described above are expected to be safe and well-tolerated. As an added precaution, the PI (Cameron Carter, M.D.) will be available on call during each session to answer any questions for research staff. A licensed physician, Dr. Carter will review the case details of any adverse event and determine whether any modifications to the protocol are needed in order to further minimize risks. If he deems it necessary, he will have the authority to stop a tDCS research session or to halt further tDCS studies.

In the unlikely event that a subject experiences serious side effects or injury due to the experiment, these details will be immediately communicated to the IRB. These subjects will also be provided with the necessary medical care. Our personnel will call 911 upon a medical emergency, such as a seizure, while ensuring that the subject does not cause further harm to him or herself.

Specifically, we will report serious adverse events as well as other unanticipated problems to the IRB within five days of becoming aware of such an event, provided that the event or problem occurred at UC Davis, suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized, was unanticipated, and was related or possibly related to the research. In the report, we will either justify why no changes to the protocol or consent form are needed or attach proposed modifications to the report. Responses to all requests from the IRB for further information will be made within 10 working days of receipt of the request.

IX. Seizure: Although risk of seizure is very low, steps will be taken to minimize this risk. Any subjects with a history of epilepsy or seizures will be excluded. Furthermore, any subjects who are currently (less than 1 month prior to enrollment) taking the antipsychotic clozapine will be excluded as this antipsychotic associated with the greatest risk for seizures (Devinsky et al., 1991)

13) Potential Benefits to Subjects

Subjects may receive some benefit from participation. Previous studies indicate that tDCS may produce transient improvements in cognitive performance. For instance, reports have demonstrated improvements in working memory performance in healthy adults (Fregni et al., 2005; Keeser et al., 2011) as well as patients with schizophrenia (Hoy et al., 2014). Improved social cognition after tDCS stimulation of the DLPFC has been observed in schizophrenia as well (Rassovsky et al., 2015).

14) Sharing of Results with Subjects

N/A

15) Provisions to Protect the Privacy Interests of Subjects

The data and/or specimens will be labeled with a code that the research team can link to personal identifying information when acquired. The code sheet will be secured and kept separate from the dataset. All data will be stored on password-

protected computers and/or networks. Information regarding personal information will only be requested from the subject by the recruiter and experimenter. No personal identifiers will be attached to data. During the experiment, the experimenter will thoroughly explain all procedures to ensure that the subjects feel at ease with the procedures.

16) Economic Burden to Subjects

N/A

17) Drugs or Devices

This study uses the Starstim device. Although not approved by the FDA, this device is specifically designed for non-invasive stimulation and EEG research, and is widely used across academic institutions worldwide. This device has demonstrated safety, and is also CE-Certified with approval in Europe. This device does not involve greater than minimal risk. A brochure for this product has been attached. The device will be stored in a locked laboratory that is supervised by investigators on the protocol during working hours. All authorized investigators will be trained on the procedures outlined in this protocol for the proper use of this device on subjects.

In additional to the manuals, brochures and other info re: this device are attached to this submission.

☐ I confirm that all investigational devices will be labeled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

18) ClinicalTrials.gov Registration

FDAAA 801 establishes penalties for Responsible Parties who fail to comply withClinicalTrials.gov registration or results submission requirements. Penalties include civil monetary penalties and, for federally funded studies, the withholding of grant funds.

Section 1: NIH Funded Studies
If yes to BOTH, the study must be registered on Clinicaltrials.gov.

Yes	
☐	This study is funded by the NIH. (If this study is not funded by NIH, go to Section 2.)
☐	One or more human subjects will be prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Section 2: Studies subject to FDA jurisdiction
If yes to ANY the study must be registered on Clinicaltrials.gov.

Yes	

☒	This is a prospective clinical study of health outcomes in human subjects that compares an intervention with an FDA-regulated device against a control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.
☐	This is a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act.
☐	This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click here.

Section 3: Publishing the results
If yes to BOTH the study must be registered on Clinicaltrials.gov.

Yes	
☒	This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome.
☒	The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations.

This requirement includes studies of behavioral interventions.

Section 4: Registration on Clinicaltrials.gov is not required

Yes	
☐	I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research.

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