Study Protocol

Official Title: Modulating Default Mode Function: A Transcranial Direct Current Stimulation (TDCS) Pilot Study

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Scientific Background

Several theories about depression and anxiety suggest that a broad dimension of negative affectivity is shared by the disorders.[1,3,10,11,15] This dimension represents the tendency to experience negative emotions and to cope inadequately with emotional distress.[16] Recent work in our laboratory has begun to identify and describe one specific component of the broad dimension of negative affectivity, Excessive Self-Consciousness (ESC), that holds promise as a specific phenotype underlying depression and anxiety in adults. This dimension reflects the tendency to feel shame, embarrassment, humiliation, and inadequacy around others. Preliminary work suggests that it is uniquely associated with impairments in interpersonal functioning over and above psychiatric symptoms, and it is associated with a specific pattern of disruption in the functioning of neural systems during emotional regulation. Specifically, among adults with depression, we have observed that higher levels of ESC are associated with: 1) decreased top-down control from the dorso- and ventrolateral prefrontal cortex (DLPFC, VLPFC; portions of the cognitive control network)[17,18] during regulation of an initial emotional response in the amygdala; 2) heightened activity during emotion regulation in the precuneus and posterior parietal cortex, regions typically active when thinking about on oneself;[19-21] and 3) an abnormal pattern of interference by which the abnormally elevated activity in parietal regions alters the patterns of connectivity in the cognitive control network – specifically, decreasing the communication between the DLPFC and the dorsal Anterior Cingulate Cortex (ACC), a region critical for the adaptive regulation of emotional experience.[17,22] The goal of the proposed project is to determine whether direct, temporary hyperpolarization of portions of the posterior parietal cortex associated with self-referential processing can alter the patterns of abnormal functioning described above and provide a more effective and targeted treatment option for individuals with high levels of ESC, regardless of diagnosis.

Transcranial direct current stimulation (tDCS) provides a safe method for intervening directly on the functioning of brain regions. The technique involves passing a weak current through the brain using a montage of electrodes, pre-selected to target a specific location. Anodal tDCS results in depolarization of cortical pyramidal cells, increasing neuronal excitability and neuronal-neuronal connections. Cathodal stimulation, by contrast, results in hyperpolarization, decreasing neuronal excitability and reducing neuronal-neuronal connections.[23] tDCS has been tested as a potential treatment for both major depressive disorder[24-27] and anxiety disorders.[28] Approximately half of the randomized controlled trials of tDCS have observed significant effects, and half have not.[24] When studies are meta-analytically combined, the efficacy of tDCS as a treatment for depression is similar to that observed for standard treatments whereby effect-sizes are small[24,27] and only 1/3rd of patients respond to the treatment.[27] We believe that outcomes from direct interventions like tDCS can be dramatically improved by individualizing them to target the specific pathophysiological mechanisms associated with a particular individual's illness. As such, we hypothesize that by combining our initial results demonstrating that the ESC phenotype is associated with specific patterns of cortical network dysfunction with the targeted intervention capability of tDCS, we will be in a position to develop and test a truly personalized, circuit-based intervention that has the capability of improving treatment outcomes.

Study Objectives

There is growing recognition that strict distinctions between clinical psychiatric disorders such as anxiety and depression, on the one hand, and trait-like dispositions to experience negative emotions, on the other, fail to capture the true nature of psychopathology and are ultimately unhelpful.[1-3] We contend that by examining specific dimensional phenotypes that are associated with the experience of negative emotions and that cut across depression and anxiety disorders, we will be better able to identify the neurobiological processes associated with an individual's

distress and to develop better, individually targeted interventions. Recent work in our laboratory has identified one such phenotype, Excessive Self-Consciousness (ESC), that cuts across depression and anxiety disorder presentations, predicts specific impairments in real-world interpersonal functioning, and correlates with a particular pattern of dysfunction in neural systems. In this study, we propose to test whether the ESC phenotype can be used to guide a novel, transcranial direct current stimulation (tDCS) intervention to target specific abnormalities in cortical network functioning.

ESC has long been recognized as one component of the general trait-like disposition to experience negative emotions. It describes the tendency to feel shame, humiliation, and inadequacy around others. In our work with depressed adults, we observed that higher levels of ESC were associated with the following neurofunctional abnormalities during emotion regulation: 1) inefficient functioning of the top-down, cognitive control network necessary to regulate negative emotions; 2) abnormally increased activity in regions of the parietal cortex that are typically active during self-reflection; and 3) a pattern of network interference by which the elevated activity in the parietal regions interfered with communication in the cognitive control network.

In this study, we propose to test whether the ESC dimensional phenotype can be used to guide a novel tDCS intervention to target the network-based abnormalities described above. tDCS involves passing a weak current through the brain. One variant, cathodal tDCS, can be used to temporarily hyperpolarize cortical pyramidal cells, thereby decreasing neuronal connections. tDCS has been explored as a possible treatment for depression, but results to date are mixed. No work has examined whether tDCS can be used in an individually guided manner to target locations in the parietal cortex and alter the patterns of circuitry dysfunction described above. The aims of this study were designed to provide pilot data for a competitive future funding proposal:

1) Determine the impact of acute cathodal tDCS to regions of the left posterior parietal cortex associated with self-reflection on the patterns of abnormal neural activity and connectivity described above. We will compare this to a sham condition whereby no active tDCS will be applied.

2) Determine if the impact of the intervention is greater for those with higher vs. lower levels of ESC, controlling for symptoms of depression and anxiety.

3) Document the feasibility and acceptability of the intervention, and explore whether the tolerability or efficacy of the intervention differs as a function of demographic variables or psychiatric symptoms.

Study Design & Methods

Sample: In order to demonstrate that the patterns of functional neural abnormalities associated with ESC can be specifically altered by cathodal tDCS, we will recruit a sample of 44 adults (18-30 years old, 50% male/female), all of whom will have clinically significant levels of depression ($\geq$ 10 on the Quick Inventory of Depressive Symptoms[29,30]) or anxiety ($\geq$ 60 on the PROMIS Anxiety Short-form[31]). We are selecting a sample of depressed and anxious adults so that we can confirm that it is the ESC dimensional phenotype, and not psychiatric symptom severity, that is associated with the patterns of cortical functioning abnormalities described above. To ensure an adequate range of ESC scores, the sample will be stratified to require that half (N=22) fall in the upper tertile of ESC scores expected among adults with depression or anxiety[2] and half (n=22) fall in the bottom tertile.

Procedures: The proposed study will be carried out at the University of Pittsburgh, Magnetic Resonance Research Center (MRRC). Participation will occur over three assessment periods. If participants appear eligible after a telephone screen, they will be scheduled for Visit 1 (which may be virtual or in-person), during which a more thorough set of screening procedures will

determine full eligibility and demographic, symptom, trait, functioning, and life history information will be collected. If participants continue to be eligible following Visit 1, they will be scheduled for two scan visits (Visits 2 and 3) to be held on separate days, approximately one week apart. The following data will be collected:

Initial Eligibility Screening (Visit 1). To determine eligibility, participants will complete the Quick Inventory of Depressive Symptoms (QIDS[30]) and the Patient Reported Outcomes Measurement Information System Anxiety 7-item short form (PROMIS-A[31]). The QIDS is a 16-item, self-report measure of depression symptoms.[29,30] Item-response theory analyses suggest cut-offs for moderate depression severity at total scores of 10.[29,30] The PROMIS-A is an 7-item, self-report tool assessing anxiety. Instrument developers recommend a cutoff for clinical significance at T scores of 60.[32] To determine scores on the ESC phenotype, participants will complete the NEO-PI-R,[16] a 240-item inventory that measures the constructs associated with the Five Factor Model of personality, along with the facets of each broad domain. We will use scoring algorithms developed in our laboratory and validated in three separate samples to determine ESC scores.

fMRI Protocol (Visits 2 and 3): At each scanning visit, symptoms (i.e., QIDS, PROMIS-A) will be reassessed. During fMRI at each visit, participants will complete the Cognitive Reappraisal Task. This widely used task examines the functioning of the neural circuitry associated with exerting cognitive control over the response to emotionally salient stimuli.[34,35] Each trial begins with an instruction cue (2s) to either "attend" or "reappraise" the image that will follow. Next, a negatively or neutrally valenced interpersonally relevant picture is presented (8s) during which participants follow the instructions given for that trial. The task consists of three trial types: attend neutral, attend negative, and reappraise negative. During attend trials, participants view the scene and experience their natural emotional response. During the reappraise trials, participants are asked to reframe the meaning of the scene so as to diminish the negative emotional impact.[36] Participants practice the task prior to the scan, and they are provided feedback on their reappraisals of practice items. The stimulus display is followed by an emotional rating probe (4s) and finally a fixation cross (4s) to mark the end of the trial. Twenty trials of each type are presented in a pseudorandom order over two 10 minute, 20 second runs. Two versions of the task have been developed to facilitate repeated testing. These will be counterbalanced across subjects and visits. This task has been used in several studies of healthy adults,[37-39] and Dr. Fournier has successfully used the task in a sample of depressed individuals. Prior to fMRI scanning, structural brain data will be collected for all participants. Following the final visit, participants will complete a short, self-report questionnaire regarding their experience of the intervention and will be debriefed by study personnel.

tDCS Protocol (Visits 2 and 3): TDCS will be administered concurrently with the emotion regulation paradigm in the scanner using procedures already in place at the MRRC. TDCS is applied to the scalp, typically providing the equivalent of what a 6V battery would produce (and providing no more than 15V). The TDCS sponge electrodes and connecting wires are non-ferromagnetic and thus can be used safely within the MRI facility. These will be connected to the main apparatus situated outside of the facility. Investigators have determined the optimal placement of wires in the scanning environment to reduce occurrence of scanning artifacts. The montage for left posterior parietal cortex stimulation and the sham will be based on our prior work, the published literature[26], and neurotargeting software. We will employ left posterior parietal cortex cathodal stimulation and anodal stimulation on the shoulder. Cathodal stimulation of -1mA will be used, as this produces neural inhibition[41], and because higher cathodal stimulation currents can yield paradoxical excitation[42]. Voltage is controlled by the device to maintain a constant electrode -1mA current. Cathodal stimulation will be applied for the duration of the emotion regulation task (approx. 20 minutes), and it will be slowly ramped up to start and ramped down to end. Previous findings indicate that effects of acute TDCS can last about 2 hours after the procedure but not into the next day[42]. Side effects: mild skin sensations under

the electrode (itching, prickling), dizziness, visual flickering; much less frequently, nausea, headache and more serious atopic skin reactions. There is a built-in safety mechanism to prevent shorting and discomfort. Participants indicate, using a squeeze ball, if they feel scalp warmth. Sham stimulation will be slowly ramped up and down to a nominal low level (1ua).

Eligibility Criteria

Inclusion Criteria:

1) Between 18-30years old
2) Score > 10 on the QIDS or > 60 on the PROMIS-A
3) We will use a flexible extreme groups recruitment strategy to ensure an adequate distribution of ESC scores. We will ensure that at least 62% of the sample will be composed of those scoring .5 SD above or below the mean, as measured by the NEO-PI-R. This value corresponds to the expected values assuming a normal distribution of the trait.
4) Normal or corrected to normal vision
5) Able to provide informed consent in English
6) Right-handed (Annett criteria)

Exclusion Criteria:

1) Have a history of head trauma with loss of consciousness.
2) Have a systemic medical illness that may impact fMRI measures of cerebral blood flow.
3) Meet standard exclusion criteria for fMRI scanning (e.g. claustrophobia, cardiac pacemakers, neural pacemakers, surgically implanted metal devices, cochlear implants, metal braces, or other MRI non-safe metal objects in the body).
4) Are pregnant (self-report and tested for as part of any scan by the scanning center)
5) Not native English speaking or not fluent
6) Premorbid NAART IQ estimate<85;
7) Visual disturbance (<20/40 Snellen visual acuity) with correction
8) Left/mixed handedness (Annett criteria), to ensure a uniform hemispheric dominance for interpretation of neuroimaging data
9) Active suicidal ideation in need of immediate treatment
10) Scoring below the cutoffs on both the QIDS and the PROMIS-A
11) History of alcohol/substance use disorder (including nicotine) and/or illicit substance use (except cannabis) over the last 3 months, determined by the MINI. Lifetime/present cannabis use (non-disordered levels) will be allowed, given its common usage in individuals in this age range.
13) Current or past psychotic-spectrum disorder
14) History of seizures

Statistical Considerations

A1: Repeated-measures ANOVA models will be used to determine whether acute cathodal tDCS to the left posterior parietal cortex, compared to the sham condition, alters patterns of neural activity in and connectivity with the posterior parietal cortex and corresponding patterns of activity and connectivity within the cognitive control network during emotion regulation. A2: Repeated measures ANCOVA models will determine whether the impact of tDCS is stronger for those with higher ESC scores, controlling for concurrent depression and anxiety symptoms. A3: Feasibility and tolerability of the intervention will be assessed by examining attrition rates between the fMRI/tDCS visits and by examining responses on the self-report questionnaire regarding the acceptability of the intervention. Differences in acceptance, tolerability, and efficacy will be explored as a function of demographic variables and psychiatric symptoms.