ANCILLARY REVIEWS

DO NOT DELETE. Submit the completed checklist below with your protocol.

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☒ **Yes** ☐ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide*	
☒ **Yes** ☐ **No**	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups each have their own**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) or MR from Masonic Institute for the Developing Brain (MIDB) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu*	

			application process.
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☒ **Yes** ☐ **No**	Plan to use CTSI Monitoring services, and/or have an IND, IDE, or designated NSR-IDE by the UMN IRB?	*The CTSI monitoring ancillary review will be assigned to your study by IRB staff. Please note eligibility criteria here.* *Contact: fencl003@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ **Yes** ☒ **No**	Use data from CTSI Best Practices Integrated Informatics Core? Formerly the AHC Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: bpic@umn.edu*	
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: Jenny Pham* *Pham0435@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact:* fencl003@umn.edu	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

PROTOCOL COVER PAGE

Protocol Title	tDCS and cognitive training for restrictive eating disorders
Principal Investigator/Faculty Advisor	Name: Lisa M. Anderson, PhD
	Department: Psychiatry and Behavioral Sciences
	Telephone Number: (763) 742-8136
	Email Address: ande8936@umn.edu
Student Investigator	Name:
	Current Academic Status (Student, Fellow, Resident):
	Department:
	Telephone Number:
	Institutional Email Address:
Scientific Assessment	HRPP facilitated scientific assessment
IND/IDE # (if applicable)	N/A
IND/IDE Holder	N/A
Investigational Drug Services # (if applicable)	N/A
Version Number/Date:	Version 8/ 13 AUGUST 2025

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	05.14.2024	• Clarified storage and handling of the tDCS device in Section 4.2. • Added description of safety precautions taken by study staff for accessing tDCS device in section 13.1.	
2	07.25.2024	• Specified that tDCS sessions will occur 5 consecutive days per week over a 2 week period • Specified that remote consent will utilize Zoom audio and video. • Clarified in sections 9.3 and 14.1 that there are no proven benefits to being in this study and that it is only meant for preliminary data. Also added to 14.1 that effects of tDCS on eating disorder symptoms is unknown.	Yes
3	09.16.2024	• Adding Eating Behavior Questionnaire to assess ED symptoms between sessions • Changing to only administering the Pearson DKEFS trail making test for baseline and follow up cognitive assessments. • Adding BIS-BAS questionnaire at baseline to assess for general reward and aversion sensitivity and responsivity. • Clarified in section 18.2 that the medical monitor will be able to access reported events in study Box. • Clarified in section 18.1 CTSI monitoring process for this study.	No
4	10.21.2024	• Changing study visit locations to Non-Invasive	Yes

		Neuromodulation Lab or Masonic Institute of the Developing Brain. This is where the StarStim device will be housed. • Updating security precautions for device access to account for new intervention visit location. • Adding clarification about using a ground if impedence is high. • Adding that StarStim can be administered using bluebooth OR wifi. Bluetooth is often unreliable and wifi will be used in these cases.	
5	01.16.2025	• Updating tDCS study visit locations to include the Ambulatory Research Center (ARC) inside of the Unversity of Minnesota Medical School.	Yes
6	04.04.2025	• Adding clarification to section 15.4 that unanswered items on questionnaires will not result in protocol deviations. Missing data will not need to be reported. Unanswered questions on self report measures will not be documented as a PD as participants are given several reminders that all responses to questionnaires are optional. • Adding clarification to section 18.2 that tDCS associated sensations reported on tDCS side effect questionnaires will only be reported in the adverse event (AE) log if they raise to the severity level of severe. • Adding update in section 18.2 to timeline of medical monitor reviewing participant safety data. Medical monitor	No

		will now review participant safety data quarterly. Participant medical history will still be reviewed at baseline by study physician to determine medical stability for eligibility purposes.	
7	08.13.2025	• Adding clarification of randomization of participants' treatment arm (active vs.sham) and the blinding process that is conducted through the StarStim program. • Detailing the unblinding process that may be conducted by the study medical monitor • Replacing the term "DSMB" or "data safety monitoring board" to "medical monitor" as the study's medical monitor will act as the data safety monitor as well. • Removal of statement that the study will send annual reports to the IRB and FDA. Study auditor clarified to the study team that this is not required for this study. • Clarification of training process for tDCS administration • Clarification of discussion held with participant during participant withdrawal including referral for care. • Addition of health update form to Visits 12 and 13 to document any adverse events unrelated to tDCS that may occur. • Addition of pregnancy test to determine study eligibility as this is a potential contraindication of tDCS that	yes

		needs to be ruled out at baseline visit.	

Table of Contents

1.0 Objectives 10
2.0 Background 10
3.0 Study Endpoints/Events/Outcomes 12
4.0 Study Intervention(s)/Investigational Agent(s) 12
5.0 Procedures Involved 14
6.0 Data and Specimen Banking 22
7.0 Sharing of Results with Participants 23
8.0 Study Population 23
9.0 Vulnerable Populations 24
10.0 Local Number of Participants 27
11.0 Local Recruitment Methods 27
12.0 Withdrawal of Participants 29
13.0 Risks to Participants 30
14.0 Potential Benefits to Participants 31
15.0 Statistical Considerations 31
16.0 Health Information and Privacy Compliance 32
17.0 Confidentiality 35
18.0 Provisions to Monitor the Data to Ensure the Safety of Participants 35
19.0 Provisions to Protect the Privacy Interests of Participants 37
20.0 Compensation for Research-Related Injury 37
21.0 Consent Process 37
22.0 Setting 39
23.0 Multi-Site Research 40
24.0 Coordinating Center Research 40
25.0 Resources Available 40
26.0 References 40

ABBREVIATIONS/DEFINITIONS

- ARC: Ambulatory Research Center
- ED: Eating Disorder
- EMA: Ecological Momentary Assessments
- IDE: Investigational Device Exemption
- NSR: Non-Significant Risk
- tDCS: Transcranial direct current stimulation
- UBACC: University of California, San Diego Brief Assessment of Capacity to Consent
- UMMC-FV: University of Minnesota Medical Center – Fairview
- NNL: Non-Invasive Neuromodulation Lab

1.0 Objectives

1.1 Purpose: The overarching purposes of this study are to: First, establish feasibility and tolerability of a tDCS-augmented cognitive training program (tDCS + CT) designed to improve cognitive flexibility among treatment-seeking individuals with restrictive EDs (R-EDs; anorexia nervosa, atypical anorexia nervosa). Second, we will use a randomized controlled trial study design to compare active tDCS + CT vs sham tDCS + CT within this sample, in efforts to evaluate the potential additive benefits of tDCS to cognitive training for individuals with R-EDs.

- Objective 1: Determine the feasibility and acceptability of a brief (10-session) tDCS+CT intervention for treatment-seeking adults with R-EDs.
    - Hypothesis 1a: Participants receiving active tDCS+CT will demonstrate similar retention rates as participants receiving sham tDCS+CT, indicating successful administration of a 10-session tDCS+CT intervention via a remote platform.
    - Hypothesis 1b: Participants receiving active tDCS+CT will report similar treatment acceptability ratings as participants receiving sham tDCS+CT.
- Objective 2: Determine the extent to which cognitive flexibility is modulated by tDCS+CT in R-EDs.
    - Hypothesis 2: Participants receiving active tDCS+CT will demonstrate greater improvement in task performance on cognitive flexibility training tasks and un-trained measures of cognitive flexibility domains, as compared to participants receiving sham tDCS+CT.
- Objective 3: Evaluate the extent to which active tDCS+CT relates to changes in eating disorder relevant cognitive flexibility (ED-FLIX self-report measure), rigid eating disorder cognitions (fear of weight gain, weight/shape concerns) and inflexible behaviors (restrictive eating behaviors), as compared to participants receiving sham tDCS+CT at end of treatment and 1-month follow-up.
    - Hypothesis 3: Participants receiving active tDCS+CT will demonstrate greater improvement in eating disorder relevant cognitive flexibility and eating disorder symptoms, as compared to participants receiving sham tDCS+CT.

2.0 Background

2.1 Significance of Research Question/Purpose: Restrictive eating disorders (R-EDs), including anorexia nervosa (AN) and atypical anorexia nervosa (AAN), are serious psychiatric disorders characterized by persistent engagement in behaviors leading to severely low weight or significant weight loss (1). Individuals with R-EDs have elevated physical and psychological morbidity (2-4) and the second-highest mortality rates of any psychiatric illness (5-6). Current evidence suggests that individuals affected by R-EDs, such as AN, often maintain a chronic illness course or die prematurely (7-9). Treatments for adults with R-EDs have limited proven efficacy (8-9). This gap in clinical care is due in part to limited translation of basic findings on

the neurobiological mechanisms that maintain R-EDs into targeted interventions. There is an urgent need to develop novel interventions that can directly alter the key neurobiological mechanisms underlying maladaptive behaviors that promote and maintain R-EDs.

To address this need, we propose to conduct a feasibility study to examine the effects of tDCS and cognitive training in adults with R-EDs (AN, atypical AN) who are enrolled in treatment programming at a local eating disorders treatment center.

2.2 Preliminary Data: In our team's pilot randomized controlled study in adults with alcohol use disorder (AUD; n=60; Camchong PI), we used a similar active/sham tDCS+CT approach designed to enhance executive functioning (including cognitive flexibility) via application of tDCS to the DLPFC. Findings from this work suggest that active tDCS+CT can increase prefrontal-incentive salience connectivity, a neural network known to support abstinence, and reduces relapse rates AUD. These promising findings for AUD indicate the critical importance of exploring the effect of tDCS+CT on other disorders characterized by difficulties with cognitive flexibility, including R-EDs.

No preliminary data has been collected in an R-ED sample.

2.3 Existing Literature:

Deficits in Cognitive Flexibility Maintain Maladaptive R-EDs Symptoms. Cognitive flexibility is a key component of executive function, and relates to the ability to adaptively shift thoughts and actions in response to changing environments and demands (10). Individuals with R-EDs often report significant difficulties with cognitive flexibility that relate to symptom severity and impairment (11-12). Recent findings suggest that improvement in cognitive flexibility contributes to significant symptom improvements in patients with R-EDs (13). Evidence from studies of cognitive remediation therapy, which targets cognitive flexibility and inflexible eating disorder behaviors, suggests that adjunctive cognitive training approaches can improve both cognitive flexibility and clinical R-ED symptoms (14-16).

Dorsolateral Prefrontal Cortex (DLPFC) Disturbances Underlie Cognitive Flexibility Difficulties. Imaging research has identified a range of brain structures involved in the pathophysiology of eating disorders (17-21). In particular, the DLPFC has been associated with cognitive flexibility difficulties (22-24). Ultimately, the DLPFC may play a key role in over-regulation of cognition and behavior often observed in R-EDs (e.g., rigid regulation of food intake via restriction).

Transcranial Direct Current Stimulation: A Novel Brain Based Approach to Improve Cognitive Flexibility, When Paired with Cognitive Training. The proposed project will apply recent advances in non-invasive neuromodulation by combining transcranial direct current stimulation (tDCS) with cognitive-flexibility-focused training. TDCS is a non-invasive neuromodulation technique that prepares neurons to fire in targeted brain regions and influences targeted brain networks (25). Drawing from Hebbian theory (26), which suggests that neurons that "fire together, wire together," tDCS may enhance cognitive training outcomes. To our knowledge, Khedr and colleagues (27) have published the only investigation of tDCS for R-EDs to date. In their open label, single-arm study, seven patients with treatment-resistant AN received anodal tDCS for 25 minutes over the left DLPFC for 10 days. Changes in self-report measures of eating disorder symptom were examined from pre to post intervention; results indicated that responses to tDCS were

variable with several participants showing consistent improvement at end-of-treatment and follow-up. Importantly, tDCS without cognitive training was used in this study (27). Because emerging literature supports the enhanced response associated with the combination of cognitive training and neuromodulation (28-29), we propose that combining tDCS with cognitive training (tDCS+CT) will enhance the desired neuroplastic changes, needed to increase cognitive flexibility.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

- Feasibility and Tolerability: To evaluate feasibility (Objective 1), participant withdrawal and retention policies are described in Section 12.0. To evaluate tolerability (Objective 1), we will use the Treatment Side Effects Questionnaire to record intervention side effects. Based on our team's previous alcohol tDCS study and studies from other research groups, we hypothesize that the intervention will be feasible and safe, such that participants will tolerate the procedures and remain in the study with less than 20% dropout over the course of active tDCS and cognitive training.
- Changes in cognitive flexibility performance: To evaluate cognitive flexibility performance changes (Objective 2), we will compare cognitive flexibility task performance change from pre-intervention to post-intervention) between groups (active tDCS+CT vs. sham tDCS+CT). We hypothesize that the group receiving active tDCS sessions will have a larger improvement in cognitive flexibility performance than the group receiving sham tDCS (cognitive flexibility task battery includes: Reversal learning task, set-shifting task)
- Treatment outcome: To evaluate and compare treatment outcome for each group (sham tDCS +CT vs active tDCS + CT) (Objective 2), eating disorder symptom severity measures will be administered at baseline and again after completion of tDCS/sham tDCS + CT: Eating Disorder Flexibility Index (ED-FLIX), Eating Disorder Examination (EDE), Clinical Impairment Assessment (CIA).

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

- To determine generalization and durability of cognitive training, participants will be asked to complete pre-intervention, mid-intervention, post-intervention, and follow up assessments assessing cognitive flexibility to examine generalization and durability effects of training.

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description: Participants are randomly assigned to receive one of two arms of transcranial direct current stimulation (tDCS) intervention: (i) 10 active (2-mA) tDCS sessions, or (ii) 10 sham tDCS sessions over the course of 10 treatment sessions. Sessions will occur for 5 consecutive days per week for a 2 week period. This study will add to the literature by having participants with R-EDs train in engaging cognitive flexibility tasks during tDCS intervention, to enhance paired neuromodulation. While patients perform cognitive flexibility tasks, half of the patients will receive active tDCS stimulation to the left DLPFC to enhance top-down control and improve the tuning or gating of the extraneous information and the other half will receive sham tDCS.

Transcranial Direct Current Stimulation

The tDCS will be performed using the Neuroelectrics Starstim Enobio 20 (Neuroelectrics Barcelona, Spain) device. For all conditions, the cathodal electrode will be placed over F4 (right DLPFC) and the anodal electrode will be placed over F3 (left DLPFC). Stimulation will consist of three periods: RampUp (30 sec), Constant (20 min), RampDown (30 sec). During the Ramp periods, 2 mA current will be delivered to both F3 and F4 with an ascending (RampUp) and descending ramp (RampDown) over 30 sec via two saline soaked electrode sponges (~ 25cm^2; current density = 0.08 mA/cm^2). In this way, all participants experience the same sensation on both sides. Only for the active tDCS condition, during the Constant period, current will be set to 2mA applied to F3 anode-F4 cathode.

StarStim is battery powered, communicates with the control computer via Bluetooth or wifi and monitors impedance and delivered current. The tDCS device does not present a potential for serious risk to the health, safety, or welfare of the participant. The participant does not need to undergo any additional procedure as part of this investigational study (e.g. no surgical procedure). In addition, the device has built in safety mechanisms which allow for the immediate cessation of stimulation should the subject become uncomfortable or impedance levels too high.

Before and during the tDCS session, the impedance of the electrodes is automatically reported, checked and verified. If the impedance during a session is too high, the stimulation is automatically terminated for safety. The current and impedance will be recorded for every session (Ruffini, 2016).

If impedence is high (low current flow) the study team may need to use a ground, as suggested by the manufacturers of tDCS. A ground may not need to be used in all situations, but there is a possibility of need for its use.

To assess subject perceptions of the intervention, we will ask what treatment they believe they received each session (active tDCS or sham tDCS).

Cognitive flexibility focused training occurs on a computer and consists of a variety of exercises selected to (i) place demands on the participant's ability to adaptively shift attention and behavior between task sets, (ii) adapt to challenge the participant's current ability level, (iii) provide ongoing feedback, and (iv) present novel stimuli across verbal, visual and spatial modalities. Training tasks are developed in-house. Tasks (described below) for each subject are delivered from our HST server (cnc2.med.umn.edu). Responses of subjects and session audio and video are saved on our HST server for analysis of training performance and engagement. The aim of using multiple tasks that require cognitive flexibility is to engage brain network functional connectivity in a number of different ways to promote generalization. In this scheme, experimenters will monitor each participant's training and customize the intervention to balance challenge and engagement. In addition, at pre- and post-intervention timepoints participants will perform 4-minute versions of a word and a spatial N-back task that will remain

the same across all weeks (but differ from the assessment versions) to allow us to track training improvements using a constant difficulty level.

Specific task descriptions are provided in the Measures section.

Participant effort will be rated by experimenters at each session using the Work Behavior Inventory (Bryson, Bell, Lysaker, & Zito, 1997). Just before the end of each training session, subjects will complete a brief questionnaire that also asks about their perceived engagement in the training that day, as well as their mood, previous night's sleep, discomfort, and their perceived experimental condition.

4.2 Drug/Device Handling: tDCS will be applied using the StarStim system. Investigators will follow all abbreviated IDE requirements per 21CFR812.2(b) (labeling the device appropriately, securing appropriate IRB approvals, securing participant consent, study monitoring, record maintenance, and adhering to standards for promotion, etc.). The tDCS device will be housed either at the Ambulatory Research Center (ARC) at the University of Minnesota Medical School or the Non-Invasive Neuromodulation Lab at the University of Minnesota Medical School when not in use. The StarStim system has built in safety mechanisms which allow for the immediate cessation of stimulation should the participant become uncomfortable or if the impedance of the stimulation electrodes is too high.

The administration procedures used in the current protocol are in line with other protocols that have outlined the safe use of tDCS in adult populations.

tDCS device administration training will be conducted by research professionals from the Non-Invasive Neuromodulation Lab within the Masonic Institute of the Developing Brain or Dr. Jazmin Camchong, who has expertise in tDCS administration and use of the StarStim device.

Biosafety: N/A

4.3 Stem Cells: N/A

4.4 Fetal Tissue: N/A

5.0 Procedures Involved

5.1 Study Design: This study is double-blind, and sham-controlled. The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design includes: In a double-blind randomized design, 20 individuals who meet DSM-5 criteria for atypical anorexia nervosa or anorexia nervosa with mild symptom severity specifier, based on BMI (greater than or equal to 17 kg/m^2), age 18-65 years old, at baseline will be recruited from local eating disorder treatment centers in the Twin Cities metro area. While all participants will complete a total of 10 brain training sessions, participants will be randomly assigned to receive one of two arms of tDCS intervention: (i) 10 active (2-mA) tDCS sessions, (ii) 10 sham tDCS sessions over the course of 10 treatment sessions. Sessions will occur for 5 consecutive days per week for a 2 week period. All subjects will engage in executive functioning tasks for cognitive training during tDCS intervention (active or sham) to engage brain circuitry associated with cognitive flexibility. All subjects will complete one

screening/baseline assessment session before the start of tDCS + cognitive training interventions, one post-treatment assessment after 10 tDCS interventions, and one at the 1-month follow-up visit after last intervention day. Clinical assessments (including eating disorder assessments) will be collected before the first and after the last day of tDCS sessions. Follow-up clinical interviews will be conducted at the 1-month follow-up period after intervention completion to query ED status depending on participant availability. This follow-up assessment visit will also include collection of cognitive data. Dependent variables will be (i) change in cognitive performance, (ii) change in self-report measures of eating disorder symptom severity, and (iii) ED status 1 month after study participation. The Specific Aims are to determine if the 10-session intervention: (Objective 1) is feasible and safe in individuals with R-EDs, (Objective 2) is related to cognitive flexibility performance changes, and (Objective 3) induces change in ED symptom severity.

5.2 Study Procedures: After the initial consent form is signed, participants will undergo:

Randomization: Participants will be randomly assigned to receive one of two tDCS arms: (i) 10 active (2-mA) tDCS sessions, or (ii) 10 sham tDCS sessions.

Double blinding occurs automatically by the StarStim device - there is an option to indicate "double blind" when setting up a participant's cognitive training + active/sham stimulation session, and the group assignment is automatically documented by StarStim which ensures that the study team remains blinded while administering study intervention sessions).

Blinding: Participants will not be informed on their assigned protocol. During consent, they will be informed that there is a 50% chance of being assigned to one of two tDCS arms: (i) 10 active (2-mA) tDCS sessions, or (ii) 10 sham tDCS sessions.

If the medical monitor deems it necessary, the study arm assignment for individual participants may be disclosed on a case-by-case basis. Request to unblind will be shared with the PI (Dr. Anderson) in writing. Urgent, unplanned unblinding prior to the conventional unblinding date is done to protect participant safety, e.g., for treatment arm identity during an acute reaction. Unblinding of participants must be implemented through the medical monitor (Dr. Lim). The medical monitor holds the responsibility for assessing and making recommendations to correct any possible abuses of the disclosure privilege.

VISIT 1 / Screening & Baseline Assessment Visit:

Informed Consent. Participants will be presented with copy of the Combined Consent/HIPAA Form prior to the baseline interview visit, will be asked standard University of California, San Diego Brief Assessment of Capacity to Consent (UBACC; Jeste et al.) questions to assess comprehension of the consent document.

Baseline/Screening Assessments. Should the participant decide to consent into the study, trained research staff will interview and administer self-report measures related to

medical history, demographic information, and behavior, personality, and eating disorder symptoms. The following well-validated clinical interview assessments and self-report questionnaires will be used:

The following assessments are interview measures or self-report format questionnaires that will be used for screening purposes; questionnaires will be administered via RedCap:

- Participant Demographics Questionnaire will be administered to the participant as part of the screening visit. This takes less than 5 minutes to complete.
- Medical History Questionnaire will be administered to assess for medical or psychiatric conditions, medications, or prior medical procedures that would impact inclusion/exclusion criteria. This takes approximately 10 minutes to complete.Course of Illness Questionnaire will be used to assess chronicity and current state of symptoms of restrictive eating pathology. This takes approximately 5 minutes to administer.
- Eating Disorder Examination (EDE) is a structured interview that will be used to assess eating disorder symptoms and confirm AN diagnosis, and will be administered as part of the screening visit. This interview takes between 45-75 minutes to administer. The EDE will be repeated at post-intervention and follow-up assessment sessions to assess symptom change.
- Mini International Neuropsychiatric Interview 7.0 (MINI) is a brief diagnostic interview for use in research that takes approximately 20-30 minutes to administer. The MINI covers mainly current symptomatology including substance use and dependence, major depressive disorder, posttraumatic stress disorder, and generalized anxiety disorder, in addition to approximately 12 other psychiatric diagnoses. This will be used during Visit 1 for diagnostic screening purposes. The MINI Suicidality Module will also be used to screen for and assess baseline suicidal ideation (see eligibility criteria).
- Clinical Impairment Assessment (CIA) is a self-report questionnaire that will be used to assess degree of clinical impairment associated with eating disorder symptoms. This takes approximately 5 minutes to complete. This will be administered at the screening visit, and will be repeated at post-intervention and follow-up assessment sessions.

Medical Screening Procedures and Vitals/Anthropometric Measures.

Participants will undergo a brief medical screening with study staff (i.e., study coordinator), who will provide the Medical Screening form (described above) to the study physician to review and determine study eligibility, including medical stability of AN participants for outpatient research. During this examination, the following information will be collected to determine if the participant meets eligibility the AN group: a) height, measured on a stadiometer; b) weight measured on a calibrated scale; c) temperature; d) pulse and blood pressure; and e) brief medical and medication history. Although enrollment in outpatient eating disorder treatment inherently indicates that an individual has been deemed medically stable by their current treatment team and ED medical providers, the study medical screening will be used to formally verify eligibility criteria related to current AN medical stability. The medical screening is expected to take approximately 30 minutes to complete. If further clarification is needed to determine participant medical stability, the study physician will directly contact the participant (e.g.,

via encrypted email, telephone, or HIPAA-compliant Zoom call) to obtain necessary information. The study physician will provide final study participation approval once medical stability is established.

The following standard eating disorder guidelines[57] will be used to inform the judgment of suitability for outpatient research, which will be ultimately determined by medical personnel: 1) Heart rate < 40 beats/minute; 2) Blood pressure < 90/60 mmHg or orthostatic hypotension (with an increase in pulse of > 20 beats/minute or a drop in blood pressure of >10-20 mmHg; 3) Body temperature <97.0º; 4) Self-report of recent electrolytic imbalance or hepatic, renal, or cardiovascular organ compromise requiring acute treatment; or 5) Assessment by M.D. that individual is otherwise medically unfit for participation in outpatient research. Height and weight will be measured for all participants to determine if they meet eligibility criteria (e.g., mild AN diagnostic severity, determined based on BMI).

Participant weight will be assessed by research staff at baseline, mid-intervention, post-intervention, and follow-up assessment visits to monitor AN illness severity. Participants will be withdrawn from the study by research staff if an individual's illness severity increases during the course of the study - evinced either by decrease in BMI to moderate (or more severe) AN symptom severity categories or by weight loss of >2lbs per week. In the case that this occurs, participants will be provided with contact information for local clinical resources, and encouraged to seek clinical care from their treatment provider/eating disorder program treatment team.

The following measures are self-report format questionnaires that assess R-ED symptom covariates of interest, which relate to cognitive control/self-regulation processes; measures will be administered via RedCap:

- Eating Disorder Flexibility Index (ED-FLIX) is a self-report questionnaire that will be used as a brief measure to assess changes in levels of cognitive flexibility and central coherence. This takes approximately 5-8 minutes to complete. This will be administered at Visit 1 (baseline cognitive assessment session) and will be repeated at the mid-point of intervention period (intervention session 5), and post-intervention and 1-month follow-up assessment visits.
- Beck Depression Inventory (BDI) is a self-report questionnaire that will be administered to assess depressive symptoms. This takes approximately 5 minutes to complete. This will be administered at Visit 1, and will be repeated at post-intervention and follow-up assessment sessions to assess change in depressive symptoms. The suicide risk item (item #9) on the BDI, which has been shown to be predictive of death by suicide and repeated attempts, will be administered at each study visit (intervention and assessment) to assess for changes in acute suicidality throughout the study. In the case that acute suicidal ideation is endorsed, study staff will contact a PI or co-investigators with suicide/risk management expertise (Dr. Lisa Anderson, Dr. Carol Peterson, Dr. Kelvin Lim). Study staff will follow the risk assessment and safety protocol outlined in the MCEDR Suicide Risk Assessment Protocol.
- State-Trait Anxiety Inventory (STAI) is a self-report questionnaire that will be used to assess state and trait measures of anxiety. This takes approximately 5 minutes to complete. The STAI will be administered at Visit 1, and will be

repeated at post-intervention and follow-up assessment sessions to assess change in anxiety symptoms.

- Positive and Negative Affect Schedule (PANAS) is a self-report questionnaire that will be administered as a measure of positive and negative emotion states. This takes approximately 5 minutes to complete. This will be administered at Visit 1, and will be repeated at post-intervention and follow-up assessment sessions.
- Behavioral Inhibition System/Behavioral Avoidance System (BIS/BAS): This self-report is 24 items, and assesses general reward and aversion sensitivity and responsivity. This will be administered at Visit 1 for baseline symptoms.

Urine pregnancy test: All participants capable of becoming pregnant will be asked to provide a urine specimen for pregnancy testing. The test will be performed and reviewed by study staff during the review of inclusion and exclusion criteria.

Baseline Cognitive Assessments: To establish and control for individual differences in baseline executive functioning performance, participants will complete one part of the Pearson cognitive battery assessment, the DKEFS trail making test (Delis et al 2004; Weis et al 2010).

Baseline/Pre-intervention Behavioral Tasks: Participants will complete behavioral tasks designed to assess aspects of cognitive flexibility (reversal learning, set-shifting) prior to beginning tDCS+CT intervention.

- Probabilistic Reversal Learning Task: This computer based reversal learning task will be used to assess generalization effects of tDCS + cognitive training intervention on executive functioning and cognitive flexibility. Reversal learning tasks require participants to choose, in each trial, between two different stimuli (by mouse-clicking on one of them), requiring working memory and cognitive flexibility to update performance in response to changes in task feedback. This is administered via computer and takes approximately 14 min to complete. Demo available here: The Experiment Factory probabilistic-selection (expfactory-experiments.github.io)
- Intra-Extradimensional Set-Shifting Task: This computer based set-shifting task will be used to assess generalization effects of tDCS + cognitive training intervention on executive functioning and cognitive flexibility. Set-shifting tasks require participants to decide whether each stimulus in a sequence matches the one that appeared n items ago, requiring working memory and cognitive flexibility to shift between task sets. This is administered via computer and takes 10 min to complete. Demo available here: The Experiment Factory dimensional-set-shifting (expfactory-experiments.github.io)

Visit 1 assessments will take approximately 3-4 hours total and will be completed either remotely or in person. The baseline assessments can be split into two days if needed.

VISITS 2-11/ Intervention Visits (10 total intervention visits): This study day will involve executive functioning training combined with a daily tDCS intervention. All participants will receive daily active tDCS sessions while they perform executive functioning tasks for

10 consecutive intervention visits. Sessions will occur for 5 consecutive days per week for a 2 week period. We will first explain to the participant what the training tasks entail and detail tDCS procedures. During tDCS interventions (active or sham) the participant will be seated while they complete cognitive training tasks in the computer. tDCS sessions may be audio or video recorded for monitoring training performance and engagement. These data will be reviewed by the study team only to achieve reliability and consistency between different interviewers and to arrive at consensus ratings for assessment scores. Assessment audio/video data will be stored on a secured UMN Box server and will only be accessible by the study team. At each intervention session participants will complete a questionnaire that asks about their perceived engagement in the training that day, as well as their mood, previous night's sleep, discomfort, and their perceived experimental condition. Total participation time for each intervention day will be about 1 hour each day.

Intervention sessions will be scheduled to begin within 2 weeks of the baseline/screening visit (Visit 1). These intervention sessions may be completed either while enrolled in ED treatment program or remote, depending on each participant's discharge date from their ED treatment. Remote intervention days will be supervised by research staff over zoom meetings. In the case that the participant completes their intervention sessions over zoom meetings, the study team will invite the participant to attend a practice session on-site in the ARC, to ensure that the participant will have had enough practice to ensure that tDCS sessions can be successfully completed remotely. If desired, participants will have the option to attend tDCS intervention sessions on-site in the ARC (e.g., the tDCS intervention would be delivered in person vs. remotely). The StarStim tDCS intervention software will have programmed conditions that will keep the participant and the research staff blind to the type of intervention each participant is randomly assigned to.

Specifics to remote intervention operations will involve the following

- Will occur via Zoom using audio and video.
- tDCS cognitive training will be self-administered using remote contact with research staff.
- Research staff will provide a package(s) to the participant containing the following:
    - 1 HST supported windows laptop. Collected data is stored on an HST (Health Sciences Technology) supported server, cnc2.med.umn.edu. The appliance will have the capacity to provide computerized assessment, tDCS training, training tasks, and an integrated HIPAA-compliant video connection platform
    - 1 tDCS stimulation device and headband
    - Sufficient saline vials for the anticipated duration of remote training
    - Other materials as may be needed to complete the protocol, including return labels and packaging as needed for laptop and tDCS device
    - All materials will be disinfected before and after shipping

Overall description of the cognitive training program: During each daily 45-minute intervention session, participants will perform four training exercises (10 mins each) in which individuals with psychiatric disorders have previously shown poor performance, presented in a randomly selected order: N-back task, Flanker task, Dot-pattern expectancy task, Set-shifting task. Tasks are described in detail below:

- "Restaurant Rush" -N-back task, requires participants to decide whether each stimulus in a sequence matches the one that appeared n items ago, requiring working memory. In our version, participants are a restaurant server, and are presented with a sequence of food items. Participants need to decide whether to pick up or not a food order, depending on whether the food order matches one that appeared n items ago.
- "Nebula" -Flanker task requires participants to engage selective attention and inhibitory function. In our version, participants are a spaceship pilot navigating back to Earth by following left or right arrows on the screen. However, pirates hacked the navigation system, and only the center arrow shows the correct navigation. Participants need to inhibit responses to the flanking confounding arrows.
- "Night Sailing" -Dot Pattern Expectancy task, requires cognitive control and context processing. In our version, participants sail a boat at night to meet a long-lost friend, navigating based on the sequence of constellations presented. One set of constellations is the valid cue (A) and another set an invalid cue (B). There is also a probe constellation. This probe can be valid (X) or invalid (Y). Participants are instructed to only follow the valid probe and cue combinations (targets – AX combinations) with a key press and all others (non-targets) with a different key press.
- "Scuba Diving" -Intra-Extra Dimensional Set-shifting task, requires cognitive flexibility. In our version, participants are scuba divers searching for sea life. They need to learn the rule for choosing the "correct" fish. However, this rule changes periodically, and they need to adapt to the new rule. This task tests rule acquisition and reversal, visual discrimination and attentional set formation maintenance, shifting and flexibility of attention.

TDCS will be applied during the first 20 mins of the 45 mins of cognitive training. Evidence suggests tDCS effects persist 1-5 hours after stimulation, thus, the effects of the 20 minutes of tDCS will continue through the remaining 25 mins of training. Exercises were designed and selected to (1) place demands on the executive function system (e.g. working memory, inhibition, decision making, and cognitive flexibility), (2) adapt to challenge participant's current ability level, (3) provide ongoing feedback within animated stories, and (4) make tasks relatable and fun. The following cognitive training exercises were developed under Drs. Camchong and Lim laboratory collaborations, and are currently used under five ongoing NIH and VA funded tDCS studies (>1000 intervention sessions across studies).

The following questionnaires will be administered by research staff at each tDCS/sham tDCS intervention session:

- tDCS Side Effect questionnaire: This questionnaire will be administered to the participant before and after each tDCS/sham intervention.
    - This is an assessment tool to monitor for common, specific side effects noted across many existing tDCS studies, including but not limited to itching, prickling, burning sensation, nausea, fatigue and headache.

- Assessment takes approximately 3-5 minutes to administer and is typically performed twice during each intervention session (once before and once after the session).
- Furthermore, participants will be continuously monitored by a member of the study staff throughout each intervention session to ensure comfort and safety.
- In addition, at the end of each intervention visit, the subject will be asked if they think they received the active or sham condition.

- Eating Disorder Behavior Questionnaire: This questionnaire will be administered to the participant before each tDCS/sham intervention starting at Visit 3.
  - This is an assessment to monitor ED behaviors in the past 24 hours before tDCS sessions.

VISIT 12/ Post-Intervention Assessment: At the endpoint of interventions, which is after 10 intervention sessions, participants will complete the same baseline behavioral tasks, self-report measures, and clinical interview assessments as completed during Visit 1. The tDCS Side Effect questionnaire will also be administered. Total participation time for Visit 12 will last approximately 1.5-2 hours.

VISIT 13/ 1-Month Follow-up Assessment: Approximately 1 month after the intervention, participants will complete the same behavioral tasks, self-report measures, and clinical interview assessments as completed during Visits 1 and 12.

Note: Visit 13 may not happen exactly at the one-month follow-up date depending on participant's and research staff availability. Total participation time for Visit 13 will be about 1.5-2 hours.

In the case that a participant misses a follow-up, an allowance of up to 1 additional month post-intervention will be granted to participants who are not available in order to accommodate relapse complications, lack of telephone availability, changes in residence, and ED treatment plans, such as residential treatment. Efforts to maintain contact with the participant are described below.

Retention: To maximize participant retention we will have all consented participants fill out a "contact information" document in which they will be asked for at least one telephone number to be reached at, their preferred email address, and one home address. For appointment reminders, we will call participants over the phone, send them an encrypted email through the University's preferred encryption service, send a reminder card through regular mail, and/or send them an unencrypted email with their informed consent.

5.3 Study Duration:

- The anticipated duration an individual participant's participation in the study including follow-up is approximately 2 months since enrollment.

- The duration anticipated to enroll all study participants: Anticipated end date Winter 2024.
- The duration anticipated to complete all study procedures and data analysis: Anticipated end date Spring 2024.

5.4 Use of radiation*:* N/A

5.5 Use of Center for Magnetic Resonance Research*:* N/A

5.6 Remote and Limited Study Operations: Research procedures may be completed using remote data collection and task administration. We will provide subjects with the necessary software and hardware to support remote research procedures.

The following remote research procedures will be used:

- Study visits will occur Zoom using audio and video.
- tDCS cognitive training will be self-administered using remote contact with research staff.
- Consent, HIPAA authorization, and UBACC will be collected electronically prior to the baseline visit (see section 20.0 for information on eConsent).
- After the consent, research staff will provide a package(s) to the participant containing the following:
  - 1 HST supported windows laptop. Collected data is stored on an HST supported server, cnc2.med.umn.edu. The appliance will have the capacity to provide computerized assessment, tDCS training, training tasks, and an integrated HIPAA-compliant video connection platform
  - 1 tDCS stimulation device
  - 2-3 tDCS headbands
  - Sufficient saline vials for the anticipated duration of remote training
  - Other materials as may be needed to complete the protocol, including return labels and packaging as needed for laptop and tDCS device

6.0 Data and Specimen Banking

6.1 Storage and Access:

All data management servers will meet all relevant privacy and security standards for electronic clinical trial data entry as storage, as well as HIPAA standards for confidentiality and privacy.

Access to study data, particularly data with identifying information, will be limited to individuals listed on the delegation of authority log, or those who have authority to review study records. Identifying information will not be shared outside of the UMN study team unless required by law. Study staff will only be provided with access to the study data that they need to perform their work duties.

All identifying information will be maintained for a minimum of six years after the completion of the study in compliance with HIPAA regulations. Any data use agreements that allow for the sharing of study data will be maintained for a minimum of two years past their expiration.

Consent documents: Consent documents, including HIPAA Authorizations and UBACC assessments, will be collected and stored in REDCap with a Part 11 compliant REDCap eConsent. If necessary, participants may still complete paper consent documents that will be stored with any other physical regulatory files in a private space behind two locks (in a locked cabinet in a locked office). Copies of physical consents will be uploaded into a dedicated folder within Box. These records will only be made available to study staff and will not be shared with any collaborators. Identifying information will not be shared outside of the research study team unless required by law.

Assessment data: Some study data may be collected in physical forms or directly into RedCap. Physical forms of data will be kept behind two locks in an office space until they can be entered electronically to RedCap or Box.

HST-managed devices will be used to collect this data for in-person appointments. Any assessments collected in REDCap during a remote appointment will be completed using a participant-owned device. Data from the REDCap database may be extracted to Box during interim analyses and at the end of the project for final storage. The data will remain in Box indefinitely.

Task assessment data will contain no direct identifiers, though they may contain the date of data collection. Collected task performance data will be stored on an HST supported server, cnc2.med.umn.edu

6.2 Data:

All diagnostic and other sensitive data will be kept behind two locks and be available only to authorized research team members involved in this study. Identifiers will include name, birthdate, address, and telephone numbers. The PI will keep the datafile containing the link between subject number and identity. This will be kept in a password-protected computer file and also in printed form in a locked file cabinet. Research staff will have access to the identifiers only after a subject has agreed to participate in the study. They will use this information only for making contact to schedule visits, etc.

6.3 Release/Sharing:

The data collected may represent a unique resource for some investigators. Following HHS/CDC (Department of Health and Human Services/Centers for Disease Control and Prevention) policy, we will make the de-identified data available to interested investigators who contact us for access to the data. As the proposed work is a clinical trial, the most appropriate database for our collected data appears to be clinicaltrials.gov. The study will be registered in clinicaltrials.gov. The investigator, co-investigator, and research staff will permit trial-related monitoring, audits, IRB/IEC(s) review and regulatory inspection(s) by providing direct access to source data/documentation.

7.0 Sharing of Results with Participants

7.1 No results will be shared with participants.

8.0 Study Population

8.1 Inclusion Criteria:

● Age 18-65 years

● Self-reported enrollment in outpatient-level treatment at local eating disorder treatment centers in the Twin Cities region, and meeting DSM-5 criteria for AN (mild severity, based on BMI greater than or equal to 17.0 kg/m^2) or atypical AN diagnosis (based on MINI and EDE assessments).

● Participant must be capable of giving informed consent, based on UCSD Brief Assessment of Capacity to Consent (UBACC) risk assessment.

● Sufficient spoken English so as to be able to comprehend testing procedures. ● Normative ranges on a C-RENAL blood panel (panel and ranges specified here: https://labguide.fairview.org/showtest.asp?testid=3321)

8.2 Exclusion Criteria:

● Substance abuse in the participant

● Neurological condition or other developmental disorder

● Serious psychiatric disorder known to affect brain functioning and cognitive performance (e.g., schizophrenia, schizoaffective disorder)

● Medical instability, which will be evident based on required outpatient treatment status. In standard eating disorders treatment, individuals who are not medically stable are referred to higher levels of care (e.g., residential treatment, inpatient). Therefore, if a participant is enrolled in higher level care for their eating disorder diagnosis, this indicates medical instability and they will be excluded from enrollment in this study.

● tDCS contraindication (e.g., history of craniotomy, history of metallic cranial plates, screws, implanted devices, pregnancy or suspected pregnancy in participants capable of becoming pregnant (assessed with urine pregnancy test)).

.● Acute suicidality (suicidal ideation with a plan or intent), assessed via MINI suicidality module and Beck Depression Inventory suicide item

● Acute homicidality (homicidal ideation with a plan or intent), assessed via MINI ● Moderate, severe or extreme AN diagnostic severity, based on BMI as per DSM-5 criteria (e.g., BMI <17.0 kg/m^2)

8.3 Screening:

Advertisement flyers will be available in common areas in eating disorder treatment programs throughout the Twin Cities metro area. Eating disorder treatment programs will also post media advertisements via social media platforms if applicable. Those interested will call or email our research staff using the study contact information listed in our flyer and media advertisements to express interest in our research study. Participants will be asked to complete a brief phone screen with study staff to determine eligibility. If the caller is deemed eligible, they are given more detailed information about the study and research staff will answer any questions about the study. If the caller is still interested, they will be invited for a baseline appointment (Visit 1).

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be focus of the research (targeted), included, but not necessarily the focus or excluded from participation in the study.
Children	Excluded
Pregnant women/fetuses/neonates	Excluded
Prisoners	Excluded
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded
Non-English speakers	Excluded
Those unable to read (illiterate)	Excluded
Employees of the researcher	Excluded
Students of the researcher	Excluded
Undervalued or disenfranchised social group	included but not the focus
Active members of the military (service members), DoD personnel (including civilian employees)	included but not the focus
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	included but not the focus

Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Excluded
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Excluded
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded

9.2 Additional Safeguards, if any, to ensure inclusion is appropriate:

- Justification for inclusion of AN**.**
    - Investigating novel intervention methods (i.e., tDCS) may inform treatment optimization efforts for individuals with AN. Given the chronic nature, severe medical and psychological comorbidities, and elevated mortality risk associated with AN, research of this kind is sorely needed.
    - Because the current study seeks to evaluate the feasibility of utilizing tDCS as an adjunctive intervention alongside treatment-as-usual in patients with AN, the inclusion of individuals with AN is necessary for the current study. We believe that the inclusion of individuals who are enrolled in outpatient-level eating disorder treatment represents the least degree of impairment compatible with aims of this study, as this level of care will ensure that individuals enrolled in the study are being closely monitored by an on-site medical and psychiatric treatment team, and can therefore be ensured to be medically stable throughout the duration of the study.
- Additional Safeguards:
    - Participants will all undergo a formal informed consent process.
    - Participant capacity to consent will be assessed with the UBACC.

      Individuals who are unable to consent will not be enrolled.

Notably, one of the hallmark features of psychiatric illnesses such as eating disorders, is potentially diminished cognitive functioning. That is why the current protocol may recruit adults with slight cognitive dysfunction. However, the current protocol will **not recruit those who lack capacity** to consent. All participants must have capacity to provide informed consent at enrollment and throughout the study as per UBACC. To

protect vulnerable populations, if the participant has been determined to lack capacity to consent (based on UBACC), they will not be included in the study. Participants are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior

Importance of knowledge to be gained: There are increasing data supporting specific cognitive and brain functional connectivity abnormalities in R-EDs. An understanding of whether these specific abnormalities can be modulated with cognitive training and non-invasive brain stimulation interventions will hold significant promise in designing new targeted interventions that can reduce vulnerability to relapse and improve treatment outcome.

Protection Against Risk. Trained research staff will be instructed to keep the content of the records confidential. During the initial consent process subjects will be told that they have the right to refuse to answer questions; however, this may affect whether they continue in the study. At all points in the study subjects will be warned at the beginning of procedures which involve the disclosure of personal and sensitive information. These warnings will occur in the introductory comments of interviews or in the instructions of questionnaires and surveys.

Recruitment will be conducted to conform to HIPAA requirements regarding protection of private health information.

We will include formal assessment (suicide risk item on the BDI, described in the Measures section) to assess for acute suicidality (ideation with intent or plan). We will administer the BDI suicide risk item at each assessment time point (baseline, mid-intervention, post-intervention, follow-up) to monitor SI throughout the course of the study. In the case that an individual is deemed at risk to themselves or others, we will follow our laboratory's standard risk assessment protocol (see "MCEDR Crisis Management Plan" documents, uploaded to ETHOS).

9.3 If research includes potential for direct benefit to participants, provide rationale for any exclusions indicated in the table above: There are no known direct benefits, and the study only is designed (with no power analysis) to collect preliminary data for a possible efficacy.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented: 20

11.0 Local Recruitment Methods

11.1 Recruitment Process: Potential participants will initiate contact themselves.

Patients at local eating disorder clinics may see flyers and brochures describing the study at the time of their clinic appointment, although they will not be recruited directly by their clinician. All recruitment materials will be submitted for IRB approval upon development, before use in the study. Telephone scripts will be utilized.

Participants will be recruited from local eating disorder programs in the Twin Cities region. Participants will be recruited from individuals who self-identify as individuals who are currently receiving outpatient treatment for a restrictive eating disorder at the

time of consent and enrollment. Flyers and internet advertisements will be posted at treatment programs for individuals with eating disorders.

The Minnesota Center for Eating Disorders Research has developed an infrastructure for recruiting patients at local eating disorder treatment programs into research studies at the University of Minnesota, which has been used successfully in recent studies. All recruitment materials and telephone scripts submitted for IRB approval upon development have been uploaded to ETHOS. Recruitment materials will provide information about the study and how to contact the study coordinator.

If during the consenting process, it is found that the participant does not qualify to be in the study, research staff will notify the participant of their ineligibility and thank them for their time.

11.2 Identification of Potential Participants: Participants will be recruited via advertisement flyers and social media advertisements displayed in eating disorder treatment programs in the Twin Cities metro area.

- No private/protected records will be used to identify potential participants
- Potential participants will self-identify and express their interest after learning about the study on IRB approved flyers posted on IRB approved boards in the treatment program.
- Potential participants will self-identify and express their interest after learning about the study on IRB approved social media advertisements shared with eating disorder treatment programs.
- No **MEDICAL** records will be used to identify potential participants.

11.3 Recruitment Materials:

- Participants will self-identify based on the information on the study poster or media posting which eating disorder treatment centers will post in their clinics and social media platforms (if applicable; e.g., clinic Facebook page or Instagram platform). If they believe they are eligible and are interested in research they will call or email our research staff using study contact information listed in our recruitment materials to express interest in our research study. Participants will be asked to complete an initial telephone screener with research staff will complete a brief phone screening to determine eligibility. If the caller is deemed eligible, they will be given more detailed information about the study and research staff will answer any questions about the study. If the individual is still interested, they will be invited to attend a diagnostic screening and baseline assessment appointment (Visit 1).

11.4 Payment: Participants will receive payment for participation. Payment will be

made at the completion of the study (final visit) or at the time that a participant ends involvement in the study. Payment will be based on procedures attempted and/or completed as follows:

- $60 for Visit 1 – screening/baseline visit

- $30 for end of treatment follow-up session – Visit 12
- $30 for 1-month follow-up session – Visit 13

The total amount a participant could receive if he/she completes all study visits and optional activities is $120. Compensation will be awarded through Amazon.com gift cards.

Participants may be reimbursed for parking or transportation expenses at follow-up visits.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances: The prospective participants will be able to discontinue study participation at any time. The participants may choose to discontinue stimulation at any time during the session if experiencing excessive discomfort or side effects, or any other reason. Criteria for discontinuation related to intervention: i) sores at the tDCS administration site; ii) headaches that impair global functioning. If subjects choose to stop their participation, they will be released from the study. To protect vulnerable populations, if a patient that was deemed capable of providing consent goes through unforeseeable situations that may affect their capacity to consent, their capacity will be reassessed, and if not deemed capable, they will be withdrawn from the study. Participants are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

Participants will be withdrawn by study staff from the study, if an individual's illness severity increases during the course of the study – evinced either by decrease in BMI to moderate or worse severity categories or by weight loss of >2lbs per week.

If participants want to leave the study, we will make sure that they stop the study safely. We will also talk to them about follow-up care, if needed. It's possible that we will have to ask them to leave the study before they finish it. If this happens, we will tell them why.

12.2 Withdrawal Procedures: If participants withdraw from procedures, all their data collected until the withdrawal data will be retained. No new data will be collected from any private/protected record.

12.3 Termination Procedures: If at any point research staff is concerned about participant's welfare or behavior, they will notify the participant that their participation in the study needs to be terminated because of safety reasons. The participant will be paid for their time as per "Payment" section, until their last active participation day. Data collected until the termination date will be used and considered incomplete.

This study will be stopped in order to prevent further harm to study participants in the occurrence of study-related adverse events. Specifically, a mandated discontinuation of the study (pending medical monitor review) would occur following any of the following: 1) clinically significant worsening of anorexia nervosa (e.g., consistent trend in weight loss of >2lb per week, or movement from mild to moderate AN symptom severity based on BMI); 2) two participants experience clinically significant increase in

suicidal thoughts; 3) one participant attempts suicide; and 4) any other device-specific severe adverse event.

13.0 Risks to Participants

13.1 Foreseeable Risks:

Intervention Risks: tDCS is considered to be a non-invasive investigational device that involves applying a weak electrical current to the scalp. There is currently no evidence of serious side-effects. Mild side-effects that typically resolve upon discontinuing tDCS include light itching under the electrode at the beginning of administration, headache, fatigue, and nausea. The subject may choose to discontinue stimulation at any time during the session if experiencing excessive discomfort or side effects. Although seizures are not a known risk of tDCS intervention (Fregni et al., 2006), anyone with a history or a risk for seizures will be excluded from the study. No other risks related to tDCS are anticipated. To minimize risks regarding tDCS, study staff will be using standards of administration that have been shown as safe in numerous other studies using transcranial direct current stimulation. The length of administration of the current, size of electrode sponges used, and method of applying stimulation are the same as methods of administration that have been demonstrated as safe. We have obtained FDA determination, which indicated that this "proposed clinical investigation is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under 21 CFR 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812)" (see FDA determination letter, uploaded to ETHOS).). To ensure that only approved study staff access the device, we take the following precautions:

NNL: Badge access is required to enter the building the NNL is located inside of. The NNL unit is locked, access required. The StarStim storage room is locked, access required and the StarStim device requires a username and password for use.

ARC: The device is store behind three locked doors. (1) There is a lock to get into the Psychiatry Department, after that, (2) there is a lock to get into the research area (Ambulatory Research Center) and then (3) the device is stored in our study-specific storage closet which is also locked.

Risks of Assessments and Batteries: As with all assessments, there is the potential that we will ask questions that make the participant feel uncomfortable, embarrassed, or stressed. We will remind participants that they only need to provide the information that they are willing to answer and can ask to skip questions at any time. In addition, due to the length of the assessment visits, it is possible that participants can feel fatigued or stressed by the interview. We will invite them to take short breaks in the middle of sessions to prevent fatigue when possible.

Other potential risks: The other potential risks pertain to the maintenance of confidentiality. Participants will be probed for personal information during the interviewing process. As noted in the consent form, participants will be told that all diagnostic and other sensitive raw data will be kept behind two locks and available only to authorized research team members involved in this study. To minimize confidentiality risks, as noted in the consent form, all diagnostic and other sensitive raw data will be

kept behind two locks and be available only to authorized investigators involved in this study. De-identified data will be labeled with the participant's study ID number and will not contain personally identifying information. Confidentiality is not absolute. Research staff are mandated reporters and are legally required to report suspicion of child or vulnerable adult abuse or neglect to the relevant authorities.

Confidentiality Risks: Participation in research will involve a loss of privacy due to the nature of the questions that are asked during assessment visits and data collected during training sessions. However, records will be handled as confidentially as possible. All participants will be assigned a unique study identifier that will be used to label all of their records. A link will be maintained on a private password-secured HST server (cnc2.med.umn.edu) accessible only to specific study staff listed in the Delegation of Authority log. This link will connect the participant's identifying information, such as name, etc., to their assigned ID number. No identifying information will be used in any report or publications that may result from this study. All study records will be kept in secure databases such as REDCap or Box. Paper records will be kept behind two locks (in locked cabinets in locked rooms). Data generated during training or assessments will be de-identified. All members of the study team will be current with their HIPAA, CITI, GCP, and IRB trainings to ensure full compliance with confidentiality laws.

13.2 Reproduction Risks: N/A

13.3 Risks to Others: N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits: There are no proven benefits to being in this study, and the investigators do not know whether tDCS will affect eating disorder symptoms, nor how long any changes may last.

15.0 Statistical Considerations

15.1 Data Analysis Plan: Data analyses will include traditional statistical analyses for

group differences in neurocognitive and clinical (e.g., eating disorder symptom severity) measures with control for confounding variables, multiple comparisons, etc. Specifically, we will (1) compare neurocognitive and clinical variables of interest between groups: active vs sham tDCS groups, (2) compare neurocognitive and clinical variables of interest within groups to examine time effects: before and after intervention, and (3) look for interaction effects (group x time).

15.2 Power Analysis: The study in reference is a pilot study for which a power analysis is not applicable. Data obtained from this study will inform future power analyses for a larger, future clinical trial.

15.3 Statistical Analysis:

Objective 1. To evaluate feasibility, Chi-square analysis will be used to compare retention rates between active and sham tDCS+CT groups. To assess acceptability, a 2-sample t-test will compare the TAFSQ acceptability ratings for active tDCS+CT vs sham tDCS+CT participant groups.

Objectives 2 & 3. Generalized estimating equations be conducted to examine changes in cognitive flexibility training task performance (objective 2) from baseline to post-

intervention, and changes in ED-FLIX scores, EDE scores, and EMA symptom frequency (objective 3) from baseline to post-intervention and 1-month follow-up visits.

15.4 Data Integrity: Participants with missing data points essential to primary analyses will be excluded from the central analyses. The principal investigator and co-investigator (Drs. Anderson and Camchong) will monitor data quality for this study. They will ensure that data are generated, documented (recorded), and reported – in compliance with this protocol, with Good Clinical Practice, and any other applicable regulatory requirements.

Items left unanswered on interviews and self-report measures will not result in a protocol deviation. Participants are given reminders throughout the course of the study that all answers to interviews and questionnaires are optional.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

X I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research: N/A

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

X I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☐ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☐ Other. Describe: N/A

16.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

Participants will provide informed consent to enroll in the study. Only data collected directly from participants will be used. No additional patient records will be reviewed.

16.4 Approximate number of records required for review: N/A

16.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

X Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

We will communicate via telephone and/or email format, depending on participant preferences. Email communication will be encrypted, unless the participant chooses to sign a waiver that allows the use of unencrypted email.

Zoom, a HIPAA-compliant video connection platform, will be used for communication between participants and research staff for remotely held study visits.

16.6 Explain how the research team has legitimate access to patients/potential participants:

Participants recruited from eating disorder treatment programs in the Twin Cities metro area will opt-in by calling our lab phone number and will provide all information necessary to determine eligibility. Participants will not be recruited based on information contained in private/protected records (e.g., medical records, student records; note that this also includes participants who will be recruited from the PI's or Co-PI's patient or student population).

16.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store☐ Analyze ☐ Share

X In REDCap (recap.ahc.umn.edu)

X Store ☐ Analyze ☐ Share

☐ In Qualtrics (34ualtrics.umn.edu)

☐ Store☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu)

☐ Store☐ Analyze ☐ Share

X In the University's Box Secure Storage (box.umn.edu)

X Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store☐ Analyze ☐ Share

X In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

Laptops (data will not be stored here):

Coordinator Laptop: 20191894

PI Laptop: 20211140 (Anderson laptop)

☐ Store**X** Analyze ☐ Share

X Other. Describe: Data collection

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as an tablet or smartphone not previously listed

16.8 Consultants. Vendors. Third Parties. N/A

16.9 Links to identifiable data: Most data collected in the study will be de-identified, meaning that there will be no information that on its own identifies the participant. Data will be labeled with a unique identifier (subject ID) that can be linked to identifiable information through the Enrollment Log, which will be stored securely in RedCap.

16.10 Sharing of Data with Research Team Members. Data will be shared among team members through approved and secure channels such as UMN Box and REDCap. Only team members with proper training and approval will be given access to study data.

16.11 Storage of Documents: Any paper documents generated over the course of the study will be stored behind two locks (in a locked cabinet in a locked office) in a secure department. Only team members with proper training and approval will be allowed to access these documents.

16.12 Disposal of Documents: In accordance with University policies, after the minimum retention period (6 years after study completion) of these documents is met, documents will be destroyed in a secure manner.

17.0 Confidentiality

17.1 Data Security: Trained research staff will be instructed to keep the content of the records confidential. During the initial consent process subjects will be told that they have the right to refuse to answer questions; however, this may affect whether they continue in the study.

Only research staff will have access to subject information. All records, including those containing identifying information, will be stored in one of the following manners:

- In a private research office in a locked file cabinet;
- In the University of Minnesota supported REDCap database;
- University of Minnesota secured BOX files;
- HST maintained server;

Passwords will be required to access study data stored electronically or in a database. Study data will be available only to select staff that need access to the information to conduct their research duties and to computer system administrators via password.

To minimize the volume of documents containing identifying information, all study documents or data will contain a unique participant ID that will be used when possible.

No copy of the Consent Form or other research study information will be placed in the participants' medical, employment, or educational records.

Optional unencrypted digital communication with participants: Participants have the option to provide informed consent for the study team to contact them using unencrypted email and/or unencrypted text message. This communication would primarily be used for appointment scheduling purposes.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring.

Performance on all measures will be scored, submitted to the database, and monitored for accuracy and integrity. Data sets will be locked once the information is verified as complete and accurate. The study will be monitored by CTSI in accordance with its institutionally approved monitoring plan.

Independent monitoring of the study will be conducted by the University of Minnesota's Clinical and Translational Science Institute (CTSI) clinical trial monitoring service. The CTSI monitors will confirm that study activities are in compliance with the approved protocol and applicable regulatory authorities (FDA, IRB, local and state regulations). The investigator will give the study monitors direct access to source documentation, study data, and relevant regulatory documentation.

18.2 Data Safety Monitoring.

Data Safety Monitoring Plan: We will use a Medical Monitor to ensure someone is responsible for prompt reporting of all adverse events and to monitor these events as they are reported. The Medical Monitor will be a faculty member at the University of Minnesota with expertise in mental health and/or psychiatric ethics who is not affiliated with the proposed study. They will be charged with monitoring the safety, quality and conduct of this study. The Medical Monitor will have access to the study's unblinded data. PI, Co-Is, and study staff will not have access to the study's unblinded data.

The Medical Monitor will serve as the safety monitor for this protocol. The Medical Monitor will not be enrolling any research subjects or caring for patients as part of this protocol. The Medical Monitor is qualified to review the patient safety data generated by this study because of their expertise in psychiatry, neuromodulation, and research ethics.

Study progress and safety will be reviewed monthly (and more frequently if needed). The Medical Monitor will review patient safety data quarterly. If a serious adverse event (SAE), Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) or other event causing risk to the research subjects occurs, the clinical research team will notify [Name of Physician] immediately. The Medical Monitor will assure the study is conducted in accordance with the investigator's agreement, the investigational plan, the IND/IDE and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA. Medical Monitor will have access to Box which contains all records of reported events.

PI and Co-Is (if needed) will review all unanticipated problems involving risk to participants, serious adverse events, and any participant deaths associated with the protocol. The PI will review all cases and make a determination as to the severity of the adverse event and its relation to study procedures, if any. Reports for events determined to be related to study procedures, those that are unanticipated, or those that are related to participant death will be promptly reported to the IRB. tDCS associated sensations assessed via the tDCS side effect questionnaire will only be documented in the AE log if they rise to the severity level of severe.

Other adverse events unrelated to tDCS intervention sessions will be reported via the Health Update Form. This will be administered at the post intervention session (Visit 12) and the 1-month follow-up (Visit 13). This form will assess events that the participant might not associate with and record as a treatment side effect.

This study will be stopped in order to prevent further harm to study participants in the occurrence of study-related adverse events. Specifically, a mandated discontinuation of

the study (pending Medical Monitor review) would occur following any of the following: 1) clinically significant worsening of anorexia nervosa; 2) two participants experience clinically significant increase in suicidal thoughts; 3) one participant attempts suicide; and 4) any other device-specific severe adverse event.

Study participants who become injured or ill as a direct result of the participation in the study will be able to seek regular medical care, as needed.

We will follow guidelines for medical devices in the reporting of adverse events in this trial, which defines unanticipated adverse device effects (UADEs) in the Code of Federal Regulations in 21 CFR 812.3(s) as any serious adverse effect on health or safety associated with a device.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy: Only research staff will have access to subject information. Data contained on paper records and computer files will not include names or other identifying information of subjects. Records containing identifying information will be stored in a private research office behind two locks and be accessible only by the principal investigator and research staff that has completed training data confidentiality training (e.g. HIPAA). The study coordinator or the principal investigator will review and remind research staff of this guideline on a regular basis. Paper and electronic records will be kept for a minimum 6 years. Paper records not under use will be stored behind two locks in a private research space. Any identifying information on magnetic or optical media will be stored in a similar manner or be password protected. The password for accessing this information will be available to only select staff that need access to the information to conduct their research duties. All other data will not contain identifying information. All other data will be stored on encrypted magnetic or optical media that is secured or on computer systems accessible only by research staff and computer system administrators via password.

As part of study interviews, questions may be asked which touch on sensitive or private issues which the subject may feel uncomfortable discussing. Although there is a potential for disclosure of sensitive personal information, every effort will be made to lessen the risk. The subject may refuse to answer any questions they do not wish to answer at any time; however, this may lead to their discontinuation from the study protocol.

19.2 Access to Participants*:* Research team members will not access any medical records from participants.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury: This research does not involve greater than Minimal Risk to participants. There is no compensation in the event of research-related injury.

20.2 Contract Language: N/A

21.0 Consent Process

21.1 Consent Process (when consent will be obtained): Consent will take place in a private room in the Ambulatory Research Center housed in the Department of Psychiatry at the University of Minnesota (in person)or remotely. Depending on location, consent will be

completed in person or remotely (through a video conference). If consent is completed remotely, an eConsent form will be completed in RedCap while using Zoom.

COVID-19 Adaptations: The following modifications to consent procedures may be used to mitigate pandemic-related risks while participating in this study. These modifications may stay in place even after the pandemic-related risks are considered to have diminished:

- Consent procedures will be completed remotely using REDCap, while also using Zoom with audio and video to communicate to the participant who will be in a private location of their choosing.
    - Remote consent procedures will be completed remotely using REDCap, while also using Zoom with audio and video to communicate to the participant who will be at home.
- The electronic versions of forms in REDCap may be formatted slightly different than the paper versions, due to limited formatting options in REDCap. The content will be the same.

The study research staff will thoroughly describe the study and read from the Consent Form. Then the patient will be given time to read the Consent Form and ask questions of study staff. If the patient agrees, they will sign the consent (either in physical paper or directly in RedCap) with the study staff person looking on. Part of the consent involves asking questions of the patient recording their responses to ensure they understand the study and that they can terminate participation at any point. To **protect vulnerable populations**, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included in the study. They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

To ensure ongoing consent: After consent is provided and at each intervention day, participants are monitored for any concerns they have about the intervention with the Treatment Side Effect Questionnaire. Participants who agree to continue in the study will report this in the questionnaire.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): N/A

21.4 Non-English Speaking Participants: We will not enroll participants who do not speak English

21.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): We will not recruit participants under 18 years of age.

21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

As stated earlier, participants' capacity is evaluated with the UCSD Brief Assessment of Capacity to Consent (UBACC) completed by study team members who have completed the Assessing Capacity to Consent training.

If a participant scores less than a 14 on the UBACC, the study staff obtaining consent may review the study details in a single session of remedial education, and then administer the UBACC a second time. If the individual is still unable to score a 14 or higher on the UBACC after this remedial education, they will not be included in the study.

At times when the study staff believe that the participant's capacity to consent may have diminished, study staff may redo the consent discussion and re-administer the assessment of capacity to consent to determine if the participant is still able to consent to participate. If the participant is determined unable to participate at that time, the investigators (PI or Co-I) will make a decision as to whether the participant will be placed on temporary hold or withdrawn from the study. If the participant is placed on hold, they must successfully complete the UBACC assessment again (score 14 or higher) before continuing with study procedures.

21.7 Adults Unable to Consent: We will not recruit any individual unable to consent for themselves.

22.0 Setting

22.1 Research Sites:

- Recruitment (via study flyers, media advertisements) will occur at local eating disorder treatment centers in the Twin Cities Metro Area.
  - Screening, consent, interview, assessments will take place at the Ambulatory Research Center (ARC) in the Psychiatry Departme^{nt} (2nd floor) of the University of Minnesota Medical School. These procedures will be done in person or remotely. tDCS sessions will take place either at the Ambulatory Research Center (ARC), the Non-Invasive Neuromodulation Lab (NNL) at the University of Minnesota Medical School or at the Masonic Institute for the Developing Brain. Services offered at NNL are listed below:
    - Facilities access
    - Neuromodulation and physiological recording equipment
    - Laboratory orientation and safety training, both in person and via Canvas
    - Equipment operator training
    - Theoretical knowledge and practical experience.
    - Training to satisfy NNL requirements prior to running participants.
    - First chair training is required of any staff delivering stimulation to participants. Undergraduate students may not serve in this role.
    - Second chair training is required of any staff or students who will access NNL spaces and assist with running experiments.
    - Equipment maintenance and technical support
    - Storage space for study supplies
    - Piloting assistance (i.e., NNL staffing for protocol dry run and first enrolled participant)

- Access to generic Standard Operating Procedures created by the NNL
- NNL Safety Steering Committee review of study protocol prior to study approval
- Parking for research participants (only at 717 Delaware, one space)
- Instruction in safety/adverse event monitoring procedures, access to example documents

22.2 International Research: N/A

23.0 Multi-Site Research: N/A

24.0 Coordinating Center Research: N/A

25.0 Resources Available

25.1 Resources Available:

- Recruitment: Participants that respond to our advertisement flyers or social media posts from eating disorder treatment programs in the Twin Cities metro will be recruited.
- Facilities for interview, cognitive assessment and tDCS: Baseline research appointments for this study will be conducted at a private room in the Department of Psychiatry Ambulatory Research Center (ARC). There are four dedicated appointment rooms available to meet participants for study visits at the ARC, as well as overflow space. In the case that remote sessions are needed, the participant will connect with research staff from a private space through zoom (for baseline visits). tDCS sessions will occur at either the Ambulatory Research Center (ARC), the Non-Invasive Neuromodulation Lab inside of the University of Minnesota Medical School or the Masonic Institute for the Developing Brain.
- Emergency facilities: In the case that a participant has an emergency, such as a heart attack, rescue resources will be made available to them. At the Department of Psychiatry Ambulatory Research Center, the Emergency Department is located on the ground floor below. In the case of a health emergency, study staff can call in a code to have emergency personnel come to the scene. For medical and psychiatric emergencies, study staff will call 911 for the participant to be brought to a hospital.
- Lisa M. Anderson, PhD (PI) will be available in case of unanticipated psychological issues.
- Kelvin O. Lim, MD (Co-I, medical monitor) will be available in case of unanticipated medical issues.

26.0 References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fifth ed. Arlington, VA: American Psychiatric Association; 2013.
2. Braun, D. L., Sunday, S. R., & Halmi, K. A. (1994). Psychiatric comorbidity in patients with eating disorders. *Psychological Medicine*, 24, 859–867.

3. Mitchell, J. E., & Crow, S. (2006). Medical complications of anorexia nervosa and bulimia nervosa.
Current Opinion in Psychiatry, 19, 438–443.
4. Pohjolainen, V., Koponen, S., Räsänen, P., Roine, R. P., Sintonen, H., & Karlsson, H. (2016). Long-term health-related quality of life in eating disorders. *Quality of Life Research*, 25, 2341-2346.
5. Crow, S. J., Peterson, C. B., Swanson, S. A., Raymond, N. C., Specker, S., Eckert, E. D., & Mitchell, J.
E. (2009). Increased mortality in bulimia nervosa and other eating disorders. *The American Journal of*
Psychiatry, 166, 1342–1346.
6. Arcelus, J., Mitchell, A. J., Wales, J., & Nielsen, S. (2011). Mortality rates in patients with anorexia nervosa and other eating disorders: a meta-analysis of 36 studies. *Archives of General Psychiatry*, 68, 724-731.
7. Eddy, K. T., Tabri, N., Thomas, J. J., Murray, H. B., Keshaviah, A., Hastings, E., ... & Franko, D. L. (2017). Recovery from anorexia nervosa and bulimia nervosa at 22-year follow-up. *The Journal of Clinical Psychiatry*, *78*(2), 17085.
8. Pike, K. M. (1998). Long-term course of anorexia nervosa: response, relapse, remission, and recovery.
Clinical Psychology Review, 18, 447–475.
9. Deter, H., & Herzog, W. (1994). Anorexia nervosa in a long-term perspective: Results of the Heidelberg-Mannheim study. *Psychosomatic Medicine, 56*, 20-27.
10. Ionescu, T. (2012). Exploring the nature of cognitive flexibility. *New ideas in psychology*, *30*, 190-200.
11. Brockmeyer, T., Febry, H., Leiteritz-Rausch, A., Wünsch-Leiteritz, W., Leiteritz, A., & Friederich, H. C. (2022). Cognitive flexibility, central coherence, and quality of life in anorexia nervosa. *Journal of Eating Disorders*, *10*, 1-8.
12. Arlt, J., Yiu, A., Eneva, K., Dryman, M. T., Heimberg, R. G., & Chen, E. Y. (2016). Contributions of cognitive inflexibility to eating disorder and social anxiety symptoms. *Eating Behaviors*, *21*, 30-32.
13. Duriez, P., Kaya Lefèvre, H., Di Lodovico, L., Viltart, O., & Gorwood, P. (2021). Increased cognitive flexibility mediates the improvement of eating disorders symptoms, depressive symptoms and level of daily life functioning in patients with anorexia nervosa treated in specialised centres. *European Eating Disorders Review*, *29*, 600-610.
14. Giombini, L., Nesbitt, S., Kusosa, R., Fabian, C., Sharia, T., Easter, A., & Tchanturia, K. (2022). Neuropsychological and clinical findings of cognitive remediation therapy feasibility randomised controlled trial in young people with anorexia nervosa. *European Eating Disorders Review*, *30*, 50-60.
15. Stedal, K., Broomfield, C., Hay, P., Touyz, S., & Scherer, R. (2021). Neuropsychological functioning in adult anorexia nervosa: A meta-analysis. *Neuroscience & Biobehavioral Reviews*, *130*, 214-226.
16. Meneguzzo, P., Tenconi, E., Todisco, P., & Favaro, A. (2021). Cognitive remediation therapy for anorexia nervosa as a rolling group intervention: Data from a longitudinal study in an eating disorders specialized inpatient unit. *European Eating Disorders Review*, *29*, 770-782.
17. Kaye, W. H., Wierenga, C. E., Bailer, U. F., Simmons, A. N., & Bischoff-Grethe, A. (2013). Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. *Trends in Neurosciences*, *36*, 110-120.

18. Kaye, W. H., Wierenga, C. E., Bailer, U. F., Simmons, A. N., Wagner, A., & Bischoff-Grethe, A. (2013). Does a shared neurobiology for foods and drugs of abuse contribute to extremes of food ingestion in anorexia and bulimia nervosa? *Biological Psychiatry*, *73*, 836-842.
19. Uniacke, B., Wang, Y., Biezonski, D., Sussman, T., Lee, S., Posner, J., & Steinglass, J. (2019). Resting-state connectivity within and across neural circuits in anorexia nervosa. *Brain and Behavior*, *9*, e01205.
20. Steward, T., Martínez-Zalacaín, I., Mestre-Bach, G., Sánchez, I., Riesco, N., Jiménez-Murcia, S., ... & Fernandez-Aranda, F. (2022). Dorsolateral prefrontal cortex and amygdala function during cognitive reappraisal predicts weight restoration and emotion regulation impairment in anorexia nervosa. *Psychological Medicine*, *52*, 844-852.
21. Kaye, W. H., Fudge, J. L., & Paulus, M. (2009). New insights into symptoms and neurocircuit function of anorexia nervosa. *Nature Reviews Neuroscience*, *10*, 573-584.
22. Borwick, C., Lal, R., Lim, L. W., Stagg, C. J., & Aquili, L. (2020). Dopamine depletion effects on cognitive flexibility as modulated by tDCS of the dlPFC. *Brain Stimulation*, *13*, 105-108.
23. Kim, C., Johnson, N. F., Cilles, S. E., & Gold, B. T. (2011). Common and distinct mechanisms of cognitive flexibility in prefrontal cortex. *Journal of Neuroscience*, *31*, 4771-4779.
24. Bartolo, R., & Averbeck, B. B. (2020). Prefrontal cortex predicts state switches during reversal learning. *Neuron*, *106*, 1044-1054.
25. Roy, A. V., Camchong, J., & Lim, K. O. (2019). Principles and applications of transcranial electrical stimulation. In *Engineering in Medicine* (pp. 319-334). Academic Press.
26. O.D. Hebb. (1949). *The Organization of Behavior: A Neuropsychological Theory*, New York: Wiley-Interscience.
27. Khedr, E. M., Elfetoh, N. A., Ali, A. M., & Noamany, M. (2014). Anodal transcranial direct current stimulation over the dorsolateral prefrontal cortex improves anorexia nervosa: A pilot study. *Restorative Neurology and Neuroscience*, *32*, 789-797.
28. Nienow, T. M., MacDonald 3rd, A. W., & Lim, K. O. (2016). TDCS produces incremental gain when combined with working memory training in patients with schizophrenia: a proof of concept pilot study. *Schizophrenia Research*, *172*, 218–219.
29. Camchong, Y., Roy, A., Gilmore, C., Thao, M., Kazynski, M., Fiecas, M., ... & Lim, K. (2019). Using brain stimulation to modify a brain network and support abstinence during alcohol use disorder recovery. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *12*, 510.
30. Sheehan, D., Janavs, J., Baker, R., Sheehan, K. H., Knapp, E., & Sheehan, M. (2014). *Mini International Neuropsychiatric Interview–Version 7.0.0, DSM-5*.
31. Fairburn C, Cooper Z, O'Connor M. (2008). Eating Disorder Examination. In Fairburn C.G. *Cognitive Behavior Therapy and Eating Disorders*. Guilford Press, New York.
32. Klauss, J., Penido Pinheiro, L. C., Silva Merlo, B. L., Correia Santos, G. D. A., Fregni, F., Nitsche, M. A., & Miyuki Nakamura-Palacios, E. (2014). A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. *International Journal of Neuropsychopharmacology*, *17*, 1793-1803.
33. Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain stimulation*, *6*, 424-432.
34. Engel, S. G., Wonderlich, S. A., Crosby, R. D., Mitchell, J. E., Crow, S., Peterson, C. B., ... & Gordon, K. H. (2013). The role of affect in the maintenance of anorexia nervosa: evidence from a naturalistic assessment of momentary behaviors and emotion. *Journal of Abnormal Psychology*, *122*(3), 709.

35. Lavender, J. M., De Young, K. P., Wonderlich, S. A., Crosby, R. D., Engel, S. G., Mitchell, J. E., ... & Le Grang1e, D. (2013). Daily patterns of anxiety in anorexia nervosa: associations with eating disorder behaviors in the natural environment. *Journal of Abnormal Psychology*, *122*, 672.
36. Schaefer, L. M., Smith, K. E., Anderson, L. M., Cao, L., Crosby, R. D., Engel, S. G., ... & Wonderlich, S. A. (2020). The role of affect in the maintenance of binge-eating disorder: Evidence from an ecological momentary assessment study. *Journal of Abnormal Psychology*, *129*(4), 387.
37. Dahlgren, C. L., Hage, T. W., Wonderlich, J. A., & Stedal, K. (2019). General and eating disorder specific flexibility: Development and validation of the eating disorder flexibility index (EDFLIX) questionnaire. *Frontiers in Psychology*, *10*, 663.
38. D'Cruz, A. M., Ragozzino, M. E., Mosconi, M. W., Pavuluri, M. N., & Sweeney, J. A. (2011). Human reversal learning under conditions of certain versus uncertain outcomes. *Neuroimage*, *56*, 315-322.
39. Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*, 175-191.