A Pilot Study of the Immediate Effects of DLPFC tDCS on Attention Bias in Depression

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AB	Attention Bias
ACC	Ambulatory Care Center
AE	Adverse Event/Adverse Experience
AMS	Analog Mood Scale
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory
CFR	Code of Federal Regulations
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DLPFC	Dorsolateral Prefrontal Cortex
FFR	Federal Financial Report
FPN	Frontroparietal network
FWA	Federalwide Assurance
HAM-D	Hamilton Depression Rating Scale
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
MDD	Major Depressive Disorder
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PANAS- SF	Positive and Negative Affect Schedule
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SMDDS	Symptoms of Major Depressive Disorder Scale
SOP	Standard Operating Procedure
tDCS	Transcranial direct current stimulation
US	United States
WRAT-4	Wide Range Achievement Test-4 Fourth Edition

Protocol Summary

Title	A Pilot Study of the Immediate Effects of Single-Session DLPFC tDCS on Attention Bias in Depression
Short Title	Change in Depressive Attention Bias with DLPFC tDCS
Brief Summary	Depression and other psychiatric conditions are marked by exaggerated, preferential processing (or attention bias) of negative information relative to neutral or positive information. This depression-related attention bias can be measured using the Dot Probe task and Visual Search task, that allow assessment of the degree to which one shows bias toward negative infromation in the presence of neutral or positive information. A clinically effective treatment for depression is noninvasive brain stimulation with transcranial direct current stimulation (tDCS), targeting the dorsolateral prefrontal cortex (DLPFC), delivered in repeated sessions across a period of time. Here, we will test the effect of a single session of DLPFC tDCS on attention bias in individuals with mild to moderate depression. We predict that a single session DLPFC tDCS will alter depression-related, negative attention bias. Further, we compare this effect across the mild to moderate depression to healthy controls.
Objectives	To test if we can modify or reduce negative attention bias in depression following a single session of left anodal DLPFC tDCS.
Methodology	Prospective
Endpoint	Attention bias and subjective depressive symptoms (affect/mood) at before and after a single-session tDCS.
Study Duration	One year
Participant Duration	A single 2.5 hour research visit
Population	Female participants, ages of 18-45, with mild to moderate depression for depression group, no to minimal depression for healthy control groups.
Study Sites	222 E 41st street, 10th Floor, NY, NY 10017 – NYU Dept. of Neurology
Number of participants	N=75 participants
Study Product	Transcranial direct current stimulation
Statistical Analysis	Pre-post tDCS comparison analyses using t-tests and correlations

Schematic of Study Design

Pre-Screen	• Eligibility pre-screen to determine general eligibility including BDI-II screen
Study Visit	• Obtain Informed Consent • Mini International Neuropsychiatric Interview (MINI) (Screening) • Beck Depression Inventory (BDI-II) (Screening) • Beck Anxiety Inventory (BAI) • Hamilton Depression Rating Scale (HAM-D) • Symptoms of Major Depressive Disorder Scale (SMDDS) • Healthy controls will complete a brief computer-based word puzzle task before the tDCS session, assigned to one of two conditions: difficult/unsolvable or easier
Pre-tDCS Administration	• Positive and Negative Affect Schedule-SF (PANAS); • Analog Mood Scale (AMS) • Dot Probe Task (DP) and Visual Search (VS) Task
tDCS Admnistration	• tDCS tolerability test • 30 minutes of tDCS (up to 2.0mA)
Post-tDCS Admnistration	• PANAS • AMS • DP and VS Tasks

Key Roles

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1 Introduction, Background Information and Scientific Rationale

1.1 Background Information and Relevant Literature

Depression is characterized by distinct cognitive and emotional disruptions (Mathews & MacLeod, 2005; Winer & Salem, 2016), and the symptom burdens associated with the disease are tremendously debilitating to those who are affected (Lorenzo-Luaces, 2015). Depression is highly prevalent globally, and occurs twice as often in females than in males consistently in almost every part of the world (Culbertson, 1997; Nolen-Hoeksema & Hilt, 2009; Weissman & Klerman, 1977). Cognitive models of depression have shown depression-related attention bias (AB), a selective and exaggerated preferential processing toward negative information and stimuli, as a key mechanism in the etiology and maintenance of depression pathology (Bar-Haim et al., 2007; Mathews & Macleod, 1985, 2002; Peckham et al., 2010. Particularly, AB is presented as increased attention to negative, mood congruent stimuli and reduced attention to positive, mood-incongruent stimuli in depression (Trapp et al., 2018). Furthermore, this negative AB, which could be measured and quantified by various cognitive tasks such as the Dot Probe Task (Mathews & Macleod, 1985, 2002), has shown significant difference between depressed versus non-depressed individuals, indicating that negative AB is a robust measure of depression-related cognitive disruptions (Peckham et al., 2010). Other tasks such as the Visual Search (VS) Task (Wolfe & Horowitz, 2017), which is a task that measures facilitation and interference effects of attention that are disrupted in emotional and stress-related disorders, have shown robust findings in anxiety and PTSD (e.g., Pineles et al, 2009), but less is known about depression (Bodenschatz et al., 2021; Rinck & Becker, 2005). Importantly, negative AB was shown in clinical depression, non-clinical dysphoria, research subjects undergoing depressive mood induction, and in those who have recovered from depressive episodes (Joormann & Gotlieb, 2007; Peckham et al., 2010; Trapp et al., 2018).

Noninvasive brain stimulation (NIBS) is an effective treatment for depression when applied in repeated sessions targeting the DLPFC. tDCS is one type of NIBS with a large body of clinical evidence supporting its PRIMSA Level A recommendation as “definitely effective” for the treatment of a major depressive episode (Fregni et al., 2021; Razza et al.,2020). In tDCS, low amplitude current is delivered through electrodes placed

on the scalp to the target regions of interest. tDCS has been extensively demonstrated to be a safe and tolerable treatment, with no serious adverse events reported across clinical trials to date (Bikson et al., 2016).

In treatment of MDD, the use of tDCS is based on evidence of an interhemispheric functional asymmetry in depressive states that leads to a hypoactivation of the left dorsolateral prefrontal cortex (DLPFC) and hyperactivation of the right DLPFC (Grimm et al., 2008). The DLPFC is connected to the frontoparietal network (FPN), which has been found to be underactivated in depression (Korgaonkar et al., 2013). Most importantly, past studies suggest that the use of tDCS over the DLPFC may increase cognitive performance of people with depression, mainly due to the fact that DLPFC is involved in complex cognitive processes and attentional network (Brunoni & Vanderhasselt, 2014; Dedoncker et al., 2016). This further implies that application of tDCS in the DLPFC may also modulate attention associated with negative attention bias associated with depression, as well as potentially reducing depressive symptoms.

Recent studies have noted that a single session of DLPFC tDCS administration can reduce AB in patients with anxiety disorders (Heeren et al., 2017), but more research is needed to support the impact of short-term (i.e., single-session) tDCS in modifying or reducing AB, more specifically in depression.

In summary, tDCS has an extensive record of safety and tolerability. A large body of research has demonstrated its efficacy in reducing depressive symptoms following cumulative daily treatment sessions (e.g., 20 or more). While there is no clinical treatment benefit expected from a single session of tDCS, no study to date has yet to evaluate the immediate effect of single-session DLPFC tDCS in depression-related AB. This study will be one of the first studies to evaluate the efficacy of the single-session tDCS on depression-related attention bias and depressive mood and symptoms.

Rationale

We will test the effects of a single-session of DLPFC tDCS to alter negative attention bias in individuals with mild to moderate depression. In addition, for comparison, we will include healthy control participants 1:1 assigned to one of two pre-task conditions, where they will complete either difficult/unsolvable or easier computer-based word puzzles. The difficult/unsovleable condition will serve as a situational stressor. The easier word puzzle condition will provide neutral condition normative data. Findings will inform future studies and have the potential to inform the use of tDCS reducing symptoms of depression. Findings will inform future studies and have the potential to inform the use of tDCS reducing symptoms of depression.

2 Potential Risks & Benefits

2.1 Known Potential Risks

Risks associated with tDCS:

MINDD STIM (ybrain, South Korea) is medical-grade non-invasive brain stimulation system that uses weak electrical current to stimulate brain region of interest. MINDD STIM system has been used in over 33,200 sessions and 1,000 patients, without any serious adverse event reported. The side effects reported are similar to the ones reported (e.g., tingling, itching, warmth sensation) in other studies using other tDCS devices.

According to literature and the extensive experience of our lab (> 11,000 tDCS sessions delivered so far), there are no major risks associated with tDCS. Some people report tingling, itchiness and warmth sensation at the site of the electrodes. Rarely, the use of saline-soaked sponge electrodes can provoke skin dryness. tDCs do meet criteria for non-significant risk (Bikson et al., 2016). Additionally, there are no known serious adverse events associated with this type of stimulation. The current intenisity for this study will be set at 2.0 mA. The safety and tolerability of tDCS current intensity at 2.0 mA has been assessed in multiple studies in which a single session of tDCS was found to be safe and well-tolerated.

For the reasons referenced above, tDCS meets the criteria for an abbreviated IDE (non-significant risk medical device):

1. It is ***not*** intended as an implant and **does *not*** present a potential for serious risk to the health, safety, or welfare of a subject
2. It is ***not*** purported or represented to be for a use in supporting or sustaining human life and does ***not*** present a potential for serious risk to the health, safety, or welfare of a subject.
3. It is ***not*** for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and **does *not*** present a potential for serious risk to the health, safety, or welfare of a subject: the device will not be used for subject treatment and subjects standard medical treatment will continue regardless of their participation in the study
4. It ***does not*** otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

Risks Associated with Mood Questionnaires: Completing questionnaires may produce some emotional distress in some participants. While we do not anticipate this to be a significant issue, participants will be allowed to take breaks as needed and may stop answering questions at any time without affecting their enrollment.

Risks Associated with Computer-Based Word Puzzle Task: If participants are assigned to the diffficult/unsobleable condition, they may experience situational frustration or emotional discomfort. While we expect any discomfort to be brief and transitory, participants will be able to stop if the task at any point.

Risks Associated with Attention Bias Task: There are no anticipated risks from completing a computerized attention bias tasks.

Other risks:

There is minimal risk of breach of confidentiality. All data will be kept strictly confidential and stored in locked cabinets located at NYU Ambulatory Care Center (ACC), 222 East 41st Street, 10th Floor, New York, NY 10017. Electronic data will be stored on secure, password-protected, NYU Langone computers. Participants will be assigned a unique ID that will be used on all data collection instruments.

Unforseeable risks: There may be risks associated with tDCS that are currently not known.

2.2 Known Potential Benefits

There is no direct expected benefit to the participants expected from the tDCS protocol as established. It is hoped that the knowledge gained from this study will help inform future research projects and ultimately help patients in the future.

3 Objectives and Purpose

3.1 Primary Objective

The researchers aim to test if a single-session tDCS targeting the DLPFC (left anodal) can modulate negative attention bias associated with depression and in comparison to helathy controls with and without experiencing a situational stressor.

3.2 Secondary Objective

Secondary objectives include evaluation of improvement in affect, reduction in depressive symptoms, and generation of primary data for future grant applications and basis of larger-sample studies.

4 Study Design and Endpoints

4.1 Description of Study Design

In this prospective pilot study we will recruit 25 female participants, ages 18-45 (inclusive), with mild to moderate depression (based on BDI-II score range 14-19 for mild and 20-28 for moderate) as well as 50 healthy control (defined by a BDI > 14) females of the same age range (18-45) to determine if a single-session of tDCS can alter negative attention bias. With the healthy control group, the recruited participants will be assigned to either

the easy (n = 25) or difficult/unsolvable (n = 25) pre-tDCS word puzzle task condition. The group assignment will be pseudo-randomized (counterbalanced; e.g., alternating easy and difficult anagram conditions).The primary objective is to study if single-session tDCS will affect attention bias in depression and is not meant to treat depression. Subjects may or may not be receiving treatment for mild-moderate depression. If potential participant is severly depressed during the screening, standard clinical procedures will be used such as advising them to contact their treating physician and/or providing them a crisis hotline number (SAMHSA's National Helpline: 1-800-662-HELP (4357), or to NYU Langone Psychiatry Associates at (212) 263-7419.

For this initial pilot study, we are measuring subtle changes in response time latency at the millisecond level for attention bias. Because demographic factors of both age and sex are known to influence response times on attention tasks (Dykiert, Der, & Deary, 2012; Joormann & Gotlieb, 2007), we will limit the contribution of these factors in this initial pilot study.

The study will consist of a single 2.5 hour research visit that will take place at the NYU Ambulatory Care Center (222 East 41st Street, 10th Floor, New York, NY 10017). After written informed consent is obtained (outlined in section 13.1), participants will have an eligibility screening which will include a semi structured interview (MINI). Eligible participants will complete depression and mood self-report questionnaires, two attention bias tasks (dot-probe and visual), and a single 30-minute tDCS session. Total study duration (including analysis, etc.) will be 1 year.

4.2 Primary Endpoints

We will examine if a single-session tDCS will reduce depression-related negative attention bias before and after the stimulation using the attention bias scores generated using reaction-time based data during the dot probe and visual search task. We will also compare this difference across conditions.

4.3 Secondary Endpoints

Measure if tDCS administration can improve negative/depressive mood and affect measured using self-reported questionnaires before and after tDCS, as well as across conditions.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Aged 18-45
2. Female
3. Depression group only: Mild to moderate depression (determined by BDI-II scores of 14-19 and 20-28, respectively).
4. If taking antidepressants, medication must be stable ≥ 30 days prior to screening
5. Health control group only: Minimal depression (determined by BDI-II scores of 0-13).

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Wide-Range Achievement Test-Fourth Edition (WRAT-4) Reading Subtest standard score <85 (to ensure understanding of test procedures)
2. Insufficient visual and motor ability to operate the intervention and assessments as judged by treating neurologist or study staff
3. Primary neurologic condition that would prevent ability to participate
4. History of head trauma in the last year
5. Medical device implants in the head or neck
6. History or current uncontrolled seizure disorder

7. Current substance abuse disorder
8. Pregnant or lactating women
9. Skin disorder/sensitive skin near stimulation locations
10. Depressed participants only:
11. Primary psychiatric disorder other than depression (based on MINI, only for the mild to moderate depression group)

Source documents for inclusion/exclusion criteria can include subject self-report, medical records, case report forms, and eligibility checklists. Criteria asked during the phone pre-screen will be reconfirmed after consent is obtained.

5.3 Vulnerable Subjects

Vulnerable subjects will not be recruited for this study.

5.4 Strategies for Recruitment and Retention

Subjects will be recruited through NYU Langone's iConnect, clinicaltrials.gov, word of mouth, and research flyers placed in the NYU Langone and NYC community. We will also use email blasts (e.g., listserv) to NYC schools and community (an email script attached separately). Interested participants will be able to contact a study team member via phone or e-mail. A team member will respond by phone to provide potential participants an overview of the study, including study procedures, and risks and benefits, using an IRB-approved phone script. Potential participants will be clearly informed that they have the right not to participate in the study. If interested, subjects can complete a general eligibility pre-screen over the phone. Subjects will additionally verbally confirm if they meet eligibility criteria.

5.5 Total Number of Participants and Sites

Recruitment will end when approximately 25 participants are enrolled for each condition (Total N = 75). It is expected that approximately 25 participants will be enrolled in order to produce 20 evaluable participants per each group (Total N = 60) for this pilot study.

5.5.1 Use of Epic Information for Recruitment Purposes

N/A

5.6 Duration of Study Participation

Subject participation will consist of a single visit lasting approximately 2.5 hours and will include:

- Obtain written consent (*~25 minutes*)
- Eligibility screening *(15 minutes)*
- Mood Questionaires *(30 minutes)*
- Attention Bias Tasks (DP & VS*, 60 minutes)*
- tDCS session *(30 minutes)*

6 Study Schedule

6.1 Pre-Screening

- Team member conducts phone pre-screening (including BDI-II) to determine general eligibility based on inclusion/exclusion criteria. Participants who meet the BDI-II criteria during the phone screen will not be required to repeat it if they schedule their visit within 2 days of the phone screen. Completing the BDI-II over the phone is a practical option that helps screen out those who are ineligible before

they travel to clinic and it is suitable for phone use as participants can verbally rate the BDI-II statements on a scale from 0-4.

Those who score in the severly depressed range (29-63) will be offered to contact the NYU Langone Psychiatry Associates at (212) 263-7419, or if outside the NY area the Substance Abuse and Mental Health Services Administration (SAMHSA) hotline at 800-662-HELP (4357).

All data collected for the purposes of the eligibility pre-screening will be destroyed immediately if the potential subject is ineligible or does not sign an informed consent form at their baseline.

6.2 Screening/Study Visit

- Obtain written informed consent (*25 minutes or however much time is needed*).
- Conduct eligibility screening/MINI/BDI-II *(15 minutes)*
- tDCS tolerability test *(2 minutes)*
- Administer depression surveys (BAI, HAM-D, and SMDDS) *(15 minutes)*
- Administer computerized attention bias dot-probe and visual search task *(30 minutes)*
- Administer pre-tDCS measures (PANAS and AMS; *10 minutes)*
- Complete tDCS session *(30 minutes)*
- Repeat PANAS and AMS *(10 minutes*)
- Repeat attention bias dot-probe task and visual search *(30 minutes)*

7 Study Procedures/Evaluations

After participants provide written informed consent, the following study procedures will take place during a single 2.5 hour research visit:

7.1 Screening

The PI (or team members with PhD or MA in a related field who are trained by the PI) will meet with the participant to review eligibility according to the inclusion/criteria including and administer the mood disorders portion of the Mini International Neuropsychiatric Interview (MINI). Data from screen failures will be deleted immediately after the recruitment period ends.

7.2 Mood and Depression Questionnaires

Participants will be asked to complete self-report questionnaires to assess their baseline depressive symptoms and mood.

7.3 Word Puzzle (Anagram) Task

Half of the healthy control participants (n = 25) will receive a difficult anagram task, consisted of medium to difficult mixed letter words (i.e., anagrams; e.g, TAEIGNS = TEASING). The other half (n = 25) will receive an easy anagram task for comparison). The task has been well-validated and used successfully in previous research to induce mild stress in healthy controls and those who are at risk for affective disorders (Bishop, 2009; Mogg et al., 1990; Wen & Yoon, 2019). Some of the words in the difficult anagram task are not solvable as real words. Participants will be instructed to solve 40 anagrams as accurately and quickly as possible and they will have 3 minutes to complete the task. The participants will be given a paper and pencil to write down their solutions, and all words will be programmed into present one word at a time on a laptop screen.

7.4 Attention Bias Tasks

Participants will be asked to complete two attention bias assessments: Dot-Probe Task and Visual Search Task.

7.4.1 Dot Probe Task

The dot probe task is an established procedure for measuring and manipulating biases in attention associated with depression in adults and children (MacLeod, Mathews, & Tata, 1986; Eldar et al., 2008, Joormann &

Gotlieb, 2007; Pekham et al., 2010). The dot-probe task will be used to assess depression-related attention bias before and after tDCS administration.

To complete the Dot-Probe task, participants will be shown two emotional images (e.g., sad and neutral pair or happy and neutral pair) simultaneously followed by a target in the location of one of the emotional images. Response latencies to targets replacing either the negative/positive or neutral images will be measured before and after training which will be the primary study outcome. Emotional stimuli used are a selection of negative, positive, and neutral pictures taken from a standardized and often used set of emotional faces called the racially diverse affective expression [RADIATE; Conley et al., 2018].

7.4.2 Visual Search Task

In addition, the Visual Search task (e.g., Wolf & Horowitz, 2017) will be administered to further assess attention bias, particularly examining the interference and facilitation effects in attention using emotional stimuli (Rinck & Becker, 2005). The task uses emotional faces or words as stimuli, where the participant is instructed to search for the face that does not fit into the search set with respect to gender (i.e., the only male under three female faces, or the only female under three male faces), where the target and distractors are expressing different or same emotions (i.e., neutral-neutral, sad-neutral, happy-neutral, neutral-sad, neutral-happy, sad-sad, and happy-happy). Studies have shown that individuals with emotional and stress-related disorders show interference effect (i.e., emotional stimuli being the distractor) and facilitation effect (i.e., emotional stimulus being the search target), but less is known about depression (Bodenschatz et al., 2021; Rinck & Becker, 2005; Pineles et al., 2009). This study will use this task as an outcome measure of AB alongside the DP task. For this task, mean response time (the time between display onset and button press) to the target stimulus for each stimulus type is measured as the main outcome variable.

7.5 tDCS Session

tDCS Dose Selection and Tolerability: Participants will undergo a tolerability test to ensure tolerance of the stimulation intensity. In under 2 minutes, the tDCS device ramps up to the target stimulation of 2.0mA and ramps back down to 0mA. The tolerability test can be aborted at any time if the participant is uncomfortable. If 2.0mA stimulation is not tolerated, the participant will be given the option to proceed with a second tolerability test at a lower stimulation amperage (1.5 mA). Participants who cannot tolerate 1.5mA will be excluded as a screen failure.

tDCS settings: The MINDD STIM tDCS system is composed of a management component, treatment module, single-use sponge patches and supporting patches, a headband to hold in position the sponge patches, and 2 cables. A trained study technician will program the stimulation device through the management component setting to the following stimulation parameters:

- **Stimulation intensity:** 2.0 mA or 1.5 mA
- **Stimulation duration:** 30 minutes
- **Ramp up duration:** 30 seconds (beginning of stimulation)
- **Ramp down duration:** 30 seconds (end of stimulation)

Participant preparation for tDCS session: The trained study technician will prepare the stimulation electrodes as detailed below:

- Two single-use sponge patches will be (1) inserted in the patch supporters and (2) soaked with saline solution.

- The patches will be then attached to the headband in the positions corresponding to the frontal region. The red patch (anode) will be located on the left frontal region while the blue patch (cathode) on the right region frontal region.

- The headband will be then positioned on the participant's head.

- The stimulation module will be then attached to the electrode cables.

- The study technician will connect the stimulation module via Bluetooth to the management station and then will be ready to initiate the stimulation session.

tDCS session: Participants will complete a single 30 minutes tDCS session targeting the left DLPFC while sitting in a comfortable position. At the end of the tDCS session possible side effects experienced during the tDCS session will be recorded along with their intensity (rated using the visual analogue scale, 0-10) and duration. The session can be aborted at any time for any reason if the participant wishes.

7.6 Repeat Questionnaires & Attention Bias Tasks

After the tDCS session participants will repeat two of the questionnaires (PANAS and AMS) and both attention bias tasks.

8 Study Questionnaires

Participants will be asked to complete the following self-report questionnaires:

- **Beck Depression Inventory (BDI-II):** a brief, criteria-referenced assessment for measuring depression severity. The BDI-II consists of 21 items to assess the intensity of depression. Each item is a list of four statements arranged in increasing severity about a particular symptom of depression.

- **Beck Anxiety Inventory (BAI):** a brief, criteria-referenced assessment for measuring anxiety severity and level. Participants respond to 21 items rated on a scale from 0 to 3. Each item is descriptive of subjective, somatic, or panic-related symptoms of anxiety. BAI has been found to discriminate well between anxious and non-anxious diagnostic groups in a variety of clinical populations.

- **Hamilton Depression Rating Scale (HAM-D)**: 17-item measure that was designed to assess frequency and intensity of depressive symptoms in patients with MDD. This measure contains somatic and suicidal ideation items and has demonstrated reliability, validity, and efficiency in adult populations
- **Symptoms of Major Depressive Disorder Scale (SMDDS):** a brief measure for adults with MDD and measures specific symptom dimensions. The measure has good psychometric properties including high reliablity and validity.

- **Analog Mood Scale (AMS):** is a brief measure of positive and negative mood consisting of three questions (i.e., “How anxious are you?”, “How sad are you?”, and “How happy are you?”). Participants were told to indicate their present mood by identifying a location on a horizontal line divided into 30 equally distanced segments labeled 1 (not at all) to 30 (very much).

- **Positive and Negative Affect Schedule (PANAS-SF):** a self-report questionnaire that consists of two 10-item scales (20 items total) to measure both positive and negative affect.

9 Safety and Adverse Events

9.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

9.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to study participation should be recorded and reported immediately.

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

For Narrative Reports of Safety Events
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

9.3.1 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events* that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process

The reportable events noted above will be reported to the IRB using a Reportable New Information submission and will include a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution, and need for revision to consent form and/or other study documentation. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

10 Study Oversight

10.1 Data Safety Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Data safety monitoring will occur at least every 4 months and will include PI review of reports of tDCS side effects including skin irritation, itching, warming, and discomfort, emotional distress, protocol adherence, regulatory documentation, enrollment (e.g. rate of enrollment, screen fails, withdrawals, etc.), unanticipated problems, and any issues that may arise during the course of research.

10.2 Medical Monitoring

Dr. Lauren Krupp, MD, Director of the NYU MSCCC, will serve as medical monitor for this study. Dr. Krupp will be responsible for determing SAE severity and relatedness.

10.3 Clinical Monitoring

N/A

10.4 Study Halting Rules

There are no predefined stopping rules for this study.

10.5 Participant Withdrawal or Termination

10.5.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The participant is non-compliant with study procedures

10.5.2 Handling of Participant Withdrawals or Termination

Data of participants who withdraw or are terminated from the study may be kept for analysis if the data is usable (as determined PI).

10.5.3 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IRB.

11 Statistical Considerations

11.1 Study Hypotheses

A single-session tDCS to the left DLPFC will reduce negative attention bias in people with mild to moderate depression. There will be cohort differences across mildy depressed vs. healthy controls with easy anagram vs. healthy controls with difficult anagram (situational stressor) where the reduction of negative attention bias would be greatest in the depressed group compared to the healthy controls.

The primary objective of this study is exploratory data collection. These pilot study findings will be the necessary first step to inform future study design and hypotheses. We are collecting the healthy control pilot data to better interpret the pilot findings in patients with depression, and to provide us with expected ranges of change in our task measures. This inclusion of the anagram task is exploratory to inform future study designs. The use of the challenging anagram task is based from literature where the same paradigm has been used in healthy controls to study temporary states of negative affect (e.g., frustration, anxiety; Myruski et al., 2021).

11.2 Sample Size Determination

The primary objective of this study is to test change in negative attention bias in people with mild to moderate depression following a single session of DLPFC tDCS, and see if their outcomes differ from that of healthy controls.

This is a pilot study to assess the feasibility of a single-session tDCS in a small sample, and the findings will provide preliminary evaluation of effect and inform power analyses for use in a clinical trial design.

A total of N = 75 (n=25 participants for each group) will be enrolled to obtain evaluable target of N=60 (n = 20 for each group) based on the estimated number of eligible participant for each group contacts across the study period.

11.3 Statistical Methods

For the study hypothesis to examine the preliminary effect of a single-session tDCS on depression on negative attention bias, we will use the calculated latency response times pre-tDCS and post-tDCS using the DP and VS tasks and compare change using a paired sample's t-test for each measure. Further, to compare across the groups, we will use ANOVA for before and after effect of tDCS on negative attention bias across the three groups.

As secondary and exploratory, we will also test change in pre- to post- ratings of depressive symptoms and affect. These findings will be collected to inform the power analyses for a larger controlled trial.

12 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from

automated instruments, copies or transcriptions certified after verification as being accurate and complete, subject files.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in blue or black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention. The following consent materials are submitted with this protocol: informed consent form.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by

emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

Subject capacity to provide written informed consent will be determined by the PI, or a team member trained by the PI, during the semi-structured screening interview (MINI). In addition, the WRAT-4, a cognitive measure for reading comprehension, will also be administered. A clinician is not required to administer the WRAT-4 because it is scored with normative values.

13.3.3 Posting of Clinical Trial Consent Form

N/A

13.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval. The study participant's contact information will be securely stored on NYU Langone servers for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be securely stored at the NYU Langone Health Ambulatory Care Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at NYU Langone Health Ambulatory Care Center .

Identifying information will not be presented or published to maintain participant privacy and confidentiality.

13.4.1 Research Use of Data

Consent forms, source documents, and research data will be stored in locked filing cabinets at the NYU Langone Health ACC, 222 East 41st Street, 10th Floor, New York. NY 10017.

Collected study data, including demographic information and research questionnaires, will be obtained electronically through TrialMaster, a HIPAA and 21 CFR Part 11-compliant database designed specifically for

this study. An anonymous database number will be assigned to each participant. The following study personnel will have access to the collected data and study documents: Principal Investigator, Sub-Investigators, and Research Coordinators who are specifically assigned to work on this study.

If participants request to leave the study, no additional data from the date of request will be collected. Any existing data which was previously collected will continue to be stored.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close out or 5 years after final reporting/publication. These documents should be retained for a longer period, however, if required by local regulations.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the study protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify deviations within 7 working days of the scheduled protocol-required activity. Protocol deviations will be reported to the local IRB at the time of study Continuation. The site PI/study staff is responsible for knowing and adhering to IRB requirements.

14.4 Publication and Data Sharing Policy

At the end of the study, the PI will make results of the research available to the research community and public at large.

15 Study Finances

15.1 Funding Source

This study is departmentally funded by the NYU Department of Neurology.

15.2 Costs to the Participant

There are no costs to the participant in order to take part in this study.

15.3 Participant Reimbursements or Payments

Participants will be compensated $100 for participating in this study in the form of check or GreenPhire Clincard.

16 Study Administration

16.1 Study Leadership

The PI will oversee the conduct of this study, in coordination with sub-investigators as applicable.

16.1.1 Non-traditional Volunteers

Non-traditional volunteers who are approved by the IRB to work on this study will not consent nor have direct interaction with research participants.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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