PROTOCOL COVER PAGE

Protocol Title	Mindful Breathing and Neuromodulation for Depression in Young People
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Version Number/Date:	Version 17 3/11/2021

REVISION HISTORY

Version #	Version Date	Summary of Changes	Consent Change?
1	9/16/18	Initial submission	No
2	1/23/19	Removed pre-/post-EEG during tDCS sessions 1-10, questionnaire updates, changing total at-home MBT training to 4 weeks, changes in recruitment and assessments	Yes
3	2/4/19	Added new titles corresponding with grants, updating times and adding procedure details, added PSQI, removed emotion regulation task.	Yes
4	3/4/19	Expanded age range, updated payment, added future re-contact.	
5	3/21/19	Added recruitment from clinic, re-administering the MINI depression module post-intervention, clarified study details, changed randomization to be based on sex only	
6	4/26/19	Made MRI optional and clarified procedures in the case of poor data quality and technical errors, updated outcomes to be consistent with aims, clarified details about MBT, added stress biology measurements, updated compensation, and added new recruitment material	Yes
7	8/1/19	Updates to recruitment materials and increased flexibility about rescheduling sessions	No
8	**8/14/2019**	**Changed procedure for MRI toxicology screen to reflect that participants will be scanned if**	**No**

		results are positive, and we have taken out language that stated the PI will be called if results are positive since recent drug use is not a safety issue.	
9	9/11/2019	Remote completion option for REDCap self-report online questionnaires has been added to increase flexibility with questionnaire completion when participants have time constraints at in-person appointments.	No
10	10/18/2019	1) Change in phone screen process involves the addition of an online eligibility survey link (MADRS-S via REDCap). Completion of MADRS-S during the phone screen will help reduce participant and staffing burden by allowing staff to know which participants meet the basic requirement of eligibility (MADRS-S score of 13 or more). 2) Added standardized language provided by CMRR, approved by the IRB regarding usage of CMRR subject safety screening forms. 3) Change in procedure for completing 3 weeks of mindful breathing training- participants will be given the option of doing it in person only if the study team determines it would be helpful for the participant.	No
11	1/16/2020	1) Added language regarding the risks of using text messaging and email communication with participants. 2) REDCap questionnaire (Cash Choice Task) added. 3) Clarified that the post-tDCS EEG and MRI will be completed within 1-2 business days, instead of 1-2 days.	No

		4) Added clearer language stating that participants are not required to complete all five mindful breathing sessions during the ramp-up period in order to begin in-person tDCS and mindful breathing. 5) Added new location (Department of Psychiatry at Park Plaza) for consenting and conducting clinical intervNAiews. Clarified that the Center for Neurobehavioral Development is used for consenting and clinical interviews.	
12	3/18/2020	1) Changed study exclusion criteria- removed "family history of epilepsy" as this is not a safety concern for tDCS. 2) Changed inclusion criteria regarding study population to Female, 17 to 24 year old, in order to decrease sample heterogeneity.	No
13	3/24/2020	Remote completion option for study procedures due to COVID-19.	No
14	6/8/2020	Took out language stating that participants will be randomized according to sex since the study is now recruiting females only. Added language regarding withdrawal of participants who appear to be unduly stressed (section 12.1).	Yes
15	8/28/2020	Included language to allow flexibility about repeating visits if there is a delay between baseline visits and the start of tDCS and MBT.	Yes
16	11/04/2020	Included language to allow participants to be screened using	Yes

		REDCap surveys. Updated recruitment materials for phone number.	
17	3/11/2021	Clarified in the protocol that the MADRS-S may be repeated if clinically indicated	No

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ABBREVIATIONS/DEFINITIONS

- AAI: Alpha asymmetry Index
- DLPFC: Dorsolateral prefrontal cortex
- DMN: Default Mode Network
- ECG: Electrocardiographic
- EEG: Encephalography
- ERN: Error-related negativity
- ERP: Event-Related Potential
- HRV: Heartrate variability
- LPP: Late Positive Potential
- MDD: Major Depressive Disorder
- MRI: Magnetic Resonance Imaging
- MBT: Mindful Breathing Training
- RSFC: Resting state functional connectivity
- tDCS: Transcranial Direct Current Stimulation

1.0 Objectives

1.1 Purpose: This study will investigate whether transcranial direct current stimulation (tDCS) targeting the dorsolateral prefrontal cortex (DLPFC) can enhance the therapeutic effect of mindful breathing training (MBT) for adolescent depression. The objective is to enhance connectivity between the DLPFC with the amygdala and Default Mode Network (DMN) circuits as well as to enhance emotion regulation abilities and decrease rumination to reduce symptoms of depression. This will aid in the development of novel treatments for depression.

1.2 This study will investigate the following aims:

Aim 1: To demonstrate the feasibility of recruiting and randomizing adolescents with depression to a research protocol involving MBT and tDCS. We expect that adolescents will be willing to enroll in a randomized trial involving MBT and tDCS.

Aim 2: To test the tolerability of MBT and tDCS in adolescents. We expect that MBT will be well-tolerated and that active tDCS will show no difference in tolerance compared to sham stimulation.

Aim 3: To examine whether tDCS can enhance the effects of MBT. We expect the MBT + tDCS group will show greater reduction in depressive symptoms compared to the MBT + sham stimulation group.

Aim 4: To examine the mechanisms of MBT +/- tDCS treatment. We expect that depression symptom improvement will be associated with decreased rumination, improvements in emotion regulation, increased task-based and resting state DLPFC-DMN and DLPFC-amygdala connectivity, as well as increased DLPFC activation and reduced amygdala activation during rumination and emotion processing tasks. We also expect reduced alpha asymmetry and reduced LPP amplitude during emotion regulation and emotion processing. We expect these changes will be greatest in the active tDCS + MBT group.

2.0 Background

2.1 Significance of Research Question/Purpose:

Depression, the main contributor to disability globally and a significant risk factor to premature deaths due to suicide (Friedrich, 2017), commonly arises in adolescence (Kessler et al., 2005). Forty percent of depressed adolescents do not adequately respond to existing treatments (March et al., 2004), emphasizing the urgent need to identify novel, biologically-based treatments. Recent neuroscience research has begun shed light on the pathophysiology of depression, implicating impairments in frontolimbic circuitry, including 1) an underactive dorsolateral prefrontal cortex (DLPFC), a region that supports executive control and emotion regulation (Disner,

Beevers, Haigh, & Beck, 2011; Koenigs & Grafman, 2009) and 2) an overactive amygdala, a region implicated in the experience of negative affect (Drevets, 2006). Connectivity between DLPFC and amygdala is also reduced in depression (Lu et al., 2012). Abnormal hypothalamic pituitary adrenal (HPA) functioning has been found in depression (Burke, Davis, Otte, & Mohr, 2005; Vreeburg et al., 2009) and with rumination (Zoccola & Dickerson, 2012). Since these brain systems are still undergoing development during adolescence (Luciana, 2013), the adolescent years represent a critical time during which to advance understanding of the neural basis both of depression and of novel treatments.

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that can modulate neural activity. If paired with MBT, tDCS may be able to enhance learning and neural changes associated with MBT. This study will test the efficacy of a novel treatment comprised of MBT and tDCS and will be the first to implement tDCS in adolescent depression. We propose that for patients with depression, where the core feature is persistent negative mood, a training task that engages the DLPFC's role in regulating emotion may optimally reduce symptoms of depression. Mindful breathing training (MBT) may be a suitable task to down-regulate negative affect and prime the fronto-limbic circuit. Further, this work will advance our understanding the synergistic effects of combining MBT with tDCS to target the connections between the DLPFC with the default mode network (DMN) and limbic regions. If successful, this study will aid in the development of novel treatments for adolescent depression and improve the ability of neuromodulation to treat depression. This would improve public health by promoting remission, reducing poor outcomes like suicide, and reducing the economic burden of depression.

2.2 Preliminary Data:

Drs. Cullen, Klimes-Dougan, Mueller and Lim have conducted foundational research identifying possible targets of intervention. Using resting-state fMRI, we previously showed in 43 unmedicated adolescents with depression versus 35 controls that patients had greater resting-state functional connectivity between amygdala (a brain region that is critically involved in negative emotion) and the precuneus (a key node of the default mode network) (Cullen et al., 2014). These findings inspired us to further pursue the interactions between DMN and salience network in adolescents at risk for suicide as proposed here.

Drs. Cullen and Klimes-Dougan's collaborations have documented the feasibility for conducting intervention studies, including those employing

neuromodulation techniques (transcranial magnetic stimulation; TMS), in adolescents with depression (Cullen et al., 2016). Notably, this TMS protocol required 30-daily TMS intervention visits in addition to pre- and post- MRI and assessment visits.

2.3 Existing Literature:

Mindfulness-based interventions (MBI), which include MBT, involve focusing on the present experience. During MBI, one becomes aware of mind-wandering, disengages and shifts attention back to the present experience. In depression, this can serve to regulate emotion by redirecting attention away from spontaneous thoughts, which tend to be negative and ruminative in nature. MBI has been shown to improve emotion regulation abilities and to reduce negative affect (Keng, Smoski, & Robins, 2011). Neurally, MBI may be able to prime the connections between the DLPFC with limbic and DMN regions as mindfulness has shown to activate the DLPFC (Hasenkamp & Barsalou, 2012), reduce amygdala activation (Goldin & Gross, 2010), increase connectivity between the DLPFC and the amygdala (Hölzel et al., 2013) and increase connectivity between the DLPFC and the DMN (Jang et al., 2011; King et al., 2016).

Transcranial direct current stimulation (tDCS) is a safe and cost-effective technique that has been studied in adult depression, typically targeting the DLPFC (Kalu, Sexton, Loo, & Ebmeier, 2012). Notably, the DLPFC subserves multiple regulatory functions, including emotional and non-emotional behavior. Prior neuroimaging studies have shown that tDCS stimulating the left DLPFC upregulates DLPFC activity, can decrease amygdala activity (Ironside et al., 2017) and increase connectivity between the DLPFC and the DMN (Keeser et al., 2011). Although tDCS has been shown to be safe for adolescents (Krishnan, Santos, Peterson, & Ehinger, 2015), its efficacy for adolescent depression has yet to be explored (Vicario & Nitsche, 2013). Further, while adult depression studies have demonstrated effectiveness of tDCS versus sham, the effect size has been only small to moderate (Hedge's $g = 0.74$), with response rates, ranging from 0-80% and only an average of 8.5% of patients achieve full remission with tDCS (Kalu et al., 2012), highlighting significant room for improvement with this treatment.

An important advance in this line of work shows that the effects of MBT and tDCS may interact synergistically. tDCS establishes a neuroplastic state which can accelerate the learning and neural effects of mindful breathing (Fritsch et al., 2010). The effects of tDCS can be augmented by priming the targeted neural networks by having participants perform a task that requires activation of the targeted neural system in conjunction with stimulation (Romei, Thut, & Silvanto, 2016). In adult depression, cognitive

control training has been combined with tDCS to enhance DLPFC activity with a response rate of 25-44% (Brunoni et al., 2014; Segrave, Arnold, Hoy, & Fitzgerald, 2014).

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome: Primary outcome measures of feasibility and tolerability include side-effects, number of participants enrolled, and dropout rate. The primary clinical outcome measure will be change in depression symptoms and DLPFC connectivity with the salience network and the default mode network.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s): Additional outcomes may include mindfulness, rumination, cortisol, cognition as assessed by executive functioning tasks, change in biological measures (e.g., RSFC, task-based neural activation, alpha asymmetry, and LPP amplitude),

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

4.1 Description:

Mindful Breathing Training (MBT): All participants will undergo mindful breathing training (MBT). MBT is a mindfulness-based intervention that guides participants to pay attention to the present experience. Participants will be trained to become aware of mind-wandering, disengage, and shift attention back to the present experience. Participants will practice mindful breathing using a computerized application that they will be able to access on the web. This training will be administered through a University of Minnesota server on an internet browser (e.g., Google Chrome). During this task, participants will close their eyes and focus on their breath, tapping at the end of each breath. Participants will first complete five sessions (for 10, 12.5, 15, 17.5, and 20 minutes) of mindful breathing training at home using a personal laptop, tablet, or cell phone over five days. Following this training, participants will be randomized to undergo either ten 20-minute sessions of active or sham tDCS concurrent with MBT across two weeks in lab. Participants are not required to complete all five mindful breathing sessions prior to starting in-person treatment. Following lab MBT training with either active or sham tDCS, participants will complete 15 sessions of MBT training across three weeks at home or in-person.

tDCS: We will use transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique that can modulate brain activity and connectivity, to stimulate the dorsolateral prefrontal cortex (DLPFC). Weak electrical current (~2mA) is applied to the scalp using anodal and cathodal

electrode sponges, which increase or decrease cortical excitability respectively. Research has shown in both healthy participants and patients (e.g. Alzheimer's disease, Parkinson's disease, and depression) that tDCS has the potential to modulate synaptic strengthening and neurotransmitter-dependent plasticity underlying changes in behavior and learning (Lang et al., 2005). Sham stimulation will serve as a control condition with current applied only for the first and last 30 seconds of the 20-minute session.

4.2 Drug/Device Handling:

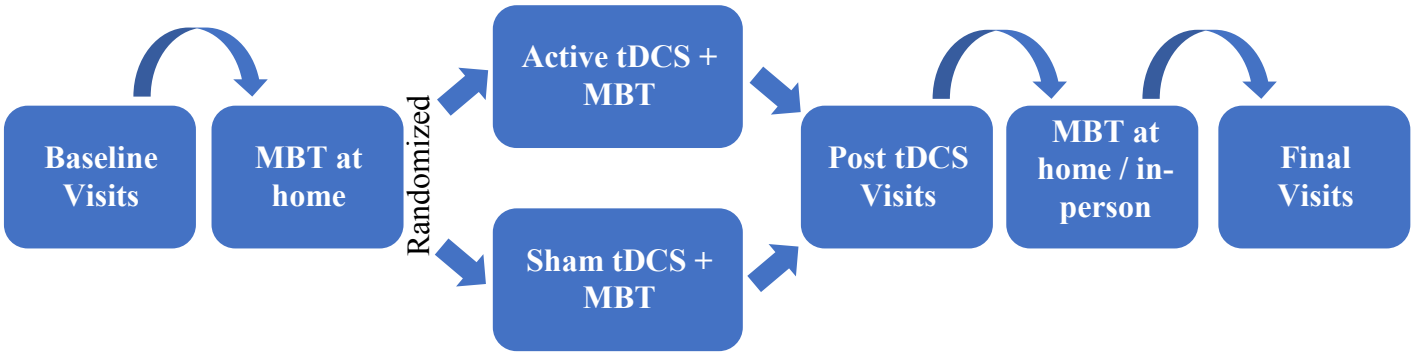
- tDCS will be applied with a StarStim Enobio system (Neuroelectrics, Barcelona, Spain) using a bipolar stimulation montage.
- This device has been approved for use in research without an investigational device exemption due to meeting criteria for non-significant risk (NSR).
- In addition, the device 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 current will be administered via two saline soaked electrode sponges during each intervention session, using a current strength of 2.0 mA.
- These administration procedures are in line with other protocols that have outlined the safe use of tDCS in pediatric populations (Krishnan et al., 2015).
- The tDCS cap and stimulation electrodes/sponges will be washed and disinfected after each intervention session and stored under lock and key in 717 Delaware Street SE.

4.3 Biosafety: N/A IND/IDE

5.0 Procedures Involved

5.1 Study Design: Participants will undergo ten daily sessions of one of two conditions: 1) active tDCS + Mindful Breathing Training or 2) sham tDCS + Mindful Breathing Training (approximate final n of 15 per group). A randomized block design will be used to assign each subject to a condition (sham or active tDCS). This study will be double-blind to +/- tDCS stimulation.

Figure 1



5.2 Study Procedures: Participants will complete a baseline assessment (including a diagnostic interview, clinical assessments, behavioral tasks, questionnaires, an EEG/ECG visit, and an optional MRI scan) prior to intervention, an interim assessment (clinical assessments and questionnaires) after 5 intervention sessions, a post-intervention assessment (including clinical assessments, behavioral tasks, questionnaires, an EEG/ECG session, and an optional MRI scan) after the tDCS intervention, and a final assessment (clinical

assessments, behavioral tasks, questionnaires, and an EEG/ECG session) following the at-home/in-person MBT intervention. The intervention will consist of MBT completed at home or in-person and MBT completed in the laboratory concurrent with active or sham tDCS (see Figure 1 and Table 1 for an outline of study activities). All self-report questionnaires will be administered online through REDCap, a HIPAA-compliant survey system, or on paper. All online self-report questionnaires administered through REDCap will be completed by participants either in-person or remotely. Participants who are unable to complete all online self-report questionnaires in-person due to time constraints will be emailed an access code for each questionnaire and a link to the REDCap website. Upon opening the website link, they will be prompted to enter their access code in order to fill out questionnaires. Questionnaires administered on paper will be entered into REDCap by research staff.

Remote Conduct of Study Procedures- In the interest of disease containment and prevention, study staff will use HIPAA-compliant communication platforms approved for use at the University of Minnesota (e.g., Zoom) at their discretion to conduct necessary study procedures when possible during the period of heightened public health concern due to COVID-19. This will allow for participants to be given the option for remote study visits when deemed necessary by either the participant or by research staff.

Week		1	1, 5, and 9	1 and 5	3-4	3	5	9
	Time	Baseline Assessment	EEG 1, 2, & 3	MRI 1 & 2	tDCS + MBT Visits 1-10	Interim Assessment	Post-tDCS Assessment	Final Assessment
Consent		X						
tDCS Safety Screen		X						
MINI	20 min	X						
MINI Depression Module							X	X
MADRS-S		X				X	X	X
C-SSRS (LV or SLV)		X				X	X	X
MAAS		X				X	X	X
FMI		X				X	X	X
RSS		X					X	X
IDAS-II		X						
DAS		X					X	X
DERS		X					X	X
AAQ-II		X					X	X
Cash Choise Task		X					X	X
Side Effects Questionnaire					X			
tDCS Perceptions Questionnaire		X					X	X
PSQI		X					X	X
CRT	20 min	X					X	X
Rest Eyes Open/closed + ECG	6 min		X					
Rumination	3 min		X					
Distraction	3 min		X					
Mindful Breathing + ECG	10 min		X (only EEG					

			2 & 3)					
Flanker	20 min		X					
Go/No-Go	10 min		X					
Manipulation Check Questionnaires			X	X	X			
Safety Screen				X				
UTox				X				
Pregnancy Test				X				
Anatomical Scan	15 min			X				
RSFC	12 min			X				
Mindful Breathing Scan	12 min			X (only MRI 2)				
Harari Task	5 min			X				
Rumination Task	20 min			X				
Active/Sham tDCS + MBT					X			
PANAS			X	X	X			
Pre-/Post tDCS Questions					X			
Saliva Samples		X					X	

Table 2: Schedule of activities

- **Baseline Visit (2 Hours)**
    - Participants will complete a diagnostic interview, self-report clinical measures, and behavioral tasks.
- **Active/Sham tDCS and MBT Intervention Visits (10 sessions; 45 minutes each)**
    - 20 minutes to set up
    - 22 minutes of mindful breathing training with 20 minutes of active or sham tDCS
    - 5 minutes of assessments
- **tDCS Description**
    - 20 minutes of active or sham stimulation will be applied at 2.0 mA in parallel with mindful breathing training using the StarStim Enobio 8 system (Neuroelectrics, Barcelona,

Spain) using a bipolar stimulation montage with the anode over the left DLPFC (F3 10-20 position) and the cathode over the right orbitofrontal cortex (FP2 10-20 position).

- The sham condition will apply stimulation only for the first and last 30 seconds of the 20-minute session.
- Stimulation will be double-blinded using StarStim settings.

- **Mindful Breathing Training Description**
  - 30 sessions of MBT: Participants will be instructed to practice mindfulness and will complete a guided computerized task. During the computerized task, they will be asked to focus on the sensations of their breaths. They will tap at the end of each breath and receive feedback. Participants will be trained to use the mindful breathing program after their last in-person baseline visit. Training will involve a brief overview of mindful breathing and a one-minute training to introduce the task. The first 5 sessions will be competed at home for 10, 12.5, 15, 17.5, and 20 minutes respectively. The first session may be completed in person during the mindful breathing training to ensure participants understand how to use the training program. Participants are not required to complete all five breathing sessions prior to starting in-person treatment. The next 10 sessions will last 22 minutes and will be done concurrent with active or sham tDCS. The remaining 15 sessions will last 20 minutes and participants will be given the option of completing these either in-person (only if the study team determines that it would be helpful for the participant to complete these sessions in-person) or at home using a personal laptop, tablet, or cell phone. This app will collect data about the quality of focus during MBT and session completion information. See Figure 1.

- **Clinical Assessments:**
  - **MINI:** The Mini-International Neuropsychiatric Interview (MINI) (D. V. Sheehan et al., 1998; D. Sheehan et al., 1997; Lecrubier et al., 1997; Amorim, Lecrubier, Weiller, Hergueta, & Sheehan, 1998; D. V. Sheehan et al., 2010) is a brief structured interview designed to quickly diagnose major DSM-5 Axis I disorders. The mean completion time of the MINI is 26 minutes (12 to 60 minutes). The diagnostic interview will be clinician administered with the participant by trained research staff and overseen by a licensed psychologist. Diagnoses will be based on the MINI

evaluation, case discussion during weekly research team meetings and biweekly group supervisions, and brief report reviewed by a licensed psychologist. Diagnoses will be confirmed by the research team prior to randomization. The MINI depression module will be repeated at the post-tDCS and final assessments to assess changes in depression.

- **MADRS:** Montgomery-Åsberg Depression Rating Scale – self-assessment (MADRS-S) (Bondolfi et al., 2010; Montgomery & Asberg, 1979). As in antidepressant trials, a ≥50% reduction in depression severity will be used to indicate treatment response. Total scores range from 0 to 27. The MADRS-S is strongly correlated with the clinician administered MADRS and has shown to be sensitive to change. Although it has not been validated in adolescents, it has been used in several previous treatment studies of adolescent depression (Berard et al., 2006; von Knorring et al., 2006). A cutoff score of 13 will be used to determine the presence of mild depression (Svanborg & Ekselius, 2003). The MADRS-S may be repeated over the course of the study if clinically indicated.
- **Ruminative Response Scale (RRS)** focuses on thoughts related to depressive symptoms 10/2/2022 10:46:00 PM
- **Freiburg Mindfulness Inventory (FMI)** assesses curious attitude toward the mindfulness experience (Walach, Buchheld, Buttenmüller, Kleinknecht, & Schmidt, 2006)
- **Mindful Attention and Awareness Scale (MAAS)** measures presence or absence of awareness of what is happening in the present (Brown & Ryan, 2003).
- **Difficulties in Emotion Regulation Scale (DERS)** assesses dimensions of emotion regulation (Gratz & Roemer, 2003).
- tDCS Safety Screen: We will administer a question to assess for tDCS contraindications at the baseline visit
- We will use a questionnaire developed to assess side effect of tDCS (Gillick et al., 2018) before and after each tDCS session.
- We will use a questionnaire to assess perceptions of tDCS treatment.

- **Columbia-Suicide Severity Rating Scale (C-SSRS)** assesses the presence and severity of suicidal ideation and behavior (Posner et al., 2011). The C-SSRS will be clinician administered with the participant by trained research staff and overseen by a licensed psychologist. Answers will be reviewed by trained clinical assessors who are supervised by a licensed psychologist. This will be administered at baseline for inclusion criteria, at the interim visit, at the post-tDCS and at final assessment visits to monitor suicidality.
- **Inventory of Depression and Anxiety Symptoms (IDAS)** assesses symptoms of depression and anxiety (Watson et al., 2007).
- **Positive and Negative Affect Schedule (PANAS)** is a mood scale that assesses positive and negative affect (Watson, Anna, & Tellegen, 1987). This will be administered at the beginning of each tDCS session and before and after each MRI and EEG session as a manipulation check and to assess participant mood at the end of the scans to ensure participants are not leaving sessions in a distressed mood. A study investigator will be contacted if the participant endorses a 5 ("Extremely") for being "upset," "guilty," "distressed," or "ashamed" at the end of the session.
- **Dysfunctional Attitude Scale (DAS)** assesses maladaptive beliefs associated with depression (Weissman & Beck, 1978)
- **Action and Acceptance Questionnaire – II** assesses psychological inflexibility and experiential avoidance (Bond et al., 2011).
- **Pittsburgh Sleep Quality Index (PSQI)** assesses sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).
- **Cash Choice Task** is a single-item survey assessing delay of gratification, impulsivity, and motivation (Wulfert et al., 2002).
- Participants will be asked at the beginning of each intervention session to rate the degree of rumination they experienced the day before. At the end of each MRI scan and EEG scan, participants will be asked to rate the degree of rumination they experienced during each scan (e.g.,

resting scan). They will rate the quality of mindfulness, rumination, neutral thinking, and rest, thoughts, and mood after respective EEG, MRI, and tDCS task completion.

- At the end of each intervention session and when they engage in MBT for the EEG and the MRI, participants will be asked to rate how successful they were at engaging in the MBT (see attached).
- Additionally, at the end of the treatment, participants will be asked whether they think they were in the active or sham condition.

- **Behavioral Tasks**
  - **Choice Reaction Time (CRT) Task** is an established thought-probe task in which participants are instructed to engage in a task with low cognitive demand, and periodically queried during the task about 6 dimensions of their thoughts (past/future, self/other, negative/positive) (Hoffmann, Banzhaf, Kanske, Bermpohl, & Singer, 2016).
- **MRI**
  - **Acquisition**: All participants meeting MRI criteria to participate in the study following the clinical interview will be scanned using a 3T Siemens Prisma MR system at CMRR. The MRI scan is optional, and participants may choose to complete other study-related activities without undergoing the MRI scan. The Prisma is a fully-clinical derivation of the Connectome MRI scanner developed by Siemens and UMN at CMRR for the WashU-UMinn Human Connectome Project. All participants will be scanned at baseline, and 1-2 business days following the last day of the tDCS intervention. Participants will complete MRI safety screening. High-resolution T1 and T2 images will be collected. We will also collect a ***field map*** to correct the fMRI data for the geometric distortion caused by magnetic field inhomogeneity. This will take approximately 15 minutes.
  - The research team will utilize the CMRR Center's screening tools and adhere to the screening SOP during enrollment of all research participants in this protocol. The CMRR Center's screening tools and SOP are IRB approved under the CMRR Center's Grand (HSC# 1406M51205) and

information regarding screening procedures is publically available on the CMRR website (CMRR Policies/ Procedures).

- **Resting State and Mindful Breathing Scans**: Whole-brain T2*-weighted functional volumes will be obtained during rest, with eyes open while viewing a fixation cross (12 min) and while practicing mindful breathing (12 min). The duration and the choice of fixation cross as the resting condition are selected to optimize reliability. The mindful breathing scan will only be conducted at the post-intervention scan.
- **Rumination Task**: Participants will be instructed to think about a series of 30 statements (30 seconds each, interspersed by 10 seconds of fixation cross) that are designed to induce either rumination, non-ruminative abstract thinking, and non-ruminative concrete thinking (5 statements of a single category per block, after which participants rate the valence of their thoughts during the block and current feelings) (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010). This task will last approximately 20 minutes.
- **Hariri Task:** Participants will be asked to match angry or sad emotional faces or horizontal and vertical ellipses (Hariri et al., 2002). This task will last approximately 5 minutes.
- If the MRI data collected is not of high enough quality (e.g., due to excessive motion) or if MRI data is not acquired due to technical difficulties, the participant may be invited to repeat the MRI scan and will be compensated for the repeated MRI scan.

- **EEG**
  - We will obtain EEG to quantify band power, alpha asymmetry, entropy, coherence, the late positive potential, and phase-amplitude coupling. EEG data will be collected at baseline, within 1-2 business days following the tDCS intervention, and within 1-2 business days following the 3-weeks of MBT training at home/in-person. Lab staff will place a 32-channel EEG cap on each of the participants for a baseline and post-intervention EEG

(done at the beginning of treatment session 1 and the end of treatment session 10). The leads will be positioned to optimally obtain frontal and midline regions. All participants will undergo 2 3-minute rest EEG scans with their eyes open and closed. Participants will also be asked to describe a negative and neutral thought they have and fixate on this thought for 3 minutes each. Participants will also be asked to practice mindful breathing for 10-minutes at the post-intervention EEG.

- **Flanker task** assesses interference processing. Participants are asked to indicate the direction of a central arrow that is flanked by two arrows on each side that are either pointing in the same direction (congruent) or the opposite direction (incongruent) as the central arrow (Albrecht et al., 2008). This will be administered using Eprime.
- **Go/no-go task** assesses attention and inhibition. Participants see letters and are asked not to respond to one letter and respond to all other letters (Wodka et al., 2007). This will be administered using Eprime.
- If the EEG data collected is not of high enough quality (e.g., due to excessive motion) or if EEG data is not acquired due to technical difficulties, the participant may be invited to repeat the EEG scan and will be compensated for the repeated EEG scan.

- **Electrocardiographic (ECG)**
  - ECG data will be collected to quantify heart rate variability (HRV). ECG data will be collected concurrent with EEG data collection under rest (6 minutes), under rumination and neutral thinking conditions, and mindful breathing conditions (10 minutes). ECG data will be collected during the EEG sessions at baseline, within 1-2 business days following the tDCS intervention, and within 1-2 business days following the 3-weeks of MBT training at home/in-person.
- **Saliva Collection Procedures**
  - We will also be asking participants to provide home saliva samples prior to participating in MBT to measure cortisol levels. We will ask participants to complete eight saliva samples at home, over the course of two days. Four

samples should be collected each day following this schedule: right when waking up, 15 minutes after waking up, and 30 minutes after. The fourth sample is to be taken at bedtime (approximately 10:00PM).

- We will have participants document the times that they collected their at home saliva samples, as well as any medications, caffeine, or events that occurred during the day that could affect their saliva samples via a "Daily Diary"- a type of self-report form for the day. We will compensate participants for their time spent collecting and documenting the saliva samples.
- Participants will be asked to repeat these procedures following the tDCS sessions.
- Saliva samples will be stored without any identifying information in a freezer and sent as a complete batch to Trier, Germany to be analyzed.

5.3 **Study Activities and Schedule:** After an initial phone screen, participants will undergo an initial visit where they will complete a series of assessment and tDCS and MBT visits. At the first visit, participants will undergo a diagnosis assessment (MINI) and behavioral and cognitive assessments and questionnaires (see Table 1). Participants who are not eligible at the time of the baseline assessment but based on their history and responses are expected to meet eligibility criteria at a later point in time (e.g., depression scores as assessed by the MADRS-S are too low) may be re-contacted within 3 months of their baseline assessment to be re-assessed.

Eligible participants will undergo:

1) an EEG/ECG session (visit 2) and an optional MRI scan (visit 3)
2) Participants will be instructed to complete 5 MBT sessions using a personal laptop, tablet, or cell phone at home. Following the in-person training after all the baseline visits are completed, the first MBT session (10 minutes) will completed during the last in-person visit (MRI or EEG visit) to ensure that participants understand how to use the training program.
3) Participants will then be randomly assigned to one of two conditions: active tDCS + MBT and sham tDCS + MBT. Participants will undergo 10 daily sessions of tDCS across two weeks (visits 4-13). Missed sessions may be rescheduled. If there is a month or longer delay between the last baseline assessment visit (e.g.,

initial assessment, EEG, or MRI), participants may be asked to repeat some or all of the baseline research visits and will be paid accordingly.

4) Following the treatment, participants will complete a post-tDCS MRI scan, EEG/ECG session, and assessment visits (visit 14-16) that will include behavioral and cognitive assessments as well as questionnaires.

5) Participants will then complete 15 sessions of MBT either at home or in-person (only if the study team determines that it would be helpful for the participant to complete these sessions in-person) across 3 weeks. After they complete the home-based MBT training, all participants will complete a final EEG/ECG session and final assessment (visits 17 and 18), irrespective of how many at-home/in-person MBT sessions were completed.

In total, this study will require 18 in-person visits and 20 online MBT sessions that can be completed at home (see Figure 1 for an overview of study activities). For participants who complete the 3-weeks of MBT in-person, there will be an addition of 15 in-person visits and a total of 4 online MBT sessions.

Randomization: A randomized block design will be used to assign each subject to undergo either active or sham tDCS in a 1:1 ratio. Randomization will occur after completion of the 5 at-home MBT sessions before their first tDCS + MBT laboratory visit.

5.4 Study Duration: The total duration of research activities for individual participants will involve 18 in-person visits and 20 MBT sessions that can be completed at home or in person (only if the study team determines that it would be helpful for the participant to complete these sessions in-person) . Research-related activities will occur over the duration of up to 10 weeks.

The anticipated duration to complete all study-related activities, include data analysis and publications is 4 years (present to 2022). It is anticipated that year 1 and year 2 will involve data collection and year 3 and 4 will involve data analysis, presentations, and publications.,

5.5 Individually Identifiable Health Information: Study staff may collect individually identifiable health information (e.g., medical history, mental health diagnoses, treatment history, demographic information) during research-related procedures (e.g., diagnostic interview, questionnaires). See attached HIPCO Ancillary Review Form and HIPAA Authorization form. HIPAA Authorization may be obtained on paper or using REDCap. All individually identifiable health information will be stored as described in

the Confidentiality section. Data analyses will be conducted on deidentified data on University computers and laptops and the CMRR servers. Participants will be contacted by phone call and/or email. Email contact with participants will not contain PHI (otherwise, emails will be encrypted).

5.6 Use of radiation*:* The research does not involve the use of radiation.

5.7 Use of Center for Magnetic Resonance Research*:* The study uses the CMRR and follows all CMRR protocols and procedures.

6.0 Data and Specimen Banking

Storage and Access: Study data will be managed by Co-Investigator Michelle Thai. Data will be deidentified using an arbitrary identification number assigned to each participant. Personally-identifiable information, including participant names, birthdates, and contact information, will be maintained in order to contact patients. This personally identifiable information will be kept separately in an encrypted, password-protected file kept separate from study data. A separate file linking identifiers with identification numbers will be stored separately. Phone screen information will only be kept for participants who participate in the consent visit; this will be stored in locked cabinets. Phone screen information from individuals who do not qualify based on the phone screen or who decide not to enroll will be shredded.

Data: Include clinical assessments, self-report measures, behavioral task performance data, technical aspects of neuromodulation sessions, MRI scan data, EEG data, and ECG data. De-identified neuroimaging data will be stored locally on servers supported by the Center for Magnetic Resonance (CMRR). De-identified clinical, EEG, ECG, and behavioral data will be stored in a secure, HIPAA-compliant REDCap database and Box Secure Storage supported by the university of Minnesota or on local servers.

Release/Sharing: Data will only be released in deidentified form to research collaborators.

7.0 Sharing of Results with Participants

7.1 Study results and individual participant results may be shared with participants at their request at the conclusion of the study to preserve study blinding. Individual diagnostic results from the initial visit may be shared with participants at their request. Incidental findings from the MRI scan will be first shared with a trained radiologist after the scan to be assessed for abnormalities. The images will not include identifying information about the patient. If the radiologist recommendation is to

further investigate unusual results from the images, the investigator will contact the participant. Consent and assent may be obtained from parents and participants to share this information with the participant's primary care physician.

8.0 Study Population

8.1 Inclusion Criteria:

- Female, Aged 17-24 years old
- Diagnosis of major depressive disorder (MDD), Dysthymia, or Other specified/Unspecified Depressive Disorder based on MINI.
- Experiencing current symptoms of depression as indexed by a MADRS-S score $\geq$ 13
- Ability to access the MBT online-based application (e.g., on a personal laptop, tablet, or cell phone)
- Fluent in English

8.2 Exclusion Criteria:

- Any participant with a current diagnosis of epilepsy (must be seizure-free during the 2 years prior to consent to be included)
- Any participant with a clinically defined neurological disorder or insult indicating, but not limited to, a condition likely to increase the risk of seizure; such as, space occupying brain lesion; history of cerebrovascular accident; transient ischemic attack within two years; cerebral aneurysm; dementia; brain surgery; history of stroke
- Any participant with an increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure or history of significant head trauma with loss of consciousness for $\geq$ 5 minutes.
- Participants with active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators
- Participants with pre-existing sores or lesions at the site of tDCS or EEG electrode placement
- A hair style that would impede EEG and tDCS electrode contact (e.g., dread locks)
- Any participant with a current or possibility of current pregnancy
- Participants unable to give informed consent.
- Participation in any investigational drug trial within 4 weeks of the baseline visit

- Clinically significant laboratory abnormality or medical condition, that in the opinion of the investigator would hinder the participant in completing the procedures required by the study
- Currently actively suicidal with intent and plan determined by the C-SSRS at the baseline visit.
- A diagnosis of current or recent substance use disorder (within the past 12 months)
- A diagnosis of Schizophrenia, Bipolar Disorder, or Autism
- Unstable psychotherapy (therapy must be for at least 3 months prior to entry into the study, with no anticipation of change in the frequency or treatment focus of the therapeutic sessions over the duration of the study)
- Recent change in dose of antidepressant medication (within 6 weeks prior to entry into the study). This includes all antidepressants and any adjunctive psychotropic medications that are being used to address problems related to mood or anxiety (e.g. antipsychotic medications, mood stabilizers)
- Refusal to cooperate with study procedures

MRI Exclusion Criteria: If participants meet MRI exclusion criteria, they may not participate in the MRI scan but may still choose to participate in other study visits

- Participants with conductive, ferromagnetic, or other magnetic-sensitive metals implanted in the head excluding the mouth that cannot safely be removed. Examples include cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, jewelry and hair barrettes

8.3 Screening: Potential participants (if age 18 or older) or parents of potential participants (if under age 18) will first complete an initial, brief telephone interview with a member of the research team. Prior to the phone screen, potential participants will be informed that they will need to fill out a short online survey to determine their eligibility and so they would need email access during the phone call. During the phone call, the study will be explained to the participant and/or their parent and will include questions about the participant's medical history, their mood, and behavior. A REDCap survey link for the MADRS-S, a depression rating scale, will be emailed to potential participants or to parents of potential participants during the phone call. The phone screen MADRS-S will not include item 9 ("Zest for life") in order to reduce any risk of triggering suicidal thoughts or ideation. The phone screen and MADRS-S will serve to select participants likely to meet inclusion criteria and to screen out

participants who meet exclusionary criteria. The REDCap survey will be linked to a dummy ID that will not be attached to a name. Potential participants/parents will be told that it is recommended that they/their child fill out their responses while the study staff remains on the phone. The survey will take about 3 to 5 minutes to complete. Participants who are interested in continuing with the study and who have a score of 13 or more on the MADRS-S will be eligible to schedule in-person visits. Participants or parents (if under age 18) will provide verbal consent for the screen to be completed. See the attached phone screen. Participants may also be screened using a REDCap survey that the participant (if age 18 or older) or parent will complete.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

☒ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☐ 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
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☐ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☐ None of the above

9.2 Additional Safeguards: Adolescents are the focus of this study because adolescence represents a critical period of brain development and because depression commonly arises in adolescence. Adolescents under the age of 18 will complete written assent and parents will undergo an informed consent process. Consent and assent may also be obtained using REDCap. Participants will be checked for capacity to consent using the UCSD Brief Capacity to Consent (UBACC).

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented: 75 people will be consented and undergo the initial assessment for a minimum target of 30 participants completing the study.

11.0 Local Recruitment Methods

11.1 Recruitment Process: Participants will be recruited through the Research Experience Participation (REP) program in the Psychology Department at the University of Minnesota. Study information will be available on the REP website. Research staff may introduce the study in relevant UMN courses and emails with study information may be distributed in relevant UMN courses. No students from Dr. Klimes-Dougan's courses will be directly recruited by Dr. Klimes-Dougan or her graduate students, including Michelle Thai. Flyers and advertisements will be posted around the University of Minnesota campus, clinics, and hospitals, and surrounding area. Letters and brochures may be sent to local clinicians. Descriptions of the study may also be posted on websites, like ClinicalTrials.gov, StudyFinder, and http://radlab.umn.edu, and the University of Minnesota's Department of Psychiatry website (https://sites.google.com/umn.edu/psychiatryresearch/home/depression/mindfulness-tdcs). We will also post advertisements on social media outlets (e.g., Facebook). Our recruitment materials may include a QR code or a link (https://z.umn.edu/mbttdcs) to our landing page. Upon scanning the QR code or clicking the link, users will be brought to a REDCap survey that describes the study and asks for contact information and birthdate. The REDCap landing page survey will be managed by project coordinators and will be independent from REDCap projects used for data collection. We will recruit participants from the Riverside Behavioral Health Outpatient Clinic using multiple strategies. First, patients in this clinic are invited to participate in a research recruitment registry. Our research staff will use the research registry to contact potential participants who have indicated they are interested in research using the contact information provided in the registry. Secondly, we will use a direct, in-person recruitment approach. Research staff will connect with providers in the clinic to discuss

patients who could be potential participants. For specific patients we will ask the provider to give an IRB-approved study brochure to the patient, along with a general introduction about the study. The research staff will be available to meet with the patient and their parent in the clinic to provide further information about the study; interested families will have the option to meet briefly with a researcher in person to allow face-to-face discussion, or to have the researcher follow up with them by phone. The Behavioral Health Research Recruitment Committee has approved this process.

11.2 Identification of Potential Participants: Potential research participants will self-identify in response to REP postings, flyers and advertisements, brochures, or other recruitment methods as listed above. Following this initial contact, a member of the research staff will screen the potential participant.

11.3 Recruitment Materials: See attached.

11.4 Payment: Participants will be compensated $20 for the initial visit (consent/HIPAA & baseline assessment), $15 for the baseline and post-tDCS, and final EEG/ECG session, $40 for the baseline and post-treatment MRI scan, $5 for completing the home saliva samples and dairy at baseline and post-tDCS, $10 for the post-tDCS assessment visit, $15 for the final assessment, and $5 for a week 1 assessment for a maximum total of $185. If participants have to repeat a visit for any reason (e.g., poor data quality), they will be compensated accordingly for any repeated visits. Participants will not be compensated for intervention visits. If participants complete all in-person visits of the study, they will be entered into a $50 raffle. A winner will be selected each time 3 participants complete the study. Participants may also choose to receive course extra credit as partial or total payment instead of cash (Research Experience Points) for their participation in this study (each ½ hour of assessment is worth 1 REP point). Cash payments will be made via institutional standard Greenphire ClinCard, a prepaid debit card that we can continue to load with money as the participants complete studies. In the case of early termination, the participant will receive partial payment. Parking passes will be provided when available.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances: Participants who have MRI or tDCS contraindications or participants who experience severe adverse events (e.g., seizure, suicide attempt, acute suicidality with plan of intent) or any unanticipated problem where the principal investigator feels it would be unsafe for the participant to continue may be withdrawn from certain

study activities or withdrawn from the entire study without their consent. In the case of other serious adverse events, the principal investigator or research staff will decide with the participant whether it would be safe or prudent for the participant to continue in the study based on their situation. Participants who experience mild to moderate adverse events (e.g., discomfort or other side effects like headache) will be allowed to discontinue at any point if they choose. Participants withdrawn from study participation due to an adverse event may be replaced to reach intended sample size. Participants will be withdrawn from the study if they appear to be unduly stressed.

12.2 Withdrawal Procedures: Participants may withdraw from the study at any time and study staff can withdraw a participant at any time if there are any serious adverse events. In the event of participant withdrawal, research staff may ask participants some questions about the study and/or to participate in some procedures or tests to help participants leave the study safely and/or to collect more information for the study. Information already collected prior to participant withdrawal will still be used. Participants who withdraw or do not qualify for the study after the phone screen may choose to receive referrals for psychological assessments.

12.3 Termination Procedures: In the case of a serious adverse event, research-related activities may be terminated immediately and appropriate treatment will be provide to the participant (e.g., first aid, emergency treatment, and follow-up care as needed). Care for such injuries will be billed in the ordinary manner to the participant or the participant's insurance company. Following termination, research staff may ask participants some questions about the study and/or to participate in some procedures or tests to help participants leave the study safely and/or to collect more information for the study. Information already collected prior to participant withdrawal will still be used.

13.0 Risks to Participants

13.1 Foreseeable Risks:

Transcranial Direct Current Stimulation (tDCS): tDCS has shown to be a safe brain stimulation technique. Adverse events are rare with tDCS, and serious side effects have not been found following tDCS application. tDCS has been safely applied in psychiatry populations and in child and adolescent populations. The most common side effects are mild, including itching or discomfort under the electrode at the beginning of administration, headache, fatigue, dizziness, and nausea, which typically resolve at the end of stimulation. Our stimulation parameters will be within

established safety guidelines (Brunoni et al., 2011). There have been reported incidents of treatment-emergent hypomania and mania in unipolar and bipolar depression patients following tCS (Matsumoto et al., 2017). As such, we will rule out participants with bipolar disorder and will use the MINI to screen out participants with symptoms of mania and to monitor participants for any change in manic symptoms over the course of the study. These risks will be described to the participants during the consent process and participants may choose whether to participate or not. Participants may decide to withdraw from the study at any point.

MRI Scanning: MRI scanning will be conducted using a 3 Tesla Siemens Prisma MRI machine. The magnet in the scanner may cause electronic devices like watches to malfunction, and some metal objects can be pulled into the scanner. Participants will be screened prior to the scan to make sure they have nothing in their body which could be magnetic or affected by the magnetic field of the scanner. Participants will be asked to change into scrubs to ensure they have no metal on their person.

It may be uncomfortable lying still in the scanner for the amount of time required. The participant may experience some stiffness and soreness in the muscles from being still. To make participants as comfortable as possible, we will provide soft pads to help support the next, back, and legs.

The scanner itself makes a lot of noise while it is running. This can be uncomfortable and may affect the participant's hearing. Participants will be asked to wear ear plugs which will significantly reduce the amount of noise. Participants will also be wearing headphones in addition to the earplugs to allow them to hear the investigators and listen to music.

Some people may become uncomfortable in the scanner because they are not comfortable being in enclosed spaces. We will screen for claustrophobia before we bring the participant to the scan center. They will have the option of using a mock scanner prior to going into the scanner to assess their level of comfort. They will not be required to participate in the scan or continue the scan if they are uncomfortable.

If a participant has a positive pregnancy test, they will not be scanned. We will not inform the participant's parent of the results unless we feel the pregnancy would cause serious problems for the participant. Adult participants will be notified of their pregnancy test results, if positive. We may also obtain a false positive with the urine toxicology screen or pregnancy test. We will inform participants of the risk of obtaining a false positive and encourage them to follow up with their primary care

physician. If the toxicology screen is positive, results will be noted on the MRI CRF form and the participant will continue on with the MRI scan.

There is a chance we might find something abnormal when we look at the images of the participant's brain. We will send all images to a trained radiologist after the scan so they can be assessed for abnormalities. These images will not have any identifying information about the patient. If the radiologist recommendation is to further investigate the unusual results of the pictures, the investigator will contact the participant. The participant is responsible for further evaluation and follow-up in response to any MRI incidental findings.

Clinical Assessments: Participants may also experience mild stress, discomfort, or fatigue during the clinical assessment or while completing self-report or behavioral assessments. The assessments may involve questions about feelings, past experiences, and family history. Participants are encouraged to only share what they feel comfortable with and will not be induced to discuss anything that will make them too uncomfortable. The results of this study may be published and/or presented, but identifying information about participants will not be released unless required by Federal Law.

Behavioral Tasks: These tasks may be tiring. Some tasks may ask participants to think about negative thoughts or involve negative stimuli that may cause mild stress, discomfort, or fatigue.

Suicide/Self-Injury Risk: The population being researched in this study has a higher risk for suicidal ideation, suicide attempts, and serious injury due to depression. The research team will monitor depression (MADRS-S), suicidal ideation (C-SSRS), and self-harm behaviors (C-SSRS) at baseline, midway through the intervention assessments at the interim assessment, and post-intervention. Answers will be reviewed by the clinical assessor who is trained and supervised by a licensed psychologist. Participants who indicate suicidal ideation or significantly increased self-harm behaviors based on the C-SSRS will be asked to meet with one of the investigators of the study to assess risk.

Participants with suicidal ideation with no plan or intent who agree to a safety plan (either developed with the investigator or a pre-existing safety plan) will be allowed to continue in the study. The investigator will inform parents of the discussion and safety plan (if applicable).

Participants with severe self-harm (requiring stitches or

hospitalization), suicidal ideation with intent, or those who cannot or will not agree to a safety plan will be escorted to the Emergency Room located 1 floor below the Ambulatory Research Center (ARC) in the West Building of the Fairview Riverside Hospital.

EEG/ECG: Mild skin irritation may occur at the electrode placement site (e.g., redness).

13.2 **Reproduction Risks**: The effects of tDCS, EEG and MRI scans on the unborn fetus are not known, and participating females should not be pregnant. Pregnant participants will not undergo the stimulation, EEG or MRI scans. Participants and parents if participants are under the age of 18 will be told that the participant should not undergo study procedures if there is a pregnancy or possibility of a pregnancy. Participants will be informed about pregnancy risks during the consent process and will be encouraged to use a reliable form of birth control. Participants will take a mandatory pregnancy test before each MRI scan. If the urine pregnancy test is positive, the participant will not undergo the MRI scan or any tDCS sessions. If the pregnancy test is positive at the post-tDCS session, participants will not undergo the MRI scan but may choose to complete the 3-week at-home / in-person MBT training and clinical assessments. Participants will be asked to inform study staff at any other point of the MRI and tDCS visits if they have any concerns that they may be pregnant. Additional pregnancy tests can be offered at any point during other visits. Pregnancy and toxicology screens will be conducted at the CMRR by research staff. Participants will provide urine samples and we will use a pregnancy test strip (Clarity Diagnostics; Manufacturer # DTG-HCG100) to test for pregnancy and an Integrated E-Z Split Key Cup Urine Drug Screening with Adulteration for 5 Drugs for the toxicology screen (Manufacturer # DUD157023019). Both of these tests have a CLIA waiver (see attached materials for more details on the tests and for CLIA waiver documentation). These tests will be purchased through UMarket. Results will be recorded on CRF forms for MRI scanner sessions. Urine will be disposed of by being flushed down the toilet and used testing materials will be disposed of in the garbage.

13.3 **Risks to Others**: There are no anticipated risks to others who are not participants.

13.4 **Email Risks:** Participants will be able to opt in to communicating with study staff via unencrypted email to arrange their appointments and receive study instructions. There are risks associated with email communication, and these risks increase when the emails are sent without an encryption

service. Risks of sending or receiving emails without encryption include, but are not limited to:

- Others can intercept messages.
- If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The internet or cell-phone provider may also have the right to save and read email messages.
- A copy of the messages may be saved on a device or computer system, even if it is deleted.
- If an email address is not typed correctly, it can be sent to the wrong person.
- Emails can spread computer viruses.
- Others may be able to access messages on devices that were lost, stolen, or thrown away.
- If a user changes emails without notifying study staff, they may miss communications.

13.5 **Text Message Risk:** Participants will be able to opt in to communicating with stud staff via text message to arrange their appointments and receive study instructions. There are risks associated with communication via text message. Risks of sending or receiving text messages include, but are not limited to:

- Others can intercept messages
- Text messages may be viewed by University of Minnesota staff depending on the nature and timing of said messages, and may be monitored by the University to ensure appropriate use.
- If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The cell-phone provider may also have the right to save and read text messages.

14.0 Potential Benefits to Participants

14.1 Potential Benefits: It is possible that a participant may have an improvement in depressive symptoms from this treatment but there are no anticipated direct benefits to participation in this research project. The contribution to general knowledge on the research topic may be a societal benefit.

15.0 Statistical Considerations

15.1 Data Analysis Plan:

Effectiveness analyses: Repeated measures ANOVAs will examine the effect of condition (active tDCS + MBT and sham tDCS + MBT) on pre- and post-intervention MADRS scores, rumination scores, mindfulness scores, and emotion regulation scores. EEG outcomes will include alpha asymmetry, LPP amplitude, coherence, and entropy at rest, during rumination, during mindfulness, and during emotion processing. ECG outcomes will include heartrate variability. MRI outcomes will include DLPFC-DMN, DLPFC-limbic system, and within-DMN RSFC, as well as DLPFC, limbic, and DMN activation to rumination and emotional processing tasks. Additional analyses will be conducted to assess whether changes in emotion regulation, mindfulness, and rumination moderate changes in depression symptoms. Regression analyses will be run on baseline measures to identify predictive biomarkers of MBT/tDCS treatment response. Correlation analyses will be conducted between the degree of change in clinical scores (depression symptoms, rumination, emotion regulation) with degree of change in neuroimaging and mindfulness indices.

Neuroimaging data analysis: We will optimize components from the HCP minimum processing pipeline to fit our imaging protocols and will include gradient non-linearity distortion corrections, distortion correction caused by magnetic field inhomogeneity, co-registration of functional and anatomical images, non-linear registration to MNI template brain, intensity bias corrections, highpass filtering, re-sampling of the data onto the cortical mesh (surface analyses), and denoising of the data using ICA-fix (Griffanti et al., 2014). Network Analysis. We will quantify RSFC within fronto-limbic and default mode networks as described in our prior work.

EEG: *Change in alpha band asymmetry*: Eyes-open and eyes-closed resting-state EEG alpha power (8-13 Hz) will be calculated for left and right prefrontal electrodes using a fast-fourier transform approach. We will define the alpha asymmetry index (AAI) as the ratio of the left prefrontal alpha power to the right prefrontal alpha power. A similar AAI analysis will be carried out for the rumination EEG data. *Coherence Analysis*: We will investigate resting-state EEG correlates of DMN functional connectivity by computing the coherence between posterior and prefrontal cortical regions. In order to specifically assess alpha and beta band coherence changes within the DMN, we will choose channel Pz to represent the precuneus/posterior cingulate and channel Fz to represent the medial prefrontal cortex/anterior cingulate. We will further assess changes in coherence between the DMN (channels Fz, Pz) and the DLPFC (channels F3, F4). *P300 Amplitude.* P300 ERP responses will be measured during the

Go/No-Go and Flanker tasks and will be compared across different types of trials (e.g., go versus no-go trials and congruent versus incongruent trials). *ERN Amplitude.* Error Related Negativity (ERN) ERP responses will be measured during the Go/No-Go and Flanker tasks and will be compared across different types of trials (e.g., trials after correct versus incorrect responses).

ECG: Estimates of HRV will be calculated based on recommendations by an international committee (Malik et al., 1996). Power spectral analyses will be used to estimate contributions from sympathetic (low frequency) and parasympathetic (high frequency) components.

Number of study visits completed may be used as a covariate in analyses.

15.2 Power Analysis:

Since we do not have pilot data with adolescents using either of these interventions, we were unable to conduct a power analysis to calculate an appropriate sample size. Budget and time constraints necessitate a relatively small sample size. While some studies in the literature have reported significant effects using similarly small samples, we cannot be certain that the study is powered appropriately to confirm or refute our hypotheses. Therefore, we have framed the project with a primary goal of establishing feasibility (our ability to recruit, adolescents' acceptance of randomization, adolescents' tolerability of the interventions) and of collecting data that will allow a power calculation to determine the sample size necessary for the federal grant to follow this work.

15.3 Statistical Analysis: A p-value of .05 will be used to determine significance for behavioral measures and a p-value of .005 will be used to determine significance for neuroimaging measures. Paired t-tests will be used to compare baseline versus post-tDCS and post-MBT intervention for both intervention groups for biological, clinical, and behavioral measures. Between-group t-tests will be conducted on the side-effects to examine group differences in prevalence of side effects. Feasibility will be determined by looking at descriptive statistics about enrollment and eligibility of people that express interest in the study and enroll as well as retention of enrolled participants. Correlation analysis will be conducted to assess how changes in clinical and behavioral relate to biological measures following intervention. Mixed repeated measures ANOVAs will test our hypothesis that the active tDCS group will show greater change than the sham tDCS group with condition (active or sham) as the between participant measures; within-participant measures will include behavioral,

clinical, and biological indices. Regression models will also be conducted on baseline measures (e.g., RSFC, task activation, trait mindfulness and emotion regulation) to assess biomarkers of treatment response. Behavioral indices include performance on the GoGreen, Middle Fish, and CRT. Biological indices include EEG (e.g., AAI, coherence, entropy at rest and during mindful breathing, as well as LPP amplitude during the Emotion Regulation Task, P300 and ERN during the GoGreen and Middle Fish tasks), ECG data (HRV), and MRI data (e.g., DMN, DLPFC, and Limbic activation to Hariri and Rumination Tasks and functional connectivity at rest and during mindful breathing). Clinical measures include depression symptoms, rumination scores, and mindfulness scores.

15.4 Data Integrity: Outlier analyses will be conducted and data values that exceed three standard deviations will be removed or winsorized. Neuroimaging data will also be examined for excessive motion. Data will be checked by Michelle Thai.

16.0 Confidentiality

Data Security:

16.1 All participants will be identified by a research identification number. All research data will be de-identified using ID numbers. Hard copies of documents will be stored in a locked cabinet. The participants name will be retained on consent and assent forms and these forms will be stored in a separate, locked cabinet. Both cabinets will only be accessible to the research team on the protocol. Behavioral and clinical data will be entered electronically using the ID numbers onto the HIPAA-compliant REDCap database that is managed by the University of Minnesota. Clinical data and questionnaires may be completed using REDCap or paper documents. Raw behavioral and EEG/ECG data will be stored on the HIPAA-compliant Box Secure Storage. Data may also be stored on password protected databases and files on AHC-IS servers (cnc2.med.umn.edu). De-identified neuroimaging data will be stored locally on servers supported by the Center for Magnetic Resonance (CMRR). Access to these electronic directories will be limited to the research staff. Copies of the consent form and other research study information will not be included in their medical, employment, or educational records to maintain confidentiality.

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

17.1 Data Integrity Monitoring: The principal investigator and/or co-investigator 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. Data will be stored in de-identified format. Study staff will monitor side effects forms and the CSSR-S for safety upon collection. Confidentiality may be broken in situations such as active suicidal ideation or other situations required by law.

17.2 Data Safety Monitoring. During all stimulation sessions, a member of the research staff will constantly monitor participants to ensure comfort and safety. A licensed clinical psychologist (Dr. Bonnie Klimes-Dougan) or a supervising psychiatrist (Dr. Kathryn Cullen) will be contacted in the case of a clinical emergency to determine whether intervention is necessary. Emergency incidents will be documented and reported to the IRB. Documentation will include a description of the incident, action taken, and individuals involved. A 0 (*No adverse event or within normal limits*) to 5 (*Fatal adverse event*) rating scale will be used to evaluate the severity of adverse events and a 0 (*Unrelated*: *The adverse event is clearly not related to investigational agent*(s)) to 5 (*Definite*: *The adverse event is clearly related to investigational agent(s))* will be used to determine the relationship between the adverse event and the proposed intervention. Any events rated 2 or higher will result in a notification to the supervising psychologist and events rated 3 or higher may warrant breaking the blind. Intervention will be determined by the supervising psychologist. Examples of incidents requiring immediate intervention and discontinuation from the study include active suicidal or homicidal ideation with plan, current self-harm requiring medical intervention, and a seizure. Data and safety monitoring will be discussed during weekly staff meetings with members of the research team to ensure that all adverse events are reported in compliance with the protocol, Good Clinical Practice, and other applicable regulatory requirements.

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy:

The records of this study will be kept private. In any publications or presentations, participants will not be identified by name or any other identifiable information. Any records, results, or publications related to the study will remain as confidential as possible and will be disclosed only with participant permission. Each participant will be provided with a unique numerical identifier at the beginning of the study in order to protect their actual identification and maintain complete confidentiality.

Mental health professionals are mandated reporters, and as such, are obliged to report alleged or probable abuse, as well as known abuse. Any

concerns about maltreatment will be reported in accordance to the law. If research staff learn that someone (including the participant) is in danger of serious harm), research staff may need to obtain outside assistance.

Only research staff associated with this study and authorized personnel will have access to the records. Research records will be kept in a locked file. Any publications from this study will not include any information that can identify participants. Data will be stored on a password protected electronic database.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include any information that can identify participants. At most, this website will include a summary of the results.

18.2 Access to Participants*:* The research team will not access any medical records or other sources of private information outside of information without the participants written consent. HIPAA Authorization will be obtained for all participants.

19.0 Compensation for Research-Related Injury

19.1 Compensation for Research-Related Injury: In the event that research-related activities result in an injury, treatment will be provided to the participant (e.g., first aid, emergency treatment, and follow-up care as needed). Care for such injuries will be billed in the ordinary manner to the participant or the participant's insurance company.

19.2 Contract Language:

"In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury let the study doctor or study staff know right away. You do not give up any of your legal rights by signing this form. Be aware that your health-care payer/insurer might not cover the costs of study-related injuries or illnesses."

20.0 Consent Process

20.1 Consent Process (when consent will be obtained): Consenting will take place in a private office in the Department of Psychology, or the Ambulatory Research Center (ARC), or at the Center for Neurobehavioral Development, or at the Department of Psychiatry (Park Plaza) at the University of Minnesota. Consent will be documented in writing or electronically through REDCap. For participants 18 years-old or over, one of the members of the research staff will review the study procedures, risks and benefits as described in the consent form

with the potential participant. Participants will be given time to read the materials and ask any questions they have about the study. The research staff member will pose a set of questions to the participant to ensure that they fully understand the procedures, risks, and voluntary nature of the study. The participant and research staff will sign the document to complete the consent process. Research staff will have completed human participants research training, and this information will be maintained on file. For participants under the age of 18, one of the members of the research staff will review the study procedures, risks and benefits as described in the consent form with the parent/guardian and in the assent form with the adolescent. The families will be given time to read the materials and ask any questions they have about the study.

20.2 Waiver or Alteration of Consent Process (when consent will not be obtained): We are requesting a waiver of documentation of the consent for only the phone screen portion of the study. Participants would be consented prior to any other study activities. We need to collect sensitive information from the parent/guardian prior to the first visit and documented consent process in order to determine basic eligibility. All parents will be read the attached script and asked to verbally consent to the phone screen only. If participants are screened using REDCap, they will be presented the same script on the survey and indicate their consent to the screen on the survey.

20.3 Non-English Speaking Participants: N/A

20.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): Participants in this study may include minors (under 18 years of age) at the time of enrollment. Parental consent (from at least one parent) and child assent will be obtained in applicable cases at enrollment and documented with a signed form.

20.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

20.6 Adults Unable to Consent: N/A

21.0 Setting

21.1 Research Sites: Potential participants will be recruited by flyers and advertisements posted around the University of Minnesota campus and surrounding local areas, including local clinics that allow research postings, and through the REP system. Clinical and behavioral assessments may be completed in the Department of Psychology, the Ambulatory Research Center, or at the Center for Neurobehavioral Development, or at the Department of Psychiatry

(Park Plaza) at the University of Minnesota. Stimulation and EEG/ECG visits will take place on the University of Minnesota, Twin Cities Campus, at 717 Delaware St. MRI scanning will take place at the Center for Magnetic Resonance Research (CMRR).

21.2 International Research: N/A

22.0 Multi-Site Research

N/A

23.0 Resources Available

23.1 Resources Available: We will recruit participants from the University of Minnesota's undergraduate population of over 30,000 students (21% of whom have a lifetime diagnosis of depression and 8% of whom have been diagnosed with depression in the last year; 2015 College Student Health Survey Report: Health Related Behaviors, University of Minnesota—Twin Cities Students). We will have access to tDCS equipment and MRI scanners through the Neuromodulation laboratory and the Center of Magnetic Resonance Research on campus, it is feasible that we will be able to reach recruitment targets. Research staff will meet on a weekly basis to discuss study progress. Approximately 20 hours/week of Michelle Thai's time will be dedicated to this study, and more time will be dedicated to this study as needed. Michelle Thai will coordinate day-to-day logistics of the study with research staff and investigators.

Research-related activities will be conducted in dedicated lab space within the Departments of Psychology and Psychiatry. Dr. Cullen has office space in Psychiatry. Dr. Klimes-Dougan has laboratory space on the 3rd floor of Elliott Hall. Michelle Thai and Dr. Klimes-Dougan have office space on the 4th floor of Elliott Hall.

Dr. Cullen has access to office space within the Ambulatory Research Center. This research space will be used to conduct consent, clinical and behavioral assessments.

MRI scans will be conducted at the Center for Magnetic Resonance Research (CMRR). The CMRR houses state of the art MR instrumentation with experts in imaging physics, engineering, and signal processing. The interdisciplinary experts and advanced MR technology will ensure quality imaging data to be collected.

tDCS will be applied at the Neuromodulation Laboratory. The Neuromodulation Laboratory was established to support research using noninvasive neuromodulation The Neuromodulation Laboratory has state

of the art equipment, including electroencephalography (EEG) equipment and the Neuroelectrics StarStim transcranial current stimulation system.

Data may be stored and analyzed using the Minnesota Supercomputing Institute (MSI). MSI has software, hardware, and experts to support the proposed neuroimaging analyses.

Research related activities may also be conducted at the Center for Neurobehavioral Development (CNBD). The CNBD is a research center that supports research on brain development in relation to cognitive and behavioral development. The CNBD has research space as well as brain imaging equipment, tDCS equipment, and software. EEG and tDCS sessions may also be conducted at the CNBD.

Dr. Cullen is a licensed child and adolescent psychiatrist with expertise in adolescent depression. Dr. Klimes-Dougan is a licensed psychologist who runs a practicum for clinical psychology trainees and will oversee clinical assessments and training in clinical assessments. Either Dr. Cullen or Klimes-Dougan will be available to provide consult in the case of any adverse events. All study staff will complete appropriate IRB and institutional trainings.

24.0 References

Albrecht, B., Brandeis, D., Uebel, H., Heinrich, H., Mueller, U. C., Hasselhorn, M., … Banaschewski, T. (2008). Action Monitoring in Boys With Attention-Deficit/Hyperactivity Disorder, Their Nonaffected Siblings, and Normal Control Subjects: Evidence for an Endophenotype. *Biological Psychiatry*, *64*(7), 615–625. https://doi.org/10.1016/j.biopsych.2007.12.016

Amorim, P., Lecrubier, Y., Weiller, E., Hergueta, T., & Sheehan, D. (1998). DSM-IH-R Psychotic Disorders: procedural validity of the Mini International Neuropsychiatric Interview (MINI). Concordance and causes for discordance with the CIDI. *European Psychiatry*, *13*(1), 26–34. https://doi.org/10.1016/S0924-9338(97)86748-X

Bond, F. W., Hayes, S. C., Baer, R. A., Carpenter, K. M., Guenole, N., Orcutt, H. K., … Zettle, R. D. (2011). Preliminary Psychometric Properties of the Acceptance and Action Questionnaire–II: A Revised Measure of Psychological Inflexibility and Experiential Avoidance. *Behavior Therapy*, *42*(4), 676–688. https://doi.org/10.1016/j.beth.2011.03.007

Bondolfi, G., Jermann, F., Rouget, B. W., Gex-Fabry, M., McQuillan, A., Dupont-Willemin, A., … Nguyen, C. (2010). Self- and clinician-rated Montgomery–Åsberg Depression Rating Scale: Evaluation in clinical practice. *Journal of Affective Disorders*, *121*(3), 268–272. https://doi.org/10.1016/j.jad.2009.06.037

Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: Mindfulness and its role in psychological well-being. *Journal of Personality and Social Psychology*, *84*(4), 822–848. https://doi.org/10.1037/0022-3514.84.4.822

Brunoni, A. R., Boggio, P. S., De Raedt, R., Benseñor, I. M., Lotufo, P. A., Namur, V., … Vanderhasselt, M. . (2014). Cognitive control therapy and transcranial direct current stimulation for depression: A randomized, double-blinded, controlled trial. *Journal of Affective Disorders*, *162*, 43–49. https://doi.org/10.1016/j.jad.2014.03.026

Burke, H. M., Davis, M. C., Otte, C., & Mohr, D. C. (2005). Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology*, *30*(9), 846–856. https://doi.org/10.1016/j.psyneuen.2005.02.010

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213.

Cooney, R. E., Joormann, J., Eugène, F., Dennis, E. L., & Gotlib, I. H. (2010). Neural correlates of rumination in depression. *Cognitive, Affective, & Behavioral Neuroscience*, *10*(4), 470–478. https://doi.org/10.3758/CABN.10.4.470

Cullen, K. R., Jasberg, S., Nelson, B., Klimes-Dougan, B., Lim, K. O., & Croarkin, P. E. (2016). Seizure Induced by Deep Transcranial Magnetic Stimulation in an Adolescent with Depression. *Journal of Child and Adolescent Psychopharmacology*, *26*(7), 637–641. https://doi.org/10.1089/cap.2016.0070

Cullen, K. R., Westlund, M. K., Klimes-Dougan, B., Mueller, B. A., Houri, A., Eberly, L. E., & Lim, K. O. (2014). Abnormal Amygdala Resting-State Functional Connectivity in Adolescent Depression. *JAMA Psychiatry*, *71*(10), 1138–1147. https://doi.org/10.1001/jamapsychiatry.2014.1087

Disner, S. G., Beevers, C. G., Haigh, E. A. P., & Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience*, *12*(8), 467–477. https://doi.org/10.1038/nrn3027

Drevets, W. C. (2006). Neuroimaging Abnormalities in the Amygdala in Mood Disorders. *Annals of the New York Academy of Sciences*, *985*(1), 420–444. https://doi.org/10.1111/j.1749-6632.2003.tb07098.x

Friedrich, M. J. (2017). Depression Is the Leading Cause of Disability Around the World. *JAMA*, *317*(15), 1517. https://doi.org/10.1001/jama.2017.3826

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning. *Neuron*, *66*(2), 198–204. https://doi.org/10.1016/j.neuron.2010.03.035

Gillick, B. T., Gordon, A. M., Feyma, T., Krach, L. E., Carmel, J., Rich, T. L., … Friel, K. (2018). Non-Invasive Brain Stimulation in Children With Unilateral Cerebral Palsy: A Protocol and Risk Mitigation Guide. *Frontiers in Pediatrics*, *6*. https://doi.org/10.3389/fped.2018.00056

Goldin, P. R., & Gross, J. J. (2010). Effects of Mindfulness-Based Stress Reduction (MBSR) on Emotion Regulation in Social Anxiety Disorder. *Emotion (Washington, D.C.)*, *10*(1), 83–91. https://doi.org/10.1037/a0018441

Gratz, K. L., & Roemer, L. (2003). Multidimensional Assessment of Emotion Regulation and Dysregulation: Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation Scale. *Journal of Psychopathology and Behavioral Assessment*, 15.

Griffanti, L., Salimi-Khorshidi, G., Beckmann, C. F., Auerbach, E. J., Douaud, G., Sexton, C. E., … Smith, S. M. (2014). ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. *NeuroImage*, *95*, 232–247. https://doi.org/10.1016/j.neuroimage.2014.03.034

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., … Weinberger, D. R. (2002). Serotonin Transporter Genetic Variation and the Response of the Human Amygdala. *Science*, *297*(5580), 400–403.

Hasenkamp, W., & Barsalou, L. W. (2012). Effects of Meditation Experience on Functional Connectivity of Distributed Brain Networks. *Frontiers in Human Neuroscience*, *6*. https://doi.org/10.3389/fnhum.2012.00038

Hoffmann, F., Banzhaf, C., Kanske, P., Bermpohl, F., & Singer, T. (2016). Where the depressed mind wanders: Self-generated thought patterns as assessed through experience sampling as a state marker of depression. *Journal of Affective Disorders*, *198*, 127–134. https://doi.org/10.1016/j.jad.2016.03.005

Hölzel, B. K., Hoge, E. A., Greve, D. N., Gard, T., Creswell, J. D., Brown, K. W., … Lazar, S. W. (2013). Neural mechanisms of symptom improvements in generalized anxiety disorder following mindfulness training. *NeuroImage: Clinical*, *2*, 448–458. https://doi.org/10.1016/j.nicl.2013.03.011

Ironside, M., Browning, M., Ansari, T., Harvey, C., Sekyi-Djan, M., Bishop, S., … O'Shea, J. (2017). Prefrontal cortex regulates amygdala response to threat in trait anxiety. *BioRxiv*, 19.

Jang, J. H., Jung, W. H., Kang, D.-H., Byun, M. S., Kwon, S. J., Choi, C.-H., & Kwon, J. S. (2011). Increased default mode network connectivity associated with meditation. *Neuroscience Letters*, *487*(3), 358–362. https://doi.org/10.1016/j.neulet.2010.10.056

Kalu, U. G., Sexton, C. E., Loo, C. K., & Ebmeier, K. P. (2012). Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. *Psychological Medicine*, *42*(09), 1791–1800. https://doi.org/10.1017/S0033291711003059

Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., … Padberg, F. (2011). Prefrontal Transcranial Direct Current Stimulation Changes Connectivity of Resting-State Networks during fMRI. *Journal of Neuroscience*, *31*(43), 15284–15293. https://doi.org/10.1523/JNEUROSCI.0542-11.2011

Keng, S.-L., Smoski, M. J., & Robins, C. J. (2011). Effects of mindfulness on psychological health: A review of empirical studies. *Clinical Psychology Review*, *31*(6), 1041–1056. https://doi.org/10.1016/j.cpr.2011.04.006

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593. https://doi.org/10.1001/archpsyc.62.6.593

King, A. P., Block, S. R., Sripada, R. K., Rauch, S., Giardino, N., Favorite, T., … Liberzon, I. (2016). ALTERED DEFAULT MODE NETWORK (DMN) RESTING STATE FUNCTIONAL CONNECTIVITY FOLLOWING A MINDFULNESS-BASED EXPOSURE THERAPY FOR POSTTRAUMATIC STRESS DISORDER (PTSD) IN COMBAT VETERANS OF AFGHANISTAN AND IRAQ: 2015 Donald F Klein Investigator Award Finalist: Mindfulness-Based Exposure Therapy and Resting DMN Connectivity. *Depression and Anxiety*, *33*(4), 289–299. https://doi.org/10.1002/da.22481

Koenigs, M., & Grafman, J. (2009). The functional neuroanatomy of depression: Distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural Brain Research*, *201*(2), 239–243. https://doi.org/10.1016/j.bbr.2009.03.004

Krishnan, C., Santos, L., Peterson, M. D., & Ehinger, M. (2015). Safety of Noninvasive Brain Stimulation in Children and Adolescents. *Brain Stimulation*, *8*(1), 76–87. https://doi.org/10.1016/j.brs.2014.10.012

Lang, N., Siebner, H. R., Ward, N. S., Lee, L., Nitsche, M. A., Paulus, W., … Frackowiak, R. S. (2005). How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *European Journal of Neuroscience*, *22*(2), 495–504. https://doi.org/10.1111/j.1460-9568.2005.04233.x

Lecrubier, Y., Sheehan, D., Weiller, E., Amorim, P., Bonora, I., Harnett Sheehan, K., … Dunbar, G. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *European Psychiatry*, *12*(5), 224–231. https://doi.org/10.1016/S0924-9338(97)83296-8

Lu, Q., Li, H., Luo, G., Wang, Y., Tang, H., Han, L., & Yao, Z. (2012). Impaired prefrontal–amygdala effective connectivity is responsible for the dysfunction of emotion process in major depressive disorder: A dynamic causal modeling study on MEG. *Neuroscience Letters*, *523*(2), 125–130. https://doi.org/10.1016/j.neulet.2012.06.058

Luciana, M. (2013). Adolescent brain development in normality and psychopathology. *Development and Psychopathology*, *25*(4pt2), 1325–1345. https://doi.org/10.1017/S0954579413000643

Malik, M., Bigger, J. T., Camm, A. J., Kleiger, R. E., Malliani, A., Moss, A. J., & Schwartz, P. J. (1996). Heart rate variabilityStandards of measurement, physiological interpretation, and clinical use. *European Heart Journal*, *17*(3), 354–381. https://doi.org/10.1093/oxfordjournals.eurheartj.a014868

March, J., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., … Treatment for Adolescents With Depression Study (TADS) Team. (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*, *292*(7), 807–820. https://doi.org/10.1001/jama.292.7.807

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry*, *134*(4), 382–389. https://doi.org/10.1192/bjp.134.4.382

Nolen-Hoeksema, S., Morrow, J., & Fredrickson, B. L. (1993). Response styles and the duration of episodes of depressed mood. *Journal of Abnormal Psychology*, *102*(1), 20–28. https://doi.org/10.1037//0021-843X.102.1.20

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., … Mann, J. J. (2011). The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. *The American Journal of Psychiatry*, *168*(12), 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704

Romei, V., Thut, G., & Silvanto, J. (2016). Information-Based Approaches of Noninvasive Transcranial Brain Stimulation. *Trends in Neurosciences*, *39*(11), 782–795. https://doi.org/10.1016/j.tins.2016.09.001

Segrave, R. A., Arnold, S., Hoy, K., & Fitzgerald, P. B. (2014). Concurrent Cognitive Control Training Augments the Antidepressant Efficacy of tDCS: A Pilot Study. *Brain Stimulation*, *7*(2), 325–331. https://doi.org/10.1016/j.brs.2013.12.008

Sheehan, D., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., … Dunbar, G. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry*, *12*(5), 232–241. https://doi.org/10.1016/S0924-9338(97)83297-X

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59*(suppl 20), 22–33.

Sheehan, D. V., Sheehan, K. H., Shytle, R. D., Janavs, J., Bannon, Y., Rogers, J. E., … Wilkinson, B. (2010). Reliability and Validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). *The Journal of Clinical Psychiatry*, *71*(3), 313–326. https://doi.org/10.4088/JCP.09m05305whi

Svanborg, P., & Ekselius, L. (2003). Self-assessment of DSM-IV criteria for major depression in psychiatric out- and inpatients *. *Nordic Journal of Psychiatry*, *57*(4), 1.

Vicario, C. M., & Nitsche, M. A. (2013). Non-invasive brain stimulation for the treatment of brain diseases in childhood and adolescence: state of the art, current limits and future challenges. *Frontiers in Systems Neuroscience*, *7*. https://doi.org/10.3389/fnsys.2013.00094

Vreeburg, S. A., Hoogendijk, W. J. G., van Pelt, J., DeRijk, R. H., Verhagen, J. C. M., van Dyck, R., … Penninx, B. W. J. H. (2009). Major Depressive Disorder and Hypothalamic-Pituitary-Adrenal Axis Activity: Results From a Large Cohort Study. *Archives of General Psychiatry*, *66*(6), 617. https://doi.org/10.1001/archgenpsychiatry.2009.50

Walach, H., Buchheld, N., Buttenmüller, V., Kleinknecht, N., & Schmidt, S. (2006). Measuring mindfulness—the Freiburg Mindfulness Inventory (FMI). *Personality and Individual Differences*, *40*(8), 1543–1555. https://doi.org/10.1016/j.paid.2005.11.025

Watson, D., Anna, L., & Tellegen, A. (1987). *Development and Validation of Brief Measures of Positive and Negative Affect: The PANAS Scales*. 8.

Watson, D., O'Hara, M. W., Simms, L. J., Kotov, R., Chmielewski, M., McDade-Montez, E. A., … Stuart, S. (2007). Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). *Psychological Assessment*, *19*(3), 253–268. https://doi.org/10.1037/1040-3590.19.3.253

Weissman, A. N., & Beck, A. T. (1978, March). *Development and Validation of the Dysfunctional Attitude Scale: A Preliminary Investigation*. Retrieved from https://eric.ed.gov/?id=ED167619

Wodka, E. L., Mahone, E. M., Blankner, J. G., Larson, J. C. G., Fotedar, S., Denckla, M. B., & Mostofsky, S. H. (2007). Evidence that response inhibition is a primary deficit in ADHD. *Journal of Clinical and Experimental Neuropsychology*, *29*(4), 345–356. https://doi.org/10.1080/13803390600678046

Wulfert, E., Block, J. A., Santa Ana, E., Rodriguez, M. L., & Colsman, M. (2002). Delay of gratification: Impulsive choices and problem behaviors in early and late adolescence. Journal of Personality, 70(4), 533–552. https://doi.org/10.1111/1467-6494.05013

Zoccola, P. M., & Dickerson, S. S. (2012). Assessing the relationship between rumination and cortisol: A review. *Journal of Psychosomatic Research*, *73*(1), 1–9. https://doi.org/10.1016/j.jpsychores.2012.03.007