Enhancing Cognitive Restructuring with Repetitive Transcranial Magnetic Stimulation: A Proof of Concept Study

Study Protocol and Statistical Plan

Objects and Significance

This study was based on the overall hypothesis that an integrating high frequency (HF) rTMS with an evidence based psychotherapeutic intervention (cognitive restructuring- CR) while engaging a neural mechanism that is impaired in adults with psychopathology (the dlPFC-amygdala circuit), will lead to quick improvements (after one session) in emotion dysregulation that will have long-lasting effects. This short intervention we hypothesized would be feasible, tolerable and acceptable to patients who have difficulties with managing their emotions.

Design and Procedures

This protocol was designed to provide preliminary data for the efficacy of a TMS/CR approach to emotion dysregulation. Dr. Neacsiu received three sources of funding for the study: a Brain and Behavior young investigator award (NARSAD), the Duke PRIDe award, and a CTSA KL2 award. The NARSAD grant application included an N of 40 subjects; the Duke PRIDe award added additional 20 participants to this study; the KL2 award added an additional 40 participants. Therefore, we planned for the target enrollment of 100 eligible subjects through study completion. The NARSAD and PRIDE projects were combined, aiming to examine the differences in administering neurostimulation over the right dorsolateral prefrontal cortex (dlPFC) versus left dlPFC versus sham, in conjunction with cognitive restructuring practice. The KL2 project was a supplement where the specific neurostimulation targeting was done using functional neuroimaging over the left dlPFC only. Recruitment for these two studies proceeded in parallel, and participants were given the choice for the study as available or the PI decided the study in which to enroll a participant. Therefore, participants were not randomly assigned to one of the two studies. Nevertheless, they were randomly assigned to a condition once they were enrolled in one of the two studies.

Interested participants complete an online or a phone screen. If eligible after the screen, participants were invited to a baseline assessment session where inclusion/exclusion was evaluated, and baseline measurements were collected. KL2 participants were called back for a brain imaging session where the ideal target for neurostimulation was identified with the use of an emotion regulation paradigm. The target was established using the 10-20 system for NARSAD/PRIDE participants. All participants returned for a one-time CR/TMS intervention

session lasting for 4 hours. Next, participants received automated phone calls for one week examining use of CR and emotion distress. At the end of the week, participants received an online questionnaire examining outcomes and those in the neuroimaging sub-study were asked to return for a follow up MRI. All participants returned one month later for a follow up assessment that included outcome measures, and an exit interview to examine feasibility and acceptability. Subjects were clinically evaluated for safety before the intervention and before each imaging session. Urine pregnancy tests are administered and interpreted by study staff who have completed training from the Department of Obstetrics and Gynecology (OB-GYN). The urine pregnancy test used is a commercially available test kit specified by OB-GYN (Quidel Quick Vue one-step HCG test; Product #: B6775-26DU).

Study Flow

Online/Phone Screening: Participants were recruited between 4/27/2016 and 2/17/2020 through online websites (e.g., Craigslist), flyers, and physician referrals. Interested participants completed an online screen and were subsequently called for additional screening if they did not report meeting any exclusion criteria. We aimed to recruit 20 participants in each of the five conditions across the two studies to align with other neurostimulation studies where 6-20 individuals per condition were sufficient to demonstrate proof of concept for novel treatments (1-3).Participants who meet criteria were scheduled for a clinical screening interview and baseline assessment session.

Clinical Screening Interview and Baseline Assessment (~4 hours):Participants went through a consent process and, for those who consented, the UWRAAMP was administered.

UWRAAMP. The University of Washington Risk Assessment and Management Protocol (UWRAAMP) is a paper and pencil established protocol to identify increased distress that may result from clinical interviewing and offers appropriate interventions as needed. Study staff who was involved in assessments was trained in the UWRAAMP by the PI who has over 10 years of experience with research studies that have employed this protocol. Briefly, suicidality, urges to self-harm, and stress were assessed before and after each clinical assessment. If the participant increased on either dimension after the assessment, the assessor walked through a mood induction protocol to alleviate distress. In the rare event that a high rating of ideation or distress continued past the use of this protocol, the trained study staff would work with Dr. Neacsiu and the participant to address these suicidal thoughts and if they were deemed to be at imminent risk of suicide after the conversation, we would call 911 or obtain a commitment from the participant to go to the nearest hospital emergency room, (e.g. Duke ER). The UWRAAMP

was used during the initial assessment, and during the 1-week and 1-month follow-up assessments. No hospitalization or ER visit occurred from the study procedures.

Clinical Interviews. Next, inclusion/exclusion criteria was reviewed. First, the participant completed the Emotion Regulation Questionnaire (ERQ) and the Difficulties in Emotion Regulation Scale (DERS). Low use of CR was operationally defined as a mean score lower than 4.7 on the cognitive reappraisal subscale (range: 1-7) of the Emotion Regulation Questionnaire (ERQ)(4) at the intake assessment. This cutoff was computed by pooling ERQ reappraisal means from 18 studies (N = 4331 participants) published before 2014 that examined the ERQ on US samples (4-21). The pooled mean across these studies was 4.70 (SD_{pooled} = 0.99). We considered adults who scored below this pooled mean to have "low use" of CR strategies and therefore to be the optimal candidates for a one-time CR intervention. ITT participants scored an average of 3.35 (SD = 0.81) on the ERQ cognitive reappraisal subscale, with no significant difference in scores between treatment conditions ($F(2, 43) = 0.29$, $p = .75$). High emotional dysregulation was defined as a score of 89 or higher on the DERS to align with prior studies done by our group.

Participants qualified for the main study only if their ERQ score was less than 4.7. Participants qualified for the neuroimaging sub-study only if their DERS score was above 89, indicating moderate emotion dysregulation. For those above the DERS threshold in the KL2 study, the ERQ score was used to decide if participants could be included in the study or not. We planned to enroll 14 low ERQ participants (score <=4.7), 13 moderate ERQ participants (4.66 < score <= 5.8), and 13 high ERQ participants (score >5.8).

If these criteria were met, a member of the study team would then interview the subject about current and past psychiatric disorders, using the Structured Clinical Interview for DSM-5 Disorders (SCID-5). From the SCID modules, we administered the modules relevant to exclusion first, followed by the remaining modules if the participant did not meet exclusion criteria. Therefore, the manic, psychotic, and substance disorders modules were administered first. Intelligence Quotient (IQ) was assessed with the Peabody Picture Vocabulary Test—Third Edition (PPVT-III). Participants with a PPVT score of <70 were excluded. For included participants, the assessor continued with the mood, anxiety, personality disorders and all other remaining modules. Excluded participants were paid for their partial assessment and referred to other treatment resources as needed.

Next, the assessor conducted a brief interview examining medical and treatment history. A Medical History Questionnaire (MHQ), the TMS Adult Safety Screen (TASS) and an abbreviated version of the Treatment History Interview (THI) were used to assess previous and

ongoing psychiatric services received. The modified THI was administered at the initial assessment visit and at the 1-month follow up. An MRI screening form was also used to assess safety for participants in the neuroimaging sub-study.

Personally-Relevant Emotional Stressor. Qualified participants underwent an interview to identify four autobiographical stressors to be used for emotional induction. Using the method developed by Pitman and colleagues (22) and used in studies of adults with affective disorders (23), we created four negative emotional arousal scripts, three of which were used in a random order during the intervention day and one during the 1-month follow-up assessment. In brief, the assessor asked the participant to describe three moderate stressors from the past month, as well as a stressor that tended to reoccur for them. Participants wrote a description of each event, and the assessor worked with the participant to establish a clear story for each event that could be recited in 30-40 seconds. Following the assessment, these scripts were narrated by the PI and digitally recorded into .wav audio files to be presented during the subsequent testing sessions. The PI decided whom to enroll in the study and was kept blind to treatment condition assignment until the end of the study.

Self-Report Questionnaires. Included participants were then be administered a packet of self-report questionnaires intended to collect baseline data about demographics handedness, emotional dysregulation, coping, functional impairment, and psychopathology (see measures). These self-reports could be administered via a Qualtrics link on one of the study computers or on the study tablet.

Emotional Memory Selection task (Participants in the neuroimaging sub-study only). Following the methods of Kross, Davidson, Weber, & Ochsner (24), participants were asked to generate a set of negative and neutral autobiographical experiences and to rate the extent to which thinking about them feels a) negative and b) arousing. A short questionnaire about each memory was then answered. These cues and memories were subsequently used in the neuroimaging task.

Assessment location and video recording. All assessments were conducted in the PI's office, or in her staff's office. For the subjects who consent to record, their assessments were video/audio recorded for reliability purposes and recordings. These video files will be destroyed 6 years after the study completion date.

At the end of the clinical interview/baseline assessment day participants were scheduled for the intervention day or for the baseline imaging session depending on the study that they were assigned to. The baseline imaging and the intervention session had to happen within 1

month of the initial assessment. The intervention day/baseline imaging day were planned for at least one day later, and at most 1 month later (time at which the assessment was no longer be valid).

Randomization procedures: Following intake, participants from the main study were randomly assigned to active right dlPFC stimulation, active left dlPFC stimulation, or sham stimulation. Participants were matched according to sex and use of psychotropic medication as dichotomous variables. When a participant withdrew before the intervention, they were unrandomized and their randomized condition reassigned to a new participant with the same matching specifications to maintain balance between the ITT groups. Randomization was done using a minimization algorithm (25, 26) using the QMinim software (http://rct.mui.ac.ir/q/index.php) by an independent staff member and kept blind from the assessor, PI and participant. A parallel clinical trial design was used with equal ratio assignment to each condition. The randomization information was saved in a password protected database to which only the staff member responsible for randomization had the password. Two sealed envelopes were created for each participant, one to be opened at the end of the study by the assessor and participant to discuss randomization, and one to be opened by the TMS technician who set up the coil before the intervention for either the sham or active paradigm. Sham participants were further randomized to receive TMS to either the right or left DLPFC. From the 15 participants in the sham treatment condition, 8 had the TMS coil placed over the left dlPFC and 7 over the right dlPFC.

Participants in the neuroimaging sub-study were randomized to one of two treatment conditions (sham, left dlPFC stimulation) matching for gender (M/F), use of psychotropics (Yes/No), and ERQ CR score (low/moderate/high) using the same randomization and blinding procedures.

Medical Screen: After the intervention, a de-identified copy of the medical history questionnaire and the TASS was sent to the study doctor, Dr. Szabo. He reviewed these documents and informed the study team if the participant could be cleared to do rTMS. In the event that the participant was deemed inappropriate the participation ended at that point and the subject was compensated. If the participant passed the medical screen, the participant proceeded to the next appointment.

Baseline Brain Imaging Session (participants in the neuroimaging sub-study only): The session took approximately 2 hours, with 1 hour in the scanner itself. The MRI Session included:

- Training in the emotion regulation task to be performed in the scanner, including practice in reappraisal, distraction, and feel strategies.
- A memory cue assessment to rehearse cuing of memories selected in the Emotional Memory Selection Task at the Assessment Session.
- Female participants of childbearing potential had a urine *pregnancy test* on the day of the MRI scan to ensure that the participant was not pregnant. Urine pregnancy tests was completed using QuickVue+ One-step hCG test. The QuickVue One-Step hCG Urine test is a sensitive immunoassay for the qualitative detection of human chorionic gonadotropin (hCG) in urine for the early detection of pregnancy with >99% accuracy and 20mIU/mL sensitivity in urine. This pregnancy test was administered by members of the Brain Imaging and Analysis Center who have completed training as directed by the Chair of Obstetrics and Gynecology of the Duke University School of Medicine. The test was conducted at the MRI Center where the scan took place, and subjects were not allowed to participate until the pregnancy test was completed and a negative reading was determined by trained MRI Center staff.
- A “mock scan” was administered to participants who had not had a previous research brain MRI. This procedure familiarizes the participant with the scan environment.
- The MRI Safety Screening was administered and reviewed by the scan technicians to ensure the absence of MRI risk factors (implanted metal, etc)
- Both structural and functional MRI images were collected.
- During the functional MRI scanning, participants completed an emotion regulation task, where they were asked to recall an emotional memory from the Emotional Memory Selection task, and then were cued to reappraise, distract, or allow for unregulated experience of emotions. At the end of each trial, participants were asked to rate their current emotional state. Strategies were blocked (e.g., 3-4 trials of reappraise followed by 3-4 trials of distance), and each trial began with a brief non-emotional control task (e.g., indicate the direction of an arrow.)

Personalized target identification (participants in the neuroimaging sub-study only): Following the intake session, fMRI analyses were performed to define, for each subject, the TMS target as the spot within the dlPFC showing the strongest activation in the “Restructure vs. Feel Negative” contrast. To obtain this contrast, data were first preprocessed with fMRIprep (27).
Separate events were then modeled for the attentional task (duration: 10 seconds), the negative and neutral cues (duration: 5 seconds), for distancing, reframing, and feel of negative or neutral

cues, (duration = 10 seconds), and for the ratings of their emotional state on the SUDS (duration: 10 seconds). The onset of each event was recorded by the Matlab script used to launch the MRI acquisition. A weight of 1 was attributed to each event. At the first level, functional data were analyzed as individual runs, using a general linear model (GLM) in which trial events were convolved with a double-gamma hemodynamic response function. The 'Restructure' contrast defined as the combination of distancing and reframing instructions was contrasted with the 'Feel Negative' contrast. This contrast was then used to generate Level 2 analysis, in which BOLD activity for each of the four runs were combined using a fixed-effect model. The statistical map obtained in MNI space were then transformed into native space using ANTS transformation, and overlaid onto the anatomical image in the neuronavigation software. The region within the dlPFC showing the strongest positive z-value was defined as the TMS target. The coil orientation was visually set up so that the rTMS induced E-field was perpendicular to the closest sulcal wall. When this orientation was not feasible (e.g., coil handle in front of participant's face), the symmetric orientation was used and the current was reversed.

Intervention Day (all participants): Participants returned for the 3.5-hour intervention session within a month of intake.

Behavioral Intervention. The first 45-60 min of this session was spent on skills training, one-on-one with the first author or a trained psychologist, and was focused on learning CR and practicing on standardized and personal examples. Skills training used standardized procedures blending psychotherapeutic approaches (28, 29) with instructions in CR that matched prior neuroimaging studies (30). Participants were told that one validated way to change emotional experiences is by thinking differently about the situation that prompts the emotion (29, 31-33) or by reorganizing the cognitive elements involved in the emotion (34).

Following Gross's model (35), we defined CR as interpreting emotional stimuli in a way in which the target emotional relevance is de-emphasized or the interpretation leads to a different emotion (36). First, participants were taught to adopt a detached and unemotional attitude as they thought about their autobiographical situation (37). Detachment was instructed by examining the situation with objectivity or putting spatial or temporal distance between the current moment and the situation. We called this strategy **distancing** (38).

Second, participants were taught **reframing** using an adapted version of existing paradigms (30, 39, 40). Specifically, we emphasized with pictures and examples the relationship between thoughts and emotions, identified helpful ways of thinking, and instructed participants to find interpretations that are less toxic in order to be effective rather than right when upset.

Participants learned to ask about elements of the situation that they did not pay attention to or information that was missing, and to reframe their cognitions based on the full picture with an eye towards reducing distress. Participants were also taught to examine the worst-case scenario, the probability of it occurring, and the likelihood of survival if it occurred. The CR training ended with a quiz that included definitions as well as hypothetical scenarios for practice purposes.

rTMS Parameters. Active or sham rTMS was performed with a figure-8 coil (A/P Cool-B65) and a MagPro X100 stimulator with MagOption (MagVenture, Denmark). The TMS device was configured to biphasic pulses with the electric field current flowing in the normal direction (AP-PA). For the main study, stimulation was delivered over the left or right dlPFC (depending on randomization), defined according to the 10-20 system (41). For the neuroimaging sub-study, active or sham stimulation (depending on randomization) was delivered over the functionally derived left dlPFC target. A stereotaxic neuronavigation system was used (Brainsight, Rogue Research), and a template brain (MNI) was registered to each participant's head using anatomical landmarks. These procedures allowed for online monitoring and adjustment of TMS coil position throughout the session to ensure proper targeting.

rTMS was performed with standard FDA-approved parameters (42, 43). Twenty trains of 10 Hz stimulation were delivered over 4 s with a 26-s inter-train interval at 120% of the resting motor threshold (rMT). To determine rMT, electrodes (Neuroline 720, Ambu) were placed in a belly-tendon montage on the participant's opposite from the site of stimulation hand to record activity in the first dorsal interosseous (FDI) muscle, and motor evoked potentials (MEP) were recorded in Brainsight. The motor hot spot was defined as the position over the left/right motor cortex that elicited the largest MEP, and rMT was then defined as the TMS pulse intensity that induced, on average, a MEP of 50 μV amplitude, using a maximum likelihood estimator (TMS Motor Threshold Assessment Tool, MTAT 2.0, clinicalresearcher.org /software.html). If the participant could not tolerate full intensity of the intervention, we dropped the intensity to rMT and ramped up during habituation to target intensity. Only participants who received the majority of stimulation above rMT were included in the analyses leading to 5 participants (including the pilot participant) to be excluded.

Each TMS session was conducted by the principal investigator (PI; first author) with the assistance of a TMS technician. The PI led the participant through the session, decided on dose adjustments and course of action for any protocol deviations, and stayed blinded to the active/sham manipulation. The technician was not blind to the assigned condition and prepared

the coil but did not influenced the course of the session in any way.

Sham stimulation was delivered using the opposite face of the same A/P coil, which included a magnetic shield to greatly attenuate the induced field. When positioned in the sham configuration, the coil also produced electrical current through two electrodes placed approximately one centimeter apart near the participant's hairline on the side of the stimulation. This electrical current was matched in intensity to create a somatosensation similar to the active stimulation, thereby creating a reliable sensory blinding to the two conditions. The electrodes were put near the hairline for all participants and were only activated for sham participants. Therefore, the presence of the sham electrodes, the scalp stimulation, the sounds and the coil position over the identified target, and the pre-determination of the motor threshold were all elements of the neurostimulation procedure that were identical between the treatment conditions. The difference was the presence or absence of HF rTMS.

Combined rTMS-CR Intervention. First, a 600 s habituation period was performed when participants received active or sham rTMS alone while listening to white noise via headphones. Participants were not instructed to think of anything in particular during this time. Then, the intervention proceeded as follows: (1) participants sat quietly for a 300 s baseline while listening to white noise, (2) participants were instructed to imagine as vividly as possible one of the stressful experiences constructed at intake, (3) the stressor was heard via headphones followed by silence when participants were instructed to continue to imagine the stressful situation (120 s total), and (4) instructions in reducing distress using CR followed. The rTMS began within 10 s after the CR instructions appeared. Reminders of reframing and distancing appeared in random order 180 s and 360 s post-stimulation onset. White noise was played throughout when instructions were not presented. After 600 s, there was a break, followed by a second and third administration of the stressor task using the procedures outlined above, but with a different personalized stressor recording each time presented in a randomized order. After each baseline, stress induction, and regulation period, the participant was asked to rate subjective units of distress (SUDS; 0-9 scale). At the end of the intervention, manipulation check questions ensuring compliance with the instructions and asking participants to guess the blinded condition assignment were administered.

Physiological Measurements. Psychophysiological measurements were collected continuously during the intervention using the BIOPAC MP-150 recording system (Goleta, CA). Electrodes recording heart rate (HR) were placed on the participant's wrist, ankle, and fingers. Amplified analog data recorded with a 200 Hz sampling rate were converted to digital recording

and filtered using BIOPAC's AcqKnowledge 4.1 software.

Introduction of the Ambulatory Assessment. At the conclusion of the intervention, the experimenter oriented participants to the follow up assessments including the ambulatory assessment week. Over the following week, participants would receive eight calls each day (approximately one call every two waking hours), with each call lasting 30- 60 seconds. For all experimental conditions, calls were used to assess daily psychological distress (SUDS; 0-9), and use of CR since the previous call (Y/N). Calls were randomly generated and automatically placed for 7 days. Participants used their own phones for this portion of assessment. If participants missed a call, they were encouraged to call into the study server where they were prompted for the same information. All calls were conducted using a dedicated server and existing software at the CBRTP (Telesage, Inc., Chapel Hill, NC). Before programing the random calls, we asked participants of their typical wake hours and programed calls during this time to maximize likelihood of compliance.

Ambulatory Assessment Week: Calls started the day following the intervention day and stopped after 7 days of daily calls. In addition, as in our previous trials, participants were paid (at the end of the study) to complete calls they answer each day ($0.25 per call; maximum of $2 per day). Participants received compensation for the calls at the 1-month follow-up assessment. If more than 8 calls/day occur, participants were only be compensated for a maximum of 8 calls. Each call (either placed or initiated) asked the participant to: 1) enter their study id, 2) enter their current level of distress (SUDS, 0-9), 3) enter 0 if they have not used CR since the previous call, or 1 if they had used CR at least once since the previous call.

One Week Follow-up: At the conclusion of the ambulatory assessment week, participants had the option to complete the battery of self-reports assessed at intake online on a Qualtrics questionnaire or via phone with a study coordinator. Participants received an e-mail with the link to the questionnaires. A self-report was included to assess compliance with medication, changes in medication, and any other changes in treatment in the past week. Participants had up to 2 weeks to complete this assessment. Participants in the neuroimaging substudy could choose to complete the 1 week questionnaire packet during the follow up MRI session.

Follow up Brain Imaging Session (participants in the neuroimaging substudy only): The session took approximately 2.5 hours, with 1 hour in the scanner itself. This session was

identical to the intake MRI session.

1-Month Follow-up: Upon arrival, all subjects went through the UWRAAMP followed by the administration of the same self-report packet as given during the initial assessment. These self-reports were administered via a Qualtrics link on one of the study computers or on the study tablet. Participants were then connected to physiological recording equipment (BIOPAC) and, after 5 minutes of baseline, heard their last stressor followed by prompts to regulate the emotion without specific instructions in cognitive restructuring. SUDS and dissociation was assessed before the procedure, after baseline, after induction, and after a 5-minute regulation period. Participants were asked what they did during the regulation period and were debriefed and guided through the relaxation procedure if distress continued to be high. The behavioral emotion regulation task followed where participants were asked to respond to emotion cues on the screen. Next, the participant was asked a series of questions about feasibility and acceptability of procedures (exit interview), were debriefed with regards to the blind treatment assignment and were offered referrals for other mental health services as needed. At this point, participants were compensated up to $50 for their participation including $10 for having completed the 1-week follow up, $26 for completing the 1-month follow up, and up to $14 for the ambulatory assessment component (exact sum depending on the # of calls completed). Sub-study participants were also compensated $50 for each MRI session.

Study Inclusion Criteria

1. Age between 18-65
2. DERS/ERQ cutoffs:
    a. For main study: ERQ reappraisal subscale <=4.7
    b. For neuroimaging sub-study: DERS score >= 89 & ERQ reappraisal subscale <=4.7 for 14 participants; 4.7< reappraisal score <= 5.8 for 13 participants; reappraisal score > 5.8 for 13 participants.
3. Meets diagnostic criteria for a current DSM-5 depressive, anxiety, obsessive-compulsive, somatic, personality, eating, or trauma and stress-related disorders (including in partial remission): major depressive disorder, bipolar II disorder, other bipolar disorder, persistent depressive disorder, cyclothymic disorder, premenstrual dysphoric disorder, panic disorder, agoraphobia, social anxiety disorder, specific phobia, generalized anxiety disorder, obsessive-compulsive disorder, trichotillomania, excoriation disorder, hoarding disorder, body dysmorphic disorder, other specified, or

unspecified obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, adjustment disorders, somatic symptom disorder, conversion disorder, anorexia nervosa (unless severe and requiring hospitalization), bulimia nervosa, binge-eating disorder, adult attention-deficit and hyperactivity disorder, intermittent explosive disorder, gambling disorder, illness anxiety disorder, borderline personality disorder, narcissistic personality disorder, histrionic personality disorder, antisocial personality disorder, paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, avoidant personality disorder, dependent personality disorder, obsessive-compulsive personality disorder, personality disorder NOS, other depressive disorder, other anxiety disorder.

4. Willing to provide informed consent.
5. Subjects are willing and able to participate in the intervention and all required study visits, stay on the same dose of psychiatric medication (if any) throughout the study, not participate in cognitive-behavioral therapy throughout their participation in the study.
6. Has cellphone that can be used during the ambulatory assessment portion of the study.

Study Exclusion Criteria

1. Current or recent (within the past 6 months) substance dependence disorder (excluding nicotine and caffeine)
2. Current serious medical illness, including current migraine headaches
3. Currently on psychotropic medications with dosage unchanged for <u>less than four weeks</u> prior to study entry OR plan to make changes in medication within 2 months after starting the study
4. History of seizure except those therapeutically induced by ECT (childhood febrile seizures are acceptable and these subjects may be included in the study), history of epilepsy in self or first degree relatives, stroke, brain surgery, head injury, cranial metal implants, known structural brain lesion, devices that may be affected by TMS (pacemaker, medication pump, cochlear implant, implanted brain stimulator).
5. Subjects are unable or unwilling to give informed consent.
6. Diagnosed with the following conditions (current unless otherwise stated):
    a. psychotic symptoms.
    b. Any DSM disorder secondary to a general medical condition, or substance-induced.
    c. Bipolar I disorder (current or lifetime),

   d. Life-threatening anorexia or any other disorder requiring immediate hospitalization
   e. High-risk for suicidal behavior, including current suicidal ideation with a method and plan, or hospitalization for suicidal behavior within 1 year before the study.
   f. Subjects currently engaged or planning to engage in other treatment during the course of the study (including behavior therapy, or other types of individual, family, or group psychotherapy/counseling).
7. Subjects with a clinically defined neurological disorder including, but not limited to:
   a. Any condition likely to be associated with increased intracranial pressure.
   b. Space occupying brain lesion.
   c. History of stroke.
   d. Transient ischemic attack within two years.
   e. Cerebral aneurysm.
   f. Dementia.
   g. Parkinson's disease.
   h. Huntington's disease
   i. Multiple sclerosis.
8. Increased risk of seizure for any reason, including prior diagnosis of increased intracranial pressure (such as after large infarctions or trauma), currently taking medication that lowers the seizure threshold (including Welbutrin, Aderall, Clorzaril)
9. Subjects with any of the following treatment histories:
   a. TMS treatment at any point in their lifetime.
   b. Use of any investigational drug or device within 4 weeks of the screening.
10. Subjects with cochlear implants
11. Women who are pregnant
12. Chronic absence of shelter or impending jail that would make consistent participation in the study difficult
13. Cannot easily come to Duke several times for the study procedures
14. Does not have a mobile phone or is unwilling to use mobile phone for ambulatory assessment
15. Does not speak/understand English enough to benefit from the psychotherapeutic intervention
16. Verbal IQ <70

Measures

Diagnostic Assessment: The SCID-5 (44) and SCID-PD (45) were used to assess DSM-5 disorders. Participants were led through both structured interviews by either the first author (76.4% of cases) or one of three trained diagnostic assessors under the supervision of the first author. In the cases where the first author did not conduct the interview, she reviewed in detail with the assessor the questions asked to confirm diagnostic profile. In case of disagreement, she reassessed the disorder at the next visit.

Self-reports:

Emotion Regulation Questionnaire (ERQ). The ERQ (4) is a 10-item self-report inventory that assesses the routine use of two cognitive emotion regulation strategies: expressive suppression and cognitive reappraisal. The items use a 7-point Likert scale with responses ranging from one (*strongly disagree*) to 7 (*strongly agree*). In our study, Cronbach alpha at intake for ERQ Reappraisal was .87. The correlation between phone screen and intake reappraisal scores for 98 participants was .57. ERQ suppression scale scores were collected but not examined for the current study.

Difficulties in Emotion Regulation Scale (DERS). The DERS (46) is a 36-item self-report measure of individuals' typical levels of emotion dysregulation across six domains. Participants respond on a Likert scale ranging from 1 (*almost never*) to 5 (*almost always*), and the total sum score indicates high dysregulation. In the present study, Cronbach's alpha for the total score at intake was .89. The correlation between phone screen and intake total DERS scores for 93 participants was .66.

Outcome Questionnaire-45 (OQ-45). The OQ-45 (47) is a 45-item self-report measure used to track severity of psychopathology throughout treatment. It consists of subscales that identify three types of problems that lead to general stress: psychological symptoms, interpersonal conflicts, and problems with social roles (48). Items are rated on a Likert scale ranging from 0 (*never*) to 4 (*almost always*). At pretreatment, Cronbach's alpha for the total score was .83.

The Work and Social Adjustment Scale (WSAS). The WSAS (49) is a 5-item self-report inventory examining the functional impairment attributable to an identified problem. In this study, we asked participants to rate the level of impairment that was related to their emotional dysregulation (e.g., "Because of my difficulties managing emotions, my ability to work is

impaired"). These questions are rated on a 9-point Likert scale (0 = *my problem does not affect this at all*; 8 = *my problem affects this very seriously*) A total WSAS score above 10 suggests clinical levels of functional impairment. At pretreatment, Cronbach's alpha for the total score was .71.

Subjective Units of Distress Scale (SUDS). During the experimental sessions and ambulatory assessments we asked participants to rate their current distress on a scale from 0 – no distress to 9 – extreme distress (50).

Manipulation Check. After each baseline and regulation period we examined dissociation during that segment using a 4-item scale (51). At the end of the intervention and at the 1-week and 1-month follow-up assessments, participants rated their confidence in the assigned condition to which they were kept blind (1 = "I am certain I received sham stimulation" to 9 = "I am certain I received active stimulation"). We also asked after the intervention for participants to give their best guess whether they received real or sham neurostimulation (forced- choice question).

Tolerability Questionnaire. Before and after the intervention session, participants rated on a scale from 0–3 (absent, mild, moderate, severe) the intensity of their headache, neck pain, scalp pain, seizure (as observed by technician), hearing impairment and any other side effect that they might have experienced from the TMS treatment.

Exit Interview. We refined a previously developed in-house interview (52) to examine feasibility and acceptability as directly relevant to the study and to collect participant feedback (available upon request). The interview was administered at the 1-month follow up, and it included open-ended questions about the overall experience, positives, and issues with the current treatment, as well as Likert-type questions about feasibility of the intervention (e.g., difficulty with limiting movement, level of comfort, ability to concentrate given the TMS noise, distress about the procedures, ease to hear and understand clinician, connection with clinician, and session engagement), acceptability (of session length, skills training, TMS procedures, personalized stressors use, ambulatory phone assessment) and overall satisfaction (i.e., likelihood to recommend to someone else). Feasibility and acceptability questions were rated on a scale from 0 (not at all) to 9 (extremely) and averaged to compute an overall feasibility and acceptability score. Satisfaction was rated on a 0 (low) to 100 (high) continuous scale.

Psychophysiological Measures: Raw ECG data were visually inspected and artifacts cleaned prior to calculation of HF-HRV following established guidelines (53, 54). The

AcqKnowledge software tool detects R-waves in the cleaned ECG to create a series of inter-beat intervals that is converted to a continuous, time-domain representation of HR using cubic-spline interpolation, which is resampled at 8 Hz. Spectral analysis yields summary report values for HRV frequency bands. Each session period (e.g., baseline, habituation, stressor, regulation) was divided into 120 s bins, and HF-HRV was extracted from each bin. The bin size was chosen because the stressor induction portion was 120s long, and segments were intended to be equivalent in length across the experiment. Therefore, two HF-HRV values for each baseline, one for each stressor, and five values for each regulation period and habituation were computed. HF-HRV was intended to be a primary outcome measure but was added later to clinicaltrials.gov record as primary because of an administrative omission at the beginning.

The 'Find Rate' function of AcqKnowledge was used to transform the ECG signal into beats per minute or heart rate (HR), using a moving average with a window of 15 s. For each baseline, HR was averaged from the last 240 of the total 300 s. We excluded the first 60 s from each baseline because often during this time participants were still settling into their chair and task and therefore, we considered the first minute not a true representation of physiological baseline. In cases where there was a clear spike in HR (e.g., because the participant coughed, talked, moved abruptly, etc), the average baseline HR was calculated from the maximum time available excluding any amount of time with disruptions.

Regulation Duration. Time to return to one's heart rate baseline (regulation duration) was defined for each regulation period as the amount of time it took from the beginning of regulation for the continuously monitored HR to reach a value that was lower or equal to the average baseline HR. If the person started the regulation period below the average baseline, we coded the return to baseline as "never stressed" and did not include it in analyses. If the participant never returned to baseline in the 600 s allocated to the regulation period, we set the return to baseline time to be 600. This data was analyzed with mixed models ANOVA which requires covarying the baseline measurement of the outcome. To create a baseline value for regulation duration, we measured the time it took during the habituation period for the person to return to HR baseline after increased arousal induced by neurostimulation. If the person was not above HR baseline at the beginning of neurostimulation, this covariate was set to 0. If the person never returned to HR baseline during habituation, the covariate was set to 600. At follow up, regulation duration was defined identically. Because only one measurement of regulation duration was achieved, a simpler ANOVA model was planned and a baseline value for this outcome was not needed. An additional difference was that the maximum value the variable could take was 300 s.

Statistical Analyses

All analyses compared the effect of sham to active rTMS over the left and right dlPFC in the main study and active rTMS versus sham in the neuroimaging sub-study. Preliminary analyses including analysis of variance (ANOVA) and chi square tests were conducted to assess demographic differences between groups. We also examined any differences between groups on randomization variables (gender, use of medication) and other potential confounding variables like presence of a depressive disorder, dissociation during regulation, or arousal induced by rTMS alone. Significant differences were included in subsequent analyses as covariates. Planned covariates included baseline measurements of the outcomes. Analyses were conducted using SPSS version 25.0.

Mixed-effects hierarchical linear models (MMANOVA) with analytically determined covariance structures were used to analyze the repeated measures data (55). All MMANOVA models used a restricted estimated maximum likelihood model to account for missing data (56) (i.e., cases with missing data were not discarded, but slopes for each participant were computed with the data available). Estimated marginal means (EMMs) were compared using LSD corrections for significant main and interaction effects. Effect sizes for these models were computed using Feingold's formula (57) and interpreted using Cohen's (58) specifications.

To test immediate effects of the intervention, we conducted three analyses in each study examining HF-HRV, regulation duration, and SUDS. The treatment condition (active left, active right, or sham), the experimental condition (regulation 1, 2, and 3), the time within each experimental condition (coded 0-4 for each 120 s segment within that period) were used to predict HF-HRV. Baseline HF-HRV was measured at the beginning of the experiment (session baseline) and right before each autobiographical stressor presentation (pre-stimulus baseline). Because active rTMS may have cumulative effects (59) that could influence the pre-stimulus baselines we included both session baseline and pre-stimulus baseline as covariates in the analyses. Because the two HF-HRV values extracted from each baseline (one from the last 120 s, one from the middle 120s) were very highly correlated (rs ranging from .93 to .98, ps < .001), we only included one of the values for each session and pre-stimulus baseline, corresponding to the last 120 s of the baseline. A MMANOVA examining regulation duration during each regulation period was also conducted using treatment condition, experimental condition, and return to emotional baseline during habituation as predictors in each study.

SUDS data were collected and analyzed with two main questions in mind: (a) were the

procedures successful in getting participants to feel increased distress after the autobiographical stressors presentation and decreased distress after regulation, and (b) did participants experience lower distress after rTMS enhanced CR when compared to CR alone. Therefore, all SUDS values collected after each pre-stimulus baseline, stressor, and regulation period during the combined intervention were included in the analysis. SUDS after habituation were covaried as the closest 'baseline' measurement before the intervention began. Treatment condition, time period of the experiment (post-baseline, post-habituation, post-stressor 1, post-regulation 1, etc.), were used to predict SUDS throughout the experiment. Two generalized estimated equations models (GEE) (60) using ordinal logistic models and an independent covariance structure examined differences between treatment conditions in side effects.

To test near-term effects of the intervention two hierarchical linear models (HLM) (61) were used to examine condition differences in SUDS and use of CR during the ambulatory assessments in each study. Data was aggregated by either obtaining a mean (SUDS) or a sum (use of CR – yes/no) for that day's data. To include a baseline covariate in the SUDS model, we utilized the SUDS rating at the beginning of the intervention day (before any procedures were conducted) which was also the day before the ambulatory assessment started. We used intake ERQ reappraisal as the baseline for the ambulatory CR use analysis.

To test the long-term effects of the intervention, six MMANOVA models were conducted in each study: four examining between-condition differences at the 1-week and 1-month follow-up assessments in ERQ, DERS, OQ-45, and WSAS; and two examining HF-HRV and SUDS during the follow-up stressor task. An ANCOVA examined differences in time period to return to baseline at follow up in the main study and a t-test examined between condition differences for this outcome in the neuroimaging sub-study. For the longitudinal self-reports (DERS, OQ-45, WSAS, and ERQ Reappraisal), intake measurements were used as covariates in the analyses. HF-HRV was extracted from the first 120 s period and the next 120 s period out of the total 300 s regulation period. The treatment condition and baseline HF-HRV (extracted from the last 2-min of baseline) were added as covariates. Treatment condition, time period in the follow-up stressor task (post-baseline, post stressor, post regulation), SUDS baseline (collected at the beginning of the 1-month follow-up day) were used to predict SUDS at follow up. In the regulation duration analyses at follow up, no covariates were included.

fMRI processing for group analysis (participants in the neuroimaging substudy only). The first hypothesis of the neuroimaging sub-study stated that the self-reported difficulties with cognitive restructuring would be inversely correlated with activation in the right and left

dorsolateral prefrontal cortex (dlPFC) and the amygdala during the emotion regulation task. Therefore, parameters estimate from each subject in these regions were extracted from the individualized statistical map obtained for TMS targeting, using 'featquery' and correlated with the self-reported difficulties.

The second hypothesis stated that the functional connectivity between the dlPFC and the amygdala would positively correlate with behavioral self-reported difficulties. To test this hypothesis, a psychophysiological interaction (PPI) analysis was conducted, using the dlPFC as the seed. First, the time series of the dlPFC was extracted using "fslmeants", and used as the physiological regressor. Three intermediary PPI were performed as the interaction between the time course of the dlPFC, and: the "Reframe Negative" event, the "Distance Negative" event, and the "Feel Negative" event as the task regressor. At the contrast level, the PPI of interest ("Reframe vs. Feel Negative") was generated as the combination between reframe and distance events, both contrasted with the Feel event (reframe + distance – 2* feel). This method was used for all subject and each run. Statistical PPI map from each of the four runs were then combined into a second level analysis using a fixed-effect model. To test our hypothesis, the parameter estimate of the amygdala obtained from this PPI map were extracted and correlated with self-reported difficulties.

To assess whether active rTMS increased dlPFC activation compared to sham, during the second imaging visit compared to the intake one, a group analysis was performed. The same process used for the targeting approach (see above) was performed on the follow-up images in order to generate the 'Restructure vs. Feel Negative' contrast for each subject and each run. For the second level analysis, this contrast obtained for the four runs of the Follow-up and the four runs of the Intake visits were included in the model and contrasted with a mixed-effect model to generate a 'Follow-up > Intake' contrast at the subject level. This follow-up > Intake contrast was then entered into a third level analysis assessing the differences between active and sham rTMS.

The third hypothesis of this sub-study concerned rTMS effects on functional connectivity: it was expected when compared to baseline, participants treated with active rTMS in conjunction with CR will show greater increases in dlPFC-amygdala connectivity during the emotion regulation task, compared to participant receiving sham rTMS and CR. To compare the effects of active and sham rTMS on functional connectivity a psychophysiological interaction (PPI) analysis was performed. First, a bilateral functional dlPFC mask was generated. To do so, the group activation in the "Restructure vs. Feel Negative" contrast obtained during the intake

session was binarized to only keep significant activations ($z > 1.96$). The thresholded statistical map was then multiplied by the anatomical mask of the dlPFC available on Mindboggle, to only display significant activation in the bilateral dlPFC. The time series from this functional mask were then extracted and used as the physiological regressor. To generate the PPI contrast for restructure vs. feel negative, three intermediary PPI contrasts were generated. The first PPI used the 'reframe' event as the psychological regressor, the second one used the 'distance' event, and the third one used the 'feel negative' event. For all, the PPI was defined as the interaction between this event and the physiological regressor. At the contrast level the PPI of interest (restructure vs. feel negative) was defined as the combination between reframe and distance events, both contrasted with the feel event (reframe + distance – 2* feel). This method was performed for each subject and for each run. A second level analysis was performed to obtain the pre-post TMS-CR statistical map for each subject, and a third level analysis was then performed to assess the differences between participants receiving active and sham rTMS.

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