Neurofeedback Enhanced Cognitive Reappraisal Training

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DETAILED IRB PROTOCOL

1. Objective

Anxiety disorders are the most common mental health condition worldwide and a leading cause of disability. The development of novel interventions to treat anxiety has lagged the advancements made regarding the neurobiology of emotion and cognitive processes directly related to treatment. This proposal will utilize real-time functional magnetic resonance imaging neurofeedback (NF) to modulate key brain regions involved in emotion regulation to enhance effectiveness of cognitive reappraisal, a central skill taught in evidenced-based psychotherapies. This innovative project will identify 1) the ability of adults with anxiety to self-modulate brain function in regions specific to healthy emotion regulation using NF and 2) the potential impact of neuromodulation on improved emotion regulation ability and anxiety reduction.

2. Specific Aims/Hypotheses

Aim 1A. Evaluate the ability of adults with anxiety to increase prefrontal cortex activity during CR based on NF.

Primary outcome 1A: BOLD activation. Change in PFC activity (baseline to transfer run) from the reappraise > look contrast.

Hypothesis 1A: Participants receiving veritable-NF will show a greater activation increase in the PFC compared to sham-NF.

Aim 1B. Determine the relationship between prefrontal cortex activity recruitment and CR ability in adults with anxiety.

***Primary outcome 1B*:** Negative affect ratings. Decrease in negative affect ratings (baseline to transfer run) from reappraise > look contrast.

Secondary outcome 1B: Prefrontal-amygdala connectivity. Change in amygdala-PFC functional connectivity (baseline to transfer) from reappraise > look contrast.

Hypothesis 1B1: Participants receiving veritable-NF will show greater CR ability compared to those receiving sham-NF.

Hypothesis 1B2: prefrontal cortex activation will positively correlate with CR ability.

Aim 1C. Assess the impact of NF on anxiety symptoms and CR use over time (exploratory).

Primary outcome 1C1: Clinician-rated anxiety severity: Change in score on the Hamilton Anxiety Rating Scale (HAM-A) from initial assessment to one-month follow-up.

***Primary outcome 1C2*:** Self-reported cognitive reappraisal use. Change in score on the reappraisal subscale of the Emotion Regulation Questionnaire (ERQ) from initial assessment to one-month follow-up.

Hypothesis 1C1: The veritable-NF group will report decreased symptom severity and increased CR use compared to the sham-NF group.

***Hypothesis 1C2*:** Increase in NF-induced brain activation will correlate with decreased symptom severity and increased CR use at follow-up.

3. Background Information

Burden of anxiety disorders. Anxiety disorders are the most common mental health condition worldwide and a leading cause of disability,[2] associated with increased risk for suicide[3] and chronic health problems[4]. Over the lifespan, prevalence rates of anxiety increase most dramatically during young adulthood (age 18-24)[5], pointing to a critical developmental period for prevention and treatment. Moreover, heterotypic continuity of anxiety disorders is observed from adolescence to young adulthood suggesting common underlying mechanisms[6]. Although cognitive behavioral therapy (CBT) is regarded as a gold-standard treatment for anxiety, associated with moderate effect sizes in meta-analyses[7,8], remission rates are low[9] and relapse is common,[10,11] resulting in an unmet need to improve beyond existing evidence-based treatments.

Emotion regulation and anxiety disorders. Emotion regulation is the process of modulating emotions towards a particular goal[12]. Cognitive reappraisal (CR) is a type of emotion regulation strategy in which one changes the meaning of a situation to alter its emotion content. For example, interpreting a poor grade on a test as an opportunity to learn instead of a personal failure. CR matures linearly over the course of development[13] and is associated with better mental health and higher life satisfaction[14]. In longitudinal studies, greater CR use is associated with greater social connection and buffers against anxiety during the transition to college[15,16]. However, anxious individuals habitually use CR less often than avoidance or emotional suppression[17]. One reason for this decreased use may be that CR is effortful and more difficult to deploy than other emotion regulation strategies[18,19]. In contrast, other work has found no differences in CR frequency between those with and without anxiety, but that CR attempts are less effective in individuals with anxiety[14]. With practice, however, CR becomes less effortful and results in desired emotional changes[19], suggesting that CR training can improve ability to deploy CR to reduce anxiety symptoms. In support of this hypothesis, gains in CR mediate CBT response in anxiety[14].

Neurobiology of cognitive reappraisal. Decreased CR ability in anxious individuals may stem from hypoactivation of prefrontal brain regions necessary for CR implementation[20]. Meta-analyses show that effective CR is associated with frontoparietal activations, particularly the left ventrolateral prefrontal cortex (vlPFC) and dorsomedial prefrontal cortex (dmPFC)[21–23] (Figure 1). The left vlPFC is involved in appraisal selection and inhibition and the dmPFC supports monitoring and self-reflection on the meaning of emotional states[21,24]. Deficits in vlPFC recruitment during CR are common amongst clinical populations (e.g., anxiety, mood, substance use, and personality disorders), while deficits in dmPFC recruitment during CR, extending to the dorsal anterior cingulate cortex (dACC) and supplementary motor area (SMA), appear to be a signature of patients with anxiety[20,25,26]. In theory, enhancing left vlPFC and dmPFC recruitment during CR could improve CR efficacy for individuals with anxiety disorders.

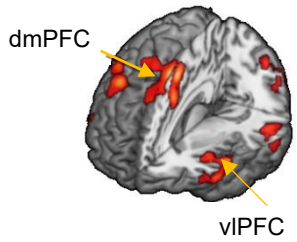

Figure 1. Brain regions involved in CR[23]

Real-time fMRI neurofeedback. Despite advances made in our understanding of the brain, translation of knowledge from functional magnetic resonance imaging (fMRI) research into clinical practice has been[27], possibly stemming from the correlational nature of fMRI design, and the reliance of fMRI inferences on group averages. To make fMRI clinically applicable, reliable, and valid methods are needed at the level of the individual patient. Real-time fMRI neurofeedback (NF) is a tool that has the potential to translate neuroimaging research to clinical practice. In this technique, participants see feedback based on their own neural signal as they engage in different psychological processes, which provides them an opportunity to become aware of and self-regulate their own brain signals[28]. As such, NF can test causal relationships about brain and behavior[29] and can teach individuals a self-regulatory skill that could then be applied in real life. The field has cohered around practice standards[30] and two recent meta-analyses[31,32] evaluating NF efficacy across psychiatric conditions reported medium-large effects sizes for neural activity and anxiety symptoms.. Thus, NF could be used to directly target vlPFC and dmPFC activity, potentially enhancing CR efficacy and use in adults with anxiety.

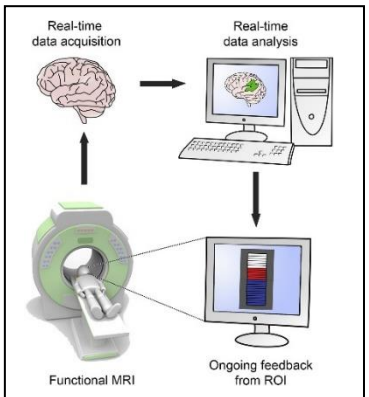

Figure 2. Illustration of NF[30]

Critical lessons learned from prior work. To demonstrate the ability of NF to enhance CR efficacy for patients with anxiety, studies need to consider the following factors. 1) Use of an appropriate control group. To date, eight studies have examined CR with NF[33–39], however, much of this work consists of feasibility studies with small sample sizes, lacking adequate control groups. As NF is rewarding and promotes self-efficacy[40],it is important to select a control group that gains the same proportion of success in auto-control of brain function as verifiable NF. 2) NF should target brain regions implicated in CR. only one research group[35,41] has targeted the left vlPFC, an area specific to CR[23], reporting positive changes for emotion regulation in depression and PTSD. No prior studies, however, have evaluated vlPFC-NF in primary anxiety. To our knowledge, no studies have evaluated the effects of dmPFC modulation with NF, despite evidence that is specifically under-recruited during CR in patients with anxiety[20,25,42]. 3) Measurement of affect or mood change. Few studies have examined the relationship between NF-induced change in brain activation and change in CR ability. Of note, Zilvestand et al.[34] found that insula downregulation was associated with decreased anxiety during the CR, while Keller et al.[35] reported that increased left vlPFC activity was associated with increased CR use at one-month follow-up. Such results are promising, but further well-controlled studies are needed to elucidate the causal role between change in brain function and CR ability. 4) Careful instruction to ensure participants are practicing CR during NF training. If instruction on how to use CR is brief, participants may inadvertently adopt maladaptive strategies, whose use is reinforced with NF. For example, when interviewed post-training, participants can report using a variety of strategies in addition to CR, including suppression[38].

In sum, the existing literature has demonstrated feasibility in using CR in the context of NF, however, lack of control groups, differences in brain regions targeted, failure to link change in brain function to change in behavior and to provide explicit CR training, as well as limited work in patients with anxiety, indicate the critical directions for this line of research to proceed, as we propose here.

4. Methodology

4.1 Overview

This project will examine the effects of NF training on CR efficacy and use in adults with clinical anxiety. The project will occur in 4 phases. In Phase 1 (Task Development), we will scan subjects using pilot funds from the fMRI lab to modify and optimize the Emotion Regulation Task (ERT) to measure reappraisal-related brain activity. Healthy participants will complete the ERT without neurofeedback to evaluate offline that the task activates areas of interest using traditional fMRI analytical methods. In Phase 2 (Neurofeedback Development), healthy participants will perform the ERT with veritable- NF to optimize NF delivery. In phases 1 and 2, participants will be recruited in groups of 4-8 to test continued iterations of task parameter modifications (e.g., timing, directions, number of trials, images) until significant activation is reached in the contrast of interest (reappraise > look). Performance from the participants with veritable-NF will be used to develop the sham condition for Phase 3 Randomization. Based on the results of Phase 2, we will pick the region of interest in the PFC for Phase 3. In the unblinded arm 1, participants will receive veritable-NF targeted at the PFC to optimize NF delivery. In the blinded arms 2 and 3, adults with anxiety will be randomized to receive either veritable-NF (arm 2) targeted at the PFC or sham-NF (arm 3).

4.2 Participants

4.2.1 Inclusion/Exclusion Criteria

1. Age 18-55
2. Primary diagnosis (primary source of distress and/or interference) of generalized anxiety disorder, social anxiety disorder, panic disorder or illness anxiety disorder based on structured interview. Comorbid phobic disorders allowed, but these cannot be the primary source of interference or distress due to the lowered chances of encountering anxiety-provoking stimuli during the study period,
3. Score of 2 or more on at least 1 question from the GAD/CROSS-AD composite
4. Medically and physically able to consent
5. Vision greater or equal to 20/30 (± correction)
6. Not taking any medication, prescription or non-prescription, with psychotropic effects other than:
    a. Buspirone, or antidepressant (e.g., selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI)) with stable dosage for past 4 weeks
    b. Hormonal contraceptives of any type for any duration
    c. If taking PRN medications not within this scope, must be willing to refrain from use for approximately 5 half-lives of the drug leading up to the training and MRI
7. No current diagnosis of Obsessive Compulsive Disorder, Bipolar Disorder, or Posttraumatic Stress Disorder
8. Current substance abuse or dependence (past 6 months)
9. No active suicidality with plan or intent
10. No current psychosis
11. No history of serious neurological illness or current medical condition that could compromise brain function, such as liver failure
12. No history of closed head injury, e.g., loss of consciousness > ~5 min, hospitalization, neurological sequela

13. For females, not currently pregnant or actively trying to become pregnant
14. Ability to tolerate small, enclosed spaces without anxiety
15. No metals, implants or metallic substances within or on the body that might cause adverse effects to the subject in a strong magnetic field, or interfere with image acquisition, e.g., aneurysm clips, retained particles (metal workers excluded), neurostimulators, foil-backed transdermal patches, carotid or cerebral stents, CSF shunts, magnetic dental implants, ferromagnetic ocular implants, pacemakers, automatic implantable defibrillators
16. Size compatible with scanner gantry, e.g., men over 6 feet tall that weigh more than 250 lbs, men under 6 feet tall that weigh over 220 lbs, women over 5'11" tall that weigh more than 220 lbs, or women under 5'10" tall that weigh more than 200 lbs. Subjects of these weights or greater typically have difficult fitting into the fMRI scanner properly

4.3 Recruitment

Adults of all genders will be recruited from several sources. First, participants will be recruited through the *Psychology Department Subject Pools*. Each semester, the Psychology Department maintains a list of individuals who are interested in participating in research. Subjects are asked for demographic and contact information, as well as handedness and vision. From this list, we will contact potentially eligible participants and ask them if they would be interested in hearing about a research study involving an MRI scan. Second, participants will be recruited from the *University of Michigan Health Research Registry*, a website (UMHealthResearch.org). Potential study participants go to the website and search for protocols in which they can participate. The website also features an email notification system that will let potential participants know when a new study is recruiting subjects. Third, participants will be recruited through *community and internet advertisements.* Flyers may be posted throughout southeastern Michigan, including in mental health treatment clinic waiting rooms, with relevant permissions. Flyer and social media advertising may direct participants to a series of prescreening questions on Qualtrics or UMHR before they are contacted by study staff for an official phone screening.
Participants in Phase 3 will be recruited from the *Psychiatry Department Anxiety Disorders Treatment Clinic*. As the proposed study requires that participants are not currently in psychotherapy treatment, information about the study will be distributed to clinical staff, who can inform waitlisted patients and those who are only on antidepressant medication about the study. We will also use the University's self-served data tools (DataDirect PHI, EMERSE, Best Practice Alerts, etc.) to *query electronic medical records and identify potential patients*. We will target patients aged 18 to 55 who meet the above inclusion criteria.

4.3 Procedure

4.3.1 Screening

Interested participants from the above sources will be asked to complete a telephone screening. The screening will include questions from the Generalized Anxiety Disorder – 2 (GAD-2) and Cross-Cutting Symptom Assessment (CROSS-AD), demographic and medication information, as well as questions to assess MRI safety. Participants who meet inclusion/exclusion criteria will be invited to schedule Study Visit 1. Study Visit 1 will take place either remotely via Zoom or in-person at the Rachel Upjohn Building. *In person procedures will be conducted following the University of Michigan's COVID safety protocols*.

4.3.2 Study Visit 1: Informed Consent, Diagnostic Interview

Informed Consent. The informed consent form will be mailed in advance of the visit. During this first study visit, participants will be given detailed information about the study. During this meeting, the potential subject will be encouraged to ask questions about the study, after which the informed consent form will be reviewed and signed. Study staff will go through and explain the informed consent document to the participant, which will be available and visible on SignNow. After the participant digitally signs the document, the research assistant will sign the document.

Diagnostic Interview and Questionnaires. Consented participants will then undergo a diagnostic interview, including the clinician-administered SCID-5 and CGI (see Section 4.5.1)This diagnostic assessment will be used to make the final determination about study eligibility. Participants will also be given the HAM-A to assess baseline anxiety severity in the past week. This visit may take 1-3 hours in total, depending on how many symptoms a subject endorses.

Randomization. Participants who meet eligibility criteria following the diagnostic interview will be invited to schedule Study Visits 2 and 3. Study Visit 2 will occur 1-5 days before Study Visit 3. In arms 2 and 3, a designated member of the study staff who will remain *unblinded* during the duration of the study will randomly assign participants to one of the two groups (veritable-NF or sham-NF). Approximately one-half of the sample will be assigned to each group. All staff interacting with the participant, including the participant themself, will be *blinded* to group assignment. To this end, the unblinded staff member will code the MRI scanning sequences with sets of random numbers that will be used to communicate to the MRI Technician which neurofeedback protocol should be employed during each study visit without revealing visually or by name if true feedback is being generated.

4.3.3 Study Visit 2: Reappraisal Practice

Cognitive Reappraisal Practice Training. During Study Visit 2, participants will first complete a series of self-report questionnaires assessing mental health symptoms and use of emotion regulation strategies (see Section 4.5.1). Next, participants will complete a 30–45-minute practice session with a member of the study staff. Negative images, like those that will be shown during the MRI session, will be displayed via Zoom if the visit is remote or displayed using the mock scanner if the visit is in-person. Participants will be guided to reinterpret situations to reduce negative affect (‘reappraise’ trials). During ‘look’ trials, participants will be instructed to passively view a picture as they normally would without trying to alter the emotional response. Research staff will be recording participants responses and performance on the pre-fMRI Scan Image Questions survey in REDCap. This visit may take up to an hour.

4.3.4 Study Visit 3: fMRI Scan

Study Visit 3 will follow the same procedures as Study Visit 2 of Phases 1 and 2, including pregnancy testing of female participants. However, half of the participants will be randomized to complete the ERT with veritable neurofeedback from the dm/vlPFC, while the other half will be randomized to complete the ERT with sham neurofeedback. Participants in the sham group will complete the same ERT as the veritable NF-group, however, the thermometer will display a pseudo-random feedback signal. This signal is generated to match the spectral characteristics of true feedback (from phases 1 and 2), including the same average success rate to control for the rewarding aspects of receiving feedback.

In the event of unexpected technical difficulties involving the scanner or neurofeedback software, subjects may be invited to complete additional fMRI sessions.

4.3.5 Study Visit 4: Follow-up Assessments

Two-week post questionnaires. Two-weeks after the fMRI visit, participants will complete online self-report measures from home via REDcap (see Section 4.5.3). These measures will take 15-20 minutes to complete in total.

One-month post interview. One month after the fMRI visit, participants will complete Study Visit 4, either in person or by phone, with a member of the study staff who is blinded to group assignment. During this study visit, participants will undergo a follow-up interview to assess anxiety symptom severity and complete a series of self-report measures. They will also be asked about how many psychotherapy sessions they attended over the course of the study, as well as the psychotropic medications they are on, to determine if there was a change in dose or a new medication. The visit may take up to an hour.

4.5 Measures and Assessments

Procedures	Pre-Screening (Pre-Consent)	Visit 1 Eligibility	Visit 2 Baseline + Training	Visit 3 fMRI			Visit 4 2-Week Follow-Up	Visit 5 1-Month Follow-Up
Eligibility				Pre-NF	NF	Post-NF		
Phone Screen	X							
Informed Consent		X						
Demographics			X					
Handedness[43]			X					
Structured Clinical Interview for the DSM-5 (SCID)[47] *		X						
Columbia Suicide Severity Rating Scale (C-SSRS)[48] * **		X						X
Treatment Follow-Up								X
Clinical Assessment								
Hamilton Anxiety Rating Scale (HAM-A[49]) *		X						X
Clinical Global Impressions Scale (CGI)[50] *		X						X
Depression, Anxiety and Stress Scales-21 (DASS-21)[44]			X				X	X
Penn State Worry Questionnaire (PSWQ)[45]			X				X	X
Emotion Regulation								
Emotion Regulation Questionnaire (ERQ[46])			X				X	X
Regulatory Emotional Self-Efficacy Scale (RESE)[51]			X				X	X
Experiences Questionnaire (EQ)[52]			X				X	X
Heidelberg Form for Emotion Regulation Strategies (HFERST)[53]			X				X	X
Perth Emotion Regulation Competency Inventory (PERCI)[54]			X				X	X
Beliefs & Personality								

Items from Stanovich Dualism Scale (DS)[55]			X			X		
Theories of Anxiety Scale (TOA)[56]			X				X	X
Theories of Intelligence Scale (TOI)[57]			X				X	X
Temporal Experience of Pleasure Scale (TEPS)[58]			X					
Task Training								
ERT Training			X					
Pre-NF IAPS Appraisals			X					
Randomization (Arms 2 & 3)			X					
fMRI								
fMRI Safety Screen				X				
Pre-NF Interview				X				
Short form composite of the Marlowe-Crowne Social Desirability Scale (SDS)[59]			X					
fMRI Neurofeedback Scan					X			
Post-NF Image Appraisals						X		
Post-NF Interview						X		

* = Clinician administered
** = As needed

4.5.2 Scan-Related Measures

Pre-NF interview.

- Belief about brain self-control[35]
- Motivation[64]
- Expected success to regulate brain during NF and in using CR[35]

fMRI Scan.

fMRI scanning will occur on a 3.0T GE Discovery MR750 scanner with a 32-channel receiver array head coil and a multi-band slice accelerated echo-planar imaging (EPI) sequence: 2.4mm isotropic resolution, 60 slices; TR/TE 800/30ms, flip angle=52°; multiband factor=6. Whole-brainT1-weighted scans will be acquired with a 3D MPRAGE sequence: 1mm isotropic resolution; TR/TI/TE/FA=2850ms/1060ms/2.3ms/8°; parallel acceleration factor=2. This imaging protocol matches that of the ABCD Protocol, providing high spatial- and temporal-resolution imaging of the functional and structural brain networks and is excellent in signal recovery in areas of high susceptibility artifact.

Emotion Regulation Task - Phase 1. Participants will complete 4-6 runs of the Emotion Regulation Task (ERT), adapted from Keller et al.[35]. Each run consists of 18 alternating 'look' and 'reappraise' trials. Each trial will begin with a 1s instruction cue to either 'look' or 'reappraise, followed by a presentation of a 6-30s negatively-valanced image from the International Affective Picture System[65] and the Open Affective Standardized Image Set[66], and a 4-6s fixation screen. At the end of the run participants will rate their negative affect.

Participants in Phase 1 will complete the ERT without neurofeedback to evaluate offline that the task activates areas of interest using traditional fMRI analytical methods. Participants will be recruited in groups of 4-8 to test continued iterations of task parameter modifications (e.g., timing, directions,

number of trials, images) until significant activation is reached in the contrast of interest (reappraise > look) averaged across subjects ($p < 0.05$ small volume corrected for multiple comparisons).

Note: Design parameters are anticipated, as task piloting in Phase 1 may reveal a need to make minor changes. Any such changes will not affect subject risk. Changes that do will be submitted for approval to the IRB.

Emotion Regulation Task. Half the participants will be randomized to complete the ERT with veritable feedback from the PFC as described in Phase 2. The specific region of interest (dmPFC or vlPFC) will be determined by the results of Phase 2 and arm 1 of Phases 3 and 4. Participants in the sham group will complete the same ERT as the veritable nf-group, however, the thermometer will display a pseudo-random feedback signal. This signal is generated to match the spectral characteristics of true feedback (established from Phase 2), including the same average success rate to control for the rewarding aspects of receiving feedback. As participants are blind to group assignment, inclusion of a sham-group controls for practice effects, fatigue, and learning that may occur without NF. On each trial of the task, a 4s presentation of vlPFC/dmPFC activity (reappraisal trials) or a crosshair (look trials) will appear following the image presentation screen. In the first functional run ('baseline'), participants complete the ERT without NF to establish baseline activity in the two regions of interest (ROIs: vlPFC and dmPFC), based on masks from previous CR meta-analyses (e.g., [20,21]). In the middle runs, participants complete the ERT with NF. In the final functional run ('transfer'), participants again complete the ERT without NF to establish ability to implement learning from NF training.

The NF set-up will utilize custom software, developed by co-investigator Scott Peltier. This includes motion correction, linear trend removal and spatial smoothing for each image presentation. The BOLD percentage signal change within the ROI is calculated using most recent "reappraise > look" contrast and fed back as a visual display reflecting BOLD signal change. The feedback display shows a thermometer whose minimum is initially set at 0% signal change. Bars fill the thermometer image to correspond to the increase in participant's brain activity using custom MATLAB scripts. On no feedback runs (baseline and transfer), the display shows a crosshair or a static thermometer.

Post-NF interview.

- Difficulty to complete the task
- Comments and suggestions about the task, including appraisals, affect, and arousal ratings of the images
- Perceived control of brain activity and perceived success of CR during NF[35]
- Tolerability and acceptability of NF
- Manipulation check of group assignment

4.6 Compensation

It is important that participants feel adequately compensated for the time spent participating in the various components of the study, including completing the diagnostic interview, being scanned, performing the NF task, completing self-report measures, and traveling to the research site.

	Amount
Baseline Assessment:	$20
Training:	$20
MRI Scan:	$50
Follow-Up Assessments:	$20

Participants who complete the study will be eligible to receive up to $110.

These values are similar to those used by other fMRI studies at the University of Michigan. If participants withdraw from the study early, they will be paid for the parts of the study they completed. Participants will be paid by check or gift card.

If a participant is asked to return for a second MRI scan brought on by scanner or neurofeedback malfunction, they will be compensated accordingly.

5. Participant Withdrawal

Participants may withdraw from the study at any time for any reason. The reasons a participant may withdraw include, but are not limited to:

- feeling claustrophobic in the MR scanner
- not desiring to continue

Researchers may withdraw a participant from the study if they have a reason to doubt the quality or validity of the data the participant would provide. Reasons may include, but are not limited to:

- participant being unable to hold still in the scanner
- participant no longer meeting criteria
- participant being unable to perform required tasks
- participant not complying with researcher or MRI tech instructions

6. Statistical Design

Aim 1. Evaluate the ability of adults with anxiety to increase prefrontal cortex activity during CR based on NF.

The task will be processed and analyzed using the same methods as Aims 1 and 2. To assess group differences in neuromodulation ability (**hypothesis 1**), a repeated-measures linear mixed effects model (LME) with participant as a random intercept, will examine the 3-way interaction of group (veritable-NF, sham-NF) x condition (reappraise, look) x time (baseline, NF1, NF2, NF3, transfer) on extracted BOLD activation from the dm/vlPFC mask.

Aim 1B. Determine the relationship between prefrontal cortex activity recruitment and CR ability in adults with anxiety.

To assess group differences in CR ability (**hypothesis 1B1**), a repeated-measures LME with participant as a random intercept, will examine the interaction of group (veritable-NF, sham-NF) x condition time (baseline, NF1, NF2, NF3, transfer) on negative affect ratings and prefrontal-amygdala connectivity during the ERT. We will use a psychophysiological interaction analysis to measure prefrontal-amygdala connectivity. Deconvolved time series from anatomical bilateral amygdala seeds for each participant will be multiplied by a vector for the reappraise > look contrast at each run. Regressors for the seed time series, the original condition and the interaction term will be convolved with the canonical hemodynamic response function. Contrast maps will be entered into second-level random effects analyses to test if veritable-NF shows greater prefrontal-amygdala connectivity than sham-NF.

For hypothesis 1B2, linear regressions will examine run-by-run associations between dm/vlPFC activity and 1) negative affect ratings and 2) prefrontal-amygdala connectivity, across all participants irrespective of training condition.

Aim 1C. Assess the impact of NF on anxiety symptoms and CR use over time (exploratory).

To examine the effect of NF on anxiety (**hypothesis 1C1**), a repeated-measures LME with participant as a random intercept, will examine the effect of time (baseline, 1 month) x group (veritable-NF, sham-NF) on the HAM-A. To examine the effect of NF on CR use (**hypothesis 1C1**), a repeated-measures LME with participant as a random intercept will examine the interaction of time (baseline, 2-week, 1-month) x group (veritable-NF, sham-NF) on the ERQ.

Linear regressions will examine the association between dm/vlPFC change (transfer-baseline) and change in HAM-A and ERQ scores (1 month – baseline) across all participants (**hypothesis 1C2**). Exploratory: Mediation will test if change in dm/vlPFC activity mediates the relationship between NF group and change in HAM-A or ERQ scores.

7. Data and Safety Monitoring Plan

7.1 Overall framework

Study monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s)

7.2 Roles & responsibilities for regular operations

PI: The PI will meet with study staff on a weekly basis to monitor the progress of the study. During phases when subject recruitment is occurring, the PI will review screenings and scheduling of assessments, as well as strategies to improve recruitment yield at weekly meetings with the study team. Issues such as maintaining confidentiality and privacy of participants during screening, assessment and data collection, protocol deviations and adverse events will be reviewed. For serious adverse events, the PI will be notified as soon as the SAE comes to the attention of study staff.

***Study coordinator/research assistant*:** This bachelors level individual will carry out the screening and informed consent, and they will provide additional study information, all under the supervision of the PI. The individual will be trained in screening, administering consent and information to the participants. Questions about eligibility will be discussed with the PI.

7.3 Frequency and type of other study monitoring

Institutional Review Board monitoring: Approval of all procedures, advertisements and materials given to subjects will be secured from the University of Michigan IRBMED. Annual reviews will be conducted by IRBMED, including the number of subjects screened, enrolled and withdrawn. The IRB will also review protocol deviations, adverse events (according to the reporting timetable of IRBMED) and complaints that arise in connection with the study.

Data monitoring: Data entry will be audited by study staff, who were not involved in primary data entry. Patient questionnaire data will be entered largely through electronic data capture, e.g., REDCap. Research data will be maintained on password protected computers, behind UM firewalls. All enrolled participants will receive participant identifiers, which will be used to code all research records for this project. Paper records with no identifying data beyond the research code are stored in locked cabinets. Copies of executed consent forms will be stored in separate locked cabinets. Demographic data will be entered into spreadsheets, and behavioral data will be merged into files. Password-protected electronic files separated from the research data will track consents, including the link between the research identifier and individual participants. This tracking file will be the sole link between participant identifiers and research data. By deleting the field linking identifiers with participant names, research records can be effectively anonymized.

7.4 Management of withdrawals and drop-outs

When participants drop out during the assessment, but before enrollment, all data will be destroyed. The consent form will be retained until study closure for regulatory purposes. Limited, de-identified data regarding ethnicity, age, gender, and diagnosis will be retained through the screening process in order to establish the sampling frame. If a participant drops out due to substance use but would otherwise meet the inclusion criteria, all data will be retained until the closing of the project, in case the participant becomes eligible and wishes to be reconsidered for the study before conclusion of recruitment. When participants drop out after enrollment, data may be destroyed, depending upon the wishes of the participant. However, consent forms and the research number will be retained.

8. Benefits/Risks

8.1 Benefits

Participants will be taught cognitive reappraisal, an evidenced-based emotion regulation skill. Previous work has found a brief single-session CR training to be of benefit to healthy individuals and those with anxiety (e.g., Dryman & Heimberg, 2018[14]). Thus, in our study, some may find participation to be a positive experience, and some may experience reduced negative affect, however, participants will be informed that the primary purpose of the study is not to directly benefit participants, but to inform our scientific understanding of the neural basis of cognitive reappraisal and the effects of real-time fMRI

neurofeedback. This information will be used to design new or improve existing treatments, which may benefit those with psychiatric disorders in the future.

8.2 Risks

8.2.1 Subject Confidentiality

Measures to protect patient privacy. Study staff will make every effort to limit identifiable information on potential subjects during recruitment. Conversations in which a patient's name must be mentioned, e.g. to determine potential eligibility, will occur in private settings of the clinic. The minimum amount of information will be recorded, and staff are alerted to the dangers of printing, faxing and emailing sensitive information. Phone conversations with potential research subjects will occur behind closed doors, and staff will ask callers if they are in a location where sensitive information can be discussed without danger of revealing confidential information. Any information gathered on subjects who prove ineligible will be destroyed as soon as possible (a list of patients who have declined or screened out will be maintained through the recruitment phase to avoid contacting these subjects again).

8.2.2 Known Potential Risks and Minimization of Risks

(1) Confidentiality risks and Protected Health Information (rare) - Loss of confidentiality around sensitive information such as psychiatric status, history of substance abuse, etc.

Minimization of Risk:

- Investigators and research staff who are responsible for conduct, management, and oversight of the study will be required to fulfill all training requirements for Good Clinical Practice (GCP). All investigators and research staff will be required to handle protected health information as outlined by the Health Insurance Portability and Accountability Act (HIPAA).
- Confidentiality of participant records is assured by assigning a research code and identifying all computer and paper files only by this code, except for a single tracking file. Paper records are kept in locked drawers in a locked room and electronic records are kept on secure server, to which only authorized research personnel have access.
- Screening forms for subjects who do not qualify for the study will be destroyed, except for anonymous information (such as age, gender and education).
- After the completion of data analysis, the record linking subjects to the research codes will be destroyed, thereby anonymizing the data.

(2) Risk of psychological discomfort, stress, or symptom exacerbation (infrequent) - Risks of psychological discomfort associated with the questions asked in the clinical interview or on some of the questionnaires.

Minimization of Risk:

- During the assessment process, subjects are reminded that they do not have to answer questions that make them feel uncomfortable.
- Participants are also reminded during the study that they may choose to terminate participation at any time throughout the study.

- Staff will check in with the participant frequently to if they are alright. Breaks will be offered to reduce any fatigue or stress.
- Interested participants will also be provided with a list of counseling resources.

- Suicide protocol: The suicide protocol begins with assessment of suicidal thoughts, plans, intentions, and behaviors with the C-SSRS (at initial screening). If assessment uncovers suicidal plans or intentions or recent behaviors, emergency evaluation will occur, and an appropriate plan of action will be followed, e. g. referral to psychiatric emergency room. The PI (a licensed clinical psychologist) will be contacted and will join the decision-making process about how to manage the suicidal thoughts or behaviors. Subjects who experience severe symptom worsening, including suicidal thoughts or behaviors, will be withdrawn from the protocol.

(3) The risks associated with potentially disturbing material (e.g., IAPS and OASIS pictures): There is a risk that subjects may become uncomfortable viewing the negative content of the IAPS and OASIS pictures.

To minimize risk:

- The research team has had extensive experience with the IAPS picture set, in over 200 subjects, including persons with psychiatric diagnoses such as schizophrenia and post-traumatic stress disorder. This image set has been used at laboratories all over the world, and subjects tolerate the images without significant difficulty. The most aversive pictures consist of images that one would encounter in a "very gory R-rated movie," as we explain this to our subjects. The OASIS picture is a well-validated dataset, designed at Harvard, to include updated images with similar content to the IAPS. When we inform our subjects about the study, we remind them they maintain control over their experience, and we encourage them to close their eyes for any image they find too intense. We also remind them that they can terminate the study, at any time. We have presented the images and discussed the protocol with members of the University of Michigan IRB, as well as community members at the local mental health agency. Mindful of potential psychological harm that some images could present for vulnerable psychiatric patients, we have excluded images suggestive of suicidal behavior from those we would present to our subjects. If any participant should become upset while viewing the pictures, the PI would be available to counsel the subjects and reinforce positive coping strategies to deal with the experience.

Risks Associated with fMRI Scanning:

(4) Discomfort or anxiety (occasional, not serious). There is a minor risk of discomfort or anxiety/panic from being in the confined space of the MRI scanner.

Minimization of Risk:

- The risks of discomfort and anxiety will be minimized by custom pads and pillows to make the subject as comfortable as possible. The subject can communicate with the machine operator via an intercom and may trigger an audible alarm at any time.
- Before the subject rolls into the bore of the magnetic, he or she is always reminded that they are free to stop the study at any time if they become uncomfortable.

(5) Peripheral nerve stimulation (rare, not serious). Fast imaging sequences, such as those employed in this study, have the potential to induce peripheral nerve stimulation (PNS). PNS can be described as a light touching sensation on the skin surface and may cause mild discomfort but is not harmful to the subject.

Minimization of Risk:

- The MRI machine is operated within FDA guidelines so the potential for inducing PNS is low.

(6) Slight dizziness, light-headedness or nausea (rare, not serious). Sometimes subjects report these symptoms during or immediately after the scanning session.

Minimization of Risk:

- If a subject feels light-headed, we will have them get up from the scanner bed very slowly, resting with the feet dangling for several seconds or more before attempting to stand.

(7) Incidental finding: Magnetic resonance image will reveal a minor or significant lesion in the brain, e. g. a tumor, previously unknown to the subject, and requiring additional follow-up. (rare, serious).

Minimization of Risk:

- Subjects will be made aware of the risk of learning about an anomalous finding in the study that might require further evaluation with a clinical MRI study. We will also inform the subject that many abnormalities will not be picked up in this study, since the scanning sequences we use are not sensitive to many forms of brain pathology. However, in the event that we find something that is very obvious, such as a large tumor, the PI will personally inform the subject by phone call, or in person.
- A neuroradiologist is available through the fMRI laboratory to review suspicious findings and provide guidance about the urgency and advisability of clinical follow-up. No diagnosis will be offered, but the P.I. may recommend that the subject pursue a follow-up study with their primary care clinician.
- The PI and study team will facilitate referrals and may provide copies of the brain image if these would be deemed helpful.

(8) Hearing damage - from loud, vibrating noises made by the scanner (very rare, serious).

Minimization of Risk:

- All subjects will wear earplugs and/or earphones throughout the procedure, which attenuate high decibel sounds, but still enable a subject to hear the intercom and respond to questions from the investigator while they are in the scanner.

(9) Injury (very rare, serious). Because the strong electromagnetic fields can move metal objects and cause heating, there is a risk that loose objects (jewelry, keys) outside the body could be accelerated by the magnetic field, striking and injuring a subject. There is also a risk that the magnetic fields could disturb

a metal fragment in the body, interfere with an implanted device, such as a pacemaker or neurostimulator, or cause metal (including foil-backed medication patches) on or in the body to heat up, causing harm.

Minimization of Risk:

- The MRI suite is kept clear of all objects that could be picked up by the magnetic field, and all subjects complete a comprehensive MR screening form prior to entering the scanner, which is reviewed by the MRI technologist (trained in clinical MRI) before scanning begins.

9. Quality Assurance and Audits

9.1 Audits and Inspections

A regulatory authority (e.g. FDA) may wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the study staff must immediately inform IRB, Medical School Regulatory Affairs, MIAP, etc.

9.2 Event Windows, Missed Assessments, Missed Sessions and Protocol Deviation Reporting

Any safety-related assessments (AE Questionnaire, etc.) which are missed will be reported to the IRB as a protocol deviation. For the other assessments, missing assessments will not be reported as protocol deviations unless they constitute > 10% of the total assessments. The time elapsed between the initial assessment and sessions are intended to be approximately 1 week, but scheduling logistics may mean this is not possible for all subjects, and may be longer for some (~ 30 days). These deviations are expected to be minor and will not be reported, although they will be recorded. These allowances should affect neither the scientific integrity nor the safety monitoring provisions of the protocol.

10. References

1. Haugg A, Renz FM, Nicholson AA, et al. Predictors of real-time fMRI neurofeedback performance and improvement – A machine learning mega-analysis. *Neuroimage*. 2021;237:118207. doi:10.1016/J.NEUROIMAGE.2021.118207
2. Baxter AJ, Vos T, Scott KM, Ferrari AJ, Whiteford HA. The global burden of anxiety disorders in 2010. *Psychol Med*. 2014;44(11):2363-2374. doi:10.1017/S0033291713003243
3. Moitra M, Santomauro D, Degenhardt L, et al. Estimating the risk of suicide associated with mental disorders: A systematic review and meta-regression analysis. *J Psychiatr Res*. 2021;137:242-249. doi:10.1016/J.JPSYCHIRES.2021.02.053
4. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *Med J Aust*. 2009;190(7 SUPPL.):S54-S60. doi:10.5694/J.1326-5377.2009.TB02471.X
5. Goodwin RD, Weinberger AH, Kim JH, Wu M, Galea S. Trends in anxiety among adults in the United States, 2008–2018: Rapid increases among young adults. *J Psychiatr Res*. 2020;130:441-446. doi:10.1016/J.JPSYCHIRES.2020.08.014
6. Ranøyen I, Lydersen S, Larose TL, et al. Developmental course of anxiety and depression from adolescence to young adulthood in a prospective Norwegian clinical cohort. *Eur Child Adolesc Psychiatry*. 2018;27:1413-1423. doi:10.1007/s00787-018-1139-7
7. Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JAJ, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: A meta-analysis of randomized placebo-controlled trials. *Depress Anxiety*. 2018;35(6):502-514. doi:10.1002/DA.22728
8. Van Dis EAM, Van Veen SC, Hagenaars MA, et al. Long-term Outcomes of Cognitive Behavioral Therapy for Anxiety-Related Disorders: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2020;77(3):265-273. doi:10.1001/JAMAPSYCHIATRY.2019.3986
9. Springer KS, Levy HC, Tolin DF. Remission in CBT for adult anxiety disorders: A meta-analysis. *Clin Psychol Rev*. 2018;61:1-8. doi:10.1016/J.CPR.2018.03.002
10. Lorimer B, Kellett S, Nye A, Delgadillo J. Predictors of relapse and recurrence following cognitive behavioural therapy for anxiety-related disorders: a systematic review. *Cogn Behav Ther*. 2021;50(1):1-18. doi:10.1080/16506073.2020.1812709/SUPPL_FILE/SBEH_A_1812709_SM1565.DOCX
11. Bruce SE, Yonkers KA, Otto MW, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: A 12-year prospective study. *Am J Psychiatry*. 2005;162(6):1179-1187. doi:10.1176/APPI.AJP.162.6.1179/ASSET/IMAGES/LARGE/P221F2.JPEG
12. Gross JJ. Emotion Regulation: Current Status and Future Prospects. *Psychol Inq*. 2015;26(1):1-26. doi:10.1080/1047840X.2014.940781
13. Garnefski N, Legerstee J, Kraaij V, Van Den Kommer T, Teerds J. Cognitive coping strategies and symptoms of depression and anxiety: A comparison between adolescents and adults. *J Adolesc*. 2002;25(6):603-611. doi:10.1006/JADO.2002.0507
14. Dryman MT, Heimberg RG. Emotion regulation in social anxiety and depression: a systematic review of expressive suppression and cognitive reappraisal. *Clin Psychol Rev*. 2018;65:17-42. doi:10.1016/J.CPR.2018.07.004
15. Zahniser E, Conley CS. Interactions of emotion regulation and perceived stress in predicting emerging adults' subsequent internalizing symptoms. *Motiv Emot*. 2018;42(5):763-773. doi:10.1007/S11031-018-9696-0/TABLES/3
16. English T, John OP, Srivastava S, Gross JJ. Emotion regulation and peer-rated social functioning: A 4-

year longitudinal study. *J Res Pers*. 2012;46(6):780-784. doi:10.1016/j.jrp.2012.09.006
17. Cisler JM, Olatunji BO. Emotion regulation and anxiety disorders. *Curr Psychiatry Rep*. 2012;14(3):182-187. doi:10.1007/s11920-012-0262-2
18. Troy AS, Brunner A, Shallcross AJ, Friedman R, Jones MC. Cognitive Reappraisal and Acceptance: Effects on Emotion, Physiology, and Perceived Cognitive Costs. *Emotion*. 2018;18(1):58. doi:10.1037/EMO0000371
19. Ortner CNM, Marie MS, Corno D. Cognitive costs of reappraisal depend on both emotional stimulus intensity and individual differences in habitual reappraisal. *PLoS One*. 2016;11(12). doi:10.1371/journal.pone.0167253
20. Wang HY, Zhang XX, Si CP, et al. Prefrontoparietal dysfunction during emotion regulation in anxiety disorder: A meta-analysis of functional magnetic resonance imaging studies. *Neuropsychiatr Dis Treat*. 2018;14:1183-1198. doi:10.2147/NDT.S165677
21. Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U. Corrigendum to "Neural network of cognitive emotion regulation - An ALE meta-analysis and MACM analysis." *Neuroimage*. 2015;111:631. doi:10.1016/j.neuroimage.2015.03.003
22. Buhle JT, Silvers JA, Wage TD, et al. Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cereb Cortex*. 2014;24(11):2981-2990. doi:10.1093/cercor/bht154
23. Dörfel D, Lamke JP, Hummel F, Wagner U, Erk S, Walter H. Common and differential neural networks of emotion regulation by Detachment, Reinterpretation, Distraction, and Expressive Suppression: A comparative fMRI investigation. *Neuroimage*. 2014;101:298-309. doi:10.1016/J.NEUROIMAGE.2014.06.051
24. McRae K, Gross JJ, Weber J, et al. The development of emotion regulation: An fMRI study of cognitive reappraisal in children, adolescents and young adults. *Soc Cogn Affect Neurosci*. 2012;7(1):11-22. doi:10.1093/scan/nsr093
25. Zilverstand A, Parvaz MA, Goldstein RZ. Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. *Neuroimage*. 2017;151:105-116. doi:10.1016/J.NEUROIMAGE.2016.06.009
26. Picó-Pérez M, Radua J, Steward T, Menchón JM, Soriano-Mas C. Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2017;79:96-104. doi:10.1016/j.pnpbp.2017.06.001
27. Henderson TA, van Lierop MJ, McLean M, et al. Functional Neuroimaging in Psychiatry—Aiding in Diagnosis and Guiding Treatment. What the American Psychiatric Association Does Not Know. *Front Psychiatry*. 2020;11:276. doi:10.3389/FPSYT.2020.00276/BIBTEX
28. Thibault RT, Lifshitz M, Raz A. The self-regulating brain and neurofeedback: Experimental science and clinical promise. *Cortex*. 2016;74:247-261. doi:10.1016/J.CORTEX.2015.10.024
29. Robineau F, Meskaldji DE, Koush Y, et al. Maintenance of Voluntary Self-regulation Learned through Real-Time fMRI Neurofeedback. *Front Hum Neurosci*. 2017;11. doi:10.3389/FNHUM.2017.00131
30. Ros T, Enriquez-Geppert S, Zotev V, et al. Consensus on the reporting and experimental design of clinical and cognitive-behavioural neurofeedback studies (CRED-nf checklist). *Brain*. 2020;143(6):1674-1685. doi:10.1093/brain/awaa009
31. Dudek E, Dodell-Feder D. The efficacy of real-time functional magnetic resonance imaging neurofeedback for psychiatric illness: A meta-analysis of brain and behavioral outcomes. *Neurosci Biobehav Rev*. 2021;121:291-306. doi:10.1016/j.neubiorev.2020.12.020
32. Pindi P, Houenou J, Piguet C, Favre P. Real-time fMRI neurofeedback as a new treatment for psychiatric disorders: A meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2022;119:110605. doi:10.1016/j.pnpbp.2022.110605

33. Sarkheil P, Zilverstand A, Kilian-Hütten N, Schneider F, Goebel R, Mathiak K. fMRI feedback enhances emotion regulation as evidenced by a reduced amygdala response. *Behav Brain Res*. 2015;281:326-332. doi:10.1016/J.BBR.2014.11.027
34. Zilverstand A, Sorger B, Sarkheil P, Goebel R. fMRI neurofeedback facilitates anxiety regulation in females with spider phobia. *Front Behav Neurosci*. 2015;9(June). doi:10.3389/fnbeh.2015.00148
35. Keller M, Zweerings J, Klasen M, et al. fMRI Neurofeedback-Enhanced Cognitive Reappraisal Training in Depression: A Double-Blind Comparison of Left and Right vlPFC Regulation. *Front Psychiatry*. 2021;12. doi:10.3389/FPSYT.2021.715898/PDF
36. Hamilton JP, Glover GH, Bagarinao E, et al. Effects of salience-network-node neurofeedback training on affective biases in major depressive disorder. *Psychiatry Res Neuroimaging*. 2016;249:91-96. doi:10.1016/J.PSCYCHRESNS.2016.01.016
37. Brühl AB, Scherpiet S, Sulzer J, Stämpfli P, Seifritz E, Herwig U. Real-time neurofeedback using functional MRI could improve down-regulation of amygdala activity during emotional stimulation: A proof-of-concept study. *Brain Topogr*. 2014;27(1):138-148. doi:10.1007/S10548-013-0331-9/TABLES/3
38. Herwig U, Lutz J, Scherpiet S, et al. Training emotion regulation through real-time fMRI neurofeedback of amygdala activity. *Neuroimage*. 2019;184:687-696. doi:10.1016/J.NEUROIMAGE.2018.09.068
39. MacDuffie KE, MacInnes J, Dickerson KC, Eddington KM, Strauman TJ, Adcock RA. Single session real-time fMRI neurofeedback has a lasting impact on cognitive behavioral therapy strategies. *NeuroImage Clin*. 2018;19:868-875. doi:10.1016/J.NICL.2018.06.009
40. Tsuchiyagaito A, Misaki M, Al Zoubi O, et al. Prevent breaking bad: A proof of concept study of rebalancing the brain's rumination circuit with real-time fMRI functional connectivity neurofeedback. *Wiley Online Libr*. 2021;42(4):42. doi:10.1002/hbm.25268
41. Zweerings J, Sarkheil P, Keller M, et al. Rt-fMRI neurofeedback-guided cognitive reappraisal training modulates amygdala responsivity in posttraumatic stress disorder. *NeuroImage Clin*. 2020;28:102483. doi:10.1016/j.nicl.2020.102483
42. Fitzgerald JM, Klumpp H, Langenecker S, Phan KL. Transdiagnostic neural correlates of volitional emotion regulation in anxiety and depression. *Depress Anxiety*. 2019;36(5):453-464. doi:10.1002/DA.22859
43. Body JV-LA of, Cognition B and, 2014 U. Edinburgh handedness inventory–short form: a revised version based on confirmatory factor analysis. *Taylor Fr*. 2013;19(2):164-177. doi:10.1080/1357650X.2013.783045
44. Antony MM, Cox BJ, Enns MW, Bieling PJ, Swinson RP. Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. *Psychol Assess*. 1998;10(2):176-181. doi:10.1037/1040-3590.10.2.176
45. Brown TA. Confirmatory factor analysis of the Penn State Worry Questionnaire: Multiple factors or method effects? *Behav Res Ther*. 2003;41(12):1411-1426. doi:10.1016/S0005-7967(03)00059-7
46. Gross JJ, John OP. Individual Differences in Two Emotion Regulation Processes: Implications for Affect, Relationships, and Well-Being. 2003;85(2):348-362. doi:10.1037/0022-3514.85.2.348
47. First MB, Williams JBW, Karg RS, Spitzer RL. *SCID-5-RV: Structured Clinical Interview for DSM-5 Disorders, Research Version*. Arlington, VA: American Psychiatric Association; 2015. https://www.appi.org/Structured_Clinical_Interview_for_DSM-5_Disorders-Clinician_Version_SCID-5-CV.
48. Posner K, Brown GK, Stanley B, et al. The Columbia-suicide severity rating scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266-1277. doi:10.1176/appi.ajp.2011.10111704
49. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;(32):50-55.

50. Guy W, Bonato R. *CGI: Clinical Global Impressions*. Chevy Chase, MD: National Institute of Mental Health; 1970.
51. Caprara GV, Di Giunta L, Eisenberg N, Gerbino M, Pastorelli C, Tramontano C. Assessing Regulatory Emotional Self-Efficacy in Three Countries. *Psychol Assess*. 2008;20(3):227-237. doi:10.1037/1040-3590.20.3.227
52. Fresco DM, Moore MT, van Dulmen MHM, et al. Initial Psychometric Properties of the Experiences Questionnaire: Validation of a Self-Report Measure of Decentering. *Behav Ther*. 2007;38(3):234-246. doi:10.1016/j.beth.2006.08.003
53. Izadpanah S, Barnow S, Neubauer AB, Holl J. Development and Validation of the Heidelberg Form for Emotion Regulation Strategies (HFERST): Factor Structure, Reliability, and Validity. *Assessment*. 2019;26(5):880-906. doi:10.1177/1073191117720283
54. Preece DA, Becerra R, Robinson K, Dandy J, Allan A. Measuring emotion regulation ability across negative and positive emotions: The Perth Emotion Regulation Competency Inventory (PERCI). *Pers Individ Dif*. 2018;135:229-241. doi:10.1016/j.paid.2018.07.025
55. Stanovich KE. Implicit philosophies of mind: The dualism scale and its relation to religiosity and belief in extrasensory perception. *J Psychol Interdiscip Appl*. 1989;123(1):5-23. doi:10.1080/00223980.1989.10542958
56. Schroder HS, Dawood S, Yalch MM, Donnellan MB, Moser JS. The role of implicit theories in mental health symptoms, emotion regulation, and hypothetical treatment choices in college students. *Cognit Ther Res*. 2015;39(2):120-139. doi:10.1007/s10608-014-9652-6
57. Hong Y, Chiu C, Dweck CS, Lin DM-S, Wan W. Implicit theories, attributions, and coping: A meaning system approach. *J Pers Soc Psychol*. 1999;77(3):588-599. doi:10.1037/0022-3514.77.3.588
58. Gard DE, Gard MG, Kring AM, John OP. Anticipatory and consummatory components of the experience of pleasure: A scale development study. *J Res Pers*. 2006;40(6):1086-1102. doi:10.1016/j.jrp.2005.11.001
59. Ballard R. Short forms of the Marlowe-Crowne Social Desirability Scale. *Psychol Rep*. 1992;71(3 Pt 2):1155-1160. doi:10.2466/pr0.1992.71.3f.1155
60. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x
61. Connor KM, Kobak KA, Churchill LE, Katzelnick D, Davidson JRT. Mini-SPIN: A brief screening assessment for generalized social anxiety disorder. *Depress Anxiety*. 2001. doi:10.1002/da.1055
62. Katherine Shear M, Brown TA, Barlow DH, et al. Multicenter collaborative panic disorder severity scale. *Am J Psychiatry*. 1997. doi:10.1176/ajp.154.11.1571
63. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097. doi:10.1001/archinte.166.10.1092
64. Freund PA, Kuhn JT, Holling H. Measuring current achievement motivation with the QCM: Short form development and investigation of measurement invariance. *Pers Individ Dif*. 2011;51(5):629-634. doi:10.1016/j.paid.2011.05.033
65. Lang Bradley, M.M., & Cuthbert, B.N. PJ. *International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual*.; 2008.
66. Kurdi B, Lozano S, Banaji MR. Introducing the Open Affective Standardized Image Set (OASIS). *Behav Res Methods*. 2016;49(2):457-470. doi:10.3758/s13428-016-0715-3