Study title: Enhancing Transdiagnostic Mechanisms of Cognitive Dyscontrol
Clinical trials identifier: NCT04912089
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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

Enhancing transdiagnostic mechanisms of cognitive dyscontrol using computer-based training

2. PRINCIPAL INVESTIGATOR

Jessica Bomyea, Ph.D., Assistant Professor, Department of Psychiatry, UCSD

3. FACILITIES

UCSD Keck Center for Functional MRI

UCSD Altman Clinical and Translational Research Institute Building, 9452 Medical Center Drive
La Jolla, CA 92037

4. ESTIMATED DURATION OF THE STUDY

5 years

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Mood, anxiety, and traumatic stress disorders are common psychiatric conditions - affecting over 40 million U.S. adults - and are leading causes of disability worldwide. People with these conditions are commonly plagued by difficulty controlling distressing personal thoughts and memories, collectively referred to as repetitive negative thinking symptoms. Models suggest that repetitive negative thinking is driven by executive functioning deficits, such that cognitive resources are insufficient to downregulate unwanted thoughts. Executive functioning deficits could be a promising treatment target but are not typically addressed with existing interventions. The long-term goal advanced by this project is to develop effective, mechanistic cognitive training programs that can improve cognition and reduce symptoms associated with mood, anxiety, and traumatic stress disorders. The objectives of this proposal are first to determine the optimal dose of a cognitive training program designed to improve executive functioning in this population using behavioral and neural outcomes. Our central hypothesis is that repeated training exercises will enhance executive functioning and will lead to a reduction of repetitive negative thinking in mood, anxiety, and traumatic stress disorders. The project will randomize participants with depression, anxiety, and/or traumatic stress disorders to one of two doses of cognitive training or a no-treatment control condition. We will examine executive functioning change with cognitive task performance and functional neuroimaging assessments. We will assess the relationship between change in executive functioning and clinical symptoms.

6. SPECIFIC AIMS

Improving control over working memory interference is theorized to be the most effective executive functioning manipulation for targeting clinical symptoms for mood, anxiety, and traumatic stress disorders. We will test whether two doses of COGnitive Enhancement Training (COGENT; 8 vs. 16 sessions) modify control over working memory interference across multiple units of analysis as compared to a no-training control condition.

Aim 1: Identify the cognitive effects and optimal dose of COGENT to improve executive functioning measured behaviorally (cognitive task) and neurally (fMRI). We hypothesize that individuals completing COGENT will show improved executive functioning on behavioral and neural measures relative to those assigned to the waitlist condition. An effect size benchmark will be used to evaluate whether there is added

benefit to completing more training sessions (16 versus 8) over the four week period to evaluate optimal dosing.

Aim 2: Evaluate the clinical effects of the COGENT program. We hypothesize that individuals completing COGENT will show a reduction in repetitive negative thinking. We will assess whether there are additional reductions in mood and anxiety symptoms.

7. BACKGROUND AND SIGNIFICANCE

Mood, anxiety, and traumatic stress disorders are prevalent and disabling conditions. These disorders share a number of etiological and clinical similarities, including elevated repetitive negative thinking symptoms (frequent, distressing thoughts about the self and/or the world that are perceived as uncontrollable). Despite slight differences in the clinical presentation of this symptom by disorder (e.g., rumination in depression, worry in anxiety, re-experiencing following trauma), types of repetitive negative thinking load on a single higher order factor rooted in shared neurobiological processes. Addressing repetitive negative thinking in treatment is critical because it relates to the onset, persistence, and recurrence of affective symptoms[2].

Executive functioning is a hypothesized causal mechanism of transdiagnostic repetitive negative thinking symptoms. Executive functioning is the neuropsychological domain that supports higher-order cognitive activities, including updating and monitoring information in working memory, inhibiting irrelevant information or behaviors, and shifting between mental activities[2]. Neural substrates of executive functioning include the frontoparietal network, consisting of the dorsal anterior cingulate (dACC), dorsal parietal cortex, dorsolateral prefrontal cortex (dlPFC), and the inferior frontal gyrus (IFG). These regions share connections with subcortical and posterior regions in order to maintain goal-directed cognition[31]. Neuropsychological deficits are observed in people with mood, anxiety, and traumatic stress disorders across behavioral (cognitive tests) and neural (functional neuroimaging) indicators of executive functioning[32-39]. Executive functioning deficits are associated with functional disability and poor quality of life, suicide attempts, and poor treatment response in individuals with these disorders, highlighting the importance of this cognitive domain for well-being and functional outcomes. Repetitive negative thinking is thought to arise from difficulty using executive functioning resources to remove irrelevant information from working memory, causing individuals to get “stuck” in negative thoughts. Thus, executive functioning deficits likely contribute to repetitive negative thinking symptoms in individuals with mood, anxiety, and traumatic stress disorders.

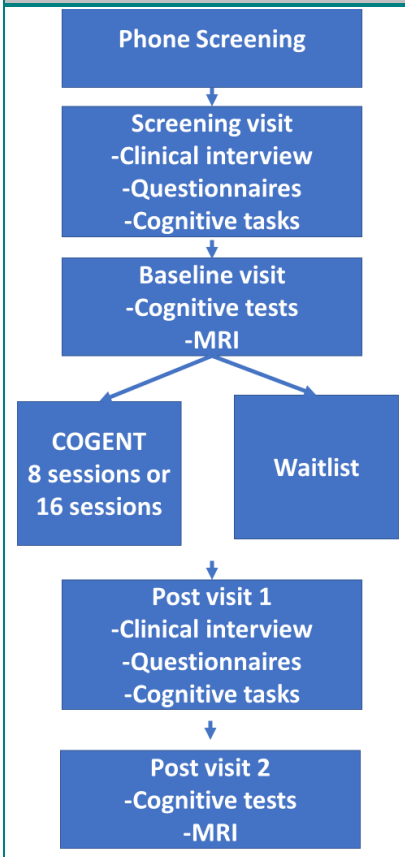
Targeted interventions for executive functioning represent an unmet therapeutic need. Estimates of non-response following first-line pharmacotherapy ranges from 30-70% and up to half of patients with mood, anxiety, and traumatic stress disorders do not adequately respond to cognitive behavioral therapy. Executive functioning deficits do not consistently remit in individuals with these disorders who complete standard treatments. Most psychosocial and pharmacological treatments are distal to cognitive mechanisms and only indirectly address cognitive skills. There is a continued need for treatment development to improve clinical response and reduce the burden of these disorders, particularly approaches that address executive functioning.

Targeting executive functioning in treatment would likely result in clinical symptom improvement for several reasons. First, work from our team and others suggest that improving executive functioning directly improves thought regulation, resulting in less repetitive negative thinking. Second, improving executive functioning would likely have helpful downstream effects because repetitive negative thinking exacerbates other clinical symptoms (e.g., negative mood, suicidality), including preceding and predicting worsening affective symptoms. Third, improving executive functioning could mitigate certain stressors that are partially rooted in ineffective cognitive functioning and worsen symptoms. This proposal seeks to test an executive functioning training program previously tested in our group in healthy participants and participants with PTSD in a broader transdiagnostic group of individuals.

8. PROGRESS REPORT

n/a

9. RESEARCH DESIGN AND METHODS



The proposed study is a randomized controlled trial of COGENT versus a no-training control (repeated assessment only) in participants with clinically elevated repetitive negative thinking symptoms. We will use a parallel group design. Primary assessment will include behavioral (cognitive task performance) and imaging-based assessments (fMRI) of control over working memory interference at two time points: baseline pre-training and immediately post-training. Neural activation will be used to assess generalization of training effects across multiple units of analysis. Within the COGENT intervention arm of the study, 8 and 16 sessions will be tested to determine optimal dose. Doses were selected based on our pilot work and empirical recommendations for maximizing cognitive training effects. **Hypotheses:** We hypothesize that COGENT will 1) improve behavioral performance on a cognitive task that assesses control over working memory interference, and 2) increase neural activation within the frontoparietal network during task-based fMRI compared to the control condition. We hypothesize that COGENT will improve symptoms relative to waitlist.

All procedures are considered experimental (i.e., not standard care) and solely for research purposes.

Participants

Approximately **95** participants endorsing elevated mood, anxiety, and/or traumatic stress symptoms who endorse repetitive negative thinking will be recruited and enrolled. Previous validation studies suggest that a cutoff score of 32 on the Repetitive Thinking Questionnaire-10 adequately detects clinically severe repetitive negative thinking. We anticipate that the sociodemographic makeup of the sample will reflect the distribution of biological sex, race, and ethnicity of the San Diego community. As prevalence of internalizing disorders is higher in women than men, it is possible that women may be overrepresented in the sample.

Procedures

Telephone screening: Prior to scheduling a study visit, participants will complete a brief phone screening. This screening will ask specific questions regarding eligibility to reduce participant burden, including questions to assess severity of mood and anxiety symptoms, clear exclusions (e.g., medication and psychotherapy status), and MRI safety. No medical record screening will occur. Participants will complete the Repetitive Negative Thinking Questionnaire-10 (RTQ-10), a psychometrically validated self-report measure that assesses disorder non-specific repetitive negative thinking. Clinically elevated repetitive negative thinking for eligibility purposes is defined as scoring above the cutoff recommended for diverging clinical samples (>32).

Screening Visit and Post Visit 1: Assessment of psychiatric disorders (MINI for DSM-5), past and current suicidality (Columbia Suicide Severity Rating Scale; C-SSRS), medications and treatment history, MRI safety screening, and history of head injury (Ohio State University Traumatic Brain Injury Identification Method Short Form; OSU TBI-ID) will occur during assessment for eligibility. Clinical interview measures will be audio and/or videorecorded for reliability assessment for participants who provide A/V consent.

A comprehensive assessment battery will be used to characterize the sample and measure change from pre to post-training. Participants will complete: a) Demographic Characteristics: PhenX Toolkit Mental Health Research Core Tier 1 assessment. b) Psychopathology symptoms: GAD7 items about anxiety and somatic symptoms. The PhenX Depression measure consists of symptoms from the Quick Inventory of Depressive Symptoms. General psychopathology will be assessed using the PhenX DSM-5 Level 1 Cross-Cutting

Symptom Measure, consisting of 23 questions assessing mental health domains, and the Positive Negative Affect Schedule. PTSD symptoms will be assessed with the PTSD Checklist-5 and the Childhood Trauma Questionnaire will query specific types of PTSD-related events. c) Repetitive negative thinking: Ruminative Response Scale (RRS) includes 22 items about tendencies to dwell on negative thoughts during periods of low mood; and the Penn State Worry Questionnaire (PSWQ) includes 16 items assessing pathological worry; the RNT-10 will be given at the screening visit; the Attention Control Scale will assess difficulty controlling thought content. The emotion regulation questionnaire will assess how participants attempt to control/regulate negative thoughts. D) Physical health and pain: WHODAS will be used to assess current self-rated health, the Insomnia Severity Index will evaluate sleep. e) drug and alcohol screening: the AUDIT, DAST, and PhenX nicotine screeners will be used to evaluate substance use; f) Cognitive assessments: Test My Brain assessments. These tasks ask participants to attend to, memorize, and process stimuli to measure neuropsychological abilities, and include the following tests:

Matrix Reasoning – test of the ability to identify "rules" to a puzzle (viewing a series of visuospatial patterns) and guess the next right answer.

Digit span – assesses working memory and attention. Digits are presented which the participant must repeat back.

Trail making task – measures executive functioning. Participants must draw a line between numbers and letters that are presented in random spatial locations, in the correct serial order.

Digit symbol matching – measures processing speed. Participants are shown a series of digits and must fill in the matching symbol using a "code" provided.

Participants will complete a modified Treatment Credibility Questionnaire for qualitatively assessing acceptability, satisfaction, and feedback about design features. All questionnaires and interviews administered are validated/published measures.

Baseline Visit and Post Visit 2: During the Baseline Visit, further cognitive assessments will be administered. NIH Toolbox Cognition Battery and a computer administered Operation Span task will be administered to further characterize cognitive functioning. This includes the following tests.

Flanker Inhibitory Control and Attention - measures allocation of one's limited capacities to deal with an abundance of environmental stimulation by asking participants to decide on the direction of an arrow that is contained within a row of visual stimuli.

Picture sequence – measures cognitive processes involved in the acquisition, storage and retrieval of new information. Participants are given a word verbally and asked to select the picture that corresponds to the word's meaning.

List sorting – measures the ability to store information until the amount of information to be stored exceeds one's capacity to hold that information. Participants are given a series of words and corresponding images and must recount the items in the correct order.

Oral reading recognition - Measures reading decoding skill and crystallized abilities. The participant is asked to read and pronounce letters and words as accurately as possible.

Dimensional Change Card Sort - The capacity to plan, organize and monitor the executive of behaviors that are strategically directed in a goal-oriented manner. Participants must guess the rule for matching a series of cards and update the rule when the game changes using only correct/incorrect feedback.

Pattern comparison - Assesses the amount of information that can be processed within a certain unit of time. Items are simple so as to purely measure processing speed. Participants are shown a set of two visual stimuli and are asked to choose whether the stimuli are the same or not.

Ospan task - In this task, participants try to memorize stimuli presented on the screen (e.g., letters, numbers) while simultaneously solving math puzzles. Each word appears on the screen, followed by a math puzzle, then another word, and another puzzle, with the number of stimuli ranging from 2 to 7. After a series of items and math puzzles have been presented, a recall screen appears where the participant indicates which items were seen.

Rspan task - In this task, participants try to memorize stimuli presented on the screen (e.g., letters, numbers) while simultaneously deciding if sentences make sense. Each word appears on the screen, followed by a sentence, then another word, and another sentence, with the number of stimuli ranging from 2 to 7. After a series of items and sentences have been presented, a recall screen appears where the participant indicates which items were seen.

Cognitive tasks have been split between the two appointments to minimize cognitive fatigue.

Baseline and Post Visit 2 MRI Assessments: fMRI scanning sessions will occur at baseline and post-training assessment points on a General Electric MR 750 3-Tesla MRI scanner using multiband protocols established by the Human Connectome Project. Each session will consist of a three-plane scout scan (16s), field mapping, a standard anatomic al protocol for standardizing and localizing activation maps) using 3D MPRAGE (TR=2500ms; TE=2ms; TI=1s; flip angle=80; FOV=256x256; 208 sagittal slices; 1mm isotropic voxels [6 minutes 9 seconds]). Functional runs will use a series of BOLD scans collected with Gradient-echo echo planar imaging (EPI) T2* (TR=800ms; TE=30ms; flip angle=520; FOV=216x216mm; 60 axial slices; 2.4mm isotropic voxels). These parameters enable us to cover the entire brain. Functional tasks will include:

Reading Span. This task assesses cognitive control under conditions of high and low interference. In this task, participants try to memorize stimuli presented on the screen (e.g., letters, numbers) while simultaneously solving secondary puzzles (e.g., decide if this sentence makes sense or not). Behavioral outcomes from this task include overall task performance (% correctly recalled stimuli) and reaction times.

Emotional working memory task. In this task, participants view neutral and valenced words, followed by a delay that contains distractor word stimuli. Participants try to remember the words presented to them. Behavioral outcomes from this task include overall task performance (% correctly recalled stimuli) and reaction times.

Participants may also complete resting state (approximately 10 minutes) and additional structural scans (approximately 5 minutes) if time permits, which do not require participant responses. Participant scans will be booked in a one hour block. Participants will complete both scans if they have 15 minutes left following the tasks. They will complete only resting state if they have 10 minutes left following the tasks. They will complete only the structural scan if they have 5 minutes left following the tasks.

COGENT, dose, and randomization: Following the baseline assessments, participants will be randomized to receive COGENT for 4 weeks (n=32) or an assessment-only control condition that receives clinical, cognitive, and MRI assessments at the same time points (n=32), stratified by diagnostic category (primary mood vs. primary anxiety/traumatic stress). In the basic COGENT training program framework, participants will view a series of items to be remembered, following by a secondary processing task where sentence puzzles are

solved. Participants will receive feedback about their accuracy at the conclusion of each set, and an adaptive algorithm will be used to ensure enough difficulty is maintained. The algorithm titrates advancement to the next trial based on meeting at least 85% accuracy on the prior set of trials. Our preliminary data indicate that a session frequency of 8 sessions, delivered twice weekly for 4 weeks (approximately 30 minutes per session) sufficiently improved cognitive performance. Participants assigned to COGENT will be randomized to complete dosing previously established in our work, 8 sessions over 4 weeks or a dosing of 16 sessions over 4 weeks based on literature indicating that training durations of 8 hours may be most effective. Randomization will be generated by Dr. Thomas and will be securely transmitted to the study coordinator. Task-based adherence data will be collected (number of sessions, frequency). Participants assigned to waitlist will be given the option to complete COGENT after all assessments if they wish.

COVID-19 Considerations: During the COVID-19 crisis, participants may be asked to complete the consenting, screening and screening measures, and cognitive paradigms using HIPAA compliant UCSD Zoom telehealth technology to minimize in-person contact. For in-person tasks, all UCSD and Keck safety procedures will be implemented based on the current Ramp Up phase.

Clinical monitoring: We will administer a brief questionnaire at the treatment mid-point, including the GAD7, PhenX depression, and RNT-10 for purposes of identifying individuals with increased symptoms. Any individual reporting >20% increase in inventories will be referred to the PI for evaluation per the Risk Management plan below.

Table: Assessments by visit	Active groups	Waitlist group
Screening visit MINI CSSRS MRI safety OSU-TBI RNT-10 Demographics GAD-7 Phenx Depression PhenX DSM RRS PSWQ WHODAS CTQ PANAS ACS ERQ PCL-5 AUDIT/DAST/Phenx Nicotine ISI Suicide Cognitions Treatment credibility	X	x
Midpoint clinical check GAD7 Phenx Depression RNT-10	X	
Baseline visit Cognitive assessments MRI	X	X

Cognitive training	X	
Post visit 1 (same as screening visit)	X	X
Post visit 2 (same as baseline visit)	X	X

STATISTICAL DESIGN AND POWER

Primary outcomes: Change in working memory and repetitive negative thinking. To determine whether COGENT engages the target as hypothesized (i.e., improving Ospan behavioral performance), we will analyze the effect of COGENT versus the control on the Ospan total correct score in a 2 (group: combined COGENT conditions, control) x 2 (time: pre-training, post-training) analysis of variance (ANOVA). Our hypothesis will be supported by a significant training by time interaction effect (p<.05; medium-large effect size based on power calculations). To investigate optimal dosing of COGENT training, effect size estimates will be compared by dose (8 vs. 16 sessions) for differences in mean change pre- to post-training. This analytic approach will be repeated for the RNT-10 Repetitive Negative Thinking and other symptom measures.

Secondary outcome of cognitive training neural generalization effects: Images will be co-registered using AFNI's 3dvolreg program conducted with the EPI image that results in the smallest adjustment in motion parameters (x, y, z, roll, pitch, yaw). Data will be preprocessed for despiking, censoring outliers, and blurred with an applied Gaussian blur of 4.0mm and transformed into MNI coordinates. The time series of motion parameters will be used to obtain an average for these six motion parameters for each subject, and subjects will be excluded if the average in any one of these parameters exceeds 2 standard deviations from the mean of the distribution of these average motion parameters. A multivariate regressor approach detailed below will be used to relate changes in EPI intensity to differences in task characteristics. A 0-1 reference function will be convolved with a gamma-variate function to model a prototypical hemodynamic response (6-8 second delay) and to account for the temporal dynamics of the hemodynamic response (typically 12-16 seconds). The convolved time series will be normalized and used as a regressor of interest. A series of regressors of interest, polorts for detrending, and the motion regressors will be entered into the AFNI program 3dDeconvolve to determine the height of each regressor for each subject. Voxel-wise normalized relative signal change will be obtained by dividing the regressor coefficient by the sum of the zero-order regressor and the mean first-order regressor. AFNI 3dREML will be used to reduce the false positives induced by cross correlations of the time series.

Group level analyses- the outcomes for the fMRI tasks are the difficulty regressor for the Rspan and emotional working memory tasks. The data will be entered into a mixed effects model, which offers a flexible framework to model the sources of variation and correlation that arise from grouped data (AFNI 3dLME). Once voxel-wise statistics have been calculated, we will use a threshold adjustment based on Monte-Carlo simulations in *a priori* functional regions of interest (ROIs) defined by neuroanatomical atlases of the frontoparietal circuit (NeuroSynth v5 "working memory" Topic 045) with FDR correction (p<.05) to guard against identifying false positive activations. The linear mixed effects model will include Group (COGENT vs. control) and Condition (interference vs. baseline) as between-subject factors and Time (pre-training, post-training) as the within-subjects factor, with subject included as a random factor.

10. HUMAN SUBJECTS

The current study will recruit 95 individuals enrolled at UCSD with a diagnosis of mood, anxiety, or traumatic stress disorder from psychiatric and primary care clinics. The study will overrecruit with the goal of randomizing 75individuals for a final evaluable sample of 65.

Inclusion criteria will include:

1) age 21-55
2) fluent in English (sufficient to understand and complete assessments in English)
3) diagnosis of mood, anxiety, or traumatic stress disorder
4) clinically elevated repetitive negative thinking

5) outpatient status
6) 6-week stability if taking SSRI medications

Exclusion criteria will include:
1) past year diagnosis of severe alcohol or moderate or greater substance use disorder
2) lifetime history of psychotic or bipolar I disorder
3) acute suicidality necessitating immediate clinical intervention
4) neurodegenerative or neurodevelopmental disorders
5) history of moderate or severe traumatic brain injury or other known neurological condition
6) sensory deficits that would preclude completing tasks
7) conditions unsafe for completing MRI scanning (e.g., metal in body)
8) currently receiving psychosocial treatment
9) currently receiving psychiatric pharmacotherapy, except SSRIs

There are no inclusion/exclusion criteria pertaining to gender, ethnic background, or health status aside from MRI safety requirements stated above.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Individuals will be recruited through IRB-approved announcements and advertisements posted throughout university, community settings, online media (e.g., craigslist), social media (e.g., Facebook), and ResearchMatch. The text of the proposed recruitment message is on a separate page labeled "ResearchMatch Message to Potential Participants." Individuals will also be recruited from other IRB-approved studies in the laboratory and only individuals who previously consented to be contacted for other research will be recruited. Clinical providers may be given recruitment materials to share with patients who express interest in research. All prior studies conducted in our lab ask individuals to provided written consent to be recontacted if they are interested in learning about future research by our team. Those who endorsed permission to be recontacted in these studies will be phoned and informed that there is a new study for which they may be eligible. Verbal consent will be obtained to provide information about the study and complete the screening if they are interested in participating. The investigator will make clear that this is a separate study and is completely voluntary and up to the discretion of the participant whether or not to participate.

12. INFORMED CONSENT

For the current study, all participants will undergo written informed consent. Participants will be of legal consenting age and capable of having study procedures explained to them. The IRB-approved consent form will be described with appropriate care, as documented by signature of the person giving permission.

Prior to in-person consenting, individuals will be contacted via phone for verbal consent and will be informed about the purpose of the study and asked to provide verbal consent for screening procedures. Verbal consent will be attained using the IRB approved Verbal Consent and Telephone Screening Form. Waiver of Documented Consent for recruitment screening purposes is justified because the only record linking the subject and the research would be the consent document and the principal risks would be the potential harm resulting from a breach of confidentiality. Each individual will be asked if they want documentation linking themselves with the research, and the individual's wishes will be respected. We will provide our contact information so that the individual is able to contact us at any time.

Documented informed consent will be obtained in-person at the ACTRI or via secure and HIPAA compliant telehealth during COVID-19. All procedures will follow FDA guidance ("FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" and "Use of Electronic Informed Consent Questions and Answers") for participant and staff safety. To do electronic consenting, research staff will 1) identify the participant via telehealth communication, 2) review the informed consent with the participant and response to any questions the patient may have; 3) confirm that the participant's questions have been

answered; 4) confirm that the participant is willing to participate in the study and sign the informed consent document while the witness is listening via telehealth technology; and 5) obtain verbal confirmation by the patient that they would like to participate in the study. The IRB-approved consent form will be provided to participants via telehealth using the screen share function which will allow for capture of a handwritten signature on the pdf form using the stylus function. Alternatively, participants will be sent a copy of the consent form via UC San Diego Health sponsored Docusign, after reviewing it with study staff. They will then sign the consent in real-time. The consent form will be sent to the person conducting the informed consent, who will also sign in real-time. All other elements of the consenting process will be the same as in-person.

For documented consent completed in-person, all procedures of the study, as described in the consent form, are reviewed with the prospective subject by a member of the research staff. If the individual agrees to participate, they are asked to sign the consent document and are provided a copy of the consent document and Experimental Subject Bill of Rights to keep. Consent documents will be reviewed for completeness and stored in a locked file cabinet in a locked office. Specific consent to be videorecorded will be obtained. All informed consent processes will occur in English. To participate, individuals must have sufficient proficiency in English language to understand and complete interviews, questionnaires, and all other study procedures.

13. ALTERNATIVES TO STUDY PARTICIPATION

Participants may opt not to enroll in the study.

14. POTENTIAL RISKS

Interview and Behavioral Assessments: The principal risks associated with completing the assessments are discomfort with the nature of questions, fatigue, and irritability with the testing procedure. These questions and procedures have been well-tolerated in previous studies with participant with anxiety disorders. All participants will be provided with information about local mental health resources, including information about crisis contacts.

Loss of confidentiality: By participating in this project, there is a very slight risk that sensitive personal information including psychiatric information or drug-use information which the subject has provided could become known outside the research setting. If some of the information collected, e.g. whether the subject had used illegal substances, were to become public, it may place the subject at risk for criminal or civil liability or may be hinder the subject's ability to get a job, affect his/her reputation, or have otherwise unforeseen consequences. In addition, there is some stigma associated with drug use; therefore divulging information regarding illicit drug use could be associated with adverse peer reaction. Subject information obtained during this study will remain confidential and be disclosed only with a subject's written permission.

Risks associated with functional magnetic resonance imaging: According to the FDA, there is currently no evidence that MRI with approved scanners of up to 7 Tesla signal strength are associated with adverse effects. However, there are two major sources of risk. First, the subject may experience discomfort being in the confined and sometimes noisy environment of the scanner. The main risks associated with these procedures are fatigue, boredom, and irritability with the testing procedure. The investigator and research assistants are trained to frequently check the subjects about their willingness and ability to continue with testing. If the subjects express concerns about continuing with testing, the investigator has instructed the research assistants to stop testing, offer a break, or, in case the subject is not willing to continue, to terminate the testing session. Overall, however, previous studies have not resulted in any significant discomfort or anxiety expressed by the participating subjects.

Second, the strong magnetic field and data acquisition pose some risks. These include

- The brief loud noises during the functional tasks may be physically uncomfortable.
- Physical discomfort: the subject may experience physical discomfort from being in the confined environment of the scanner for an extended period of time.

- The strong magnetic field will affect electronic, magnetic, and metal devices that subjects carry with them or that have been implanted in the subject's body. Subjects will be screened to prevent any metal from entering the scanner.
- Claustrophobia: Some subjects may get anxious in the confined space.
- Peripheral Nerve Stimulation effects: At times, some individuals may experience harmless muscle twitching or paresthesias, especially in the torso.
- Dizziness: Some individuals experience brief light-headedness while in the scanner or when rising from the MRI gurney too rapidly.
- Hearing: hearing damage may occur if appropriate hearing protection is not used because the MRI scanner produces a loud high frequency tone.

During the COVID-19 crisis, all UCSD mandates for mitigating risk of on-campus in person activities will be followed pursuant to the appropriate "phase", including the specific guidelines established by the Keck Imaging Center where study activities take place.

15. RISK MANAGEMENT

Confidentiality (see also section 16): Confidentiality will be maintained by keeping all identifying information (such as names and phone numbers) in a separate location from the study results. Records and data will be linked to coded numbers and anonymity will be rigorously enforced. All record keeping will in accordance with the stipulations of the local Institutional Review Board. Moreover, when contacting agencies, family, or friends who were provided by the subject, no information will be provided about the nature of the participant. To minimize social and legal risk, all of the data will be kept in locked cabinets or in electronic databases with secured passwords.

Discomfort and other risks related to completing computer, behavior, and fMRI assessments: The computers will be checked regularly for proper and safe operation. Patients and comparison subjects will be carefully screened and subsequently informed about the fact that the principal investigator or delegated clinical coverage will be available at all times during the experiment. Subjects are informed that they may end the test session at any time and that participation in this research is voluntary. Examiners will be clinically trained and sensitive to signs of stress, anxiety, or fatigue so that testing will be immediately terminated should any subject experience signs of discomfort.

In terms of other fMRI related issues, to minimize the risk of fear of closed spaces while in the MR scanner, patients will be extensively interviewed and informed about the nature of the task. We have previously used pictures of the MR scanner to familiarize subjects with the scanner environment. During scanning the investigator can hear the subject at all times and if, at any point in during the scanning, the subject expresses increasing discomfort, the operator will immediately intervene and terminate the scanning procedure. There is the possibility of an abnormal finding on the fMRI scan. However, the fMRI scans are not being done for clinical purposes, and the fMRI scan procedure is not sufficient for the clinical diagnosis of a possible brain disorder. The purpose of this scan is not to diagnose abnormalities, but on rare occasions a finding is observed that might be clinically important. Should there be cause for concern, we will forward to neuroradiology. Participants will be told about the potential discomforts associated with lying in the scanner for approximately 60 minutes. During scanning, subjects' heads and necks will be supported for maximum comfort, and earplugs and headphones will be required in the MRI scanner to protect from the noise produced by the scanner. The individuals will be given an alarm button, which they will be able to press if there is any discomfort or distress. Pregnancy testing with immediate results will ensure that no pregnant individual receives an MRI. Pregnancy testing results will be discussed with participants, and counseling will be provided should the participant indicate significant distress. In order to address any concerns regarding coercion, subjects will be informed that they are free to choose not to participate and may withdraw at any time (this is included in the consent form).

Participants may terminate the study or any parts of the study at any time. During scanning the investigator can hear the subject at all times and if, at any point in during the scanning, the subject expresses increasing discomfort, the operator will immediately intervene and terminate the scanning procedure.

Procedures for ensuring professional intervention: If a participant expresses significant distress or discomfort during any study procedure, the PI will be notified. The PI (a licensed clinical psychologist) will meet with the individual to evaluate clinical status and level of risk. Subjects may be referred for intervention as deemed appropriate based on level of distress or other clinical factors. The PI will also provide appropriate referrals for outside mental health services for all consented participants, even if the participant elects not to complete the assessment. Information reported will be kept in confidence with the exception that disclosure of suicidality, homicidality, or child or elder abuse warrant reporting to appropriate authorities. In cases of clinical emergency (e.g., current risk of suicide), participants will be escorted to the Emergency Department, which is immediately adjacent to the ACTRI.

The PI will bear final responsibility for the oversight of participant safety monitoring during the study. The UCSD IRB will be provided with annual reports on recruitment, data, and adverse effects associated with the study. Any incidences of serious adverse effects will be provided to the IRB in an official report as directed by the program's current guidelines. The PI and research staff will meet weekly to address issues in recruitment, data entry and quality, training plan progress, and any clinical or adverse effects issues as they arise.

The study will have an independent safety monitor who will be responsible for ongoing monitoring of the study and reporting to the IRBs any issues regarding the safety of study participants or threats to data integrity. The monitor and research team will meet via teleconference annually (more if needed). The PI will submit the protocol for approval by the monitor prior to initiating the study activities. The monitor will document minutes from each meeting, and the PI will provide a report to the IRB each year. The monitor will review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. The safety monitor will be selected based on their experience and competencies with respect to ensuring the safety and integrity of the study. The monitor will function independently of the research team and be free of career and financial interests of the team. The monitor will possess experience in conducting clinical and/or experimental pharmacologic trials, expertise in biostatistics, and a thorough knowledge of clinical trial ethics and human subject protection issues. This monitor will not be involved in the study in any other way, and will be named and approved by the UCSD IRB prior to any initiation of study procedures.

Summary of Safety Monitor activities:

1. Safety Reporting to the safety monitor. Serious Adverse Events – Immediate review will occur for Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, or event requiring or prolonging inpatient hospitalization. All SAEs will be required to be reported to the safety monitor regardless of any judgment of their relatedness to the study. Reporting to local IRBs will be completed within 24 hours of the SAE; reporting to the NIH will be made according to their respective regulations governing SAE reporting. Non-Serious Adverse Events – The safety monitor will be provided with annual summaries of the numbers and rates of adverse events. These reports will include types of events, severity, and intervention phase. Other Safety-Related Reports –The monitor will receive summary reports of participant retention and reasons for dropout by experimental condition (provided by Dr. Thomas) and study phase.
2. Study Stopping Rules – This study will be stopped prior to its completion if there is evidence that study procedures are associated with adverse effects that call into question the safety of the procedures; recruitment or retention difficulties preclude the ability to evaluate the study endpoints; new data becomes available during the trial that necessitates stopping the trial; the safety monitor has deemed it necessary to stop the trial for any other reason out of safety or data integrity concerns.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

All data are solely collected for research purposes and all study data will be de-identified. Records and data will be linked through coded number identifiers and anonymity will be rigorously enforced. The research team will be thoroughly trained by the PI on procedures to maintain confidentiality and on all study procedures. In cases when the participant contact information is no longer valid and we contact family or friends who were provided by the subject, no information about the nature of the participant will be provided, i.e. the research assistant will state that the individual had participated in a research study at UCSD and that the project requires a follow up interview.

To minimize social and legal risk, all data will be kept in locked cabinets in locked rooms, or in electronic databases located behind secure firewalls with secured password protection and access will be strictly limited to the research team within the PI's laboratory. All study records that contain identifying information (including contact information such as phone number and email address) will be kept in a locked cabinet in a locked office and only specific approved study personnel will have access to this information. The key needs to be maintained in order to inform participants of new information that may be derived from the results of the study. The key that relates the code numbers to participants will be kept in a locked cabinet, separate from any study records, in the principal investigator's office. Videorecordings of participants will be immediately transferred to electronic storage encrypted on our UCSD-based server. Once this data has been transferred it will be destroyed from the local machine. Destruction and responsibility of hard copy and speech data will be destroyed in accordance with UCSD policy and electronic study records will be destroyed in coordination with UCSD HRPP policy.

As per requirements by the NIMH for clinical trials, de-identified data containing a subject identifer, sociodemographic variables, and clinical data collected will be uploaded to the NIMH Data Archive (NDA; https://nda.nih.gov/).

17. POTENTIAL BENEFITS

Individuals deciding not to participate will be referred to community clinics offering mental health services on a sliding fee scale. The results of this study will provide information to inform novel treatments to benefit individuals experiencing symptoms of anxiety, depression, or PTSD. There may be a direct benefits to participants if they experience symptom reductions.

18. RISK/BENEFIT RATIO

Those modest risks that have been identified (e.g. feeling transient fatigue or anxiety) have combined to produce no known untoward effects or significant problems over the years in our clinical and imaging studies. Given that the risks are minimal and the benefits are potentially great for new insights into improving treatment outcomes in anxiety, mood, or PTSD we consider the ratio acceptable.

19. EXPENSE TO PARTICIPANT

There is no expected expense to study participants other than the time to complete study procedures.

20. COMPENSATION FOR PARTICIPATION

If an individual completes the baseline clinical assessment but is them deemed ineligible (e.g., unable to safely complete MRI) they will be compensated $30.Otherwise participants will be compensated $100 per completed set of assessment visits (maximum $200), $10 for each week of completed treatment or wait time (maximum $40), and a $10 completion bonus for all parts. These rates are on par with those established in current ongoing MRI research at UCSD. If the participant wishes, we will provide a copy of their brain scan image.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Principal Investigator

Jessica Bomyea, Ph.D.is an Assistant Professor in the Department of Psychiatry at the University of California, San Diego (UCSD) and licensed clinical psychologist

Co-Investigators

Alan Simmons Ph.D. is a Professor in the Department of Psychiatry at the University of California, San Diego (UCSD)

Raeanne Moore, Ph.D. is an Associate Professor in the Department of Psychiatry at the University of California, San Diego (UCSD)

Michael Thomas, Ph.D. is as Assistant Professor in the Department of Psychiatry at the University of California, San Diego (UCSD) with a concurrent appointment at Colorado State University

TBN Project Manager. A staff research associate will lead project management, screen potential subjects, conduct scanning, and work with the lab assistant to administer the experimental protocols and oversee the training and management of other research personnel. They will also liaise with recruitment sites in primary care and elsewhere, and manage recruitment and participant databases. She will assist with data management and sharing. The manager will meet once a week (or more often as needed) with Dr. Bomyea to review new participants and to discuss any concerns with data collection. They will monitor aspects of the budget, liaise with the UCSD Research Office including preparation of IRB protocols for submission and renewal, prepare documents and files necessary for study operation and scheduling, and engage in administrative duties necessary for study performance and completion.
TBN, Lab Assistant II . The lab assistant will be responsible for participant recruitment, phone screening, and scheduling, and will assist with conducting the behavioral tasks. They will also assist the project manager in data processing and management, including data entry and back up. The lab assistant will work with the database administrator and other project staff to assure data accuracy and completeness. Salary support is titrated to expected participant accrual rates and other project staff roles.

All personnel associated with this project will complete the online HRPP Human Subjects training and certificates will be kept on file in the study office.

22. BIBLIOGRAPHY

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23. FUNDING SUPPORT FOR THIS STUDY

NIMH R61 MH127005

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER
Not applicable.
26. IMPACT ON STAFF
Not applicable.
27. CONFLICT OF INTEREST
Not applicable.
28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES
Not applicable.
29. OTHER APPROVALS/REGULATED MATERIALS
Not applicable.
30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT
Not applicable.