Transdiagnostic Brain-Behavior Profiling to Enhance Cognitive Behavioral Therapy Response

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LIST OF ABBREVIATIONS

[Add frequently used abbreviations here. Delete any abbreviations that are not applicable to your research.]

ACC	Anterior Cingulate Cortex
CBT	Cognitive Behavioral Therapy
COI	Conflict of Interest
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
EG	Emotion Generation
EMG	Electromyography
ER	Emotion Regulating
FLARES	Fronto-Limbic Affect Regulation and Emotional Salience
fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practice
gSAD	General Social Anxiety Disorder
HIPAA	Health Insurance Portability and Accountability Act
ICD	Informed Consent Document
IPs	Internalizing Psychopathologies
IRB	Institutional Review Board
MDD	Major Depressive Disorder
OHRP	Office of Human Research Protections
OPRS	Office for the Protection of Research Subjects
PHI	Protected Health Information
PI	Principal Investigator
PS	Preliminary Studies
QA/QI	Quality Assurance/Quality Improvement
SAE	Serious Adverse Event
ST	Supportive Therapy

1.0 Project Summary/Abstract

Major Depressive Disorder (MDD) and generalized Social Anxiety Disorder (gSAD) are prevalent major public health problems. These internalizing psychopathologies (IPs) are characterized by excessive negative emotion and attention-memory bias. They are also associated with low levels of positive emotion though to a lesser extent in gSAD than MDD. Together, these symptoms of emotion dysregulation may reflect a shared neural dysfunction involving a Fronto-Limbic Affect Regulation and Emotional Salience (FLARES) network. Cognitive behavioral therapy (CBT) is 'gold standard' psychotherapy for MDD, gSAD, and other IPs. However, response is frequently unpredictive and varied. Critically, only a minority of patients achieve meaningful clinical improvement (e.g., 14% to 48%) leaving those with sub-optimal treatment response in persistent illness and at risk for relapse. These outcomes are daunting given CBT is a labor- and cost-intensive intervention of limited availability. CBT attempts to improve emotion regulation with techniques that draw on implicit (e.g., attentional control) and explicit (e.g., cognitive reappraisal) strategies that engage nodes within the FLARES network. Accumulating data indicate nodes in this network set the stage for clinical change and/or interact with the 'skills' developed by CBT during the course of treatment. Published data from our lab and others, and our theoretically-relevant and robust Preliminary Data (n=70-87 IP patients) comprising of MDD and gSAD patients show anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) function during implicit and explicit emotion regulation predict CBT success better than clinical or demographic measures, and that aberrant activation in FLARES network is ameliorated after 12 weeks of CBT. Translation of these findings into clinical practice requires new prospective and confirmatory studies adequately powered to demonstrate validity and reproducibility (i.e., testing/training data sets), and validation of less expensive, more portable/accessible psychophysiological (e.g., EEG, EMG) and cognitive/behavioral measures that are as equally good as (vs. fMRI) predictors and assays ("targets") of CBT treatment. In parallel, there is a need to examine how CBT exerts its mechanisms of action over the course of CBT. This work can lead to more precise mechanism-based interventions aimed at enhancing 'strengths' or at correcting 'deficits' that exist before CBT and/or when therapeutic gains are not being attained during course of treatment. The broad objectives of the proposed project are to: 1) Determine the accuracy and replicability of ACC and DLPFC function as a prospective predictor of CBT treatment response; 2) Determine how, where and when CBT treatment exerts its mechanisms of action; and 3) Develop new 'pragmatic' markers that predict CBT outcome. To carry out these aims we will consent 500 participants (including 100 healthy control participants and 400 patient participants) in order to enroll a total of 300 patients (100 with MDD, 100 with gSAD) and randomize them to 12 weeks of CBT or 12 weeks of 'placebo' psychotherapy (supportive treatment) (1:1 ratio). All patients will undergo fMRI and EEG scans before (Week 0), at midpoint of treatment (Week 6), and after CBT (Week 12). All patients and healthy controls (n=40 completers) will complete the same measures at the same time points to delineate FLARES dysfunction, CBT effects, and test-retest reliability of our measures.

2.0 Background/Scientific Rationale

Mood and anxiety disorders such as Major Depressive Disorder (MDD) and Social Anxiety Disorder (SAD) carry substantial chronic burden in the U.S. and worldwide1–3. They are amongst the most prevalent, disabling and costly mental illnesses in the U.S. (e.g., 12-mo. prevalence estimates of 8.6% in MDD, and 7.4% in gSAD;1,4–7. Adding to public health relevance, MDD and gSAD are independent risk factors for suicide8–12. Effective treatments can ameliorate this burden. Cognitive behavioral therapy (CBT) is empirically-supported, and similarly efficacious, psychotherapy for MDD and SAD13. CBT is also evidenced-based psychotherapy for other internalizing psychopathologies (IPs) suggesting active CBT components generalize across disorders. Nonetheless, CBT response is unpredictably varied and few achieve meaningful clinical improvement. Meta-analyses based on RCTs show that less than half of depressed and/or anxious patients (~42%) achieve meaningful change (e.g., >50% decrease in symptom severity) following CBT14. In real-world settings, recovery following CBT ranges from 14% to 48%15. Sub-optimal treatment response means millions of individuals continue with persistent illness placing them at high risk for relapse or recurrence14,15,16,17–19. Although data indicate MDD and SAD are illnesses rooted in behavioral-brain dysfunction and that CBT works by correcting this dysfunction, there is insufficient data to explain how and when CBT works and for whom.

Understanding how, when, and where CBT works and for whom is essential to tailoring treatment to improve clinical outcomes. In doing so, precise “targets” can be identified and “predictors” can be used to guide patients to CBT or an alternative treatment. Yet, critical gaps in the literature have hampered this pursuit. Most studies of CBT mechanisms examine only one unit of “change” limited to measures of behavior or brain. Also, the use of ‘distal’ measures of cognitive-behavioral-emotional change such as symptom severity and other patient characteristics has done little to advance precision medicine. Another challenge is the development of a ‘biomarker’, which requires large sample sizes, well-controlled designs, and formal tests of predictive power. Data across labs and our Preliminary Data (see below) have shown fMRI measures of neural function can accurately predict treatment response20–22 better than clinical measures. While fMRI has increased our understanding of the neurobiology and neural correlates of treatment change in MDD and SAD, it is limited in its clinical utility due to costs and data collection logistics (e.g., data analysis demands, contraindications to fMRI). Thus, the field needs more clinically-portable, low-cost measures that can be implemented in outpatient settings where CBT is delivered in an effective and efficient way. Also, for a biomarker to be clinically impactful, large samples are needed to establish its classification validity, reliability, and generalizability. We propose to address these challenges by: 1) advancing our fMRI-based mechanistic predictor by testing newly collected data against, and in combination with, preliminary data; 2) discover non-fMRI predictors; 3) examine both fMRI and non-fMRI measures of change over the course of CBT; 4) employ intent-to-treat analyses and directly compare CBT against Supportive Therapy; and 5) integrate multiple units of measures to improve predictive performance and examine factors that load on predictive validity and change.

3.0 Objectives/Aims

Aim 1. Determine how, where, and when CBT exerts its mechanisms of action on FLARES function. Hypothesis 1a: CBT (not ST) will normalize assays of ER and EG dysfunction with negative stimuli in MDD and gSAD. Hypothesis 1b: CBT (not ST) will normalize reward responses in MDD (not gSAD) and fear responses in gSAD (not MDD). Hypothesis 1c: Compared to ST, CBT-related symptom change will be partially mediated by FLARES-related changes at Week 6 and fully mediated by FLARES changes at Week 12.

Aim 2. Determine the predictive validity of baseline measures in FLARES function in CBT response. Hypothesis 2a: Baseline ER-related frontal activity with negative stimuli will specifically predict CBT (not ST) outcome at 12 weeks and 6-mo. follow-up, confirming and extending published/Preliminary Data in MDD and gSAD. Hypothesis 2b: Non-fMRI measures of ER and EG function with negative stimuli will specifically predict CBT (not ST) outcome at 12 weeks and 6-mo. follow-up. Hypothesis 2c: fMRI and non-fMRI predictors of CBT (not ST) response in MDD and gSAD will distinctly relate to reward and fear processes, respectively.

Aim 3. Integrate brain, behavior, and clinical units in the mechanism and prediction of CBT outcome and develop a new integrated assay of change and prediction. Hypothesis 3a: Integrating across multiple units will yield a composite measure that is sensitive to change specific to CBT. Hypothesis 3b: Integrating across multiple units will improve prediction performance. This integrated change and predictor index be more accurate, specific, and sensitive than any measure alone. We will compare the validity of change and predictive markers that represent brain function (a 'mechanistic' index that includes fMRI data) and those that represent FLARES function more distally (a 'pragmatic' index that does not include fMRI data) (exploratory).

Study Duration:

Patient participants will be in the study for approximately 38 hours over approximately 22 visits. 21 of the 22 visits will occur during a 15-19 week period. Patient participants will also be asked to complete questionnaires at a 6 month follow up visit. Control participants will be in the study for approximately 20 hours over approximately 8 visits spanning approximately 15-19 weeks.

4.0 Eligibility

Eligibility for patient participants will be determined in two phases:

First: Potential adult (ages 18-65) participants will be screened over the phone and those who report IP symptoms/distress in the clinical range will be invited for an interview. **Due to COVID-19, screening and all clinical assessments will be done virtually over a secure network (i.e., WebEx or by phone) whenever possible.** The interview will comprise the Structured Clinical Interview for DSM-5 (SCID)[148]. Primary diagnosis of MDD or gSAD will be based on SCID and standard cutoffs on clinician-administered assessments (see below).

Second: At the screening appointment, a clinical psychologist will review the patient's prior treatment history (type, duration, adherence) and this information, along with SCID

and clinical measures, will be used to decide if the patient is appropriate for CBT treatment. The screening clinician will *not* be the therapist who delivers treatment. A **Best-Estimate/Consensus Panel** of at least 3 study staff members (an assessor of at least bachelor's level [master's when possible] who has been trained by the primary investigator, PhD clinical psychologist, and MD psychiatrist) will confer following each assessment to determine eligibility for enrollment into the treatment study. Once participants are determined to be eligible for the study they will be randomized to receive either CBT or supportive therapy (ST).

Randomization: Following initial screening procedures, eligible patients will be randomized to 12 weeks of individual CBT or 12 weeks of individual supportive therapy. Because randomization does not guarantee comparability across groups, we will use covariate adaptive randomization, in which a new participant is sequentially allocated to a condition by taking into account baseline characteristics (e.g., symptom severity, age, sex)[149–153]. This approach will ensure patients are matched on the comorbidity that is allowed.

Eligibility for Healthy Control participants will be determined in two phases:

First: Potential adult (ages 18-65) participants will be screened over the phone and those who meet criteria to be a healthy control participant will be invited for an interview. **Due to COVID-19, screening and all clinical assessments will be done virtually over a secure network (i.e., WebEx or by phone) whenever possible.** The interview will comprise the Structured Clinical Interview for DSM-5 (SCID)[148]. Determination of history or current Axis I disorder will be based on SCID. While most interviews will be conducted by one rater, several raters/assessors will be associated with the project, and so inter-rater reliability studies will be conducted.

Second: At the screening visit, the primary investigator will confer with the assessor following each assessment to determine eligibility for enrollment into the study.

Eligibility will be documented in the participants research file.

4.1 Inclusion Criteria

Inclusion criteria will be: a) generally medically and neurologically healthy, including no evidence of mental retardation or serious cognitive impairment that would interfere with protocol adherence and/or task performance; b) between the ages of 18 – 65 years old, inclusive; c) primary diagnosis of MDD or gSAD based on the SCID DSM-5. Patients will be permitted to have limited comorbid and/or history of internalizing psychopathologies (e.g., generalized anxiety disorder, specific phobia, adjustment disorder). In addition to Inclusion Criteria stated above, MDD and gSAD participants for the treatment study must meet the following criteria: a) Liebowitz Social Anxiety Scale[145] (LSAS) Total Score at screening visit ≥ 60 for gSAD[246] and b) Hamilton Depression Scale[154] (HAM-D) Total Score at screening visit ≥ 17[247] or Beck Depression Inventory (BDI-II) Total Score at screening visit ≥16 for MDD.

4.2 Exclusion Criteria

Subjects with the following will be excluded from the study: a) personal current or past manic/hypomanic episode or psychotic symptoms; b) active suicidal ideation as determined by the Columbia Suicide Severity Rating Scale[248] (C-SSRS); c) ; d) prior history of standard CBT (failure or success) as determined by screening psychologist or PI; e) any current or recent (past 4 weeks) use of medication (prescription or non-prescription) with psychotropic effects; f) psychotherapy other than CBT/ST or psychotropic medication use during study; g) cognitive dysfunction (traumatic brain injury, mental retardation, dementia); h) active moderate or severe alcohol and/or substance use disorders; i) evidence of chronic self-injurious behavior in the past six months (i.e., cutting, burning, etc.) as determined by self-report and the Primary Investigator. To reduce overlap between MDD and gSAD, patients with MDD will not have current diagnosis of gSAD as determined with SCID and conventional diagnostic cutoffs; patients with gSAD will not have current diagnosis of MDD or Persistent Depressive Disorder (PDD) as determined with SCID and conventional diagnostic cutoffs.

For healthy controls: history or current Axis I disorder based on the SCID.

Additional exclusion criteria for all participants pertaining to the fMRI scan include: a) presence of ferrous-containing metals within the body (e.g., aneurysm clips, shrapnel/retained particles) or b) inability to tolerate small, enclosed spaces without anxiety (e.g., claustrophobia).

Termination Criteria: Subjects may be terminated for any of the following: (a) development of suicidal or homicidal ideation requiring hospitalization; (b) alcohol or drug use to the extent that psycho-social or vocational functioning is markedly impaired; (c) non-compliance with study protocol requirements; (d) development of a systemic, medical, neurologic or psychiatric illness requiring hospitalization; and (e) significant clinical deterioration (see below).

Noncompliance: Patients will be asked to discontinue their participation if they fail to appear for three sessions. We will make every effort to ensure that the treatment is accessible (i.e., scheduling treatment sessions during evening and weekend hours). The protocol for noncompliance is to ensure that patients receive appropriate treatment. If a patient decides to end treatment, which they are free to do at any time without consequence, the PI will coordinate a thorough exit evaluation and coordinate treatment referrals to community agencies or at the University of Illinois at Chicago. Patients will be informed of this protocol before starting treatment.

The study is meant to be completed over 15 weeks. We will allow for participants to miss up to 3 study sessions during the course of the study. We will allow for make-up sessions to occur within a study week on a case by case basis. The initial treatment session is to occur the 2nd week after the initial screening session and the fMRI/EEG and

neuropsychological assessment are to occur the 1st week after the initial screening session (they can occur during the 2nd- 3rd week after the initial screening session if there are scheduling constraints). The mid-treatment fMRI and EEG are to occur between session 5 and session 7 of the treatment sessions. The final fMRI/EEG and neuropsychological assessment are to occur before or after the final treatment session (they can occur during the 2nd- 3rd week before or after the final treatment session if there are scheduling constraints).

Inadequate Clinical Improvement or Clinical Deterioration: A potential risk exists that several patients will not achieve clinical improvement, as expected, or could experience clinical deterioration, during this protocol. This risk will be explained fully to the subject at study entry and during informed consent. If, and when, clinical deterioration warrants ending a patient's participation, the PI or treating psychologist will immediately refer the patient to receive appropriate clinical treatment by the outpatient clinic of the University of Illinois at Chicago, Department of Psychiatry, or another appropriate clinical referral.

Emergent Suicidal or Homicidal Risk: The clinician or research staff may remove a subject from the treatment trial if the PI thinks the subject is at imminent suicidal or homicidal risk, which will be evaluated during each treatment session. Endorsement of suicidal or homicidal ideation will be addressed in session. If the patient is deemed to have specific active suicidal or homicidal ideation the C-SSRS will be completed and the PI will be immediately notified. The subject will meet with the PI, or a psychiatrist, psychologist, or master's level clinician on the investigative team, and an appropriate clinical decision for emergent psychiatric evaluation will be made, including an evaluation of the need for psychiatric hospitalization.

4.3 Excluded or Vulnerable Populations

No individuals will be allowed to participate in the study if they are < 18 years of age or > 65 years of age. The study will exclude individuals who are pregnant or are trying to get pregnant to ensure safety during laboratory procedures. The study will also exclude non-english speaking individuals due to the inability to provide CBT/ST treatment in their native language.

5.0 Subject Enrollment

Recruitment and Attrition: We expect to enroll 40 patients (20 MDD, 20 gSAD) and 8 healthy control subjects per year in this 5-year project. In order to achieve our goal of 70 MDD and 70 gSAD patient completers we will over recruit - 400 - patient participants into the study. In order to reach our goal of 40 healthy control participant completers we will over recruit – 100 – healthy control participants.

Recruitment: Subjects will be recruited from several sources including flyers, mass emails, social media (only recruitment, no participant contact will occur via social media) and webpage advertisements. Current staff in the department will be informed about the study to pass along the information (in flyer format) to their patients. Potential subjects

will be given an information sheet regarding the project and contact information. Once a potential subject contacts the research staff, they will explain the study to the potential subject and if they appear to be eligible for the study the research staff will schedule the subject for an initial assessment through WebEx (participants are allowed to use their phone for this as well). Potential participants at the Mood and Anxiety Clinic will also be contacted and informed of the research study. We have a recruitment script that will be used to introduce the study and if they agree to hear more information, we will follow the same protocol for conducting phone screens. A waiver of signed consent will be requested for the phone screens in order to save a high number of ineligible subjects from coming in for the initial assessment session. During the initial assessment, the subject will be provided with the informed e-consent form on REDCap, along with an oral presentation of the material in the consent form by a research staff member. Only after signing the consent form will the subject be evaluated for participation in the study.

Disposition of drop outs and withdrawals: When subjects drop out during the assessment, but before enrollment, all research data will be destroyed. However, consent forms will be retained, as will the research number. Limited, coded data regarding ethnicity, age, gender, and diagnosis will be retained through the screening process in order to establish the sampling frame. A Waiver of Informed of Consent will be obtained for the screening and recruitment process to enable the retention of anonymized data.

When subjects drop out after enrollment, data may be destroyed, depending upon the wishes of the subject. However, consent forms will be retained, as will the research number. If any subject withdraws from treatment, efforts will be made to make contact to ascertain the reasons for dropping out. If after this discussion, the subject chooses to withdraw from the study, arrangements will be made to provide the best available treatment including pharmacotherapy and/or locally available psychosocial treatment.

Minimizing coercion and undue influence on participants: As the PI and her research team have clinical responsibilities the following procedures will be enacted in order to maintain separation from clinical responsibilities and influence and research responsibilities and influence. The mental health care providers involved in this study are interested both in the participant's clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, participants are informed they may ask for a second opinion about their care from another clinician who is not associated with this project. They are also informed that they are not obligated to participate in any research project offered by their clinician. Their participation in this research study is voluntary and they do not have to participate. The decision to not participate will not affect their clinical care now or in the future.

6.0 Study Design and Procedures

Study Design: We will consent a total of 500 participants (including 100 healthy controls and 400 patient participants) in order to enroll a total of 300 patients: 100 with MDD and 100 with gSAD. To balance disorder-specific effects with generalizability,

certain comorbidity/history of IPs will be permitted – MDD may have comorbid of IPs, except for gSAD. The gSAD group may have concurrent of IPs except for MDD. Using a 1:1 ratio, 50 MDD and 50 gSAD patients will receive 12 weeks of CBT and the remainder (50 MDD; 50 gSAD) will receive 12 weeks of a 'placebo' psychotherapy (i.e., supportive therapy/ST)[146]. Patients in the ST arm will be offered CBT at the end of 12-weeks. Therapy will be conducted virtually. Different units of measure (i.e., neurofunctional, neurophysiological, behavioral, self-reports) will be collected before treatment (Week 0), midway through treatment (Week 6), and immediately after treatment (Week 12). There will be a 6-mo follow-up at which time patients will complete standard clinical measures of symptom severity, impairment, and functional status. All patients will complete the same measures at the same time points. A healthy control (HC) group will also be recruited. HCs will complete the same measures at the same time points as patients; however, scans will be limited to Week 0 and Week 12 and they will not complete a 6-mo follow-up. The MRI scans will be done at the Center for MR Research. The EEG appointments and neuropsychological appointments will be done on the 3rd floor of the PI building. Questionnaires will be sent in a link to complete at home.

Participants will be asked to complete the following study procedures:

VISIT 1, Screening, Approximately 3 hours- Virtual

Participants will first be asked to complete a series of questionnaires which will take approximately 1.5 hours. They will meet with one of our study staff to determine if they are eligible to participate.

During this visit they will take part in a series of interviews about their feelings, thoughts, moods, impulses, and behavior. These interviews will take approximately 1.5 hours. Please note that some of the questions may be of a personal and/or sensitive nature. They do not have to answer any individual questions that make them feel uncomfortable if they do not want to.

If they are eligible for the study we will schedule them for further visits. If it is determined that they are not eligible to take part in this study, they will be referred for further evaluation and possible treatment to a clinical treatment program, if appropriate. All participants are given emergency contact information, including study staff and community resources, regardless of eligibility.

To reduce barriers, those who do not have access to internet or have equipment set up at home have an alternative option of participating and completing the screening appointment. You may have the option of coming into the building and use one of our private assessment rooms to complete the screening appointment and your clinical assessments.

National Institute of Mental Health (NIMH) National Database for Clinical Trials Related to Mental Illness (NDCT)

Data from this study may be submitted to the National Database for Clinical Trials Related to Mental Illness (NDCT) of the National Institute of Mental Health Data Archive (NDA). NDCT is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share deidentified information with each other. A data repository is a large database where information from many studies is stored and managed. Deidentified information means that all personal information about research participants such as name, address, and phone number is removed and replaced with a code number. With an easier way to share, researchers hope to learn new and important things about mental illnesses more quickly than before.

During and after the study, the researchers will send deidentified information about participant's health and behavior, to NDCT. Other researchers nationwide can then file an application with the NIMH to obtain access to their deidentified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to their privacy.

Participants may not benefit directly from allowing their information to be shared with NDCT. The information provided to NDCT may help researchers around the world treat future children and adults with mental illnesses so that they have better outcomes. NIMH will also report to Congress and on its web site about the different studies that researchers are conducting using NDCT data. However, participants will not be contacted directly about the data they contributed to NDCT.

Participants may decide now or later that they do not want to share their information using NDCT. If so, they can contact the researchers who conducted this study, and they will tell NDCT, which can stop sharing the research information. However, NDCT cannot take back information that was shared before they changed their mind.

Epic:EMR

Since this study involves treatment, data from this study will be submitted to Epic, a secure electronic record system at the University of Illinois at Chicago. Participants data will be assigned a unique medical record number as part of a restricted access account. To help protect participants data, Epic uses a variety of technical safeguards to protect the confidentiality, integrity, and availability of data including supporting Transport Layer Security (TLS)/Secure Sockets Layer (SSL) certificate technology and encryption. Keeping a record of the health and

behavior related to the treatment participants receive may help with their current or future health care.

Epic is an optional part of the study. The goal of including information in Epic is to increase standard of care; it is not related to research. The information that will be included in Epic is the same information reported by mental health workers who perform psychotherapy in the Mood and Anxiety Clinic at UIC and use Epic. For example, demographic information for those participants who are not already part of the UI health care system and information about mood and topics covered during a psychotherapy session. Psychotherapy session notes avoid unnecessary details and are written in a manner that assumes the participant will read it. Only licensed clinical psychologists on the team performing psychotherapy will record information in Epic.

VISIT 2, EEG & Behavioral Tasks, Approximately 3 hours- 3rd floor PI building:

During this visit they will also be given a medical screen to check that they are generally physically healthy and have no medical reason against taking part in this study. Part of the testing will include a urine screen for drugs of abuse and a pregnancy test. During this visit they will perform the following tasks on a computer while we monitor electrical signals from their brain (EEG):

Behavioral Tasks during EEG

a) Guessing Reward Task in which they will choose between one of two doors, they will then see a point on the screen followed by a response representing a gain of $.50 (‘↑’) or a loss of $.25 (‘↓’) with the chance to win between $0 and $15.00; b) Threat Sensitivity Task in which they will be shown different images, one at a time. They should look carefully at the images because an unpleasant stimulus (e.g. loud noise burst/mild hand shock) may occur before, during, or after the image is presented while other images may never be followed by the shock. They should try to predict whether the loud noise burst/shock will occur or not based on which image is shown. They will be asked to rate their anxiety and the degree to which they would avoid experiencing the shock again. The shock that they will receive will be uncomfortable but it will not be painful; c) Reward Sensitivity Task is the same as the Threat Sensitivity Task, except that instead of unpleasant stimulus (e.g. loud noise burst/mild shock), they may receive a monetary award of $0 to $15 after completing the task;d) Flanker Task in which they will be making rapid and accurate decisions about stimuli that are presented on the screen. They will see arrows on the screen and their job will be to respond to the direction of the middle arrow and ignore the other arrows; e) Reappraisal Task in which they will be asked to think about emotional pictures (e.g., scenes, facial expressions) and reduce or maintain their emotional response; f) Resting Task in which they will be asked to look at a point on the screen and remain still while they relax and let their mind wander. In any of the tasks, they may be

asked to rate pictures or faces (e.g., pleasantness/unpleasantness, low/high arousal level).

During all of these tasks, they will be connected to an Electroencephalography (EEG) machine. They will wear a special cap that contains 32 to 64 little disks (sensors). These disks need to be filled with a gel that helps the sensors record brain activity from their scalp. The gel washes off easily with water. This visit will occur after their screening visit.

VISIT 3, Neuropsychological Assessment, Approximately 1.5 hours- 3rd floor PI building:

During this visit, they will be asked to take part in a neuropsychological assessment. This includes completing a variety of activities involving concentration, attention, and memory administered on the computer. This assessment can be done as a separate visit or on the same day as one of their other study visits.

VISIT 4, fMRI Scan & Behavioral Tasks, Approximately 2.5 hours- Center for MR Research building:

During this visit, they will be asked to take part in one scanning session that includes a series of behavioral tasksand MRI scanning. Efforts will be made to schedule the fMRI visit after the EEG visit

fMRI scans take pictures of the way their brain physically appears and the way it responds to tasks of some kind (that is, looking at pictures, thinking about pictures in different ways, or making decisions about images). For the fMRI scans, they have to lie down on a table while a large machine makes images of their brain. They will undergo the fMRI scan session on a 3T GE MRI Imaging System at the fMRI Lab at the University of Illinois at Chicago. The scan does not hurt, but the machine makes a loud noise and they must lie still on a small table. They will be in the scanner for approximately 90 minutes.

They may be at the fMRI Lab for about 2.5 hours for the visit, which includes the time in the scanner and the preparation time for the fMRI assessment. The fMRI scan will be done by the staff at the UIC fMRI Lab.

Behavioral Tasks during fMRI

They are being asked to undergo the following behavioral tasks inside & outside the fMRI scanner. : a) Expression Matching Task in which they will match one of two presented faces with a target face based on their expression; b) Reappraisal Task in which they will be asked to think about emotional pictures (e.g., scenes, facial expressions) and reduce or maintain their emotional response; c) Face Interference Task in which they will identify a single target letter (N or X) in a string of letters while looking at faces; d) Monetary Incentive Delay task, in which they respond to a target (e.g., square, circle) to win or avoid losing $5.00; on

some trials there is no gain or loss; e) Passive Avoidance Task in which participants respond to an object (e.g., schematic face) and may win or lose $1.00 or $5.00; participants can also choose to avoid responding to an object, in which case a blank screen will occur instead of a monetary outcome; f) Resting Task in which they will relax in the scanner while looking at a blank screen for a few minutes. In any of the tasks, they may be asked to rate pictures or faces (e.g., pleasantness/unpleasantness, low/high arousal level)..

Prior to undergoing the EEG/MRI scan/computer tasks they will be given a urine drug test (testing for the presence of Cocaine, Amphetamines, Methamphetamines, Opiates, Benzodiazepines, Marijuana, and Methadone in their urine) and a breathalyzer (as deemed necessary by the research staff) to assure that they are not under the influence of alcohol or drugs. They will also be given a pregnancy test, if female before the fMRI scans. If they do not pass these tests, they will not undergo this study session and, if after the test the research staff has determined that it is safe for they to leave our unit, they will be released to go home. In this case, they may be terminated from this research project. Throughout the course of the study if their treatment provider or other research staff are concerned about their use of drugs or alcohol or that they may be pregnant they will be given a urine drug test, breathalyzer, or pregnancy test (if female).

VISITS 5-18, Cognitive Behavioral Therapy or Supportive Therapy Treatment, Approximately 1-2 hours- Virtual:

Cognitive Behavioral Therapy (CBT) and Supportive Therapy (ST) include 12 weekly, 60 minute individual therapy sessions with a single therapist. These visits will occur after their first EEG/fMRI visit. Once started in CBT or ST, at Weeks 2, 4, 6, 8, 10, and 12 they will also complete interviews and questionnaires lasting about 30 minutes to assess their mood and behavior. If they do not follow through with this program and do not keep their appointments, they may be removed from the study.

CBT and ST are types of talk therapy. CBT will involve three main components: 1) educational topics related to anxiety and/or depression and CBT principles; 2) modifying the way they think about things; and 3) making personalized behavior modifications and “homework assignments.” Behavior modifications practiced in session and outside of session as “homework” include doing things that may temporarily increase distress in the short term in order to reduce distress in the long term. For example, facing social fears and anxiety-producing situations they may be avoiding in a repetitive, prolonged fashion so that their anxiety is reduced naturally. Or participating in adaptive behaviors and activities (e.g., socializing, getting out of bed when the alarm goes off) even if they don’t feel up to it. Patients are encouraged by their therapist and reminded that they are fighting back actively against anxiety or depression, which is often empowering. Most

importantly, they will participate in negotiating the difficulty level of their homework, so that they will always stay in control of the experience. At the end of the study they and their study doctor will discuss their options for aftercare, if appropriate and provide them with any referrals as necessary.

In ST, they will be asked to talk about their feelings. Therefore, the therapist will ask open-ended questions to help they explore their feelings and related thoughts, which may bring to mind negative situations or experiences. Talking about such situations or experiences in a supportive, non-judgmental therapy setting can help people feel understood. It can also help they come up with strategies to better cope with anxiety or negative mood. Unlike CBT, they will not be asked to modify thoughts or behaviors. Therefore, they will not be asked to face fears or participate in behaviors that may cause temporary distress in session or outside of session as "homework."

All assessment and treatment visits will be done virtually due to COVID.

At the end of the study they and their study doctor will discuss their options for aftercare, if appropriate and provide them with any referrals as necessary.

VISITS 11 & 19, EEG & Behavioral Tasks- 3rd floor PI building, Approximately 3 hours:
During these visit they will repeat the EEG Assessment and Behavioral Tasks that they did in Visit 2.

VISIT 20, Neuropsychological Assessment- 3rd floor PI building, Approximately 1.5 hours:
During this visit they will repeat the neuropsychological assessment they did in Visit 3.

VISITS 12 & 21, fMRI Scan & Behavioral Tasks- Center for MR Research, Approximately 2.5 hours:
During these visit they will repeat the MRI Scanning and Behavioral Tasks that they did in Visit 4.

6 MONTH FOLLOW-UP- Virtual, Approximately 30 minutes:
During this visit they will repeat the interviews and questionnaires to assess their mood and behavior that they completed at their Week 2, 4, 6, 8, 10 and 12 visits. This visit will last about 30 minutes. This visit will occur approximately 6 months after their last treatment visit.

All assessment and treatment visits will be done virtually, unless the participant is not able to engage in virtual visits (e.g., does not have access to internet or other necessary equipment). Participants may have the option of coming into the building and use one of

our private assessment rooms to complete the screening appointment and their clinical assessments.

Study Visit Type, Location, and Length
Screening (**Visit 1**) – 3 hrs – **PI/ virtual (WebEx/phone)**
First EEG (**Visit 2**) – 3 hrs –**PI**
First Neuropsychological Assessment (**Visit 3**) – 1.5 hrs –**PI**
First fMRI (**Visit 4**) – 2.5 hrs – **Center for Magnetic Resonance Imaging**
1st CBT or ST Treatment Visit (**Visit 5**) – 1 hr – Session 1 – Wk 1 – **PI/virtual (WebEx/phone)**
2nd CBT or ST Treatment Visit & Surveys (**Visit 6**) – 1½ hrs – Session 2 – Wk 2 – **PI/virtual (WebEx/phone)**
3rd CBT or ST Treatment Visit (**Visit 7**) – 1 hr – Session 3 – Wk 3 – **PI/virtual (WebEx/phone)**
4th CBT or ST Treatment Visit & Surveys (**Visit 8**) – 1½ hrs – Session 4 – Wk 4 – **PI/virtual (WebEx/phone)**
5th CBT or ST Treatment Visit (**Visit 9**) – 1 hr – Session 5 – Wk 5 – **PI/virtual (WebEx/phone)**
6th CBT or ST Treatment Visit (**Visit 10**) – 1½ hrs – Session 6 – Wk 6 – **PI/virtual (WebExphone)**
Second EEG (**Visit 11**) – 3 hrs – Wk 6 (may occur after session 5) –**PI**
Second fMRI (**Visit 12**) – 2.5 hrs – Wk 6 (may occur after session 5) – **Center for Magnetic Resonance Imaging**
7th CBT or ST Treatment Visit (**Visit 13**) - 1 hrs – Session 7 – Wk 7 – **PI/virtual (WebEx/phone)**
8th CBT or ST Treatment Visit & Surveys (**Visit 14**) - 1½ hrs – Session 8 – Wk 8 – **PI/virtual (WebEx/phone)**
9th CBT or ST Treatment Visit (**Visit 15**) - 1hr – Session 9 – Wk 9 – **PI/virtual (WebEx/phone)**
10th CBT or ST Treatment Visit (**Visit 16**) - 1½ hrs – Session 10 – Wk 10 – **PI/virtual (WebEx/phone)**
11th CBT or ST Treatment Visit (**Visit 17**) - 1hr – Session 11- Wk 11 – **PI/virtual (WebEx /phone)**
12th CBT or ST Treatment Visit & Surveys (**Visit 18**) - 1½ hrs – Session 12 – Wk 12 – **PI/virtual (WebEx/phone)**
Third EEG (**Visit 19**) – 3hrs – Wk 12 –**PI**
Second Neuropsychological Assessment (**Visit 20**) – 1.5 hrs –**PI**
Third fMRI (**Visit 21**) – 2.5 hrs – Wk 12 – **Center for Magnetic Resonance Imaging**
6 month Follow-Up (**Visit 22**) (30 mins) 6 months following completion of treatment – **PI/virtual (WebEx/phone)**

Healthy Control Subjects only complete Visits 1, 2, 3, 4, 11, 19, 20, and 21. HC subjects complete the assessments listed below for the screen, S6 (completed at Mid-EEG), and S12.

Session 6 assessments may be done at the S6 treatment visit or at the mid-treatment EEG or fMRI session.

Assessments at Study Entry, During, and After the Treatment Phase

						Mid-Scan Completed*								
Assessment	**Screen**	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**	**6mos**
Demographic History	■													
Treatment History	■													
SCID	■													
C-SSRS **also as needed*	■													
General Health Questionnaire	■													
WTAR	■													
SES	■													
Ethnicity/Race	■													
AUDIT	■													
DAST	■													
BIS-BAS	■													
CTQ	■													
Credibility/Expectancy		■					■							
MAIA	■						■						■	■
PANAS	■						■						■	■
RSAS	■						■						■	■
PDSS-SR	■						■						■	■
PSWQ	■						■						■	■
IDAS-II	■						■						■	■
PSQI	■						■						■	■
RRS	■						■						■	■

STAI Y1 & Y2														
SDS														
HAM-A														
HAM-D														
LSAS														
BDI-II														
ERQ														
ACQ														
ADUI														
Brief Medication Questionnaire														
PCL-5														
IUS														
UPPS														
TEPS														
SNI														
fMRI EEG Survey														
CCTS_SR														
6-mo follow-up Tx Hx														
AEUPM														
CGI														
Session Notes														
BiAffect														
RSQ-COVID 19														

*Mid scan forms completed at mid-MRI.

Safety Measures: If a participant (patient or healthy control) reports use of alcohol or drugs or the potential for being pregnant during the course of the study to any research staff or treatment provider they will be given a urine drug screen or pregnancy test to see if they test positive for any drugs or pregnancy. The results of the drug and pregnancy screen will be kept confidential. If the participant does screen positive on the drug or pregnancy screen this would be grounds to terminate their study participation. If a participant arrives to an appointment smelling like alcohol or acting inebriated they will be given a breathalyzer to ensure they can participate in the scheduled study activities and that they are safe to leave the appointment.

Recruitment: Subjects will be recruited from several sources including flyers and webpage advertisements. Current staff in the department will be informed about the study to pass along the information (in flyer format) to their patients. Potential subjects will be given an information sheet regarding the project and contact information. Once a potential subject contacts the research staff, they will explain the study to the potential subject and if they appear to be eligible for the study the research staff will schedule the subject for an initial assessment through WebEx (this can also be done over the phone). A waiver of signed consent will be requested for the phone screen in order to save a high number of ineligible subjects from coming in for the initial assessment session. During the initial assessment, the subject will be provided with the informed e-consent form on REDCap along with an oral presentation of the material in the consent form by a research staff member. Only after signing the consent form will the subject be evaluated for participation in the study.

Behavioral Intervention Studies

Cognitive Behavioral Therapy (CBT) and Supportive Therapy (ST): Subjects will meet and initiate treatment with a licensed clinical psychologist who will deliver individual manualized CBT or Supportive Therapy. The trained Assessor of at least bachelor's level will meet with the assigned treating therapist to discuss the findings obtained from the initial assessment.

CBT: The clinical psychologist will use a manualized CBT approach tailored to MDD[162,245] or gSAD[161].Over a 12-week period sessions will include core CBT strategies -- psychoeducation, cognitive intervention (e.g., cognitive restructuring), behavioral changes (i.e., fear exposure, behavioral activation strategies) and relapse prevention.
ST: The clinical psychologist will use an ST approach that resembles client-centered therapy of Carl Rogers (1951) which has been used as a control psychotherapy[146,249,250]. The manual is based on supportive psychotherapy principles[251,252]. Over a 12-week period sessions will emphasize reflective listening and elicitation of affect. In contrast to CBT, therapists allow patients to determine the focus of each session, pulling for emotion, validating emotions when possible, and offering empathetic comments. Therapists will refrain from delineating any CBT theoretical framework and avoid cognitive and behavioral techniques that might overlap with CBT.

As noted in the Exclusion Criteria, no enrolled patient will be on, or start, psychotropic medication of any kind during the 12-week CBT or ST protocol. Both CBT and ST sessions will last one hour.

Therapy Training, Competence, Integrity. *Training.* All therapists will have a PhD in clinical psychology and have had advanced training (i.e., at least 2 years of experience) in CBT and other standard psychotherapies. They will be required to demonstrate adequacy in treatment delivery, therapists will complete two videotaped CBT training cases and two videotaped ST training cases under Dr. Craske's supervision. *Treatment integrity* is defined as how well therapists restrict themselves to the rationales of a specific treatment. Therapists will be assigned to both CBT and ST to reduce therapist effects. While this increases the risk that therapists may inadvertently introduce prohibited treatment strategies from one intervention to the next, integrity will be maximized by three factors: (1) standardized treatment manuals, (2) ongoing adherence and competency checks, and (3) weekly supervision with Dr. Duffecy at UIC and bi-monthly supervision with Dr. Craske. Supervision will include review of treatment techniques, session objectives for each patient, and problem-solving to maintain adherence to protocols. Also, all study sessions will be taped for fidelity assessment and supervision purposes (the videotapes will be erased two years after the completion of the study). Session tapes (~20% randomly selected) will be rated for fidelity by raters who did not treat the patients[253]. Subjects in ST arm will be offered standard CBT after completion of ST treatment.

Fidelity Assessment. Coded videotapes will be sent to Dr. Craske at UCLA to complete the fidelity assessment. No other research will be conducted at UCLA.

7.0 Expected Risks/Benefits

Diagnostic/Assessment Procedures: The diagnostic interviews (and questionnaires) are time consuming and may be boring to some individuals. These are, however, necessary in order to determine eligibility for the study. In addition, questions about alcohol/drug use, interpersonal relationships, abuse/trauma history, and questions related to history of suicidal and/or homicidal behavior may be considered sensitive by some subjects. The collection of such data poses a potential risk of loss of confidentiality around sensitive information such as psychiatric status, history of substance abuse, etc. Subjects will also be informed in the consent document that confidentiality will be limited in cases where the subject reveals intentions to harm themselves or others, and the investigator feels that the proper authorities may need to be notified in order to prevent the occurrence of harm to the subject, or others. Interviews will be conducted by experienced mental health workers who will maintain confidentiality and all data from interviews and questionnaires will be numbered so as to conceal the identity of the subject.

Other Tasks: There is little risk to participating in the tasks except possible mild boredom. Any distress experienced while participating in the study is unlikely to persist beyond completion of study procedures. There is little risk to participating in the other behavioral tasks (viewing emotional faces/emotional pictures), other than boredom or mild subjective anxiety; the PI will be available during all behavioral tasks in order to evaluate and recommend treatment for the emergence of any anxiety/panic attack or elevated levels of anxiety. Regarding the NPU task, some subjects may feel anxiety in response to the acoustic startle probes used during the startle tasks. Finally, the threat and experience of electrical stimulation during the startle and certain tasks involving pictures/faceselicit temporary mild anxiety by design. Any distress experienced while participating in the study is unlikely to persist beyond completion of study procedures.

Magnetic Resonance Imaging: Magnetic resonance imaging is non-invasive, widely used, and safe. The potential risks such as static magnetic field, radio-frequency field, magnetic field gradients, and acoustic noise are rarely dangerous or life threatening. Additional minor and/or rare risks include: (a) discomfort or anxiety from being in the confined space of the MRI scanner; (b) 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; (c) risks of hearing damage due to loud noises produced by the scanner; (d) risk that the 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; (e) risk of injury from objects accelerated by the strong magnetic field of the magnet, striking the subject; or metallic substances on the skin or foreign bodies implanted deliberately or accidentally in the subject that acquire kinetic or thermal energy from the magnetic or radiofrequency emissions of the

MRI, causing tissue injury to the subject; (f) sometimes, subjects report a temporary, slight dizziness or light-headedness when they come out of the scanner; (g) potential risk for pregnant women: According to the NIMH Council Workgroup on MRI Research and Practices (September, 2005), “there is no known risk of MR brain scanning of a pregnant woman to the developing fetus for scanning at 4T or less, and no known mechanism of potential risks under normal operating procedures.” Nevertheless, subjects should be warned about potential risks not yet discovered.

Discovery and disclosure of incidental finding or abnormality on MRI scans: During the formal consent process, all subjects will be informed about the potential risks of discovering an incidental finding or abnormality on their MRI scan. If an abnormality is found in a subject’s MRI scan, the PI will contact the subject and refer the subject for medical follow-up for the problem if the subject requests, including a referral to a primary care physician. If a subject has a primary care physician, the PI will contact the subject’s doctor, at the request and with permission from the subject, to inform him/her of the finding on the MRI scan and to help him/her get the subject appropriate follow-up. The decision as to whether to proceed with further examination and/or treatment lies solely with the subject and his/her primary care physician.

EEG Assessment: Foreseeable risks or discomforts associated with EEG procedures include the potential for psychological fatigue arising from the completion of the EEG tasks. During the EEG recordings there is also a small possibility of mild skin irritation (redness) where rubbing alcohol and the electrodes contact the skin. This, however, is usually temporary. There may be minor discomfort from wearing an EEG cap, which is similar to wearing a fabric swim cap. There is also a small possibility of skin irritation (redness) from the gel used in the EEG cap. Participants may feel local pressure points developed during the EEG procedure from some of the electrodes. This, however, is usually temporary. There are no known risks in the procedure of measuring EEG activity. The system used in the proposed study is one of the most popular and widely-tested systems available for EEG. EEG has not been associated with adverse effects in humans when conducted using appropriate protocols.

Treatment with Cognitive Behavioral Therapy (CBT) or Supportive Therapy (ST): Risks of CBT or ST participation are no more than minimal. Participation in CBT does produce temporary increases in anxiety, but this is by design and is a critical component of the efficacy of these techniques. Levels of anxiety are carefully moderated and titrated by the licensed therapist to keep them in a therapeutic and non-detrimental range. Thousands of patients have been treated successfully with this approach, without any long or short-term negative consequences. Supportive Therapy resembles client-centered therapy (aka person-centered therapy) of Carl Rogers (1951) which can be considered ‘treatment as usual’ in terms of psychotherapy and as such has been used as a ‘control’ psychotherapy as it comprises common factors to psychotherapy such an empathetic therapist[146,249,250].

Neuropsychological Indices: Procedures for neuropsychological tests as well as neuropsychological aspects of the tasks are considered minimal risk. There are no more

than minimal risks associated with attention and executive function (CANTAB) as the tasks are very similar in form to standard neuropsychological measures and involve experiences people undergo on a regular basis.

8.0 Data Collection and Management Procedures

Sources of material from human subjects include: (a) informed e-consent, (b) telephone screen form, (c) diagnostic interviews, (d) clinician-administered and self-report questionnaires, (e) urine drug screen, (f) urine pregnancy test (women only), (g) fMRI data, (h) behavioral data (e.g., startle data, mood ratings, reaction times), (i) EEG data, (j) neuropsychological data

Each subject is given a unique number and there is a password-protected master key database separate from study data linking the subject with the code only accessible to UIC research team members. This file is a password-protected master key database, which links the participant with unique participant codes; it is stored on the password-protected server, and kept separate from study data. The information in this file could be used to *indirectly* identify participants. The record linking participants to the research codes will be destroyed 6 years after completion of the study, thereby anonymizing the data.

All research materials from participants will be labeled with the unique participant code (not participant name).

Paper forms with the participant code will be kept in a locked cabinet where only official study staff has access. The data will be entered by research staff into a REDCap database.

Data collected from fMRI and EEG tasks, the computerized neuropsychological assessments, clinical data, and behavioral data for each participant will be saved with a research identifier number only and stored in computer files without reference to any personally identifiable information. These files will be stored on the lab server, which is joined to the Psychiatry Department's username and password-protected, Windows 2008r2 active directory domain. In addition to password-protection, the server is behind UIC's Academic and Computing Support firewall, which implements network address translation, meaning that no one from outside of the domain can connect to the server. These measurements will be obtained solely for the purposes of research. All research materials will be maintained in strict confidentiality.

Only official UIC study staff has access to the data. If any member of the research study leaves, his or her access to the network and all files will be removed immediately, thereby terminating access to this file and other files associated with the study.
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9.0 Data Analysis

fMRI Data Collection and Processing: All MR scanning will be performed at the UIC Center for Magnetic Resonance Research on a 3.0 Tesla GE Discovery MR750 System (Milwaukee, WI) using a state-of-art 8-channel radiofrequency coil and updated software (Discovery 20.0, Neuro-optimized gradients). Whole-brain blood-oxygen-level dependent (BOLD) fMRI signal measures will be acquired using a T2*-weighted Echo-Planar Imaging sequence with BOLD contrast to measure task-related effects, optimized to reduce susceptibility artifact in the ventral frontal cortex and medial temporal lobe. A high-resolution T1 scan will provide precise anatomical localization and structural analyses. We will assess T2* images from all participants and measure signal quality with signal-to-noise ratios. Only scans with high quality and scan stability with minimum motion will be analyzed. All data will be processed and analyzed with Statistical Parametric Mapping SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) using conventional methods, in terms of spatial realignment, smoothing, and time series convolution – recently described in our published papers[143,205]. Condition effects are modeled with regressors representing the occurrence of each event type, and effects will be estimated at each voxel, and for each subject. We will employ a random effects analysis, which handles within and between subjects variance. Covariates for each event type will be generated by convolving a stick function with the canonical HRF and entering it into the GLM.

Exploratory Whole Brain Analyses: Whole brain analyses for activation and connectivity maps will be generated by the first-level analyses. Brain images will be entered into second-level analyses implemented in standard software packages (e.g., SPM, AFNI) to mirror analyses performed with extracted values.

EEG Data Collection and Processing: The EEG assesses brain electrical activity through surface recording disks (electrodes) which are placed near the participant's head. The electrodes transmit the signals, which are then amplified and stored on a computer. The procedure is entirely non-invasive. A custom designed 32-electrode lycra cap will be placed on the participant's head. In order to record the brain's activity, these disks need to be filled with a gel which allows the electrodes to better record brain activity at the scalp. The gel is completely water soluble, and the procedure is painless. After an accurate signal is assured, the signal derived from the electrode cap is then amplified, transmitted to a computer, and stored for later analysis. In addition to the EEG recording, several facial electrodes to measure muscle movements and eye blinks will be placed. For EEG processing, separate averages will be computed for each condition noted above including experimental and control trials. Analyses will focus on, but are not limited to, the positive and negative event-related potential (ERP) mean amplitude (e.g., LPP, P3, P1, N2, reward positivity) obtained for specific sets of frontal electrodes (fronto-central: FCz, FC3, FC4; frontal: F3, Fz, F4; centro-parietal: CP1, CP2, Cz, and Pz; and occipital). EEG will be recorded continuously allowing capture of windows (e.g., 100ms-200ms, 220ms-400ms, 400ms-1000ms) robust to ERPs of interest.

10.0 Quality Control and Quality Assurance

Please see below for description on how MRI and startle data is evaluated for adherence with the protocol. All self-report data will be double entered, checked for discrepancies, and cleaned. Analyses will assume that 'missingness' occurred at random, with data imputed when necessary. Type 1 error rates will be adjusted using Bonferroni corrections.

The PI of the study and her research staff are responsible for the monitoring of the research and the evaluation of the data quality. After each MRI scan the scan data is transferred from the MRI center within approximately 24hrs to the lab storage drive and during that transfer. The data is closely reviewed to ensure its quality and that nothing is missing.

The startle, EEG and MRI data are processed using automated scripts; however, the PI and study staff examines each file by hand to ensure acceptability and high quality data.

11.0 Data and Safety Monitoring

Weekly meetings of the research staff of this study will be conducted that will include review of accrual, consenting procedures, protocol adherence, adverse events, and quality control of all data obtained from the study in the previous weeks. Minutes of these meetings will be recorded, signed by the PI, and archived in a Data and Safety Monitoring Binder. Please note that serious adverse events (SAEs) will be reported by the PI to the IRB and NIH as appropriate within 5 business days of her (or her team's) knowledge of the SAE. A Serious Adverse Event (SAE) is any adverse experience occurring during the study that: (a) results in death, (b) is life-threatening (e.g., suicidality, homicidality), (c) results in hospitalization or prolongation of hospitalization, (d) results in persistent or significant disability, (e) results in congenital anomaly or birth defect, or (f) events not meeting the above criteria but requiring intervention to prevent one of these outcomes are also considered serious adverse events. Finally, any unanticipated problems (its occurrence, frequency or severity is new or greater than previously known or as expected based on subject characteristics, including natural progression of disease). They are always unanticipated by definition and will be reported to the IRB and NIH as appropriate within 5 business days of the PIs (or her team's) knowledge of the event.

Adverse events (AEs) not determined as serious will be graded as moderate or mild. Moderate is defined as any non-serious event which causes discomfort and requires treatment, but does not pose any significant or permanent risk of harm to the subject or require in-patient hospitalization, including social or psychological trauma causing moderate or temporary distress, significant embarrassment, stigmatization of individual or community/ group, disruption of familial/social relationships or nontrivial emotional

distress. Moderate AEs will include evaluation in the emergency room not leading to hospitalization. Mild is defined as any non-serious event of less than moderate severity.

Moderate AEs that are expected or are not associated with a greater risk of harm to subjects or others than previously known will be reported to the IRB and NIH as appropriate at the scheduled continuation review. Moderate AEs that are unexpected and indicate that the research is associated with a greater risk of harm to subjects or others than previously known will be reported to the IRB and NIH as appropriate within 15 business days of the PIs (or her team's) knowledge of the event.

Mild AEs that are expected, unexpected, or are not associated with a greater risk of harm to the subjects or others than previously known will be reported to the IRB and NIH as appropriate at the scheduled continuing review.

A data safety monitoring board (DSMB) will be established for this study; members of this board are Dr. Tory Eisenlohr-Moul and Dr. Jaclyn S Weisman.. It will meet at regular intervals, not less than twice per year in February and September, and more frequently if deemed necessary. Members of this DSMB will include clinical researchers from the Department of Psychiatry, who are not affiliated with this project/grant. The DSMB for this trial will: 1) review reports filed by the PI to the DSMB regarding the conduct of this study; 2) review interim analyses of outcome data and recommend whether the study should continue without modification, require modification, or require termination based on these analyses; 3) review the nature of any serious adverse event that occurs during the trial, as it occurs during the trial (please note that serious adverse events will be reported to the DSMB within 5 business days of the time that the research team becomes aware of the event). 10% samples of patient's charts may be audited to confirm eligibility, documentation of informed consent, and adherence to the protocol.

12.0 Statistical Considerations

Aim 1. Determine how, where, and when CBT exerts its mechanisms of action in FLARES network.

Hypothesis 1a: CBT (not ST) will normalize assays of emotion regulation and emotion generation dysfunction with negative stimuli in MDD and gSAD. A mixed-effects model[209] will be used to estimate separate slopes for distinct time periods with logit link and indicators for the intervention groups to adjust for within-therapist correlation. The model will include an intercept representing the baseline differences between two intervention groups (CBT,ST), a slope representing the magnitude of change in units of measure from baseline to Wk 12, a variable for intervention (CBT, ST), and a covariate for diagnostic group (MDD, gSAD) to assess disorder-specific effects. Terms for interactions between the intervention variable and the slopes will assess differences in change in units of measure during treatment and post-treatment. Treatment outcome, based on primary symptom measure (other units of measure to be tested are fMRI, EEG, behavioral, self-report) will be compared at Wk 6 and post-treatment. For dichotomous response data (responder/non-responder), a mixed effects logistic regression model will be used to include multiple random effects related to units of

measures. Planned comparisons will include regression analysis for separate measures and simple effects analyses (e.g., t-tests).

Hypothesis 1b: CBT (and not ST) will normalize reward processes in MDD (but not gSAD) and fear in gSAD (but not MDD). The same analysis above will be performed and include measures of reward (e.g., VS activity, money accumulated in MID) and fear (e.g., subcortical reactivity to fearful faces, EMG to unpredictable threat).

Hypothesis 1c: Compared to ST, CBT-related symptom change will be partially mediated by FLARES-related changes at Week 6 and fully mediated by FLARES changes at Week 12. Similar to above, this hypothesis will also be tested using a series of random coefficient regression models. For example, we will consider FLARES-related changes as a predictor of primary symptom measure. If the inclusion of this variable eliminates or partially reduces the significant difference in trajectories between intervention (CBT, ST), they will be considered putative mediators of condition effects. Formal methods for explicitly testing mediated effects in the context of random coefficient regression models have been developed by Krull and MacKinnon[210]. In short, these authors generalize the OLS point estimates and standard errors of mediated effects[211] to the context of random coefficient regression models. A covariate for diagnostic group (MDD and gSAD) will also be included in the model. While models presented in Krull and MacKinnon[210] are of a simpler form than the models discussed here, we will attempt to generalize their work to accommodate inclusion of a time-varying mediator variable.

Aim 2: Determine the predictive validity of baseline measures in FLARES function in CBT response.

Hypothesis 2a: Baseline ER-related frontal activity with negative stimuli will specifically predict CBT (not ST) outcome at 12 weeks and 6-mo. follow-up, confirming and extending published/Preliminary Data in MDD and gSAD. Frontal activity from *a priori* ROIs (ACC, DLPFC) and 'cognitive masks' comprising multiple regions (larger search volumes) consistently recruited in previous studies of implicit and explicit emotion regulation[38,212,213] will be subject to conventional accuracy metrics of discrimination (sensitivity, specificity, d', AUC)[214]. And generalizability to CBT (vs. ST) will be determined with common replicability procedures (split-sample validation, cross validation, bootstrapping – note below)[214]. Random permutation testing (1,000 times) will be used to calculate the significance of the discrimination (percent correct, d') for "Significant Responders", "Minimal Responders" and "Non-Responders" (see above) to determine how well indices of each construct predicts responder status. Second, mixed effects regression models will be used to examine frontal predictive ability with dichotomous and continuous clinical outcomes. GLMs and simple effects analysis (e.g. chi-square tests) will be used for planned comparisons. Testing predictive performance between CBT and ST: AUC based on neural activity will be estimated with an empirical (nonparametric) method[215] and binormal method[216,217] from which the complete (and partial) AUC may be calculated. For the empirical method, a *z*-test will be used for comparing AUC between treatments in a paired design[218]. Regarding binormal approach, the *z* statistic will involve a logistic transformation[217].

Hypothesis 2b: Non-fMRI measures of regulation and emotion generation with negative stimuli will predict CBT response (not ST) immediately after treatment (Week 12) and at 6-month follow-up. Hypotheses will be tested with analogous analytic methods used in Hypothesis 2a. Also, AUCs will be compared between fMRI-related predictors and non-fMRI related predictors.

Hypothesis 2c: fMRI and non-fMRI predictors of CBT (not ST) response in MDD and gSAD will distinctly relate to reward and fear processes, respectively. The same analysis above will be used to test units of measure sensitive to reward and fear processes in predicting response within CBT, within ST, and across treatments. Planned comparisons will include chi-square analysis contrasting fMRI and non-fMRI predictive units based on multinomial analysis with diagnostic category with responder status.

Hypothesis 2a-2c: Machine learning procedures (e.g., SVM, Random Forest) will be used to examine classification validity for dichotomous and continuous (extent of change) outcomes at the single-subject level.

Aim 3. Integrate brain, behavior, and clinical units in the mechanism and prediction of CBT outcome and develop a new integrated assay of change and prediction.

Hypothesis 3a: Integrating across multiple units will yield a composite measure that is sensitive to change specific to CBT.

Hypothesis 3b: Integrating across multiple units will improve prediction performance. This integrated change and predictor index be more accurate, specific, and sensitive than any measure alone. We will compare the validity of change and predictive markers that represent brain function (a 'mechanistic' index that *includes* fMRI data) and those that represent FLARES function more distally (a 'pragmatic' index that *does not include* fMRI data) (exploratory). Confirmatory factor analytic (CFA) measurement models will be parameterized such that measures will each load on a latent dimensional factor[219,220], representing true score variance. Method factors will be included to extract extraneous variance sources (e.g., method and time point effects)[183]. Ordered categorical (ordinal) measures will be treated as such analytically, with polychoric relations modeled, and a robust maximum likelihood estimator will account for non-normal distributions in continuous measures[221]. The result of this approach will be a latent factor that provides a *single, best estimate* of CBT-predictor and CBT-change measure for each participant, incorporating information *across all* modalities and measures. Factor scores for each participant will be estimated, and these scores will be submitted to regression analyses. We also intend to pursue alternative strategies as needed, including multi-group (i.e., each treatment modality [CBT vs. ST] as a separate group) structural equation modeling (SEM;[219]), where the latent CBT-predictor and CBT-change factor (as estimated above in the CFA measurement model) at post-treatment would be regressed on the pre-treatment latent factor. CFA and SEM analyses will allow for direct comparison of latent CBT-predictor and CBT-change factor means and

variances across time points. These planned analyses are intended to derive a variable (serving as a *bridge* between clinical and brain domains) that can be assembled jointly from the multitude of units of measurements in this experiment. After the model is specified, its parameters from the data are estimated and assessed for model fit to test the prediction that circuits-neurophysiology-behavior-self-report will load on a CBT-predictor and CBT-change latent variable that relates to treatment outcome and change. These procedures will be based on recommendations made by Muthén[222] and performed in SAS. Final model fitting will be performed using Akaike Information Criterion and Bayesian Information Criterion. These approaches are not intended to describe fully what we plan but rather to illustrate the feasible analytic approaches to address the importance of integrating data. We intend to take an exploratory, iterative approach that compares alternative models and a multidimensional 'framework' of multiple composites, continually testing/confirming variables and models. Additionally, we will integrate and compare multiple units using a multiple-kernel SVM based multimodality classification or regression strategies. For each modality, features with significant discriminative power will be selected using *t*-tests. For high dimensional features we will employ feature selection strategies such as sparse regression or Regularized trees[223] embedded into a with a learning algorithm. Individual kernel matrices will be then constructed from the selected features of each modality before they are integrated to form a single mixed-kernel matrix. The constructed mixed-kernel will be employed to train SVM classifiers/regressors in a leave-one-out fashion using the LIBSVM solver. Multiple-kernel SVM based multimodality classification approach will be compared with the single modality approach and the direct data fusion method. In addition, we will follow three approaches for linking brain and behavioral data[224]: (1) using the neural data to constrain a behavioral model, (2) using the behavioral model to predict neural data, and (3) modeling both neural and behavioral data simultaneously.

Exploratory Analyses: We limited the scope to FLARES activity and connectivity, and specific ERPs, however, we will perform complementary analyses: 1) outside of FLARES circuit using whole-brain voxel-wise analyses and other relevant ERPs and sites using univariate and multivariate analyses; 2) using FLARES circuit seeds for functional (psychophysiological interaction analyses)[225] and effective (dynamic causal modeling) connectivity[226] analyses; 3) and to evaluate EEG connectomics in the context of both task-based and resting-state predictors and CBT-related change.

Missing Data: Using the intent-to-treat (ITT) sample model, we will account for dropouts by examining the primary outcome variables using (longitudinal, if applicable) mixed effects models using PROC GLIMMIX in SAS® and assess the effect of missing 'at random' on the inference[227–229].

Power and Sample Size Estimates: Due to the complexity and number of the analyses, and the novel approach described here, we cannot fully provide a valid and/or comprehensive power estimate for the planned analyses across multiple predictor and change measures. We will employ appropriate tests for correction for the multiple comparisons, such as false discovery rate[230,231] and Monte Carlo simulation (e.g., AlphaSim), methods as in the case with fMRI BOLD data[230]. Published papers showing

significant and generalizable findings of fMRI, ERPs, EMG and behavioral indices of change following CBT and/or predictors of CBT response in anxiety or depression are generally in the moderate range with samples of 20-50 subjects[22,86,98,100–102,104,109,114,118,121,122,126–128,131–133,178,200,201,232–244]. Predictors of CBT response: Preliminary fMRI, ERP, EMG, and behavioral data yielded effect sizes in the moderate to large range (odds ratios = 2.2 to 3.0). Pre-to-post CBT changes: Preliminary fMRI (frontal and subcortical activity), ERPs, EMG, and self-report data (e.g., regulation, avoidance tendencies) yielded moderate effect sizes (Cohen's *d*=0.35 to 0.50). Considering attrition, loss of data/excessive movement during fMRI, treatment dropout/withdrawal, failure to complete post-treatment fMRI/EEG scan, we have determine a sample of 70 MDD and 70 gSAD CBT completers will have at least 80% power to detect small-medium size effects, using Cohen's convention. Since much of the analysis will occur with region of interests, we will use data from prior analyses of brain reactivity to estimate variance and approximate effect sizes. This study will provide much needed effect sizes for these kinds of analyses to inform subsequent studies.

13.0 Regulatory Requirements

13.1 Informed Consent

Upon being scheduled for a screening visit, a written summary, in lay terms, of the research project will be provided to the subjects via email to review. **Subjects will be encouraged to look over the consent ahead of their screening assessment. When their screening assessment starts, they may ask any questions after the research assistant goes through the informed consent process. If all questions are answered and the participant agrees to participate in the study, they will sign an e- consent on REDCap. As soon as the designated lab member receives the signed e-consent through REDCap, they will continue with the screening visit. Participants will be sent their signed consent via email. Consenting will be done virtually through a secure network such as WebEx. This can also be done over the phone for those who do not have access to internet or other necessary equipment**. The consent document will inform the subjects of the voluntary nature of the study procedures, the purpose of the study, the procedures to be followed, the duration of the study, the risks associated with EEG/MRI scanning, as well as the potential benefits to the community at large. Women will agree that they are not pregnant and not planning to become pregnant. Subjects will be informed that a urine sample for a pregnancy/toxicology screen will be obtained prior to the MRI scanning session. Written informed consent will be obtained by the PI or designated research staff and the subject will receive a copy of the signed consent form. Subjects will be informed that they can discontinue participation at any time without penalty.

13.2 Subject Confidentiality

Confidentiality: All data from subjects will be marked with a research identifier number only and kept in locked cabinets. No data will have subject names on them, except for

consent forms, which will be stored separately from other questionnaires in a locked file cabinet. Paper records will be kept in locked file drawers in a locked room, to which only authorized research personnel have access. Confidentiality of subject records is assured by assigning each subject with a research identifier number/code, and such data, as well as fMRI, EEG, neurocognition, and task performance data, are stored in computer files (except for a single tracking file) without reference to name, hospital registration number, or any other type of personally-identifiable information (e.g., birth date, social security number, etc.). Data that may be reported in scientific journals will not include any information that identifies any person as a subject in this study.

Limits of Confidentiality on Clinical Information: Confidentiality is limited, however, when a danger to self or others is present. If the subject is discovered to be acutely homicidal or suicidal during the evaluation period, the subject will be evaluated for hospitalization in a mental health facility (either voluntarily or involuntarily as necessary). If, for whatever reason, the subject is not hospitalized when it is determined that he/she is either homicidal or suicidal (e.g., we receive a phone call from the subject or another person) the police will be alerted to bring the subject to a psychiatric emergency room.

Confidentiality of Drug/Pregnancy Tests Prior to Scans or Assessment: The results of the urine drug and pregnancy screens will remain confidential. The only individuals who will have knowledge of the results of these tests are research staff directly working on the project. This information will be stored in a secure computer database that uses subject codes (rather than names) as identifiers.

13.3 Unanticipated Problems

Any unanticipated problems (its occurrence, frequency or severity is new or greater than previously known or as expected based on subject characteristics, including natural progression of disease). They are always unanticipated by definition and will be reported to the IRB within 5 business days of the PIs (or their team's) knowledge of the event.

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APPENDICES

Summary Sheet

Inclusion Exclusion Checklist

MRI Safety Form

Questionnaires (See separate attachment of questionnaires)

Participant Screen Summary

Participant ID: _____

Date & Time of Informed Consent: _____

Date & Time Study Participation began: _____

Eligible: Y/N

If no, reason for exclusion: _____

_____

Gender: M/F

Race: _____

Ethnicity: _____

Age: _____

Education: _____

Handedness: L/R/A

Form completed by: _____ Date: _____

Inclusion/Exclusion Criteria Reviewed by Primary Investigator? Y ☐ N ☐

Primary Investigator: _____ Date: _____
Heide Klumpp, PhD

ID # _____

General - Inclusion Criteria

Yes _____ No _____ 1. Age 18-65

Yes _____ No _____ 2. Participant is able to give informed consent

Yes _____ No _____ 3. Generally medically and physically healthy as confirmed by medical history

gSAD Patient - Inclusion Criteria

Yes __ No __N/A__ 4. Current diagnosis of gSAD based on the SCID

Yes __ No __N/A__ 5. LSAS score of ≥ 60

Yes __ No __N/A__ 6. **NO** current diagnosis of PDD based on the SCID

Yes __ No __N/A__ **7. NO** current diagnosis of MDD based on the SCID

MDD Patient - Inclusion Criteria

Yes __ No __N/A__ 7. Current diagnosis of MDD based on the SCID

Yes __ No __N/A__ 8. HAM-D score of ≥ 17 or BDI-II score of ≥ 16

Yes ___ No __N/A_ 9. **NO** current diagnosis of gSAD based on the SCID

Healthy Controls – Inclusion Criteria

Yes __ No __N/A__ 10. Free of a lifetime diagnosis of Axis I disorder

ID # _____

General - Exclusion Criteria

Yes _____ No _____ 1. Clinically significant and active medical or neurological condition

Yes _____ No _____ 2. Primary comorbid anxiety disorder (defined by which disorder was the more debilitating and clinically salient than SAD or MDD)

Yes _____ No _____ 3. Life history of bipolar disorder, schizophrenia, or presence of an organic mental syndrome, mental retardation, or pervasive developmental disorder

Yes _____ No _____ 4. Life history of or current psychotic symptoms

Yes _____ No _____ 5. Current moderate or severe AUD/SUD or in the past 6 months based on the SCID

Yes _____ No _____ 6. Current active suicidal/homicidal ideation based on the C-SSRS

Yes _____ No _____ 7. Evidence of chronic self-injurious behavior in the past six months (i.e., cutting, burning, etc.) as determined by self-report and the Primary Investigator

Yes _____ No _____ 8. Prior treatment of a clinical dose of cognitive behavioral therapy as determined by the Primary Investigator

Yes _____ No _____ 9. Ongoing active psychotherapy (e.g. CBT) treatment of any kind

Yes _____ No _____ 10. Current treatment with any psychotropic medication (anti-depressants, anti-obsessionals, anxiolytics, anti-psychotics, mood stabilizers); prior treatment with a psychotropic medication is not an exclusion criteria as long as the treatment was discontinued at least 4 weeks prior to study entry.

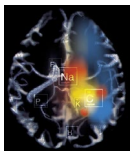
Yes _____ No _____ 11. Positive drug screen

Yes __ No __ N/A __ 12. Pregnancy (positive pregnancy test), trying to become pregnant (females only).

Exclusion Criteria for fMRI Studies

Yes _____ No _____ 13. Presence of ferrous-containing metal in the body

Yes _____ No _____ 14. Inability to tolerate small, enclosed spaces



Center for MR Research

Research Subject Assessment

Name _____

Weight _____

Consent obtained (indicate with signature subject/investigator)? x_____

Please answer the medical history questions below:

Are you left handed or right handed? _____

	Yes	No		Yes	No
Aneurysm clip	_____	_____	Tattoos/Piercing	_____	_____
Pacemaker/stimulator	_____	_____	Cardiac/Respiratory problem	_____	_____
Ear Implant	_____	_____	Strokes/Seizures	_____	_____
Heart Valve Replaced	_____	_____	Liver/Kidney disease	_____	_____
Other Implant	_____	_____	Cancer	_____	_____
History of Metal Work	_____	_____	Brain Surgery	_____	_____
Hx of Metal in eyes	_____	_____	Diabetes/High BP	_____	_____
Bullets/Shrapnel	_____	_____	Claustrophobia	_____	_____
Dentures/Braces/Wigs	_____	_____	Prior MRI: yes ____ no ____ Where: _____		

Onset of Symptoms (date/time) _____

Expanded Medical History _____

_____

Current Meds _____

Allergies _____ Contrast to be given? Yes _____ No _____

Pregnant? Yes _____ No _____ Unsure _____

Source of Screening Info. _____ Screened by _____

x_____ _____

Signature of Consent Date