Title of Project: **Approach-Avoidance Conflict-a multi-level predictor for therapy response**

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Sponsor: Laureate Institute for Brain Research (LIBR)

ABSTRACT

The aim of this study is to identify whether neural and behavioral responses related to the arbitration of conflicting avoidance and approach instincts can predict behavior therapy response for anxious and depressed individuals. This aim will be accomplished using behavioral and functional magnetic resonance imaging (fMRI) analysis pre and post behavioral therapy (BT). Research subjects will include treatment-seeking individuals with clinically significant symptoms of anxiety or unipolar depression. Diagnosis will be assessed using structured clinical interviews. Anxious and depressive symptom severity, personality characteristics, and general functioning will be collected via self-report paper-and-pencil questionnaires. Objective measures of approach, avoidance, and conflict behavioral responses will be collected using computer-administered testing and related neural responsivity will be measured using fMRI. This research has the potential to identify neural and behavioral approach-avoidance characteristics that can help predict which patients are likely to respond to standard behavior therapy for anxiety and depression (i.e., predictors of treatment effectiveness) and reveal targets for future treatment modifications.

A. SPECIFIC AIMS

The current study will accomplish the following aims:

Aim 1: Clarify the potential contribution of approach-avoidance behaviors and neural responses to anxiety and depression symptom severity.

> **Hypothesis 1.1*:*** Approach-related behaviors and conflict arbitration behavior will explain a significant amount of variance in anxious and/or depressive symptoms, above and beyond avoidance-related behavior.
> **Hypothesis 1.2:** Activations within approach-related (i.e., striatum) and conflict arbitration (i.e., lateral PFC) neural circuitry will explain significant variance in anxiety and depressive symptom severity above and beyond activations within avoidance-related (i.e., amygdala) neural circuitry. Specifically, we expect increased levels of anxiety to relate to increased striatal responsivity while increased depression relates to reduced striatal responsivity.

Aim2: Identify approach-avoidance behaviors and neural responses that predict the effectiveness of exposure-based behavioral therapy (EXP) for anxious subjects and behavioral activation therapy (BA) for depressed subjects.

> **Hypothesis 2.1:** Approach-related behaviors and/or conflict arbitration behavior will help predict treatment response above and beyond avoidance-related behavior and baseline symptom severity. Specifically, we expect that difficulties with conflict arbitration will predict nonresponse of anxiety patients to EXP and that decreased reward sensitivity will predict nonresponse of depressed patients to BA.
> **Hypothesis 2.2:** Approach-related and conflict arbitration neural circuitry will help to predict treatment response above and beyond activations within avoidance-related neural circuitry. Specifically, we expect prefrontal responsivity during conflict arbitration to predict response of anxiety patients to EXP and striatal responsivity to reward to predict response of depressed patients to BA.

Aim 3: Identify whether functional improvement with EXP or BA is associated with change in approach-avoidance behaviors.

> **Hypothesis 3.1:** The level of change in conflict arbitration behavior will positively relate to the level of improvement in overall functioning with EXP.
> **Hypothesis 3.2:** The level of change in reward sensitivity will positively relate to the level of improvement in overall functioning with BA.

Aim 4: Identify whether functional improvement with EXP or BA is associated with baseline metabolic and inflammatory markers, as measured via blood assays.

> **Hypothesis 4.1:** The elevation of inflammatory biomarkers (i.e., ratio of uinolinic acid [QA] relative to kynurenic acid [KynA]) will relate to less improvement with treatment.

Aim 5: Identify whether Behavioral Activation is as or more effective for Generalized Anxiety Disorder (GAD) than exposure therapy.

Hypothesis 5.1: Behavioral Activation will be equally effective to exposure therapy for individuals with GAD as their primary mental health diagnosis.

B. BACKGROUND AND SIGNIFICANCE

Current Anxiety and Depression Treatment Effectiveness

Anxiety and mood disorders are the most prevalent class of mental health disorders, with lifetime prevalence estimated at 32% and 18%, respectively[1]. These disorders have tremendous personal and socioeconomic impacts (cost >$1500 per-patient/year) due to days lost at work, increased health care utilization, and increased risk of mortality (e.g. cardiovascular disease)[2-8]. First-line treatments for anxiety and depressive disorders include pharmacologic (e.g. SSRIs) and psychotherapeutic interventions (e.g. cognitive behavioral therapy [CBT] and behavioral therapy [BT]). While both are superior to placebo treatments, only 40-60% of patients experience significant improvement[9-13] and 15-25% of responders relapse within one year[12, 14-17]. Thus, we are producing long-lasting improvements in *less than 50% of patients*. This ineffectiveness has been moderately associated with symptom severity, illness duration, and comorbidity[18-20] but these findings do not provide any strategies for improving treatment effectiveness. The current study will seek to identify behavioral or cognitive-affective predictors that indicate how well a patient is responding to treatment so that interventions can be further individualized to more effectively treat refractory patients.

Anxiety and Depressive Disorder Comorbidity

Studies emerging from both primary care and psychiatric settings have shown substantial comorbidity between anxiety and depression[21-24]. These results have been seen across various demographics including children, adolescents, and adults. When self-report rating scales for anxiety and depression are used, typically only two or three dimensions of symptoms are found in which symptoms of depression emerge distinct from symptoms of anxiety[21-24]. When anxiety and depression are assessed at syndrome or diagnostic levels, high correlations remain. Moreover, studies of adults suggest that both disorders often share common risk factors and that similar interventions may be effective[25]. However, there have been important neural differences identified, particular in relation to striatal circuitry and reward processing [26-30] . Thus, the current study will attempt to identify similar or unique therapy predictors for primary anxiety and primary depression (using EXP and BA, respectively). We will also include those with comorbid anxiety and depression, but will enroll them in the treatment that corresponds to the disorders/symptoms of most concern for the patient. As the comorbidity is extremely high (i.e., 88%) between generalized anxiety disorder (GAD) and depression in particular [31], this makes it difficult to determine which treatment these individuals should be provided. It has often been proposed that GAD is a form of depression with slight variance in symptoms [31]. Thus, it is possible that therapies effective in reducing depressive symptoms may also be effective for individuals with GAD. Thus, in the current study, those who meet criteria for GAD as their primarily clinical complaint, will be randomized to receive either BA or EXP. This will allow us to address Aim 5.

Approach and Avoidance in Anxiety and Depression

Most neuroscientific research in anxiety and depression has focused on avoidance-related processes, or responses to threat (e.g. amygdala activity to fearful faces). Theories stemming from this research focus on inadequate top-down regulation of amygdala and/or insula regions by the prefrontal cortex (PFC: usually anterior cingulate cortex [ACC], medial PFC [mPFC], or lateral PFC [lPFC]). Meta-analyses support amygdala hyperactivity in SAD and specific phobia[32]. Various studies have also shown up to 70% greater activity in the amygdala in response to negative stimuli among depressed individuals versus healthy ones[33, 34]. GAD and panic on the other hand have shown inconsistencies in regards to the exact region and directionality of PFC and amygdala hyperactivity for GAD and panic[35-38]. Three previous fMRI studies have examined predictors of therapy response for adult anxiety disorders, all focused on reactivity to negative emotional stimuli. Results suggest that greater activation in cognitive-emotional processing (dorsal ACC and dorsomedial PFC) or secondary visual areas (temporal and occipitotemporal

cortex) in response to threat faces in SAD[39] predicted better CBT treatment response. On the other hand greater frontal, temporal, and insula activation during emotion reappraisal predicted better CBT treatment response in subjects with GAD/panic[40]. Functional MRI studies in depression have similarly focused on negative affective stimuli and have reported greater rostral anterior cingulate cortex (ACC) or reduced sgACC activation to predict better treatment response [41, 42]

However, anxiety in particular has been conceptualized as being driven not only by threat reactivity, but also by simultaneous and balanced activation of both avoidance and approach systems, and generation of approach-avoidance conflict[43-45]. For example, conflict can arise between motivations to obtain the praise or promotion from presenting a public speech at work, teamed with motivations to avoid the anxious sensations and embarrassment that could also result. Difficulties arbitrating these types of conflicts can lead to chronic distress, uncertainty, "freezing" behavior, and often, avoidance. Conflict paradigms have been observed extensively in animal models of anxiety, with conflict approach behavior being modulated using anxiolytic agents[43, 46]. In these animal studies, e.g. the Vogel and Geller-Seifter paradigms[47, 48], behavior (i.e., approaching a platform) is associated with both a punishment (e.g. shock) and reward (e.g. food). Some anxiolytic agents, such as benzodiazepines, reliably increased approach behavior, while other agents, such as cholecystokinin antagonists, did not. The results of these studies offer translational support for the conflict model[43, 46, 47]. However, there has been a lack of human research investigating conflict processes in relation to anxiety (and depression).

Avoidance is among the most dominant focuses of neuroscientific research in depression. Individuals with depression use escape and avoidance coping strategies when stressed by focusing attention away from internal or external stimuli to manage, reduce, or eliminate stress[49, 50]. This is done both cognitively (i.e., denying, minimalizing, ruminating, or making passive decisions that stressful or unpleasant situations are unchangeable) and/or behaviorally (i.e., participating in alternative activities, engagement in temporarily satisfying albeit maladaptive behaviors such as substance use, binge eating, etc.)[51, 52]. Furthermore, longitudinal investigations have shown that avoidance directly contributes back to the etiology and maintenance of depression symptoms[52, 53]. This positive feedback cycle of depression and avoidance leads to individuals persistently missing out on opportunities for reward. Behavioral theories explain the development and persistence of depressive symptoms as being the result of decreased environmental reward, associated reductions in positively reinforced healthy behavior, reinforcement of depressive or passive behaviors, and punishment of healthy behaviors[52, 54]. However, neuroscientific investigations concerning therapy predictors in depression have remained focus on threat processing or the negative valence system, despite theoretical and scientific evidence that dysfunction in reward circuitry may play a role in depression and in the observed avoidance and withdrawl behaviors. Also, while depression is associated with decreased striatal response, anxiety and behavioral inhibition are associated with enhanced striatal activation to reward[26-30]. Further, adolescent research suggests that greater striatal and less medial PFC activation to reward anticipation predicts lower anxiety symptoms after CBT[55]. Thus, reward processing may need to be incorporated into theoretical models of anxiety and depression related treatment, but to understand exactly *how*, studies in adults samples using fMRI tasks probing both threat and reward responsivity are needed[55].

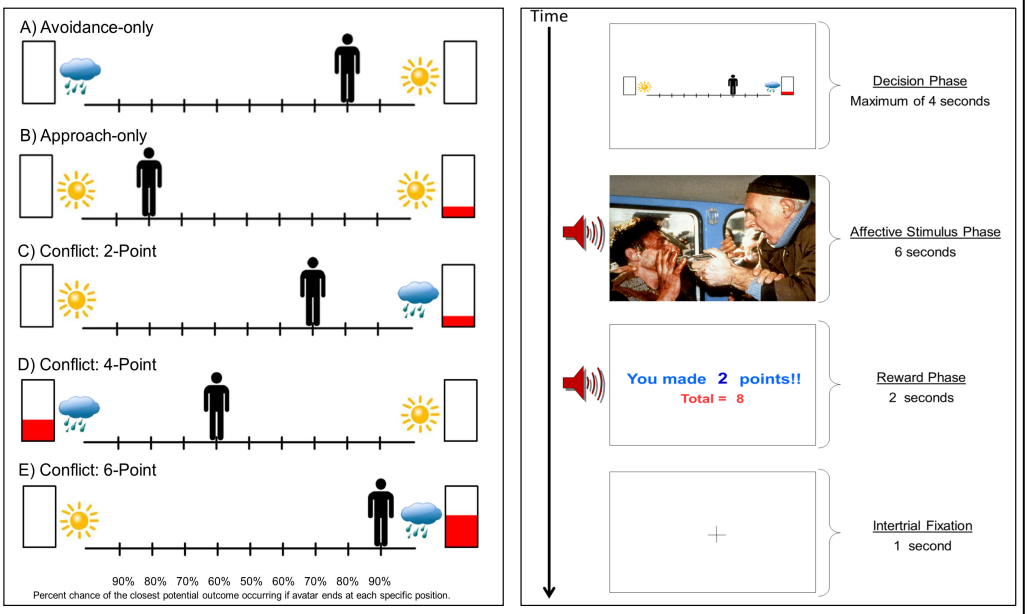
The current study will seek to find which behaviors/neural responses among approach, avoidance, and conflict arbitration provide the best predictions of behavioral therapy effectiveness with respect to disorders characterized across the anxiety-depression comorbidity.

C. PRELIMINARY STUDIES

Our project will use cross-sectional (Aim 1) and longitudinal (Aims 2,3) designs to identify factors contributing to anxiety and depression severity, and treatment outcome, focusing on approach-avoidance conflict. The PI has a record of research related to approach-avoidance processes and neural predictors of anxiety treatment. Her previous work and preliminary data support the rationale and feasibility of the proposed study.

Approach-avoidance conflict:

Figure 1. Approach-avoidance conflict (AAC) task



Shown on the left are examples of each decision (avoidance-only, approach-only, and three levels of conflict). Shown on the right is the timeline of screens shown for one trial, including the decision phase, followed by the affective stimulus and reward presentation phases.

Dr. Aupperle developed the approach-avoidance conflict (AAC) task to probe decision-making processes when faced with a conflict between approaching rewarding stimuli and avoiding negative affective stimuli. On each trial, the subject decides between two outcomes, represented on each side of a runway. A cloud indicates that a negative affective image/sound pair will be shown while a sun indicates that a positive image/sound pair will be shown (images obtained from International Affective Picture System [IAPS] and sounds obtained from International Affective Digitized Sounds system IADS [56, 57]). The amount of red in a rectangle indicates the number of potential points awarded for each option. In conflict trials, negative stimuli are paired with reward points (2, 4, or 6) while positive affective stimuli are paired with no points. Thus, the same behavior leads to both affective punishment and reward. For non-conflict 'approach' trials, both outcomes include positive affective stimuli, but only one offers reward points. For 'avoid' trials, neither outcome offers reward, but one involves a negative affective image. There are 92 trials (18/condition). For each, the subject moves the avatar, knowing that the probability of each outcome (10-90%) depends on their end position (-4 to +4). Behavioral variables include: (1) approach behavior (end avatar position), (2) response time (RT) for initial button press, and (3) number of oscillations (change of direction). In previous behavioral research (N=95 healthy adults) [58], approach behavior was modulated by conflict and reward levels in the expected directions ($F(2,188)=35.30$, $p<.001$). Conflict conditions were associated with longer RT $t(94)=3.67$, $p<.001$) and more oscillations (trend: $t(94)=1.89$, $p=.062$) compared to non-conflict and these measures related to self-reported difficulty making decisions on the task (RT: ρ=.334, $p=.001$; oscillations: ρ=.311, $p=.003$). Thus, while end position indexes approach behavior, RT and oscillations seem to index conflict arbitration. Furthermore, greater scores on measures relevant for both panic and GAD (anxiety sensitivity index (ASI); intolerance of uncertainty (IUS)) related to slower RT (ASI: ρ=.26, $p=.011$) and more oscillations (ASI: ρ=.27, $p=.008$; IUS: ρ=.22, $p=.029$). This research supports the use of the AAC task to assess behavioral avoidance and conflict arbitration, with greater levels of anxiety relating specifically to difficulties in conflict arbitration.

FMRI research with the AAC (N=15 healthy adults) showed that areas involved in processing interoceptive salience (insula), reward (caudate), and conflict monitoring and decision-making (ACC, dorsolateral PFC [dlPFC]) are activated during conflict (vs non-conflict) decisions. Greater caudate and ACC activation related to less approach behavior while greater dlPFC (BA 9) activation related to self-reported difficulties in decision-making. Thus, caudate and ACC may signal approach-avoidance motivations, while dlPFC is involved in conflict arbitration specifically. We therefore hypothesize that greater dlPFC activation to conflict reflects arbitration difficulties, and could thus contribute to anxiety and treatment response.

Prediction of therapy response:
The PI has been involved in previous project investigating neural predictors of CBT response for PTSD[59] and, most relevant to this application, GAD and panic disorder. For the latter, subjects completed a cued anticipation paradigm, which combines a continuous performance task with presentation of affective images. Analyses focus on anticipation of positive (API) and negative images (ANI), cued with blue and yellow backgrounds respectively. We used a linear mixed model with post-treatment OASIS as the dependent variable, diagnosis and baseline OASIS as covariates, and ANI and API entered sequentially as predictors. Whole-brain analyses (p<.05, Monte Carlo corrected) revealed that greater baseline ANI activation in the medial PFC (BA 9; 34 voxels, $F(1,37)=6.80$) and left amygdala (32 voxels, $F(1,37)=8.20$) predicted worse CBT response. However, greater API activation in the right caudate/putamen (17 voxels; $F(1,37)=5.99$) further predicted worse response. These results indicate that striatal activation to positive affective stimuli may enhance our ability to predict and understand treatment effects. This study was limited in that (1) affective images may not activate approach drives and striatal activation as reliably as reward and (2) we had no behavioral data to determine if activations related to avoidance/ approach motivations versus conflict, or deficiencies vs. compensatory efforts. The current study addresses these limitations, combining fMRI with behavioral indices to provide a more holistic understanding of how activations relate to treatment.

D. CRITERIA FOR SUBJECT SELECTION

Recruitment
Subjects will be recruited using the pre-approved LIBR screening protocol (WIRB #20101611) and from the Laureate Psychiatric Clinic and Hospital (LPCH), community mental health clinics, and the general community through clinician referral, Facebook ads, and print advertisement. Advertisement materials are included with this application.

Inclusion Criteria
1. Age: 18-55
2. All genders
3. All races
4. Eligibility as clinically significant anxiety and/or depression will be determined by:
    a. Scoring greater than 9 on the Patient Health Questionnaire (PHQ-9) and/or greater than 7 on the Overall Anxiety Severity and Impairment Scale (OASIS)
    b. Self-report that they are interested in obtaining treatment for anxiety or depression.
    c. Through structured diagnostic interviews, it is determined that anxiety symptoms (generalized anxiety, panic, or social anxiety) or depressive symptoms are the primary disorder of concern. For subjects with comorbid anxiety/depression, they will be assigned to therapy for the symptoms (anxiety or depression) they report as their primary concern. Those with a PHQ-9 score >17 (moderately severe to sever range) will be asked to complete the therapy for depression, as Behavioral Activation has been shown effective for severe depression (while exposure therapy has not been shown effective in severe depression). Those who meet diagnostic criteria for GAD will be randomized to BA or EXP due to the high comorbidity and similarities with symptoms of depression.
5. Able to provide written, informed consent
6. Have sufficient proficiency in English language to understand and complete interviews, questionnaires, and all other study procedures

Exclusion Criteria:
1. Has a history of unstable liver or renal insufficiency; glaucoma; significant and unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic disturbance; or any other condition that, in the opinion of the investigator, would make participation not be in the best interest

(e.g., compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.

2. A history of drug abuse in the past 6 months, including alcohol, cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine, benzodiazepines, barbiturates, methadone, and oxycodone. Current alcohol use will be ruled out using a breath test and urine testing will be used to rule out current use of other drugs of abuse.
3. Has any of the following DSM-5 disorders:
    a. Schizophrenia Spectrum and Other Psychotic Disorders
    b. Bipolar and Related Disorders
    c. Obsessive-Compulsive and Related Disorders
    d. Anorexia or Bulimia Nervosa
    e. Substance use disorder within 6 months
4. Moderate to severe traumatic brain injury (>30 min. loss of consciousness or >24 hours posttraumatic amnesia) or other neurocognitive disorder with evidence of neurological deficits, neurological disorders, or severe or unstable medical conditions that might be compromised by participation in the study (to be determined by primary care provider)
5. Active suicidal ideation with intent or plan
6. Current use of a medication that could affect brain functioning (e.g., anxiolytics, antipsychotics, or mood stabilizers). However, participants reporting current use of prescribed antidepressants (selective serotonin reuptake inhibitors [SSRIs]) will be included as long as the dose has been stable for 6 weeks prior to enrolling in the study, as they are the most commonly prescribed medications and have less of an acute impact on symptoms and emotional processing. SSRIs will be included to increase generalizability to clinical populations.
7. Prescription of a medication outside of the accepted range, as determined by the best clinical practices and current research
8. Taking drugs that affect the fMRI hemodynamic response (e.g., methylphenidate, acetazolamide, excessive caffeine intake > 1000 mg/day).
9. MRI contraindications including: cardiac pacemaker, metal fragments in eyes/skin/body (shrapnel), aortic/aneurysm clips, prosthesis, by-pass surgery/coronary artery clips, hearing aid, heart valve replacement, shunt (ventricular or spinal), electrodes, metal plates/pins/screws/wires, or neuro/bio-stimulators (TENS unit), persons who have ever been a professional metal worker/welder, history of eye surgery/eyes washed out because of metal, vision problems uncorrectable with lenses, inability to lie still on one's back for 60-120 minutes; prior neurosurgery; tattoos or cosmetic makeup with metal dyes, unwillingness to remove body piercings, and pregnancy
10. Unwillingness or inability to complete any of the major aspects of the study protocol, including magnetic resonance imaging (i.e., due to claustrophobia), biopsy, blood draws, or behavioral assessment. However, failing to complete some individual aspects of these assessment sessions will be acceptable (i.e., being unwilling to answer individual items on some questionnaires or being unwilling to complete a behavioral task)
11. Non-correctable vision or hearing problems

Informed Consent

All participant interactions including consenting will be conducted in private interview/exam rooms. All subjects will be old enough to give informed consent (age 18 or older), and have all procedures fully explained to them. Care is taken to ensure the subject understands completely the IRB-approved consent form and that the form is appropriately endorsed with a signature as acknowledgement of his/her consent.

Participation Compensation

Participants will be compensated for their efforts during this study as follows:

- Completion of clinical, self-report, and behavioral assessment, estimated 7 hours total at both pre-treatment and post-treatment and an additional 15 minutes per each of the 10 weeks of treatment): $10 for every half hour, equating to a total of $140 for completion of the pre-treatment session, $140 for completion of the post-treatment session, and $50 for 10 weekly assessments, for a total of $330.
- Completion of self-report assessments, estimated at 30 minutes total at both 3 and 6 months following completion of treatment. These assessments will be completed online (via RedCAP) or via phone and therefore won't require an in-person session. To encourage completion of these follow-up questionnaires, participants will be provided $20 compensation for each of these two time points (for a total of $40).
- Completion of self-report assessments, estimated at 10-15 minutes, if they withdraw from the study prior to completion of treatment. These assessments will be completed online (via RedCAP) or via phone and therefore won't require an in-person session. Participants will be compensated $10 for completion of these measures.
- Completion of MRI scanning (estimated 2.5 hours total, conducted at pre- and post-treatment): $25/half hour, equating to a total of $125 for completion of each MRI scanning session and a total of $250.
- Completion of blood draws for bioassay analyses (estimated 30 minutes): $50 per half hour, equating to a total of $50 at pre-treatment and $50 at post-treatment, for a total of $100.
- Given the above compensation rates, total compensation for completing all study procedures is estimated to be $680.
- Participants that withdraw part way through any of the assessments will be compensated on a half-hour basis, according to the compensation rates noted above.
- Participants may also be provided additional compensation of $0-55 at each pre- and post-assessment session based on their participation in and decisions made during the risk-based decision-making tasks described below.

E. RESEARCH DESIGN AND METHODS

Screening Assessment

Potential participants will be screened by phone or in-person using the WIRB screening protocol 20101611 to determine initial eligibility. The inclusion/exclusion criteria listed above will be obtained using screening questionnaires included in that protocol and the PHQ-9 and OASIS questionnaires. Patients will accordingly complete a diagnostic interview with study personnel using an abbreviated version of the Mini International Neuropsychiatric Interview (MINI V6.0)[60]. We will include sections on Panic Disorder (PD), Social Anxiety Disorder (SAD), Posttraumatic Stress Disorder (PTSD), Generalized Anxiety Disorder (GAD), Obsessive-Compulsive Disorder (OCD) and Major Depressive Disorder (MDD) and several modules to provide further clinical information or to determine ineligibility (Suicidality, Manic/Hypomanic Episode, Eating Disorders, and Psychotic Disorders). If it is found through this interview that a subject does not meet the inclusion criteria of the study (i.e., meeting criteria for OCD, for example), they will be excluded from the remaining procedures.

After determining eligibility participants will be required to complete The Wide Range Achievement Test (WRAT-4) in order to estimate IQ[61]. Additionally participants will be instructed to complete self-report assessments and participate in behavioral tasks both inside and outside of an MRI (refer to Figure 2). The descriptions of the self-report assessments and behavioral tasks are described below.

Self-Report:

Participants will be asked to complete pencil-and-paper questionnaires related to clinical symptoms, traits and personality characteristics, daily life function, and medical and mental health history. These questionnaires are listed in Table 1. Pre-treatment self-report assessments are estimated to take approximately a maximum of 4 hours to

complete in total. Post-treatment self-report assessment is estimated to take a maximum of 3 hours total. Most assessments listed will be completed at both pre- and post-treatment sessions, except as follows. The PHQ-9 will only be used for screening purposes pre-treatment and will not be repeated. Even if the MINI was completed as part of previous LIBR studies or screening protocol, it will be repeated pre-treatment for the current study as well as post-treatment. The Life Chart Interview will be conducted in full at pre-treatment, but will only be updated at post-treatment (thus, decreasing the amount of time required to complete post-treatment assessments). If participants would like, they will be provided a summary chart of the important life events and mood ratings provided during the initial Live Chart Interview. The homework Rating Scale, Credibility Expectancy Questionnaire, and Working Alliance Inventory will only be conducted during weekly therapy sessions and the PROMIS Anxiety, PROMIS Depression, SDS, GAD-7, and the BADS will also be completed weekly (in addition to pre- and post-treatment) to assess severity of symptoms throughout the study protocol. At the 3 and 6-month online/phone followups, the PROMIS Anxiety, PROMIS Depression, SDS, BDI-II, OASIS, PSWQ, LSAS, PDSS, BADS, GAD-7, and the Treatment FollowUp Form will be completed. The Withdrawn Questionnaire, PROMIs Depression, PROMIS Anxiety, GAD-7, and SDS will be administered to individuals who withdraw from the study after beginning treatment. Those who withdraw from treatment will still be invited to complete the 3 and 6-month assessments. The questionnaires for those who withdraw and at the 3 and 6-month time points will be administered via phone or online (via RedCAP). In addition, the Health Anxiety Inventory[62] (modified for the current study, revised measure attached) and the Dimensional Obsessive–Compulsive Scale (DOCS)[63] may be given pre-treatment, 2-3 weeks throughout the therapy intervention, and at post-treatment and at the withdrawn timepoint. Participants who complete therapy interventions by videoconferencing technology will also be asked to complete the Telehealth Usability Questionnaire [64] (modified for the current study, revised measure attached).

In addition, participants will be provided the workbook, “Overcoming Depression One Step at a Time” [65] (http://www.amazon.com/Overcoming-Depression-One-Step-Time/dp/1572243678) for free, as a companion to the group therapy. Within this workbook are descriptions of the treatment rationale and the various exercises used during therapy, as well as handouts for them to use. In particular, there are activity charts they use to monitor their daily activities hour by hour (see attached measures). As an alternative to completing these charts on paper, they will be provided access to a web-based application developed by Laureate Institute for Brain Research. To use this application, they will create their own username and password and indicate their mood level associated with activities throughout the day. This information will then be accessible by the therapists, to help inform therapy. Those completing hard copies will be asked to bring their copies into treatment each week and a copy will be made for the purposes of research records.

Self-Report Measures	
DIAGNOSTIC AND DEMOGRAPHIC ASSESSMENT	
Diagnosis	MINI 6.0
Demographics	Demographics and Psychosocial Form
History	Assessment of Medical and Medication History
Substance Use	Customary Drinking and Drug Use Record (CDDR)
Handedness	Edinburgh Handedness Inventory
Compliance	Medication Compliance History Questionnaire
Compliance History	Therapy Compliance History Questionnaire
Medical and Treatment Followup	Treatment Followup Form
History	Life Chart Interview

STANDARD SELF-REPORT SCALES	
Negative Valence	Symptoms of Depression Questionnaire (SDQ)
Negative Valence	Overall Anxiety Severity and Impairment Scale (OASIS)
Negative Valence	State Trait Anxiety Inventory (STAI)
Negative Valence	Anxiety Sensitive Index (ASI-3)
Negative Valence	Generalized Anxiety Disorder – 7 item (GAD-7)
Negative Valence	Intolerance of Uncertainty (IUS) Scale
Negative Valence	Penn State Worry Questionnaire (PSWQ)
Negative Valence	Liebowitz Social Anxiety Scale (LSAS)
Negative Valence	Panic Disorder Severity Scale (PDSS)
Negative Valence	Beck Depression Inventory-II (BDI-II)
Negative Valence	Patient Health Questionnaire – 9 (PHQ-9)
Negative Valence	Behavioral Activation Depression Scale (BADS)
Trauma	Traumatic Events Questionnaire (TEQ)
Trauma	Child Trauma Questionnaire (CTQ)
Positive / Negative Valence	Positive and Negative Affect Schedule (PANAS)
Positive / Negative Valence	Behavioral Inhibition System/Behavioral Approach Scale (BIS/BAS)
Positive Valence	Snaith–Hamilton Pleasure Scale (SHAPS)
Personality	Big Five Inventory (BFI)
Arousal / Interoception	Multidimensional Assessment of Interoceptive Awareness (MAIA)
Sleep	Pittsburg Sleep Quality Index (PSQI)
Physical Activity	International Physical Activity Questionnaire (IPAQ)
Disability	Sheehan Disability Scale (SDS)
Therapy expectancies	Credibility/Expectancy Questionnaire (CEQ)
Therapy compliance	Homework Rating Scale
Therapy Process	Working Alliance Inventory
Therapy dropout	Withdrawn Questionnaire
PROMIS MEASURES	
Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Cognitive	PROMIS Cog Abilities
Cognitive	PROMIS Cog General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related impairment
Alcohol	PROMIS Alcohol Use
Social	PROMIS Social Satisfaction DSA

Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social
Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrumental Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity
Nicotine	Nicotine Dependence
Negative Affect-Anger	NIH Toolbox Anger-Affect Survey
Negative Affect-Anger	NIH Toolbox Anger-Hostility Survey
Negative Affect-Anger	NIH Toolbox Anger-Physical Aggression Survey
Negative Affect-Fear	NIH Toolbox Fear-Affect Survey
Negative Affect-Fear	NIH Toolbox Fear-Over Anxious Survey
Negative Affect-Fear	NIH Toolbox Fear-Somatic Arousal Survey
Negative Affect-Sadness	NIH Toolbox Sadness Survey
Psychological Well-Being	NIH Toolbox General Life Satisfaction Survey
Psychological Well-Being	NIH Toolbox Meaning and Purpose Survey
Psychological Well-Being	NIH Toolbox Positive Affect Survey
Social Relationships	NIH Toolbox Friendship Survey
Social Relationships	NIH Toolbox Loneliness Survey
Social Relationships	NIH Toolbox Positive Peer Interaction Survey
Social Relationships	NIH Toolbox Social Withdrawal Survey
Social Relationships	NIH Toolbox Empathic Behaviors Survey
Social Relationships	NIH Toolbox Peer Rejection Survey
Social Relationships	NIH Toolbox Perceived Hostility Survey
Social Relationships	NIH Toolbox Perceived Rejection Survey
Stress & Self-Efficacy	NIH Toolbox Perceived Stress Survey
Stress & Self-Efficacy	NIH Toolbox Self-Efficacy Survey
Health Anxiety	Healthy Anxiety Inventory
OCD Symptoms	Dimensional Obsessive–Compulsive Scale (DOCS)
Telehealth	Telehealth Usability Questionnaire

Behavioral Paradigms

These tasks will be conducted in private examination rooms and will be conducted via computer interface or verbally reported responses to the examiner. Some tasks will be completed in the MRI scanner; these tasks are identified in the descriptions below. All tasks will be completed at pre- and post-treatment assessment sessions. At the pre-treatment session, any task that has been completed within 2 weeks as part of any other research protocol at LIBR will not be repeated.

Approach-Avoidance Conflict Paradigms

AAC Task: The assessment of approach-avoidance conflict behavior will be conducted using the AAC task described in the "Preliminary Studies" section of this protocol except that points will be replaced with cents so that participants will be reward $0-3 depending on their performance. The AAC task will last approximately 25 minutes and will be conducted once during an fMRI scan at baseline and repeated behaviorally post-treatment. This task will allow us to assess conflict-arbitration-related behavioral and neural processes.

Exploratory paradigm: This paradigm will assess for naturalistic exploratory approach and avoidance behavior by recording subjects' motor behavior when in a naturalistic setting (an office) filled with objects that invite exploration. This task is meant to mimic paradigms used in animal studies to quantify approach-avoidance behavior (open field tests) and will provide a more "real-world" task to complement the computer-based tasks.

For this paradigm, the subjects will be fitted with an Equivital Life Monitoring Sensory system (Hidalgo, 2010), an ambulatory, multi-sensor, continuous monitoring vest for collecting, analyzing, and reporting health data. The Equivital System is able to collect reliable objective physiologic data through various sensors, which measure electrical activity of the myocardium via a 3-lead EKG, and activity/posture via a two-axis accelerometer. The sensor array of the Equivital System is embedded in a strap worn across the chest, made of washable material that fits snugly and can be worn comfortably for extended periods by individuals of varying girth. A rectified and integrated accelerometer signal is used to detect periods of physical activity and rest. An on-board PDA continuously encrypts and stores the patient's activity and posture physiologic data on a compact flash memory card. VivoSense™, a proprietary PC-based software, decrypts and processes the recorded data, and provides the viewing of- high-resolution waveforms and trends over time. Summary reports are generated that present processed data in concise, graphical, and numeric formats. Data are then exported in ASCII format for analysis in other software programs. Accelerometry data is sampled at 10 Hz and stored numerically in digital units. From these data, we will derive changes in posture, average activity levels, periods of peak activity, and total activity levels for specified time frames.

In order to assure that the subject doesn't alter their natural behavior/instincts because of the Equivital vest the subjects will be told that the vest is intended to efficiently measure rough baseline readings to calibrate the more robust sensors that will be worn during the remaining behavioral tasks described below. Subjects will then be led into an office room that is equipped with various objects that may prompt exploring (e.g. books, stuffed animals, globe, etc.) and minimal furniture. A small video camera will be mounted on the ceiling of the room that will record the subject's activities during the 15-minute period. The camera will feed live images via a monitor to the experimenter's office. The purpose of videotaping subjects' activities is two-fold: 1) to be able to validate the physiological movement measures from the monitoring vest using "real-life" motor behavior and 2) for safety reasons, so that the experimenter can ensure that the subject is safe at all times. The combined time of instruction, sensor set up, and the 15-minute exploratory period will be 30 minutes.

Reward-related Paradigms

Monetary Incentive Delay Task (MID)[66-68]: The MID is among the most robust methodologies in eliciting striatal activation and identifying reduced caudate activation in depression. On each trial, subjects are given a cue for potential reward (circle), loss (square), or no reward/loss (circle/ square). Horizontal lines in the cue indicate three reward/loss levels. To receive reward or avoid loss, subjects quickly press a button after seeing a target (white square). Task difficulty is adjusted to reflect each subject's skill level on the task using pre-scan reaction time

assessment so that each subject will succeed on ~66% of trials and earns $0-40. The MID lasts 18 minutes and will be conducted during fMRI at baseline and again without fMRI post-treatment.

Signal Detection Reinforcement Task (SDRT)[69]*:* For each *SDRT* trial, a cartoon face (without a mouth) is displayed. A short or long mouth is shown for 100ms (pseudo-randomized and counterbalanced). Subjects identify by button press the type of mouth presented. One mouth type is associated with three times more positive feedback (monetary value) than the other. The task difficultly is similarly rigged as in the MID so that out of 300 total trials the subject will be awarded for 120. For the entire task, subjects are awarded ~$6. Severity of depression has been shown to relate to deficiencies in developing response biases for rewarded trials on this task*(89)*. The SDRT lasts 10 minutes and will be conducted both at baseline and post-treatment.

Threat-Relevant Paradigms

Backward Masking Task (BMT)[70]: At the beginning of the run the subject will be sequentially shown two images of emotionally neutral faces. This is the target. For each of the proceeding trials the subjects will be shown an emotional face followed by another neutral face. The pairs include sad-neutral (SN), happy-neutral (HN), fear-neutral, neutral-neutral (NN; only shown at the beginning of the run), and the contrasting orders (i.e., NF). The goal is to identify if the pair of faces in each trial match the target. The images will be obtained from the NimStim Faces database*(71)*. The first face is shown for 26ms, followed by the neutral or “masking" face for 107ms. Each pair type is shown eight times during each of four runs in mixed-trial design. The BMT lasts 18 min. and will be conducted during fMRI at baseline and again post-treatment without fMRI. This task is expected to elicit amygdala activation according to the emotional stimuli of each trial. We believe that this task will elicit amygdala activations such that:

- Depression severity will correlate to greater activation in response to SN or NS faces.
- Anxiety severity will correlate to greater activation in response to FN or NF faces.
- The correlations between depression/anxiety severity and HN or NH faces will be observable.

Approach-Avoidance Task (AAT): This task will assess the behavioral avoidance tendencies associated with anxiety. For this tasks subjects will be shown a picture of a face (happy, angry, or neutral) framed by a blue or yellow border and instructed to pull a joystick (approach) when the border is one color and push away (avoid) when it is the other (counterbalanced). The picture zooms out and in accordingly. Mean response latency for push is subtracted from pull (e.g., angry faces pull - angry faces push) to obtain an avoidance bias score. Preliminary analyses by the PI suggest that greater trait anxiety relates to greater avoidance bias for negative stimuli. This replicates previous research in SAD[71] and spider phobia[72]. This task will be conducted at baseline and post-treatment behavior sessions and lasts 12 minutes.

Modified Probe Detection Task (MPDT): Attentional bias for positive and negative information will be measured using a version of the modified probe detection task [73]). Each trial consists of the identification of a cue location, brief presentation of a cue at that location (a small line oriented either horizontally or vertically), presentation of a pair of images (one representational, one non-representational), and presentation of a target, which is another line in either of two locations and is either horizontal or vertical. This target is presented until the participant responds, indicating whether the target is of the same or different orientation from the cue. Representational [73] stimuli will comprise IAPS images taken from positive, negative, or neutral valence sets. Each representational image is paired with one non-representational image, taken from a set of images of abstract art. Participants are presented with a total of 192 trials: 64 from each of positive, negative, and neutral images. The following traits are balanced across trials: representational image location, cue location, cue orientation, target location, target orientation, image duration (500 or 1000ms). The main outcome measures are the positive and negative engagement and disengagement biases [74].

Neuropsychological Assessment:

The neuropsychological assessments will be administered by a trained examiner
Wide Range Achievement Test (WRAT-4 reading): The WRAT-4 is an individually administered test of reading designed to measure general academic competence. The main variable of interest will be the total words pronounces correctly [193].
Delis-Kaplan Executive Function System (D-KEFS) Color-Word Inhibition Test: The D-KEFS Color-Word Inhibition Test is designed to assess verbal response inhibition and attentional switching. Participants are asked to name patches of colored ink (Color Naming subtest), read color-related words (Word Reading subtest), or to name the ink that color-related words are written in (Inhibition subtest). The speed at which participants complete the task and the number of mistakes made during completion are recorded. The main variables of interest for this study are the total time to complete the word reading, color naming, inhibition, and inhibition/switching subtests [75].
Delis-Kaplan Executive Function System (DKEFS) Verbal Fluency: This test is meant to measure information retrieval that is under conscious cognitive control and presumably an aspect of executive functions. On each of six one-minute trials, the examinee is asked to say as many distinct words as possible that meet a certain criterion. For the first three trials, the words must begin with a particular letter, for the next two trials, the words must belong to a particular semantic category, and for the last trial, words must alternate between two semantic categories. The main variable of interest is the total number of words correctly identified for the letter subtests and the semantic category subtests [75].
Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span: This sub-test of the WAIS-IV is used to assess attention and working memory and requires participants to repeat a series of numbers in forwards and backwards order (Digit Span). The accuracy of their responses is recorded. The main variables of interest are the total score forward and backward [76].
Finger Tapping Test (FTT): The FTT is a neuropsychological test that examines motor functioning, specifically, motor speed and has also been shown as a sensitive measure of testing effort [77]. The main variables of interest are the average number of taps with the index finger per 10 seconds for dominant and non-dominant hands.
WAIS-IV Digit Symbol Coding [76] The Digit Symbol is a neuropsychological test of visuomotor speed and working memory. The test requires individuals to match a symbol to a number according to a key at the top of the page. The main variable of interest will be the number of symbols matched in the time limit (90 seconds).

Neuroimaging using MRI

We will conduct the MRI behavioral tasks described above simultaneously with both EEG and MRI in order to ascertain the relationship between anxious systems and neural responses during emotional, cognitive, and interoceptive processing. If there is reason to believe a subject may not be able to tolerate the MRI, the subject may be asked to complete a mock MRI scan to verify MRI tolerability. If they are unable to tolerate MRI scanning, they will be withdrawn from the study and be provided prorated reimbursement for the time spent on the study. The mock scanner simulates the look, sound and feel of a real MRI scanner. The mock scan appointment takes about 30 minutes.
Prior to scanning, each subject will complete (1) self-report assessment of sleepiness (2) review of fMRI procedures and MRI safety screen, (3) review of instructions to complete the tasks (described above), and completion of practice tasks to ensure comprehension of instructions. This pre-scan preparation is estimated to take approximately 15 minutes. Participants will be scanned in a GE Discovery MR750 3.0 Tesla scanner (GE Medical Systems) at the Laureate Institute for Brain Research. The scanner is equipped with system-standard 8- and 32-channel brain coils. The multi-element brain arrays are highly sensitive MRI signal detectors offering vastly improved sensitivity for the detection of functional activation induced signal changes at high spatial and temporal resolutions, as well as anatomical MRI at very high spatial resolutions. The receivers allow for shorter readout times and reduced signal distortions and ventromedial signal dropout. During the functional neuroimaging scanning session, EEG data recordings will be collected via a state-of-the-art 8-channel MRI-compatible EEG system (Brain Products, GmbH, Germany, USA branch: Brain Vision LLC, Morrisville, NC). The customized system allows for accurate correction of MRI artifacts and high-quality EEG signals acquired simultaneously during fMRI. Each of the

two imaging sessions (conducted pre and post treatment) will take approximately 60 to 120 minutes. Each subject will be thoroughly screened for MRI safety.

MRI preparation

MRI eligibility will be confirmed prior to entry into the scanner. The subject will be asked to remove all ferromagnetic items. The subject will be trained on all fMRI tasks and given time to practice. If the subject requires vision correction, he or she will be fitted with plastic glasses closely matching his optic prescription. A urine sample will be collected for a pregnancy test (for female participants). Earplugs will be inserted prior to entering the scanner. The audio system will be explained so the participant will know how to communicate with the scanner operator and headphones will be placed over the ears. The subject will be reminded of the importance of staying still in the scanner. To minimize motion, the participant's head will be stabilized with a specially designed pillow under the neck and wedge-shaped cushions between the sides of the head and head-holder. Padding will be arranged to maximize comfort and a pillow will be placed under the knees to provide lower back relief. The MRI operator will put the head coil in position over the participant's head, localize the head position on the scanner, and ensure that the subject can fully view the display screen at the end of the scanner gurney, where task images will be displayed, by looking in the mirror directly above their eyes. The response box will be positioned in the subject's dominant hand and the subject will test the buttons. In the subjects' non-dominant hand, the pulse oximeter is placed on one finger and the subject is provided the emergency squeeze ball. Once the subject is comfortable, the gurney will move into the magnet. The MRI technician will secure the scan room door, dim the scan room lights, and communicate with the participant through the console.

Plan of Action for Incidental Findings

Upon detection of incidental findings during MRI scanning, the researcher or medical doctor at LIBR will verbally and/or in writing communicate the discovery to the subject. The communication will guide the subject to make the discovery known to their primary-care physician and that the Laureate Institute for Brain Research will provide a digital copy of the suspect MR scans to the primary-care physician upon request once the subject provides written consent authorizing the release of these medical records. Additionally, detection and disclosure of incidental findings will be documented in a database contained on the Laureate Institute for Brain Research computer cluster.

Physiological Monitoring

Physiological noise estimation and correction will be acquired through physiological monitoring of pulse rate using a fingertip pulse oximeter throughout the MRI session. An elevated pulse rate will generate a query from the scanner operator. Pulse rates above 90 beats per minute will prompt the scanner operator to ask participant if they are okay. The pulse oximeter sensors are connected to an In Vivo physiological monitoring system. Collection of physiological data during the scan will be linked to the behavioral tasks by a pulse marker generated by the magnet console and recorded on the physiological tracings. The concurrent information on pulse rate will be used to remove physiological fluctuations from the fMRI data.

Psychophysiological Recordings:

Subjects will perform behavioral tasks (outside of the scanner) while having their psychophysiological activity recorded using the measures described below. All measures will be taken using BIOPAC instrumentation (Lehigh, Pennsylvania). BIOPAC Systems provides both hardware for collection of these measures (BioPac MP150 system) and software (AcqKnowledge software) for analyzing these measures. All of these measures are commonly used in emotional processing research and are non-invasive. The use of all of these measures concurrently allows for a more thorough understanding of sympathetic and parasympathetic nervous system influences on physiological responses to negatively and positively-valenced stimuli, interoceptive stimuli, cognitive processing and decision-making. The combined time for both sensor set up and task completion is 2.5 to 3 hours.

Galvanic Skin Conductance Level and Response: Electrodes are used to measure variations in sweat gland activity that has been shown to vary due to stress and emotional arousal. Galvanic skin conductance responses to emotional stimuli have been shown to vary with individual anxiety levels. To measure galvanic skin conductance small electrodes are placed on the skin at either the fingertips, palm of the hand, or soles of the feet with isotonic gel (0.5% saline in a neutral base). Skin conductance has long been considered as a physiological marker of emotional arousal[78] and is often described as a non-specific measure of arousal, regardless of the valence of a stimulus[79]. Skin conductance measures have been shown to vary not only with the arousal state of the individual, but also by the more chronic emotional state – for example, with those reporting higher levels of trait anxiety demonstrating increased skin conductance responses[80].

Heart rate: Measures related to heart rate will be obtained from (1) pulse oximetry and (2) electrocardiogram (ECG). For pulse oximetry, BioPac systems use Nonin's PureLight® sensors to noninvasively measure blood-oxygen percentage levels via light-emitting diodes (LEDs) placed onto either the earlobe or fingertip. Light absorption differs between oxyhemoglobin and its deoxygenated hemoglobin and thus can be used to obtain the oxyhemoglobin/deoxyhemoglobin ratio and pulse rate. Heart rate has consistently been shown to increase under states of high arousal, particularly emotional arousal and anxiety. State changes in arousal and anxiety have been consistently found to relate to increased heart rate, which is considered primarily under sympathetic nervous system control[81, 82]. For ECG, Biopac systems will again be used, along with three Ag/AgCl electrodes placed on the subject's chest (to the right or left clavicle and to the left of the belly button) in order to obtain a measure of the electrical activity of the heart. Data collected from this measure can be used to estimate heart rate variability (oscillations in the interval between consecutive heart beats) and, when combined with measures of respiration rate, respiratory sinus arrhythmia (RSA; variation in heart rate that occurs during a breathing cycle). While skin conductance and startle responses are thought to be primarily controlled by sympathetic nervous system inputs, heart rate variability and RSA are thought to result from the interaction of sympathetic and parasympathetic inputs[83]. Individuals with a variety of mood and anxiety disorders have been reported to decrease HRV and RSA[81, 84].

Respiration Rate: Respiratory effort will be measured using BIOPAC's Respiration Transducer, which measures changes in thoracic or abdominal circumference that occur as the subject breathes. This is accomplished via a belt that wraps around the abdominal or thoracic region of the body, which noninvasively measures changes in stretch of the belt with circumference change. High levels of anxiety, particularly anxiety sensitivity and/or panic disorder have been associated with increased respiratory rate in response to anxiogenic stimuli[85]. In addition respiration rate will be used in conjunction with ECG to estimate RSA, as indicated above.

Startle Reflex Electromyogram: Electromyogram (EMG) responses will be measured from the orbicularis oculi using two electrodes filled with electrode gel and fitted with adhesive collars. One electrode will be placed directly underneath the left eye, and another one approximately 1 cm to the left below the outside corner of the left eye. The startle reflex is sensitive to habituation, sensitization, and affective context and modulation. Eye blink startle is a reflexive response and thus, no heavily influenced by intentional control or response biases that can interfere with self-report, and represents a translational tool that has been used with both humans and other animals. Startle amplitude has been consistently shown to vary with induced affective state as well as trait levels of mood and anxiety. It represents the one psychophysiological measure that may track valence rather than arousal only[86, 87].

Facial Expressions: Advances in computer vision and machine learning over the past 15 years have led to the emergence of technology for automatic analysis of affective behavior[88]. During this time, the Machine Perception Laboratory at UCSD (MPLab) has focused on development of systems for automatic analysis of facial behavior, including audio-visual speech recognition [89-91] and recognition of facial expressions [90-94]. The output of the face detector is scaled to 90x90 and fed directly to the facial expression analysis system. First the face image is passed

through a bank of Gabor filters at 8 orientations and 9 scales (2-32 pixels/cycle at 0.5 octave steps). The filterbank representations are then channeled to a classifier to code the image in terms of a set of expression dimensions. Research at the MPLab has demonstrated that performing feature selection on the Gabor filters prior to classification enhances both speed and accuracy. This approach combines feature selection based on Adaboost with feature integration using support vector machine. *Automatic Facial Expression Analysis*: A video camera will record each subject during the behavioral tasks described above in order to permit coding of facial expressions. Automatic facial expression analysis will be conducted by the EMOTIENT [95], software developed and validated by our collaborators at the Machine Perception Laboratory at UCSD (MPLab). EMOTIENT analysis corresponds to the well-validated Facial Action Coding System (FACS [96, 97]), a comprehensive method to objectively code facial expressions. EMOTIENT automatically codes the intensity of 26 component facial movements referred to as action units (Aus).

Blood biomarkers:

Under the direction of the Dr. Jonathan Savitz, biochemical assays will be performed on biological samples collected at baseline and post-treatment to quantify biomarkers linked with changes in functional improvement with therapy for anxiety and depression. Participants will be asked to have fasting blood drawn by a trained phlebotomist (conducted prior to 11am to reduce the length of fasting and increase consistency across samples drawn). This will be scheduled to occur the morning of one of the visits, or at a time convenient for the participant. Resting blood pressure and heart rate will be assessed. Extra blood samples will be obtained to examine a standard panel of metabolic and inflammatory biomarkers, including leptin, glucose, insulin, a lipid panel, soluble cellular adhesion molecules (sICAM, sVCAM), C-reactive protein, IL-6, and TNFa. Additionally, in order to lay the foundation for future studies, we also propose to collect and process a small quantity of blood (40 mL) to be banked for potential future endocrine, immune and/or genomic analyses.

Sample collection, processing distribution and storage procedures: Approximately 100 mL of blood is needed per subject during both the baseline and post-treatment follow-up sessions, including biomarker and genetic samples, for a total of 200 ML, which is well within the safety limit of ~450 mL. Blood will not be drawn from subjects with a hematocrit below 30%. A trained phlebotomist will obtain blood samples. Samples for genetics will be delivered to the University of Oklahoma laboratory for processing and storage. Blood samples for plasma and serum preparation will be processed at the Laureate Institute for Brain Research. Plasma and serum will be collected and temporarily stored at -20ºC and then transported to the University of Oklahoma laboratory for long term storage in locked freezers at -80ºC. Freezers will be maintained in a specially equipped room with emergency backup power and an automated telephone alarm system that is programmed to call in case of failure. Additional aliquots of samples will be stored at -80^{o}C should repeat analyses be required at a later date.

F. TREATMENT

The treatments that we will be providing to the subjects will be catered to their specific disorder, including exposure therapy (EXP) for anxiety symptoms and disorders (i.e., SAD, panic disorder, phobias) and behavioral activation (BA) for depression. However, individuals who meet criteria for GAD will be randomized to receive either EXP or BA. This randomization will be conducted in blocks of 4, stratified by gender. The randomization will be determined prior to enrolling any GAD participants using computer generated allocations.

The interventions described will usually be conducted as group-based, in-person therapy. However, if in-person meetings are made impossible for a reason that is not specific to any one individual (e.g., natural disasters, contagious diseases that require social distancing), then participants will be provide the option to continue participating in these interventions and complete interview-based assessments through videoconferencing. Participants who are provided this option will be required to sign an informed consent addendum specifically addressing this situation. Only participants who consent to the utilization of videoconferencing technology will be asked to complete these procedures. Consent may be obtained in person (in a private interview/exam room) with

hard copy consent, in person using e-consent (on computer or tablet) or remotely (by phone/video chat) with signed consent returned via email, mail or fax. If the consent process is conducted remotely, the researcher will send the consent to the participant in advance of the consent discussion to allow participant and family/friends time to review. The researcher will then review the consent by phone with the participant in detail, giving the participant an opportunity to ask questions, have all questions answered and allowing time for participant to consider whether he/she wishes to participate prior to signing consent. If participant agrees to participate, he/she will sign consent and return by email, mail or fax. The person obtaining consent will sign the consent form received from the participant and date with current date. A note will be entered in the participant's record to explain the reason consent was signed on different dates.

For videoconferencing, GoToMeeting will be utilized, which has put protections in to place for protecting confidentiality, privacy, and security (see https://www.gotomeeting.com/meeting/resources/hipaa-compliant-video-conferencing for more detail). However, participants will be informed that confidentiality of information shared during videoconferencing cannot be guaranteed. Participants will be allowed to participate via audio only connections as requested.

EXP is a treatment that motivates individuals to experience situations that cause them distress in a controlled and safe environment, allowing for habituation/extinction of the fear response and processing of the emotions that arise from such experiences. BA is a treatment that focuses on increasing engagement in one's world, e.g. through work/academic/life goals, physical lifestyle, and social connections. These treatments will be delivered by a licensed clinical social worker (Sydney Nelson-Hunt, LCSW) in conjunction with the PI (Robin Aupperle, PhD, a clinical psychologist) and clinical psychologist in training (Ashley Stillman, TU doctoral student). Dr. Aupperle and Ms. Nelson-Hunt will receive training in the treatments being provided via clinical workshops from Michelle Craske, PhD (Professor, UCLA and author of several treatment manuals for exposure-based treatment of anxiety[98-101]) and Christopher Martell, PhD (private practitioner and author of the manual for Behavioral Activation Therapy for Depression [102]). Dr. Michelle Craske has agreed to provide monthly (and as-needed) clinical consultation throughout the study regarding both interventions. However, she will not be privy to any identifiable information. Clinical psychologists in training will be provided training and supervision in the treatment protocols from Dr. Aupperle and Ms. Nelson-Hunt. We chose to use treatment protocols focusing on behavioral techniques (exposure; behavioral activation) rather than those involving cognitive techniques (e.g., restructuring) as both exposure-only and behavioral activation-only treatments have been associated with equivalent clinical benefits compared to those involving cognitive techniques [103-105]. This will also allow for a more direct interpretation concerning how the predictive variables (e.g., approach, avoidance, and conflict varaibles) may relate to treatment mechanisms.

Measures will be taken to help ensure treatment fidelity, according to previous recommendations[106]. Each therapy session will be recorded and 40% of sessions will be randomly selected for fidelity ratings by research personnel. Skill acquisition and fidelity will be assessed using BT competencies developed for the Improving Access to Psychological Therapies (IAPT) Program[107] (for exposure therapy) or the Quality of Behavioral Activation Scale (Q-BAS) for Behavioral Activation therapy, provided by Dr. Martell. These fidelity ratings will be made by experts in each therapy (Dr. Michelle Craske, UCLA; and Dr. Christopher Martell; University of Wisconsin – Milwaukee), who will be provided de-identified audio tapes of therapy sessions via secure server access. Subject compliance will be assessed using (1) session attendance, (2) Homework Rating Scale[108] to assess between-session compliance and (3) Vanderbilt Psychotherapy Process Scale (VPPS), therapist and client versions, to assess subject compliance and therapist behavior intra-session[109]. The OASIS and PHQ-9 will be completed weekly to assess symptom severity. Each therapy session will be video and audio recorded and may be reviewed by the research team. The recordings will be destroyed by the end of the study, unless consent was given by ALL members in attendance at that group to use them for educational and training purposes (se consent form addendum).

Group-based, transdiagnostic therapy will be conducted according to a treatment manual developed by Dr. Michelle Craske at UCLA, which has been found effective in reducing anxiety symptoms for GAD, panic, and SAD[110]. This 10-week protocol (one session per week, 90 minute sessions) will be modified to focus on exposure techniques, excluding cognitive restructuring. Exposure exercises will be individualized based on anxiety foci. For example, all subjects will complete initial interoceptive exposures. However, those with SAD may complete them while looking in the mirror, focusing on their ability to concurrently deliver a speech. For those with GAD, exposure to worry-related imagery will be a treatment focus. The specific manual to be used in this study is attached to this protocol.

Behavioral Activation Treatment of Patients with Depression

BA is based on the premise that problems in an individual's life reduce their ability to experience reward from positive behaviors/events, leading to symptoms of depression. BA techniques focus on behaviorally stimulating reward activation in the subject by encouraging engagement in key aspects of life that are pleasurable or will ultimately make them feel productive. The BA sessions will occur once each week for 10 weeks (each 90 min). During the sessions the therapist and client will work together to develop reward activation assignments to be completed before the next session (i.e., in the subject's day to day life outside the therapist's office). The BA sessions will become highly individualized to target the behavioral patterns that cause depression in each subject. These behaviors will be identified early on in the sessions (first 1-2 sessions) and then subsequent sessions will consist of changing this behavior in order to stimulate feelings of reward, and thus alleviate symptoms of depression. The treatment will last 10 weeks (10 sessions, 90 minutes each) and will be conducted in accordance with the published clinician's guide on behavioral activation therapy[102] . Each subject will be provided the workbook entitled "Overcoming Depression One Step at a Time: The New Behavioral Activation Approach to Getting Your Life Back"[65], which they will complete concurrently with the group therapy sessions.

G. GENDER/MINORITY/PEDIATRIC INCLUSION FOR RESEARCH

Women and minorities will be included in the study without prejudice according to their representation in the study population. Adult subjects will be recruited from the greater Metro Tulsa area and should thus share the racial and ethnic composition of this area. All efforts will be made to ensure that our subject population closely resembles the gender, ethnic and racial composition of the greater Tulsa area. Children are not included in this protocol due to its focus on understanding the neural systems underlying adult mood and anxiety disorders**.**

H. PARTICIPANT RISKS AND PLANS TO MINIMIZE RISKS

Risks Associated with Screening and Evaluation:

Risk: The risks and discomforts of the screening evaluations are minimal. Some of the questions in the interviews may be distressing or uncomfortable to answer due to their personal or emotionally relevant nature.

Risk minimization: The researchers are trained to frequently inquire the subjects about their willingness and ability to continue with testing. If the subjects express concerns about continuing with testing, the research assistants will stop testing, offer a break, or, in case the subject is not willing to continue, terminate the testing session. If subjects report psychological distress, suicidal ideation, or intent to harm self or others, Dr. Khalsa, or his licensed designee, will be contacted immediately to ensure appropriate care and compliance with mandated reporting to authorities. Subjects may be referred for professional intervention, as deemed appropriate, including calling emergency personnel (911) if needed. A current list of local mental health treatment programs will be provided to all subjects at screening. 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.

Risks Associated with MRI and EEG:

Risk: MRI uses powerful magnetic fields and weak radio frequency pulses (electromagnetic radiation), neither of which has been associated with adverse effects in patients or laboratory animals when studied under clinical imaging protocols. However, as in the clinical setting, subjects must be free of any external or implanted ferrous material. People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, implanted delivery pump, or shrapnel fragments.

Risk minimization: Each subject, prior to entering the MR environment, will complete a safety pre-screening questionnaire. The safety pre-screening questionnaire probes for possible occupational exposure to metal slivers or shavings remnants of which may remain lodged in the subject's head or neck. Subjects with surgical clips or shrapnel, cochlear implants, or any other form of ferrous metal body implanted in or on their body will be excluded. All subjects with any form of implant wires, metal or electronic device implants will be excluded. All persons involved in this protocol will receive MR safety training conducted at the Laureate Institute for Brain Research by their MR safety officer.

Risk: While there are no known medical risks associated with EEG, placement of electrodes and continued wear of the EEG cap during fMRI may cause minor bruising and discomfort, respectively.

Risk minimization: Subjects are encouraged to inform study personnel if the EEG electrode placement and cap are causing discomfort. Study personnel will make every effort to ensure subject's comfort throughout all study procedures. In addition, should the EEG cap cause more than minimal discomfort, subjects will have the option to complete the fMRI without EEG.

Risk: MRI is performed in confined quarters and may cause feelings of being isolated or confined. It is expected that a very low percentage of subjects will be unable or unwilling to complete participation due to these feelings of discomfort.

Risk minimization: We intend to minimize claustrophobic problems using a series of procedures: 1) by giving a detailed explanation of the environment prior to scanning, 2) providing the opportunity for subjects to experience a mock scan in which all the sounds, visuals, and feelings of a real MRI scan are simulated, 3) maintaining voice contact with the subjects at all times, 4) maintaining visual contact of the patient in the scanner using observational cameras placed inside the scanner room.

Risk: The sounds that are made by the MRI scanner are very loud and are capable of causing hearing damage to an unprotected ear.

Risk minimization: All participants will be fitted with hearing protection and be required to wear the hearing protection for the duration of the MRI scanning.

Risk: It is currently unknown what effects MRI has on pregnancy. For that reason there are unforeseeable risks of birth defects forming as result of scanning a pregnant subject.

Risk minimization: A pregnancy test will be obtained from women of child-bearing potential prior to the fMRI scan. Women who are pregnant or planning to become pregnant will be excluded from the study. For women of child-bearing potential, they will be given a choice of the following: 1) to receive from the researchers a pregnancy test kit to administer at home the day of the MRI, with recommendation to follow directions on the kit (i.e., to use the first morning void); or 2) to self-administer the test after coming in to the research lab. In order to participate in the study, the subject will need to check the appropriate box and initial/sign a statement that affirms that she took a pregnancy test that day (at home or at the lab) and the results were negative. This statement has been placed at the end of the consent document with a place to date and initial the statement if multiple MRI scans are completed.

Risks associated with Blood Draws

Risk: Blood draws may be associated with mild pain, bruising, and infection at the puncture site as well as possible risk of fainting or dizziness.

Risk minimization: Samples will be taken by a trained phlebotomist and the subject will be informed that the blood draw may be associated with mild pain, bruising and infection at the puncture site, as well as a possible risk of fainting or dizziness. In addition, the

Risks associated with behavioral testing

Risk: The participants may experience feelings of discomfort and tiredness due to the lengthy nature of the behavioral testing block. In addition, participants may experience feelings of distress due to the emotional nature of the stimuli used during the tasks.

Risk minimization: The researchers are trained to frequently inquire the subjects about their willingness and ability to continue with testing. If the subjects express concerns about continuing with testing, the research assistants will stop testing, offer a break, or, in case the subject is not willing to continue, terminate the testing session. If subjects report psychological distress, suicidal ideation, or intent to harm self or others Dr. Werful, or his licensed designee, will be contacted immediately to ensure appropriate care and compliance with mandated reporting to authorities. Subjects may be referred for professional intervention, as deemed appropriate, including calling emergency personnel (911) if needed. A current list of local mental health treatment programs will be provided to all subjects at screening. 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.

Risks associated with treatment

Risk: It is not expected to occur but participants may experience adverse effects to treatment in the form of worsening anxiety or depression symptoms.

Risk minimization: All subjects will be informed of the procedures/strategies involved in the therapy protocol during the informed consent process. Anxiety and depressive symptoms will be monitored weekly throughout the intervention by using validated questionnaires (OASIS; PHQ-9). This will allow for detection of any worsening of depressive or anxiety symptoms during completion of the study. This will be supplemented by observation by the clinician leading the treatment groups (the PI). If symptoms worsen during the course of the study, the subject will be assessed individually by Ms. Nelson-Hunt, Dr. Aupperle and Dr. Khalsa as needed. If symptoms worsen significantly such that additional evaluation, emergency services, or other clinical treatments is needed, appropriate referrals will be made (as described in the contingency plan for suicidality, below). If a subject has a clinical issue in between treatment sessions that does not reflect a psychiatric emergency, they will be able to reach a LIBR clinician during official hours (weekdays between 0800 and 1700). On weekends and off-hours (evenings and nights) they will be able to call a 24-hour per day on call service for LIBR, which is provided through the Call Center of Laureate Psychiatric Clinic and Hospital. In case of clinical emergency between sessions or during videoconferencing, subjects will be instructed to contact 911 or Tulsa Community Outreach Psychiatric Emergency Services (COPES – 918 744 4800).

Contingency plans for monitoring suicidality, worsening clinical symptoms, or other mental health emergencies

All volunteers who are deemed a serious suicide risk will be excluded from the study. All research volunteers will undergo routine, state-of-the-art screening and diagnostic assessments at LIBR. The screening will be conducted by a clinician interviewer (who holds either a nursing or MD degree, or a MA or PhD degree in clinical or counseling psychology, and has received extensive training and experience in the evaluation and management of patients with major psychiatric disorders). In the evaluation of suicidal risk, we specifically will exclude from participation any volunteer who endorses having developed a plan or intent to attempt suicide, or has made a serious suicide attempt

within the preceding six months. Any volunteer who is excluded from participation for these reasons will be referred for emergency care according to written LIBR policies for managing potentially suicidal patients, as described below.

While the participants are in this study they will be monitored for the development of suicide risk or for worsening in their clinical illness by a clinician. This will be conducted using the weekly self-report assessments and clinical observation, as described above. If concerns arise when the participant is physically present at the Laureate Institute for Brain Research, psychologist Robin Aupperle, PhD is available on site to address any concerns that arise. If Dr. Aupperle is unavailable or further evaluation is deemed necessary, psychiatrists Dr. Martin Paulus, and Sahib Khalsa will be available.

For patients who are at the LIBR facility and are deemed to constitute a serious risk for suicide, the LIBR policy requires that they be escorted by two clinicians to the onsite, 24-hour emergency facility at Laureate Psychiatric Clinic and Hospital (which is located about 100 yards from the LIBR facility). If participants refuse to be escorted to this facility and leave the LIBR premises, the study clinician will contact the Community Outreach Psychiatric Emergency Services (COPES – 918 744 4800), which is available 24 hours per day to send a mobile unit to the person's home.

For participants who develop serious suicidal ideation while not on the LIBR premises, these participants will be instructed to call 911 or to go to the nearest emergency room if they feel they are a threat to themselves or others. They will also be given the contact details of the Tulsa Community Outreach Psychiatric Emergency Services (COPES – 918 744 4800).

For participants who have clinical issues that do not reflect a psychiatric emergency, they will be given a telephone number where they can reach a LIBR clinician during those hours when LIBR is officially staffed by clinicians (weekdays between 0800 and 1700). For weekends and off-hours (evenings and nights) they are provided a second telephone number where they can reach the 24-hour per day on call service for LIBR, which is provided through the Call Center of Laureate Psychiatric Clinic and Hospital.

Upon study completion, patients who are currently under treatment by an external provider will be referred to their own clinician. Subjects who are dropped from study participation, or patients who complete the study and are not under the care of a clinician, will be provided a referral to a psychiatrist or other mental health professional at one of the following clinics (regardless of the reported level of post-treatment symptoms):

Outpatient (insured)
Laureate Psychiatric Clinic and Hospital
6655 South Yale Ave
Tulsa OK, 74136
(918) 481-4000

Department of Psychiatry (sliding scale)
University of Oklahoma College of Medicine
Tulsa OK, 74136
(918) 619 4400

Outpatient (uninsured)
Tulsa Center for Behavioral Health (sliding scale)
2323 South Harvard Ave
Tulsa, OK, 74114
(918) 239 2100

Associated Centers for Therapy (sliding scale)
7010 South Yale Ave, Suite 215
Tulsa OK, 74136

(918) 492 2554

Inpatient
Laureate Psychiatric Clinic and Hospital
6655 South Yale Ave
Tulsa OK, 74136
(918) 481 4000

Shadow Mountain Behavioral Health System
6262 South Sheridan Road
Tulsa OK, 74133

Individually tailored referrals will be made for participants who reside outside of the Tulsa region, so that they will be referred to psychiatric services that are located near their home or workplace.

I. DATA STORAGE AND CONFIDENTIALITY

Only information that is required to fulfill the objectives of the study will be collected. Paper copies of consents, screening forms, the Research Privacy Form and any other forms, and testing results or papers containing Personally Identifiable Information (PII) will be stored in locked cabinets at the Laureate Institute for Brain Research. Only approved study personnel will have access to any records that have identifying information. Any electronic data will have all identifiable information encrypted and be stored on a password-protected database on a secure server managed by the Laureate Institute for Brain Research. Records of the subject's participation in this study will be held confidential except in the case when disclosure is required by law or as described in the informed consent document (under "Confidentiality"). The study doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the Institutional Review Board (IRB), will be able to inspect and copy confidential study-related records that identify the subject by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subject will not be identified.

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. Study consent records will be stored in the locked records room at the Laureate Institute for Brain Research. Only approved study personnel will have access to study records that contain any identifying information. Study data records and blood/urine/biological samples will be assigned code numbers and will not be individually identifiable. Code numbers are a combination of numbers and letters. Audio and video recordings will be destroyed after the study, unless consent was given by ALL members in attendance at that group to use the recordings for future educational and training purposes. The electronic data will be kept in a firewalled and password protected database on a secure server managed by Laureate Institute for Brain Research (LIBR). Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the information technology staff. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at Laureate Institute for Brain Research and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to LIBR researchers by both our Privacy Office and the Western Institutional Review Board (WIRB). REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (www.project-redcap.org). In addition, all subjects will be given the option of tracking their daily

activities and mood using a mobile web application (versus using the paper forms included in the Behavioral Activation workbook). Information collected by this application will be encrypted for transmission and for local (mobile client-side) and remote (the local data center at the Laureate Institute for Brain Research (LIBR)) storage. Authentication, audit and access controls will be implemented to ensure that only authorized users have access to the data and that all access is logged and monitored appropriately.

The Life Chart application, developed by LIBR, is accessed only within the LIBR network by participants and members of LIBR's research team. Life Chart data is stored behind a firewall through a password protected database on a secure server managed by LIBR that undergoes weekly security dynamic and static analysis scans through Veracode's platform under the HIPAA/Omnibus Act/HITECH/HITRUST policy. Veracode is used by over 2000+ companies in the world in making secure software (www.veracode.com).

The videoconferencing technology, GoToMeeting, utilizes encryption methods and meeting access control to avoid interception by anyone other than the invited participants. They have also implemented various mechanisms designed to address HIPAA privacy and security standards (see https://www.gotomeeting.com/meeting/resources/hipaa-compliant-video-conferencing). However, all participants will be informed prior to using this technology that confidentiality of information shared during videoconferencing cannot be guaranteed.

Subjects will not be identified in any reports or publications. Records of the participant's participation in this study will be held confidential except as disclosure is required by law or as described in the informed consent document (under "Confidentiality"). The study doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and WIRB will be able to inspect and copy confidential study-related records which identify the subject by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subject will not be identified. Paper copies of consents, screening forms, the Research Privacy Form, and any other forms, testing results or papers containing Personally Identifiable Information (PII) will be stored in a secured medical records room with access granted only to authorized personnel.

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