# Development of a Novel Transdiagnostic Intervention for Anhedonia

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# Development of a Novel Transdiagnostic Intervention for Anhedonia

**Protocol Number:** ***R61MH110027-01*** **&** ***R33MH110027-03***

**IRB Number: UNC #16-2268**

**National Clinical Trial (NCT) Identified Number:** ***NCT02874534*** **&** ***NCT04036136***

**Principal Investigator: Gabriel Dicther, PhD (Duke PI: Moria Smoski, PhD)**

**Funded by: NIH National Institute of Mental Health (NIMH)**

**Version Number:** ***for ClinicalTrials.gov***

**09 October 2023**

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# STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

| | |
|---|---|
| **Title:** | Development of a Novel Transdiagnostic Intervention for Anhedonia |
| **Study Description:** | *The overall goal of this project is to develop a novel transdiagnostic treatment for anhedonia, called Behavioral Activation Treatment for Anhedonia (BATA), using ultra-high field functional neuroimaging. There is a critical need for a validated treatment that specifically targets anhedonia, and this project will evaluate the effects of this new treatment on anhedonia and will establish how this treatment impacts brain systems that mediate reward processing, clinical symptoms of anhedonia, functional outcomes, and behavioral indices of reward processing. During the first phase of the study (R61-i.e., the first 60 participants), both groups will receive pre- and post-treatment scans as well as two mid-treatment scans (weeks 8 and 12) to evaluate treatment dose (4 scans total). During the second phase of the study (R33-i.e., the remaining 150 participants), participants will receive only pre- and post-treatment scans (2 scans total). All participants will complete interview, symptom, and behavioral measures before and after treatment. PET supplement: 30 participants that are part of the main parent NIMH grant will asked to enroll in the PET sub-study & complete up to 2 PET scans pre/post during the study. It is optional, so participants may refuse &still participate in the main study. Of the 30 enrolled in the PET sub-study, ~50% will be randomized to the investigational treatment BATA & ~50% to the control condition, MBCT.* |
| **Objectives:** | *R61 Phase: **Aim 1**: To evaluate whether BATA produces changes in neural responses to reward anticipation and reward outcomes using fMRI that exceed changes due to an active comparison treatment, specifically* |

*Mindfulness Based Cognitive Therapy (MBCT) and does not impact neural responses to threat. This aim pertains to only the first 60 participants randomized into the study (n=30 to receive BATA and n=30 to receive MBCT).* ***Aim 2:*** *To evaluate relations between BATA dose (treatment duration) and neural target engagement by examining changes in neural response to rewards with mid-treatment fMRI scans 8 and 12 weeks after starting the 15-week treatment.*
*R33 phase of this grant, pertains up to 210 participants in the study (105 randomized to BATA & 105 randomized to MBCT):*
***Aim 3:*** *To evaluate the effects of BATA versus an active comparison treatment on anhedonic symptoms and functional outcomes.*
***Aim 4:*** *To evaluate the effects of BATA versus an active comparison treatment on behavioral indices of reward sensitivity.*
***Aim 5:*** *To evaluate the effects of BATA versus a comparison treatment on neural response to rewards.*

**PET & EMA sub-study Aims:**

**Aim 1 (PET):** To evaluate the effects of BATA, relative to a comparison treatment, on PET-derived measures of DA functioning during incentive processing. We hypothesize that BATA, but not the comparison treatment, will result in increased phasic striatal DA release but will not influence background DA striatal tone. **Aim 2 (PET):** To evaluate relations between treatment-related changes in fMRI-derived mesocorticolimbic activation and PET-derived DA functioning in the BATA-treated group. We hypothesize that normalization of fMRI-derived mesocorticolimbic activation due to BATA specifically will be associated with increased phasic DA release but no change in background DA tone during incentive processing. **Aim 3 (EMA):** To evaluate if BATA, relative to a comparison treatment, produces improvements in real-world positive affect and the use of BATA skills. **Aim 4 (EMA):** To evaluate relations between treatment-related changes in fMRI-derived mesocorticolimbic activation and real-world positive affect and the use of relevant BATA skills.

**Endpoints:**

*Primary Endpoints:*
*Imaging (7T) – Tasking based activation to Monetary Incentive Delay (MID) Task; Task based activation to Emotion Reactivity task (Hammer)*
*Behavioral/Observational:-Probabilistic Reward Task (PRT) and EffortExpenditure for Reward Task (EEfRT); Changes in SHAPs scores pre/post treatment*
*Secondary & Exploratory Endpoints:*
*Imaging (7T)- Resting state connectivity*
*Behavioral/Observational -CGI-I; Homework Completion (participation and clinician-rated); ecological momentary assessment of activation, mood, reward experiences. Passive location tracking (PLT) data via the MetricWire app for the EMA sub-study to compare distance traveled before and after both treatments as a secondary, exploratory measure of behavioral activation. Follow-up analyses will evaluate relations between motion tracking, behavioral, brain, and clinical measures of response to both treatments.*

| | |
|---|---|
| | *PET Aim1: Extract dynamic change in binding potential (BPND%) before, during and after the task and then comparing these values before and after treatment between treatment groups. PET Aim2: Correlations between changes in PET striatal binding potential magnitudes and changes in fMRI.* |
| **Study Population:** | *This study will recruit participants with clinically significant anhedonia, who are 18-50 years old who are able to read & understand English, and who are seeking treatment.* |
| **Phase:** | Phase I/II |
| **Description of Sites/Facilities Enrolling Participants:** | *Recruitment and therapeutic intervention for the study managed by Duke University Medical Center, Department of Psychiatry and Behavioral Sciences and Duke PI ;Eligible participants based on the initial Duke study assessment consent at UNC-Chapel Hill in the Department of Psychiatry under UNC PI for all 7T imaging, EMA and optional PET Scans.* |
| **Description of Study Intervention:** | *BATA: modified Behavioral Activation Treatment for Depression to create Behavioral Activation Treatment for Anhedonia (BATA). Treatment in the R61 phase (Phase I) will consist of up to 15 weekly 45-minute sessions. In the R33 phase, BATA sessions will again be from 8 to 15 weekly 45-minute sessions. BATA will be compared to MBCT (Mindfulness-Based Cognitive Therapy), chosen because its mechanisms of action are hypothesized to impact different brain mechanisms than BATA. To control for nonspecific factors in BATA including clinician contact, MBCT is administered in an individual format. MBCT in the R61 phase will be compromised of up to 15 weekly 45-minute sessions. In the R33 phase, the number of sessions match that of BATA.* |
| **Study Duration:** | *72 months* |
| **Participant Duration:** | *Three to five months* |

## 1.2 SCHEMA

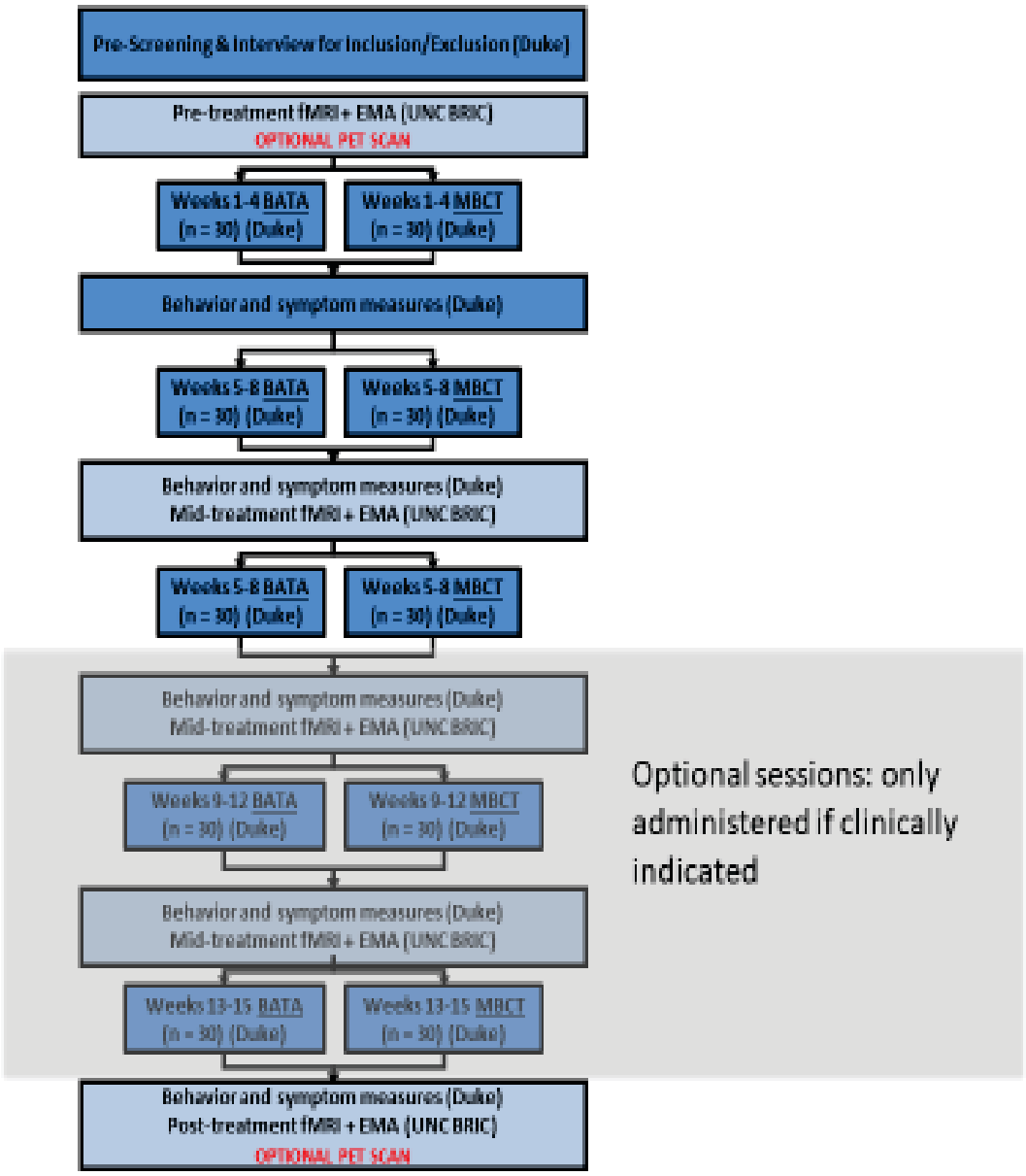


*Figure 1: R61 Study Flow*

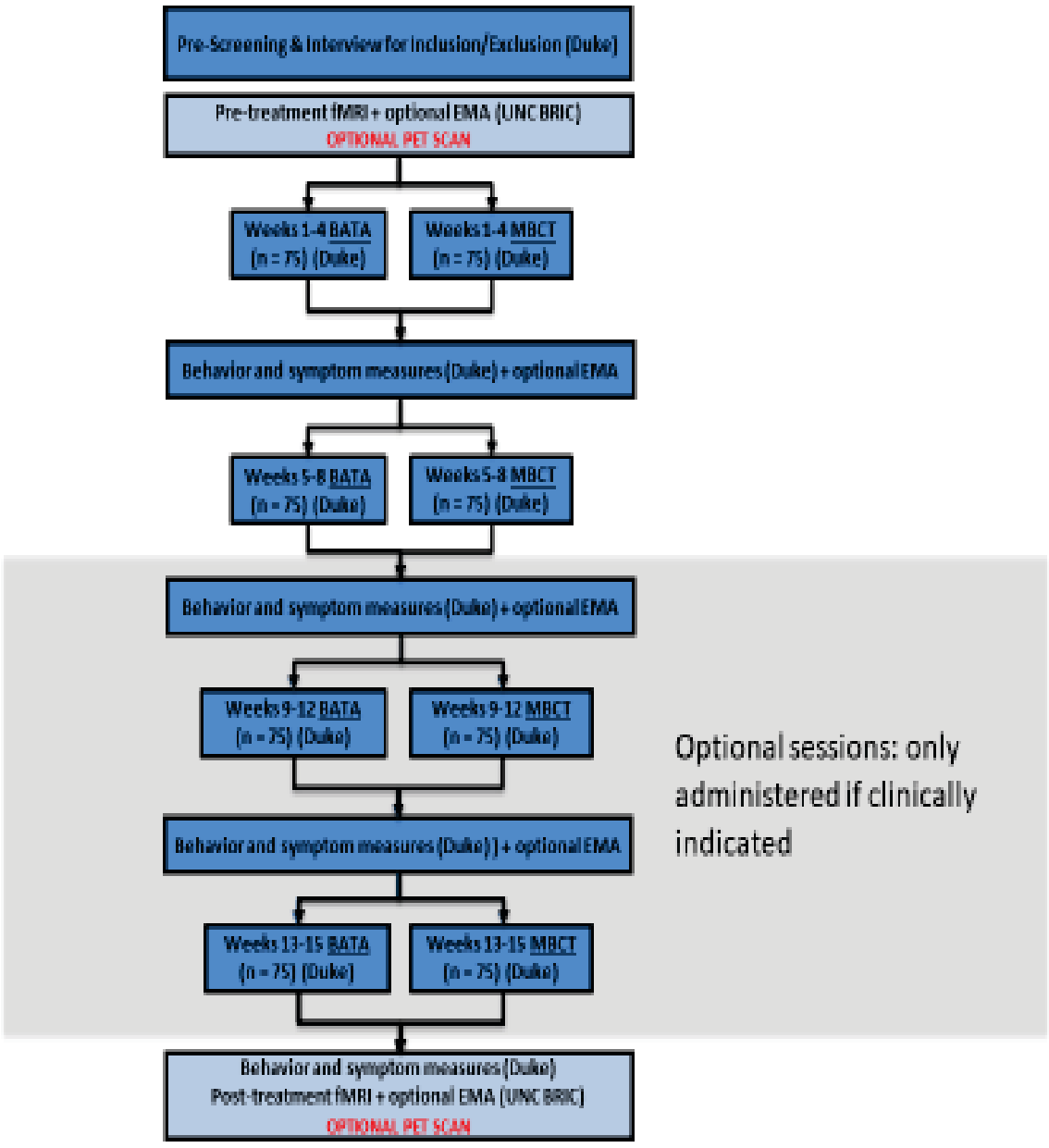


*Figure 2: R33 Study Flow*

## 1.3 SCHEDULE OF ACTIVITIES (SOA)

TIMELINE OF STUDY ASSESSMENTS AND PROCEDURES:

| Assessment/ Procedure | Online/ Phone Screen | Remote/In Person Screen (at Duke) - can be split in 1-2 visits (part remote/part in-person)** | Pre-Tx fMRI (at UNC) | Intervention therapy sessions at Duke)[1] | Wks 4, 8 & 12 (if applic-able)[2] | fMRI (wk 8 & 12)[3] | Study Completion Visit-Part I (Duke) | Part II Post-Tx fMRI (UNC) |
|---|---|---|---|---|---|---|---|---|
| Online/Phone Screen Questionnaire | X | | | | | | | |
| Informed consent | | X (via Duke REDCap econsent) | X (UNC specific consent) | | | | | |
| SHAPS | X | X | X | X | X | X | X | X |
| C-SSRS | | X | | | X (post) | | X (post) | |
| SCID5 relevant to inclusion /exclusion, NART | | X | | | | | | |
| SCID-5-RV | | X | | | | | | |
| Brief THI, DDS & Background info, CGI-S, CTQ | | X | | | | | | |
| R61 Phase: BDI-II, BAI, SF-36, PhenX depression & perceived stress, PCL-5, PSWQ, IDAS, TMS, SRS-2 | | X | | | X | | X | |
| R33 Phase: BDI-II, BAI, SF-36, PhenX depression & perceived stress, PCL-5, PSWQ, TMS, MAPS, IDS-RS, BADS | | X | | | X | | X | |
| R33 Phase: WAI | | | | | X | | X | |
| EEfRT, PRT | | X | | | X | | X | |
| Caffeine, Nicotine, Alcohol & sleep day of intake | | X | X | | X | X | X | X |
| Urine Pregnancy Test; PEERS (female only) | | | X (pre) | | | X (pre) | | X (pre) |
| CGI-I, % homework tasks completed | | | | X | | | X | |
| MID | | | X[4] | | | X | | X |
| fMRI | | | X[5] | | | X | | X |
| MRI checklist | | | X | | | X | | X |
| Urine Drug Screen | | X** | | | | | | |
| Acceptability Questionnaire | | | | | | | X | |

*[1]Between 8-15 weeks of therapy sessions (therapy will be either MBCT or BATA), in-person or remote during COVID-19 guidelines.*
*[2]At visits week 4, 8 & 12 (if applicable), subjects will complete EEfRT & PRT computer tasks at the beginning of the visit followed by the therapy session or if during COVID-19 times, at a separate in-person visit from the remote therapy session. All paperwork done at therapy visits will be done in addition to procedures noted in this column. They will then complete the REDCap questionnaires at these key assessment time points (either in-person or done remotely by REDCap survey invitation). If the final therapy visit is before week 8, there will be three assessment points (pre-treatment, week 4, and at the last therapy visit). If the final therapy visit is between week 8 and week 12, there will be four assessment points (pre-treatment, week 4, week 8, and at the last therapy visit). If the final therapy visit is after week 12, there will be five assessment points, and post-treatment assessments will be administered either at the last therapy session or separately if therapy was remote. COVID-19 Update:**Please note that the conduct of the computer tasks with CSSRS at the in-person assessment visit, wks 4, 8, 12 and final visit are contingent upon the building availability and approval of in-person visits either at Duke or UNC. If not available and approved, the computer tasks with CSSRS will be omitted until the study team have the appropriate approvals to do the tasks at an in-person visit. These omissions (skipping the in-person visit) will not be considered protocol deviations since the omissions are necessary to be able to open the study and begin to collect the main primary outcomes of imaging and therapy.*
*[3]This column is only for the first 60 subjects randomized as part of Phase I, R61.The R61 study will be entering a no-cost extension at the end of the current project period to allow for completion of data collection for this phase. Due to limited funds, the number of scans obtained is being reduced from up to 4 scans to two scans (pre- and post-treatment) for participants who are consented at UNC as of November 1.*
*[4]MID practice is included & done first to determine reaction time*
*[5]Includes mock scan and fMRI scan*
***While Duke is not open to in-person visits (COVID), this 2nd assessment visit that includes an additional CSSRS, alcohol, caffeine, sleep and 2 computer tasks, may be done at UNC. Urine drug screen would be skipped if done at UNC or there are not approvals at Duke for in-person visit and this won't be considered a protocol deviation.*

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

The overall goal of this project is to develop a novel transdiagnostic treatment for anhedonia, called Behavioral Activation Treatment for Anhedonia (BATA), using ultra-high field functional neuroimaging. There is a critical need for a validated treatment that specifically targets anhedonia, and this project will evaluate the effects of this new treatment on anhedonia and will establish how this treatment impacts brain systems that mediate reward processing, clinical symptoms of anhedonia, functional outcomes, and behavioral indices of reward processing. This work will also identify brain targets by which future novel anhedonia treatment may be evaluated.

## 2.2 BACKGROUND

Anhedonia, the loss of motivation and pleasure for enjoyable activities, is associated with impaired mesocorticolimbic activity and it is a transdiagnostic symptom associated with significant functional deficits in social and occupational domains.1-2 A novel anhedonia treatment is urgently needed given that existing therapies have minimal impact on anhedonia and given the wide range of disorders characterized by anhedonia.2, 27 In mood disorders, anhedonia is associated with risk for future depressive episodes, a more chronic illness course and poorer treatment response to both pharmacologic and neurostimulation interventions.3-6 Outside of mood disorders, anhedonia is associated with greater risk of anxiety disorders7 and reduced cognitive and social functioning as well as quality of life.8-11 Across psychiatric disorders, deficits in approach motivation (reduced reward valuation and willingness to work for rewards) and initial response to rewards (reduced hedonic responses to pleasurable stimuli) have been proposed to subserve anhedonic symptoms by reducing approach behaviors and pleasurable experiences, as well as subsequent opportunities for positive reinforcement.12-13

The clinical objective of this project is to evaluate Behavioral Activation Treatment for Anhedonia (BATA), a novel psychotherapy designed to treat anhedonia using an experimental therapeutics approach in a transdiagnostic sample characterized by clinically impairing anhedonia. BATA is a modification of Behavioral Activation Therapy for Depression, a validated treatment for patients with mood disorders.14-16 We have extensively modified this treatment to treat anhedonia in a transdiagnostic sample in a manner that is consistent with research domain criteria (RDoC) priorities.2 We propose to evaluate mesocorticolimbic response to rewards versus threat by BATA versus Mindfulness-Based Cognitive Therapy (MBCT) on anhedonia symptoms, functional outcomes, behavioral indices of reward sensitivity, and neural responses to rewards versus threat.

If hypotheses are supported, the results of this project will change real-world clinical practice given that there are currently no empirically-validated treatments, psychosocial or otherwise, that target anhedonia transdiagnostically. Given the high rates of clinically impairing anhedonia across a range of psychiatric disorders, as well as the relative ease with which BATA can be disseminated, this novel intervention has the potential to rapidly and meaningfully impact patient care in clinics that specialize in a range of disorders and conditions, including mood disorder clinics, anxiety disorder clinic, and general outpatient psychiatry services.

For the UNC optional PET supplement, the study team has added PET-derived measures of striatal DA functioning given that motivation and pleasure are mediated by ascending mesolimbic DA projections from the ventral tegmentum to limbic brain areas. It is not known whether striatal impairments in anhedonia are linked to impaired striatal DA functioning given that fMRI is sensitive only to blood oxygen level dependent (BOLD) signals. This is a critical gap in our understanding of the mechanisms of action of anhedonia treatments. PET imaging is ideally suited to bridge this gap between preclinical anhedonia research and clinical neuroimaging studies of anhedonia. PET imaging of the DA system affords the opportunity to address unprecedented new questions about how the study's novel anhedonia treatment influences striatal DA functioning in anhedonic patients. We expect that BATA will result in increased phasic DA release but will not influence background DA tone and that normalization of fMRI activation due to BATA will be associated with increased phasic DA release but no change in background DA tone.

This would be the first PET examination of the effect of an anhedonia treatment on the mesolimbic DA system. The addition of PET to this experimental therapeutics trial will address critical gaps in our knowledge given the mounting evidence that disrupted motivation systems play an etiologic role in anhedonia pathophysiology.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

**7T FMRI**

There are no known health risks from exposure to the magnetic fields and radio waves used in MRI scans. However, it is not assured that harmful effects will not be recognized in the future. Strong magnetic fields pose a safety risk because they attract metals such as iron. The radio waves can interfere with medical devices such as pacemakers. It can be dangerous for people who have medical devices, metal objects, or metal debris in their body to go into the MRI machine. Therefore, subjects will fill out an MRI screening form prior to entering the MRI 7T scan room before each scan. It is also dangerous to bring loose metal objects into the room containing the MRI machine because the objects may be pulled

towards the magnet and could injure somebody in the way. Subjects will be asked to leave all metal objects (including jewelry) in a secure location located outside of the MRI 7T scan room. They will be asked to change into a pair of scrubs to prevent any clothing parts from interfering with the MRI exam. There are rare incidental risks involved in exposure to magnetic fields, including (1) malfunctioning or movement of implanted metal objects and (2) asphyxiation due to large amounts of cryogenic gases generated during quench (i.e., the event which occurs when a magnet makes the sudden transition from superconducting to resistively conducting). Routine and strict safety procedures are in place to thoroughly screen participants prior to scanning, maintain security of the restricted MR area, and ensure that system security features are in good working order. These procedures are all in place to reduce risk. Some people can feel claustrophobic when confined by the small space of the MRI machine. If subjects feel anxious or uncomfortable inside the MRI machine, they will be able to tell the investigators over the intercom (a panic ball will also be provided to signal the technician) and they will be removed immediately from the MRI machine. It is also possible (though rare) that the subject may experience muscle twitching, dizziness, or a tingling feeling during the MRI 7T scan. This is not harmful to the subject; however, if the subject is bothered by it, they can use the panic ball to signal the technician to stop the 7T scan. Furthermore, MRI machines produce loud noises. Precautions (e.g., ear plugs) will be taken to protect subjects from possible side effects of exposure to loud sounds and to make sure that they are as comfortable as possible during the 7T scan.

-*Update to the 7T MRI language as of June 2, 2017 from UNC's BRIC re: tattoos in the 7T MRI:* Previously the UNC BRIC was limiting scanning participants who either did not have tattoos or only those who could identify the specific inks used to create their tattoos and determine that they did not pose a threat to the subject. However as of 6.2.17, the BRIC is updating their practices such that tattoos are no longer a limiting factor for recruitment into a 7T MRI protocol.

In consideration of the available literature and experience pertaining to MR procedures and patients with permanent cosmetics and tattoos, guidelines to manage these individuals include, the following:

-The screening form used for subjects should include a question to identify the presence of permanent cosmetics or decorative tattoos.

-Before undergoing an MR procedure, the subject should be asked if he or she had a permanent coloring technique (i.e., tattooing) applied to any part of the body. This includes cosmetic applications such as eyeliner, lip-liner, lip coloring, as well as decorative designs.

-The subject should be informed of the risks associated with the site of the tattoo. (rare heating)

-The subject should be advised to immediately inform the MRI technologist regarding any unusual sensation felt at the site of the tattoo in association with the MR procedure.

-The subject should be closely monitored using visual and auditory means throughout the operation of the MR system to ensure safety.

-As a precautionary measure, a cold compress (e.g., ice bag) may be applied to the tattoo site during the MR procedure. (this is of unknown effect).

*MRI Incidental Findings (rare):* On rare occasions, a participant will exhibit a frank abnormality on their research 7T fMRI scan as noted by the research MRI technician. In consultation with our Office for Risk Management, we have developed the following protocol for these infrequent events: (1) the MRI technician will inform the center director and/or associate director and the PI of the finding, and they will evaluate the images for technical artifacts; (2) if no technical artifacts are present, the anatomical images will be examined by a neuroradiologist who will evaluate the images and provide a follow-up recommendation. Because images are not of clinical quality, a definitive diagnosis is not possible, and BRIC will pay for this consultation. (3) If the incidental finding is within normal limits, no further action is taken. (4) If the finding is not within normal limits, the participant will be contacted by phone by the PI and provided with a letter that provides an additional explanation and reference material. The PI will

follow up by telephone to ensure that the process has been completed and that the participant does not have further questions.

**Optional UNC PET sub-study risks:**
Intravenous catheter discomfort (infrequent): An intravenous catheter will be placed for this study by trained UNC BRIC staff. IV injection of [11C]raclopride has a very low risk of reaction. A BRIC certified nuclear medicine technologist with training in radiotracer safety will start the IV line. The technologist will also be present for the radiotracer injection and the entirety of the scan. Additionally, Terrence Wong, MD, PhD, Division Chief of Nuclear Medicine at the UNC BRIC and Director of Molecular Imaging at the UNC BRIC will be on call as needed in case of a clinical emergency related to infusion. The subject will feel a slight pinprick, similar to a bee sting, and may feel some discomfort and have some bruising or bleeding at the site where the needle goes in. Depending on the length of time the catheter is in place, a bruise may last for a day or so. There is a small risk of fainting. Rarely an infection may occur at this site. If infection does occur, it will be treated. The UNC BRIC has staff trained in the application of IV catheters.
[11C]raclopride radiotracer (rare): This research study involves exposure to radiation from radiotracer used for the PET/MR scan. The radiotracer that will be used will be produced at the BRIC cyclotron facility and go through required initialization trials. The radiotracer exposure only involves a small risk and is necessary to obtain the desired research information. The effective radiation dose received in this study is 3.47 mSv per PET scan. For comparison, a person in the United States receives a radiation exposure of 3mSv per year from natural background sources. This radiation exposure involves a small risk and is necessary to obtain the information desired. The radiation exposure described here is what the subject will get from this research study only. It does not include any exposure the subject may have received or will receive from other tests outside of this study that are a part of their medical care. There may be rare risks associated with [11C]raclopride administration to pregnant women, which is why pregnant & breastfeeding women will be excluded. Administration of far higher doses of [11C] raclopride has been reported to produce extrapyramidal effects. The severity and duration of these effects appear to be dose-related.

**Study Assessments**
The assessment interviews and questionnaires may be stressful for some people. Some individuals may experience increased emotional discomfort as they discuss past or present problems during the assessments. During each in-person assessment, the trained study clinical assessor will consult should discomfort become extreme and the Duke PI, Dr. Smoski is available either in person or by phone. To minimize this risk, all participants will be asked to read, discuss, and sign written consent forms that describe the study procedures. Assessors will first give a narrative of the consent, and then have the subjects read it themselves. Following this, assessors will summarize the consent and answer any questions the subjects may have. The written document will not be signed until all questions and study concerns have been addressed. All participants will be told that they are free to withdraw from the study without penalty at any time. Every effort will be made to make the environment comfortable and supportive during assessment procedures: snacks and beverages may be offered, breaks will be taken, and the assessment will be stopped if the subject wishes or if stress is too high. All assessment sessions will be video and/or audio recorded and will be supervised by Duke PI Dr. Smoski, a licensed psychologist.

Should a participant's discomfort become extreme and includes strong thoughts of suicide, a trained professional will be available on-site during all active study hours. Because suicidal ideation is an exclusion criterion, we do not expect this to be likely risk. We will be using the C-SSRS and the SCID

interviews to assess suicidal ideation, intent, self-harm, and date of most recent attempt. If the patient endorses item #4 or 5 on the C-SSRS, the PI will be immediately notified. In the rare event that a high rating of ideation or distress occurs, the trained study assessor (a LCSW or PhD level clinician) will work with Duke PI, Dr. Smoski, and the subject to address these suicidal thoughts. The mood improvement and crisis management procedures successfully used in past studies will be employed to reduce suicidal urges if they occur. If the participant is deemed to be at imminent risk of suicide after the conversation, we will call 911 or obtain a commitment from the participant to go to the nearest hospital emergency room, (e.g. Duke ER).

**Women of Child-bearing Potential**
There is no evidence that MR imaging harms a developing fetus, however, since such harm might be identified in the future, pregnant women are excluded from participating in this study. All women of child bearing age will be administered a urine pregnancy test before scanning to ensure they are not pregnant.

Overall, the risks to subjects are low considering the potential benefits to them of participating in the study: the opportunity to receive therapy that can possibly help with reduction of their anhedonic symptoms. Participants will also receive compensation and any satisfaction they might receive from contributing to the progress of scientific research.

### 2.3.2 KNOWN POTENTIAL BENEFITS

There are currently no empirically-validated treatments, psychosocial or otherwise, that target anhedonia transdiagnostically. Anhedonia is a symptom of a number of psychiatric disorders, including mood and anxiety disorders, substance-use disorders, schizophrenia, and attention-deficit/hyperactivity disorder. Anhedonia is also a risk factor for the development of psychopathology and a marker of familial risk for psychopathology, suggesting that anhedonia represents a mechanism of trait vulnerability for a range of disorders. There is thus a critical need for a validated treatment that targets anhedonia transdiagnostically.

Given high rates of anhedonia across a range of DSM disorders, as well as the relative ease with which BATA may be disseminated, this novel intervention has the potential to meaningfully impact patient care in clinics that specialize in a range of disorders and conditions (e.g., mood disorder clinics, anxiety disorder clinics, substance abuse clinics, and general outpatient psychiatry services).

The addition of EMA to this project will allow for a fine-grained “real-world” assessment of positive affect, stress, cognitions, recent activities, contextual information, and relevant BATA treatment skills. We expect that greater pre- to post-treatment normalization of fMRI-based mesocorticolimbic target engagement will be associated with and greater increases in EMA reports of positive affect and use of BATA skills. Additionally, there is an urgent need for sensitive and standardized outcome measures for use in anhedonia treatment studies, and the high ecological validity of EMA suggests that this method may be a viable outcome measure.

In the PET supplement, we collect simultaneous PET/fMRI to establish linkages between striatal BOLD activation, striatal DA tone, and phasic striatal DA release during reward processing in anhedonia. Results will provide critical preliminary data for future proposals to use simultaneous PET/fMRI as a target engagement measure to evaluate novel therapeutics that impact striatal functioning in anhedonia.

We expect that patients who receive BATA will demonstrate meaningful reductions in anhedonia as well as overall improvement in functioning. We expect that patients who receive MBCT will also show overall

improvement in functioning, but their improvements specifically with respect to anhedonia are expected to be not as pronounced.

### 2.3.3 MINIMIZING RISKS

PIs Smoski and Dichter are licensed psychologists who will be on-call at all times to assist with any clinical emergencies that may arise.

Medications: Participants must be free of psychiatric medication use for at least 1 month before entering the study (8 weeks for fluoxetine or other medications with extended half-lives). The study will not remove any potential participant from medications in order to join the study or supervise a medication taper. The study team will not encourage potential participants to discontinue medication in order to qualify. Individuals who contact the study and express an interest in discontinuing their medication (which, in our experience, is not uncommon in individuals who respond to advertisements for psychotherapy trials) will be referred back to their prescribing provider regarding any medication questions.

Symptom / Behavioral Measurements: To minimize the risk of a participant becoming stressed, the laboratory space is designed to be patient friendly. Breaks will be provided as requested, and assessors will be flexible in the pace and scheduling of assessments. We will explain and demonstrate the procedures in terms participants can understand. We will make every effort to maintain a personally supportive relationship with each participant.

Treatment/Suicidality. Participants are selected for the proposed study based on problems with motivation rather than a specific diagnosis, but we anticipate that at least some participants will be experiencing clinically significant depression. The BATA treatment provided in the study is based on an empirically validated treatment for depression. Some participants may not feel better during their course of BATA treatment. Care will be taken to assure that no participant is in danger of harming themselves. Any participant who reports suicidal intent either to PI Smoski, another member of the treatment team, or on any symptom instrument, will immediately be assessed using the Suicide Risk Assessment protocol described above. Based on the level of assessed risk, patients may be escorted to the DUMC Emergency Room for further evaluation by the on-call psychiatrist. Participants who report a significant increase in psychiatric symptoms including suicidality will be excused from the research protocol, and in consultation with PI Smoski, referred for more extensive treatment, including referral for medications, if desired.

Although the utility of behavioral activation in treating suicidality has been hypothesized and supported in a case study, and MBCT has shown efficacy in reducing relapse of suicidality in individuals remitted from depression, more empirical support is necessary before using BATA or MBCT as the sole treatment for suicidal behavior. Therefore actively suicidal individuals will be excluded from the study at the intake assessment and throughout the trial.

Likewise, although both behavioral activation and MBCT have been found to improve a range of psychiatric symptoms and quality of life, they are not validated treatments for the full range of psychopathology that may present in our sample. Thus, symptom severity measures for depression, anxiety, and trauma-related symptoms will be administered every four weeks. If a participant shows a 10% or greater increase in symptom severity in any of those domains from baseline levels, he or she will be excused from the trial and referred for more intensive treatment and clinical management.

Following the conclusion of the trial, all participants will be provided with referral information as appropriate for further treatment.

# 3 OBJECTIVES AND ENDPOINTS

The overall goal of this project is to develop a novel transdiagnostic treatment for anhedonia, called Behavioral Activation Treatment for Anhedonia (BATA), using ultra-high field functional neuroimaging. There is a critical need for a validated treatment that specifically targets anhedonia, and this project will evaluate the effects of this new treatment on anhedonia and will establish how this treatment impacts brain systems that mediate reward processing, clinical symptoms of anhedonia, functional outcomes, and behavioral indices of reward processing. This work will also identify brain targets by which future novel anhedonia treatment may be evaluated.

**R61 Phase:**

**Aim 1:** To evaluate whether BATA produces changes in neural responses to reward anticipation and reward outcomes using fMRI that exceed changes due to an active comparison treatment, specifically Mindfulness Based Cognitive Therapy (MBCT) and does not impact neural responses to threat. This aim pertains to only the first 60 participants randomized into the study (n=30 to receive BATA and n=30 to receive MBCT).

**Aim 2:** To evaluate relations between BATA dose (treatment duration) and neural target engagement by examining changes in neural response to rewards with mid-treatment fMRI scans 8 and 12 weeks after starting the 15-week treatment.

**Aims 3, 4, and 5 pertain to all 210 participants randomized (n=105 to receive BATA and n=105 to receive MBCT).**

**Aim 3:** To evaluate the effects of BATA versus an active comparison treatment on anhedonic symptoms and functional outcomes.

**Aim 4:** To evaluate the effects of BATA versus an active comparison treatment on behavioral indices of reward sensitivity.

**Aim 5:** To evaluate the effects of BATA versus a comparison treatment on neural response to rewards.

PET Aims specifically refer to the 30 subjects who consent to the optional PET sub-study:

**Aim 1 (PET):** To evaluate the effects of BATA, relative to a comparison treatment, on PET-derived measures of DA functioning during incentive processing. We hypothesize that BATA, but not the comparison treatment, will result in increased phasic striatal DA release but will not influence background DA striatal tone.

**Aim 2 (PET):** To evaluate relations between treatment-related changes in fMRI-derived mesocorticolimbic activation and PET-derived DA functioning in the BATA-treated group. We hypothesize that normalization of fMRI-derived mesocorticolimbic activation due to BATA specifically will be associated with increased phasic DA release but no change in background DA tone during incentive processing.

Exploratory Aims include the data from the EMA optional study: Passive location tracking (PLT) data during the period of EMA monitoring will be collected via the MetricWire app to allow us to compare distance traveled before and after both treatments as a secondary, exploratory measure of behavioral activation. Follow-up analyses will evaluate relations between motion tracking, behavioral, brain, and clinical measures of response to both treatments.

**Specific Aim 3 (EMA):** To evaluate if BATA, relative to a comparison treatment, produces improvements in real-world positive affect and the use of BATA skills. We hypothesize that BATA, but not the comparison treatment, will be associated with improvements in real-world positive affect and the use of BATA skills.

**Specific Aim 4 (EMA):** To evaluate relations between treatment-related changes in fMRI-derived mesocorticolimbic activation and real-world positive affect and the use of relevant BATA skills in the

# 4 STUDY DESIGN & PROCEDURES

## 4.1 OVERALL DESIGN

The clinical objective of this project is to evaluate Behavioral Activation Treatment for Anhedonia (BATA), a novel psychotherapy designed to treat anhedonia using an experimental therapeutics approach in a transdiagnostic sample characterized by clinically impairing anhedonia. BATA is a modification of Behavioral Activation Therapy for Depression, a validated treatment for patients with mood disorders. We have extensively modified this treatment to treat anhedonia in a transdiagnostic sample in a manner that is consistent with research domain criteria (RDoC) priorities. We propose to evaluate mesocorticolimbic response to rewards versus threat by BATA versus Mindfulness-Based Cognitive Therapy (MBCT) on anhedonia symptoms, functional outcomes, behavioral indices of reward sensitivity, and neural responses to rewards versus threat.

**Aims 1 and 2 pertain to the first 60 participants randomized (n=30 to receive BATA and n=30 to receive MBCT).**

Aim 1: We predict that BATA will increase right caudate nucleus (CN) activation during reward anticipation and decrease rostral anterior cingulate cortex (rACC) activation during reward outcomes, and that BATA will not decrease amygdala activation to threat, confirming the specificity of BATA to these positive valence neural systems.

Aim 2: We predict that the BATA group will show increased right CN activation during reward anticipation and decreased rACC activation during reward outcomes that will plateau after the optimal dose of the intervention has been delivered.

**Aims 3, 4, and 5 pertain to all 210 participants randomized (n=105 to receive BATA and n=105 to receive MBCT).**

Aim 3: We predict that BATA will produce clinically and statistically significant improvements in anhedonia and functional outcomes that exceed those due to the comparison treatment.

Aim 4: We predict that BATA will improve behavioral indices of reward sensitivity.

Aim 5: To evaluate the effects of BATA versus a comparison treatment on neural response to rewards. We predict that, consistent with Aim 1, BATA will increase right CN activation during reward anticipation and decrease rACC activation during reward outcomes and that BATA will not decrease amygdala activation to threat, confirming the specificity of BATA for targeting these positive valence neural systems. This Aim will provide a replication and extension of Aim 1 findings with a larger sample and with an optimal treatment dose.

In the PET sub-study, Hypothesis 1- BATA, but not the comparison treatment, will result in increased phasic striatal DA release but will not influence background DA striatal tone. Hypothesis 2- that normalization of fMRI-derived mesocorticolimbic activation due to BATA specifically will be associated with increased phasic DA release but no change in background DA tone during incentive processing.

This is not a pilot study but rather a Phase I/II study. The R61 phase (Phase I) of the protocol is designed to provide preliminary data for the acceptability, identification of the optimal dose of BATA as well as the preliminary efficacy of BATA in subjects with anhedonia compared to those in the MBCT control group. Using the fMRI data, this phase of the study will test if BATA produces changes in neural responses to reward anticipation and reward outcomes that exceed changes in the MBCT group and does not impact neural responses to threat. As such, a small group (N = 60) of subjects will be in this blinded phase and they will complete up to a total of 4 fMRI scans (pre-treatment, week 8, 12 and post-treatment). The R61 study will be entering a no-cost extension at the end of the current project period to allow for completion of data collection for this phase. Due to limited funds, the number of scans obtained is being reduced from up to 4 scans to two scans (pre- and post-treatment.) for participants

who are consented at UNC as of November 1. In the R33 phase (Phase II) of the study, a larger group (N=150) of subjects will complete the study having been randomized to either BATA or MBCT and undergone a pre-treatment and post-treatment fMRI. This second phase will continue to test the efficacy of BATA over MBCT on changing anhedonic symptoms and functional outcomes for all 210 subjects from both phases. The effects of BATA on behavioral indices of reward sensitivity and neural response to reward will also be evaluated. If this study, across both phases, shows that BATA, relative to MBCT, engages brain targets in hypothesized ways and decreases anhedonia, future research with larger sampler will investigate the effectiveness and efficacy of this novel intervention. This study involves the evaluation of a novel behavioral treatment for anhedonia called Behavioral Activation Treatment for Anhedonia (BATA). It is a collaboration with the Duke Department of Psychiatry, and this protocol will be linked to a companion Duke's IRB protocol via a Data Transfer Agreement (DTA.)

**Phone/Online Screen**

Prospective participants will either 1) contact the study coordinator's office at Duke or be called for a telephone screening interview, administered by the Duke Study Coordinator/approved study team member, or

2) they may visit the websites such as ClinicalTrials.gov, Dukehealth.org, DukeList, Reddit, UNC Psychiatry site, Facebook/IG and see the study description or posting. The telephone-screening instrument (see telephone script) is designed to rule out individuals who clearly meet certain exclusion criteria. The Duke study coordinator or approved study staff member will go through the telephone script document within UNC's REDCap & will be directly entering potential participant's responses to the telephone script electronically-thus no paper copies of the telephone script will exist.

As an aid to shorten the recruitment prescreening process, prospective participants will be directed by all Duke/UNC flyers & brochures, online postings, Facebook/IG ad briefs, emails to UNC listserv & Duke's DEPRU registry, to the REDCap online screen survey within UNC's REDCap platform. Once on the REDCap online screen, they will read a description of the study (a modified version of the IRB approved phone screen) and if interested, will continue with answering the online screen questions (see online screen script for REDCap). The REDCap survey begins with an information statement designed to describe the study, risks and benefits in the absence of informed consent. If they agree to continue, they will then be asked their current age & if their age meets the study inclusion/exclusion criteria, they will continue on with the rest of the REDCap online screen as per REDCap online script. If they do not meet the age requirement, they will receive a message in REDCap indicating that they are not eligible and the survey will end. The results from the REDCap online survey will be monitored by the Duke/UNC study coordinator and other approved Duke/UNC study staff who will have access via a username and password. The data from the online survey can be imported to a SPSS or an excel .csv file which can only be accessed by the approved study team. Each day, study staff can check results of the online survey to see if any new potential participants have completed the survey and contact those people to either set up their first appointment or inform them that they don't qualify for the study per inclusion/exclusion criteria. Upon reviewing the prescreening information from REDCap by the study coordinator or Duke/UNC approved designated study staff, if it is noted that the subject did not complete all of the online screen questions, the plan is for the study coordinator/staff to contact the subject. They would thank them for starting the screen and prompt them to complete the online screen again or by phone (if easier, using the phone script) if they are still possibly interested in the study.

**Study Visits:**

Potential participants will complete the following:

1) A phone or online screen to determine initial eligibility via UNC's REDCap

2) A 1-2 clinical characterization visit(s) to determine eligible, and, if eligible, to characterize participants clinically. During COVID, can be split remote/in-person.
3) A pre-treatment 7 Tesla (7T) fMRI scan & if one of the first 60 subjects enrolled, have an initial blood draw of 10ml (2tsps). Update, the NARSAD blood protocol had entered an extension and has additional funds so up to 210 participants, in both phases, will have an initial blood draw of 10ml (2tsps). **As of 6/26/20, the blood protocol will no longer continue for any new participant enrolled in the study. As of the NCE 2022, this current amendment, imaging of new participants will end. Only enrollment into the therapy portion at Duke will continue.**
4) Patients will then be assigned randomly to the experimental treatment (BATA) or comparison treatment (Mindfulness Based Cognitive Therapy (MCBT)) for approximately 15 weeks of treatment.
5) The first 60 patients enrolled (n=30 who receive BATA and n=30 who receive MBCT) will additionally complete two additional, mid-treatment, fMRI scans as well as an additional blood draw at all other MRI visits. The 1st phase of the study entered the R61 no cost extension at the end of the project period & due to limited funds, participants will no longer be receiving up to 4 scans. Participants who consent at UNC on or after 11/1/18 will receive only pre- and post-treatment scans (2 scans total). **The R61 no cost extension has ended and the study has entered the larger R33 phase of the study and participants will continue to receive only pre and post treatment scans (2 total) and no bloodwork will be collected starting summer 2020 for new participants. **No new enrollment to imaging at UNC will occur with the approval of the June 2022 NCE amendment.**
6) A post-treatment clinical characterization visit
7) A post-treatment 7T scan

## 4.2 EFFICACY ASSESSMENTS & STUDY PROCEDURES

**Pre-Treatment eligibility and diagnostic assessment and participant characterization (at the Duke CBRTP):**
**This session will be completed by a study coordinator or assessor at Duke who is study personnel on the companion Duke IRB protocol. The following assessments will be conducted over 1-2 visits (some can be completed remotely):**

**Eligibility and diagnostic assessment measures:**
**1) The Columbia Suicide Severity Rating Scale (C-SSRS)** will be administered. Participants indicating "yes" on items 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) and/or 5 (Active Suicidal Ideation with Specific Plan and Intent) within the last month will be excused from the trial and referred to more intensive clinical management. The C-SSRS will be used during the initial assessment visit over the past 1 month and then used to assess "since the last study visit" at the in-person assessment visit, if applicable during COVID-19, and the weeks 4, 8, 12 therapy visits that include the computer tasks and the final therapy/post-treatment visit. During the 1-2 remote & in-person assessment screening visits, if the participant has a 4 or 5 on the CSSRS, they will no longer be eligible for the study as per inclusion/exclusion criteria. **COVID-19 Update:**Please note that the conduct of the CSSRS with computer tasks at the inperson assessment visit, wks 4, 8, 12 and final visit and are contingent upon the building availability and approval of in-person visits either at Duke or UNC. If not available and approved, the computer tasks with CSSRS will be omitted until the study team have the appropriate approvals to do the tasks at an in-person visit. These omissions (skipping the inperson visit) will not be considered protocol deviations since the omissions are necessary to be able to open the study and begin to collect the main primary outcomes of imaging and therapy.**

**2) T**he SHAPS will be repeated to verify a score of >= 30, corresponding to clinically significant anhedonia. **If the SHAPS score is <30, the participant will be ineligible (R33 phase);**
**3) Clinician's Global Impression Scale-Severity score (CGI-S) = 3** to assure a clinically impaired sample. If the CGI score is 2 or less, the participant will be ineligible;
**4) The Structured Clinical Interview for DSM Disorders-5 Research Version (SCID-5-RV) will be** administered to assess exclusionary conditions and to characterize the sample. Individuals with primary anhedonia but no DSM diagnosis will be included. Exclusionary axis I disorders include:
a. Those for whom medication management is the primary gold-standard treatment, including those with bipolar disorder/mania, schizophrenia spectrum, and other psychotic disorders; (to clarify, if a subject meets criteria for current or lifetime history of bipolar I and II is exclusionary).
b. Those who may have difficulty understanding the cognitive components of BATA, including those with intellectual disability, neurocognitive disorders, and dissociative disorders;
c. Feeding and eating disorders which may have confounding effects on the BOLD fMRI signal;
d. Substance Use Disorders given confounding effects of substances of abuse on the BOLD fMRI signal; At screening if subject reported use of a substance of abuse in the past week, they will be excluded to ensure acute drug effects. Lifetime history of moderate or severe non-alcohol substance use disorder on SCID-5 is also excluded. Lifetime history of severe alcohol use disorder on SCID-5 will be excluded.
**5) North American Adult Reading Test (NART)** will be administered & NART calculated IQ score should be 90 or higher for study eligibility.

Participant characterization:
Next, the assessor will conduct a brief interview examining medical and treatment history using: 1) The 7T MRI Adult Safety Screen (completed as part of prescreening & reviewed by UNC study team at pre scan visit at the BRIC. **Removed in the NCE June 2022 since no longer enrolling to MRI at UNC.**
2) an abbreviated version of the Treatment History Interview (THI) will be used to assess previous and any ongoing psychiatric services received. The modified THI will be administered at the initial assessment visit(s) ONLY. Those who have any contraindications for MRI or report taking psychotropic medications and/or being in psychotherapy currently will not qualify.
3) Urine Drug Screen-Subjects will undergo a urinalysis drug screen and those positive for cocaine, marijuana, opiates, methadone, methamphetamine will be excluded at study entry. ADHD medications (amphetamines) and benzodiazepines will not be excluded from the study if participant is taking them by prescription. (COVID-19: Will be done at the 2nd assessment visit, which is in-person, only after determining clinical assessment eligibility).

Eligible participants will complete the following assessments:
For included participants, the subject will then complete the two computer reward tasks next because fatigue can affect their performance. Thus it is important to complete these tasks as soon as eligibility is confirmed.
1) The Effort Expenditure for Rewards Task (EEfRT). The EEfRT is a computer task that takes 20 minutes and indexes the willingness to work for rewards under varying conditions of reward probability and magnitude. On each trial, participants simply select whether they wish to do an easy task (pressing a key 10 times with their dominant index finger) for a relatively smaller reward or a slightly harder task (pressing a key 100 times with their non-dominant finger) for a relatively larger reward.
2) The Probabilistic Reward Task (PRT). The PRT is a computer-task that takes 20 minutes that is sensitive to behavioral shifts driven by reward in anhedonic patients. One of two reward-based responses receives feedback more frequently; this asymmetry typically induces bias toward the more frequently rewarded response. (COVID-19: Computers tasks will be done at the 2nd visit, which is in-person with an additional completion of another CSSRS at the end of the tasks, only after determining eligibility). COVID-19

Update:**Please note that the conduct of the computer tasks with additional CSSRS at the in-person assessment visit and the urine drug screen are contingent upon the building availability and approval of in-person visits either at Duke or UNC. If not available and approved, the computer tasks with CSSRS and urine drug screen in person visit will be omitted until the study team have the appropriate approvals to do the tasks at an in-person visit. These omissions will not be considered protocol deviations since the omissions are necessary to be able to open the study and begin to collect the main primary outcomes of imaging and therapy. **NCE June 2022-tasks will only be done at Duke. Enrollment to UNC procedures is ending.**

3) *REDCap Self-report Questionnaires*

a) Demographic Data Survey (DDS)
b) PhenX Toolkit Core Tier 1 Impairment measures related to depressed mood
c) PhenX Toolkit Core Tier 2 measures of perceived stress and life events
d) The Beck Depression Inventory II (BDI-II)
e) The Beck Anxiety Inventory (BAI)
f) The Penn State Worry Questionnaire (PSWQ)
g) The PTSD Checklist for DSM5 (PCL-5)
h) Short Form-36 Health Survey, a widely used metric of quality of life
i) Childhood Trauma Questionnaire (CTQ)
j) Inventory of Depression & Anxiety Symptoms (IDAS)
k) Toronto Mindfulness Scale (TMS) to measure trait mindfulness
l) Social Responsiveness Scale, version 2 (SRS-2) to collect a rating around social deficits in the population which could impact ratings of anhedonia.

**For the R33 phase**, the Inventory of Depression and Anxiety Symptoms [IDAS] and Social Responsiveness Scale, version 2 [SRS-2] is not collected. In addition to the measures listed above, in the R33 phase, we will collect Motivation and Pleasure Scale-Self Report [MAPS] to measure motivation and pleasure domains of negative symptoms, and collect Inventory of Depressive Symptomatology-Self-Report [IDS-SR] anhedonia items and Behavioral Activation for Depression Scale [BADS] to measure change in anhedonia, avoidance and activation. Participants can either complete these in person or be sent the REDCap survey invitation link to complete at the end of the remote or in-person assessment visit.

At the end of the clinical interview/assessment visit(s) all eligible participants will be scheduled for the 7T MRI scan at UNC's BRIC. The MRI will be planned for at least one day later, and up to 2 weeks later. If a subject is unable to be logistically scheduled for an fMRI until between 2-4 weeks past screening, we will still schedule them for an MRI at the UNC BRIC. Anyone going over 4 weeks, will be considered a screen fail and not randomized and have the ability to rescreen at a later date (i.e. will sign another econsent, redo SHAPS, C-SSRS, UA drug screen [if possible during COVID times], all self-report, SCID5, THI and computer tasks [if possible & contingent on ability to have in-person visits]). Their NART will not be redone and can be used for the rescreen. Knowing this, we will aim to schedule participants for their brain scan as soon as possible after their assessment day and also have informed subjects in the online/phone screen. Subjects who are THC smokers (and do not meet criteria for a current THC use disorder & have a negative urine drug screen at intake & confirm no use in the past 1 week) will be reminded to not smoke within 24 hours of the MRI scan visit as well as the future week 4, 8, 12 & post-treatment computer tasks & additional MRI scans. Note: The 1st phase of the study entered a R61 no cost extension at the end of the project period & due to limited funds, participants will no longer be receiving up to 4 scans. Participants who consent at UNC on or after 11/1/18 will receive only pre- and post treatment scans (2 scans total).

**Update: We are in the R33 phase of the study which only has pre- and post treatment scans (2 scans total).**
Subjects who are nicotine smokers and/or caffeine drinkers will be reminded to not smoke or drink caffeine within 2 hours of the MRI scan days and computer task days. Subjects will be asked not to drink alcohol on the day of the task or scan. Users of PRN anti-anxiety medication will be asked to abstain from use on the day of scan unless medically necessary. If a subject does use these substances it will be documented; however they will not be removed from the study.

**Neuroimaging session (at the UNC Biomedical Research Imaging Center (BRIC)):**
All scan sessions will be identical. All patients will receive pre- and post-treatment scans. The first 60 patients enrolled (n=30 who receive BATA and n=30 who receive MBCT) will also receive two mid-treatment 7T fMRI scans approximately 8 and 12 weeks after starting treatment. The 1st phase of the study entered a R61 no cost extension at the end of the project period & due to limited funds, participants will no longer be receiving up to 4 scans. Participants who consent at UNC on or after 11/1/18 will receive only pre- and post-treatment scans (2 scans total). **Update: We are in the R33 phase of the study which only has pre- and post-treatment scans (2 scans total).** Patients who drop out of treatment early before reaching 8 weeks of therapy, will be asked to return for 1 final post-treatment visit to complete the computer tasks, self-report questionnaires, and MRI. They will complete this early termination/post treatment visit all at UNC to reduce the burden on participants to have to return to both Duke and UNC.

Equipment: This study will utilize a research-dedicated Siemens Magnetom 7T whole body MR scanner for MRI data collection.

7T Scan Preparation: After arrival at the BRIC, participants will undergo a final MRI screening prior to the reassessed by the BRIC technologist for any potential contra-indications to the scan. If any concerns are raised, participants will not undergo the scan. If the subject is a female of child bearing potential, she will complete a urine pregnancy test administered by UNC BRIC study personnel. If the test indicates that she is pregnant, the scan will not be done. In either situation (failed checklist or + urine pregnancy screen), subjects will be informed of this decision to cancel the MRI and thanked for their time and will no longer be eligible to continue in the study. Alternatively, if participants are cleared, they will begin out-of-scanner training in preparation for the scan.
All subjects will then be asked about their caffeine, alcohol, nicotine use and sleep habits in the last 24 hours. If female, they will complete the PEERS questionnaire regarding their current reproductive status and answer additional questions about their menstrual cycle. The UNC study team member will then have subjects complete the MID practice task to measure their reaction time. The results from the practice test will be used to calibrate the MID task to the participant's speed level for the MID task in the scanner.
Monetary Incentive Delay (MID) practice run. The practice run is to familiarize them with the computer task and measure reaction time. The results from the practice test will be used to calibrate the MID task to the participant's speed level during the fMRI brain scan.
MRI Scan: After the out-of-scanner training, participants will be escorted to a private room in which they will be asked to change into a pair of clean scrubs provided by the BRIC. They will also be asked to remove any loose objects (e.g., watches, jewelry, cellphones) that may interfere with scanning and secure their belongings in a secured locker only accessible to the participant. A trained BRIC technician will reiterate the requirements for the 7T scan (e.g., remain still, remove jewelry and any other metallic or loose objects) and then assist the participant in entering the MRI scanner. The scan will include the following:
1. Mock Scan
2. Anatomical MRI Scan
3. Resting state fMRI scan

4. Monetary Incentive Delay task (involves pressing a button as quickly as possible to receive a reward)
5. Face- and shape-matching task (involves pressing a button to indicate which two of three faces or shapes match)
6. Perivascular spaces (PVS) sequence known as 3D turbo-spin-echo
Debriefing After the Scan: Upon completion of the 7T fMRI scan, participants will be given time to change back into their own clothing. They will then be escorted back to a separate, private room. At this time, participants will be compensated and will also have the opportunity to ask any questions. At this time the technologist will ask the participant if they experienced any discomfort during the scan to report to the PI, and will tell the participants that this assessment is not meant to constitute a diagnosis.

**Treatment (at Duke between 8-15 weeks)**
Patients will complete a course of BATA or MBCT. Subjects will be assigned a specific Duke study therapist and will continue with the same therapist through the 8-15 weeks of therapy. All therapy sessions will occur in Duke CBRTP located in the Civitan building (2213 Elba Street) or via WebEx/Zoom Duke approved remote platforms. At the end of each therapy visit, the therapist will complete the Clinical Global Impairment scale in relation to improvement of symptoms (CGI-I) and the subject will complete the SHAPS. Starting at the second therapy session, the subject will be asked to give a % of how much of the homework tasks they had completed over the prior week since the last therapy session. The weekly therapy sessions will last around 1 hour, except for weeks 4, 8, 12, and the final therapy session (if not at week 8 or 12) as noted just below. All remote weekly therapy sessions will last around 1 hour.

Weeks 4, 8, and 12 (if applicable) : At these specific therapy visits, subjects will also be asked to complete the EEfRT and PRT computer tasks again. The tasks will be done and the subject will be asked about their caffeine, alcohol, nicotine & sleep habits over the past day in addition to completing SHAPS & % homework tasks completed over the past week (if not already completed during the therapy sesson). The subject may have their therapy session before or after these tasks & surveys or may be completed on a separate day during the week 4, 8, and 12. The C-SSRS will be administered after the computer tasks. They will then again be asked to complete most of the questionnaires they completed at the screening assessment visit (i.e. R61: the PSWQ, PCL-5, BDI-II, BAI, SF-36, IDAS, TMS, SRS-2, and PhenX measures of related to depressed mood and perceived stress, R33: the MAPS, IDS-RS measures related to anhedonia, BADS, WAI, PSWQ, PCL-5, BDI-II, BAI, SF-36, TMS, and PhenX measures of related to depressed mood and perceived stress). They will complete them directly in REDCap either in-person or by REDCap survey invitation. These visits will last from 2 to 2 ½ hours.

To clarify, computer tasks and REDCap questionnaires will be administered up to 5 times in the study: pre-treatment, 4 weeks 8 weeks, 12 weeks, and post-treatment (if necessary): 1) If the final therapy visit is before week 8, there will be three assessment points (pre-treatment, week 4, and at the last therapy visit); 2) If the final therapy visit is between week 8 and week 12, there will be four assessment points (pre-treatment, week 4, week 8, and at the last therapy visit); 3) If the final therapy visit is after week 12, there will be five assessment points, and post-treatment assessments will be administered at the last therapy session***.**As noted above, the conduct of the computer tasks with CSSRS at the in-person visit wks 4, 8, 12 and final visit are contingent upon the building availability and approval of in-person visits either at Duke or UNC. If not available and approved, the computer tasks and urine drug screen will be omitted until the study team have the appropriate approvals to do the tasks at an in-person visit. These omissions will not be considered protocol deviations since the omissions are necessary to be able to open the study and begin to collect the main primary outcomes of imaging and therapy.**

Final Therapy Visit/Post-Treatment participant characterization:

Duke: At the final therapy visit (anytime between 8-15 weeks as determined by Duke/UNC study team) or separately, the subject will be asked to redo the computer tasks (EEfRT and PRT), complete the SHAPS & % homework tasks 1 last time and then again be asked to complete most of the online questionnaires they completed at the screening assessment visit ((i.e. R61: the PSWQ, PCL-5, BDI-II, BAI, IDAS, SF-36, TMS, SRS-2, PhenX measures of related to depressed mood and perceived stress, R33: the MAPS, IDS-RS measures related to anhedonia, BADS, WAI, PSWQ, PCL-5, BDI-II, BAI, SF-36, TMS, and PhenX measures of related to depressed mood and perceived stress). They will complete them directly in REDCap. Next, the C-SSRS will be done and the subject will be asked a series of questions about feasibility and acceptability of procedures (exit interview), and will be offered referrals for other mental health services as needed. Finally, they will be scheduled for their final fMRI brain scan at UNC. Note: Especially during COVID-19, the final computer tasks, CSSRS, exit interview, and caffeine/alcohol questions may be done at UNC and survey invitation sent out for the REDCap questionnaires. ****Please note that the conduct of the computer tasks with CSSRS at the in-person final visit are contingent upon the building/room availability and approval of in-person visits either at Duke or UNC. If not available and approved, the computer tasks with CSSRS will be omitted until the study team have the appropriate approvals to do the tasks at an in-person visit. These omissions (skipping the in-person visit) will not be considered protocol deviations since the omissions are necessary to be able to open the study and begin to collect the main primary outcomes of imaging and therapy. If omitted, the participant will be emailed the REDCap survey invitation to complete only the self-report with exit interview, as applicable.**
UNC: If the subject's final therapy session occurs between weeks 9-11 or after week 12, they will be scheduled for the final post-treatment MRI and it will occur one last time at the BRIC at UNC. All subjects will be asked about caffeine, nicotine, alcohol, and sleep habits over the past 1 day, if female, have urine pregnancy screen, and then undergo the scan. This visit can last up to 2 hours. As noted, subjects who consented at UNC at 11/1/18 or later, will only have a pre-treatment and a post treatment MRI scan in the 1$^{st}$ phase (R61) and in the R33 phase as per the grant.

Note: If a subject decided before their final scheduled therapy session that they were actually done with therapy and they felt they didn't need to come back for a final session at Duke and the study team agreed, then the subject could do the REDCap self-report, C-SSRS and exit interview at UNC, at their post-treatment MRI visit. This would help reduce the burden on the subject so they would not have to complete 2 separate final visits. It could be done all at 1 time.

**Optional Sub-study (UNC Only)**
*Ecological Momentary Assessment*
Ecological Momentary Assessment (EMA) allows for the acquisition of naturalistic, real-time assessment of participants' self-reported mood, activities, and behaviors. *Study Procedures*-At the first MRI visit in the BRIC, the subject will review the UNC econsent form that contains the description of this EMA portion of the study. They will either choose to participate or not participate by indicating so on the consent (and can only possibly participate if they have an android or iPhone themselves). If they do agree to participate, at the end of the MRI session, the researcher will guide the participant in downloading the app to the participant's smartphone. The researcher will provide orientation to the app and answer any questions regarding the EMA assessments and data collected. The participant will need to provide an email address & password to be able to access the study specific application. MetricWire will then automatically assign them a unique ID. The EMA data (EMA specific questions are attached to the amendment application for review) will be collected over the course of four 5-day blocks (Saturday-Wednesday) following each of four MRI sessions (during weeks 1, 9, 13, and 16, if applicable).
Since the 1st phase of the study entered a R61 no cost extension & due to limited funds, participants no longer received up to 4 scans. Participants received only pre- and post-treatment scans (2 scans total) &

thus only do EMA after pre & post MRI scans. This is true for any participant who signs the UNC consent on or after 11/1/18 as part of R61.
**R33: The study has entered the R33 phase and with funds available, participants will have the option of participating in the EMA portion after the pre and post treatment scan visits as well as after wks 4, 8, and 12 (if applicable) after completing the computer task visit. These participants will follow the same prompt schedule as pre and post scan EMA timepoints.**

There will be 2 EMA assessments per day on weekdays and 3 per day on weekends. EMA assessments will occur between 9am on Saturday and 9pm on Wednesday, at specified time windows distributed throughout the day (e.g., 4-7pm). No contact will be made on weekdays between working hours of 9-5. Participants who work outside of these hours will be given the option to block off their unavailable work time. At each EMA timepoint, an alert will be sent to the participant's smartphone (iPhone or Android) and they will be instructed to answer questions regarding current affect, anhedonia (both anticipatory and consummatory), stress, cognitions, and recent activities. EMA data will be collected using the *MetricWire* application. All EMA data will be encrypted on participants' smartphones prior to being uploaded to a secure server and downloaded by the researcher to UNC CIDD secure server in the study specific folder.

In this EMA portion of the study, we will be is using **Passive Location Tracking (PLT)** to monitor patient movement during the 5 days (Saturday 9am-Wednesday 7pm) after each MRI. PLT allows us to compare distance traveled before and after both treatments as a secondary, exploratory measure of behavioral activation. With PLT, the server pings the subjects phone to collect a specific GPS location to set up a fence and then only when the phone moves outside of this location, will it wake up & send another GPS location back to MetricWire services. PLT uses what they call the **Geofencing API** of the **Android** or **iOS** operating system to do the monitoring of location changes by the participant. More specifically, once these fences are set, the app waits for the system to notify it that the device has left the specified fence. At this time, the app wakes up, determines and records its new location, updates the fences to center on its new location and returns to the inactive state.

**Optional Sub-study (UNC Only)**
*PET Scan (Pre and possibly Post)* ****As noted above, this optional PET sub-study completed the last T2 PET scan on 7/7/21 and is no longer enrolling new participants and no additional participants are pending a final PET scan.**

Equipment: The Biomedical Research Imaging Center (BRIC) utilizes a research-dedicated Siemens Biograph mMR whole-body imaging system for PET/MR data collection. The Siemens Biograph mMR allows for simultaneous acquisition of MR and PET images to produce high resolution images in addition to displaying cell metabolism and molecular events.

As part of the NIMH supplement, subjects who meet the inclusion/exclusion criteria for the main study as assessed at Duke and at UNC in the BRIC per the MRI checklist, will be offered the PET sub-study consent at their first appointment at UNC. If the subject has had a PET scan in the last 1 year or has been treated with radiation or chemotherapy in the last 2 months, they will not be eligible to participate in the sub-study. The BRIC tech will also complete the PET checklist with the subject to confirm final eligibility for the subject. The PET scan can be done on the same day as the blood & 7T fMRI and will add about 2-2.5 hours to the visit, if they sign the PET consent. If preferred, the PET scan can be scheduled for a separate day after this initial UNC blood and 7TMRI visit at their convenience. We will allow the PET scan to be completed anywhere before their 3rd therapy session at Duke. The PET scan visit done separately will be

~2.5 hours and the actual scan is about 75 minutes. Their possible post PET scan will be scheduled after their last therapy session at Duke and can be done on the same day as their blood & fMRI or separately, and we will aim to do this within 4 weeks of completing therapy.
*On the day of the PET scan (if separate from 7TMRI);* After arrival at the BRIC, participants will undergo a final PET/MR screening and the scan, conducted by BRIC's imaging staff. As part of the final screening procedures, participants will be reassessed by the BRIC technologist for any potential adverse outcomes of the scan. If any concerns are raised, participants will not undergo the scan. Instead, participants will be informed of this decision and thanked for their time. Alternatively, if participants are cleared, they will begin out-of-scanner training in preparation for the scan.
Out-of-Scanner Training (~15 minutes): Participants will practice the Monetary Incentive Delay (MID) on a computer in a separate, private room prior to the actual scan. This practice session will familiarize participants with the computer task to be completed in the scanner.
*Radiotracer Injection and PET/MR Scan:* After the out-of-scanner training, participants will be escorted to a private room in which they will be asked to change into a pair of clean scrubs provided by the BRIC. They will also be asked to remove any loose objects (e.g., watches, jewelry, and cellphones) that may interfere with scanning and secure their belongings in a secured locker only accessible to the participant. A trained BRIC technician will reiterate the requirements for the scan (e.g., remain still, remove jewelry and any other metallic or loose objects). The BRIC technician will place the IV line while the participant is in the private prep room. The technician will then assist the participant in entering the PET/MR scanner. Once in the scanner, the BRIC technician will inject 555 MBq of the radiotracer through the IV during the scan. During the scan, the participant may receive a second injection of the radiotracer. The total amount of radiation exposure the subject will receive is about the same as they would normally receive in 12 months from natural background sources from the earth and sky. During a pre-scan training session, participants will learn that on each trial they can win the opportunity to earn a monetary reward and that if they don't win on a given trial, they will not earn a reward. During this pre-scan training session, participants will learn that one cue, a circle or a triangle (counter-balanced across participants), will signal that they may receive a reward and the other cue will signal that they will not receive a reward.

## 4.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study and its design will deliver an empirically supported transdiagnostic anhedonia treatment as well as an fMRI-based quantitative index of mesocorticolimbic target engagement to use in future experimental therapeutics trials of novel anhedonia treatments. Testing whether the treatment impacts motivational circuitry specifically: The effects of many psychiatric treatments are non-specific. Pharmacologic agents, including SSRI's, have relatively equivalent and moderate effects for a range of disorders [*51*], likely due to the fact that non-specific symptoms of general worry are targeted across disorders [*52*]. This proposal includes an fMRI task that is sensitive to the negative valence system construct of "threat" which includes anxious arousal, increased conflict detection, attentional bias to threat, and avoidance and recruits the amygdala, hippocampus, and insula. We will thus be able to distinguish the impact of BATA on brain systems that subserve motivation and pleasure from those that subserve threat. Aim 2 will include mid-treatment scans to determine the optimal BATA dose, and multilevel modelling will estimate the optimal number of sessions to achieve target engagement. In this way, we will be positional to evaluate the optimal dose of BATA in the R33 phase.

In the PET sub-study, because of the relatively slow kinetics of [11C]raclopride displacement, in the present study we will use a monetary incentive delay task that has been optimized for [11C]raclopride PET imaging (Schott et al., 2008).The task will be divided into rewarded (75% reward trials) and nonrewarded (0% reward trials) blocks that are each 18 minutes long.

### 4.4 JUSTIFICATION FOR DOSE

Rationale for intended dose using BATA: The rationale for 15 sessions of BATA is based on our previous trials(MH094781 & MH078145) that indicate 15 sessions of behavioral activation for depression yielded clinical response in ~75% of patients with mood disorders and was sufficient to reduce anhedonia scores by ~40%.

### 4.5 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

## 5 STUDY POPULATION

### 5.1 INCLUSION CRITERIA

Inclusion Criteria
1) 18-50 years old and treatment seeking and willing to be video and/or audio recorded for clinical structured interviews and weekly therapy sessions. Only those subjects who agree to video and/or audio record will be allowed in the study. All recordings will occur at the Duke site for the clinical screening interviews & weekly therapy sessions.
2) SHAPS scores >= 30, corresponding to clinically significant anhedonia;
3) Clinician's Global Impression Scale-Severity score (CGI-S) >= 3 to assure a clinically impaired sample;
4) Seeking treatment for anhedonia (i.e., referred from an outpatient clinic or responded to an advertisement for anhedonia treatment; endorses desire for treatment during screening).

### 5.2 EXCLUSION CRITERIA

Exclusion Criteria
1) Those for whom medication management is the primary gold-standard treatment, including those with bipolar disorder/mania, schizophrenia spectrum, and other psychotic disorders; (to clarify, if a subject meets criteria for current or lifetime history of bipolar I and II is exclusionary)
2) Prior treatment with behavioral activation therapy for depression or mindfulness-based treatments (those with exposure to other forms of psychotherapy, e.g., supportive therapy, will be eligible);
3) Those who may have difficulty understanding the cognitive components of BATA, including those with intellectual disability, neurocognitive disorders, and dissociative disorders; Subjects with a NART calculated IQ score of <90 will be excluded from the study.
4) Feeding and eating disorders which may have confounding effects on the BOLD fMRI signal;
5) Substance Use Disorders given confounding effects of substances of abuse on the BOLD fMRI signal; At screening if subject reported use of a substance of abuse in the past week, they will be excluded to ensure acute drug effects. Lifetime history of moderate or severe non-alcohol substance use disorder on SCID-5 is also excluded. Lifetime history of severe alcohol use disorder on SCID-5 will be excluded.
6) Suicidal intent and plan; If item #s 4 and/or 5 on the C-SSRS are answered yes within the last month at the first study visit, subjects will be excused from the trial and referred to more intensive clinical management. Though it is not expected that the study would increase the risk of suicidal intent with plan especially when the subjects will be in active study therapy with trained therapists, to be even more cautious, subjects who report a suicidal attempt within 6 months of the screening visit will also be excluded. *Note: During COVID-19, as screening is done over 1-2 assessment visits, the CSSRS from the in-person visit using "since your last visit" if the participant has either #s 4 and/or #5 answered yes, they*

*will be ineligible and not scheduled for an MRI visit at UNC. However the conduct of the in-person assessment visit including the tasks and CSSRS is based upon building/room approval and if not available, then the in-person CSSRS with tasks will be omitted and not considered a protocol deviation and participant's answers on the CSSRS from the first assessment remote visit will need to meet inclusion/exclusion criteria.*
7) Psychotropic medication use in the past 4 weeks (8 weeks for fluoxetine) and/or current psychotherapy. Participants must be medication(specifically an antidepressant, mood stabilizer and/or antipsychotic)-free at study entry; study personnel will not supervise medication taper for the purpose of the study, but those who taper under the supervision of their regular provider will be eligible (those currently on a sleep, prn benzodiazepine and/or ADHD medication will be allowed in the study)
8) Currently pregnant, as measured by urine pregnancy screen immediately before MRI scans;
9) Positive urinalysis screen for cocaine, marijuana, opiates, methadone, amphetamines, and benzodiazepines (conducted on-site at study entry). [drug screen will not be conducted if in-person visit for tasks and urine drug screen is conducted at UNC while Duke is paused for Phase 3 research during COVID-19 or if unable to do in-person assessment visit at either Duke or UNC).
10) Neurological conditions (e.g., history of stroke, seizure, or TBI);
11) Contraindications for MRI imaging: Metal in the body, dental work that is not fillings or gold, any metal in the body, any metal injury – especially those to the eyes, any other type of implant unless they are 100% plastic. **Note: with amendment 2022, exclusion criteria #11 is no longer applicable for those participants in therapy since imaging procedures are being removed due to funding.**
12) Subjects who are blind or unable to read and understand English will be excluded.

**PET Supplement:** Same inclusion/exclusion apply for the parent study including the imaging. Subjects must meet the inclusion/exclusion criteria for the main study to be eligible to be offered the PET sub-study. SUBJECTS ARE UNABLE TO PARTICIPATE IN THE PET SUB-STUDY IF THEY HAVE HAD A PET SCAN IN THE LAST 1 YEAR; IF THEY'VE RECEIVED RADIATION THERAPY OR CHEMOTHERAPY IN THE 2 MONTHS PRIOR TO THE PET SCAN.

## 5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study.

Screen failures who did not meet inclusion/exclusion criteria at the first visit will be allowed to return to Duke to rescreen for the study up to a total of 3 times, if it is deemed appropriate (examples include SHAPS<30, UA drug screen is positive at screening but the subject doesn't meet criteria for abuse or dependence, CGI-S <3, C-SSRS items #4 or 5 as yes, current psychotropic medication use, positive urine pregnancy screen with delivery of child and female subject is eligible again, etc).

Any participant going over 4 weeks between the remote assessment and the 7T pre-treatment scan, will be considered a screen fail and not randomized and have the ability to rescreen at a later date (i.e. will sign another econsent, redo SHAPS, C-SSRS, UA drug screen [if possible during COVID times], all self-report, SCID5, THI and computer tasks [if possible & contingent on ability to have in-person visits]). Their NART will not be redone and can be used for the rescreen.

## 5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants may be recruited using 1) flyers and posters at Duke University Medical Center (DUMC) campus and the surrounding Research Triangle area as well as UNC IRB approved flyers/brochures on

the University of Chapel-Hill campus, 2) online advertisements used on DukeHealth.org, DukeList, Craigslist, Reddit, the UNC Psychiatry webpage http://www.med.unc.edu/psych/research, UNC's research site, Research for Me https://researchforme.unc.edu/ (formerly Join the Conquest https://jointheconquest.org/index.php/en/ 3) a print advertisement in a local newspaper, 4) direct referrals from local healthcare providers, Duke/UNC outpatient clinics, and other studies of depression 5) Our IRB-approved participant registry (IRB# Pro00000853) in the CBRTP, 6) DEPRU (Duke Early Phase Clinical Research)volunteer registry, This is a registry that the DEPRU has that contains a list of potential study volunteers who have participated in research within the DEPRU, who have said they would be interested in participating in other research. In exchange for a fee from our study team, a member of the DEPRU team will identify potential research volunteers based on our study specific inclusion/exclusion that we give them and they will send out an email with a blurb about our study (this content is first approved by the IRB) and our contact information. Interested participants would then contact our study coordinator and complete a phone screen or go directly to the REDCap online screen for the study. 7) ResearchMatch.org, The study PIs will seek approval from the institutional liaison to have ResearchMatch recruitment access where you are able to search for appropriate matches amongst the non-identifiable ResearchMatch Volunteer profiles in the system. Our study's recruitment content will be inserted into the standard ResearchMatch electronic notification that informs possible matched Volunteers that we have identified them as a potential match for our study. The secure ResearchMatch clearinghouse will route this standard ResearchMatch notification that includes the IRB approved study content that we enter on "Contacting Volunteers" steps available through ResearchMatch (i.e. similar to the content available on a flyer or poster) to each of these ResearchMatch volunteers. These potential matching volunteers will have the option of replying yes, no, or not respond through a set of quick links available in this notification to our study announcement. By responding yes, the volunteer has authorized ResearchMatch to release their contact information to us. This contact information of the Yes responding ResearchMatch Volunteers will be made available on our "Managing my Study" dashboard. Once we receive the contact information for those volunteers who respond yes, a member of our study staff would contact them to do a phone screen or direct them to our REDCap online screen after reading through the phone script information to introduce the study and see if the individual is interested in being screened. 8) The UNC Hospital Carolina Data Warehouse for Health (CDWH) will identify potential participants to receive our recruitment ad. 9) We will also send the recruitment ad to the UNC listserve. 10) Contacting Duke Patients through the Recruitment and Engagement Policy which is a *new method for R33:* Patients will be recruited from the pool of patients who present to Duke University for depressive disorders (e.g. major depressive disorder), anxiety disorders, and trauma and other stressor related disorders. Patients will be identified through a search in Deduce/Pace. Before contacting Duke patients, the study team member will ensure that patients have not 'opted out' of research recruitment by looking at the patient header, multiprovider schedule, patient lists (My List), or opt-out reporting workbench reports. Patients may be contacted via IRB approved letter &/or email template.

Patients who have opted out of research contact, will not be contacted. Patients will not be contacted more than three times, including via letter, email, or Maestro Care In-Basket Message. If a patient states to the study team member that they would like to opt out, the study team member will follow the Duke Recruitment and Engagement policy1. 1) Facebook/Instagram Paid Ads: We will use ads on Facebook to recruit potential participants from the local community. We will set ad parameters based on age (18-50) and proximity to Durham and Chapel Hill. Participants who respond to advertisements will be directed to complete the IRB approved RedCap online screener. **Discover Duke Research Facebook Page**: We have worked with the Duke RIC (Recruitment and Innovation Center) in CTSI and have developed a Duke IRB approved social media plan that involves posting IRB approved social media ads on the RIC's

"Discover Duke Research" Facebook page as well as using the RIC services to post paid ads on Facebook/Instagram. We have Duke IRB approval for this plan that includes multiple pictures, wording, headlines and hashtags that can be used as part of this advertisement plan. The post on "Discover Duke Research" Facebook page is managed by this small team in RIC and locked down by them and done 1x/month. They also manage the paid Facebook/Instagram ads that are posted. This study is able to be advertised via this method and using this specific trained group at Duke per Duke IRB and Duke Office of Research (DOCR).

We are using the UNC Hospital Carolina Data Warehouse for Health (CDWH) to identify potential participants to receive our recruitment ad. We plan to use the email language that we have submitted for IRB approval to reach out to potential participants who CDWH has identified based on certain eligibility (age & diagnoses). A member of the UNC study team will send the IRB approved language to the potential participant identified by CDWH which includes the REDCap link that describes the study & allows them to decide if they would like to complete the online screen to see if they qualify. If they choose to call the UNC team member who emailed them, they will be first given the choice to complete the online screen on their own time but if preferred, the Duke & UNC IRB approved REDCap Phone script will be used to complete the phone screen. Thus the methods for CDWH contacts are either email (with valid email address) or mailed letter & both will be done by members of the UNC study team.

Prospective participants will either 1) contact the study coordinator's office at Duke or be called for a telephone screening interview, administered by a Study Coordinator/approved study team member, or 2) they may visit the websites ClinicalTrials.gov, Dukehealth.org, DukeList or Research for Me (UNC) and see the study description or posting. Participants may choose to complete prescreening via REDCap survey or phone screen script.

Again, the main methods of recruitment for the study funnel most potential participants to complete the REDCap online screen (includes seeing a flyer, brochure, online posting or calling after receiving an email from the UNC listserv/Duke registry). Study team members attempt to contact potential study participants who have either completed the REDCap online screen, called them after seeing a flyer or online posting or calling after receiving an email from the UNC listserv/CDWH or CDWH letter. They will never leave a voicemail message that includes any information that jeopardizes the privacy of potential subjects.

UNC Hospital Carolina Data Warehouse for Health (CDWH): Supported by NCATS, the CDWH is a repository of clinical, research and administrative data on all patients seen since July 2004 by the UNC Health Care System. Updated every 48 hours, this portal is a web-based tool that allows researchers to identify patients as potential research participants. As of February 1, 2016, the patient population in the CDW-H was 3,976,932; the number of patients with at least one encounter from April 1st, 2014 - April 1st, 2015 was 559,233; and the number of encounters from April 1st, 2014 - April 1st, 2015 was 2,778,684.

Request for information cards: The study team will give these cards to interested healthcare providers (starting first within Duke and possibly later, if needed, outside Duke) along with our Duke IRB approved study brochures. For Duke Providers who are outside of our clinic, we will send a letter (or email) as the study is beginning, with the study information and IRB approved brochure. The letter/email will be brief that will include inclusion/exclusion criteria and ask them to let any potential patients know about the study. We will ask the interested healthcare providers to inquire with their own appropriate patients whether they are interested in learning more about the study. If their patient says yes, then the provider will ask the individual if they would prefer to be contacted directly by a member of the study staff or to contact the study team on their own accord, using the information on the brochure. If they prefer for one of the study staff to contact them, they will fill out the request for information card with their name

and either phone or email contact info and leave it with their provider, who would then give it directly to one of the study staff.

The phone screen will include questions about age, pregnancy, drug use, psychiatric status, psychiatric medication use, use of psychotherapy, a question about anhedonia, and administration of the MRI Safety Screening Form (**MRI safety removed with June 2022 NCE amendment).**

If the potential participant is indeed ineligible for in-person screening, the study coordinator/approved study team member will log in to REDCap and remove their contact information from the study record by the end of the study enrollment period. After removing the contact information, the record number will continue to exist in REDCap with only the subject's research information.

The lead Duke study coordinator & UNC research assistant or Duke/UNC approved study team member or UNC research assistant will have a unique log in and password to access the UNC REDCap online survey. Participants who complete the online screen will be called by the Duke study coordinator or approved Duke team member to communicate whether the study is a good fit or not and to provide referrals as needed. Participants will also be able to be screened for the study via the Duke approved phone script if they call the study coordinator's or PI's office directly. The study coordinator or approved study staff will use the REDCap phone screen script to assess certain exclusion and inclusion criteria.

Team does not specifically intend to recruit UNC-CH students or UNC-CH employees however, it is definitely feasible because of the nature of this study, that some of the participants can turn out to be a UNC-CH students or UNC-CH employees.

Study team will of course not enroll any students or employees are that were trainees or students of the UNC or Duke PI.

To reduce attrition, at Duke participants will receive $20 for the structured clinical interview, $20 for the initial self-report questionnaires, $10 for the urine drug screen, and between $32-39 for completing the 2 computer tasks. They will also receive a parking pass or a bus pass (up to $3) to cover the cost of parking or bus fare, if applicable. Thus in summary, those who complete the visit will receive $82-89 ($80 + $2-9 depending on their performance on the computer reward task). They will receive an additional $62-69 for completing the post treatment visit which again depends on their performance on the computer reward task. **If computer tasks & urine drug screen need to be omitted because approval for in-person visits have not occurred, the participant will still be paid for the 2 (urine drug screen & computer tasks) and will be paid the minimum of $32 for tasks & $10 for drug screen.**

Therapy sessions are provided at no cost to the participant and they will be given a parking pass, if applicable. At weeks 4, 8, & 12 of therapy, they will complete the computer effort/reward tasks & will receive between $12-19 ($10 + $2-9 based on task performance) at each of those 3 visits for a total of $36-57 at these 3 therapy visits in addition to parking or bus pass. **Again, during COVID-19, if tasks cannot be conducted at an in-person visit, the participant would still be paid the minimum of $12 for these visits, if applicable.**

UNC: For completing each MRI brain scan visit, subjects will receive $75 up to as much as $110 depending on their responses to the scanner task plus a parking or bus pass, if applicable. Thus total fMRI compensation for the study will be between $150-440. **Participants enrolled at UNC as of 11/1/18, will only have a pre & post treatment MRI scan and thus total fMRI compensation for the study will be between $150-220.**

Based on our previous experience, retention for psychotherapy trials from pre- to post-neuroimaging sessions is approximately 81%.

EMA Optional Sub-study: Participants will be compensated $10 per week of EMA participation, and will receive a bonus of $1 per survey completion if they complete more than 8 responses in a given week. Thus, participants will have the potential to earn up to $52 over the course of the four weeks of EMA.In the 1st phase of the study- a R61 no cost extension & due to limited funds-participants who enrolled in the 1st phase on or after 11/1/18, have been completing EMA after pre and post MRI scans & thus can earn up $26 over the course 2 weeks of EMA instead of $52.

**R33 EMA compensation: With the additional wks 4, 8, and 12 (if applicable) adding to the pre and post treatment scan timepoints, participants who agree to the optional EMA portion of the study, will have the potential to earn up to $65 over the course of 5 weeks of EMA instead of only $26 from the R61 no cost extension.**

PET sub-study: Subjects will be compensated a range of $160 - $200 per scan, to be determined by the computer activity that they complete while in the scanner. If they are unable to complete the PET imaging with computer activity after getting in the scanner, they will be paid $20/hour for that session.

# 6 STUDY INTERVENTION

## 6.1 STUDY INTERVENTION(S) ADMINISTRATION

### 6.1.1 STUDY INTERVENTION DESCRIPTION

**Behavioral Activation Treatment for Anhedonia (BATA)**

Treatment in the R61 phase (Phase I) will consist of up to 15 weekly 45-minute sessions. This duration maybe modified in the R33 phase as a result of R61 phase Aim 2 analyses. Update for R33: Duration will remain as 8-15 weeks of treatment. Session 1 provides orientation and psychoeducation on anhedonia, and activity monitoring is introduced. Sessions 2-3 include structured values assessments of 10 life areas (e.g., Family Relationships, Employment/Career) to enhance motivation for sustained behavior change and to clarify goals. Following goals clarification, an activity hierarchy is developed, establishing a set of idiographic behavioral targets across life areas prioritized by ease of implementation to scaffold task engagement during the course of treatment. Session 4 focuses on reduction of avoidance. Sessions 5 and above assess completion of goals from the previous sessions, troubleshoot barriers to goal completion, and assign goals for the coming weeks. In the R33 phase, the minimum number of sessions will be 8 to allow for all planned content to be introduced, with a maximum of 15 sessions. Inherent in this structure is therapist assistance in setting achievable goals, which is often impaired in the context of anhedonia. Embedded in the review of goal completion is heightened awareness of anhedonia and identification of behaviors that are associated with greater positive response in the form of subjective importance and enjoyment. Those behaviors then form the basis of goals for the following weeks. The therapist uses motivational techniques to elicit goal-directed behaviors outside session including tying goals to the patient's identified values, open-ended questioning and reflective listening, and functional analysis to select behaviors maximally likely to achieve the patient's goals. Increased positive affect and decreased negative affect are theorized to result from increased contact with potential reinforcers through reduced behavioral avoidance4.6,47 Maladaptive behaviors such as avoidance decrease the effectiveness of positive events in shaping future behavior, weakening the learned association between adaptive behaviors and positive outcomes. In this way, the overarching goal of BATA is to encourage the

patient to engage in activities that increase contact with personally relevant, values-consistent reinforcers, thereby strengthening links between environmental engagement, positive mood, and future approach-oriented behaviors.

Several specific new components are included in BATA: in Session 1, content specific to depression is removed and additional psychoeducation about anhedonia and response to rewards is provided. This includes education about anticipatory versus consummatory anhedonia, positive versus negative reinforcement, and how anhedonia can foster avoidance. Activity monitoring is streamlined to reduce monitoring effort for low motivation patients. Sessions 5 includes a focus on increased frequency of initiation of new behaviors to target motivation. In Session 6, once novel behaviors are established, additional exercises49, 50 will be introduced to increase present-moment savoring as a means to target pleasure.

**Mindfulness Based Cognitive Therapy (MBCT)**

Mindfulness is nonjudgmentally bringing awareness and acceptance to one's present-moment experience. Mindfulness-based interventions have demonstrated efficacy for treatment of diverse psychological symptoms including depression. To control for nonspecific factors in BATA including clinician contact, MBCT will be administered in an individual format. MBCT for individual treatment is empirically supported for a number of forms of psychopathology. Individualized adaptations of MBCT share primary components of the traditional program, including instruction and in-session practice of meditative exercises, didactics, and home practice. MBCT will be compromised of approximately 15 weekly 45-minute sessions. In the R33 phase, the number of sessions will match that of BATA. Sessions will begin with practice and discussion of a mindfulness meditation exercise, and then include: discussion of home practice, introduction to a new exercise and/or psychoeducational topic, and explanation of home practice for the coming week. Initial sessions will focus on practice and discussion of core meditation exercises to build mindfulness skills. Later sessions will focus on generalizing learned skills to cope with stressors and mood shifts. Psychoeducational content will center on identifying connections between negative thoughts, emotions, and sensations, recognizing triggers of emotional events, and developing an "action plan" to reduce stress-related symptoms. At the end of each session, participants will receive handouts that summarize the meditative exercise and/or psychoeducational content covered each week. Participants will also be asked to practice meditation exercises at home for 30 minutes each day and track practice time. Homework and logging are included to control for homework and monitoring components of BATA. Participants will receive guided meditation CDs (based on Segal et al.) to aid in home practice. Adherence will be monitored by tracking attendance; compliance of home practice will be monitored by evaluating frequency and duration of practice on weekly homework logs.

### 6.1.2 DOSING AND ADMINISTRATION

MBCT/BATA Therapy Window Visits:
Therapy sessions will be managed overall by calendar weeks, rather than trying to count days. This study is offering up to 15 weeks (as opposed to sessions) of treatment. Therapists will be instructed that they need to push to schedule at least one appointment per week, even if it's not on the same day of the week each week. The therapy portion of the study will follow this protocol:

| Therapy Week | Procedures & Window |
|---|---|
| **Week 0** | The week the first MRI scan takes place. This "starts the clock" for both therapy and assessments |
| **Weeks 1-3** | Weekly therapy sessions. Sessions can start post-scan in week 0 if preferred; up to two sessions can be scheduled in a calendar week to make up missed sessions, with no more than three sessions completed by the end of week 3. Therapy content will not be skipped: for example, the content designated for Session 1 will be administered at the first therapy session, regardless of the week in which it takes place. |
| **Week 4** | Follow-up REDCap Questionnaires, computer tasks, and therapy. REDCap questionnaires and computer tasks will take place in this week as long as at least one session was attended in weeks 0-3. If 0 sessions were attended prior to this week, assessment is delayed to Week 5. If a subject has not attended at least one therapy session by the end of Week 4, they are a study drop by the 4-miss rule. This way every subject will have at least one "dose" (=therapy session) prior to the Wk4 visit. |
| **Week 5** | Weekly therapy session. If necessary, this can be a make-up for the Week 4 assessment if they did not attend or if Week 4 was first therapy session. If the participant does not attend therapy in Weeks 4 or 5, the "Wk4 Assessments" will not be collected and will be considered missing. |
| **Weeks 6-7** | Weekly therapy sessions. Up to two sessions per week can be conducted to make up previous missed appointments. No more than 7 Sessions will be delivered by the end of Week 7. |
| **Week 8** | Follow-up REDCap questionnaires, computer tasks, therapy, MRI Scan. If the subject has not attended at least 2 sessions overall, including at least 1 session in weeks 5-7, assessments and MRI scan may be delayed to Week 9. If a subject has not attended at least 1 session between weeks 5-8, they are a study drop by the 4-miss rule. Clinical response will be assessed and discussed with participants at this therapy session to determine if therapy is complete or will continue. |
| **Week 9** | Weekly therapy session. If necessary, this can be a make-up for the Week 8 visit and/or MRI Scan. If the participant does not attend therapy and/or MRI scans in Weeks 8 or 9, the "Wk8" assessments will not be collected and will be considered missing. DECISION POINT: The study team proposes that in terms of their best use of study resources, anyone who misses both the Week 4/5 and Week 8/9 Behavioral assessments, as well as the Week 8/9 MRI scan, should be considered a study drop and will be withdrawn from the study at that time. |
| **Weeks 10-11** | Weekly therapy sessions. Up to two sessions per week can be conducted to make up previous missed appointments. No more than 11 sessions will be conducted by the end of Week 11. If treatment is completed during one of these sessions, a final Assessment will be conducted at the final therapy session, and the final MRI scan will be scheduled by the end of the week following the final therapy session. |

| | |
|---|---|
| **Week 12** | Follow-up REDCap questionnaires, computer tasks, therapy, MRI Scan. If subject has not attended at least 3 sessions overall, including at least 1 session in weeks 9-11, assessments and MRI scan may be delayed to Week 13. If a subject has not attended at least 1 session between weeks 9-12, they are a study drop by the 4-miss rule. |
| **Week 13** | Weekly therapy session. If necessary, this can be a make-up for the Week 12 assessments and/or MRI Scan. If the participant does not attend therapy and/or MRI scans in Weeks 12 or 13, the "Wk12" assessments will not be collected and will be considered missing. DECISION POINT: Anyone who misses both the Week 8/9 and Week 12/13 Behavioral assessments, as well as the Week12/13 MRI scan, should be considered a study drop and will be withdrawn from the study at that time. |
| **Week 14** | Weekly therapy sessions. Up to two sessions per week can be conducted to make up previous missed appointments. |
| **Week 15** | Follow-up REDCap questionnaires, computer tasks, therapy, MRI Scan. If the subject has not attended at least 4 sessions overall, including at least 1 session in weeks 13-15, assessments and MRI scan may be delayed to the following week ("Week 16"). No therapy sessions will be held in Week 16. |

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 ACQUISITION AND ACCOUNTABILITY

BATA therapist training: Study therapists will include Duke LCSW- or PhD-level clinicians with experience in cognitive behavioral therapy. Duke PI, Dr. Smoski will supervise weekly BATA training and supervision meetings. Additional supervision will be provided if manual adherence falls below a predetermined "redline." BATA training will include didactic seminars by Dr. Stacey Daughters at UNC and two pilot training cases supervised by Dr. Smoski. Dr. Daughters will be the adherence rater for BATA in this study.

MBCT therapist training: Study therapists will be Duke experienced LCSW- or PhD-level clinicians with experience in mindfulness-based interventions. All therapists will have previous training as meditation instructors and a personal meditation practice. Dr. Smoski will supervise weekly training and supervision meetings. Additional supervision will be provided when manual adherence scores fall below a predetermined "redline." Training for MBCT delivery will include didactic seminars by UNC's Dr. Susan Gaylord and two pilot training cases supervised by Dr. Smoski. Dr. Gaylord will serve as senior consultant and adherence rater for MBCT in this study.

Therapy Session Video and/or Audio Recordings & Treatment fidelity:
The study therapy sessions will be video and/or audio recorded to ensure that the study therapists are performing the therapy correctly. These video and/or audio recordings will be recorded directly onto the study therapist's Duke computer/laptop, using a USB connected web camera that is connected to the hard drive of that computer. The recordings do contain PHI and thus the Duke lab computer used for recording has been encrypted with PGP/Bitlocker. These video/audio files will be only temporarily stored on the local Duke computer and will be moved to Department of Psychiatry & Behavioral Sciences protected folder. These video and/or audio files will then be transferred by the Duke approved secure file-sharing program (Box) to UNC to the study specific folder on the CIDD server and will be managed & monitored by UNC IT. Thus, the recordings will no longer be stored at Duke. These therapy recordings will be used to assess study therapist adherence throughout the study. Drs. Gaylord & Daughters, as the study adherence raters, and on the UNC IRB protocol and the Duke IRB protocol as outside key personnel, will access these recordings via the study specific folder on the UNC server. They

will review a number of weekly therapy sessions and Likert-scale ratings will be made of competence and adherence to the specific session objectives in the treatment manuals. If therapist drift is detected from the specific therapy protocol, therapists will be given feedback and the problem will be corrected through supervision with either Dr. Smoski or the specific therapy expert (i.e. Drs. Gaylord or Daughters). Patient adherence will be measured through ratings of completion of therapy homework as well as through patient self-report (i.e. % they reported they completed). All therapy session recordings will be kept at UNC no longer than 7 years after the study completion date and at that time, will be destroyed.

### 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization assignment will be performed through a dynamic balancing protocol that will balance treatment assignment within groups of lower (20-30) and higher (31+) SHAPS scorers. We recognize that anhedonia is common in patients with major depression. To ensure a true transdiagnostic sample, we will monitor DSM diagnoses of enrolled subjects in both phases to ensure that no more that 40% in either phase meet DSM criteria for a current depressive episode. We will stratify groups based on SHAPS scores. **For the R33 phase**, we will no longer stratify groups based on SHAPS score as all participants will have SHAPS scores 30 or greater.
Unblinding does not apply to this study since study therapists and participants are aware of which group the participant is in for the therapy intervention.

### 6.4 STUDY INTERVENTION COMPLIANCE

A participant will be considered a drop if they miss 4 therapy sessions in a row. Up to two sessions per week can be conducted to make up previously missed weeks. No more than 4 sessions will be completed before week 4, no more than 7 sessions will be complete before week 7, no more than 11 sessions will be complete before week 11. At week 8 onward, clinical response WILL be assessed and discussed with participant to determine if therapy is complete or will continue. No Therapy sessions will be held in wk 16.

### 6.5 CONCOMITANT THERAPY

Those who are stable on a sleep, as needed benzodiazepine and/or ADHD medication will be allowed in the study are allowed to be in the study and if they need to start one of these medications per their medical doctor, they will be allowed to continue in the study. Any other psychotropic medication for mood, anxiety, OCD, mood lability, etc are not allowed in the study and if needed during the course of the study, will end in participant withdrawal.

#### 6.5.1 RESCUE MEDICINE

*Not-applicable.*

## 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1 DISCONTINUATION OF STUDY INTERVENTION

A participant will be considered a drop if they miss 4 therapy sessions in a row. Up to two sessions per week can be conducted to make up previously missed weeks.
If a participant decides to drop the study before they reached 8 weeks of therapy and they have completed at least 1 therapy session at the time they withdraw, they will be asked to return for one final visit to UNC to complete a post treatment brain scan.

If a subject who agreed to the PET sub-study, drops out of the study before week 8 of therapy & they have had at least 2 therapy sessions, they will also be asked to do the post PET scan at the time of the 7TMRI & blood at UNC.

### 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects will be informed that they have the right to discontinue their participation at any time, and that their right to obtain appropriate treatment through normal referral channels will not be affected by their decision to participate or not participate. Subjects will also be informed that they have the right to demand that their responses not be included in the study, and that any publications resulting from the research will not identify them as individuals. The study doctor may decide to take a subject off this study if their condition gets worse, if they have serious side effects, or if the study team determines that it is no longer in the subject's best interest to continue. Other reasons for the study doctor to withdraw a subject from the study includes: if the subject is female and becomes pregnant, the subject needs treatment not allowed in the study (antidepressant, mood stabilizer and/or antipsychotic), the subject misses 4 talk therapy sessions in a row and has not maintained contact with their study therapist or any member of the study team. Though starting a benzodiazepine, sleep or ADHD medication is not encouraged in the study, if the situation arises during the study where it medically indicated by their own doctor that one of these type medications is needed, they will be allowed to start these medications and asked to notify the study team so it can be documented. The reason for participant discontinuation or withdrawal from the study will be recorded on the UNC REDCap tracking log form.

### 7.3 LOST TO FOLLOW-UP

A participant is considered lost to follow-up if he or she fails to return for four scheduled therapy visits in a row and is unable to be contacted by the study site staff.

The following actions are taken if a participant fails to return for a required study therapy visit:

- The site will attempt to contact the participant and reschedule the missed visit (must complete at least 1 therapy session before week 4 and at least 1 in weeks 5-8 and again at least 1 in weeks 9-12 and 13-15, if applicable). Study team will counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and emails, if necessary, these contact attempts should be documented in the participant's study file in REDCap.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- R33-If a participant is unable to return for the task visit due to sickness, weather, travel, etc but is attending the remote therapy sessions, the scheduled week 4, 8 and/or 12 task visit may be skipped, documented as a deviation but the participant is allowed to continue.

## 8 SAFETY

### 8.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

### 8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator, DSMB, or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### 8.1.3 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.1.3.1 SEVERITY OF EVENT

*All AEs will be assessed by the study monitors (Drs. Dichter and Smoski) and monitored by the independent Data Safety Monitoring Board (DSMB), known as the BATA DSMB.*

For adverse events (AEs), the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

#### 8.1.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) that occur during the study will be captured have their relationship to study intervention assessed by the study PIs who examine and evaluate the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – The AE is known to occur with the study intervention and the temporal relationship between the study intervention and event aligns. The event occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.
- **Possibly Related -** there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE. However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as

"possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded "definitely related", as appropriate.

- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

#### 8.1.3.3 EXPECTEDNESS

*Expected adverse reactions are AEs that are known to occur for the study therapy and/or procedures being studied/used. Expectedness is assessed based on the awareness of AEs previously observed, not on the basis of what might be anticipated from the properties of the study intervention.*

*An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the device labeling or is not listed at the specificity or severity that has been observed; or listed in the participant informed consent.*

*The Study PIs (UNC and Duke)* will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. The BATA DSMB will also be able to weigh in and recommend continuation, discontinuation, modification, or termination of a study based on emerging data (in the study and literature) and evaluation of risk/benefit ratio.

### 8.1.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

We will start collecting AEs/SAEs at the pre-treatment MRI visit at UNC's BRIC and will continue to collect them through their final visit (i.e. most likely the post-treatment MRI visit at BRIC). All follow-up AEs/SAEs will end at their final study visit.

A trained study team member will ask about any changes in health and medications at each of the study visits as per the list of scheduled events table. In terms of the fMRI: After each participant is scanned, the PI, Dr. Gabriel Dichter, will communicate with co-I Dr. Weili Lin, the UNC BRIC Director, to review any unanticipated problems (including but not limited to adverse events) to monitor subject safety. A weekly team meeting will be conducted to discuss research procedures.

*Quality assurance*. The Duke and UNC study teams will meet weekly to review any research issues that may have arisen during the past week as well as to monitor progress on subject recruitment and other research-related matters. Additional meetings are conducted on an as-needed basis.

Any Adverse Events will be reviewed by the study team at UNC and Duke as the events occur.

All AEs including not meeting the criteria for SAEs will be captured in their individual REDCap form Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, the study team will discuss and it will be recorded as an AE.

In this study, if a subject experiences an SAE or study related, non-serious AE and they are not resolved at their final study visit, because it is a minimal risk study, it will not continue to be followed past the participant's final study visit.

### 8.1.5 ADVERSE EVENT, SERIOUS ADVERSE EVENT REPORTING

*Reporting mechanisms of AEs & SAEs to the IRB*. In this study we will use the FDA's definition of adverse events (AEs) and serious adverse events (SAEs). It is not expected that any such AEs or SAEs will occur in this experiment. However, AEs and SAEs will be assessed by a trained study coordinator, study therapist or other approved study team member, and discussed at the weekly research staff meetings.
Any SAE during this collection period will be brought to the attention of the PI as soon as possible and not longer than 24 hrs. Any SAE (regardless of the study relatedness), will be reported to the Duke University Medical Center Institutional Review Board and/or UNC-Chapel Hill Institutional Review Board using the appropriate documentation within 5 days of the event. Unexpected study related SAEs will be reported to the overall sponsor, NIMH within 10 business days. This will be the responsibility of the 2 PIs, Drs. Smoski & Dichter. The Duke University Medical Center IRB/UNC-Chapel Hill IRB will decide as to whether additional reporting requirements are needed.

Reporting of non-study related, non-serious AEs are not reported to the IRB, overall sponsor, and not entered on the study AE tracking log, however they will be entered on the subject's individual adverse event pages within REDCap and checked at every study visit (both at UNC & Duke).

Non-serious AEs that are deemed study related will be reported to the IRB and overall sponsor with annual reporting and entered on the subject's individual adverse event page in REDCap. These will be reported to the DSMB as per the DSMB scheduled reporting.

### 8.1.6 REPORTING EVENTS TO PARTICIPANTS

Participants will be told about new information that may affect their health, welfare, or willingness to stay in the study. The study PIs may decide to take someone off this study if their condition gets worse, if they have serious side effects, or if the study team determines that it is no longer in the participant's best interest to continue. The Duke PI (supervisor of the study therapists) meets weekly with the study therapists and if there appears to be significant worsening with no clear signs of current study potential benefits, the study therapist will then meet with the participant at the next therapy session (or sooner, if necessary) and discuss having the participant stop and be provided resources to follow-up with such as medications, therapy and other interventions outside of the study.

If the BATA DSMB suggested any changes to the risk/benefit ratio to the study, these updates are given to participants in the form of a new consent and asked to review and sign and date that they are been given the new information and still will continue to participate (or can refuse to continue).

### 8.1.7 REPORTING OF PREGNANCY

*Pregnancy is not an adverse event, but study participants who do become pregnant while enrolled in the study are asked to report this to their study therapist or a study team member immediately. They will be dropped from the study since it is not recommended they undergo a follow-up 7T MRI and if applicable, a follow-up PET scan using the radioactive tracer.*

# 9 STATISTICAL CONSIDERATIONS

## 9.1 SAMPLE SIZE DETERMINATION

**Aims 1, 2, and 5**: To evaluate whether BATA produces changes in neural responses to reward anticipation and reward outcomes that (1) exceed our *a priori* target engagement criteria; (2) exceed changes due to a comparison treatment; and (3) does not impact neural responses to threat. To evaluate relations between BATA dose and neural target engagement by examining changes in reward responding with fMRI scans 8, 12 and 16 weeks after starting the 15-week treatment.

Power is calculated for Aim 1 fMRI analyses because of its smaller sample, and the Aims that involve all 210 participants will have higher power because of the larger sample and optimized BATA dose. For Aim 1 we will enroll 30 outpatients per group to have complete data from 25 per group. Based on our pilot data demonstrating increased right CN activation during reward anticipation and decreased rACC activation during reward outcomes, we calculated an effect size of approximately z=4.1. Conservatively, we estimate the effect size for the increased right CN activation and reduced rACC activation will be in the range of z = (0.75-1.25). Our models will thus have >90% power at a=0.025.

**Aims 3 and 4**: To evaluate the effects of BATA versus MBCT on anhedonic symptoms, functional outcomes, and behavioral indices of reward sensitivity. Our power analysis addresses the effects of BATA versus MBCT on SHAPS scores (conducted with Gpower) as an ANCOVA with two groups and two timepoints. With 65 subjects per treatment group with complete data at post-treatment, a =.05, and assumed correlation between assessments of 0.35 (based on preliminary studies), we will have 98% power to detect small (*f* = .2) effects. Pilot data in depressed patients indicated a large effect from pre- to post-treatment (d=1.24, *f* = .62), and we are powered to detect these effects. We are 80% powered to detect the interactions with effects as small as *f* = .14.

*PET Power Analyses:* Samples sizes are dictated by the limitations of this funding mechanism, and we note that the majority of published molecular imaging studies have had relatively modest sample sizes. We also note that one advantage of our approach is that both phasic and tonic DA states are acquired during the same scan, thereby allowing for statistical models that use within-subjects variance calculations. Finally, we highlight that the test-retest stability of [11C]raclopride-derived DA binding potentials is very good (ICC = .82 for the NAcc [46]). Our power analysis is based on power to detect group differences in the intra-subject correlation between DA release and change in BOLD signal. Assuming a standard deviation in DA-mediated binding potential changes of 0.3 (approximately 10%), we will be powered to detect a >15% change in DA binding (?BP%) with a power of 0.85 and a false discovery rate of 2.5%. This sample size is limited by the funds available through this grant mechanism and the extremely high cost of PET imaging.

*EMA Power Analysis.* Given our sample size, we consider EMA to be preliminary data that may be used to estimate effect sizes for future grant applications that use EMA as an outcome measure for anhedonia clinical trials. Additionally, the proposed structural equation models are very complicated and may need to be adjusted. With the sample size of the R61 phase of the parent grant, the proposed analyses should have medium power (50% or more) to identify paths if the paths correspond to partial correlations of |0.10| or larger. By continuing to collect EMA data in R33, we hope to increase our sample size and also explore changes after wk 4, 8, and 12 (if applicable) computer tasks, thus EMA is not only linked to pre- and post treatment MRI scan visits.

## 9.2 DATA ANALYSES & STATISTICAL CONSIDERATIONS

fMRI Analyses for Go/No-Go Decision for phase II (R33): Analyses of target engagement will focus on activation in the right CN during reward anticipation, the rACC during reward outcomes, and bilateral amygdala in response to threat. The decision to proceed to the R33 phase will rest on reward-related activation metrics from functional CN and rACC regions of interest (ROIs) derived from our preliminary studies (from [37]). We will make these functional ROIs publically available through the UNC BRIC's website for use by other researchers. Amygdala activation during the threat task will be evaluated using an amygdala ROI defined from the Harvard-Oxford subcortical structural probabilistic atlas. Data will be preprocessed using FSL (Oxford University, UK) as described in our work.[76-78] We will ensure groups do not differ in head motion by calculating mean framewise displacement[79] which yields, for each participant, a value indicating mean head displacement from one volume to the next. Hypotheses will be evaluated with a ROI approach whereby signal intensities are extracted from ROIs for the relevant task contrasts (i.e., potential win versus non-win trials during MID reward anticipation trials; wins versus non-wins during MID reward outcome trials; fearful and angry faces > shapes during the threat task). **Our go/no-go decision will be based solely on this ROI analysis**.

Exploratory Whole-brain Activation Analyses ROI analyses will be followed-up with whole-brain analyses that will yield activation maps thresholded at a False Discovery Rate of 0.01[80] to allow for an examination of activation in other reward processing regions, including the ventral striatum/nucleus accumbens, putamen, ventral tegmental area, and orbitofrontal cortex.[81, 82] To optimize BOLD signal coverage in the ventral tegmental area we will acquire high-resolution T1-weighted images with 1x1x1 mm voxel size to allow for precise registration and will use cardiac and respiratory gated imaging during the acquisition of structural scans to address pulsatile artifacts using retrospective corrections implemented with the FSL PNM toolbox.[83]

Exploratory Connectivity Analyses: Mesocorticolimbic connectivity in central to anhedonia.[42,84] We will explore task-dependent correlations between ROIs using a psychophysiological interactions approach as in our prior work.[42, 85] Timeseries will be extracted from ROIs using FSL Featquery for each participant and trial type and correlation values will be transformed using a Fisher r-to z transformation. We also conduct whole-brain connectivity analysis, with a particular emphasis on the salience network (i.e., dorsal anterior cingulate cortex, anterior prefrontal cortex, and anterior insula),[17] by segmenting the brain based on a probabilistic atlas132, while correcting for multiple comparisons at the familywise error rate of $p < .05$.

Secondary Analysis: Secondary data analysis will be conducted examining relationship between psychological symptoms and patterns of brain activation in the functional neuro data. Data will be transferred from UNC to Duke to be analyzed by Duke study team members.

Aims 1 and 5: Only patients who complete baseline measures will receive BATA, and those who complete at least one BATA session will participate in post-treatment assessments (ITT, estimating ~90% of sample). We will compare fMRI activation in regions of interest at pre- and post-treatment. Primary analyses will address changes in regional brain activation from baseline to post-treatment.
Models will include motion parameters, gender, and age as covariates. The design is a 2 (BATA vs MBCT) X 3 (CN, rACC, amygdala) X 2 (pretreatment vs post-treatment) ANCOVA testing the change from pre- to post-treatment as moderated by treatment group and brain region in the outcome variables controlling for the covariates. Post-hoc comparisons will compare change across each region. Note that CN and rACC activation values are derived from the MID task whereas amygdala activation values are derived from the threat task.

Aim 2: We will analyze whether dose moderates treatment response via regression models that predict change in neural target (CN and dACC) activation from the number of sessions as an indicator of BATA dose. Hierarchical linear modeling where time-in-weeks is treated as a continuous variable nested within subject will provide parameter estimates of the linear, quadratic, and cubic functions for change over time in neural target engagement over the course of treatment. Standard evaluation (e.g., significant at $p < .05$) will guide our selection of the most appropriate function. From these functions, we can estimate both the point in time where the change in target engagement is greatest and where it approaches 0, meaning minimal further improvement is anticipated. Although mid-treatment scans will occur at weeks 8 and 12, we will estimate change continuously so the optimal dosage is not restricted to one of those timepoints.

Aims 3 and 4: To evaluate the efficacy of BATA, relative to MBCT, for treating anhedonia, functional outcomes, and behavioral indices of reward sensitivity, we will test for differential change over time between those who receive BATA and those who receive MBCT post-treatment. We will use an intent-to-treat (ITT) analysis for patients who receive BATA relative to those who don't. The ITT model will be a repeated-measures ANCOVA with effects for treatment condition (BATA, MBCT), outcome measure (SHAPS, PRT, etc), time (pre-treatment, post- treatment) and their interactions. The interaction tests will assess mean differences at each time point as well as differences in the degree of change between the groups. This also provides tests of each group relative to their baseline scores. We will include gender and age as covariates in these models. **We will also note any participants who were enrolled in the study and had PRT & EffRT reward tasks data omitted during COVID-19 times.

*PET Analysis:* The primary PET metrics to be evaluated will be striatal background DA tone and phasic DA release. Study UNC biostatistician will oversee all analyses. UNC will first evaluate the means and standard deviations of PET-derived striatal binding potentials. **Aim 1** (to evaluate relations between BATA response and PET-derived changes in background DA tone and phasic DA release) will be evaluated by extracting the dynamic change in binding potential ( BPND%) before, during and after the task and then comparing these values before and after treatment between treatment groups. **Aim 2** (to evaluate relations between BATA related changes in fMRI and PET-derived background DA tone and phasic DA release) will be addressed by correlations between changes in PET striatal binding potential magnitudes and changes in fMRI.

*EMA: Primary Analyses*-For EMA, the primary variables of interest will be scores on the positive/negative affect and anhedonia items over the assessment periods. Given the longitudinal (i.e., repeated waves of EMA data) and hierarchical (i.e., assessment timepoints nested within individuals) structure of the data to be collected, Hierarchical Linear Modeling (HLM) will be used to analyze EMA data.
Follow-up analyses with the Passive location tracking of MetricWire will evaluate relations between motion tracking, behavioral, brain, and clinical measures of response to both treatments. **Optional EMA enrollment ended with the NCE June 2022 amendment.**

### 9.2.1 SAFETY ANALYSES

Safety data will be collected as it comes up during the study and discussed in weekly team meetings. All safety data will be shared and monitored by the BATA DSMB team comprised of 3 independent members, not connected to the study team at Duke or UNC. Both Voting members and Advisory members for this DSMB may attend closed sessions for this Committee.
In addition, both Voting members and Advisory members will have access to monitoring data for this Committee. All reports, materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.
It is expected that all DSMB members who are identified in the table just above will attend every meeting. However, it is recognized that this may not always be possible. Therefore, the DSMB for ***BATA Study*** has established the following quorum for voting: A quorum of this DSMB is considered to be **2** voting members.
Quorum must be reached in order for an item to be voted on. At least **2** votes in favor are always needed for a decision to be final.
The goals of this DSMB are:
1) To review and report adverse events (see schedule below).
2) To monitor the level of risk posed by the study and insure that risks are minimized.
3) To review modifications to risk management protocols.
4) Review progress toward meeting enrollment goals.
5) To review procedures for maintaining the confidentiality of data, and quality of data collection, management, and analyses.
6) Serve as final arbiters of whether individual subjects should be removed from a protocol.
7) To recommend continuation, discontinuation, modification, or termination of a study based on emerging data (in the study and literature) and evaluation of risk/benefit ratio.

### 9.2.2 PLANNED INTERIM ANALYSES

*not-applicable*
*Only as R61 is ending to confirm approval of the R33 phase as noted above:* fMRI Analyses for Go/No-Go Decision for phase II (R33): Analyses of target engagement will focus on activation in the right CN during reward anticipation, the rACC during reward outcomes, and bilateral amygdala in response to threat. The decision to proceed to the R33 phase will rest on reward-related activation metrics from functional CN and rACC regions of interest (ROIs) derived from our preliminary studies (from [37]). We will make these functional ROIs publically available through the UNC BRIC's website for use by other researchers. Amygdala activation during the threat task will be evaluated using an amygdala ROI defined from the Harvard-Oxford subcortical structural probabilistic atlas. Data will be preprocessed using FSL (Oxford University, UK) as described in our work.[76-78] We will ensure groups do not differ in head motion by calculating mean framewise displacement[79] which yields, for each participant, a value indicating mean head displacement from one volume to the next. Hypotheses will be evaluated with a ROI approach whereby signal intensities are extracted from ROIs for the relevant task contrasts (i.e., potential win

versus non-win trials during MID reward anticipation trials; wins versus non-wins during MID reward outcome trials; fearful and angry faces > shapes during the threat task). **Our go/no-go decision will be based solely on this ROI analysis**.*)*

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

### 10.1.1 INFORMED CONSENT PROCESS

#### 10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Update as of 7/2020, in preparation for returning to study visits during COVID-19 guidelines, consent is moving to REDCap econsent and will remain via econsent for the rest of the study. Approved study coordinators, graduate students, clinical assessor, or the PI will conduct the consent process using Econsent.

PET sub-study consent is a separate paper consent and remained paper during the entire time participants had the option to consent.

#### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved (Duke or UNC) and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form (econsent form after 7/2020) and ask questions prior to signing. The participants have the opportunity to discuss the study with their family or doctor and think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. A copy of the informed consent document will be given to the participants for their records. An electronic copy of the econsent was sent to them for their records when the study moved to REDCap econsent (except for the PET sub-study). Study team member completes the consent/econsent checklist (initially on paper but then electronically in REDCap with the econsent).

### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause as per the BATA DSMB. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or DSMB.

### 10.1.3 CONFIDENTIALITY AND PRIVACY

All data (self-report) and clinical assessment data (SCID-5 scoresheet only, THI, NART, C-SSRS, CGI-S/I), urine drug screen results, urine pregnancy screen results, PEERs & menstrual cycle, caffeine, alcohol & nicotine use will be in REDCap at UNC. REDCap requires an individual log in & password in order to be able to access the study data. Study permissions only allow those approved to be able to access the study data & make any changes.

Any study logs or other study information will kept on the CIDD server or the equivalent approved secure Duke server in the study specific folder. All neuroimaging data will be recorded in the database using numeric identifiers that are unrelated to any personal identifying information about the participant. Neuroimaging data are coded by subject number only on password-protected servers located at the BRIC. All sources of electronic data (i.e., computerized neuropsychological test data and symptom data) are saved on a double password-protected file on a PI's hard drive. All sources of nonelectronic research data will be coded by subject number and stored in a dedicated locked file cabinet. Materials identifying participants by name (e.g., prior signed consent forms and any PET consent form) will be stored in a separate locked file cabinet. The computer file matching participant names with code numbers will be saved in a double password-protected file in the PI's study folder on the secure drive. All data will be entered into the data set using the subject identification number only. Participants are not identified by name in any analysis of these data, or any presentation or publication resulting from the analysis of these data.

To protect confidentiality, only randomly assigned ID numbers, rather than names, will appear on clinically sensitive charts and digital data. The key linking the numeric identifier and participant's identity will be maintained on a separate drive that is double password protected and to which only the PIs and coordinator have access. Contact information will be recorded separately in double password protected files with restricted access as above. The code linking the names with the ID numbers will be securely protected with limited access. Medical records will be kept confidential with access granted only to those medical and research professionals directly involved with the study. If any scientific paper based on the data collected for this study is published, no information that could be linked to any single participant will be reported.

Confidentiality will be protected to the fullest extent permitted by law. All research personnel have completed HIPAA training for researchers and CITI training. All data from Duke will be entered either directly into REDCap (UNC) or from paper to REDCap. Duke/UNC personnel have access to the CIDD server as well and thus contact information to allow MRI scheduling can be directly entered into the log on the CIDD server by them. Video/audio recordings will be transferred from the Duke protected server

to the UNC CIDD protected server via the Duke approved method of file sharing (Box) or UNC approved file sharing program.

**MetricWire (UNC Only):**
MetricWire is a cloud-based data collection and analytics platform. The MetricWire platform provides userswith the ability to log, analyze, and visualize data collected from smartphones, tablets and the web. In this study, we are using the MetricWire mobile application for the optional sub-study. MetricWire provides Android and iOS mobile applications that will allow participants who consent, to submit responses to survey questions.
UNC will have a Site Administrator(s)-these users can add, change or remove other users only within their site based on their permission settings defined by their Account Administrator. A Researcher is a user that can only access site-specific features or data based on the permissions defined by the Site Administrator. MetricWire requires participants using the Mobile Applications to be individually identified and authenticated prior to being permitted access to the application on the backend (this is by the participant signing up with their email & their own password). Once they do that, MetricWire will assign them a unique study user ID. Once logged into the Mobile Applications, we have the ability to have participants be required to enter a PIN to access specific studies as required by the Protocol. A study can be configured to require the participant to re-enter their PIN following a predefined period of inactivity that way we can confirm the data is coming from the study participant and not someone else (like a friend picking up their phone).
*Encryption in Transit*-All passwords are suppressed during entry within the MetricWire Mobile App. Passwords are encrypted when transmitted across the network using Secure Hypertext Transfer Protocol or HTTPS. All the mobile apps use the TLS v1.2 protocol.
To validate response data sent to the server from a mobile device, MetricWire utilizes an “Encrypted Token Pattern”. After successfully logging into the MetricWire mobile app, a unique token is generated for the user using the Users Id, timestamp, a unique randomly generated number and a private key that is only available on the server. The token is returned to the mobile device and every subsequent request or response from the user includes this token as a HTTP Header. When the user submits a response, the server reads and decrypts
the token with the private key used to create it, to verify that the response is coming from the correct source (in this case the participant). This also ensures that the data being captured on the mobile device cannot be modified in-transit to the server. Additionally, the data is protected in-transit using HTTPS. This method is commonly used across websites to prevent attacks called “Cross-Site Request Forgery”(CSRF). *Please refer to the MetricWire Business Risk Assessment document for further details.*

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Research information by this Certificate cannot be disclosed to anyone else who is not connected with the research unless there is 1) a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings, 2) participant has consented to the disclosure, including for their medical treatment, 3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

### 10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data will remain on secure servers at UNC overseen by the CIDD ITS team directed by Tom Gray. Study personnel will only access the data on these servers and will not store copies of the data anywhere else. This includes our collaborator, former UNC BRIC faculty, Xiaopeng Zeng and his two students, who will have onyens sponsored by the study PI, and access the deidentified neuroimaging data stored on the UNC Longleaf computing cluster for any study analyses, under the supervision of the study PI and CIDD/IT.

Data at Duke will remain on Duke secure Psychiatry Dept server and is managed by Duke OASIS. And as noted, only video/audio files will be transmitted by Duke research team to UNC specific research team via Duke approved method of Box or UNC approved file sharing program.

NIMH Database of Clinical Trials (NDCT). Data from this study will be submitted to NDCT by the study team at UNC, as required by NIMH. 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. 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 UNC researchers will send deidentified information about subjects' health and behavior, to NDCT. Other researchers nationwide can then file an application with the NIMH to obtain access to subjects' 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 privacy. Subjects 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. Subjects will not be contacted directly about the data they contributed to NDCT. Subjects can decide that they do not want to share their information using NDCT. If so, they can tell Dr. Smoski/Dr. Dichter, and they will tell NDCT, which can stop sharing the research information. However, NDCT cannot take back information that was shared before a subject changes their mind. More information about NDCT is available on-line at *https://data-archive.nimh.nih.gov/ndct/*.

Following completion of the study, all previously collected biological samples (hormone & inflammatory marker blood sample) will be discarded following standard OSHA biohazard protocols.
During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

### 10.1.5 KEY ROLES AND STUDY GOVERNANCE

| **Principal Investigator - UNC** | **Prinicipal Investigator - Duke** |
|---|---|
| *Gabriel Dichter, PhD* | *Moria Smoski, PhD* |
| *UNC-Chapel Hill* | *Duke University Medical Center* |
| *919-445-0132* | *919-684-6717* |
| *dichter@med.unc.edu* | *Moria.smoski@duke.edu* |

### 10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Per NIH requirements for multi-site clinical trials, the trial will be monitored by an independent Data Safety Monitoring Board (DSMB). The DSMB for this study is the BATA DSMB. Note that the BATA study was initiated under the review of the North Carolina Translation and Clinical Sciences Institute (NC TraCS) DSMB and data collection began on 7/7/17. The NC TraCS DSMB subsequently declined further oversight of the study, stating that the relatively low risk and low complexity of the trial did not warrant DSMB oversight. Thus, the study moved forward with the BATA DSMB. They will meet biannually to review the aspects of the study. The study staff will prepare biannual reports for the DSMB on participant accrual, safety events, clinical outcomes, and adherence/drop outs. All Serious study related adverse events will be submitted to the DSMB safety officer within 4 weeks of the event, as will any concerns regarding confidentiality. Non-serious AEs will be included in the biannual reports.

The BATA DSMB is composed of members listed in the table below and are independent from the study team. In addition, their high level roles and responsibilities are identified in the table.

| **Name of Member** | **Role on DSMB** | **High Level Responsibilities** |
|---|---|---|
| **M. Zachary Rosenthal, PhD**<br>**Associate Professor**<br>**Vice Chair, Clinical**<br>**Director, Cognitive Behavioral Research & Treatment Program**<br>**Director, Clinical Psychology Fellowship Program**<br>**Director, Misophonia and Emotion Regulation Program**<br>**Department of Psychiatry and Behavioral Sciences, and**<br>**Department of Psychology and Neuroscience**<br>**Duke University**<br>*mark.rosenthal@duke.edu* | Chair of DSMB | *Clinical Psychology* |
| **R. Alison Adcock, MD, PhD**<br>**Associate Professor**<br>**Departments of Psychiatry and Behavioral Sciences; Neurobiology; and Psychology and Neuroscience**<br>**Core Faculty, Center for Cognitive Neuroscience**<br>**Duke University**<br>*alison.adcock@duke.edu* | Voting Member | *Psychiatry and Neuroscience* |
| **Eric Youngstrom, PhD**<br>Professor<br>Department of Psychology and Neuroscience<br>Department of Psychiatry<br>University of North Carolina at Chapel Hill<br>**eay@unc.edu** | Voting Member | *Biostatistics and Research Methods* |

Both Voting members and Advisory members for this DSMB may attend closed sessions for this Committee. In addition, both Voting members and Advisory members will have access to monitoring data for this Committee. All reports, materials, discussions and proceedings of the DSMB are completely

confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.
It is expected that all DSMB members who are identified in the table just above will attend every meeting. However, it is recognized that this may not always be possible. Therefore, the DSMB for ***BATA Study*** has established the following quorum for voting: A quorum of this DSMB is considered to be **2** voting members. Quorum must be reached in order for an item to be voted on. At least **2** votes in favor are always needed for a decision to be final. The current BATA DSMB charter is uploaded for reference and the letter post the initial BATA DSMB meeting of 11/8/17 is also included to the IRB.
The goals of this DSMB are:
1) To review and report adverse events
2) To monitor the level of risk posed by the study and insure that risks are minimized.
3) To review modifications to risk management protocols.
4) Review progress toward meeting enrollment goals.
5) To review procedures for maintaining the confidentiality of data, and quality of data collection, management, and analyses.
6) Serve as final arbiters of whether individual subjects should be removed from a protocol.
7) To recommend continuation, discontinuation, modification, or termination of a study based on emerging data (in the study and literature) and evaluation of risk/benefit ratio.
The options available for the outcome of the review are:

- Recommend continuation with no modification,
- Recommend continuation with no modification(s) to the protocol but with other recommendations (e.g.,modify informed consent form, seek additional expert review),
- Recommend continuation with modification(s) to protocol,
- Recommend suspension of enrollment pending additional information,
- Recommend suspension of all study activities pending additional information,
- Recommend termination of study because of undue safety risks to subjects,
- Recommend termination of study or part of the study because of results of formal interim analyses.

### 10.1.7 CLINICAL MONITORING

The study monitors will be Drs. Smoski & Dichter. They will ensure the quality of the study and establish that the study staff is complying with the investigational plan and IRB regulations. Throughout the investigation, the monitors will ensure that the facilities being used continue to be acceptable for the purposes of the study, that the investigational plan is being followed, that any changes to the protocol have received IRB approval and have been reported to the sponsor, and that accurate, complete, and timely reports are made to the IRB. They will confirm that inclusion and exclusion criteria have been met for each subject enrolled, and compliance with all other aspects of the investigational plan are met. They will safeguard against and regularly monitor for unanticipated problems by ensuring appropriate oversight of all study and treatment procedures. A weekly joint UNC/Duke study team meeting will be conducted to discuss research procedures.

### 10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

*Quality assurance. The Duke and UNC study teams will meet weekly to review any research issues that may have arisen during the past week as well as to monitor progress on subject recruitment and other research-related matters. Additional meetings are conducted on an as-needed basis.*

*Each* site (Duke and UNC) will perform internal quality management of study conduct, data and biological specimen collection (if applicable), documentation and completion.
*Each site will have MOPs for quality management that describe:*

- *How data and biological specimens (when applicable) will be evaluated for compliance with the protocol, ethical standards, regulatory compliance, and accuracy in relation to source documents.*
- *The documents to be reviewed (e.g., CRFs, clinic notes, product accountability records, specimen tracking logs, questionnaires, audio or video recordings), who is responsible, and the frequency for reviews.*
- *Who will be responsible for addressing QA issues (e.g., correcting procedures that are not in compliance with protocol) and QC issues (e.g., correcting errors in data entry).*
- *Staff training methods and how such training will be tracked.*

Both sites will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor (NIMH), and inspection by local and regulatory authorities (Duke and/or UNC IRB).

### 10.1.9 DATA HANDLING AND RECORD KEEPING

#### 10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the study staff at the site under the supervision of the site investigator. The investigators at Duke and at UNC are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents are completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in UNC REDCap derived from source documents should be consistent with the data recorded on the source documents.

Research data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) are entered into UNC REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Therapist notes for therapy sessions will be entered directly into REDCap along with their clinical rating and decision about participant homework completion.

#### 10.1.9.2 STUDY RECORDS RETENTION

Study documents and research data with identifying links will be destroyed 7 years after the conclusion of data collection for the study.

### 10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Protocol violations that could represent serious or continuing noncompliance will be brought to the attention of the PI as soon as possible and not longer than 24 hrs. These violations will be reported to

the Duke University Medical Center Institutional Review Board using the appropriate documentation within 5 days of notification of the PIs. If these events are determined to be serious or continuing noncompliance by the Duke IRB, they will then be reported to the overall sponsor, NIMH, within 10 business days and entered on the study log. They will be reported to the DSMB < 4 weeks.

Protocol deviations around study visit windows, skipped questions on self-report measures, missed therapy sessions, etc. will not be reported to the Duke IRB. Other protocol deviations will be reported to the PIs upon discovery and will then be reported to the Duke IRB within 2 weeks. These deviations will in turn be reported to NIMH annually within the study progress report and reported to the DSMB per the DSMB designated meeting schedule. ***COVID-19 Update:**Please note that the conduct of the computer tasks with CSSRS at the in-person assessment visit, wks 4, 8, 12 and final visit and the urine drug screen are contingent upon the building availability and approval of in-person visits either at Duke or UNC. If not available and approved, the computer tasks with CSSRS and urine drug screen will be omitted until the study team have the appropriate approvals to do the tasks at an in-person visit. If omitted (skipping the in-person visit), it will not be considered a protocol deviation since the omissions are necessary to be able to open the study and begin to collect the main primary outcomes of imaging and therapy.***

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