PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL

PRINCIPAL/OVERALL INVESTIGATOR
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PROTOCOL TITLE
Examining Reward-Related Predictors and Mechanisms of Change in BA Treatment for Anhedonic Adolescents

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I. BACKGROUND AND SIGNIFICANCE
By 18 years of age, approximately 15% of adolescents will have experienced at least one major depressive episode (Avenevoli et al., 2015). Further, 66% of these individuals will experience a relapse within 5 years (Kovacs et al., 1994) and 84% will experience a recurrent episode during adulthood (Harrington et al., 1996). More recent studies have identified anhedonia and related reward circuitry dysfunctions as being critically involved in the development and maintenance of depressive symptoms in adolescents (Forbes and Dahl, 2012). Given converging evidence of functional abnormalities in reward circuitry playing a central role in the pathophysiology of anhedonic symptoms in adolescents, treatments that directly target reward-related deficits may prove particularly effective at alleviating these core depressive symptoms (Dichter et al., 2009). Moreover, anhedonia is an especially important treatment target given that amelioration of the latter symptom is a robust predictor of improvement in other depressive symptoms (Bringmann et al., 2015).

II. SPECIFIC AIMS
(1) **Specific Aim 1:** Examine baseline neural and behavioral differences in 35 treatment-seeking anhedonic adolescents and 35 healthy control adolescents. Specifically, participants will complete *neural* (fMRI reward task), *behavioral* (Probablistic Reward Task; PRT) and *self-report* (Ecological Momentary Assessment; EMA) measures of anhedonia and reward system function. Relative to the healthy control group, the anhedonic adolescents will exhibit aberrant reward function on each of these measures, as evidenced by:

(a) Blunted striatal and hyper-active medial prefrontal cortex (mPFC) response to reward-related stimuli during the fMRI reward task;

(b) Blunted response bias on the PRT;

(c) Blunted daily positive affect and increased anhedonia as assessed via EMA.

(2) **Specific Aim 2:** Examine neural and behavioral predictors and mechanisms of symptom improvement in Behavioral Activation (BA) for anhedonic adolescents: Anhedonic adolescents will undergo a 12-week protocol of BA treatment. Neural (fMRI) and behavioral (PRT) measures will be assessed at pre- and post-treatment, and the EMA protocol will involve repeated assessment waves. We hypothesize that:

(a) Pre-treatment reward dysfunction (i.e., assessed via baseline fMRI, PRT and EMA), controlling for overall pre-treatment levels of depressive symptoms, will predict anhedonic (Snaith–Hamilton Pleasure Scale [SHAPS; Snaith et al., 1995]) symptom improvement over the course of BA.

(b) Greater pre- to post-treatment normalization in neural (i.e., striatal and mPFC response to fMRI task) and behavioral (i.e., PRT performance) measures will be linked to greater anhedonic symptom improvement over the course of treatment**.**

(c) Given emerging evidence of decreased cortico-striatal functional connectivity to reward-related stimuli in depression (Admon et al., 2015), we expect that BA will result in significant increases in cortico-striatal functional connectivity to rewarding stimuli from pre- to post-treatment.

(3) **Specific Aim 3:** Examine association between changes in neural reward circuitry and real-world positive affect and anhedonia: The EMA protocol will be implemented to acquire a more fine-grained and "real-world" assessment of changes in subjective positive affect (PA) and anhedonia, as well as the acquisition and use of BA skills, over the course of treatment. We hypothesize that:

(a) Following BA, participants will report improvements in daily PA and anhedonia and increased use of BA skills.

(b) Integrating across units of analyses (i.e., neural, behavioral and self-report), we expect that greater pre- to post-treatment normalization of striatal and mPFC response, cortico-striatal connectivity, as well as PRT performance will be associated with greater improvements in daily reports of PA and reduced anhedonia, as well as use of BA skills.

III. SUBJECT SELECTION

This study will include two adolescent cohorts, and a parent for each adolescent participant. Rather than recruiting adolescents on the basis of DSM-defined Major Depressive Disorder (MDD), and in line with the NIMH RDoC initiative, the proposed study will recruit treatment-seeking adolescents with elevated anhedonia (as defined by the SHAPS) into a brief clinical trial of BA, as well as a healthy control group for comparison. Specifically, the two adolescent cohorts will consist of: (A) **Anhedonic Adolescents**: Adolescents who report SHAPS scores ≥ 3; (B) **Healthy Controls**: Adolescents with no lifetime history of psychopathology and with SHAPS scores = 0. Finally, we also propose to include (C) one parent of each participating adolescent to complete questionnaires assessing their child's, as well as their own, mental health. All participants will complete an initial assessment at McLean Hospital. Within the subsequent week, participants meeting study criteria will be invited back to the lab to collect fMRI data probing reward circuitry function. They will also complete a behavioral task (PRT) assessing reward responsiveness outside the scanner. Anhedonic adolescents completing BA treatment will also fill out self-report measures at the start of each therapy session (see **Table 1**). Following treatment, participants will complete a post-treatment assessment within 10 days of the last session, which will be identical to the pre-treatment session. Although not receiving BA, the healthy control participants will complete corresponding pre-treatment (i.e., initial) and post-treatment (i.e., final) assessments,

which will allow for modeling the effects of repeated scans and practice effects (e.g., on the PRT). In addition, a smartphone-based EMA protocol will be implemented for both the anhedonic sample and healthy control sample involving repeated assessments of positive affect (PA) and anhedonia. The EMA protocol will use a smartphone app (*Beiwe*) already approved by both the Partners IRB (protocols 2015P001303; 2012P000890; 2015P000666) and Partners Research Information Security Office (RISO; see attached *RISO Approval for Beiwe EMA Application*). The latter app will be used for Android phones. For participants with iPhones, EMA data will be collected using the *Metricwire* app previously approved by RISO (see attached *RISO Approval for Metricwire EMA Application*) and the IRB (protocol 2015P001303). The schema outlining the assessment procedure is presented in **Table 1**.

Adolescent Cohort

General Inclusion Criteria:

- Both genders, any ethnicity
- Ages 13-18
- English as first language or English fluency
- Smartphone with iOS or Android platform (for EMA)
- *Healthy Control Sample:* Total SHAPS score = 0; *Anhedonic Sample:* Total SHAPS score $\geq$ 3. The anhedonic sample must also meet criteria for elevated anhedonia on the K-SADS clinical interview (i.e., anhedonia item score > 1).

*General Exclusion Criteria***:**

- History of head trauma with loss of consciousness for two minutes or more
- History of seizure disorder
- Serious or unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic or hematologic disease
- Current use of cocaine or stimulant (e.g., amphetamine, cocaine, methamphetamine)
- Current use of dopaminergic drugs (including methylphenidate)
- Clinical or laboratory evidence of hypothyroidism
- Systemic medical or neurological illness that could impact fMRI measures of cerebral blood flow
- Color blindness
- Meet standard exclusion criteria for fMRI scanning (e.g. claustrophobia, cardiac pacemakers, neural pacemakers, surgically implanted metal devices, cochlear implants, metal braces, or other metal objects in their body);
- Positive urine pregnancy test
- Meets criteria for anorexia nervosa (DSM-5 diagnostic code: 307.1) or bulimia nervosa (DSM-5 diagnostic code: 307.51)

A. Anhedonic Adolescents: Anticipated enrollment = 65

Additional Exclusion Criteria:

- Subjects with suicidal ideation where outpatient BA treatment is determined unsafe or inappropriate by the study clinician. These patients will be immediately referred to appropriate clinical treatment.
- History or current diagnosis of any of the following DSM-5 psychiatric illnesses: schizophrenia spectrum or other psychotic disorder, bipolar disorder, OCD, substance (including alcohol) use disorder within the past 12 months or lifetime severe substance use disorder (i.e., meeting former DSM-IV criteria for past substance dependence). Simple phobia, social anxiety disorder, panic disorder, generalized anxiety disorder, and PTSD will be allowed (unless study clinician determines PTSD is primary diagnosis and requires treatment prior to depression/anhedonia treatment).
- Meet criteria for chronic depression (current episode > 2 years)
- Currently receiving psychotropic treatment or psychotherapy
- Current use of psychotropic medication with the exception of SSRIs (See section on Concomitant Medications (see p. 4))

B. Healthy Control Adolescents: Anticipated enrollment = 65 (age-matched to serve as healthy controls).

Additional Exclusion Criteria:

- Elevated depressive symptoms as assessed in phone screen
- History of meeting criteria for any DSM-5 psychiatric or substance-related disorder
- Current use of any psychiatric medications
- First degree relative diagnosed with MDD, Bipolar Disorder or Psychotic Disorder

<u>Adult Cohort</u>
C. Parent**:** Anticipated enrollment = 70
Inclusion Criteria:

- English as first language or English fluency

Concomitant Medications:

Anhedonic adolescents being treating with any SSRI (e.g., fluoxetine (Prozac), fluvoxamine (Luvox), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), and escitalopram (Lexapro)) may participate in the active treatment as long as they have not made a change in medication for at least 4 weeks prior to enrollment. Those who are being treated with any other psychiatric medications will be excluded. In order to limit attrition and to mirror real world clinical practice, participants will be permitted to make

changes in the dose of their SSRI during the course of the treatment. If a participant's clinical status worsens to the degree that a new medication is necessary, the participant will have the opportunity to complete the BA course and scheduled assessments. Analyses will be conducted to determine if there are statistical differences in symptom, behavioral, and/or neural measurements between participants on SSRIs versus participants on SSRIs plus other psychiatric medications.

Of note, participants' outpatient psychiatrists will prescribe all medications and study personnel will play no role in medication decision-making. Moreover, participants will not go through any medication washout as part of this study. Participants who are interested in coming off a medication to enter the study will be instructed to discuss this with their outpatient psychiatrist. Each participant's current medication and dosage will be tracked via communication with the participant's parents, unless the participant is an adult (18 years old) in which case we will communicate with them directly. This practice is consistent with protocol 2012P001844, a study which also focuses on psychotherapy for depressed adolescents.

Recruitment

Subjects will be recruited through the following methods:

- *Fliers.* Fliers will be hung on the McLean campus as well as throughout the greater Boston area (i.e., within a 25-mile radius of the hospital).
- *Internet advertisements.* Advertisements will be posted on websites (e.g., Craigslist, Facebook, Nextdoor, Rally)
- *Direct mail.*
    - Through a Partners-approved vendor, we will mail postcards advertising our study to families with adolescents between 13 and 18 years of age. The ad will include IRB-approved language adapted from approved study fliers. Furthermore, our lab will not receive any demographic information about the families who will receive the advertisements, as all of the mailing will be done through the approved vendor. Additionally, the ads will include the following note: "Note: You are receiving this postcard as part of a commercial mailing list of families with adolescents between 13-18 in the greater Boston area."
    - Sending a letter to "RODY Yes" patients within Research Patient Data Registry (RPDR)
- *Schools.* When invited by school administrators, the PI will make presentations in schools to school administrators, teachers, and parents. Additionally, the study staff will provide study flyers to schools that wish to hang them in guidance counselor offices. These presentations and flyers will be available to schools within a 25-mile radius of McLean.

Importantly, all study advertisements will either be directed at parents or will specify that parent permission is required. If an adolescent initiates contact with study staff, Dr. Webb/research assistant (RA) will ask to speak with a parent or ask that the parent calls

back to obtain verbal consent before the study is explained or the phone screen conducted. Participants responding to ads may either complete an online interest form on REDCap, a Partners secure website, or contact Dr.Webb/research assistant directly. If a participant contacts us via email with PHI (e.g., parent reporting that their child is diagnosed with – or may suffer from – a mental disorder and is seeking treatment), they will have to acknowledge that they understand the risks associated with receiving unencrypted emails which will be conveyed through the following language "The Partners standard is to send email securely. This requires you to initially set up and activate an account with a password. You can then use the password to access secure emails sent to you from Partners HealthCare. If you prefer, we can send you "unencrypted" email that is not secure and could result in the unauthorized use or disclosure of your information. If you want to receive communications by unencrypted email despite these risks, Partners HealthCare will not be held responsible. Your preference to receive unencrypted email will apply to emails sent from this research group/study only." This same statement is also included in study consent forms. Alternatively, participants can choose to speak with Dr.Webb/RA over the phone where they can agree verbally to receive unencrypted emails. A log will be kept to document the agreements. For short email correspondances that lack medical information or diagnoses (e.g., sending confirmatory information for appointment or date/time of scheduled phone call), formal IRB approval is not needed (https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/FAQs-Email-Communication-with-Research-Participans-and-Potential-Research-Participants.pdf). Dr. Webb/RA will provide details about the study, and if the parent and child are interested, they will complete a telephone screen.

IV. SUBJECT ENROLLMENT

Phone screening

Telephone screens will be conducted by Dr. Webb or an RA trained by Dr. Webb in assessing depression and suicidality. The telephone screens will be conducted according to a script, which is included in this submission.

The RA/Dr. Webb will first speak to a parent to ask about their adolescent's health history and MRI safety. If the child is eligible for MRI procedures and their health history meets the inclusion/exclusion criteria for the adolescent cohorts, the RA/Dr. Webb will conduct a phone screen with the adolescent while the parent is present in the home. The adolescent telephone screen will assess current depressive (including anhedonic) symptoms. At the end of the adolescent portion of the screen, the RA/Dr. Webb will again speak to the parent. If the adolescent indicated an intention to harm him/herself or others, the RA/Dr. Webb will inform the parent and encourage the parent to seek immediate help. If the phone screen is being conducted by an RA, they will then request a phone number at which the parent can be contacted, and the RA will immediately contact Dr. Webb, who will take appropriate steps to contact the parent and intervene as per his clinical discretion. Eligible adolescents, and one of their parents, will be invited to McLean for initial lab-based assessments.

Consent and Assent Procedures
At the onset of the initial assessment, eligible participants, both adolescents and parents, will complete appropriate assent and consent forms, respectively. When all questions and concerns from adolescents and parents have been addressed, adolescents and adults will be asked to sign the assent and consent forms, respectively. Adolescents who turn 18 during the course of the study will be asked to sign a consent form on the first visit after their 18th birthday in order to continue to participate.

Due to revised COVID-19 procedures, participants may elect to complete their screening session remotely. With the participant's verbal consent, the research assistant will email a copy of the Consent/assent form(s) prior to the remote session. The research assistant and participant will discuss all study procedures via telephone or a Partners-issued Zoom account (http://pcm.partners.org/services/movi.aspx). The participant will be reminded they can withdraw at any time. REDCap eConsent will be used to obtain signatures and a signed copy will be distributed to the participant electronically according to ERIS guidance (https://confluence.partners.org/display/shareit/27233366/HOX07266265b398484fada0c1b491a15c5aYOP)

V. STUDY PROCEDURES

A. Parent Initial Assessment – Day 1 (Approximately 1 hour)

Semi-Structured Clinical Interview
(1) Miniature International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) The MINI is a structured interview assessing for Axis I psychopathology symptoms (e.g., mood, anxiety, substance abuse, psychosis). Each MINI diagnostic module consists of a series of screening items followed by questions about specific symptomatology.

Self-Report Measures
(1) Beck Depression Inventory-II (BDI-II; Beck et al., 1996). The BDI-II is a 21-question self-report inventory for measuring the severity of depression.
(2) Snaith-Hamilton Pleasure Scale (SHAPS, Snaith et al., 1995). This 14-item self-report questionnaire asks participants to rate their ability to experience pleasure when doing various activities. This instrument assesses hedonic capacity.
(3) Temporal Enjoyment of Pleasure Scale (TEPS; Gard et al., 2006). The TEPS is an 18-item self-report measure assessing anticipatory and consummatory aspects of pleasure
(4) Positive and Negative Affect Schedule – Trait Version (PANAS; Watson et al., 1988). The PANAS is a 20-item self-report measure that assesses positive and negative affect symptoms.
(5) Perceived Stress Scale (PSS; Cohen et al., 1983). The PSS is a 10-item self-report questionnaire assessing the extent to which the participant perceives stress in his/her life.
(6) Contact Information & Demographic Forms (Relating to Parent & Child)

Parent-Report of Adolescent Mood and Symptoms

(7) Mood and Feelings Questionnaire – Parent Report (MFQ-PR, Angold & Costello, 1987). The MFQ-PR is the parent analogue of the MFQ, completed by adolescent participants. It is a parent report of the child's depressive symptoms.
(8) Multidimensional Anxiety Scale for Children – Parent Report (MASC-PR; March, 1997). The MASC-PR is a 39-question parent-report inventory to assess their child's anxiety symptoms.
(9) Adolescent Medical History and Physical Health Form

B. Adolescent Initial Assessment – Day 1 (Approximately 2 hours)

Semi-Structured Clinical Interview
(1) Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1996). The K-SADS is a semi-structured diagnostic interview to assess current and past episodes of psychopathology in children and adolescents. The interviewer will record the interview using an audiotape for data coding purposes.
(2) Children's Depression Rating Scale –Revised (CDRS-R; Poznanski & Mokros, 1996). The CDRS-R is a 17-item clinical interview tool designed to assess depression severity in children and adolescents.
(3) Columbia Suicide Severity Rating Scale – Children's Lifetime/Recent Version (C-SSRS-L/R; Posner et al., 2010). The C-SSRS-L/R assesses lifetime prevalence of suicidal ideation and suicidal behavior.

Self-Report Measures
(4) Tanner Staging Questionnaire (TSQ; Tanner & Davies, 1985). The TSQ is a 5-item self-report measure of pubertal development.
(5) Center for Epidemiological Studies Depression Scale (CES-D; Radloff 1977). The CES-D is a 20-item self-report scale that measures severity of depression.
(6) Mood and Feelings Questionnaire (MFQ; Angold & Costello, 1987). The MFQ is a 30-item self-report measure assessing depressive symptoms in children.
(7) Multidimensional Anxiety Scale for Children (MASC; March, 1997). The MASC is a 39-question self-report inventory to assess anxiety symptoms.
(8) Positive and Negative Affect Schedule – Trait Version (PANAS; Watson et al., 1988). The PANAS is a 20-item self-report measure that assesses positive and negative affect symptoms.
(9) Snaith-Hamilton Pleasure Scale (SHAPS, Snaith et al., 1995) This 14-item self-report questionnaire asks participants to rate their ability to experience pleasure when doing various activities. This instrument assesses hedonic capacity.
(10) Temporal Enjoyment of Pleasure Scale (TEPS; Gard et al., 2006). The TEPS is an 18-item self-report measure assessing anticipatory and consummatory aspects of pleasure
(11) NEO Five-Factor Inventory-3 (FFI-3; Costa & McCrae, 2010) The questionnaire assesses the "big five" personality traits. For this study, only the neuroticism and extraversion questions (24 items) will be asked.
(12) Cognitive Triad Inventory for Children (CTI-C; Kaslow et al., 1992). The CTI-C is a 36-item scale to assess the child's negative views of self, world, and future.

(13) Children's Depressive Experiences Questionnaire (CDEQ; Abela & Taylor, 2003). The CDEQ is a 20-item measure to assess dependency and self-criticism. Participants respond with the statements "not true," "sort of true," or "really true" to statements about themselves.
(14) Children's Response Styles Questionnaire (CRSQ; Abela et al., 2002). The CRSQ is a 25-item questionnaire, which asks participants to answer questions about how they would respond to depressive symptoms (i.e., using ruminative, distraction, or problem-solving strategies).
(15) Adolescent Cognitive Style Questionnaire (ACSQ; Hankin & Abramson, 2002). The ACSQ assesses cognitive vulnerability to depression using adolescent-specific hypothetical situations. The participant rates the extent to which the causes of each of these situations are internal, stable, global, due to flaws in the self, and likely to result in negative consequences.
(16) Perceived Stress Scale (PSS; Cohen et al., 1983). The PSS is a 10-item self-report questionnaire assessing the extent to which the participant perceives stress in his/her life.
(17) Adolescent Life Event Questionnaire – Revised (ALEQ-R; Hankin & Abramson, 2002). The ALEQ-R is a 57-item self-report questionnaire that asks participants about negative life events that have occurred in the previous week.
(18) Perceived Criticism Scale (PCS; Renshaw, 2008). The PCS consists of 4 items assessing perceived criticism from a parent.

Mock fMRI Scan
(18) Mock Scan Procedure. Each child will receive a "mock scan" that simulates the conditions of the actual scanner at the McLean Brain Imaging Center. In particular, adolescents will experience the sounds (i.e., repetitive metallic thumping), feel (i.e., enclosed within the scanner head coil), and sights (i.e., will see what fMRI equipment looks like). During the process, participants will be trained to limit movement. In the event that the mock scanner is out of commission, participants will be prepped in detail with a description of the sounds (i.e., repetitive metallic thumping), feel (i.e., enclosed within the scanner head coil), and sights (i.e., will see what fMRI equipment looks like) of the MRI. In addition to habituating to the scan environment, participants will also have an opportunity to ask questions about the process. Any and all questions will be addressed openly and honestly. Finally, in preparation for the MRI session, participants will complete a practice run of the fMRI tasks (see below).

C. Adolescent MRI Session – Day 2 (Approximately 2 hours)
Adolescent participants satisfying applicable inclusion and exclusion criteria (see above) will be invited to return to the McLean Brain Imaging Center. Entry into the scanner environment is contingent upon successful completion of an MRI safety form and a negative urine pregnancy screen for females. In addition, given the abovementioned substance use exclusion criteria, urine screens will be conducted for both male and female participants to test for current drug use. All imaging will be performed on the McLean Hospital Brain Imaging Center Siemens 3-Tesla (3T) Prisma scanner with a TIM upgrade. A 32-channel head coil will be used in order to improve the ratio of signal to noise. The entire imaging procedures are expected to last approximately 60-90 minutes.

Self-Report Measures and Behavioral Task Prior to the Scanner

Self-Report (see pg. 6-7 for descriptions for 1-4):
(1) CES-D
(2) MFQ
(3) SHAPS
(4) PANAS-State Version
(5) EMA PANAS Forecasting

Behavioral Task
Probabilistic Reward Task (PRT; Pizzagalli et al., 2005). The PRT is a behavioral reinforcement computer-based task examining reward learning in relation to depressive, particularly anhedonic, symptoms. Specifically, participants are instructed that the aim of the task is to earn as much money as possible. The task consists of 200 trials, divided into 2 blocks of 100 trials, with blocks separated by a 30-sec break. Each trial will start with the presentation of an asterisk for 500 msec in the middle of the screen that serves as a fixation point (see below). After 500 msec, a mouthless cartoon face will be presented in the center of the screen. After a delay of 500 msec, either a short mouth (11.5 mm) or a long mouth (13 mm) will be presented for 100 msec. The face without the mouth will remain on the screen until a key response is made. Participants are asked to identify which type of mouth was presented by pressing either the "z" key or the "/" key on the keyboard (counterbalanced across subjects). For each block, the long and short mouths will presented equally often in a pseudorandomized sequence, with the constraint that no more than three instances of the same stimulus will be presented consecutively. Participants will earn $15.80-$16.20.

Structural MR Imaging
All subjects will undergo an anatomic MRI protocol, which is a standard set of structural MRI images acquired in the axial and coronal planes. This initial MRI screening/data collection will be conducted using the 3 Tesla whole-body clinical MR scanner. Structural data will be utilized in three ways; to ensure specific regions of interest are visible and localized for correlation with MR data, to ensure subjects are free of significant clinical abnormalities, and for potential morphometric analyses. All structural scans will be read and interpreted by a clinical neuroradiologist; in the event that a clinical abnormality is detected, the subject will be contacted and their primary care physician will be notified. Structural scanning takes approximately 10 minutes.

Resting State Data Collection
A brief 6-minute resting state (no task) fMRI scan will be completed by all subjects. This short scanning sequence will be used to assess brain connectivity patterns in the default-mode network linked to depressive/anhedonic symptoms. fMRI images will be acquired using an EPI BOLD sequence with the following parameters: TR=2500 ms, TE=30 ms, FOV=224 mm, flip angle=82 degrees, matrix=64x64x40, slice thickness=3.5mm with 3.5 mm3 isotropic voxels.

fMRI Reward Task
(1) We will use an fMRI card-guessing paradigm commonly employed in depressed and healthy adolescents to probe striatal and mPFC activation (e.g., Forbes et al., 2009; Olino et al., 2011). Each trial includes both an anticipation period and an outcome period, and participants receive win, loss, or no-change feedback for each trial. Participants are told that their performance determines a monetary reward to be received after the scan. Trials are presented in pseudorandom order with predetermined outcomes. During each 27-sec trial, participants have 3 seconds to guess, via buttonpress, whether the value of a visually presented card with a possible value of 1–9 is higher or lower than 5. After a choice is made, the trial type (reward or loss) is presented visually for 12 seconds (*anticipation*). This is followed by the "actual" numerical value of the card (500 ms), outcome feedback (a green upward-facing arrow for win, a red downward-facing arrow for loss, or a yellow circle for neutral feedback; 500 ms), and a crosshair presented for 11 seconds (*outcome*). There are no trials involving anticipation of a neutral outcome. That is, neutral feedback trials are those with no-win or no-loss outcomes (i.e., no monetary increase or decrease). Trials are presented in four runs, with 12 trials per run and a balanced number of trial types within runs (i.e., 6 possible-win and 6 possible-loss trials, with a total of three win, three loss, and three neutral outcomes). Participants are told that they will receive $1 for each win, lose 50 cents for each loss, and experience no change in earnings for neutral outcomes. Participants are unaware of the fixed outcome probabilities and are led to believe that their performance will determine net monetary gain. All participants will be compensated $15 for playing "the money game." The task takes 23 minutes.

(2) *Self-Referent Encoding Task (SRET; Gotlib et al., 2004)*. The SRET is an information processing task that has participants encode and recall adjectives while fMRI data is being obtained. We will use 22 depressotypic, 22 socially threatening, and 22 physically threatening words. To balance the number of negative and positive words, we used 50 positive words. Examples of the words include "loving" for the positive category, "sad" for the sad emotion category, "teased" for the social threat category, and "choking" for the physical threat category. All words will be presented on a computer monitor, and at the conclusion of the task, subjects will be asked to recall adjectives presented on the screen. The task takes approximately 10 minutes.

Following the fMRI session we will re-administer the PANAS-State Version.

Sustained Attention to Response Task (SART; Van Schie et al., 2012). In the sustained attention to response task (SART; Van Schie et al., 2012), participants are instructed to press the spacebar as fast and accurately possible when frequent non-targets (numbers 0-2; 4-9) are presented on a computer screen, and to withhold response to an infrequent target (number '3'). Performance is assessed with RT and errors. A total of 72 targets (on 1040 trials) are randomly presented within four blocks of 5 mins each. In addition, 4 probe questions appear (after each block) to inquire about mind-wandering: Participants indicate if just prior to the probe, they were a) on-task, b) off-task because of an external distraction (e.g., noise), or c) had a task-unrelated thought. The frequency (%) of each category is calculated.

This SART task will allow us to collect important preliminary data on the relationship between sustained attention and depressive symptoms (including anhedonia). In addition, the K23 study includes EMA measures of rumination and mind-wandering. We wish to test the relation between ecologically valid (EMA) measures of rumination/mind-wandering (both linked to depression) and sustained attention on a computerized performance task.

D. Parent Behavioral Task and Self-Report (Approximately 1 hour)

While the child is completing their questionnaire and the behavioral task (PRT). The Parent will complete the BDI-II, SHAPS, PANAS and MFQ-PR. In addition, they will complete the PRT.

E. Behavioral Activation (BA) Treatment with Anhedonic Adolescents:

Paralleling a previously approved protocol (2012P001844), anhedonic adolescents will receive 12, 50-minute BA sessions. The study will be embedded within a 12-week protocol of BA, implemented following two treatment manuals (Martell et al., 2013; McCauley et al., 2015) co-authored by Dr. Sona Dimidjian, Ph.D. (consultant). The manuals provide detailed instructions regarding how to administer specific BA procedures and techniques, while providing sufficient flexibility for therapists to adapt treatment to the idiosyncratic needs of patients. As some 18-year-old participants may no longer live at home, 18-year-old (adult) participants who do not live with their parents can do therapy on their own without parent involvement.

During the course of treatment, adolescents will complete self-report measures prior to selected therapy sessions (see **Table 1** for schedule of MFQ, CES-D, SHAPS MASC, WAI-S-C, PSS assessments). Additionally, prior to selected sessions, the study clinicians will complete measures of depression severity (CDRS-R) and the therapeutic alliance (WAI-S-T). Similar to the abovementioned approved protocol (2012P001844), all sessions will be videotaped to assess therapist adherence to the BA treatment manual as well as competence. All participants will consent to videotaping before beginning the study and will be free to leave the study at any time if they are uncomfortable being filmed (see attached consent forms). If a participant does not attend a scheduled session, the study clinician will contact the participant's parent (if the participant is a minor) or the participant directly (if they are 18). If the study clinician leaves a message and the parent or participant does not respond within 24 hours, a second attempt will be made. All attempts to contact parents and subjects about missed sessions will be documented. If the schedule permits, the therapist will attempt to reschedule the session.

BA sessions will be conducted by Dr. Christian Webb (Ph.D. in clinical psychology), or clinical psychology Ph.D. students from McLean Hospital's psychology internship program. The internship program is co-directed by Dr. Throstur Björgvinsson, Ph.D., ABPP (consultant), who will provide weekly supervision on treatment implementation and supervision of study therapists, supplemented with monthly phone meetings with Dr. Dimidjian. Importantly, the internship is based in the Behavioral Health Partial Program

(BHPP) at McLean Hospital (Director: Dr. Björgvinsson), and rooted in CBT and BA delivered in group and individual therapy formats. Before administering treatment, clinicians will complete a 20-hour training and will receive weekly supervision from Dr. Webb. Dr. Webb currently serves as a study therapist and group supervisor for the abovementioned approved clinical trial of treatment study for depressed adolescents (2012P001844). As in the latter trial, clinical psychology Ph.D. students completing clinical practica in the BHPP may also serve as study therapists.

All study staff assessing depression and suicidality will be trained by Dr. Webb. Dr. Webb has received extensive training in conducting interviews using the K-SADS, CDRS MINI, and CSSRS. During the last 9 years, Dr. Webb has utilized all assessment tools in completing large-scale studies. Further, Dr. Webb has provided extensive training and supervision for study staff/diagnosticians conducting these interviews. Dr. Webb will provide 40 hours of didactic and practical training for all study staff that will conduct interviews. Included in this instruction is the assessment of both depressive symptoms and suicidality. Particular attention will be paid to delineating the differences between passive suicidal ideation and intent to self-harm. Additionally, all diagnostic interviews will be audiotaped (in contrast to therapy sessions, which will be videotaped) and reviewed in order to ensure reliability of diagnoses and assessment.

Self-Report Process Measures (completed by adolescents at selected therapy sessions):

(1) Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000). The CEQ is a 6-item self-report measure assessing subjects' perception of the credibility of treatment and their expectations of symptom improvement. Participants will complete this measure only at the start of session 1.

(2) Working Alliance Inventory – Short Client Version (WAI-S-C; Horvath & Greenberg, 1986). The WAI-S-C is a 12-item self-report measure assessing subjects' perception of the quality of the therapeutic alliance between themselves and their (individual or group) therapist.

(3) Five Facet Mindfulness Questionniare – Short Form (FFMQ-SF; Bohlmeijer et al., 2011). The FFMQ is a measure is an abbreviated 24-item measure assessing mindful awareness of and engagement with the present moment.

(4) Behavioral Activation for Depression Scale – Short Form (BADS-SF; Kanter et al. 2012). The BADS is a brief 9-item measure designed to assess the acquisition and use of behavioral activation skills.

(5) CES-D (see pg. 6)
(6) MFQ (see pg. 6)
(7) SHAPS (see pg. 6)
(8) MASC (see pg. 6)
(9) PSS (see pg. 7)

Clinician-Report Process Measures (completed by study clinicians at selected therapy sessions):

(1) Children's Global Assessment Scale (CGAS; Shaffer et al., 1983). The CGAS is a single-item clinician report of a child's overall functioning rated on a scale of 1-100.

(2) Clinical Global Impression (CGI; Rush et al., 2000). The CGI is a 2-item measure of a mental health subject's current illness severity and improvement over the course of treatment.

(3) Working Alliance Inventory – Short Therapist Version (WAI-S-T; Horvath & Greenberg, 1986). The WAI-S-T is a 12-item measure assessing the therapist's perception of the quality of the therapeutic alliance between the subject and clinician.

(4) Columbia Suicide Severity Rating Scale – Children's Since Last Visit Version (C-SSRS-SLV; Posner et al., 2010). The C-SSRS-SLV assesses the prevalence of suicidal ideation and suicidal behavior since the last such assessment.

(5) CDRS-R (see pg. 6)

Table 1: Assessment Schedule for Anhedonic Adolescents Completing BA

Table 1.	**Treatment Sessions (Weeks)**														
Instrument	**Pre I**	**Pre II**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Post**
K-SADS-PL	C														
TSQ	A														
CEQ			A												
NEO-FFI-3	A														A
PANAS	A	A													A
CRSQ	A					A				A					A
ACSQ	A														A
CTI-C	A														A
CDEQ	A														A
ALEQ-R	A														A
TEPS	A														A
SHAPS	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
CES-D	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
MFQ	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
C-SSRS-SLV	C		C	C	C	C	C	C	C	C	C	C	C	C	
CDRS-R	C				C			C			C				C
MASC	A				A			A			A				A
PSS	A				A			A			A				A
FFMQ	A				A			A			A				A
BADS	A		A	A	A	A	A	A	A	A	A	A	A	A	A
PCS	A														A
CGAS/CGI			C											C	
WAI-S-C			A		A			A			A			A	
WAI-S-T			C		C			C			C			C	
EMA Forecasting		A													A
Neuroimaging (fMRI)		A													A

Behavioral task (PRT)		A													A
Ecological Momentary Assessment (EMA)†		A		A		A		A		A		A		A	A
Note. Pre=Pretreatment; Post=Posttreatment; A=Adolescent; C=Clinician. Anhedonic participants complete all assessments; Healthy Control participants complete pre- and post-treatment assessments (and EMA).															

Ecological Momentary Assessement (EMA)

Consistent with prior research implementing EMA with depressed and healthy adolescents by the secondary mentor (Dr. Forbes) and her colleagues (Forbes et al., 2012), EMA data will be collected over the course of ten 5-day blocks (Thursday-Monday) distributed over the course of the 12-week BA trial, beginning the week following the initial MRI session (Day 2). Prior research from Dr. Forbes' laboratory indicates that collecting EMA data Thursday-Monday is a preferable assessment time window for several reasons (e.g., samples time intervals when freedom and behavioral choice are most variable [i.e., after school and on weekends] as well as sampling some behavior within the structure of the school schedule for comparison). There will be 2 EMA assessments per day on weekdays and 3 per day on weekends, via smartphone alerts signaling self-report items to complete. The EMA assessments will occur between 4pm Thursday and 9pm Monday at specified time windows distributed throughout each day (e.g., 4–7pm). No contact will be made during school hours or between the hours of 10pm and 11am. 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, stress, cognitions and recent activites. In addition, the smartphone application also will collect data on the participant's usage of their phone (e.g., time and length of calls and texts, GPS location, movement of the phone; For details, see attached *Smartphone EMA Data Collection*). EMA data collected from Android phones will use the *Beiwi* application ("app") designed by Jukka-Pekka "JP" Onnela, D.Sc. at the Harvard T.H. Chan School of Public Health (Dr. Onnela has a previous Partners IRB-approved protocol [#2015P000666] using the *Beiwi* app to collect the same EMA/passive data as proposed in this study. Other recently Partners-approved protocols using the *Beiwe* app include 2015P001303 and 2012P000890). EMA data collected from iPhones will use the *MetricWire* app (previously approved by the IRB: protocol 2015P001303). Data collected by both apps are encrypted on the phones and uploaded to a secure server (using HIPAA compliant software which has been reviewed and approved by Partners RISO) and downloaded by the researcher to the local research server in a de-identified format (i.e., subject ID number). 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 (see attached *Smartphone EMA Information Sheet*, which will be provided to participants).

Participants will be contacted at regular intervals to ensure high EMA completion.

F. Post-Treatment Adolescent Assessment (Approximately 3 hours):

Within 10 days of the final BA session, anhedonic participants will return for a post-treatment assessment lasting approximately 3 hours. Healthy control participants will also complete the same assessment 12-13 weeks after their initial assessment. Adolescents will be asked to complete self-report measures assessing symptoms/affect (MFQ, CES-D, SHAPS, TEPS, MASC, PANAS), stress (PSS, ALEQ-R), cognitive vulnerability (CTI-C, CRSQ, ACSQ), interpersonal vulnerability (CDEQ), personality (NEO-FFI-3), and EMA PANAS Forecasting. Adolescents will aslo complete the same fMRI task and the PRT task as completed at the pretreatment/baseline assessment.

Parents will complete the same self-report (BDI-II, SHAPS, TEPS, PANAS, PSS) and parent-report measures (MFQ-PR, MASC-PR) as they completed at the initial assessment.

Debriefing for Active Treatment Cohort and Their Parents:

Within one week of concluding post-treatment study session, the treatment group subject and parents will be debriefed. Specifically, the subject and parents will receive a summary including: (a) pre- and post-treatment diagnosis, (b) pre- and post-treatment changes in depressive and anxious symptoms, (c) recommendations for treatment moving forward (if necessary), and (d) a list of clinical resources in the greater Boston community if family is interested and/or would benefit from continuing treatment.

Debriefing for All Subjects

Following the final assessment, all subjects will be debriefed regarding the two monetary reward tasks (i.e, fMRI reward task and the PRT). Specifically, (s)he will outline the purpose of the study and explain the purposes of the scans and tasks. The study staff member will explain the differential reinforcement schedule utilized in the PRT. They will explain the partial contingency between the accuracy of the subject's choices and his/her likelihood of receiving positive feedback, and the rationale for use of this paradigm. Similarly, study staff will explain the our interest in probing reward-circuitry function during reward anticipation and outcome (i.e., wins, losses, neutral outcomes) for the fMRI task.

G. Follow-up Assessments

The anhedonic participants completing the BA treatment and the healthy control participants will complete follow-up assessments at 3-, 6- and 12- months post-treatment, and these assessments will be conducted using REDCap, a secure, Partners-approved tool for collecting participant data. During the and 3- and 6-month follow-up assessments, the adolescents will be asked to complete self-report symptom measures (CES-D, MFQ, SHAPS, TEPS, PANAS, MASC, PSS, ALEQ-R), which will necessitate approximately 20 minutes. The participating parent will be asked to complete self-report measures (BDI-II, SHAPS, TEPS, PANAS, PSS) and a parent-report measure of their child's symptoms (MFQ-PR, MASC-PR). At the 12-month follow-up assessment, adolescents

and their parents will complete the above measures, and adolescents will also complete additional measures examining cognitive and interpersonal vulnerability (CTI-C, CDEQ, CRSQ, ACSQ) necessitating approximately 25 minutes. In addition, in order to assess for any changes in diagnoses during the follow-up phase, the K-SADS (including full depression module) will be completed over the phone with anhedonic participants at the 6- and 12-month assessments. Just the depression and anxiety disorder modules of the K-SADS will be completed over the phone with healthy participants at the 6- and 12-month assessments. Study staff will schedule these assessments at a time when both the parent and participating teen will be at home, and staff will speak to the parent before and after speaking with the adolescent.

After completing the 12-month follow-up, participants will be added to an email list to receive a quarterly lab newsletter, which will communicate results from our research to participating families. Past participants may opt out of receiving this newsletter at any time.

VI. BIOSTATISTICAL ANALYSIS

Data from this study will consist of demographic information, semi-structured clinical interviews (K-SADS, MINI), adolescent self-report symptom measures (MFQ, CES-D, SHAPS, TEPS, MASC, PANAS), parent self-report measures (BDI-II, SHAPS, TEPS, PANAS, PSS), cognitive vulnerability measures (CRSQ, ACSQ, CTI-C), an interpersonal vulnerability measure (CDEQ), stress measures (ALEQ-R, PSS), a personality measure (NEO-FFI-3), EMA data, behavioral data (PRT), and MR/fMRI data.

Sample Size

The adolescent portion of the study includes the following cohorts: (a) 35 anhedonic adolescents receiving BA and (b) 35 healthy control adolescents. The primary aim is to examine whether anhedonic and healthy adolescents differ on baseline neural (fMRI), behavioral (PRT) and self-report (EMA) measures of reward function, as well as whether behavioral and neural mechanisms prospectively predict and mediate symptom improvement among anhedonic adolescents receiving BA. Importantly, within the active treatment cohort, analyses will be conducted to determine if there are statistical differences in symptom, behavioral, and/or neural measurements between medicated and non-medicated depressed adolescents. Additional analyses will examine if there are statistical differences between participants on SSRIs versus participants on SSRIs plus other psychiatric medications.

Descriptive and Exploratory Analyses:

Descriptive statistics and exploratory graphical techniques, such as frequencies, means, medians, histograms, and box plots will be used to assess skewness and/or outliers in the data. Continuous/quantitative variables will be appropriately transformed when necessary, e.g., via log transformation for positively skewed distributions. For outcomes acquired during treatment, the analytical approach will address the type of outcome, as well as accommodating the within-individual correlation due to repeated assessments. In

addition, the results will be assessed for sensitivity to dropouts or missing data. The primary analysis will be an intent-to-treat analysis, which includes all subjects. Of note, attempts will be made to continue assessing subjects even if they drop out of treatment.

Behavioral Variables:
For the PRT, the primary variable of interest will be *Reward Learning*, operationalized as the increase in response bias (RB) scores from Block 1 to Block 3 [ΔRB = RB(Block 3) - RB(Block 1)]. This variable was selected because it has been repeatedly linked to current and future anhedonic symptoms (Pizzagalli et al. 2005; 2008).

EMA-Derived Variables:
For EMA, the primary variables of interest will be scores on the positive/negative affect and anhedonia items over the assessment periods. In addition, passive accelerometer data from the Beiwe app will provide data on amount of movement per day, which will be used to predict changes in self-reported affect and depressive symptoms. 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, Growth Curve Modeling (GCM) will be used to analyse EMA data (see *Statistics* below).

fMRI Processing:
fMRI: Gradient echo T2*-weighted echoplanar images will be acquired using the University of Minnesota multi-band BOLD EPI sequence (Feinberg et al., 2010; Moeller et al., 2010; Xu et al., 2013), which achieves excellent temporal and spatial resolution (TR/TE: 1300/35ms; FOV: 224 mm; matrix: 64X64; 78 slices; in-plane resolution: 2mm; voxels 2 x 2 x 2mm, multiband factor of 6). The EPI acquisition will use prospective motion correction to minimize the effects of subject motion. Analyses will be conducted using SPM8 and FreeSurfer (Fischl et al., 2002). Pre-processing will include motion/slice-time correction, removal of slow linear trends, intensity normalization, and spatial smoothing (6-mm).

Statistics:
GCM will be used to test the hypothesis that pretreatment reward dysfunction (fMRI, PRT, EMA), controlling for overall pretreatment levels of depressive symptoms (BDI), will predict anhedonic (SHAPS) symptom improvement over the course of BA. Given our multimodal assessment of reward system dysfunction, pretreatment predictors will include: (1) self-reported anhedonia (i.e., baseline EMA), 2) neural (i.e., striatal and mPFC) response to monetary rewards on the fMRI reward task and (3) reward learning scores on the PRT. The dependent variable in these analyses will be anhedonic (SHAPS) symptom improvement. GCM is well-suited for handling repeated symptom assessments over time (i.e., session-to-session SHAPS scores), as well as accommodating missing observations in longitudinal datasets.

With regards to fMRI analyses, data will be analyzed using an ROI approach to evaluate *a priori* hypotheses, followed by a whole-brain analysis to test regional specificity of findings. In the first approach, regression coefficients ("beta weights") will be extracted

from ROIs obtained from FreeSurfer's parcellation. Informed by the relevant literature, and consistent with reward circuitry hypotheses, ROIs will include striatal (NAc, putamen, caudate) and cortical (mPFC) regions. For each subject and ROI, results of one-sample *t* tests (reward feedback > baseline) will be extracted for inclusion in growth models estimating SHAPS improvement. In the second approach, whole-brain analyses will be run predicting SHAPS improvement. For these analyses, each subject's data will first be re-sampled into Talairach space and random effects analyses will be conducted.

GCM will also be implemented to test the hypothesis that greater pre- to post-treatment normalization in neural (i.e., striatal and mPFC response to fMRI task) and behavioral (i.e., reward learning on PRT) responsiveness will be associated with greater anhedonic symptom improvement over the course of BA treatment. For fMRI analyses, for each of the above ROIs and consistent with prior work (Dichter et al., 2009), a *Group* (AH, HC) X *Time* (Pre-, Post-treatment) X *Condition* (Monetary Gains, Monetary Losses) interaction will be tested. For significant ROIs, pre- to post-treatment change in ROI activation will be entered as predictor variables in growth models estimating SHAPS improvement. For the behavioral (PRT) analyses, a *Group* (AH, HC) X *Time* (Pre-, Post-treatment) interaction will be tested, followed by correlations between reward learning scores and anhedonic (SHAPS) symptom change.

VII. RISKS AND DISCOMFORTS

(a) *Privacy*. A potential risk is a breach of confidentiality. To protect against the loss of confidentiality, we will keep all study data locked in a separate file, coded by a unique study code number (with names and other personal identifying information kept separately). Further, the consent and assent forms will clearly inform subjects of the limits of confidentiality, including the circumstances in which confidentiality may be breached such as in cases of suspected child abuse or neglect and dangerousness to self or others.

(b) *Discomfort.* In the event that participants experience discomfort when completing the study questionnaires or experimental tasks, they can refuse (a) to answer any questions and/or (b) to complete any tasks that make them uncomfortable. Further, all participants may choose to discontinue an assessment session at any time, or, if they wish, to withdraw from the study. This will be explained in the informed consent and assent forms as well as reiterated orally prior to the onset of the assessment.

(c) *Clinical Risk: Adolescents.* As in any study examining depressive symptoms, there includes the possibility that subjects may experience dangerous or suicidal thoughts. (Note that in the current study, the "anhedonic adolescents" cohort is being recruited on the basis of elevated anhedonic [SHAPS] symptoms, and are *not* required to meet DSM criteria for Major Depressive Disorder (MDD). MDD is neither an inclusion nor exclusion criteria). We do not anticipate that our study procedures will increase suicidal risk, but there is a risk that this could occur during the study period. In order to effectively monitor and address this issue, this study will employ the same suicidality protocol that has been approved by the McLean and Partners IRB for previous studies of

this population. If an adolescent indicates intent to harm themselves or others during the phone screen, the study staff member conducting the call will inform the parent and suggest that they seek immediate help. The staff member will then contact the PI or the covering clinician, who will follow up with the parent per their clinical discretion. All anhedonic participants receiving BA will complete self-report questionnaires of depression, which include items assessing suicidality, as well as a clinician-administered suicidality scale, prior to the weekly session, which clinicians will review before commencing the session. If an individual endorses increased suicidal thoughts, an appropriate clinical recommendation will be made and appropriate actions taken, if necessary; this could involve treatment either at McLean Hospital or elsewhere.

In addition, following the completion of every EMA smarphone survey, the following message appears on the screen: "*Thank you for completing the survey. Don't forget, no clinician will see your answers. So, if you need help or you're thinking about harming yourself, immediately tell your parent, a trusted adult (e.g., teacher, school counselor), call 911, or page Dr. Webb (617-855-2000).*

(d) *Clinical Risk: Adults*. Adult participants (i.e., parents of anhedonic and non-anhedonic adolescents) will be reminded that they can discontinue an assessment at any time. If an adult participant indicates an intention to harm him/herself or others during any portion of the study, staff will encourage him/her to seek immediate clinical attention, and Dr. Webb will follow up per his clinical discretion. Additionally, study staff will offer to provide lists of local resources to any participant indicating elevated symptoms.

(e) *Medication Washout*: As has been approved by the McLean/Partners IRB in previous studies, individuals who have used medication to treat depression in the past may be included in the study if there is an absence of the following psychotropic medications: 8 weeks for fluoxetine, 4 weeks for neuroleptics, 8 weeks for benzodiazepines, 6 weeks any other antidepressants. When individuals contact the laboratory for the initial screening and indicate current use of medication to treat depression (see exception pp. 4-5 SSRIs), they will not be eligible to participate in the study. In light of these guidelines, no medication washout period is permitted. These details are delineated in the applicable informed consent form.

(f) Medication Use: Depressed adolescents endorsing current use of SSRIs may participate in the active treatment if they have remained on the same type of SSRI for at least 4 weeks. During the course of the treatment, SSRI dose changes are permissible. Medication will be prescribed through an outside treater, not affiliated with the study. If during the course of the treatment, an adolescent is prescribed medication included in the exclusion criteria, the adolescent may complete the entire BA course. Participants will continue to complete scheduled assessments as outlined above.

(g) *MRI*. The study will be conducted in an MRI scanner approved for routine clinical studies in children or adults by the FDA. Although there are no known risks from these scans, there could be adverse effects that are delayed or very mild, such that they have not

yet been recognized. Most people experience no ill effects from these scans, but some people do report claustrophobia (fear of being in enclosed small spaces), dizziness, mild nausea, headaches, a metallic taste in their mouth, double vision, or sensation of flashing lights. These symptoms, if present, disappear shortly after leaving the scanner.

a) *Implants/Prostheses*: The magnetic field of the scanner exerts a force on ferromagnetic objects within the field. This force can cause a ferromagnetic implant, such as some brands of aneurysm clips, surgical clips, or prostheses, to move or be displaced and cause injury or death. If the implant is both large and ferromagnetic, sufficient currents can be induced in the metal by the magnetic field to cause heating of the implant. Individuals with any such devices will be excluded from enrolling in the study.

b) *Pregnancy*: The safety of the 3.0T MRI scanner for imaging embryos/fetuses has not been clearly established. Therefore, individuals who are pregnant or who are of unknown pregnancy status will be excluded. All participants are required to take a pregnancy test before entering the scanner environment.

c) *Collision Hazard*: The magnetic field near the scanner is strong enough to attract ferromagnetic objects with great force. Near the magnet this force can be strong enough to pull objects in and cause them to fly down the axis of the magnet. Such objects become projectiles that can cause injury or death. A security zone has been established to prevent ferromagnetic objects from coming into proximity of the magnet. The likelihood of a collision in the context of the present experiment is thought to be low, much lower than the likelihood in clinical practice.

d) *Radio Frequency (RF) and Magnetic Field Interference*: Implants electronic devices, such as cardiac pacemakers and cochlear implants, may be susceptible to interference from the magnetic and RF fields produced by the scanner. This interference may destroy or adversely affect operation of these devices. Since interference to cardiac pacemakers is observed in magnetic fields as low as 13 gauss, means have been provided to prevent persons with cardiac pacemakers or other implanted electronic devices from entering a zone where the magnetic field exceeds 5 gauss. Individuals with such devices will be excluded from the study.

e) *RF Antenna Effects*: If metal wires or electrodes, such as electrocardiograph leads, are attached to the subject during imaging, the RF energy radiated by the transmission coils of the scanner can induce sufficient electrical currents in the lead wires to cause burns where the electrodes or wires contact the skin. No such leads or wires will be employed in the present experiment.

f) *Biomagnetic Hazards*: It is possible that subtle genetic or molecular changes could be caused by the magnetic fields produced by the MR system. To date, however, no harmful biological effects have been demonstrated at the magnetic field strengths and

exposure times utilized by the scanner. At the present time, the likelihood of any significant adverse biomagnetic effect is considered to be very low.

g*) Clinical Hazards*: The confining conditions of the MRI system can precipitate claustrophobia in a subject. Subjects will be screened for possible claustrophobia before they are enrolled in the study.

h) *Access to MRI Area*: Access to all areas exceeding the 5 gauss level will be controlled by warning signs, barriers, staffed entry locations, and adequate interrogation to assure avoidance of incidents. Access to the magnet room by any personnel will be closely controlled for safety of persons, in particular to prevent accidental introduction of ferromagnetic objects that could be attracted by the magnetic field generated by the MRI system.

(h) *EMA Data Security:* Data collected by the EMA app (*Beiwe*) are encrypted on the phones and uploaded to a secure server (using HIPPAA compliant software). These data are downloaded by the researcher to the local research server in a de-identified format (i.e., under subject ID number). The same password-protections and encryptions described above for all other data will also apply to EMA data.

(i) *Treatment:* If after enrolling in the study, an active treatment participant begins medication included in the exclusion criteria, he/she will not be removed from the study. Rather, the participant may complete the treatment and study. Medication changes will be tracked throughout the course of the study by the BA therapist.

VIII. POTENTIAL BENEFITS

Short-Term. The potential benefits of BA are for anhedonic adolescents to experience improvement in their anhedonic/depressive symptoms and improved reward system functioning (Dichter et al., 2009).

Long-Term. Participants in the current study may potentially experience remittance of anhedonic/depressive symptoms, and further, these may contribute to improvement with (a) academic performance, (b) social involvement in recreational activities, (c) improved interpersonal relationships with peers, classmates, parents, (d) lower likelihood of using substance use to dowregulate negative affect or upregulate positive affect, (e) lower likelihood of engaging in risky behaviors (e.g., sexual promiscuity, aggression, rule breaking) to manage depressive symptoms, (f) improvement in self-esteem and self-efficacy, and (g) greater mastery of behavioral skills to decrease stress and symptoms of depression and anxiety.

Collectively, the research will advance our understanding of the behavioral and neurocognitive mechanisms implicated in anhedonia and reward system dysfunction, which is expected to ultimately lead to the development of more effective prevention and treatment programs that alleviate many of the mental and physical health problems as well as economic costs associated with anhedonic and depressive symptoms

IX. MONITORING AND QUALITY ASSURANCE

(a) The PI will have responsibility for continuous monitoring of data and safety of subjects in the study. Data and safety monitoring will take place continuously throughout the study's duration. For participants in the active treatment condition, the study clinicians will administer a suicidality assessment before commencing each session, in addition to reviewing depressive symptom severity scores on self-report measures. If depressive symptoms and/or suicidality increase significantly, an intervention will be made during the time of the assessment. The PI will determine if the participant should discontinue the study. Additionally, appropriate recommendations will be made and appropriate actions taken in collaboration with the adolescent and parents.

(b) We will report both adverse events and all serious adverse events that occur during the course of the trial to the Partners Institutional Review Board.

(c) At the time of the continuing review we will provide the Partners IRB with a summary of any unexpected and related adverse events as well as any other unanticipated problems that occurred since the last continuing review.

(d) We will also follow the Partners IRB policies for expedited reporting of unexpected Adverse Events and Serious Adverse Events. We will report to the IRB any nonserious unexpected adverse events and serious adverse events that are related or possibly related to a subject's participation in the research occurring: (a) while a subject is enrolled in the study or (b) after study completion, or (c) after subject withdrawal. These events will be reported to the Partners IRB within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem.

(e) All study staff assessing depression (including anhedonic symptoms) and suicidality will be trained by Dr. Webb, who has completed a doctorate in clinical psychology and a 1-year APA internship at McLean Hospital. Dr. Webb has received extensive training in conducting interviews using the K-SADS, MINI, CDRS, and C-SSRS.

(f) During the last 9 years, Dr. Webb has utilized all assessment tools in completing large-scale studies. Further, Dr. Webb has provided extensive training and supervision for study staff/diagnosticians conducting these interviews. Dr. Webb will provide 40 hours of didactic and practical training for all study staff that will conduct interviews. Included in this instruction is the assessment of both depressive symptoms including suicidality. Particular attention will be paid to delineating the differences between passive suicidal ideation and intent to self-harm. Additionally, all diagnostic interviews will be audiotaped (in contrast to therapy sessions, which will be videotaped) and reviewed in order to ensure reliability of diagnoses and assessment.

(g) Throughout the study there may be circumstances where a subject's participation may be terminated by the PI without the subject's consent. Specifically, potential reasons for participation termination may include: (a) increased participant suicidality, and (b) participant no longer satisfies inclusion criteria. Within 24 hours of any issue arising, the PI will speak to the parent and child, and if needed, the PI will also help to arrange

treatment for the child. It is important to note that this provision is explained in the consent forms.

(h) During the course of the BA sessions, private information will be collected. Such information will not be shared with parents as this may inhibit subject responses, and potentially, undermine the course of therapy. Therefore, a provision within the assent and consent forms states that parents must waive their right to access private information obtained in the context of therapy sessions. However, there are important caveats as outlined by the American Psychological Association Guidelines for Psychological Practice in Health Care Delivery: (a) subject reports imminent threat to herself, (b) subject reports imminent threat to other (i.e., Tarasoff Rule), and (c) subject reports current maltreatment and/or past maltreatment which was previously undisclosed (i.e., Mandatory Duty to Report Child Abuse and Neglect). If any of these exceptions arise, the study clinician will work collaboratively with the subject in order to disclose information as outlined in the APA Ethical Guidelines. During these occasions, the PI will be immediately contacted, and a report will be filed as early as is feasible to the IRB.

(i) During this study, we may learn information from subjects that must be reported to public health or public safety authorities. We are required by law to report known or suspected child abuse. Should a subject disclose such information, we will report it to public health or public safety authorities.

(j) *Requests for data sharing*
Some de-identified research data will be shared with Dr. Aaron Kucyi at Northeastern University. The shared data will consist of de-identified behavioral (Flanker task) and demographic data (age and gender), de-identified resting state fMRI data, de-identified structural MRI data and de-identified ecological momentary assessment (EMA) data on momentary affect and cognitions. Data shared with Dr. Kucyi will be stored on a secure, password-protected server (Northeastern University's Discovery cluster). Data will be transferred securely by using a MGB-approved data sharing service such as Syncplicity, or secure file transfer. The primary purpose of the data sharing will be to complete analyses for a planned manuscript and grant (NIMH R01) submission focused on the relation between EMA-assessed cognitions, including mind-wandering, and attentional control brain networks assessed via resting state fMRI.

Some de-identified research data will be shared with Dr. Kathleen Gates at UNC Chapel Hill (and possibly other researchers). The shared data will consist of de-identified self-report questionnaires and ecological momentary assessment (EMA) data on momentary affect and cognitions. Data shared with Dr. Gates will be stored on a secure, password-protected server. Data will be transferred securely by using a MGB-approved data sharing service such as Syncplicity, or secure file transfer. The primary purpose of the data sharing will be to complete analyses for a planned manuscript focused on the relationship between EMA-assessed variables in BA treatment.

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