Mass General Brigham

Institutional Review Board

Intervention/Interaction Detailed Protocol

Principal Investigator:	Diego A. Pizzagalli, PhD
Project Title:	SMART Trial to Predict Anhedonia Response to Antidepressant Treatment
Version Date:	December 13, 2024

1 Background and Significance

Anhedonia has emerged as a critical intermediate phenotype of MDD and constitutes a major clinical challenge (Pizzagalli, 2014). Despite significant efforts, treatment of MDD remains imprecise and involves trial-and-error to determine the most effective approach. Findings from the STAR*D trial revealed that only ~50% of individuals with MDD responded (i.e., ≥50% reduction in symptoms) to the SSRI citalopram (Trivedi, et. al, 2006) and over one-third failed to respond to two or more antidepressants (Rush et. al, 2006). The situation is even worse in primary care, where only ~30% respond to first-line antidepressants (Katon et. al, 1996) To exacerbate these issues, it takes at least 4 weeks to evaluate the efficacy of an antidepressant. This can lead to lengthy treatment that is insufficient and unnecessary, thereby increasing patient morbidity, drop-outs, and suicide risk. *These challenges are even more pronounced in the context of anhedonia*, which has been linked to chronicity, poor response to first-line antidepressants, CBT and TMS, as well as increased suicide risk.

This limited success largely stems from the fact that treatment selection is not based on identification of underlying biomarker abnormalities. Hence, some depressed individuals may benefit from SSRIs while others might be better suited to other classes of medication. Identifying *objective markers that reliably predict differential responses to distinct classes of antidepressants* would provide patients and clinicians with critical information to guide optimal treatment selection. Although single studies have identified neural (Chen et. al, 2007), behavioral (Dunkin et. al, 2000), and clinical (Farabaugh, et. al, 2010), variables that predict SSRI response, lack of replications abound (Gudayol-Ferré, 2012). *We hypothesize that the intermediate phenotype of anhedonia is critical to addressing these issues.* Two important gaps exist in prior literature. First, to the best of our knowledge, with the exception of our recent report (Ang, et. al, 2020) no prior study has examined brain-behavior factors linked to response to second-line antidepressants, especially after failing a full course of SSRI treatment. Current guidelines recommend SSRIs as first-line antidepressant treatments, and depressed patients who fail to benefit are often switched to non-SSRI agents (Fredman et. al, 2000; Ruhé, et. al, 2006;

Papakostas et. al, 2008). Prior studies have not tested whether pretreatment biological and behavioral markers can differentiate between responders to a second antidepressant, after failure on a pharmacologically distinct class of medication, and non-responders resistant to both treatments. Second, alterations in the brain reward circuitry – centered on the ventral striatum (nucleus accumbens, NAc) and medial prefrontal cortex (mPFC) and modulated by dopamine (DA) – have been strongly implicated in MDD (Pizzagalli, 2014). However, few studies have tested the degree to which markers of reward processing predict antidepressant response. *Our data suggest that* ***anhedonia is a robust predictor of differential response to antidepressant treatment.***

2 Specific Aims and Objectives

The overarching objectives of this research study are to **(1)** determine whether anhedonia is an important factor in differentiating MDD patients who respond to standard SSRIs from those who respond to a non-SSRI medication such as bupropion, and **(2)** improve our understanding of anhedonia across units of analyses (genes, molecules, cells, circuits, physiology, behavior, self-report). Based on our extensive sets of preliminary data as well as our published work, we hypothesize that:

Hypothesis 1**:** MDD patients with elevated anhedonia for whom the randomized treatment matches the pre-treatment response marker, *will have double the response rate* of patients treated with a non-matching treatment (as measured by decrease in Montgomery-Åsberg Depression Rating Scale [MADRS] score).

Hypothesis 2: MDD patients responding to treatment will show, from baseline to week 8, significant improvement in measures of anhedonia, including:

- Self-report of symptoms
- Reward learning
- Effort-based decision making
- Reward-related ventral striatal activation
- Cortico-insular activation during the effort-based task
- Reward positivity (RewP)
- Resting state functional connectivity between the NAc and mPFC.

In addition, we will conduct exploratory analyses of associations between anhedonia, treatment response, and certain biomarkers and biometrics such as facial expressions and the associations between endocrine and genetic markers in relation to anhedonia.

3 General Description of Study Design

This study is a double-blind trial in which treatment for MDD patients with elevated anhedonia will be stratified based on clinical, behavioral and neural markers we recently identified in an independent study (Ang et. al, 2020; Webb et al., 2019). We will enroll individuals ages 18-64, meeting DSM-5 criteria for current MDD with an elevated level of anhedonia (Snaith-Hamilton Pleasure Scale score ≥25) from the greater Boston area.

Prior to randomization, data from clinical assessments, behavioral tasks, and MRI will be analyzed to determine whether subjects display positive composite markers for response to

bupropion (BUP+) or sertraline (SERT+). The method for assigning response markers is described under the heading SMART Response Marker Classification in section 6.2.1.

After subjects have been classified by composite response marker, they will be randomized to one of four arms:

1. BUP+ Marker and BUP treatment
2. BUP+ Marker and SERT treatment
3. SERT+ Marker and SERT Treatment
4. SERT+ Marker and BUP Treatment

Refer to section 5.3 Randomization and Blinding, for a description of the randomization criteria.

For subjects who have both BUP and SERT markers or do not have markers for either, they will be randomized to receive either study medication and form a fifth arm. This group will serve as a control condition.

5. Indeterminant markers

Medication will be dispensed at weeks 0, 1, 2, 3, and 4. Subjects will also receive their medication for weeks 4-8 at week 3. Drug side-effects will be assessed by a board-certified psychiatrist before drugs are dispensed, and primary clinical measures will be collected (by independent clinical interviewers who will be also blind to treatment arm). At week 8, a final visit will include collection of all outcome measures and a study debrief, in addition to a check of side-effects. Overall, a subject will participate in the study for about nine to ten weeks.

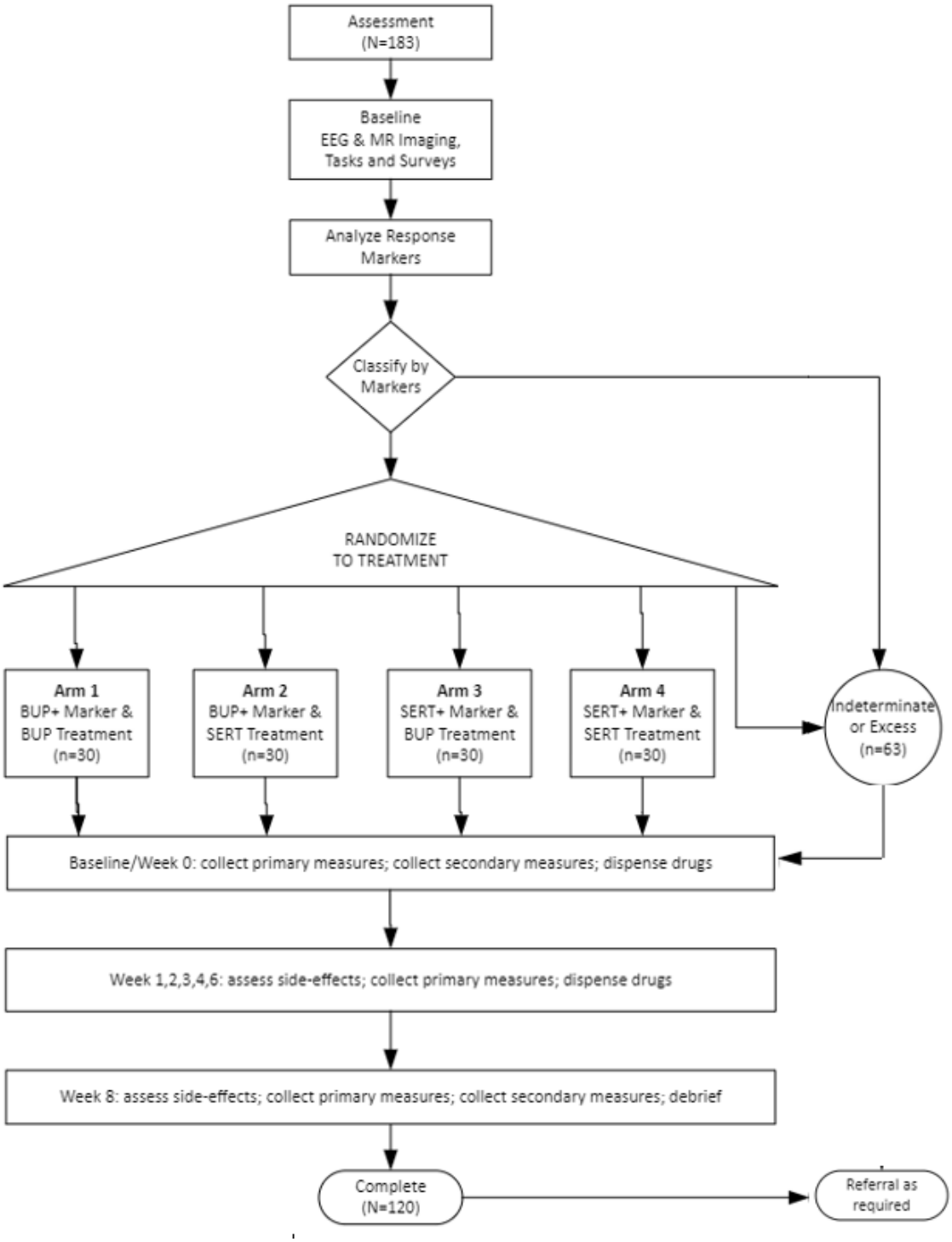


Figure 2: Study Schema

4 Subject Selection

4.1 Participants

This research study will enroll unmedicated participants ages 18-64, meeting DSM-5 criteria for current MDD and with varying degrees of anhedonia (Snaith-Hamilton Pleasure Scale score ≥25) from the greater Boston area.

To provide sufficient statistical power, 120 participants must complete the drug trial, consisting of 60 patients with the BUP+ response marker and 60 with the SERT+ response marker (for more details, see *Power Analysis*). The sample will consist of four treatment groups (N=30 per group), matched for severity of anhedonia. Based on simulations we have performed, up to 183 participants will need to be completely assessed in order to populate treatment groups that are balanced on all factors. Participants who can't be assigned to a group will form the fifth treatment arm (N = 63) and still be randomized to receive treatment.

4.2 Inclusion and Exclusion Criteria

Exclusion criteria will follow our published imaging studies in MDD (Trivedi et. al, 2016; Pizzagalli et al., 2009; Kumar et al., 2018). Inclusion and exclusion criteria are listed in Table 1. Subjects will be carefully screened for MRI contraindications. Since safety of MRI has not been established for fetuses, women who are pregnant, or suspect that they may be pregnant, will be excluded. Women will have a urine pregnancy test prior to the MRI scan. Consistent with prior protocols from our laboratory, recent use of recreational drugs, except for THC, is not permitted, so a urine drug screen will be administered at the screening visit and the scanning visit. Participants who use THC regularly will be allowed to continue in the study provided they have abstained for the two days prior to the baseline scanning session (thereby allowing the acute effects to wear off).

To avoid assigning a subject to a treatment that has already been ineffective during their current episode of depression, we will not enroll anyone who has already completed a full course of treatment with both sertraline and bupropion (i.e., six weeks of treatment with medication compliance) within the current depressive episode. Use of one study drug will not result in exclusion unless the participant has failed the other.

Table 1. Summary of inclusion and exclusion criteria. *Note*: The instruments used for assessment of these inclusion and exclusion criteria are defined in Section 6.3, Data collection.

Inclusion Criteria:
1) Ages 18 to 64 2) Any gender and all ethnic/racial origins 3) Diagnosis of MDD, established according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). MDD diagnosis will be determined via the Structured Clinical Interview for DSM-5 (SCID-5). 4) Elevated depression severity, defined as a score ≥ 16 on the Hamilton Depression Rating Scale (HAM-D) 5) Elevated anhedonia symptoms, defined as a score ≥ 25 on the Snaith-Hamilton Pleasure Scale.

6) Clinical criteria may be adjusted at clinicians' discretion in the cases where HAM-D score or scores of other clinical measurements do not meet the threshold noted in this protocol.
7) Fluency in written and spoken English
8) Ability to give signed, informed consent either written or electronic (via REDCap eConsent)
9) Normal or corrected-to-normal vision and hearing
10) Ability to adhere to the study schedule

Exclusion Criteria:

Study medication

1) Any contraindication to bupropion or sertraline deemed unsafe by the study physician, or any history of adverse reaction to either drug.
2) Failure to respond to an adequate course of treatment with both study medications (sertraline or bupropion) during the current episode. Failure (here and throughout this protocol) will be defined as less than a 50% reduction of symptoms. This will be assessed by the study physician and clinician using the MGH Antidepressant Treatment Response Questionnaire (ATRQ).
3) Participants who are determined to be treatment resistant, (i.e., having failed to respond to at least two adequate antidepressant trials in the current episode), assessed by the MGH Antidepressant Treatment Response Questionnaire.

Imaging Exclusions

4) Pregnant or currently breastfeeding women, women who gave birth within the past 12 weeks, or women of childbearing potential who have a positive result on a urine pregnancy test
5) Failure to meet MRI safety requirements including, but not limited to, any metal implants or prostheses that cannot be removed, or exposure to shrapnel
6) Claustrophobia or severe anxiety that might impact participation in neuroimaging
7) Injury or movement disorder that may make it difficult to lie still in the scanner

8) Substance and Drug Use Exclusions

9) Any current recreational/illicit drug use, with the exception of THC, as assessed by a urine drug test (covering cocaine, cannabinoids, opiates, amphetamines, methamphetamines, phencyclidine, MDMA, benzodiazepines, methadone, oxycodone, tricyclic antidepressants, and barbiturates). Participants who use THC regularly will be allowed to continue in the study provided they have abstained for the two days prior to visits involving the MRI scan.
10) Use of Monoamine Oxidase Inhibitors (MAOIs) either currently or within the past two weeks
11) Participants who are currently discontinuing the use of tobacco products. Participants who cannot abstain from tobacco products for eight hours without cravings.
12) More than 15 alcohol-induced lifetime blackouts.
13) History of regular use (5-7xs per week) of marijuana before the age of 15

14) Lifetime history of other recreational drug use beyond the following limits (for each drug individually) and/or last use within the past 3 months:
    a. Hallucinogens (mushrooms, LSD): exclude for12 uses in the past year, or 15 uses lifetime (unless last use was 5+ years ago, then allow up to 25 lifetime uses)
    b. Ecstasy: exclude for 12 uses in the past year, or 15 uses lifetime (unless last use was 5+ years ago, then allow up to 25 lifetime uses)
    c. Anxiolytics (recreational use): exclude for 12 uses in the past year, or 15 uses life time (unless last use was 5+ years ago, then allow up to 25 lifetime uses)
    d. Cocaine, meth/psychostimulants (this does not include prescribed stimulants such as methylphenidate) exclude for 5 uses in the past year, or 10 uses lifetime
    e. Prescribed opioids for a limited period (e.g., post-surgery) is OK if no use in the past 3 months
    f. 3 uses: Inhalants, IV drugs, crack cocaine, or crystal methamphetamine
15) Use of drug or herbal supplement for depression (e.g., St. John's Wort or SAMe) within the past three weeks.
16) Use of any antibiotics in the 24 hours prior to an experimental procedure (i.e. fMRI or EEG)
17) Recent use (within 4 weeks) of any medication that affects blood flow or blood pressure, or which is vasodilating/vasoconstricting (for participants undergoing fMRI)
18) Metformin use in the past 3 weeks
19) Participants with any use of psychotropic medications within the past: a) 3 months for dopaminergic drugs (including methylphenidate and Metformin); b) 6 weeks for fluoxetine; c) 8 weeks for neuroleptics; d) 2 weeks for benzodiazepines or any anxiolytic; e) 2 weeks for any other antidepressants or other psychiatric medications

Medical exclusions

20) Current serious or unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine (hypothyroidism), neurologic, autoimmune disease (such as Lyme, Crohn's), or hematologic disease. Psoriasis is allowed.
21) Current infectious illness (either transient or chronic); Current episode of uncontrolled allergic reaction or uncontrolled asthma
22) Hemophilia; Diabetes with poor glucose control; History of chronic migraine (> 15 days/mo.); History of dementia.
23) History of seizures or seizure disorder.
24) Any history of significant head injury or concussion with loss of consciousness for two minutes or more, or head injury with lingering functional/psychological impact
25) Serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems (contraindication to bupropion)- confirmed with ECG at physicians' discretion.

Comorbidity and Treatment Exclusions

26) Past/current DSM-5 diagnosis of: OCD (current only) , schizophrenia or other psychotic disorders, schizoaffective disorder, delusional disorder, psychotic disorders NOS, bipolar disorder, patients with mood congruent or mood incongruent psychotic features, autism or any other pervasive developmental disorder, organic mental disorder, PTSD (current only), somatoform disorder, severe borderline or antisocial personality disorder, anorexia or current subthreshold anorexia, binge eating disorder, or bulimia (however bulimia is allowed if it has been fully remitted in the past 2 years; binge eating disorder is allowable if it has been partially remitted within the past 3 months; current subthreshold binge eating disorder is allowable; past OCD or PTSD fully remitted for longer than one month and current partial remission of OCD or PTSD is allowable)
27) Patients with psychotic features in a current or past episodes of depression.
28) First-degree relatives with a history of a psychotic disorder or psychotic symptoms outside of the context of a mood disorder (i.e., MDD or bipolar disorder).
29) History of cocaine, stimulant, or opioid use disorder
30) Current mild, moderate, or severe substance or alcohol use disorder. Moderate or severe cannabis use disorder. Early or sustained remission is allowable, i.e., criteria for any level of abuse has not been met for at least the past 3 months (with the exception of past or current cocaine, stimulant, or opioid abuse, which will lead to automatic exclusion). Current mild cannabis use disorder is allowable.
31) Specific phobia, social anxiety disorder and generalized anxiety disorders will be allowed only if judged to be currently mild and never the principal diagnosis when co-occurring with current or past MDD. Panic disorder will be allo wed if MDD is the principal diagnosis and panic disorder has been in remission for > 2 years.
32) Patient is currently taking another antidepressant, receiving TMS OR planning to change their treatment regiments in the next three months (I.e., start/stop counseling, start TMS, etc.). Note: current psychotherapy or counseling is allowed if the participant has been in it for longer than 10 days and continues care as usual throughout the entirety of this study. TMS in the current episode is allowable as long as subject is not currently receiving it.
33) Electroconvulsive Therapy in the current episode.
34) Patient is clinically unstable, in the judgment of the clinician or physician.
35) Participants with suicidal ideation where outpatient treatment is deemed unsafe by the study clinician or study physician (these participants will be immediately referred to appropriate clinical treatment).

4.3 Recruitment Procedures

4.3.1 Recruitment Methods and Materials

Subjects will be recruited from the community by the Center for Depression, Anxiety and Stress Research (CDASR; Director: Dr. Diego Pizzagalli, Ph.D.) at McLean Hospital. All recruiting material will be submitted to the IRB for review and approval prior to being used.

Participants will be recruited using both online and physical sources. Advertisements may be posted on social media (e.g., Facebook, Instagram, Reddit, LinkedIn, Spotify, Google Ads),

online bulletin boards (e.g., Craigslist, community bulletin boards), community newsletters (e.g., Cambridge Health Alliance Newsletter), job/volunteer opportunity listings at local colleges (e.g., Boston University, Northeastern University, Tufts University, Harvard University, Bentley University, Brandeis University), radio or television advertisements, NIH-affiliated research participation sites such as ResearchMatch.org and WeSearchTogether.org, and on the MGB Rally site at rally.massgeneralbrigham.org. We may also post flyers on community bulletin boards or in doctor's offices, with permission from the staff. We may also hand out flyers at community events (e.g. NAMI's fundraising walk, etc.)

We will also work with a recruiting platform, BuildClinical, who have created a landing page for our study with a short recruitment survey. BuildClinical will advertise our landing page on social media platforms.

We may also choose to publicize our study through presentations from our Director, Diego Pizzagalli, or other study staff through media including television, news, etc.

Participants may also be recruited via the MGB Patient Gateway using targeted letters and research announcements. These participants will be carefully pre-selected from the Research Patient Data Registry (RPDR) following the above-mentioned inclusion/exclusion criteria to minimize ill-fitting research announcements. Any negative feedback or complaints pertaining to Patient Gateway advertisements will be reported to the IRB as an Other Event (OE).

Additionally, participants who have completed prior research studies in the PI's lab may be contacted if they had previously given consent to do so.

We may ask participants who have scheduled a phone screen to pass along the link to our recruitment survey to others who they believe might be interested in participating in research in our lab. We will not directly ask participants to provide any personal or sensitive information (including contact information) for these individuals; instead, potential participants will be sent our recruitment survey to determine their eligibility to continue with our study or any other research in our lab. Current participants are free to decline passing this document along without impact to their participation in our study.

Finally, we will work with clinics at McLean (e.g., Behavioral Health Partial Hospital (BHP), outpatient waitlist) as recruitment sources to disseminate study information and collect contact information for individuals interested in our study. Clinic, research staff, physicians, and other healthcare providers may share information about our study to patients who may be eligible for our study.

Study coordinators on the project will be primarily responsible for recruiting subjects. Participants responding to ads may either complete an online screening tool on REDCap, a Partners secure website, may be screened over the phone by study coordinators, or both. No employees of McLean Hospital or students or employees of Harvard Medical School affiliated with the research team will be enrolled. For participants who fill out the online survey, we will conduct a short phone screen to ensure that they are eligible for the study before scheduling them for the first session.

Our goal is to recruit a sample that is ethnically and racially representative of the population in the greater-Boston area. To enhance the enrollment of diverse individuals and underrepresented populations, our recruitment advertisements will be targeted within the greater-Boston area. To

reduce the impediment of travelling to McLean, transportation costs to and from McLean will be reimbursed.

Email communication with all subjects will utilize the "Send Secure" feature from institutional email addresses when discussing study details unless the participant consent to receiving unencrypted emails.

4.3.2 Prescreening

The online recruiting survey and all other computer-based surveys in this study will be implemented in REDCap, which is a web-based application designed to support data capture for research studies. REDCap is built around HIPAA guidelines. REDCap is operated by the MGB Research Information Systems organization, and the software and data are hosted on secure servers at a MGB data center.

Interested participants responding to certain ads will be directed to a website landing page to see more information about the research study. From this landing page, participants will have the option to complete an online screening form. Other ads will contain a direct link to the screening form.

Participants may either complete the screening survey online or they can choose to be screened over the phone by study coordinators. Candidates who fill out the online survey and appear to be eligible will be contacted for a short phone screen to verify that they are eligible for the study. Phone screens may be scheduled through Microsoft Bookings, email, or text with participant consent. During the phone screen, the information that will be solicited at this time includes: handedness, eyesight, history of mental illness, prior and current illnesses, history of recreational drug use, medication, and the presence of other contraindications.

We will also provide information about the risks of unencrypted communication (I.e., text or unencrypted email) and ask participants to indicate their preference for communication. If participants consent to allow a researcher from our team to text them, despite the risks, phone calls will be scheduled via text message. No PHI or personal information will be sent through text. Text will solely be used for scheduling a phone call. We will text participants with the blurbs that are IRB-approved. Contact name for the participant will be their recruitment ID, so their name will not be stored with the text chain. If participants do not indicate a preference for either text or email or do not consent to text, all communication will be sent using the "Send Secure" feature from Mass General Brigham email.

Individuals who may qualify for this study based on the phone screening will be invited to participate in the screening session.

5 Subject Enrollment

5.1 Prescreening

Prior to completing the initial screening session and clinical interview, participants recruited for our study may either complete an online pre-screening tool on REDCap, an MGB secure website, be prescreened over the phone by study coordinators, or both. Prior to completing the prescreening phone interview, subjects are informed that the interview contains sensitive questions, and that they can withdraw from the phone interview at any time. Participants are informed that there is no compensation for the phone screen. Subjects are also informed on how

we will maintain the confidentiality of their data during the phone interview. Study coordinators will document verbal consent prior to conducting the pre-screening phone interview.

Participants who are currently taking an antidepressant that is not working for them, but are eligible otherwise, will be told they can be re-screened for participation in the future if they are no longer taking the antidepressant. Participants will be told to discuss their medications and any changes with their own physician and recontact us for reassessment if they are interested in participating in the research study in the future. The reassessment will be a review of their initial phone screen, during which we will ask them about their current mood and discuss any recent medical or medication changes. We will reassess in this manner if less than two months have passed since their initial phone screen. The reassessment will only be about 10 minutes. If more than two months have passed between the initial phone screen and the reassessment, we will re-do the full phone screening.

Individuals who may qualify for this study based on the phone screening will be invited to the screening session. Participants will be contacted via email and phone.

5.2 Consent Procedure

When a subject is scheduled for their first session, the research coordinator will email them a copy of the consent form, so they have ample time to read it. Informed e-consent will be obtained by the study physician, who is authorized to dispense the study medications. Consent will be obtained prior to any research activity. All procedures will be fully explained to the subject, and any questions will be answered. The subject will be told that they can withdraw from the study at any time.

The Informed Consent Form will include a specific request for consent to provide a blood sample, which the subject initials to indicate their consent. We will explain to participants that the blood sample will be used to investigate genetic information and inflammatory markers related to mental health functioning. We will explain that they can participate in all other aspects of the study if they do not want to provide a blood sample, and the decision will not affect their compensation.

A portion of the clinical assessment interview may be recorded for subsequent analysis of facial expression and prosody. The subject can choose not to be recorded. The consent form contains a place where the subject will add their initials if they give consent for this procedure. This choice will have no effect on their eligibility to participate in any other study procedures.Potential risks and benefits will be explained in full. Participants will meet with the study physician, who will fully explain the potential risks of the study medications and answer any questions that they may have. Once the participant has fully reviewed the ICF and agrees to join the study, the participant along with the study physician and research coordinator will sign the informed consent.

REDCap eConsent will be used to obtain signatures and a signed copy of the consent forms will be distributed to the participant electronically according to ERIS guidance (https://confluence.partners.org/display/shareit/27233366/HOX07266265b398484fada0c1b491a15c5aYOP). After informed consent is received, additional assessments will be conducted to ensure eligibility for the trial (for details refer to Section 6.1, Study Sessions). Subjects who are enrolled and eligible will be scheduled for their Baseline visit.

5.3 Randomization and Blinding

Results from the clinical, behavioral, MRI and EEG assessments will be used to determine a subject's composite response marker (see SMART Response Marker Classification in section 6.1.2 for details). After subjects have been classified as having either SERT+ or BUP+ markers, they will be randomly assigned to receive either SERT or BUP medication such that 50% of patients with each marker will receive SERT and the other 50% will receive BUP. Thus, patients with clear response markers will be randomized in a 1:1:1:1 ratio. Patients with either both or neither marker will be randomly assigned to BUP or SERT medication in a 1:1 ratio.

	Randomized to:	
Response Marker:	**Bupropion treatment**	**Sertraline treatment**
MDD patients with BUP+ response marker	N=30	N=30
MDD patients with SERT+ response marker	N=30	N=30
MDD patients with both or neither marker	N=31	N=32

Furthermore, the sample will be stratified by SHAPS score to ensure equal distribution of anhedonic severity across all treatment groups. Thus, the randomization for patients with clear response markers is based on two factors:

1. Biomarker status: BUP+ response marker vs. SERT+ response marker
2. Anhedonic severity: SHAPS score at Baseline, in three bins: 25-34, 35-44, 45-56.

For participants with inconclusive markers, they will be randomly assigned to either study drug without consideration of balancing anhedonic severity. Randomization setup will be performed by a biostatistician selected by the study team, and the execution of the randomization will be completed by the Research Pharmacy at McLean Hospital. Assignment will be double blind so neither the participants, the experimenters, nor the study physician have knowledge of which treatment the participant is receiving. The study physician can break the blind if it is clinically required.

At the end of the study, once the participant has been debriefed, the participant can send a request to break their blind to the PI. If the PI deems the request medically necessary (I.e., the participant would like to continue the treatment they received outside of the study), the PI will send an email to the pharmacy. The pharmacy will then connect with the participant and only the participant to provide them with their treatment. No study staff beyond the pharmacy and the participant will see which drug they were assigned at this point.

5.4 Withdrawal, Termination, and Loss of Participants

Subjects are free to discontinue their participation in the study at any time and without implications for future mental health treatment. Early discontinuation in this protocol is defined as not completing the final clinical assessment and debrief session.

A subject may withdraw or be withdrawn from the study for the following reasons:

1. Subject withdrew consent.
2. Request of sponsor to terminate the study.
3. Request of primary care physician or investigator.

4. Subject is non-compliant with study procedures or eligibility criteria.
5. Protocol violation.
6. Subject is unable to continue the study.
7. Subject is lost to follow-up.
8. Subject experiences an adverse event (whether considered related to the investigational product or not) that results in a medical condition that may prevent the subject from meeting study criteria.
9. Death.

Documented attempts will be made to follow up on subjects who prematurely discontinue the study. Reasons for premature withdrawal from the study will be recorded in the study enrollment log. This includes also subjects who were screened and assigned a subject identifier but did not initiate treatment. In cases of more than one reason for early withdrawal from the study, the most severe reason will be stated. For example, if the patient withdrew consent due to adverse events the reason will be Adverse Event.

6 Study Procedures

6.1 Study Sessions

The term ’session’ is used instead of ‘visit’ because some of the procedures can be done remotely, without an in-person visit.

This study is comprised of nine sessions, summarized below. A complete schedule of activities is provided in We will try to be as flexible as possible in scheduling, including splitting sessions in half, allowing remote options when possible, and completing procedures over the course of several days.

Table 2.

- Subject Enrollment and Screening: After providing informed consent, subjects will have a clinical interview by a study clinician, an ECG exam, a pregnancy and drug screen, and complete additional surveys to determine eligibility for the study. ECG may be conducted at the Scanning session if participants have limited in-person availability.
- Scanning: Subjects will complete ECG if applicable (see above), clinical assessments, surveys, an MRI exam, an EEG exam, and series of behavioral tasks. Subjects will be given an actigraphy watch to wear for one week either after Subject Enrollment and Screening or Scanning, depending on how soon eligibility is determined and subjects' schedule.
    a. Data analysis and Randomization: After the Scanning session, the data will be analyzed to classify subjects as having either BUP+ or SERT+ response markers. This analysis will be able to classify approximately two-thirds of the participants into one of the two groups (see SMART Response Marker Classification in Section 6.1.2). All participants will be randomized to receive either sertraline or bupropion treatment.
- Baseline (week 0): Subjects will meet with the study physician remotely and will be mailed the drugs for their first week. The physician will complete a thorough medical history, review the medication instructions, and answer any questions the subject has. Subjects will also complete clinical assessments and questionnaires.
- Medication check-in (five sessions at weeks 1, 2, 3, 4, and 6): Subjects will undergo a clinical reassessment and will report on side-effects. The study physician will assess drug side-effects at each visit. Medication will be dispensed at weeks 0, 1, 2, 3, and 4. At week 3, subject will also receive their medication for weeks 4-8 through FedEx or by picking them up at the McLean pharmacy.
    a. The physician may request the participants to come in person for vital signs at any point, and participants will be made aware of this possibility during the consent process.
- Outcomes Assessment (week 8): Subjects will complete clinical surveys, MRI, EEG, and behavioral tasks. The study physician will assess drug side-effects and inform subjects of their options for continuation or discontinuation of treatment. Subjects will be given the actigraphy watch to wear for one week. Once the watch is returned, subjects will be debriefed on the study.

We will try to be as flexible as possible in scheduling, including splitting sessions in half, allowing remote options when possible, and completing procedures over the course of several days.

Table 2. Schedule of Procedures. Acronyms are defined in Section 6.3.2, Surveys and Interviews.

	Screening	Scanning	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8 (Outcomes Assessment)
Informed Consent	X								
Clinical Interview (SCID-5)	X								
MADRS (SIGMA version)			X	X	X	X	X	X	X
HAMD	X								
Audio/video Recording of SIGMA interview, the Affect Induction Prompts, and the Mood section of SCID-5 if administered	X		X	X	X	X	X	X	X
Affect Induction Prompts *only if participant consented to recording			X						X
Medical History			X						
Treatment History (ATRQ)	X								
SHAPS	X	X	X	X	X	X	X	X	X
QIDS-SR	X		X						X
NEO		X							
PVSS-21	X		X					X	X
PVSS-21-Modified				X	X	X	X		
AMI			X						X
GAD-7			X						X
WSAS			X						X
WHO-5			X						X
WHO ASSIST	X								
CNNDC Checklist	X								
Demographics	X								
Edinburgh Handedness	X								
Drug and Pregnancy Screens	X	X							X
MRI		X							X
EEG		X							X
ECG	X	***							

	Screening	Scanning	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8 (Outcomes Assessment)
Blood Draw		X							X
Randomization		(between visits)							
Actigraphy		(between visits)							X
Medical assessment			X	X	X	X	X	X	X
TESS				X	X	X	X	X	X
FIBSER				X	X	X	X*	X*	X
CHRT				X	X	X	X*	X*	X
Dispense medication			X	X	X	X	**	**	
Debrief									(after actigraphy) X
Adverse Events Reporting	X	X	X	X	X	X	X	X	X

* Side-effects reports will also be collected remotely at week 5 and week 7

** Medication may be dispensed if dose changes at physician's discretion

*** May happen at Session 2 if participants were not able to complete it at Session 1

6.1.1 Session 1: Subject Enrollment and Screening

The Screening session will take place in person at McLean Hospital. During the Screening visit, potential candidates will receive complete information regarding the study, (i.e., information about the MRI and EEG procedures, schedule of medication and clinical assessment visits), and their questions will be addressed. Subjects volunteering to participate in the study will read and sign the Informed Consent prior to any study-related procedure. The study physician will consent the participant regarding medication and side effects, review the ATRQ responses, and ask any necessary follow-up questions.

In cases where a participant wishes to stop an excluded medication prior to signing the informed consent document, the participant will be referred to his/her primary healthcare provider or treating psychiatrist for management of the medication washout. The participant will be asked to contact study staff following medication washout if he/she is still interested in participating in the study and would like to set up a screening visit.ECG Test

An electrocardiogram (ECG) will be performed as a measure of heart health for all participants. Any subjects with abnormal lab results or signs of possible heart disease will be excluded from the study at the physicians' discretion. While this exam is not for diagnostic reasons, the participant will be informed of these results and encouraged to consult with their primary health provider for follow up care, if necessary.

Bupropion has been associated in clinical trials with a fast or irregular heartbeat as well as increases in blood pressure. In addition, studies suggest that left ventricular dysfunction can result in decreased metabolism of bupropion, theoretically increasing the chance of side effects. While not an absolute contraindication, Wellbutrin (bupropion) needs to be used cautiously in those with pre-existing cardiac disease or arrhythmia.

If scheduling limits participants availability to complete the ECG in-person at Session 1, study staff will arrange ECG to be performed at Session 2. Our study physicians will review the results prior to scheduling session 3. In this case, participants may become ineligible after they finish Session 2.

Clinical Interview
After obtaining the signed Informed Consent, subjects' eligibility for participation in the study will be assessed using the specified criteria, by a trained clinical assessor, licensed psychologist, nurse practitioner, or physician/MD. A focused clinical interview (SCID-5) with a cannabis addendum will be performed and documented by the investigator or qualified designee to identify whether the subject is eligible to be included in the study. Determination of eligibility also will be guided by use of the Hamilton Depression Rating Scale (HAMD) which informs about depression severity.

The clinical interviews will take place in person at McLean Hospital or remotely via telephone or an MGB-issued Zoom account (http://pcm.partners.org/services/movi.aspx). These structured interviews will be used to assess psychiatric, medical, and neurological history as well past and present psychiatric diagnosis(es). In cases of remote interviews, the clinician will get some indication of the participant's location if any emergencies arise. Study staff will also have an emergency contact for the participant on hand.

The Mood section of the SCID will be recorded, with the subject's consent, for subsequent assessment of prosody and facial expressions. Nonverbal behavior plays an important role in human communication and is an essential part of all clinical interactions, especially in mental health settings. Facial expressions, gaze, body gestures and vocal prosody can reveal information about a person's emotions, mental state and social intentions, and is routinely used by both patients and their doctors in a variety of ways that ultimately can impact healthcare outcomes.

Our video analysis will comprise behavioral cues based on facial action and audiometric signals (such as smile, brow raise, speech rate and quantity). These features can be contextualized and correlated with respect to clinical variables, or other validated psychiatric scales.

Additional self-reported scales will be administered through REDCap (see Table 2, Schedule of Procedures). For the measures that are administered through REDCap, the participant will receive a link to complete these surveys independently.

Treatment History
The Antidepressant Treatment Response Questionnaire (ATRQ) will be used to assess whether subjects are treatment resistant, defined as having failed to respond to at least two adequate antidepressant trials in the current episode. Responses will be reviewed by study staff along with other questionnaires. Clinicians and physicians will have a chance to follow up on the participant responses at session 1. If subjects are determined to be treatment resistant, they will be excluded from the study.

Urine Drug Test and Pregnancy Test
A urine drug test, such as the AmediCheck™ CLIA waived 12 panel cups (Amedica Biotech, Inc., Hayward, CA) will be administered to all subjects at session 1. Participants who test positive for drug use, with the exception of THC, will be terminated from the study.

A urine pregnancy test will also be administered to women of child-bearing potential at session 1, using the QuPID® hCG Pregnancy Test Set (StanBio Laboratory, Boerne, TX). Participants who test positive for pregnancy will be terminated from the study

If, at any point during the study, a participant becomes suicidal, homicidal, manic, or psychotic, they will be withdrawn from the study and appropriate care will be provided (see Plans for dealing with at risk individuals, suicidality, and referral for psychiatric treatment in section 7, Risks and Discomforts).

Confirmation of eligibility will be documented, and the next study session will be scheduled with the subject.

Actigraphy

We will provide the participant with and activity watch at the end of the first session or the scanning session that tracks motion, participant skin conductance, and skin temperature. The timing of this instrument will depend on how soon subjects' eligibility is determined and their schedule. They will wear it continuously for one week. Additionally, the participant will be asked to wear the watch for one week following their post-treatment scanning visit. They will either return the watch to McLean or ship it after the week is complete.

Participants will be asked to wear the watch at all times with the exception of activities during which the watch would be completely submerged in water. The watches also have sufficient battery life, so the participant will not need to charge them during the week in which they are wearing it.

6.1.2 Session 2: Scanning

The Scanning session will take place within four weeks following the screening session. If more than four weeks passes between the sessions, the subject will be reassessed by the clinician over the phone, by readministering the MDD symptom section of the SCID.

The Scanning session will last about 6 hours and consist of MRI and EEG exams, questionnaires, behavioral tasks, and a blood draw.

MRI Scanning

The MRI scans will be conducted at the McLean Imaging Center (MIC). Participants will arrive at the MIC, where they will complete a urine drug test, and female participants will complete a urine pregnancy test. Participants will also complete again the MRI Safety Screening form, which will be reviewed by the MRI Technologist. Participants who do not pass the MRI safety screen will not be allowed to continue. Participants who test positive for drug use, not including THC, will be terminated from the study. Additionally, female subjects who test positive for pregnancy will be excluded from the remainder of the study.

Before the MRI procedure, participants will experience a mock scanner, which simulates the environment of the 3T Prisma scanner.

Subjects will be offered hospital scrubs to change into. If they remain in their own clothes, they must remove any items that may contain metal including certain zippers, underwire bras, clothing with metallic buttons or decorations, and shoes. Subjects will be required to remove any metal objects from their person such as (but not limited to): watches, rings, bracelets, pierced jewelry, belts, coins, and wallets (with credit cards). Prior to entering the scanner environment, MRI techs will use a metal detecting wand on all participants.

The MRI scan will last approximately 90 minutes. The scan will include a functional MRI scan conducted while the subject performs the Guessing Monetary Reward Task (Forbes et al., 2009), which ascertains ventral striatal activation during reward motivation. The fMRI will continue while the participant performs the Effort-based Decision-making task (Bonnelle et. al., 2016). Additional scanning will include a structural scan and a resting-state scan. Refer to Section 6.3.4 for additional details about these sequences.

Peripheral psychophysiological measures (e.g., heart rate and respiration) will be collected throughout the scanning session using MRI-compatible equipment. Heart rate will be collected using a non-invasive wireless physiological monitor that clips on to the participant's pointer finger. Respiration will be collected by attaching a respiratory cushion to the participant using a belt fastened to the lower chest. Both the sensor and the belt can be easily applied and removed. The experimenter will ensure that the clip and belt are securely attached to the participant and that the participant is comfortable. This wireless monitoring system is a standard Siemens system, which comes with the FDA-approved Siemens 3.0 magnetic resonance scanner and is MRI compatible.

Prior to the research scans, a screening scan (VA Brain sequence) will be acquired and later reviewed by a certified neuroradiologist. Any reports with potential abnormalities are reviewed by the MIC Clinical Director, Dr. Gordana Vitaliano, and forwarded to the PI. If an abnormality is present, the PI will coordinate the process of contacting the subject so that an appointment can be made to discuss the findings. The MIC Clinical Director may also assist with this process when requested and appropriate. If a follow-up scan is recommended by the radiologist, we will offer the subject a cost-free clinical scan (with contrast if indicated) at the MIC. A copy of both the clinical report and the MRI scan is offered to subjects to take to their primary care or other consulting physicians, at no cost.

Urine Drug Test and Pregnancy Test
Prior to the MRI exams a urine drug test, such as the AmediCheck™ CLIA waived 12 panel cups (Amedica Biotech, Inc., Hayward, CA) will be administered to all subjects. Participants who test positive for drug use, with the exception of THC, will be terminated from the study.

A urine pregnancy test will also be administered to women of child-bearing potential prior to each MRI scan, using the QuPID® hCG Pregnancy Test Set (StanBio Laboratory, Boerne, TX). Participants who test positive for pregnancy will be terminated from the study

Break

Participants will be given time to eat in the middle of the study session. They will be encouraged to provide their own food, but may also choose to purchase food at the cafeteria.

EEG Exam
After the MRI scan is complete, a research assistant will bring the participant to the PI's EEG laboratory in the deMarneffe Building at McLean Hospital. Participants will be fitted with a 96-channel electrode cap, then undergo 8-minutes of resting state EEG recording (4 minutes with eyes open, 4 minutes with eyes closed), followed by administration of the Probabilistic Reward Task (20 min) and Flanker Task (18 min). These EEG recordings will be used to derive metrics of reward learning and cognitive control, respectively. All EEG recordings will be administered in an acoustically and electrically shielded room within the PI's laboratory, using a 96-channel EEG data collection system (Brain Products GmbH).

After the EEG exams are finished, participants will perform the Effort-Reward Trade-off task, which is detailed in Section 6.3.4.

Blood Draw
After verifying that the participant has agreed during the Informed Consent process to provide a blood sample, we will collect approximately 32.5 mL of blood in four vacutainer tubes. Blood samples will be collected by certified staff nurses, MRI Technicians, or study staff who have completed MGB-sponsored phlebotomy training according to the routine clinical procedures and good clinical practice guidelines.

a.) approximately 20 mL of blood in two 10 mL EDTA tube
b.) approximately 10 mL of blood into one 10 mL serum tube
c.) approximately 2.5mL of blood into one PAXgene Blood RNA tube

A barcoded label will be affixed to each tube with the following information: site ID, participant ID, date and time of collection. The samples will be transported to the McLean Biorepository where they will be processed and stored at -80° C for future analysis of endocrine, biomarker, and genetic/genomic contributions to anhedonia. The portion of blood samples earmarked for RNA-based assays will then be transported to Circular Genomics for RNA extraction and processed immediately for analysis starting January 2025. Partial samples will be returned to McLean Biorepository from Circular Genomics for long-term storage and future studies and analysis.

Behavioral Tasks and Questionnaires

The subject will complete some questionnaires about their mood and feelings. They will also complete the Effort-Reward Trade-Off task (Berwian et al., 2020) on a desk top computer, if time permits.

Intersession Data Analysis and Randomization

Following the second session, the results of the MR imaging, EEG, and behavioral tasks listed above will be analyzed to determine the subject's clinical response markers (i.e., BUP+ or SERT+). This assignment uses a regression analysis called "Sequential Multiple Assignment for Randomized Trial" (SMART), which is based on results of prior research by the investigators (see Section 3, General Description of Study Design).

Processing the MR imaging data will take a day or more.

SMART Response Marker Classification
The following measures are considered when assigning response markers to subjects:

BUP+ Response Marker:

- Functional Connectivity: rsRC metric between the NAc and the rACC
- Greater reward bias on the Probabilistic Reward Task (resp)
- Greater reward sensitivity on the Probabilistic Reward Task (reward)
- Optimal cut-off:
    a. $4 * resp + 1.9*reward + 11.8*NAc\text{-}rACC \geq 2.9$

b. Subjects who satisfy the above inequality are identified as BUP responders (BUP+)

SERT+ Response Marker:

- Functional Connectivity: rsRC metric between the NAc and rACC
- Higher depression severity (determined from pre-treatment HRSD score)
- Higher level of cognitive control (determined by better performance in the Flanker Interference Task)
- Being currently employed
- Neuroticism (determined from the NEO score)
- Optimal cut-off
  a. -11*NAc-rACC + 0.03*w0 – 5.9*flanker + employ – 0.08 * neo2 ≥ -4.5
  b. Subjects who satisfy the above inequality are identified as SER responders (SERT+)

Based on these criteria, some participants will not fit the profile of either of the two response markers (or will be assigned to both) and so will not be assigned to either group by the SMART regression analysis. These unclassified participants will still be randomized to receive treatment and complete the rest of the study, forming a fifth, control arm.

Notification to Research Pharmacy
The resulting response marker or unclassified status will be conveyed to the Research Pharmacy along with the other data that are required for randomization as part of the medication order (see Section 5.3, Randomization and Blinding). The pharmacy will conduct the randomization and then package the appropriate medication. A member of the study team will bring the package to the participant.

If a subject cannot be randomized for any reason or chooses to withdraw between scanning and baseline, they will meet with study staff to be debriefed and receive appropriate referral material so they can seek treatment outside of our study. They will be compensated for the study activities that they have completed.

6.1.3 Baseline - Initial Medication session (week 0)

Once randomization is complete, eligible subjects will be scheduled for their Baseline session remotely. Subjects may be required to participate in-person at McLean Hospital to have their vitals taken if physicians decide there is a need. The following activities will be performed during the baseline visit:

- They will complete the SIGMA interview and the Affect Induction Prompt with a study clinician, which will be recorded with the participants' consent
- They will complete clinical surveys online through REDCap (see Table 2, Schedule of Procedures).
- They will meet with the study physician who will collect detailed health history and review the subject's medication history. The study physician will describe the treatment procedures once again for the subject and answer any question, they will then dispense the initial week's medication.
- Medication will be shipped to the participant

Three additional days of pills will be given to subjects to allow for flexibility in scheduling subsequent visits. The remaining number of pills will be checked by the physician at each visit.

6.1.4 Weekly Check-In sessions (weeks 1, 2, 3, 4, 6)

Check-in sessions will occur 1, 2, 3, 4, and 6 weeks after the Baseline session. These visits will be conducted on an MGB-issued Zoom account unless the physician decides that vitals need to be tracked. Then the participant will come into McLean for the specified week. The following activities will be performed during the check-in sessions:

1. Participants will repeat the SIGMA interview with a study clinician, which will be recorded with the participants' consent.
2. They will complete interim assessments of depressive and anhedonic symptoms using the PVSS-21-Modified, and SHAPS surveys.
    a. Note: A modified PVSS-21 for these weekly visits that asks about the past week since the last visit will be used. The original PVSS-21 asks about the past two weeks which would be redundant and potentially confusing for participants who are reporting symptoms weekly.
3. They will complete three surveys that probe possible side-effects of the medication: the Treatment Emergent Signs and Symptoms scale (TESS); the Frequency, Intensity, Burden of Side Effects Rating scale (FIBSER); and the Concise Health Risk Tracking scale (CHRT). The TESS will be administered by the physician.
4. They will meet with the study physician, who will review the side-effect surveys. If the study physician determines that it is safe to continue, they will dispense the medication for the upcoming period. Three additional days of pills will be given to subjects every week during week 0, 1, and 2 to allow buffer time between the current session, shipping, and the next check-in sessions. The physician will check the extra number of pills at the next visit. Subjects will receive their medications for week 3-8 at week 3 with three additional days of pills via FedEx, or they can pick up the medication at the McLean pharmacy.

6.1.5 Outcomes Assessment session (week 8)

The Outcomes Assessment session will take place eight weeks after subjects receive their first dose of medication at McLean Hospital. The session will include the same procedures as those conducted in the Scanning session (see above). Participants will meet with the study physician for a final assessment of side-effects and will be debriefed about study procedures.

The following activities will be performed as part of the Outcomes Assessment:

- Urine drug screen and if applicable, urine pregnancy screen
- MRI Safety Form and mock scanner practice
- Clinical interview measures (SIGMA, Affect Induction Prompts)
- Self-report measures (QIDS-SR, SHAPS, PVSS-21, AMI, GAD-7, WSAS, WHO-5)
- MRI Scan
    - Structural MRI
    - fMRI while the participant completes the Guessing Monetary Reward Task, and the Effort- and Reward-based Decision-making Task

- Behavioral task
  - Effort-Reward Trade-off Task
- 96 Channel EEG
  - Baseline recording (8 minutes)
  - Probabilistic Reward Task (20 minutes)
  - Flanker Interference Task (18 minutes)
- Break for lunch/snack
- Blood Draw
- They will have their vital signs collected by a study staff at physicians' discretion
- Side-effects surveys (TESS, FIBSER, CHRT)
- Meet with study physician to assess side-effects and vitals, and review possible treatment options
- Provide participants with the actigraphy watch
- Once the watch is returned, subjects will be debriefed

6.2 Study Drugs

6.2.1 Sertraline & Bupropion

Sertraline (SERT) and bupropion (BUP) are both FDA-approved for treatment of major depressive disorder. Sertraline is an SSRI commonly used to treat depression. Bupropion is an atypical antidepressant. Although its mechanisms of action are unclear, the overall effect of BUP appears to be a dose-dependent increase in brain extracellular dopamine and norepinephrine concentrations.

Due to contraindications from these drugs, participants will be excluded for any of the following known risk factors: seizure disorder or known risk for seizures, bipolar disorder, bulimia, anorexia nervosa, current use of pimozide, use of Monoamine Oxidase Inhibitors (MAOIs) within the past two weeks, or a history of adverse reaction to either study drug. Participants who are currently discontinuing the use of tobacco products will be excluded, and all subjects will be instructed to not discontinue tobacco use while taking the study drugs. Participants will also be told not to abruptly discontinue use of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs.

Because participants are blind to the medication they will receive, they will be informed of all the common side effects of either drug. The most common side effects of sertraline are: nausea, diarrhea/loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido. The most common side effects of bupropion are: headache, dry mouth, insomnia, dizziness, pharyngitis, constipation, agitation, anxiety, abdominal pain, tinnitus, tremor, palpitation, myalgia, sweating, rash, and anorexia.

As part of their assessment at each weekly medication visit, the study physician will assess the participant for these warning signs as directed in the product inserts: increase in blood pressure, symptoms of mania, psychosis, or other neuropsychiatric reaction. These are in addition to other assessments of side effects.

6.2.2 Dosing

Dosing will follow the schedule shown in Table 3. Dose is raised only if tolerated. All medication will be taken in the morning as a single dose of four identically matched capsules. To

preserve blinding, participants in all four arms will always take four identical capsules, which may include placebo capsules as shown in Table 3. The extended release form of BUP (i.e., bupropion XL) will be used to enhance adherence with single daily dosing, which is made safer by using the XL formulation.

The starting dose of sertraline will be 50 mg, and will be titrated in increments of 50 mg up to the target dose of 200 mg. The starting dose of bupropion is 150 mg, titrated in increments of 150 mg to the target dose of 450 mg. Blinding will be achieved by over-capsulating commercially available tablets.

Table 3. Dosing Schedule

Study Week	Sertraline						Bupropion XL				
	Dose	Dispense					Dose	Dispense			
Baseline (Week 0)	50 mg	50	pbo	pbo	pbo		150 mg	150	pbo	pbo	pbo
Week 1	100 mg	50	50	pbo	pbo		300 mg	150	150	pbo	pbo
Week 2	150 mg	50	50	50	pbo		450 mg	150	150	150	pbo
Week 3	200 mg	50	50	50	50		450 mg	150	150	150	pbo
Weeks 4-8	200 mg	50	50	50	50		450 mg	150	150	150	pbo

Side effects will be monitored at each weekly visit by the study physician.

The Frequency, Intensity, Burden of Side Effects Rating (FIBSER) scale is designed by Dr. Stephen Wisniewski for use in the U.S. STAR*D effectiveness study. It is a 3-item scale to assess side effects from antidepressant treatment. We will evaluate three areas of drug side effects through patient self-report and rank the drug impact: frequency (how many adverse reactions caused by depression drugs in the past week), intensity (how serious adverse reactions caused by depression drugs in the past week), and burden (how much adverse reactions caused by depression drugs affect your daily activities in the past week). To use the FIBSER in our dosing assessments, we will consider item #3 (Burden).

- If the score is 0 to 2 (None to Mild interference with activities), no change in medication is needed.
- If the score is 3-4 (Moderate to Marked interference with activities), the side effects need to be addressed (i.e., the dose needs to be decreased).
- If the score is 5-6 (Severe interference with activities or Unable to Function), the dose needs to be decreased or the medication needs to be discontinued.

The FIBSER scale will be reviewed by our physician and used with Treatment Emergent Symptom Scale (TESS) to further evaluate severity of treatment-emergent signs and symptoms. Additional treatment-emergent side-effects reported by subjects will also be collected and evaluated based on TESS criteria. The severity level of symptoms will be evaluated on a 4-point scale (from no symptoms to mild, moderate to severe symptoms). The dosing will be adjusted based on FIBSER criteria for dosing assessment (e.g., burden scores 3 to 6) and TESS criteria for severity (e.g., moderate to severe). The dosing may also be decreased at the physician's discretion.

Concise Health Risk Tracking (CHRT) is a brief 14-item scale that will be used to assess suicide risk and ideation in the past week. If, at any point during the study, a patient becomes suicidal

he/she would be withdrawn from the study and appropriate care will be provided. Also, if serious adverse reactions occur patient would be withdrawn from the study at the physician's discretion and appropriate care will be provided.

As noted, the physician may be able to predict a drug based on its side effects. For example, sexual side effects are usually caused by SSRIs (e.g., sertraline) but not bupropion. Bupropion is used to treat sexual side effects. However, depression can also cause sexual side effects. Therefore, these predictions will not necessarily be accurate, and the physician will remain blinded for the duration of the study. Possible unblinding of the physician due to side effect profile is further mitigated because separate clinical interviewers administer the clinical scales used to evaluate clinical response.

6.3 Data collection

6.3.1 REDCap Electronic Data Capture System

Throughout the study, participants will complete standardized surveys using the REDCap online data collection system. REDCap is a web-based application designed to support data collection for research studies. REDCap meets all HIPAA requirements and has been certified by the MGB Research Information Security Office (RISO). The REDCap software and data are hosted on secure servers at the MGB Research Data Center.

6.3.2 Surveys and Interviews

- **Structured Clinical Interview for DSM-5 (SCID):** diagnostic interview tool to assess Axis I disorders.
    - **Cannabis Addendum:** assesses details of cannabis use
- **Montgomery–Åsberg Depression Rating Scale (MADRS):** a 10-item clinician-administered questionnaire assessing symptoms of depression.
- **Structured Interview Guide for the MADRS (SIGMA)**: a version of the MADRS with guidance for administering the instrument. This version improves reliability.
- **Hamilton Depression Rating Scale (HAMD):** a 17-item clinician-administered scale for assessing depression severity
- **Affect Induction Prompts:** a 7-item clinician-administered interview with open-ended questions related to mood and memories.
- **Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR):** a 16-item depression scale, yielding scores from 0-27, which covers the symptom domains of major depressive disorder, for the time frame of the past week: mood; concentration; suicidal ideation; anhedonia; loss of energy; insomnia; appetite change; psychomotor agitation/retardation; as well as self-esteem.
- **Snaith Hamilton Pleasure Scale (SHAPS):** 14-item self-administered measure of anhedonic symptoms. The purpose of this assessment is to evaluate the ability to enjoy/experience pleasure in activities in the past week.
- **Positive Valence Systems Scale (PVSS-21):** 21-item assessment of the positive valence system, including things such as reward valuation, reward expectancy, effort valuation, reward anticipation, action selection, and initial responsiveness.
- **Positive Valence Systems Scale Modified (PVSS-21-Modified):** 21-item assessment of the positive valence system, including things such as reward valuation, reward expectancy, effort valuation, reward anticipation, action selection, and initial

responsiveness. This is the exact same as the PVSS-21 except this modified questionnaire asks participants to respond based on their experiences in the past week.

- **Apathy Motivation Index (AMI):** 18-item self-report measure of apathy. The AMI covers behavioral activation, social motivation, and emotional sensitivity over the past two weeks.
- **General Anxiety Disorder scale (GAD-7**): 7-item scale used to screen for anxiety or to measure its severity. The GAD-7 score is calculated by assigning scores of 0, 1, 2, and 3, to the response categories. Scores of 5, 10, and 15 are taken as the cut-off points for mild, moderate, and severe anxiety, respectively. When used as a screening tool, further evaluation is recommended when the score is 10 or greater.
- **Work and Social Adjustment Scale (WSAS):** a 5-item self-report measure that assesses functional impairment as a result of a specific disorders and/or symptoms. In our study we will use the WSAS to assess functional impairment brought on by depression.
- **World Health Organization Well-being Index (WHO-5):** a 5-item self-report measure of current mental well-being.
- **National Network of Depression Centers self-administered Comorbidity questionnaire (C-NNDC):** a 15-item self-report measure that assesses current medically relevant conditions (e.g., thyroid disease, ulcers, kidney disease) to depression.
- **NEO Five-Factor Inventory-3** (FFI-3; Costa & McCrae, 2010): This abbreviated NEO questionnaire assesses the "big five" personality traits. There are 60 items total (12 items/subscale). We only included the 12-item neuroticism subscale.
- **World Health Organization Alcohol, Smoking and Substance Involvement Screening Test (WHO ASSIST)**: an 8-item clinician administered assessment of current and lifetime substance use.
- **MGH Antidepressant Treatment Response Questionnaire (ATRQ):** a self-report questionnaire assessing the use of antidepressants and additional medications taken to boost antidepressant effects during a participant's current depressive episode. Dosage of medication and self-reported clinical improvement is also assessed.
- **Edinburgh Handedness Inventory:** a 10-item self-report measure used to assess the dominant hand of an individual.
- **Demographics Questionnaire:** information about gender, race/ethnicity, education, occupation, income, and BMI.
- **Treatment Emergent Symptom Scale (TESS):** physician-administered survey that assesses side-effects and adverse reactions to psychiatric medications.
- **Frequency, Intensity, Burden of Side Effects Rating scale (FIBSER):** a 3-item self-report scale to assess side effects of antidepressant treatment in the past week.
- **Concise Health Risk Tracking (CHRT):** a brief 14-item self-report scale assessing suicide risk and ideation in the past week

6.3.3 MRI Sequences

All MRI scans will be done on an FDA-approved Siemens 3.0 Tesla magnetic resonance scanner with a 64-channel brain array coil. The scanning session will utilize sequences routinely collected at the facility. The total acquisition time will be 1.5 hours.

- Structural MRI: High-resolution, T1- and T2-weighted MPRAGE anatomical images will be collected at 3T using the Human Connectome Project – Development/Adult (HCP-D/A) acquisition protocol for 3T scanners (Harms et. al, 2018).
- Functional MRI: fMRI imaging will be acquired using a gradient echo T2*-weighted echoplanar image (EPI) multiband (MB) sequence which achieves excellent temporal and spatial resolution
- Resting state fMRI: We will acquire multi-echo multi-band resting-state fMRI scans adapted from Lynch et al. (2020).
- Iron scan: If time permits, we may acquire a standard turbo spin echo imaging (TSE) sequence to assess tissue iron to compute a proxy variable for dopamine availability, allowing measurement of dopamine function in reward circuitry.
- Diffusion Tensor Imaging: If time permits, we may acquire DTI images using the HCP-D/A protocol (Harms et. al, 2018, Neuroimage).

6.3.4 Behavioral and Neurophysiological Tasks

Probabilistic Reward Task (during EEG)
The Probabilistic Reward Task (PRT) has been successfully used by the PI to assess reward responsiveness (Pizzagalli et. al, 2008). In each trial, participants choose which of two difficult-to-differentiate stimuli was presented. Stimuli consist of simple cartoon faces (diameter: 25 mm; eyes: 7 mm) presented in the center of the monitor. At the beginning of the trial, the face has no mouth. After a given delay, either a straight mouth or nose of 11.5 mm ("short") or 13 mm ("long ") is presented for 100 ms. Subjects are instructed to press an appropriate button to decide whether a long or small mouth or nose had been presented. Unbeknownst to participants, correct identification of one stimulus ("rich stimulus") is rewarded three times more frequently (*"Correct! You won 20 cents"*) than the other ("lean") stimulus. In healthy controls, this reinforcement schedule leads to a response bias (i.e., a preference for the more frequently rewarded stimulus). The degree of response bias toward the more frequently reinforced alternative will be used for operationalizing sensitivity to reward.

Flanker Interference Task (during EEG)
The PI's lab has successfully implemented Flanker tasks in behavioral, EEG, and imaging studies that have excellent test-retest reliability (r=0.75-0.84). In this task, participants will complete an 8-trial practice session that includes 4 congruent and 4 incongruent trials and is used to individually titrate task difficulty in the main blocks. The flanking and target stimuli are presented with a 200ms duration. Participants are asked to indicate whether the center arrow is facing left or right, and accuracy and RT are recorded. Participants then complete 12 blocks of 20 trials, for a total of 240 trials (120 congruent, 120 incongruent).

Effort-and Reward-based Decision-making task (during MRI)
The aim of the Effort- and Reward-based Decision-making Task (also known as the Bonnelle task) is to investigate whether effort or reward is most critically involved in anhedonia observed in healthy individuals (Bonnelle et al., 2016). In this simple computer game, participants are presented on a trial-by-trial basis with an offer, which they can accept or reject. They are presented visually with a combination of a "stake" (or incentive) and an "effort" level. If they accept the offer, they are required to engage in an effortful physical response (i.e., squeezing a handgrip) to obtain a "reward." As in real-world situations, the actual reward obtained depends

both on the stake on offer and on the physical force produced. If an individual rejects the offer, a new offer is presented.

During the Bonnelle task, effort will be measured using a BIOPAC MR-compatible Hand Clench Dynamometer. This hand-held device is MRI compatible. The trace conductive parts of the transducer are electrically and thermally isolated from the subject.

Guessing Monetary Reward Task (during fMRI)
The Guessing Monetary Reward Task is a number-guessing task that lasts approximately 18 minutes and involves pressing buttons to earn money. The participants are told that their guesses on each trial can be correct or incorrect, influencing the amount of money they earn.

Instead, outcomes are fixed, and trial outcome order is pseudorandom and predetermined. This approach ensures that all participants have the same experience of the task (e.g., for the first trial in the Baseline Assessment session, all participants will have a win outcome) and any variability in response will be more specifically attributable to individual differences. Following the task, participants will answer questions about the task in the post-card guessing task questionnaire which asks questions about their experience with the task.

After the Outcome Assessment session (detailed below), we will provide debriefing about this deception and explain the scientific rationale for this approach. We will also assess whether participants experience distress over the deception and allow them to communicate any related concerns.

Effort-Reward Trade-off task (desktop computer)
The goal of the task is to assess reward and effort anticipation and experience (Berwian et. al, 2020). On each trial, patients decide between investing little effort (fewer button presses) for a small reward (points) or more button presses for a larger reward. Effort levels include 20, 40, 70, 100 and 130 button presses. Rewards include 3,4,5,6 and 7 points. Patients indicate their decision with a button press within 4 sec, and then have 40 sec to execute the effortful behavior, allowing us to measure effort experience. We collect data on the choices subjects make as well as the time it takes them to make the choice (decision time) and the time between button presses (effort execution time). Every third trial participants are asked to rate their momentary happiness on a slider ranging from 0 to 100, which we use as a proxy to assess reward experience.

This task is performed on a local desktop computer. The software interacts with a secure webpage and server controlled by our collaborators, Dr. Yael Niv and Dr. Isabel Berwian at Princeton University. This interaction and exchange of data is described in detail in Section 6.8, Data Transfer. A Data Transfer Agreement has been approved.

Actigraphy (Activity Watch)

The watch measures motion of the participant with an accelerometer which is a neurophysiological metric important to psychomotor symptoms of depression. The band is a standard for use in sleep studies, and we have chosen the smallest, light weight version. The band is similar to a Fitbit, and participants will be asked to wear it continuously with the exception of activities that would cause it to be completely submerged in water.

The activity watch we are using the the GeneActiv Original which has:

1. Accelerometer
2. Direct Skin temperature sensor

3. Peripheral Skin temperature sensor
4. Microelectromechanical System (MEMS) for the sensors and gyroscope

We will collect the raw data from the device itself, rather than solely proprietary derivatives of raw data using these sensors. GeneActiv watches do not contain a microphone, cameras, or any other sensors that could generate identifiable data streams.

6.4 Definition of Primary Endpoint

The endpoint of the study is having 120 participants with either SERT or BUP response markers complete all medication and measurement procedures, with 30 of these participants in each of the four arms (see Section 3). In addition, there will be 63 participants that were found to have both or neither marker in a fifth arm. The projected rate of completion is shown in **Table 4**.

Table 4. Projected rate of completion

	Randomized for Drug Trial	BUP/SERT Responders who Completed Drug Trial	Control (neither or both markers) who Completed Drug Trial
Year 1	N = 61	N = 40	N = 21
Year 2	N = 61	N = 40	N = 21
Year 3	N = 61	N = 40	N = 21
Total	N = 183	N = 120	N = 63

6.5 Standard of Care

The standard of care for major depressive disorder usually consists of antidepressant medications. Antidepressants are usually administered following a diagnosis of major depression by clinical interview and/or use of a variety of diagnostic questionnaires. For this study, diagnoses will be obtained primarily by the SCID. At the present time, there is no commonly agreed upon standard of care for MDD resistant to SSRIs. Treatments include switching to a second SSRI, switching to a non-SSRI agent, or augmenting the SSRI with a second compound. In our study subjects will be randomly assigned to receive either bupropion, a noradrenaline/dopamine reuptake inhibitor, or sertraline, an SSRI. We hypothesize that participants who are assigned to receive the medication that aligns with their clinical response marker (i.e., SERT+ response marker/SERT medication and BUP+ response marker/BUP medication) will display twice the response rate relative to non-matched participants.

Additional treatments for major depressive disorder include psychotherapy and Transcranial Magnetic Stimulation (TMS). Standard care for treatment resistant depression, which will not be included in this study, often involves electroconvulsive therapy (ECT). Participants who are either deemed ineligible or who chose to terminate participation in our study and note interest in other methods of treatment for MDD will be provided with a list of resources.

At the end of our study, during week 8, participants will meet with our clinicians and study physicians to assess current symptoms and side-effects. Participants who have responded to treatment and/or remitted from depression (MADRS score improvement of 8 or 9) will be

encouraged to speak with their primary care physician to continue treatment. Participants who have not responded to treatment will be referred to other treatment centers.

6.6 Remuneration

All subjects will be compensated for the completion of study tasks. The breakdown of compensation is as follows:

1. Enrollment and Screening session: If the participant is found ineligible or drops out before visit completion, they will be paid $20 per hour spent participating.	$60
2. Scanning Assessment session: a. $50 for completing behavioral tasks b. $50 for completing the EEG c. $100 for completing the MRI scan d. Up to an additional $65 based on performances on behavioral tasks e. $10 for completing one week of actigraphy	$210 (+$65)
3. Baseline and Check-ins	8 weeks of antidepressant at no cost
4. Outcomes Assessment session: a. $50 for completing behavioral tasks b. $50 for completing the EEG c. $100 for completing the MRI d. Up to an additional $65 based on performances on behavioral tasks e. $10 for completing one week of actigraphy	$210 (+$65)
5. Bonus for subjects who complete all study activities:	($100)
TOTAL:	$480 (+$230)

These payments will be managed according to the MGB policy, Cash Control and Accountability for payments to Human Subjects for Participation in Research. Researchers will keep a Cash Payment Log, recording which participants have received this form of compensation.

Costs for travel to and from McLean will be covered. Travel reimbursement will be given to subjects using eCheck. All other compensation for the study will happen through Advarra. Further payments will be issued after each session. If the subject does not complete the entire study, they will be compensated for the visits that were completed. If a visit is started but not completed, compensation will be prorated based on the expected length of the visit at a rate of $20 per hour using eCheck.

6.7 Specimen Transfer

Not applicable. No specimens will be transferred.

6.8 Data Transfer

Participants will complete the Effort-Reward Trade-off task developed by our collaborators at Princeton University, Dr. Yael Niv and Dr. Isabel Berwian. The task is written in JavaScript and runs in a web browser. It connects with a secure webpage hosted on a server located at Princeton University. The server is encrypted and requires authentication and authorization to gain access. The data from this task can only be accessed by our collaborators Dr. Yael Niv and Dr. Isabel Berwian and authorized members of their team.

No personal identifying data are collected during this task, and none are sent to the Princeton server at any time. The behavioral measurements are collected and scored by the software at Princeton, and the results are returned to McLean.

A Reciprocal Data Transfer and Use Agreement between McLean Hospital and Princeton University has been created and approved.

7 Risks and Discomforts

All studies will be performed with the approval of the MGB Human Research Committee (PHRC). Every effort will be made to provide information to participants to reduce their anxiety about the procedures. All clinical assessors have extensive experience in clinical psychiatric assessment. Measures to minimize risks include the careful assessment of each participant before the study, and close clinical scrutiny during all aspects of the study. Research interviews or experimental assessments will be interrupted if participants become distressed or object to answering questions. Screening for suicide risk factors and suicidality is described below. If an adverse event occurs during the imaging protocols, appropriate medical intervention will be provided. A physician will be available in the Imaging Center during the MRI scans.

The consent form will clearly specify that a participant may stop the study at any time for any reason. For example, if during the MRI session a subject becomes uncomfortable, the study will be stopped, and the participant may speak with a study clinician if this becomes necessary. Dr. Pizzagalli will oversee any issues that may arise.

If, at any point during the study, a patient becomes suicidal, homicidal, manic, or psychotic, they will be withdrawn from the study and appropriate care will be provided. Further, participants will be informed that a study clinician will be available for consultation.

We have successfully implemented these procedures in >10 independent samples involving more than 500 unmedicated individuals with MDD recruited from the community and have not encountered any adverse reactions or issues. In addition, this team has successfully performed neuroimaging studies with multiple sessions in depressed, at-risk, or remitted samples with high completion rate.

7.1 Complications of Surgical and Non-surgical Procedures

Screening and evaluation
The risks and discomforts of the screening evaluations are minimal. No discomfort is expected to be associated with the clinical interview other than potential stress of answering personal questions.

Plans for dealing with at risk individuals, suicidality, and referral for psychiatric treatment
After consent is obtained, a full medical and psychiatric history will be taken. In the case of a remote screening session, the research coordinator will ask for participant's current location at the beginning of the call, in case of an imminent risk situation. In addition, an emergency contact form will be completed at the screening session following consent procedures. All clinical assessors (e.g., board-certified psychiatrists and licensed clinical psychologists) have extensive experience in clinical psychiatric assessment with currently and previously depressed populations and will make every effort to implement protocol procedures in a sensitive and supportive manner. Research interviews or experimental assessments will be interrupted if participants become distressed or object to answering questions. If, at any point during the study, a participant becomes suicidal, homicidal, manic, or psychotic, they will be withdrawn from the study and appropriate care will be provided.

In the unlikely event that any of the interviews or instruments administered during the screening session are highly distressing to the subject, the clinical interviewer will make a further assessment of current suicidal intent and planning. If the interviewer judges that the patient is at imminent risk of self-harm, the interviewer will walk the person to the nearby McLean Emergency Services (Clinical Evaluation Center). The PI will also be informed of the situation. If the participant refuses to take part in the plan above, we will call 24-hour McLean Crisis Mental Health Care service (800-333-0338) for immediate assistance and evaluation for possible hospitalization and inform the staff of the subject's location and risk level.

If the session is occurring remotely, the clinician will keep participants on the phone while contacting (or enlisting the help of colleagues to contact) clinician/people in support network to inform them of level of risk and enlist their assistance in getting subject to a clinician or psychiatric emergency room. If subject refuses to do this, the clinician will call 911 and inform of subject's location (to be collected at the beginning of the study session) and risk level. If risk is judged to be serious but not imminent, the interviewer, in consultation with the PI and the study physicians, will provide crisis phone numbers as well as relevant referrals for therapy, and to verify that the subject understands how best to access these resources. See the LATN Suicidality Procedures and Managing Suicide Risk Remotely documents for more information.

Behavioral Tasks
We foresee no risks from the behavioral tasks required for the proposed research (the PRT, Flanker Task, Effort-Reward Decision-making Task, Effort-Reward Trade-off Task, and the Guessing Monetary Rewards Task). The Guessing Monetary Rewards Task has been used in over 800 participants, and this approach (as well as debriefing participants about it) has not elicited distress in participants. At the end of the study, we will debrief the deception used during the tasks and explain the scientific rationale for this approach. We will also assess whether participants experience distress over the deception and allow them to communicate any related concerns.

Questionnaires
Possible discomfort may occur while answering personal questions while completing the questionnaires and interviews. Assessments will be interrupted if participants become distressed, and questions will be skipped if the participant objects to answering them.

Risks associated with blood draw
A staff nurse, a trained MRI Technician, or MGB-certified phlemotomist will draw blood from each patient at the day of the MRI scanning visit. A slight risk for psychological discomfort exists when assessing depression and clinical/behavioral phenotyping. There may also be some anxiety or discomfort associated with the blood draw. This may include minor pain of the needle stick, some risk of slight bleeding, bruising, and, rarely, infection and fainting. The risk of syncope will be minimized by having the participants recline during the blood draw as and when necessary. The total blood draw will be about 32.5 mL.

A subject can decline the blood draw procedures, and still participate in all other study procedures, with no penalty. This is stated in the Consent Form.

Activity Watch Risks:

Infrequently, participants may feel some irritation on the skin from wearing the wristband device. If this happens to the participant research staff can attempt to change the wristband to a more comfortable one. The watch does not contain any personal information, nor does it contain cameras or microphones.

Risks associated with genetic research
DNA and RNA will be extracted from the blood sample. The major concern in this or any genetic study is patient confidentiality. To protect confidentiality, blood samples and genetic information will be stored in research files identified only by code. The code key connecting IDs to identifying information will be kept in a separate secure location. Study staff will at no time have access to the code keys required to match patient identifiers to patient names. Data in databases are similarly identified only by coded ID number and are password-protected. Data will not leave our institution in any form that would identify individual participants or their families. The results of genetic analyses will be kept confidential and will not be returned to participants in this study. Consequently, the potential risks of participants' learning potentially sensitive genetic information, or of discrimination related to participation in a genetic study should be avoided.

Protection against biohazards
Blood samples are collected at the McLean Imaging Center, so all McLean Hospital and MIC procedures for handling biohazards will be followed. Blood samples transported to collaborators will follow universal procedures for handling biohazards. Risks will be minimized by having trained staff collect, handle, transport, and process blood samples using universal biohazard precautions.

Discomfort during ECG exam:
ECG is a common medical procedure used to measure electrical activity on the surface of the chest. The electrodes placed on the chest may cause slight pain when removed, similar to ripping off a bandaid, but we will allow participants to remove the electrodes, if they prefer.

7.2 Risks Associated with MRI

Participants who have metal implants, cardiac pacemakers, and potential pregnancy will be excluded. Some patients experience claustrophobia (fear of being in a closed space) while inside the machine. In these cases, the examination will be terminated immediately, and the participant will be rapidly removed from the scanner. Overall, the risks associated with MRI procedures are minimal. A detailed list of risks associated with the MRI scan can be found below.

- 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.
- Pregnancy: The safety of MRI scanners for imaging embryos/fetuses has not been clearly established. Therefore, women who are pregnant or who are of unknown pregnancy status will be excluded
- 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.
- RF and Magnetic Field Interference: Implanted 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.
- 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.
- Neurostimulation: Some participants undergoing functional MRI have experienced minor neurostimulation effects, such as muscle twitches and “tingling” sensations, due to the rapidly oscillating magnetic field gradients used in these examinations. There are no known risks associated with these effects. Specifically, the potential for cardiac stimulation has been examined and judged not to be a problem. The devices used in our research create field gradients that are within the limits specified by the FDA. Likewise, the head resonator for the McLean 3.0T scanner operates within FDA guidelines.
- Clinical Hazards: The confining conditions of the MR system can precipitate claustrophobia in a subject. Participants will be screened for possible claustrophobia before they are enrolled in the study.

- Access to MR 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 MR system.

MRI sessions are conducted on the grounds of McLean Hospital which ensures immediate access to crisis services if needed.

7.3 Risks Associated with EEG

Collecting EEG data is a common and widespread procedure used to measure electrical brain activity on the surface of your head. The only known risk is that on rare occasions, individuals with very sensitive skin may experience a slight irritation at the site of sensor application due to the pressure from the blunted end of the needle that is used to enter the gel which ensures a good connection between the scalp and the electrode. The EEG cap may become uncomfortable after a long exam, but we will do our best to adjust it on our subject's head so this will not happen.

7.4 Drug Side Effects and Toxicities

Side effects commonly associated with sertraline include sleep problems, nausea, increased sweating, decreased libido, agitation, and tremors. Side effects associated with bupropion XL include agitation, anxiety, insomnia, dry mouth, and nausea. To maintain blinding, the information about side effects for both drugs will be given to all participants.

Once the participant is in the drug trial, the study physician will record vital signs during the first three weeks of drug titration and collect reports of side-effects at every session. If at any time the study physician feels that worsening symptoms may be hazardous or harmful to the patient's safety, they may be removed from the study at the discretion of the study physician or PI. The subject's options for follow-up treatment will be explained. During the drug trial if the participant withdraws from the study or does not attend a medication visit, study staff will make repeated attempts to contact them so the study physician can assess their condition and present options for follow-up treatment.

7.5 Privacy/Confidentiality Risks

All information about participants will be treated confidentially. Confidentiality will be maintained throughout the project period. Personally identifiable information will be strictly segregated from research data. No personal identifiers will be kept on data records, and a standardized code will be used for each subject's data. Participants will be identified only by a code number. The code key connecting IDs to identifying information will be kept in a separate secure location. Any paper records with subject-specific information will be kept in a locked file cabinet in the PI's laboratory. Data in databases will be similarly identified only by coded ID number and be password-protected. Data will not leave our institution in any form that would identify individual participants or their families. No research data will be linked or added to a participant's medical records.

8 Benefits

8.1 Benefits to Participants

All participants will enter the study during a major depressive episode and will be given an antidepressant medication that is indicated for this condition. This may relieve their depressive symptoms.

8.2 Differences by Group

Not applicable.

8.3 Potential benefits to society

From a scientific perspective the study may benefit people with depression by developing a novel method to prospectively assign MDD patients with anhedonia to a treatment that could double their response rate. Given the magnitude of human and economic costs associated with depression, the ongoing debate about the effectiveness of available treatments beyond the placebo effect and the relatively low risks involved in study participation, we believe that the minimal risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

9 Statistical Analysis Plan

9.1 Outcomes Analysis

To test the hypothesis that patients with matched assigned treatment will have better outcome than non-matching patients, we will run a linear model for the primary outcome, where the assigned treatment and an indicator encoding matching status of the pre-*treatment* predictive analytics and the assigned treatment are included as covariates. A secondary analysis on the dichotomized primary outcome indicating response status (defined as ≥50% reduction in MADRS scores) will also be performed using a logistic regression model with the same covariates. To test *Hypothesis 2*, changes of reward learning, effort-based decision making, reward-related ventral striatal activation (Guessing Monetary Reward Task), cortico-insular activation during the effort-based task, Reward Positivity during the PRT, and NAc-mPFC rsFC from baseline to week 8 will be used as outcomes, and separate linear models will be employed to test their associations with response status. The assigned treatment at baseline as well as its interaction with response status will be included as covariates. Bonferroni correction will be used to correct for multiple comparisons.

Imaging from the DTI scan will be used to test hypotheses related to structural connectivity between NAc, amygdala, mPFC and other regions associated with reward. Fractional Anisotropy (FA) maps will be generated, after skull-stripping with FSL, using DTIfit in the FMRIB Diffusion Toolbox.

9.2 Power Analyses

Monte-Carlo simulations were performed to estimate power. For each simulation, patients were sampled with replacement from the preliminary data, and their pre-treatment predictive analytics were generated based on the models from our papers (Ang et. al, 2020; Webb et al., 2019). A treatment (BUP vs. SERT) was then randomly assigned with equal probabilities to these sampled

patients and observed response status for the assigned treatment in the preliminary data were considered as the simulated outcomes. This sampling process was repeated until 30 participants were obtained for each of the four groups, defined by the combinations of assigned treatments and predictive analytics. Patients sampled when their associated baseline was full were considered as screen failed. The proposed statistical analysis for the binary treatment response outcome was applied to the simulated data to test whether patients for whom pre-treatment predictive analytics match the randomized initial treatment have higher response rate than non-matching patients. The simulation was repeated 1,000x and the estimated power is the proportion of replicates with significant results. Based on the simulations, the power of sample size N=120 is estimated as 0.9 and the average number of patients to be screened was 183.

10 Monitoring and Quality Assurance

10.1 Adverse Event Criteria and Reporting

Definition
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a therapeutic product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of study drugs, whether or not related to the study drugs. A new condition or the worsening of the pre- existing condition will be considered an AE. Stable chronic conditions, such as arthritis, that are present prior to study entry and do not worsen during study will not be considered as AEs. Hospital admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered adverse events if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).

Symptoms that are related to an AE will not be reported as separate events but described under the primary event.

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it:

- results in subject's withdrawal by the investigator
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- is considered by the physician to be of clinical significance

Severity Definition:

Mild: AE that is easily tolerated.
Moderate: AE sufficiently discomforting to interfere with daily activity.
Severe: AE that prevents normal daily activities.

A serious adverse event (SAE) is any adverse event that at any treatment dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,

- Results in persistent or significant disability/incapacity,

Or

- Is a congenital anomaly or birth defect.

Hospitalization for elective treatment of a pre-study condition that did not worsen during the study and hospitalizations for treatment of non-adverse events (e.g., cosmetic surgery or diagnostic procedure) are not considered as Serious Adverse Events.

Reporting of Adverse Events
Unanticipated problems involving risks to subjects or others including adverse events will be reported to the Partners Human Research Committee (PHRC) in accordance with PHRC unanticipated problems reporting guidelines. If clinical interviewers, study staff members, or study physician responsible for data collection become aware of a participant experiencing an adverse event as a result of the research study, they will be directed to contact the principal investigator and, if necessary, relevant emergency services immediately. All unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines. The sponsor will be informed of any actions taken by the IRBs as a result of such adverse events.

10.2 Planned Safety and Outcomes Monitoring

10.2.1 Safety Monitoring

MRI Safety Monitoring
Study staff members responsible for MRI data collection must be trained and certified for MRI safety procedures according to the standards of the McLean Imaging Center. For screening purposes, all subjects scanned at the MIC are required to have a structural brain MRI scan of clinical quality within the past 12 months. The results are reviewed by a board certified radiologist or neurologist and a clinical report is generated usually within 2-4 days. Subjects will not receive more than one screening scan within a given 12-month period unless a follow-up scan is recommended by the radiologist who reads the scan.

Abnormal reports are reviewed by the Clinical Director of the McLean Imaging Center (MIC), Dr. Gordana Vitaliano and forwarded to the Principal Investigator, in this case, Dr. Pizzagalli and the designated study physician. If an abnormality is present, the study physician and PI will coordinate the process of contacting the subject so that an appointment can be made to discuss the findings. The MIC Clinical Director may also assist with this process when requested and appropriate. If a follow-up scan is recommended by the radiologist, we will offer the subject a cost-free repeat scan (with contrast if indicated). A copy of both the clinical report and the MRI scan is offered to subjects to take to their primary care or other consulting physicians, at no cost.

Drug Safety Monitoring
Side effects from the study medication will be monitored at each weekly visit by the study physician. A participant reporting a serious medication side effect or other serious adverse event will be directed to go to the nearest emergency room. Participants will be removed from the study under the following conditions:

- Participants display adverse reactions to the assigned study medication (i.e., seizures, allergic reactions, harmful increase in blood pressure)
- Symptoms worsen

- Participants become suicidal, homicidal, manic, or psychotic

10.3 Study stopping rules

Participants will be closely monitored by the study staff during study visits. They will be instructed to immediately inform the study staff if they feel anxious or experience any discomfort. The study staff present during the visits will have authority to terminate the experiment. Participants also reserve the right to withdraw from the study at any point. If subjects withdraw from the study while they are receiving medication subjects will be encouraged to contact their PCP and/or our study physician to discuss how to safely discontinue medication use.

10.4 Internal Quality Monitoring

A quality review meeting will be conducted twice a year. The PI will be responsible for the review, and all members of the study staff who are directly engaged in study activities will attend. The status of the regulatory binder will be reviewed, including both IRB-approved and internal documents, by study coordinators and the PI. The logs will be brought up to date (for example, protocol exception log and equipment maintenance logs). Gaps in procedures or documentation will be identified, and plans will be put in place to fill them. A representative sample of subject folders will be reviewed, including paper records and database records. Once they are available, trial datasets will be processed through statistical analysis to validate the data collection procedures.

The principal investigator and co-investigators will be in charge of the oversight of the clinical interviews, as well as the study staff involved in data collection and analyses. Study staff members responsible for MRI data collection must be trained and certified for MRI safety procedures according to the standards of the McLean Imaging Center. Additionally, study staff members involved in conducting the EEG will be trained and certified on collecting EEG data through standards established by the Center for Depression, Anxiety, and Stress Research at McLean. Throughout the data collection period, the Principal Investigator, co-investigators, and study staff will review the data for completeness and signs of physiological and technical artifact.

11 Privacy and Confidentiality (checklist)

☒ Study procedures will be conducted in a private setting

☒ Only data and/or specimens necessary for the conduct of the study will be collected

☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)

☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g., locked storage spaces, laboratory areas)

☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol

- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g., encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

12 References

Ang, Y. S., Kaiser, R., Deckersbach, T., Almeida, J., Phillips, M. L., Chase, H. W., ... & Pizzagalli, D. A. (2020). Pretreatment reward sensitivity and frontostriatal resting-state functional connectivity are associated with response to bupropion after sertraline nonresponse. *Biological Psychiatry*, *88*, 657-667.

Berwian, I. M., Wenzel, J. G., Collins, A. G., Seifritz, E., Stephan, K. E., Walter, H., & Huys, Q. J. (2020). Computational mechanisms of effort and reward decisions in patients with depression and their association with relapse after antidepressant discontinuation. *JAMA Psychiatry*, *77*, 513-522.

Bonnelle, V., Manohar, S., Behrens, T., & Husain, M. (2016). Individual differences in premotor brain systems underlie behavioral apathy. *Cerebral Cortex*, *26*, 807-819.

Chen, C. H., Ridler, K., Suckling, J., Williams, S., Fu, C. H., Merlo-Pich, E., & Bullmore, E. (2007). Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biological Psychiatry*, *62*, 407-414.

Dunkin, J. J., Leuchter, A. F., Cook, I. A., Kasl-Godley, J. E., Abrams, M., & Rosenberg-Thompson, S. (2000). Executive dysfunction predicts nonresponse to fluoxetine in major depression. *Journal of Affective Disorders*, *60*, 13-23.

Harms, M. P., Somerville, L. H., Ances, B. M., Andersson, J., Barch, D. M., Bastiani, M., ... & Yacoub, E. (2018). Extending the Human Connectome Project across ages: Imaging protocols for the Lifespan Development and Aging projects. *Neuroimage*, *183*, 972-984.

Farabaugh, A., Sonawalla, S., Johnson, D. P., Witte, J., Papakostas, G. I., Goodness, T., ... & Harley, R. (2010). Early improvements in anxiety, depression, and anger/hostility symptoms and response to antidepressant treatment. *Ann Clin Psychiatry*, *22*, 166-171.

Fredman, S. J., Fava, M., Kienke, A. S., White, C. N., Nierenberg, A. A., & Rosenbaum, J. F. (2000). Partial response, nonresponse, and relapse with selective serotonin reuptake inhibitors in major depression: a survey of current" next-step" practices. *Journal of Clinical Psychiatry*, *61*, 403-408.

Forbes, E. E., Hariri, A. R., Martin, S. L., Silk, J. S., Moyles, D. L., Fisher, P. M., ... & Dahl, R. E. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *American Journal of Psychiatry*, *166*(1), 64-73.

Gudayol-Ferré, E., Herrera-Guzmán, I., Camarena, B., Cortés-Penagos, C., Herrera-Abarca, J. E., Martínez-Medina, P., ... & Guàrdia-Olmos, J. (2012). Prediction of remission of depression with clinical variables, neuropsychological performance, and serotonergic/dopaminergic gene polymorphisms. *Human Psychopharmacology: Clinical and Experimental*, *27*, 577-586.

Huys, Q. J., Pizzagalli, D. A., Bogdan, R., & Dayan, P. (2013). Mapping anhedonia onto reinforcement learning: a behavioural meta-analysis. *Biology of Mood & Anxiety Disorders*, *3*, 1-16.

Katon, W., Robinson, P., Von Korff, M., Lin, E., Bush, T., Ludman, E., ... & Walker, E. (1996). A multifaceted intervention to improve treatment of depression in primary care. *Archives of General Psychiatry*, *53*(10), 924-932.

Lynch, C. J., Power, J. D., Scult, M. A., Dubin, M., Gunning, F. M., & Liston, C. (2020). Rapid precision functional mapping of individuals using multi-echo fMRI. *Cell Reports*, *33*(12), 108540.

Papakostas, G. I., Fava, M., & Thase, M. E. (2008). Treatment of SSRI-resistant depression: a meta-analysis comparing within-versus across-class switches. *Biological Psychiatry*, *63*, 699-704.

Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annual Review of Clinical Psychology*, *10*, 393-423.

Pizzagalli, D. A., Iosifescu, D., Hallett, L. A., Ratner, K. G., & Fava, M. (2008). Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *Journal of Psychiatric Research*, 43, 76-87.

Pizzagalli, D. A., Jahn, A. L., & O'Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biological Psychiatry*, *57*, 319-327.

Ruhé, H. G., Huyser, J., & Schene, A. H. (2006). Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. *The Journal of Clinical Psychiatry*, *67*, 20568.

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., ... & Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. *American Journal of Psychiatry*, *163*(11), 1905-1917.

Trivedi, M. H., McGrath, P. J., Fava, M., Parsey, R. V., Kurian, B. T., Phillips, M. L., ... & Weissman, M. M. (2016). Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design. *Journal of Psychiatric Research*, *78*, 11-23.

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., ... & Star* D Study Team. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR* D: implications for clinical practice. A*merican Journal of Psychiatry*, *163*, 28-40.

Webb, C. A., Trivedi, M. H., Cohen, Z. D., Dillon, D. G., Fournier, J. C., Goer, F., ... & Pizzagalli, D. A. (2019). Personalized prediction of antidepressant v. placebo response: evidence from the EMBARC study. *Psychological Medicine, 49*(7), 1118-1127.