Neurobiological Underpinnings of Placebo Response in Major Depressive Disorder
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Table of Contents

1. Background and Significance

1. A. Major Depressive Disorder (MDD)

MDD is a debilitating illness that affects 16.6% of the US population (1) and costs the U.S. over $80 billion/year (2). All FDA-approved antidepressants used as monotherapy have shown only modest benefits (3). One of the most critical issues in developing new treatments is the very high placebo rate in clinical trials. The administration of placebo under double-blind conditions can often mimic the effects of antidepressants and lead to improvements in about 35% of MDD patients (4). Over the past 20 years, research programs failing to confirm the expected superiority of antidepressants over placebo have become the rule rather than exception (4).

1.B. Placebo Effect in Medicine

In its broadest sense, the placebo effect encompasses the self-healing capacity of the ritual of medicine, the patient-physician relationship, and the power of imagination, expectation, hope and empathetic witnessing. For illnesses defined by self-appraisal and subjective outcomes, placebo response can be indistinguishable from response to medications (5). Furthermore, the effects of many known pharmaceutically active classes of medications – including gastrointestinal drugs, analgesics, anxiolytics, β-blockers, antihistamines, and asthma drugs – are frequently indistinguishable from placebo in well-designed randomized clinical trials (RCTs) (6).

1.C. Placebo Effect in MDD

The placebo effect is particularly critical in MDD (4). After more than 1,000 randomized controlled trials, the debate continues as to the clinical value of antidepressants beyond placebo effect, and the exact nature of the placebo effect in MDD (4, 7-10). The lack of understanding of the mechanisms underlying placebo effects in MDD is a major obstacle in drug development and in clinical trials. Most of the studies in MDD have compared subjects defined as “placebo responders” with “placebo non-responders”, or with “drug responders”. In recent years our group has published numerous papers reviewing different aspects of placebo effect in the context of RCTs in MDD (Dr. Fava) (11-21) and other medical conditions (Drs. Kaptchuk and Kelley) (5, 22-24). Dr. Fava’s group has also conducted the first trial of open-label placebo in MDD (25) and has developed a new design for conducting clinical trials (4). Attempts to distinguish placebo responders from non-responders from a clinical perspective have largely been unsuccessful and plagued by replication failures (26). Recently, attempts at identifying regionally specific placebo responses for analgesia in specific brain areas have yielded especially promising results (27-29). With the exception of two studies probing putative resting brain state correlates of placebo responses (30, 31), the anatomical, biochemical and neurobiological mechanisms underlying placebo response in MDD remain unknown. The goal of the proposed research is to fill this critical gap.

1.D. Psychological Mechanisms of Placebo Response: Expectation of Improvement

Two important contextual factors in placebo response are knowledge, or degree of certainty that active medication has been received, and expectations about the therapeutic efficacy of the medication. In different conditions, knowledge of treatment has been found to have a significant effect on medication and placebo outcomes. Numerous studies (e.g., (32, 33)) have shown that, in post-operative oral surgical patients, the effect of saline injections coupled with the deceptive “knowledge” that the patient received morphine can equal the effect of morphine given by hidden

infusion, and the analgesic doses of medications required for post-operative pain or anxiety were much higher with hidden infusions than open infusions (34), (35).

Studies in pain, Parkinson's disease, and addiction clearly show that placebo response rates can be influenced by verbal cues that modulate subject's expectations (36). In a recent meta-analysis from our group including 146 clinical trials in MDD, the placebo response was significantly higher when subjects were informed that the probability of receiving placebo was lower (between 20 and 33%) than the usual 50% (18). Regarding the timing of placebo response, initial observations suggested that antidepressant drug effects and placebo effects are most likely to occur after the first 2 weeks of treatment (37 , 38). Our review of 13 clinical trials comparing antidepressants vs. placebo showed that the majority of improvement during both placebo (mean 79.5%) and antidepressant treatment (80.2%) occurs in the first half of the antidepressant trials regardless of their duration (21). Accordingly, we hypothesize that both subjects' and clinicians' expectations of timing of response contribute significantly to the placebo effect, and that these expectations are affected by the duration of the antidepressant trial itself. Based on these data, the current application proposes a design in which the expectations of subjects are modulated by (1) the increased chance of receiving active treatment (~75%), (2) by the description of the antidepressant as "fast-acting", and (3) by setting the primary assessment of outcome at the end of the first half of the trial.

1.E. Neurobiological Mechanisms of Placebo Response: Focus on Mesolimbic DA pathways

Recent experiments that administer noxious stimuli (e.g. pain) and followed by placebo treatment, coupled with an expectancy manipulation, have demonstrated reliable symptom improvement (e.g., analgesia) as well as biochemical (e.g., opioid and dopamine transmission) and neural correlates of such change (e.g., rostral anterior cingulate cortex, nucleus accumbens (NAc), putamen) (27, 39, 40); see (41) for review).

Decades of animal research have indicated that dopamine (DA) is critically implicated in coding the occurrence, prediction, and expectation of reward-related stimuli. As a result, current models strongly emphasize the role of DA in placebo effects (42-44), and recent empirical studies and reviews have provided additional support for the notion that placebo can be conceptualized as a reward mechanism (45, 46). Of note, in studies in which both DA and opioid transmission were assessed, DA release in the NAc contributed to the largest amount (25%) of variance of the placebo effects and fully mediated placebo-related improvements in mood (47). Recent neuroimaging laboratory studies in collaboration with Dr. Kaptchuk (27, 48, 49)) have shown that manipulation of expectancies can produce symptom improvement and is linked to measurable biochemical and neuroanatomical correlates (50). In several conditions, expectation/reward-related mechanisms seem to play a crucial role in placebo responses. Specifically, PET raclopride studies in subjects with Parkinson's disease (PD) have shown that administration of placebo produced significant DA release in striatal regions (51, 52) as well as changes in basal ganglia and thalamic neuron firing (50, 53). Notably, DA release in the ventral (i.e., NAc) – but not dorsal striatum – was linked to the *expectation* of symptom improvements (42), particularly when the declared probability of receiving active medication was 75% (43). Similarly, raclopride PET studies have uncovered DA release in the NAc during placebo administration under expectation of analgesia (44). Notably, DA release in the NAc contributed to the largest amount (25%) of variance of the placebo analgesic effects and mediated participants' expectation of analgesia and placebo-related increase in positive affect (47). Relevant to the current proposal, among healthy controls, both DA release in the NAc (as assessed by PET) and placebo analgesia correlated with NAc BOLD signal (as assessed by fMRI) during *anticipation of monetary reward* (40).

Additional evidence pointing to the NAc stems from other imaging modalities. In a PET study in MDD, placebo administration was linked to increased NAc metabolism (31). Among healthy individuals, placebo administration while *expecting to* receive a psychostimulant (methylphenidate) elicited increased NAc metabolism (54). Finally, DA-related traits (e.g., novelty seeking and reward responsiveness) and gray matter density in the ventral striatum (and PFC) predicted a significant portion of placebo analgesia (55). Together, these data indicate that DA

release in the NAc plays a pivotal role in the belief of improvement. Specifically, it has been suggested that DA transmission in the NAc (as well as PFC) represents a "'permissive component', integrating motivational and reward-expectation circuitry enabling the belief that there will be improvement in one's symptoms. This state of expectation, driven by prefrontal cortical and limbic areas, may in turn trigger a downstream biochemical response specific to the condition in question; in the case of PD, dopamine release in the dorsal striatum, and in placebo analgesia, endogenous opioids release." (56) Using a multi-model integration of *in vivo* molecular imaging, fMRI, and objective measurements of reward responsiveness, the proposed study will test, we believe for the first time, the hypothesis that mesolimbic DA mechanisms are critically implicated in placebo responses in MDD.

1.F.1. Preliminary Studies

In the following sections, we summarize data that highlight the feasibility of the proposed approaches and corroborate our hypotheses. In *Section 1.F.2*, we summarize selected findings that highlight our experience with implementing prospective manipulations of placebo effects. In *Section 1.F.3* we present behavioral findings derived from the probabilistic reward task proposed here, including evidence that performance in this task is related to reward-related striatal responses and modulated by DA. In *Section 1.F.4*, we review recent fMRI findings indicating that unmedicated MDD subjects display reduced activation in the caudate and NAc to reward feedback delivered in the proposed task. Critically, preliminary data indicate that reduced NAc responses to rewards characterize treatment non-responders. In *Section 1.F.5*, we review promising PET findings indicating that the molecular imaging technique proposed here can be used to assess task-induced release of striatal DA in MDD. Finally, in *Section 1.F.6*, we provide evidence of our ability to simultaneously probe molecular and hemodynamic mechanisms using the MGH integrated PET-MRI system.

1.F.2. Preliminary Study 1: RCTs demonstrating our ability to augment placebo responsiveness

Our team has extensive experience investigating placebo effects by integrating concepts, research designs and analytic methods drawn from the basic, clinical, and social sciences. For example, our collaborator Dr. Kaptchuk has written on the influence of psychological and provider variables on placebo response (24), in addition to several bioethics studies of placebo, (57, 58) and historical studies of placebo effects, (23, 59). Over the past five years, Dr Kaptchuk has also led two NIH-funded R01s testing placebo treatment for chronic pain (n=270) (60) and irritable bowel syndrome (IBS) (n=262) (61), and a third smaller study also in IBS (n=80) (62). From these studies, it is noticeable how the investigators were able to "augment" the placebo effect in subjects with chronic pain (61). Briefly, 262 subjects were randomized for 3 weeks to one of 3 groups: (1) a no-treatment waitlist; (2) "limited" (duration <5 minutes) placebo (sham acupuncture) treatment administered with minimal subject-practitioner interaction; or (3) "augmented" placebo, wherein placebo/sham treatment was administered with a supportive patient-practitioner. The results showed that, in the sample randomized to 'augmented' sham treatment (with supportive subject-practitioner interaction) the 'augmentation' of placebo response can be very effective. We believe that, in order to investigate the neurobiology of placebo response, we need to rigorously assess and control for all those elements that are likely to be involved (selection of subjects, setting the expectations, treatment delivered, and attitude of the provider).

1.F.3. Preliminary Study 2: Behavioral Studies of Reward Responsiveness in MDD

In recent years, our group has developed a reward task rooted within signal-detection theory that provides an objective assessment of a core component of anhedonia: reward responsiveness (63). Prior studies have shown that a higher frequency of reward delivery for correct identification of one stimulus versus the other induces a response bias, i.e., a systematic preference for the response coupled with more frequent reward, irrespective of which stimulus was actually

presented (64). Thus, the degree of response bias can be used to objectively assess reward responsiveness. Using this task, our team has found that subjects with elevated depressive symptoms (63) and MDD (65) (66) showed reduced reward responsiveness. Moreover, reward responsiveness negatively correlated with anhedonic symptoms in non-clinical (63) and clinical (65) samples, predicted these symptoms one month later (63), and predicted worse outcome after 8-week antidepressant treatment (66). Of particular relevance, reward responsiveness (1) correlated with individual differences in striatal regions in response to monetary rewards, as assessed in a separate fMRI session (67), and was reduced by catecholamine depletion (68) and administration of a single dose of the D2/D3 agonist pramipexole. Blunted reward responsiveness with pramipexole was assumed to result from activation of presynaptic DA autoreceptors, leading to decreased phasic DA bursts in response to unpredictable rewards (69, 70). Together, these data indicate that MDD is characterized by an impaired tendency to modulate behavior as a function of reinforcements and that the proposed behavioral measure of anhedonia is sensitive to DA modulations and striatal function. Based on these findings, we expect that placebo response will be linked to increased response bias in our reward task.

1.F.4. Preliminary Study 3: fMRI Studies Investigating Reward Responsiveness in MDD

Based on prior studies (71), our group developed a modified version of a monetary incentive delay (MID) task to identify activation specific to reward anticipation vs. consumption. Trials featured cues indicating a potential reward (+$), loss (-$), or no-incentive (0$), followed by a target to which participants responded with a key press. Participants were informed that faster response time (RT) increased the chances of obtaining rewards and avoiding losses. Trials ended with presentation of monetary gains, penalties, or no-incentive feedback. In healthy samples the task induces motivated responding: mean RT was fastest on reward trials, intermediate on loss trials, and slowest on no-incentive trials ($p<.001$) (67, 70, 72).

In an fMRI study, we administered the MID task to unmedicated MDD subjects and controls (65). Relative to controls, MDD subjects showed weaker activation in (1) the left putamen during reward anticipation, and (2) the bilateral caudate and left NAc to gains. Subjects showing treatment response (≥50% drop in HAM-D scores) after an 8-week treatment with escitalopram showed significantly increased NAc responses to gains at baseline ($p<.009$). Critically relevant to the current proposal, a similar pattern emerged when comparing placebo responders vs. non-responders. Moreover, we implemented psycho-physiological interaction (PPI) analyses to investigate whether striatal connectivity would predict treatment response. Relative to controls ($n = 31$), MDD subjects ($n = 30$) showed decreased effective connectivity between the caudate and dorsal anterior cingulate cortex (dACC) in response to monetary gains, yet increased connectivity between the caudate and a different, more rostral, dACC sub-region in response to monetary penalties. Critically, a composite score of caudate-dACC connectivity across both incentives predicted 36% of variance in symptom change 12 weeks later in response to 2 active treatments and placebo (73). A significant positive correlation was seen also in subjects randomized to placebo ($r = 0.48$). Finally, as a first step to probing DA in MDD, we administered a single 150 mg dose of bupropion ($n=10$) or placebo ($n=11$) to MDD subjects performing the MID task. Relative to placebo, bupropion (assumed to increase DA through partial DAT blockade) increased responses to gains within the midbrain, NAc, and orbitofrontal cortex (74). Bupropion increased anticipatory valence ratings and correlations between reward-related basal ganglia responses and reward valence ratings, suggesting that the drug's influence on positive experience may involve effects on brain reward circuitry. Based on these data, we expect that placebo response will be linked to increased dorsal (caudate) and ventral (NAc) striatal responses as well as corticostriatal connectivity to rewards.

1.F.5. Preliminary Study 4: PET Studies Assessing DA Release (Raclopride Displacement Studies)

Over the years, Dr. Alpert's lab has developed a modified molecular imaging method to dynamically assess striatal DA release during performance of tasks using a single-session design

(75, 76). In all experiments, subjects received a single intravenous injection of ^{11}C-raclopride before task initiation. The concentration of the ligand was dynamically measured during the experiment. A decrease in the concentration (ligand displacement) after task initiation was taken as an indication of task-induced DA release. Striatal DA release has been detected during: (1) motor planning (77); (2) implicit motor memory (78), and (3) explicit motor memory (79). In a recent pilot study, we have implemented a revised version of the MID task, in which a 25-min control condition is immediately followed by a 25-min reward condition, where reward-predicting cues and monetary gains are presented (see *Section C.8* for detail). At this stage, 2 unmedicated MDD and 2 healthy subjects have been scanned. Preliminary analyses reveal significant, reward-related tracer displacement in striatal regions**,** which were defined using the clusters emerging from our prior fMRI study in MDD using a similar MID task (65). The preliminary analyses showed that striatal DA released was substantially diminished in the two MDD subjects tested so far (Pizzagalli, El Fakhri, Alpert, unpublished observation).

1.F.6. Preliminary Study 5: Dual PET-MRI Studies

A Siemens integrated MR-PET scanner is fully operational at the Athinoula Martinos Center for Biomedical Imaging at MGH. This scanner consists of a dedicated brain PET scanner ("BrainPET") that can be operated in the bore of a 3T whole-body MR scanner. We have been using the BrainPET device and have demonstrated that high quality PET data can be acquired. We have developed MR-based methods for generating attenuation correction maps, and have shown that simultaneous MRI motion tracking can enable retrospective PET motion correction, and thus improved image quality (80). Technical specifications and detailed comparisons have been published elsewhere (81, 82). The key advantage of this system is that both advanced and conventional MRI data can be acquired simultaneously with PET data without substantial artifacts (83). A study investigating the relationship between changes in D2/D3 receptor occupancy with raclopride and changes in brain activity inferred by fMRI was recently published by our collaborators (84). The device has been qualified by the American College of Radiology Imaging Network (ACRIN) for quantitative measurements of SUV for ACRIN 6684 and ACRIN 6689, studies that involve PET with F-MISO and FLT, respectively. Thus, we expect to achieve excellent image quality and quantitative imaging.

2. SPECIFIC AIMS

The mechanism of placebo response in Major Depressive Disorder (MDD) is poorly understood.

The objective of this pilot study is to investigate possible dopaminergic mechanisms underlying the placebo response in MDD.

We expect that mesolimbic DA mechanisms implicated in reward anticipation, reinforcement learning, and expectation play a critical role in mediating placebo responses in MDD. A better understanding of the neurobiological basis of placebo has enormous potential on different levels. On a clinical level, the understanding of placebo mechanisms could lead to a number of applications for therapeutic purposes, such as developing drugs that could enhance the effects of a therapeutic relationship or accelerate the onset of action of an antidepressant by manipulating the placebo-related mechanisms, even if the subject is hopeless or severely anhedonic. On a level of clinical trial innovation, if we confirm the role of dopamine in placebo response and we comprehend how the placebo response mechanistically takes place, this could lead to developing new drugs that could block the placebo effects in clinical trial participants and greatly decrease if not eliminate the placebo effect nested even in those subject who are drug responders, therefore increasing the effect size and decreasing the sample size of studies. Moreover if we can identify biosignatures of placebo effect and use them to predict response, we could potentially enrich samples with subjects who are less likely to be placebo responders and again this would result in increased signal detection in a clinical trial. Finally, with this initial study we plan to lay the

foundation for other studies to investigate how this dopaminergic circuitry is affected by other treatments, such as psychotherapy, and what are the changes that are similar or different between antidepressants, placebo and specific forms of psychotherapy, transcranial magnetic stimulation, electroconvulsive therapy or deep brain stimulation.

2.A. Specific Aim 1:
To generate a large cohort of placebo responders through a sequential parallel comparison design trial with manipulation of expectancies designed to increase placebo response. We expect that 35% (n=25) of the 70 subjects receiving placebo in the first phase of the trial will be responders at week 4 **(Hypothesis 1).**

2.B. Specific Aim 2:
To investigate the role of mesolimbic dopaminergic mechanisms in placebo response in MDD. When considering changes from baseline to week 4, relative to placebo responders, placebo non-responders will show:
- Reduced raclopride displacement (i.e., reduced task-induced DA release) in response to reward-related stimuli within ventral (nucleus accumbens) and dorsal (caudate, putamen) striatal regions **(Hypothesis 2a);**
- Reduced BOLD signal in ventral and dorsal striatal regions as well as reduced corticostriatal connectivity to reward-related stimuli **(Hypothesis 2b);**
- Reduced ability to modulate behavior as a function of reinforcement history (reward responsiveness) in a probabilistic reward task **(Hypothesis 2c).** We further hypothesize reward responsiveness will positively correlate with ligand displacement (PET) and BOLD signal (fMRI) in striatal regions **(Hypothesis 2d).**

2.C. Specific Aim 3:
To develop statistical algorithms with the goal of better identifying placebo responders. To maximize the clinical utility of the proposed research, we will develop statistical models based on multivariate logistic regression analyses, bootstrapping strategies, and receiver operating characteristic (ROC) curves that will integrate various predictors with the aim of better identifying placebo responders. We predict that multivariate models will further improve our ability to identify placebo responders in MDD (**Hypothesis 3**).

In summary, the proposed research is novel with respect to design, technology, and its multi-level integration probing psychological and neurobiological constructs assumed to be crucially implicated in placebo response and has significant clinical and research implications for the future. Specifically, the future implications include: 1) identification of biomarkers and biosignatures of placebo responders, 2) new possibilities to understanding and manipulating the system, 3) possibly decreasing or eliminating a major confounder in clinical trials and drug development, and 4) refining treatments with novel drugs that decrease (in clinical trial) or increase (in clinical practice) the placebo response.

2.D. Design:
An innovative sequential parallel comparison design, in which 87.5% of MDD subjects will be initially randomized to placebo for 4 weeks followed by a second 4-week phase in which the odds of placebo assignment at randomization will be reversed (12.5%), will be implemented in order to maximize (1) number of placebo responders, (2) the subject's expectation of therapeutic benefits, and (3) power to detect significant differences.

2.E. Technology:

Imaging will be performed using a Siemens integrated MR-PET scanner, which involves a dedicated brain avalanche photodiode-based PET scanner (BrainPET) that can be operated in the bore of a 3T whole-body MR scanner. As shown in *Preliminary Study 5*, PET and MRI data can be acquired concurrently without artifacts.

3. Subject Selection

3. A. Inclusion Criteria

In addition to fulfilling the diagnostic criteria for MDD, the following conditions must be met for subject eligibility:

1. Virtually signed informed consent form using REDCap eConsent module
2. Men or women aged 18 to 60 years old
3. A score of 16 or greater on the Hamilton Depression Rating Scale –32 items (HAM-D- 32)
4. Continuing to meet criteria for current MDD at baseline and Clinical Global Impression Improvement (CGI) scores ≤ 3 (i.e. minimally improved or less) from the screen to the baseline visit
5. No more than one prior failed antidepressant in the current episode or are currently taking an antidepressant as defined by the MGH-ATRQ, in the current episode and are willing to take bupropion or placebo as augmentation, since we are using subjects as their own controls and we are comparing changes within subjects. Subjects with secondary anxiety disorders, like panic, GAD or simple phobia will be allowed, in order to make the population studied more representative of the general population of MDD.

3.B. Exclusion Criteria

1. Pregnant women or women of child bearing potential not using a medically accepted means of contraception.
2. Serious suicide or homicide risk.
3. Unstable medical illnesses, any history of seizure disorder.
4. Failure to meet standard MRI or PET safety requirements (e.g. claustrophobia, non-removable piercings, implanted medical devices, other non-removable metals) as determined by the MRI-contraindication form
5. The following DSM-IV diagnoses: a) organic mental disorders; b) substance use disorders, including alcohol abuse, within the last year; c) psychotic disorders; d) bipolar disorder; e) acute bereavement; f) severe borderline or antisocial personality disorder; g) history of eating disorder unless if in remission for ≥5 years prior to screening and presenting no current electrolyte abnormalities; h) current primary diagnoses of panic disorder, social phobia, PTSD, GAD, or OCD; i) mood congruent or mood incongruent psychotic features.
6. History of hepatic impairment or congestive heart failure.
7. Any history of abuse of stimulants or opiates.
8. Currently taking any exclusionary medications (i.e., antipsychotics, anticonvulsants, stimulants, dopaminergic agents), potential augmenting agents (e.g., T3, SAMe, St. John's Wort, lithium). Subjects who are on a benzodiazepine dose above the acute treatment dose (e.g. clonazepam 1.5 mg, lorazepam 2mg, alprazolam 2mg) will be excluded from the study. Monoamine oxidase inhibitors are excluded. Subjects must have either no antidepressant treatment or stable (for at least 4 weeks prior to screening). No dose changes are allowed during the study. Gabapentin and pregabalin are allowed.–Concomitant use of trazodone (up to 200 mg daily) is allowed. In agreement with subject's treating provider and under clinical monitoring, exclusionary drugs can be tapered and washed out prior to baseline visit. Any drugs or antidepressants below the adequate treatment dose, or atypical antipsychotics, benzodiazepines below the acute treatment dose, secondary antidepressants, thyroid hormones, and lithium used as augmentation medications, or any other medications

used as antidepressant augmentation will be eligible for washout with our licensed MDs.
9. Any investigational psychotropic drug within the last year.
10. Subjects who have not responded to two or more antidepressant trials of adequate doses (e.g., fluoxetine 40 mg/day or higher) and duration (e.g., ≥6 weeks) over the past five years according to the ATRQ.
11. History of inadequate response/poor tolerability to bupropion.
12. Subjects with medical contraindications to bupropion (e.g., history of seizures, uncontrolled electrolyte imbalance due to eating disorders, etc.) unless stable for 8 weeks prior to screening and there will be no changes during participation in the study.
13. Any unstable concomitant form of psychotherapy (depression-focused). Concomitant psychotherapy would be allowed if the frequency and the modality have been stable for the 8 weeks prior to screening and there will be no changes during the participation to the study
14. Receiving or have received during the index episode VNS, ECT or rTMS.
15. Color-blindness for blue or green (see fMRI task).

3. C. Subject Recruitment

Subjects will be recruited through the DCRP at MGH. This will be an outpatient sample of subjects with MDD, diagnosed by the use of the Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition. Subjects will be recruited through advertisements and clinician referrals. Signed informed consent will be obtained from all subjects using the REDCap eConsent module before carrying out any procedures.

Subjects will also be recruited via the Research Patient Data Registry (RPDR). RPDR will be used to identify potential subjects across MGB based on key inclusion criteria (e.g., ICD codes indicative of Major Depressive Disorder, age 18 and over, English speaking) and key exclusion criteria (e.g., exclusionary diagnoses and medication). These potential subjects may be contacted with research invitations, unless they have opted out (in accordance with July 2021 revised MGB policy).

4. Subject Enrollment

4. A. Randomization and Treatment assignment

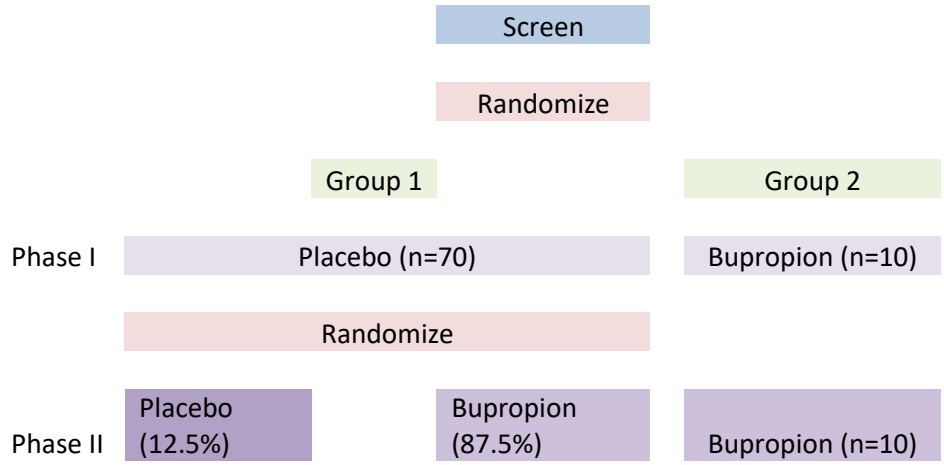
After a screening visit, the subjects will undergo baseline assessment and will be randomized to bupropion XL of up to 300 mg or placebo. The initial dose of bupropion XL will be 150 mg/day, and if tolerated adequately will increase to the target dose of up to 300 mg/day as early as day 4 with at least 24 hours between successive doses. To maximize the number of placebo responders, we will apply the SPCD developed by Fava et al. (4), coupled with a manipulation of expectations of receiving "*fast acting antidepressant treatment*". In accordance with the SPCD, the 8-week, double-blind treatment with bupropion or placebo is divided into two phases (4 weeks each), with assessments performed every 7 days. During the first phase of double-blind treatment, eligible subjects (n=80) are randomized to drug or placebo with an unbalanced ratio for placebo versus drug. In the phase 1 of the design, the subjects are randomized to placebo: drug with a ratio of 7:1 (i.e., 87.5% assigned to placebo), while in phase 2 both placebo responders and non-responders are randomized with inverse proportion (i.e., 87.5% are assigned to active drug). For the first 4 weeks, subjects will receive either bupropion (12.5%; n=10) or placebo (87.5%; n=70). With this 2-phase design, we can truthfully state in the consent

form that the odds of being on an active treatment is 75% at some time during the study, which is associated with a placebo response rate of approximately 40% (18). Due to the high expectation of receiving active medication (see below), we expect that the responders at week 4 will be a sample enriched in placebo responders. The manipulation of expectation will include: (1) a script with the description of bupropion as fast-acting antidepressant and the expectation of a symptomatic improvement within 4 weeks (first endpoint); (2) the description of an overall 75% probability of being assigned to the active arm at some point during the study. Because of this manipulation, we expect that at least 35% (conservative estimate) of subjects receiving placebo will be responders at week 4, for a total estimated N=25 (placebo non-responders: N=45). Assuming an overall 20% drop-out rate at week 4, the placebo responders (estimated N= 20) and non-responders (N = 36) who have not dropped out will be re-randomized with a reversed ratio to drug (87.5%) or placebo (12.5%) for the second 4-week phase. Accordingly, 32 of the Phase 1 placebo non-responders and 17 Phase 1 placebo responders will receive bupropion in Phase 2. Consequently, over the entire 8 weeks, 59 (~74%) of the subjects [=(10+17+32)/80] will have received bupropion at some point during the study. Note that, although all 80 subjects will be assessed with neuroimaging, only data from Phase 1 placebo responders and non-responders (total N=70) will be entered in the analyses due to our focus on mechanisms of placebo responses. In sum, the proposed design is expected to maximize placebo response using a highly efficient paradigm in which only 12.5% of participants' data will not be considered for the primary analyses.

The sample size was estimated after considering effect sizes (Cohen's d values) obtained in our work or pilot studies that have used proposed paradigms (see below). For analyses involving covariates, the denominator df was adjusted accordingly. Based on these estimates, and in light of the randomization schema, response rate, and attrition rate assumptions summarized in Section C.4 (Design of the Modified Randomized Clinical Trial), the sample size will be n=80, yielding an estimated 25 placebo responders and 45 placebo non-responders for analyses. Effect sizes were calculated using $\alpha = 0.05$ for detecting differences between 25 placebo responders vs. 45 non-responders and G*Power 3.0 (106). In a behavioral study, we found that unmedicated MDD subjects had significantly reduced response bias compared to controls (Cohen's d = -0.70; (65)). In a separate study, we found that healthy subjects receiving a single dose of pramipexole had significantly lower reward learning than those receiving placebo (d = -1.45; (69)). In an fMRI study using the MID task proposed here, unmedicated MDD subjects showed weaker activation than controls in response to gains in the caudate (d = -0.98) and left NAc (d = -0.73) and left putamen (d = -0.78) during reward anticipation (65), yielding a mean effect size of -0.87. Of note, among this sample, those subjects showing treatment response (≥50% drop in HAM-D scores) after an 8-week placebo-controlled trial with escitalopram showed significantly higher NAc response to gains at baseline, compared to non-responders (d = 1.25). In a pharmacological fMRI study in unmedicated MDD, we found that a single 150 mg dose of bupropion increased reward-related responses in components of the brain's reward circuit, including the midbrain (d = -1.88), subcallosal gyrus (d = -1.64), and SLEA (d = -1.89), leading to an mean effect size of -1.80 (74). In sum, based on the effect sizes we have observed for the behavioral (mean d = 1.08) and fMRI (mean d = 1.30) components, a total sample of 70 subjects (25 placebo responders, 45 placebo non-responders) leads to a power >0.95 of detecting group differences. If effect sizes involving placebo responders vs. non-responders are smaller than the ones we have observed in MDD, a group of 70 subjects will afford us the ability to detect an effect size of 0.76 with 0.85 power, or an effect size of 0.91 with 0.95 power. For the PET study, based on the variance observed in our earlier studies, we estimate that 70 subjects will provide adequate statistical power to detect differences. The sample size is the number of independent resolution elements (resells) times the number of subjects. However, because adjacent voxels are spatially correlated, it is difficult to determine

the exact number of independent resells. Since the estimates of striatal resells range between 25-40 (107), data from 70 subjects will yield 1,750-2,800 samples, which will yield an appropriate empirical estimate of variance. Prior raclopride studies have typically used <25 subjects (e.g., (108, 109)). For references, see the National Institutes of Health grant application.

5. Study Schema



6. Study Procedures

6.A. Screening Visit (Day -45 to -1)

The Screening Period will range from a minimum of 1 day to a maximum of 45 days. The purpose is to ensure that appropriate subjects are entered into the study. The investigator will determine that the subjects meet eligibility criteria and will collect the demographic and medical data permitting full characterization of the subjects. The Screening period begins when informed consent is signed. Only a study physician will perform the informed consent procedures. The study clinician will review screening data prior to the baseline to assess any drastic changes if the baseline occurs nearer to the 45 days.

The Screening Period is also designed to allow the gradual taper and discontinuation of any prohibited concomitant medications under the supervision and monitoring of a study physician. A study physician and/or site medical staff will maintain ongoing telephone contact with the subject during the washout period in order to ensure subject safety during this time.

With current COVID-19 procedures, we will enroll and consent research subjects remotely. Subjects will be emailed a PDF copy of the informed consent document prior to the initial screening visit. A study clinician will review the consent form with the subject during the virtual screening visit. The subject will sign the consent form using REDCap eConsent, and a signed copy of the consent form will be emailed to the them. Once subjects agree to participate in the study by signing consent, the screening procedures listed in the Schedule of Assessments (Table

1) will be performed. The clinician and self-rated measures listed in Table 1 will be administered virtually using REDCap surveys. The physical exam, laboratory tests, urine pregnancy test, and urine drug test will be conducted in person at MGH DCRP.

To assess expectations, we will include a modified version of the CGI Improvement Scale at the screening visit and change the wording: "*At the end of the first 4 weeks I expect no change or worse, or to be mildly/moderately/markedly improved*." This is a standard measure of cognitive expectancies in clinical trials.

Blood samples will be drawn to study genetic factors (DNA, mRNA) and to measure proteins. These blood samples will be stored and frozen at the DCRP. At screening, a total of 60mL of blood (two 8.5 mL blood samples, four 10 mL blood samples, one 3 mL blood sample) will be drawn for safety labs and biomarkers. Detailed instructions for blood sample preparation and storage are found in the study Manual of Operations.

Part or all of the screening interview may be audio recorded for rater training and quality assessment purposes. The recordings will be de-identified and labeled with an alpha numeric study code. The recordings will be accessible only to the clinicians and study staff associated with this study and will be destroyed after a year.

6.B. Baseline Visits 2 and 6 (Day 0 and 28)

During the first baseline visit, the study physician will review the I/E criteria in order to determine that the subject remains eligible for the study. Following completion of the study procedures listed in the Schedule of Assessments, the subject will be randomized and provided with study drug for 10 days. In instances when more than 10 days have lapsed between visits, participants will be mailed additional study drug.

With current COVID-19 procedures, the study medication will be mailed to the research subjects. The subject will take their first dose of study drug remotely, and will be instructed to take 1 pill on Days 1, 2, 3 and 4. If the subject is tolerating the medication adequately, then he or she will be instructed to take 2 pills thereafter beginning on Day 5.

6.C. Imaging Visits 2 and 5 (Day 0 and Day 21)

Participants will undergo two imaging sessions, 3 weeks apart (+/- 7 business days), at the Athinoula Martinos Center for Biomedical Imaging. A detailed description of the imaging procedure and the assessments to be administered during the visit are provided in the study Manual of Operations. The assessments to be administered can be found in the Schedule of Assessments (Table 1). To avoid craving effects, subjects will be asked to consume their usual amount of caffeine and/or nicotine on the day of imaging (105).

6.D. Interim Visits 3 and 4 (Days 7 and 14), Visits 6-10 (Days 28, 35, 42, 49, 56)

Subjects will be virtually assessed weekly (+/- 5 business days for scheduling availability) for the entire study, either by HIPAA-compliant Zoom video conferencing or Doximity Dialer. In the instance that more than a week has lapsed between study visits, a DCRP clinician will call the participant for a safety and clinical check. Subjects will complete the procedures listed in the Study Schedule of Assessments (Table 1), which include: the HAM-D-32 (96), Clinical Global

Impression (CGI) - Severity Scale (97), and Improvement Scales, Symptoms of Depression Questionnaire (SDQ) (98), concomitant medications record, Medical Outcome Survey–Short form–36 items (SF-36) (99), SAFTEE-SI Side Effect Scale and Adverse Events (100), Snaith-Hamilton Pleasure Scale (101), Concise Health Risk Tracking Scale–Clinician Report (CHRT-CR) (102), a Visual Analog Scale (VAS), and Credibility/Expectancy questionnaire (CEQ; (158)) by a clinician with at least a master's level degree. At Visit 10, a total of 40 mL of blood (four 10mL tubes) will be drawn for biomarkers. Blood samples will be drawn, frozen, and stored at the DCRP for future use. Once funding is available to run biomarker and pharmacogenetic analyses, study staff will measure inflammatory markers and cytokines, such as hsCRP, IL-6, TNF-alpha, IL-1beta, and genetic polymorphisms associated with placebo response with serotonin 5HTR2A, serotonin transporter, glucocorticoid receptor gene NR3C1, and monoamine oxidase A gene.

At all visits, the clinician will record other variables found to affect DA function. During the Interim Visits, subjects complete the procedures outlined in the Schedule of Assessments. Non-imaging visits 3-4 and 6-10 will be administered remotely by a clinician via HIPAA-compliant Zoom video conferencing or Doximity Dialer, in addition to subject completing the self-rated questionnaires administered by the research assistant, who will send to the subject in a secure online REDCap survey.

6.E. Study Drug Dispensation

The research pharmacy at MGH will be providing the medication, as film-coated placebo-matched tablets. The target dose of bupropion XL is up to 300 mg/day. The initial dose of bupropion XL will be 150 mg/day, and if tolerated adequately will increase to the target dose of up to 300 mg/day as early as day 4 with at least 24 hours between successive doses. With current COVID-19 research, a two-week supply of the study drug with a buffer of 2 doses will be mailed to the subject every two weeks for the entire study, and pill counts will be performed virtually using HIPAA-compliant Zoom video conferencing in order to assess compliance.

6.F. Procedures for Discontinuation from Study Treatment

A subject who decides to discontinue participation in the study will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Section 7.) until resolution.
If a subject discontinues from the study before randomization, then no further follow-up will be expected. If a subject discontinues from the study before completion and has received at least 1 dose of study drug, the subject will be asked to return for a final study visit, at which the procedures outlined in Visit 10 will be completed. Every effort will be made to follow up with subjects who discontinue from the study prior to Day 56. If subjects refuse to return to the MGH DRCP for the study-related assessments, a modified follow-up through, for example, regular telephone contact or a contact at study closure will be arranged, if agreed to by the subject and in compliance with local data privacy laws/practices. If the subject refuses follow-up, the reason for the refusal and last contact date will be documented in the eCRF and source documents.

Subjects who discontinue from the study will not be replaced.

6.G. Remuneration

For participation in the study, subjects will be compensated with up to $952 for their time and travel expenses.

Table 1: Study Schedule of Assessments

Study Assessment	Screen Visit 1	Baseline and Imaging Visit 2	Visit 3	Visit 4	Imaging Visit 5	Visit 6	Visits 7	Visit 8	Visit 9	Visit 10[6]
Study Day	-45 to -1	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56
Visit Window		(+2 days)	(+ 5 days)	(+ 5 days)	(+7 days)	(+ 5 days)	(+ 5 days)	(+ 5 days)	(+ 5 days)	(+ 5 days)
MINI 6	X									
HAM-D32	X	X	X	X	X	X	X	X	X	X
CGI-S, I	X[1]	X	X	X	X	X	X	X	X	X
CHRT-CR	X	X	X	X	X	X	X	X	X	X
MGH-ATRQ	X									
Concomitant meds	X	X	X	X	X	X	X	X	X	X
Psychiatric History	X									
Medical History	X									
Anger Attacks	X									
SDQ	X	X	X	X	X	X	X	X	X	X
CEQ		X	X	X	X	X	X	X	X	X
VAS	X	X	X	X	X	X	X	X	X	X
TEPS		X			X					
SAFTEE-SI (AEs)	X	X	X	X	X	X	X	X	X	X
SF-36	X	X	X	X	X	X	X	X	X	X
Snaith-Hamilton Pleasure Scale	X	X[2]			X[2]					
Fagerstrom	X									
General Habit Questionnaire	X									
NCQ Withdrawal Questionnaire		X [5]			X [5]					
PANAS (trait)	X									
PANAS (state)		X [5]			X[5]					
STAI (trait)	X									
STAI (state)		X[5]			X[5]					
Physical Exam	X									
Review I/E Criteria	X	X								
Laboratory Tests	X									
DNA, mRNA Sample	X									X
Urine Pregnancy Test	X									
Serum Pregnancy Test		X			X					
Urine Drug Screen	X	X			X					

Randomization		X				X				
Monetary Incentive Delay Task[3]		X			X					
Face game (PRT)		X			X					
PRT and MID Post Task Questionnaires					X					
Option Generation Paradigm		X			X					
Menstrual Cycle Info		X			X					
Drug Dispensation		X	X	X	X	X	X	X	X	X
Pill Count			x	x	x	x	x	x	x	x
Test Scanner at CNY		X[4]								
MRI safety checklist	X	X			X					

[1]CGI-I is a modified version for this visit only. [2]Performed prior to imaging study
[3]Completed during imaging study. [4]Tested at least 24 hours before scheduled imaging day. [5]Before and after scan.
[6]May also serve as the Early Termination Visit Procedures.

6.H. Laboratory Tests

At the Screening Visit, blood will be collected for a Complete Blood Count (CBC), Chemistry and TSH.
Table 2 lists the Exclusionary laboratory values for the study.

Exclusionary Laboratory Values - Table 2

Hematology	
Leukocytes	<2 or >17.5 x $10^3/mm^3$
Platelets	<75 or >700 x $10^3/mm^3$
Chemistry	
AST	>3 times upper limit of the reference range
ALT	>3 times upper limit of the reference range
GGT	>3 times upper limit of the reference range
Creatinine	>1.3 times upper limit of the reference range
BUN/Urea	>1.3 times upper limit of the reference range
Glucose	<70 mg/dl or >2 times the limits of the reference range
TSH	0.450-4.500 µIU/mL

7. Evaluation of Adverse Events (AEs)

7. a. Definition of AEs

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational)

product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH]).

This definition includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

7.b. Reporting of AEs

Observed and spontaneously reported adverse events will be recorded at each visit. Spontaneously-reported adverse events will be classified as mild, moderate or severe. Subjects shall be encouraged to contact the investigator or a member of study staff at any time between visits concerning adverse events or worsening of symptoms.
All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated Informed Consent Form (ICF) is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the site-investigator from the time a signed and dated ICF is obtained until within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. MGH DCRP will evaluate any safety information that is spontaneously reported by a site investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the Case Report Form (CRF). Whenever possible, diagnoses will be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion will be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to MGH DCRP instructions.
MGH DCRP assumes responsibility for appropriate reporting of adverse events to the regulatory authorities and IRB.

7.b.1. Time Period for Collection of Adverse Events

Adverse events and SAEs will be collected from the time of signature of informed consent throughout the treatment period and including the observation period. Unsolicited SAEs will be collected for 30 days post last study treatment.

7.b.2.Unresolved Adverse Events

Any AEs that are unresolved at the subject’s last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF.

7.b.3. Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity or intensity or changes in intensity
- Whether the AE is serious or not
- Expectedness
- investigator causality rating against study drug (yes or no)
- Action taken with regard to the study drug
- AE caused subject's withdrawal from the study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to study drug
- Causality assessment in relation to other medication
- Description of AE

Intensities will be reported for each AE in the following categories: a) Mild (awareness of sign or symptom, but easily tolerated); b) Moderate (discomfort sufficient to cause interference with normal activities); c) Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section H.4.d. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

Worsening symptoms of the primary study condition (i.e., MDD) will not be recorded as an AE. However, if inpatient hospitalization results from worsening psychiatric symptoms or suicidal ideation, the hospitalization will be recorded as an SAE in the eCRF.
Study drug abuse is an SAE, even when there are no symptoms or additional AEs, and will be reported according to the guidelines in Section 7.b.. Misuse of study drug is an AE, but is not considered an SAE unless accompanied by serious sequelae.

Should an overdose of study drug occur, it must be reported in accordance with the procedures described below. An overdose associated with symptoms must be reported as an AE, while an overdose without associated symptoms, must be reported only on the separate Clinical Study Overdose Report Form.

7.b.4. Pregnancy

If a subject (or subject's partner) becomes pregnant during the study, it must be reported within 24 hours of the time the investigator becomes aware of the event and in accordance with the procedures described on the Pregnancy Report Form. Pregnancy in itself is not regarded as an SAE/AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs from Visit 2 to 30 days following the last dose given will be followed for gestational outcome. A pregnant female subject will be discontinued from study medication.

7.b.5. Causality Collection

The investigator will assess the causal relationship (i.e., the relationship to study treatment) between the study drug and AEs, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?" Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility. For SAEs, causal relationship will also be assessed. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as "yes."

7.b.6. Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject in response to the open question from the study personnel: "Have you had any health problems since the previous visit?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.b.7. Adverse Events Based on Examinations and Tests

Abnormal and clinically significant lab values will be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the study drug. The t Principal investigator and the study biostatistician will establish the rules for what will constitute abnormal and clinically significant lab values based on established site-specific lab normal ranges. Adverse events, including abnormal lab values (clinically significant and clinically non-significant), will be reviewed monthly for trends by the Contract Principal investigator and the Contract Medical Monitor. Should any abnormal lab values exceed rates described in the IB, the FDA and NIMH will be notified within regulatory timelines. If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator will use the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters will be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

7.b.8. Disease Progression or Worsening Depression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the study drug is being studied. It may be an increase in the severity of

the disease under study and/or increases in the symptoms of the disease. The development of worsening depression will be considered as disease progression and not an AE. Events (except for suicidal ideation or behavior) which are unequivocally due to disease progression will not be reported as an AE during the study.

7.b.9. Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unexpected if it is not listed in the package insert, or the nature or severity is not consistent with the applicable reference in the package insert.

7.b.10. Serious Adverse Events

The RedCap system will be programmed to provide a mechanism for collecting information in order to reportSerious Adverse Events (SAE).

7.b.11. Definition of SAE

The following criteria define a Serious Adverse Event:

- Death
- Life-threatening event
- Inpatient hospitalization or prolongation of inpatient hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Medically important event, as defined in this protocol*

*Medical and scientific judgment will be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These will usually be considered serious.
If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (e.g., death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

7.b.12. Reporting of SAEs

When a SAE is discovered, it will be reported immediately (within 24 hours, as described below (Section 10).

7.b.13. Protocol Violation Reporting

Protocol violations will be reported as described in the Study Operations Manual.

8. Biostatistical Analysis

Efficacy and Treatment Outcome Data: The primary measure of clinical improvement for **Hypothesis 1** will be reduction of HAM-D-32 total scores over the course of the first 4 weeks as

well as response (≥50% reduction in HAM-D-32) in subjects assigned to placebo treatment. Our primary analysis will be an intent-to-treat analysis. The HAM-D-32 scores will be analyzed as continuous and dichotomous variable.

General Statistical Approach: To identify neurobiological mechanisms underlying placebo responses in MDD, the main variables of interest will be change scores (week 4 – baseline) for the *a priori* behavioral, PET, and fMRI data. Across domains, a hierarchical regression approach will be used, whereby four covariates (baseline HAM-D-32 score, age, gender, smoking status) will be entered in the first step, followed by the behavioral or neuroimaging predictor of interest, with group (placebo responders vs. placebo non-responders; dummy coded) or changes in HAM-D-32 score as criterion variables. For regression sets, follow-up (control) analyses will be performed to probe the respective contribution of the baseline and week 3 behavioral and neuroimaging data to the findings. We expect that change scores will have the strongest predictive validity.

PET data: The magnitude of DA activity will be estimated using two comparisons: 1) the mean BP, and 2) the mean γ (the rate of change in ligand displacement) for each group (placebo responders, non-responders), conditions (control, reward condition), and time (baseline, week 3). The BP maps will provide a quantitative estimate of the number of available binding sites per unit volume. These maps will be stereotactically transformed, pooled, and averaged across subjects. Mean BP in two groups will be compared to estimate the number of binding sites activated during the task. To test **Hypothesis 2a**, mean γ change score (week 3 – baseline) will be entered as the predictor in the second step of the hierarchical regression. We hypothesize that relatively larger changes in task-induced release of DA will predict placebo response (dichotomous variable – logistic regression) and change in HAM-D-32 scores (continuous variable – linear regression).

fMRI data: fMRI data will be analyzed using two approaches: a ROI approach to evaluate *a priori* hypotheses and a whole-brain approach to test finding specificity. In the first approach, regression coefficients ("beta weights") will be extracted from ROIs obtained from FreeSurfer's parcellation of sub-cortical and cortical structures and selected based on previous literature (143) and prior findings from our laboratory (65, 72). For the anticipatory phase, ROIs will include the NAc, caudate, putamen, and globus pallidus, and dACC. For the outcome phase, ROIs will include five regions implicated in reward consumption: medial and lateral OFC, rostral ACC (rACC), dACC, and striatal regions. For each ROI, a contrast comparing beta weights between the reward and no-incentive condition [reward – no-incentive] will be computed to isolate reward-related activations. To test **Hypothesis 2b**, contrast change scores (week 3 – baseline) will be entered as the predictor in the second step of the hierarchical regression. We hypothesize that relatively larger increases in reward-related striatal responses **as well as increased corticostriatal connectivity** will predict placebo response status and HAM-D score changes. In the second approach, whole-brain analyses will be computed. Each participant's data will first be re-sampled into Talairach space. Using random effects analyses, a GLM will be performed to identify additional regions whose reward-related activity changes (from baseline to week 4) predicts group (placebo responders vs. non-responders) or changes in HAM-D, while considering covariates.

Behavioral data: The main variable of interest will be response bias, which captures participants' ability to modulate behavior as a function of rewards. As in our prior studies (63, 144), a difference score (ΔResponse Bias = Block 3 – Block 1) will be computed, for each session, to assess the overall amount of reward learning. To test **Hypothesis 2c**, ΔResponse Bias change scores (week 4 – baseline) will be entered as the predictor in the second step of the hierarchical regression. We hypothesize that relatively larger reward responsiveness changes will predict placebo response status as well as change in HAM-D scores. Finally, to test **Hypothesis 2d**, a forward stepwise regression analysis will be run with response bias as the criterion variable, and the four covariates, mean γ (PET), and beta weights in striatal ROIs (fMRI) as predictors.

Statistical Modeling Integrating Various Markers of Placebo Response (Cross-modal Integration)

To test **Hypothesis 3**, a logistic regression approach will be used to develop multivariate models aimed at identifying predictive variables that distinguish placebo responders vs. non-responders, wherein the dependent binary outcome will be the response status and the predictor variables will the changes (week 3 – baseline) in the proposed biobehavioral variables. We will first identify a set of predictors of clinical (e.g., anhedonia), behavioral (e.g., ∆Response Bias), fMRI variables (e.g., NAc activation to rewards), and PET variables (e.g., mean γ value) showing significant univariate group differences. Appropriate transformations will be considered for variables with skewed distributions. Prior to group dichotomization, we will examine potential non-linear relationships of each variable with HAM-D-32 total scores. Variables emerging with $p<0.05$ will be entered as the candidate predictor variables in the multivariate logistic modeling. The final model will be determined via forward stepwise selection procedure, with a classification cutoff of 0.5, to include only the significant predictors at 5% alpha level as well as to identify variables with the strongest predictive value. The log-likelihood ratio chi-square will be evaluated to assess the improvement in fit when the predictor variables are in the model vs. the null model, and Nagelkerke's R^2 will be used to test the strength of association between the treatment outcome and the predictor variables. Overall, the receiver operating characteristic (ROC) curve will be measured for each continuous variable to define the cut-off point with the best sensitivity and specificity, and thus will better characterize findings in a clinical sense.

9. Risks and Discomforts

General: By agreeing to take part in this study, participants will be temporarily forgoing the opportunity to receive routine clinical psychiatric care in the community. This will be clearly explained to all participants, along with the treatment strategies that are generally used in subjects with depression.

Pharmacological component: The antidepressant used in the study, bupropion, is commonly prescribed for treatment of depression and it is considered to be relatively safe, as has been used in million of subjects in the US and there is a large well-validated safety database for it. The dose in the study is a commonly prescribed antidepressant dose. Most common side effects include nausea, constipation, dry mouth, dizziness, insomnia, hypertension and tachyarrhythmias. Rare side effects include severe cardiac arrhythmias, allergic reactions,and seizures (0.1-0.4%). All subjects will be informed of the risks associated with the treatment.

Risks of Placebo: Since placebo is an inert compound, we do not expect that it may directly cause side effects, although subjects may report some adverse events during the treatment anyway. In addition, we will acknowledge to subjects the fact that foregoing active medication could lead to worsening or no improvement in symptoms.

Risk of delaying treatment: By taking part in this study, participants are likely to experience some delay in the initiation of treatment due to the performance and imaging studies prior to treatment assignment. For each participant, the delay will not exceed two weeks, which is close to the typical time period between the screen and baseline visits in clinical trials conducted at MGH. During this period, it is possible that the participants' condition could worsen and lead to increased disturbances in mood, sleep, appetite, and cognition. This could result in work loss, loss of social function, and possibly increased risk of suicide. However, the risk should be minimized as there are several safety precautions in place and participants will remain in close contact with study clinicians (see below). We expect that approximately 35% of subjects assigned to placebo will respond and 40% of subjects assigned to bupropion. Because of the design of the study, the subjects will have an overall chance greater than 50% of being assigned to the active drug during the 8-week period. Therefore the maximum delay from the

baseline visit to the beginning of an antidepressant will be 8 weeks. At the end of their participation in this DCRP research study, all subjects are offered 6 months of clinical follow-up with a staff psychiatrist at the DCRP, during which the subject can receive treatment according to best clinical judgment, completely free of charge. During this period, a plan for long-term care is developed and at the end of this 6-month period the subject, if so he/she wishes, can be referred to a clinician (primary care physician, psychiatrist, therapist) for continuation of care.

All subjects will be instructed on how to contact (via pager, cell phone) the on-call study clinician in the case of an emergency, such as worsening of depressive symptoms or emergence of suicidal ideation. They will also be instructed on how to contact MGH's Acute Psychiatry Service (APS), which provides emergency psychiatric care on a 24hr/day basis. Any subject who, based on the investigator's judgment, poses an imminent risk of suicide should be discontinued from the study and appropriate level of care will be implemented. All investigators involved in assessments at the DCRP have extensive clinical experience in the treatment of MDD and treatment-resistant depression, and can make the decision(while blinded) as to remove subjects from the trial, particularly in the event of clinical deterioration or emergence/worsening of suicidal ideation.

Behavioral component/Questionnaires: We foresee no risks from the behavioral tasks required for the proposed research. Answering detailed questionnaires may create a mild degree of inconvenience for subjects but this is minimal. There is always a chance that a subject's confidential record might somehow be disclosed to some other source. The procedures to protect against or minimize potential risks against such occurrence include the following: (1) the assignment of unique study subject numbers to subjects, (2) the use of these primary identifiers throughout the study, (3) all information will be kept in locked file cabinets, and (4) only study personnel will have access to these file cabinets and data.

fMRI component: The risks associated with the MRI procedure are minimal. Subjects who have non-MRI compatible metal implants, cardiac pacemakers, and potential pregnancy will be excluded. Some subjects 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.

PET component: The principal risk to subjects enrolled in this study is exposure to ionizing radiation. Subjects will receive a single IV injection of 11C raclopride for each PET scan for this study. Previous significant radiation exposure either for clinical or research purposes, is one of the exclusion criteria. There is also a small risk of bleeding, bruising, and infection associated with blood drawing and placing a catheter into an arm vein. Throughout the PET session, it will be ensured that participants are comfortable. Their status will be assessed after each scan and any adjustments required to facilitate participant comfort will be made when necessary. The exposure to radiation may involve risks to an unborn child that are currently unforeseeable. Therefore, women who are pregnant or are at risk of becoming pregnant and not agreeing to use approved methods of contraception will be excluded from the study. A serum pregnancy test will be obtained on the day of each imaging session. For the serum pregnancy test, a 6 mL blood sample will be drawn. The results will be evaluated by a physician. Some subjects may experience minimal discomfort from the PET procedure, as they lie for up to 90 minutes in the supine position, with head movement restrained by a custom-molded facemask. Experience in hundreds of similar procedures has shown that this discomfort is easily tolerated by the vast majority of subjects. In any event, subjects will be told that they may withdraw from the study should they find the procedure to be overly taxing.

Risks of Radiation Exposure: As a result of your participation in this study you will be exposed to radiation from two PET scans of your brain. Please note that this radiation is not necessary for your medical care and is for research purposes only.

The total amount of radiation exposure you will receive from participation in this study is equal to a whole body exposure of approximately 9 milliSieverts (mSv). A milliSievert is a unit of radiation dose. This amount of radiation is about the same as you would normally receive in 2.9 years from natural background sources from the earth and the sky. Since the effects of radiation can be cumulative (add up over time), it is important to know of your past research related radiation exposure. If you have taken part in other research studies in the past 12 months that have involved radiation exposure, please inform the investigators or study staff. If we determine that your prior radiation exposure from research studies is more than we allow, you will not be able to take part in this study. Please write your initials next to your answer below.

Risks to an Embryo or Fetus: You cannot take part in this study if you are pregnant or nursing. Radiation exposure may be harmful to an embryo or fetus (developing baby still in the womb) or to a nursing infant. We will do a blood test for pregnancy before you have the MR-PET scan.

Risks of allergic reaction: You may have an allergic reaction to raclopride, the dye used in the PET scan. Allergic reactions can be mild or serious, and can even result in death in some cases. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.

Risks of the IV: Placing the IV catheter into your arm may cause some pain, discomfort where we place the IV, bruising, bleeding, swelling, redness, and temporary loss of pulse at the wrist could occur. This area may have a bruise or feel painful or uncomfortable for 2 - 3 days after the tube is removed. Rarely, an infection may occur at this site. If you develop an infection, it will be treated.

Risks of Drawing Blood: You may have a bruise (black-and-blue mark) or pain where we take the blood samples. There is also a small risk of feeling lightheaded, fainting, or infection.

9. Potential Benefits

To Participants: There will be no direct benefits to the subjects themselves for participating in the imaging portion of this research.

To Others: From a scientific perspective, the study may benefit people with depression by furthering our understanding of the role of dopamine in the mechanism of placebo. 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 risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

10. Monitoring and Quality Assurance

Data and Safety Monitoring Board (DSMB)
A Data and Safety Monitoring Board (DSMB) will be created **at the beginning of year 1**, as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support those purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality.

10.1. Membership of the DSMB:
We propose that the DSMB consist of one member with experience in conducting clinical trials for unipolar depression, one with experience in psychopharmacology, and one member with expertise in biostatistics of clinical trials. Drs. Perry Renshaw, Mark Pollack, and Gheorghe Doros will serve as the DSMB committee for this study.

10.2. Monitoring of Safety Data by the DSMB
Unblinded Reporting: Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.

10.3. Range of Safety Reporting to the DSMB:
It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but other data that may reflect differences in safety between treatment groups. This includes treatment retention rates, reasons for drop-out, and clinical outcome.

10.4 Serious Adverse Events:
Expedited review will occur for all events meeting the FDA definition of SAEs as described in Section 7 above. For purposes of this study, all SAEs will be required to be reported to the DSMB, regardless of any judgment of their relatedness to the study drug. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, dosing history of all study drugs, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by e-mail and/or fax of all related study forms shall be made to the DSMB within 2 days of the occurrence of any SAE. Information will be reviewed and a determination made of whether there was any possible relevance to the study drug. Additional reporting to local IRBs will be done within 5 business days of the SAE; reporting to NIH, and FDA will be made according to their respective regulations governing SAE reporting. PET-related events will be reported directly to the Radioactive Drug Research Committee within five days as required by the FDA.

10.5. Adverse Events:
At periodic intervals (yearly during the course of the study and then again at its completion), the DSMB will be provided with unblinded summaries of the numbers and rates of adverse events

by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.

10.6. Other Safety-Related Reports:
At twelve-month intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for drop-out, by treatment arm and study phase.

10.7. Study Stopping Rules:
If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

10.8 Monitoring of Data Quality by the DSMB:
At least on a yearly basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of subject intake and retention; summary reports describing subject compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize subjects, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

10.9 Annual DSMB Report to NIMH:
Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve subject safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

10.10 Policies and Procedures for Adverse Event Reporting to NIMH:
The PI will contact NIMH within 24 hours after the detection of a SAE. The PI will also report all PET-related adverse events directly to the Radioactive Drug Research Committee (RDRC) within five days of the detection of an AE.

10.11. ClinicalTrials.gov Requirements
The trial will be registered with ClinicalTrials.gov by the PI (Dr Cusin) prior to enrollment of the first subject.

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