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Research paper

Novel multi-modal methodology to investigate placebo response in major depressive disorder

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ABSTRACT

The neurobiological mechanisms underlying the placebo phenomenon in patients with major depressive disorder (MDD) remain largely unknown. The progressive rise in rates of placebo responses within clinical trials over the past two decades may impede the detection of a true signal and thus present a major obstacle in new treatment development. Understanding the mechanisms would have several important implications, including (1) identifying biomarkers of placebo responders (thereby identifying those individuals who could benefit therapeutically from such interventions), (2) opening new avenues for manipulating such mechanisms to maximize symptom reduction, and (3) refining treatments with approaches that decrease (in clinical trials) or increase (in clinical practice) the placebo response. Here we investigated the research question: is the dopaminergic system one of the neurobiological underpinnings of the placebo response within MDD? Inspired by preclinical and clinical findings that have implicated dopamine in the occurrence, prediction, and expectation of reward, we hypothesized that dopaminergic activity in the mesolimbic system is a critical mediator of placebo response in MDD. To test this hypothesis, we designed a double-blind, placebo-controlled, sequential parallel comparison design clinical trial aimed at maximizing placebo antidepressant response. We integrated behavioral, imaging, and hemodynamic probes of mesocorticolimbic dopaminergic pathways within the context of manipulations of psychological constructs previously linked to placebo responses (e.g., expectation of improvement). The aim of this manuscript is to present the rationale of the study design and to demonstrate how a cross-modal methodology may be utilized to investigate the role of reward circuitry in placebo response in MDD.

1. Introduction

Major Depressive Disorder (MDD) is a debilitating psychiatric condition characterized by features such as persistent low mood, anhedonia, and reduced motivation. While antidepressants are approved to treat MDD (Cipriani et al., 2018), it is difficult to determine whether improvement results from the medication versus cognitive processes like expectations and anticipation of symptom improvement, i.e., a placebo response.

Very little is known about the neurobiological underpinnings of the placebo phenomenon. Developing such an understanding is crucial, as placebo response rates in MDD clinical trials are often in the 35–50 % range, suggesting that antidepressant effects can be produced by an inert substance (Ioannidis, 2008; Fournier et al., 2010; Fava et al., 2003; Walsh et al., 2002; Dunlop et al., 2012). In fact, the placebo response rate in clinical trials has increased over several decades, and this has hampered the development of effective therapeutic agents not only for MDD (Dunlop et al., 2012), but also for pain (Tracey, 2010), and other conditions (Kaptchuk et al., 2009). In a meta-analysis of monotherapy, FDA-approved antidepressant trials in MDD (Iovieno and Papakostas,

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2012), a higher placebo response rate correlated with a lower risk ratio of responding to antidepressant versus placebo ($P < .001$) and correlated with higher antidepressant response rates ($P < .001$), with the number needed to treat for response being approximately 4, 6, and 9 in trials with placebo response rates <30 %, ≥ 30 % and < 40 %, and ≥ 40 %, respectively. This implies that the ability to detect a therapeutic effect depends on how well the placebo response is managed (Fava, 2023). Unfortunately, high placebo responses have called into question the effectiveness of antidepressants, which can contribute to the stigmatization of patients and can discourage them from accessing mental health care (Rutherford and Roose, 2013). Further research is clearly needed to better understand the placebo phenomenon.

Current understanding of the placebo neurobiology in MDD focuses on its association with brain reward circuitry, which comprises, among other regions, the mesolimbic dopamine (DA) pathway connecting the midbrain ventral tegmental area (VTA) to the nucleus accumbens (NAc) in the ventral striatum (Schweinhardt et al., 2009; Scott et al., 2007; de la Fuente-Fernández et al., 2002; Peciña and Zubieta, 2015). This line of research has been primarily conducted using neuroimaging, clinical, and behavioral methods. For example, DA release in the ventral striatum might influence the expectation of reward and symptom improvement (Vrieze et al., 2013; Scott et al., 2007). Recent studies by Pecina and colleagues have shown placebo-induced changes in functional magnetic resonance imaging (fMRI) signal in areas involved in cognitive control (dorsolateral prefrontal cortex) and reward processing (nucleus accumbens or NAc) (Peciña et al., 2021, 2023). Additionally, raclopride positron emission tomography (PET) studies have described DA release in the NAc during placebo administration under expectation of analgesia (Tracey, 2010).

Mesolimbic DA activity and reward responses can also be manipulated using pharmacological agents. Bupropion is an FDA-approved antidepressant that functions as a DA and norepinephrine (NE) reuptake inhibitor and has been shown to modulate NAc activity during reward-related anticipation induced by the monetary incentive delay (MID) task (Ikeda et al., 2019). We previously showed (Pizzagalli et al., 2008; Whitton et al., 2020) that the antidepressant properties of bupropion may be influenced by pre-treatment sensitivity to reward and functional connectivity of the NAc with other regions of the mesolimbic reward pathway. Hence, bupropion was chosen in this study as pharmacological probe to modulate mesolimbic DA activity in the context of reward processing and reinforcement learning. Additional studies used approaches such as the MID task to assess brain activity during anticipatory and consummatory stages of reward processing (Knutson et al., 2000), as these stages—especially reward anticipation—are known to evoke strong dopaminergic activity. One shortcoming of the MID task is that it uses cues that explicitly signal the potential delivery of monetary gains and losses, which means that it does not permit examination of reinforcement learning. This shortcoming is important because DA is well-known for encoding reward prediction errors, which are a teaching signal that drives reinforcement learning (Schultz, 1998). Therefore, for the current investigation of the neurobiology of placebo responses, we developed a modified version of the MID that entailed a learning component. Within our clinical trial, we aim to address the following question: what are the possible dopaminergic mechanisms underlying the placebo response in MDD?

Inspired by preclinical and clinical findings that have implicated dopamine in the occurrence, prediction, and expectation of reward, we hypothesized that dopaminergic activity in the mesolimbic system is a critical mediator of placebo response in MDD. To test this hypothesis, we designed a double-blind, placebo-controlled, sequential parallel comparison design clinical trial aiming at maximizing placebo antidepressant response. This design was coupled with an integration of behavioral, molecular imaging, and hemodynamic probes of mesocorticolimbic dopaminergic pathways within the context of manipulations of psychological constructs previously linked to placebo responses. With trial data currently in the analysis phase, the aim of this manuscript is to review and discuss the use of novel cross-modal methodology within our study design.

2. Methods

To investigate the placebo response in MDD, we developed a modified MID task to assess brain regions activated by anticipatory (goal-directed behavior) vs. consummatory (experience of pleasure) stages of reward processing, but also by reinforcement learning, thus maximizing sensitivity to variation in mesolimbic DA function (Dillon et al., 2008). The task is completed twice, prior to randomization to bupropion or placebo, and again after three weeks of treatment, during PET/fMRI scanning. This approach permits direct assessment of DA receptor occupancy (PET) and hemodynamic responses elicited by rewards and reward-predicting cues (fMRI), both of which may be related to individual differences in susceptibility to placebo responses. Critically, the second scan is timed to maximize the detection of early changes associated with placebo response. To our knowledge, this is the first multimodal study examining the placebo response observed during clinical trials for MDD. This research protocol has been approved by the Massachusetts General Hospital Institutional Review Board (Protocol #2014P000889) and is registered with ClinicalTrials.gov. Data and safety were monitored by a Data and Safety Monitoring Board (DSMB), 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. Written informed consent was obtained from all participants by a study physician before carrying out any procedures.

3. Design

The overall design of this research study consists of experimental procedures within a randomized controlled study. Subjects with MDD are randomized to active drug (bupropion XL 300 mg/day) or placebo as either monotherapy or augmentation of SSRI/SNRI. We use the sequential parallel comparison design (SPCD) (Fava et al., 2003) to maximize the number of placebo responders. Briefly, the 8-week study is divided into two Stages. In Stage 1, participants are randomized to placebo or drug in a ratio of 7:1 (87.5 % placebo vs. 12.5 % bupropion). In Stage 2, those participants randomized to bupropion in Stage 1 stay on bupropion, whereas placebo non-responders are re-randomized to placebo or bupropion in a 1:7 ratio (12.5 % placebo vs. 87.5 % bupropion, with these percentages computed separately for the placebo responder and non-responder groups). Placebo responders from Stage 1 stay on placebo in Stage 2. For the first four weeks, subjects will receive either bupropion (12.5 %; $n = 10$) or placebo (87.5 %; $n = 70$). Given these percentages, the informed consent document accurately states that there is a 75 % probability of being assigned to an active treatment arm at some point during the study; other statements are included as a way to heighten expectations of improvement (Fava et al., 2003), such as a description of bupropion as a "fast-acting antidepressant" (Zubieta and Stohler, 2009), as expectations have also been shown to affect activity in dopaminergic reward circuits (Lidstone et al., 2010). See Fig. 1 for a visualization of the study flow. Subjects are asked to complete weekly assessments and the timepoints of interest are baseline, week 4 follow-up, and week 8 follow-up.

The inclusion criteria include: (a) meeting the Diagnostic and Statistical Manual IV (DSM-IV; First et al., 2002) criteria for MDD; (b) age 18–45 years old; (c) a score > 17 on the Hamilton Depression Rating Scale-32 (HAMD-32 Williams, 1988); (d) continuing to meet criteria for current MDD and Clinical Global Impression (CGI; Guy, 1976) improvement scores ≤3 (i.e., minimally improved or less) between the screen and baseline visit. Exclusion criteria include: (a) pregnancy or childbearing potential without a medically accepted contraceptive; (b) serious suicide or homicide risk; (c) unstable medical illness; (d) the presence of any of the following —organic mental disorders, substance use disorders including alcohol abuse within the last year, psychosis,

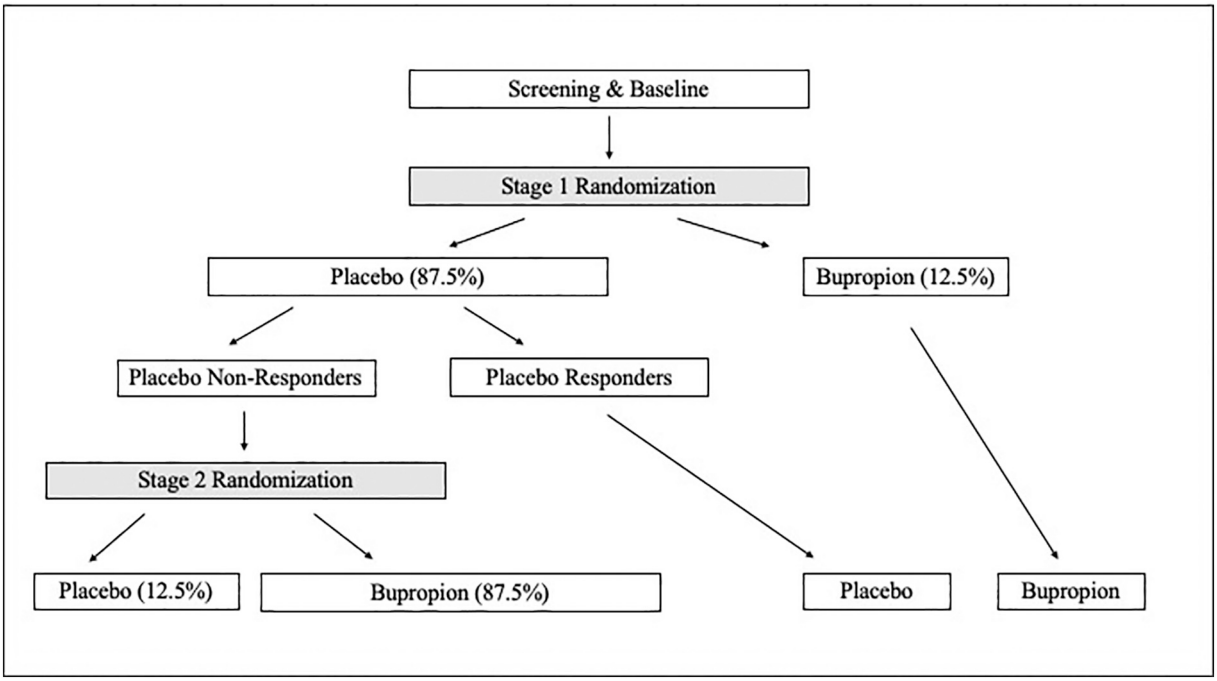

Fig. 1. Study flow and randomizations sequence.

bipolar disorder, acute bereavement, severe borderline or antisocial disorder, current primary diagnosis of panic disorder, social anxiety disorder, eating disorder, post-traumatic stress disorder (PTSD), generalized anxiety disorder, or obsessive compulsive disorder (OCD), mood congruent or incongruent psychotic features; (e) history of abuse of stimulants or opiates; (f) current use of antipsychotics, anticonvulsants, stimulants, or augmenting agents [e.g., T3, SAMe, St. John's Wort, lithium, buspirone]; (g) use of any investigational psychotropic drug in the last year; (h) non-response to two or more antidepressant trials of adequate dose and duration, as defined by the Massachusetts General Hospital (MGH) Antidepressant Treatment Response Questionnaire (ATRQ; Fava et al., 2003), over the last five years; (i) history of inadequate response to, or poor tolerability of bupropion; (j) any concomitant form of psychotherapy focused on depression; (k) current or prior treatment with electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagal nerve stimulation (VNS); or (l) red/green colorblindness (due to a task used with the PET/MRI scan). Depression severity is assessed throughout the trial with the HAMD-32. All subjects are 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. Any patient who, based on the investigator's judgment, poses an imminent risk of suicide is discontinued from the study and appropriate level of care is implemented. For patients receiving antidepressant treatment during the screening period, tapering takes place before the baseline randomization visit under clinical monitoring of the study doctor, in agreement with the patient's treating provider. The antidepressant used in the study, bupropion, is commonly prescribed for treatment of depression and it is considered to be relatively safe.

Neuroimaging measures focus on mesolimbic reward circuitry. A modified version of the MID paradigm (see below) is administered during the imaging sessions. Baseline data measure pre-treatment reward circuitry function. Pre-to-post changes in function between baseline and a 4-week follow-up investigate differential responses to bupropion vs. placebo. Neural activity of non-responders to bupropion is measured to investigate neuroimaging biosignatures for this group.

Subjects receive a single IV injection of [11C]-raclopride prior to each PET scan. Raclopride is selected due to: (1) strong a priori hypotheses targeting striatal regions; (2) prior findings from our group highlighting reduced activation in striatal regions in response to reward-related stimuli in MDD (Pizzagalli et al., 2009); (3) preliminary evidence of reduced reward-related raclopride displacement in unmedicated MDD subjects (Schneier et al., 2018); and (4) the fact that all prior PET studies investigating the role of DA in placebo response in pain or Parkinson's Disease have used raclopride (de la Fuente-Fernández et al., 2002; Lidstone et al., 2010; Tracey, 2010; Scott et al., 2008; de la Fuente-Fernandez et al., 2001; Strafella et al., 2006).

3.1. Imaging and behavioral tasks

3.1.1. Modified MID task

A modified version of the MID task (Knutson et al., 2001a, 2001b, 2000) is used to elicit dopamine release in striatal regions by adding a reinforcement learning component. In the standard MID task, each trial begins with a reward, penalty, or no-incentive cue that explicitly signals the potential outcomes on the trial; to earn rewards and avoid losses, participants must respond quickly to a target that follows each cue. This design is ideal for studying reward (and penalty) anticipation, but there is little to no learning involved, and DA is well-known for its crucial role in reinforcement learning (Schultz, 1998). To address this limitation, we modified the task by replacing the traditional cues with several shapes, each of which predicted a different outcome. Participants are not informed of the shape-outcome relationships, but have to learn them by experience, thus driving reinforcement learning in an effort to maximize DA release in the striatum.

Participants completed four blocks of the modified MID task in which they could win rewards; the task is programmed in PsychoPy (Peirce et al., 2019). Each trial began with a blue triangle, square, pentagon, or hexagon (duration: 1.5 s; radii = 3.92–6.32 cm), centrally presented on a light gray background; the cues are accompanied by the sound of a card being dealt (0.27 s;). After a jittered interstimulus interval (ISI: 1.5–5.0 s), during which time a black fixation cross is visible, a green circle (radius = 3.57 cm) is shown for 365 ms; the participant's task is to respond to the circle as quickly as possible by pressing a button. After a second jittered ISI (1.5–5.0 s), one of six outcomes is shown (duration: 1.5 s); each outcome is accompanied by a brief (0.5 s) sound. If response

time (RT) is <100 ms, the words "Too Fast!" are centrally presented in dark red, accompanied by a middle "E" tone. If RT exceeds a response threshold (see below), the words "Too Slow!" are centrally presented in dark red, accompanied by a falling tone (see "reward_fail.wav" in the Supplement). The remaining four outcomes indicate different reward magnitudes. On no-incentive trials, participants see a dark gray rectangle and hear a middle "C" tone: this indicates that their response is on-time, but no monetary reward is delivered. On small, medium, and large reward trials, participants view images of two U.S. quarters, a $1 bill, and $5 bill, respectively, indicating that they have won the corresponding amount of money. Delivery of these four outcomes is accompanied by a rising tone (see "reward_success.wav" in the Supplement) that is simply the failing tone played in reverse. Each cue shape deterministically predicts one of these reward outcomes, and assignment of cue shapes to outcome magnitudes is counterbalanced across participants; for each participant, the cue-outcome assignments are reversed from the first to the second imaging session such that the no-incentive cue becomes the large reward cue, the large reward cue becomes the no-incentive cue, and so on. A jittered interval (1.5–5.0 s) separates the trials.

Three steps are taken to increase engagement of the dopamine system throughout the session. First, no monetary penalties are used. Second, the number of large rewards on offer increase over the runs (run 1: 5; run 2: 8; run 3: 11; run 4: 14; note that there are 34 trials in runs 1 and 4, and 33 trials in run 2 and 3). Third, after runs 1–3, the participants view screens that show coins, stars, or fireworks, each with text indicating that the participant has qualified for the next "level" where they could win even more money.

Importantly, whether the participant receive the expected outcome on a given trial depends on their RT. In each of the four reward runs, the task code is designed to maintain a success rate of approximately 75 %. Thus, the code monitors the preceding four trials: if all four previous trials are "successful" (i.e., no "Too Fast!" or "Too Slow!" feedback), then the response threshold is decreased by 5 %; if three of four trials are successful, then the threshold is not changed; and if two, one, or none of the trials are successful, then the threshold is increased by 5, 10, or 15 %, respectively.

The response threshold on the first reward run is equal to the 70th percentile of the RT distribution obtained in a "neutral" run that precedes the four reward runs. The neutral run is structured exactly like the reward runs, except that just one cue is presented and only three outcomes are possible: too fast, too slow, or no-incentive. The neutral run includes 63 trials and is preceded by structural MRI scans and an 8-min resting state scan. The sessions are structured in this way so that the reward runs began approximately 25 min after injection of [11C]-raclopride, when peak DA receptor occupancy is expected; in this way, displacement of the radiotracer by reward-elicited dopamine release would be facilitated.

Finally, participants rate the valence (1 = very negative, 5 = neutral, 9 = very positive) of their emotional responses to the four shape cues and the four main outcomes (no-incentive, small/medium/large rewards) before the first reward run, and again after the second and fourth reward runs. Changes in cue shape valence ratings over the session are designed as a measure of reinforcement learning: we anticipate that the cues would elicit similar (neutral) emotional responses prior to the first reward run, but that, as the session progresses, participants would learn the cue-reward associations and come to prefer cues associated with larger rewards. Because the response threshold is adjusted to maintain an overall 75 % success rate, it is not possible to use cue effects on RT as a measure of reward responsiveness (as participants have to respond quickly to all cues due to the thresholding).

3.1.2. Probabilistic reward task (PRT)

The probabilistic reward task (PRT) is used to examine subjects' ability to modulate behavior in response to rewards, both pre- and post-treatment (Pizzagalli et al., 2005). In the PRT, subjects complete three blocks of 100 trials in which monetary rewards are delivered 3× more often for correct identifications of a "rich" versus a "lean" stimulus. Subjects typically develop a response bias towards the rich stimulus that can be used to measure reward responsiveness. We examine reward responsiveness in correlation with ligand displacement (PET) and blood oxygenation level dependent (BOLD) signal (fMRI) in striatal regions.

3.2. Clinical data

We define clinical improvement or response (either to the active treatment or placebo) as a $\geq$ 50 % reduction in the total HAM-D-32 score between baseline and follow-ups. The primary variable of interest is the difference in depressive symptom scores between baseline and the 4-week and 8-week follow-ups. A two-step regression model is used. We utilize covariates in the first step (e.g., baseline severity, age, gender, smoking status), followed by behavioral and neuroimaging predictors. Group (responders vs. non-responders) or change in HAM-D-32 score are the criterion variables.

3.3. Neuroimaging analysis

The goal is to examine raclopride displacement (i.e., task-induced dopamine release) and BOLD signal to cues and reward outcomes in ventral (NAc) and dorsal (caudate, putamen) striatal regions, to compare placebo responders vs. non-responders and bupropion responders vs. non-responders at the group-level.

3.3.1. Positron emission tomography (PET)

Subjects are scanned headfirst, supine on a hybrid PET/MR (positron emission tomography/magnetic resonance) scanner (Biograph mMR, Siemens Healthineers) for 90-min in list mode following intravenous bolus injection of ~17 mCi of [11C]-raclopride. All the dynamic [11C]-raclopride PET images are processed with a kinetic analysis approach based on the linear parametric neurotransmission PET model ('lp-ntPET'(Normandin et al., 2012). The lp-ntPET method is implemented in a direct reconstruction framework inclusive of motion correction (Petibon et al., 2020) for the estimation of striatal D2 receptor availability and task-induced dopamine release. Dopamine activity is estimated using two comparisons of mean binding potential (BPnd) and mean γ (rate of change of ligand displacement). Comparisons are made across group (responders vs. non-responders), condition (neutral vs. reward), and time (baseline vs. follow-up). BPnd maps provide a quantitative estimate of the binding sites available per unit volume. The maps are stereotaxically transformed, pooled, and averaged across subjects. Mean BPnd is compared between groups to estimate the number of binding sites activated during the MID task. Mean γ change score is entered as a predictor variable in the second step of the hierarchical regression.

3.3.2. Functional magnetic resonance imaging (fMRI) acquisition

Structural and functional magnetic resonance imaging scans are acquired on a 3Tesla MR scanner using a 32-channel head coil. A T1-Magnetization Prepared Rapid Gradient Echo Imaging (T1-MPRAGE) structural image is collected (TR: 2530 ms; TE1/TE2/TE3/TE4: 1.69/3.55/5.41/7.27 ms; voxel size = 1 mm^3 isotropic; 176 slices). Five functional runs of the modified MID task (one neutral, four reward runs) are collected with the following parameters: TR: 3000 ms; TE: 30 ms; voxel size =3.3 mm^3 isotropic; 51 slices; 222 volumes.

3.3.3. fMRI Preprocessing

The first three volumes of each run are removed for magnetic field stabilization. Standard preprocessing is conducted using the software Statistical Parametric Mapping 12 (SPM12), including slice timing correction, realignment of functional images to the first image, co-registration of functional and anatomical images, warping to Montreal Neurological Institute (MNI) space, and spatial smoothing (6-mm

FWHM). The Artifact Detection Toolbox is used to identify outlier fMRI volumes (https://www.nitrc.org/projects/artifact_detect). Outlier volumes are those that exceed a composite threshold of 2 mm framewise displacement or where global mean intensity is over 3 standard deviations away from the mean intensity across volumes.

3.3.4. fMRI analyses

The fMRI analyses focused on activation during the reward runs. A first-level general linear model includs regressors for each cue (no incentive, small, medium, large) and outcome (no incentive or small, medium, large reward) separated by block. Standard nuisance covariates (e.g., motion parameters) are included. Analyses focused on activation in the NAc, caudate, and putamen, as per Harvard-Oxford atlases. Beta-weights are extracted from the three striatal regions of interest for cues and outcomes, separated by blocks. Analyses include a *Cue Type* (no incentive, small, medium, and large) x *Block* (1–4) x *Session* (1,2) x *Responder Status* whole-brain ANOVA, and an *Outcome Type* (no incentive, small, medium, and large) x *Block* (1–4) x *Session* (1, 2) x *Responder Status* whole-brain ANOVA.

3.4. Cross-modal integration using statistical modeling

We plan to identify the clinical, behavioral, and neuroimaging predictors that demonstrate significant univariate group differences. A logistic regression approach is used to develop multivariate models and identify predictive variables that distinguish groups of responders vs. non-responders for both placebo and bupropion. Response status is the dependent binary outcome Transformations are performed for variables with skewed distributions. Non-linear relationships of variables with total HAM-D scores are examined before group dichotomization. The model is determined using forward stepwise selection, with a classification cutoff of 0.5. The chi-square ratio is evaluated to assess fit improvement with predictor variables in the model relative to the null model. Nagelkerke's R^2 is used to test the association strength between treatment outcome and predictor variables. The receiver operating characteristic (ROC) curve is measured for each continuous variable to define cut-off points with the best sensitivity and specificity.

4. Discussion

Our novel study design involves experimental procedures conducted within a double-blind, randomized, placebo-controlled study to investigate the neurobiological underpinnings of the placebo response among MDD patients. Several strategies were implemented to maximize the number of placebo responders in the study, including the choice of SPCD design and manipulation of expectations (Fava et al., 2003; Zubieta and Stohler, 2009). The ultimate goal is to compare the biosignatures of placebo responders and non-responders.

Although our study had rigorous exclusion criteria, as participants are excluded if they met criteria for other primary psychiatric diagnoses, like substance use disorders, patients with comorbid anxiety disorders or stable medical conditions were included to increase generalizability. Finally, to enhance generalizability and facilitate recruitment, bupropion was administered as either monotherapy or augmentation of a stable antidepressant.

In summary, the "Neurobiological Underpinnings of the Placebo Response in Major Depressive Disorder" study (ClinicalTrials.gov ID NCT02562430) is a double-blind, randomized, placebo-controlled study examining the relationship between reward circuitry and placebo response in individuals with MDD. The current study design is intended to provide clinicians and patients with an improved understanding of the role of reward circuitry in symptom improvement. Utilizing a combination of neuroimaging techniques, objective behavioral measures of reward responsiveness, and clinical measures, the current study provides a novel framework for future studies investigating reward circuitry to ultimately develop effective pharmacotherapeutic interventions for MDD.

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CRediT authorship contribution statement

Cristina Cusin: Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Daniel G. Dillon:** Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Emily Belleau:** Visualization, Formal analysis, Data curation. **Marc D. Normandin:** Methodology, Conceptualization. **Yoann Petibon:** Software, Methodology, Formal analysis. **Georges El-Fakri:** Supervision, Conceptualization. **Maeva Dhaynaut:** Formal analysis, Data curation. **Jacob Hooker:** Supervision, Formal analysis, Data curation, Conceptualization. **Ted Kaptchuk:** Formal analysis, Data curation. **Madison McKee:** Project administration, Data curation. **Emma Hayden:** Writing – original draft, Project administration, Data curation. **Ashley Meyer:** Writing – review & editing, Writing – original draft, Project administration, Data curation. **Aava Jahan:** Writing – original draft, Project administration, Data curation. **Julianne Origlio:** Writing – review & editing, Project administration, Data curation. **Yuen-Siang Ang:** Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Devon Brunner:** Project administration. **Min Kang:** Project administration, Data curation. **Yinru Long:** Project administration, Data curation. **Maurizio Fava:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Diego A. Pizzagalli:** Visualization, Supervision, Software, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

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