Study Protocol

Official Title: Study of Neural Responses Induced by Fast-Acting Antidepressant Effects (SONRISA)

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Scientific Background
For unknown reasons, certain diseases, such as depression, show remarkably and increasingly high placebo rates, significantly hindering the development of novel therapeutics and predictors of treatment response. The failure to differentiate between placebo and antidepressant responses has caused large pharmaceutical companies to reduce or discontinue research focused on treatments for depression and other mental illnesses. Several strategies have been used to improve assay sensitivity in clinical trials, primarily by reducing the number of placebo responders that enter a trial. Examples of these strategies include the use of placebo-lead phases or, more recently, sequential parallel comparison designs. One limitation of these approaches is that the results from these trials, obtained primarily from placebo non-responders, may not be generalizable to all patients with depression. It is likely that placebo responders may require lower doses of antidepressant treatment, or no treatment at all, which will result in reduction of the overall cost and risk of using antidepressants. Furthermore, currently used ratings scales to measure both placebo and antidepressant effects are imprecise and highly influenced by other factors, such as regression to the mean or natural fluctuation of symptoms. As a consequence, placebo effects continue to be a great barrier to the development of novel and successful therapeutics. The work proposed in this application is significant because, rather than excluding placebo responders from clinical trials, it aims to objectively define neural responses to placebo, in order to predict placebo effects and assess drug effects on placebo-related neural networks in clinical trials. This information will be accounted for in the statistical analysis of clinical trials in order to improve the ability to detect drug-placebo differences in clinical trials. Results from this study, would be generalizable to all patients with depression. Ultimately, a better understanding of the neurobiology of placebo effects will advance personalized medicine for depression and provide new insights into novel targets for drug development.

Study Objectives
The study intent is to identify biological mechanisms associated with inter-individual variations in placebo responses in patients with Major Depressive Disorders (MDD) as a model syndrome with high placebo responses. It is hypothesized that the identification neural responses during an fMRI placebo experiment will predict sustained responses to placebo in an 8-week double-blinded randomized controlled trial (RTC) of escitalopram and allow the investigation of the effect of antidepressant treatment on placebo related neural networks.

AIM 1: We will first define the neural correlates of placebo response in MDD. We hypothesize that simulated neurofeedback will be associated with acute mood improvement and increased Blood-oxygen level dependent (BOLD) responses.
AIM 2: We will determine the extent to which mood and neural responses to simulated positive neurofeedback at baseline will predict placebo responses in an RCT.
AIM 3: We will assess whether antidepressant treatment enhances placebo-related neural networks in an RCT.

Study Design & Methods
This study is a single site double-blinded 8-week placebo control RTC randomized controlled trial of 20mg of escitalopram or placebo that incorporates neuroimaging measures before and after the RTC. During the fMRI scanning session participants undergo the “Simulated Real-Time Neurofeedback” fMRI task, previously described (1, 2). In summary, **the Simulated Real-time Neurofeedback fMRI Task** features two components of the placebo effect: expectancies and their reinforcement, each followed by an expectancy and mood rating cue, respectively. The expectancy condition involves an “antidepressant infusion” cue and a “no-infusion” cue, described as periods of equipment “calibration”. During the “antidepressant infusion” cues (4s),

a bar is filled at four 1s-periods representing 0%, 33%, 66%, and 100% of the dose administered. During the "calibration no-infusion" cue (4s) the bar remains empty. For the reinforcement condition (10s), sham neurofeedback acts as a secondary reinforcer of the "antidepressant" effects. In the high-reinforcement condition, sham neurofeedback is positive 75% of the trials (vs. 25% baseline). Participants rate their expected and actual change in mood (YES/NO) in response to each infusion/neurofeedback signal, respectively, by using a keypad and their index fingers. Inter-stimulus interval duration was randomly sampled from an exponential distribution bounded between 0.33 and 2 s. Inter-trial intervals were sampled from the uniform distribution with bounds 4-6 s.

1. **Peciña M.,** Chen J., Lyew T., Karp J.F., Dombrovski A.Y. μ-Opioid antagonist naltrexone partially abolishes the antidepressant placebo effect and reduces OFC encoding of reinforcement. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021 Mar 6;S2451-9022(21)00055-0. doi: 10.1016/j.bpsc.2021.02.009. Online ahead of print.
2. **Peciña M**, Heffernan J, Wilson J, Zubieta JK, Dombrovski AY. Prefrontal expectancy and reinforcement-driven antidepressant placebo effects. Transl Psychiatry. 2018 Oct 15;8(1):222. doi: 10.1038/s41398-018-0263-y. PMID: 30323205; PubMed Central PMCID: PMC6189213.

Eligibility Criteria

List the inclusion criteria:

• Adults, age 18-55 years; fluent in English and with the capacity to understand the nature of the study and sign the written informed consent since the research instruments used in this study are not available in other languages;
• Written informed consent obtained;
• Outpatients with a current primary diagnosis of nonpsychotic Major Depressive Disorder (MDD) per the Mini-International Neuropsychiatric Interview (M.I.N.I) with or without certain anxiety disorders (e.g., generalized anxiety, panic, agoraphobia, social phobia, and specific phobia); HDRS-17 score of ≥ 16 at Screening Visit. Patients with MDD in the context of a chronic major depression will also be allowed. Other forms of chronic depression in the absence of MDD will not be allowed;
• No more than one failed antidepressant trial of adequate dose and duration of the current episode, as defined by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ);
• Participants will need to be antidepressant medication-free for at least 21 days prior to collection of imaging data (five weeks for fluoxetine). However, individuals currently taking antidepressants will not be eligible to enroll in the study, even if they are willing to stop their medications.

List the exclusion criteria:

• Pregnant or breastfeeding or plan to become pregnant over the duration of the study;
• History (lifetime) of psychotic depressive, schizophrenic, bipolar (I, II, or NOS), schizoaffective, OCD, ADHD or other Axis I psychotic disorders;
• History of intolerance to or contraindications to escitalopram, fluoxetine, and sertraline.
• Meeting M.I.N.I. criteria for substance dependence in the last 6 months, except for nicotine, or substance abuse in the last 2 months;
• Requiring immediate hospitalization for psychiatric disorder or have an unstable general medical condition (GMC) that will likely require hospitalization or to be deemed terminal (life expectancy < 6 months after study entry);
• Requiring medications for their GMCs that contraindicate treatment with escitalopram, fluoxetine or sertraline;
• Having epilepsy or other conditions requiring an anticonvulsant;
• Receiving or have received vagus nerve stimulation, ECT, or rTMS.

• Currently taking any psychiatric medication or other potential augmenting agents (e.g., T3 in the absence of thyroid disease, lithium, buspirone); Taking thyroid medication for hypothyroidism may be included only if they have been stable on the thyroid medication;
• Receiving therapy that is depression specific, such as CBT or Interpersonal Psychotherapy of Depression (participants can participate if they are receiving psychotherapy that is not targeting the symptoms of depression, such as supportive therapy, marital therapy);
• Currently actively suicidal or considered a high suicide risk;
• Currently enrolled in another study, and participation in that study contraindicates participation in this study;
• Any reason not listed herein yet, determined by the site PI and research staff that makes participation in the study hazardous.
• Having any contraindication for the performance of an MRI, such as: the presence of metal implants or foreign metallic objects (e.g., braces or extensive dental work), severe claustrophobia, or inability to tolerate the scanning procedures.

Statistical Considerations

Image acquisition and data processing. Functional MR images are acquired at MR center at the Presbyterian Hospital on a 3 Tesla scanner (Philips Achieva, Best, Netherlands) using a single-shot echo planar imaging (EPI) sequence (TR=2000, TE=35ms, FA=90, FOV =20cm, 64 x 64 matrix). The "Simulated Real-Time Neurofeedback fMRI Task" described above has been programmed using PsychToolbox-3 software (13) and can be presented to subjects via a display placed behind the gantry. In each of the 6 runs of the task, 228 functional images will be acquired. Two sets of anatomical MR images will be acquired on the same scanner, including a high resolution anatomical scan for anatomical standardization to the Montreal Neurological Institute (MNI) template and a lower resolution scan acquired in the same locations as the functional scans to improve standardization. All newly collected fMRI data is analyzed using standard procedures (14).

Imaging data statistical analysis. Subject-level analysis. Each participant's effects is analyzed using general linear model. The regressors included in the model will be anticipation of infusion/no-infusion (6s), and neurofeedback (16s). Additionally, first order parametric regressors will be constructed for the neurofeedback regressor, modelling the effect of expectancy (drug infusion vs. calibration) and reinforcement (positive vs. baseline neurofeedback), where each will be weighted 1 and -1, respectively. All regressors of interest will be convolved with the standard hemodynamic response function.

Group-level analysis. At the group-level, a random effects analysis determines the main effects of the regressors of interest (e.g., expectancy) resulting in statistical parametric maps (t or F statistics). The resulting voxel-wise parametric maps are thresholded with height and extent values generated by Monte Carlo simulations with 3dClustSim to protect against overall type I error at $p < 0.05$. To control for potential confounders, sex and depression severity will be entered as covariates in statistical models.

Mood ratings during the fMRI task data statistical analysis. Linear regression analyses will examine the relationship between changes in mood improvement and neural responses during the simulated real-time neurofeedback fMRI task and changes in the MADRS scores from baseline treatment with placebo or escitalopram for 8 weeks. **RCT statistical analysis.** A series of models will examine whether behavioral and neural response during the simulated real-time neurofeedback fMRI task will predict the improvement of depressive symptoms after treatment with placebo for 8 weeks. For each, the effect will be modeled using an interaction between placebo responsiveness and time (week). The main effect will be interpreted as the effect of the predictor on MADRS scores at the beginning of the RCT, and the interaction term will be interpreted as the degree to which the trajectory of MADRS score over the 8-week trial varies by level of the predictors.