Title: An fMRI Study of Stimulant vs. Non-Stimulant Treatment of ADHD

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Hypothesis Testing

Primary Objective: Vyvanse (lisdexamfetamine; LDX) reduces impulsivity by normalizing cognitive control and reward processing circuits, whereas Intuniv (guanfacine, extended-release; G-EX) reduces impulsivity by normalizing cognitive control but not reward processing circuits.

We will first examine whether there are significant pre- vs. post-treatment changes in cognitive control and reward processing circuits. **Task-based functional MRI (fMRI) analyses:** We will enter each participant's task-related contrast map into a 2 x 2 repeated measures factorial model, treating Time as a repeated measure with two levels (pre- and post-treatment), and Treatment as a between group factor with two levels (LDX and G-EX). We will isolate an interaction term (Time x Treatment) to determine differential effects of treatment on task-related activation and then conduct post-hoc t- tests to determine the nature of the interaction. **Resting-state functional connectivity MRI (Rs-fcMRI) and Diffusion Tensor Imaging (DTI):** Analyses will be similar to those for task-based fMRI, but dependent variables will be seed based connectivity and FA maps.

For mediation analysis of treatment effects, we first estimate the changes in cognitive control and reward processing circuits that result from treatment (described in paragraph above). We then establish that the changes in these circuits, in turn, affect impulsivity, while controlling for treatment group. To estimate **path a (Fig. 1)**, we will use a linear regression model with pre-post changes in cognitive control and reward processing circuits as the outcome variable and treatment as the predictor variable. If we find a significant effect of treatment on both reward and cognitive control circuits, we will pursue multiple mediation analyses; otherwise, we will include only the circuit in which there is a significant effect of treatment. To estimate **path b**, we will use a linear regression model with pre-post change scores in impulsivity (based on parent report) as the outcome and pre-post change in cognitive control or reward processing circuits as primary predictors, while controlling for baseline impulsivity and treatment group. The mediation effect is then estimated by taking the product of the estimates for **path a and b** and using the bootstrap method to obtain standard errors, confidence intervals, and the test for statistical significance.

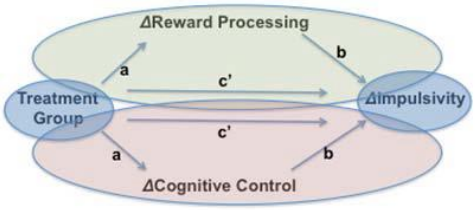

Figure 1 Mediation Model

To test whether treatment effects on cognitive control or reward processing circuits are specific in mediating improvements in impulsivity, we will explore whether treatment-related changes in other neural networks also mediate the effect of treatment on impulsivity. We will first screen these additional neural networks based on a significant effect of treatment on connectivity within these networks. Only networks that show significant change with treatment will be added to the multiple mediation analyses described above. The indirect effects of the cognitive control or reward processing circuits will be tested in the existence of the mediation effects of other neural networks using the bootstrapping method.

Power: Power for detecting the mediation effect depends on the size of the associations between (a) treatment group and changes in cognitive control and reward processing circuits, and (b) changes in cognitive control and reward processing circuits and changes in impulsivity. Based on tabulated recommendations for sample sizes needed to test mediation effects, with a sample size of n=60, we have more than 80% power to detect a significant mediation effect with medium effect size of both paths a and b.

Secondary Objective: ADHD patients with baseline MRI anomalies within reward processing circuits will respond to Vyvanse, but not Intuniv, treatment. Conversely, ADHD patients with baseline MRI anomalies that are circumscribed to cognitive control circuits (i.e., reward processing comparable to healthy controls) will predict response to either Intuniv or Vyvanse.

We will test the moderation effect of the baseline MRI measures cognitive control and reward processing circuits on the treatment response. We will use linear regression models with pre-post change scores in impulsivity measures as outcomes and Group, baseline measures of cognitive control and reward processing circuits measured in predefined regions of interest (ROIs), and their interactions as predictors. Likelihood ratio tests will be used to test the effect of moderation with combination of multiple brain imaging measures.

Power: With sample size of n=60, the minimum detectable effect size of Cohen's f^2 is 0.09 (smaller than medium effect size 0.15) with 80% power for a two-sided test at the 5% significance level. If the effect size of interactions between baseline measures within cognitive control and reward processing circuits and Group is greater than f^2 is 0.09, we would be able to detect such effect size.