Neuroimaging predictors of relapse during treatment for Opiate dependence
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C**4. Data Analysis**

A priori ROI analyses will be our primary method for quantifying task-related effects for hypothesis testing, while analyses involving the functionally defined ROIs will serve to validate our *a priori* findings.

We will test hypotheses using lapse as the grouping variable and then with relapse. Three markers (altered response, disorganized response, and compensatory mechanisms; see Aim 1) will be evaluated in both the stable opiate use state and during opiate withdrawal.

We will compare lapsers and nonlapsers on pre-quit behavioral and FMRI measures hypothesized to predict lapse (Aim 1) followed by application of Cox regression models predicting time to relapse among the full sample to determine if neuroimaging measures provide additional utility in predicting lapse (Aim 2). Although Aim 1 hypotheses are designed to be tested as group contrasts based on lapse within 1 week of quitting, we will group by median split of time to lapse if this results in unacceptable differences in group size.

Aim 1. 1) Altered response to targeted challenges. These hypotheses will be tested using independent samples t-tests using mean task-associated activity in each ROI (listed in Table 1) as the dependent measure. For contrasts of cognitive persistence during the WM challenge, a linear mixed effects model for repeated measures will be conducted that allows estimates of contrasts of group over time and interactions. Parallel contrasts of behavioral measures will also be conducted for each task. 2) Disorganization of neural networks. Functional connectivity analyses will be conducted to determine the strength of relationships between the nodes of each network listed in Table 1. These will be converted to z-scores using Fisher's transformation and contrasted across groups using independent samples t-tests. 3) Compensatory mechanisms. Compensatory overactivation will be assessed using voxel-wise independent samples t-tests. Voxel threshold will be <.05 corrected for multiple comparisons. We expect more recruitment of regions outside of the *a priori* ROIs among the lapsers during all FMRI paradigms. Although assessed qualitatively due to a lack of *a priori* spatial extent, we will count both clusters of significant activity and total volume of significant activity outside of a priori ROIs in order to perform exploratory group contrasts. Compensatory underactivation will be assessed using independent samples t-tests of mean task-related responses (i.e., DD, WM, *WMCP,* IC) in regions identified as the DN in the independent functional connectivity analyses of the resting state imaging run. We expect that while FMRI predictors for lapse and relapse will be related, they will not be identical. We plan primary analyses to separately examine both lapse and relapse. Although they are strongly associated, this permits identification of differential relationships between each and FMRI challenges, if present. Prediction and prevention of relapse is the most important goal of this line of research; however, we still include lapse, since it has been used as the outcome measure in most relevant studies.

Aim 2. For each targeted relapse-risk domain, comparisons of behavioral and FMRI markers will be examined per ROI using logistic regression (lapse) and Cox proportional hazards survival models predicting time to relapse conditional on planned covariates including gender, age, social support, self-efficacy, *comorbid alcohol and drug use,* and mood. The unique explanatory contribution of FMRI responses will be evaluated by comparing a full model (including FMRI response, behavioral data acquired during the FMRI challenges, and covariates) to a reduced model, which includes only the behavioral data and covariates.