Title: Striatal Effective Connectivity to Predict Treatment Response in Cocaine Misuse

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Data analysis plan

Initial analyses will evaluate group differences on demographic and baseline variables, will use contingency tables with chi-square testing, ANOVA's, and examination of correlations between baseline variables and snDCM results. The Friston et al. network discovery technique, Bayesian model selection (BMS), and Bayesian family level inference (BFLI) will be used to select the optimal model based on the exceedance probability of the DCM (or family of DCMs) in which DLPFC causally affects ventral striatum vs. exceedance probability of the DCM (or a family of DCMs) in which the ventral striatum causally affects the DLPFC. The parameter estimates for the endogenous DLPFC-striatal connectivity will be compared between groups using Bayesian model averaging (BMA) and also compared using analysis of covariance.

Urn randomization, a form of stratified randomization, will help ensure comparability of treatment groups on baseline severity and duration of cocaine abuse. Pretreatment task behavioral performance or demographic variables on which group differences are detected, and which are correlated with outcomes, meet the definition of confounders. In such cases, analyses will evaluate the robustness of findings after statistically controlling for the confounder. If conclusions remain unchanged after covarying for the confounder, the more parsimonious model will be reported along with a statement indicating its robustness to covariation for potential confounding. If inclusion of the covariate alters the conclusions of the analysis, both models will be reported. Treatment success is a function of two elements: (a) retention and (b) demonstrating cocaine-free status using the SRPHK1 criteria. The Treatment Effectiveness Score (TES) provides a metric for this composite outcome. TES is the sum of all cocaine-negative tests (according to SRPHK1 rules). Higher TES indicates that participants both continue to participate in the study and are negative for cocaine. For each group, BMA is conducted across all DCMs in the model space. Group difference in the gating effect by the dorsal striatum is assessed using Bayesian confidence probability. In addition, BMA is conducted across all DCMs in the model space for each subject in the medication group and in the placebo group. Evaluation of differential treatment response, measured by the TES, as a function of the averaged (across the DCM model space) gating effect, will use Poisson regression. Violations of assumptions of dispersion will result in the use of more appropriate approaches such as zero-inflated Poisson, negative binomial, or zero-inflated negative binomial models. Regression of treatment, averaged gating, and their interaction will permit evaluation of differential treatment response as function of gating. The critical element in doing so is the evaluation of the interaction term. Given that the current study is powered to detect group differences, it is likely underpowered to detect an interaction. Brookes, et al. demonstrate that for studies with 80% power to detect a between-groups effect, power to detect an interaction effect of the same magnitude as the main effect is approximately 29%. One solution is to adopt a Bayesian subgroup analysis approach. This approach utilizes the posterior distribution of the interaction parameter to estimate the probability that it exceeds some number (e.g., for Poisson regression a Risk Ratio of 1.0). Specification of vague neutral priors will reflect uncertainty regarding parameter values, utilizing prior distributions for the lower order effects that are neutral and diffuse with specification ~N(0, 1×10^{-6}) on the log scale (i.e., centered at the null hypothesis with a 95% Credible Interval of ± 1960) for all coefficients, and ~U(0,100) for any required dispersion terms. Examination of the interaction of treatment and the subgroup index forms the crux of the evaluation of the subgroup effect. For evaluating the interaction representing the differential subgroup effect, analysis will be conducted in two ways: (a) utilizing diffuse, indifferent priors (~N(0, 1×10^{-6}) on the log scale for the interaction coefficients, and (b) using informative skeptical priors for the coefficients will evaluate sensitivity of statistical conclusions to specification of priors. Informative, skeptical priors will be derived via the method first proposed by Dixon and Simon. Evaluation of resulting posterior distributions will permit conclusions regarding the probability that subgroup/interaction effects of varying magnitudes obtain. Examples of this use of the posterior distribution may be found in Green et al. (2009). Bayesian modeling will use SAS v9.2 (Proc Genmod and Proc Monte-Carlo Markov chain [MCMC]), and in WinBugs 1.4.3 (http://www.mrc-bsu.cam.ac.uk/bugs). Convergence of Bayesian analyses on the posterior distributions via MCMC will be assessed via graphical (Trace Plot, Autocorrelation Plot) and quantitative (Geweke Diagnostics, Gelman-Rubin Diagnostics, and Heidelberger-Welsh Diagnostics) evidence. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data.

While the use of urn randomization will likely result in comparable groups, substantial heterogeneity may still exist within conditions on baseline variables such as severity, duration of use, and impulsivity. We propose subgroup analyses following the procedures described above. This will determine the degree to which baseline variables moderate the interaction of treatment and snDCM.