

## *Meta-Analysis and Machine Learning: Towards Neuromarkers of Craving and Relapse*

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The experience of drug craving is known to increase drug use and relapse after treatment. Specifically, drug-related stimuli are known to elicit cue-induced craving, as well as physiological and neural responses, called cue reactivity, which have all been directly linked to drug use and relapse across addictions, including gambling. To date, hundreds of studies investigated neural cue-reactivity; however, there is little consensus in findings, due to significant variation in methods, drug types, cue types, and analysis procedures. Further, prior meta-analyses used suboptimal methods and inclusion criteria, and were underpowered.

As part of R01 DA043690 we used state-of-the-art meta-analytic methods – Multilevel Kernel Density Analysis – to summarize findings from 127 published imaging studies, representing ~4000 participants during neural cue reactivity/cue-induced craving (3x larger than any prior meta-analysis). Following our prior meta-analytic work in other domains, we used optimized inclusion criteria and correction methods, and accounted for multiple methodological differences in studies across substances (e.g., cigarettes, alcohol, cocaine, cannabis) and gambling, a behavioral addiction. Further, we tested for differences across drug types (e.g., cigarettes vs. alcohol) and different cue-types (e.g., pictures vs. video) to resolve several open questions in the field (e.g., role of insula in cigarette craving vs. drug craving in general; effects of pre-scan abstinence).

Next, we have gone beyond meta-analysis to address an urgent need in addiction research: development of predictive biomarkers, which are stable indicators of biological processes. Biomarkers have been developed in other areas of medicine, and psychology (including recently in pain, negative emotion, and empathy). To do this, we combined the meta-analytic results noted above with person-level fMRI data from our lab (of cue-induced craving) using machine learning models, to establish multivariate patterns of neural activity that can differentiate between drug-cue reactivity and reactivity to other cues, and between drug users and controls. We are currently working on a multivariate pattern to predict craving self-report from neural activity – a predictive neuromarker for craving. Given the associations between neural cue reactivity, craving, and drug use outcome, such a multivariate neuromarker could provide a powerful neural predictor of outcomes.

Our next step is to validate this neuromarker on data from two ongoing clinical trials of cigarette smokers and cocaine users collected at Yale's Psychotherapy Development Center (P50 DA09241; Center PI: Carroll; Project PI: Kober). Here, the neuromarker will be used on pre-treatment fMRI cue-reactivity data to predict both self-reported craving and long-term clinical outcomes (e.g., cocaine abstinence). The validated neuromarker will provide well-defined brain targets that can then be used to test the efficacy of interventions to reduce craving and drug use, such as pharmacotherapies, brain

stimulation, or cognitive training, and to monitor patient progress in both research and clinical settings.