Addiction-associated genetic variants implicate cell type- and region-specific cis-regulatory elements in addiction neurobiology

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Recent large genome-wide association studies (GWAS) have identified multiple confident risk loci linked to addiction-associated phenotypes. Genetic variants from complex behavioral and neurological traits, including addiction, tend to lie within non-coding cis-regulatory elements (CRE). We leverage the high degree of cell type-specificity of CREs to hypothesize that addiction-associated genetic variants lying in CREs of some cell types, but not others, might play functional role in the process of addiction.

We applied LD score regression to intersect addiction-associated variants with cell type- and region-specific CREs from human, mouse, and macaque to predict cell populations and circuits of addiction. We find that addiction-associated variants enrich in NeuN+ nuclei from human dorsolateral prefrontal cortex, orbitofrontal cortex, putamen, and the nucleus accumbens (Fullard et al. 2018), and excitatory and inhibitory neurons of human occipital cortex (Lake et al. 2018).

We note concordant enrichment in orthologous CREs specific to mouse bulk striatum as well as mouse excitatory and VIP+ cortical neurons from INTACT sorted nuclei (Mo et al. 2015). We find further concordant enrichment within orthologous non-coding regions around medium spiny neurons and interneuron sub-types marker genes of the macaque striatal cell populations. Lastly, machine-learning models trained on sequences of cell type-specific CREs predict the impact of addiction-associated variants on CRE function.

The enrichments patterns that we find within cell type- and region-specific CREs across species point to the conservation of neural circuits and translatable inferences of studying addiction genetics in model organisms.