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Prioritizing Brain Cell Types and Biological Processes Associated with the Shared Addiction Risk Factor

Substance use disorders (SUDs) are genetically correlated, and some of their risk is shared in a drug-agnostic manner. The common polygenic architecture across SUDs reflects inherited vulnerability to addiction, rather than substance-specific vulnerability. However, it is unknown which brain regions, cell types, and pathways are causal of addiction risk in the brain. Functional interpretation of these genetic variants is challenging because many are located in non-coding regions of the genome and exert small effects. Additionally, postmortem tissue from affected donors is scarce, and observed molecular changes in tissues often reflect both genetic vulnerability and consequences of chronic drug exposure. Thus, there are substantial obstacles in linking addiction-associated genetic variation to specific cellular mechanisms in the brain.

We used scPagwas to prioritize brain cell types and cell-specific biological processes identified in the general addiction risk-factor GWAS (Hatoum et al., 2023, Nature Neuro.). ScPagwas is a novel polygenic regression approach that aggregates genetic variant effects from GWAS onto genes and biological pathways in single-nuclei expression datasets to prioritize tissues, cell types, and pathways associated with the traits. In applying this method, we used single-nuclei expression profiles from brain tissues implicated in the addiction circuit: amygdala, dorsolateral prefrontal cortex (DLPFC), and hippocampus.

Our functional analysis revealed region-specific localization of shared SUD genetic liability. We found significant enrichment in GABAergic neuronal populations ($p=5e-03$ – $7e-03$) and glial cell types ($p=1.9e-14$) of the DLPFC. While we observed glial enrichment within limbic regions, including the amygdala ($p=0.01$ – $3.5e-14$) and hippocampus ($p=2e-03$ – $6.7e-13$). Prioritized genes converged on biological processes related to myelination and neuronal ensheathment in the DLPFC ($p_{adj}=1e-03$), amygdala ($p_{adj}=1e-03$), and the hippocampus ($p_{adj}=2e-03$).

We identified key addiction brain cell types and biological processes and suggested that shared addiction genetic risk could influence myelination programs across brain regions and inhibitory neuronal biology in the DLPFC.

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