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Prioritizing Brain Cell Types and Biological Processes Linked to OUD-Associated Common Genetic Variants

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Background
Substance use disorders (SUDs) are a current health crisis, with opioid use disorder (OUD) showing the highest death toll and health care system costs. OUD susceptibility has a significant genetic component, with 12% SNP-based heritability and multiple risk variants identified. However, research is needed to understand its underlying biological and functional relevance. In this study, we aimed to prioritize the brain cell-types and cell-specific biological processes associated with OUD genetic variants.

Methods
We employ scPagwas, a novel polygenic regression approach that integrates single-cell RNAseq (scRNA-seq) and GWAS summary statistics, to prioritize cellular types and pathways. We integrated the most recent multi-ancestry OUD GWAS with human brain single-cell gene expression profiles from striatum, amygdala, dorsolateral prefrontal cortex, hippocampus, and hypothalamus. To confirm OUD specificity, we compared these to other SUDs, such as alcohol, cannabis use disorder, and general addiction risk-factor GWAS.

Discussion
OUD-associated genetic variants were significantly linked to gene expression specifically in neurons of the amygdala (p=9.8e-13), dorsolateral prefrontal cortex (p=2.6e-07), striatum (p=6.2e-05), hypothalamus (p=0.002), and hippocampus (p=0.002). Interestingly, association of neurons across all brain regions was unique to OUD as other SUDs showed association patterns in glial cells and neurons. The top associated biological processes included neuronal signaling, such as modulation of chemical synaptic transmission (q= 5.0e-39), regulation of trans−synaptic signaling (q= 5.0e-39), synapse organization (q=6.0e-27), and others. Alternatively, the other SUDs were associated to gliogenesis and neuronal myelination. These results suggest that the genetic basis of OUD is functionally distinct from other SUDs.