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Elucidating neurobiological processes underlying cigarette smoking and alcohol use traits

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Alcohol and tobacco are prevalent substances used in the United States. Despite their health burden, there is a lapse in treatment options for individuals with substance use disorders, which can be attributed to insufficient understanding of their underlying neurobiology. Genome-wide association studies (GWAS) have identified over 400 genomic loci to be associated with alcohol use and cigarette smoking. However, given that the majority of risk variants reside in non-coding regions of the genome, deciphering their target genes and neurobiological processes remain a challenge. To investigate functional impact of common variants associated with cigarette smoking and alcohol use, we used Hi-C coupled MAGMA (H-MAGMA) developed from cortical neurons (CN) and midbrain dopaminergic neurons (DN) to delineate the biological impact of substance use variation. We applied cell-type specific H-MAGMA to GWAS summary statistics of problematic alcohol use (PAU), drinks per week (DPW), nicotine dependence (ND), and cigarettes per day (CPD). After the identification of risk genes, we found that pathways including ethanol metabolic process and alcohol catabolic process to be associated with PAU and DPW, while response to nicotine and acetylcholinergic pathways were identified for ND and CPD. Lastly, we employed single-cell analyses to identify specific cell types enriched for the risk genes. Using CN H-MAGMA-associated genes, we identified cigarette smoking and alcohol use traits to be enriched for excitatory neurons. Moreover, we identified DN H-MAGMA-associated genes to be enriched for dopaminergic, GABAergic, and serotonergic neurons in the midbrain, suggesting them as relevant cell types that may contribute to substance use etiology.