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Inter-Linking the Developmental Brain Transcriptome and GWAS Risk Variants Revealed Neural Circuits Prognostic of Nicotine Use Severity

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GWASs have identified many risk variants for smoking-related traits, but the neural bases of these risk variants remain unclear. We linked brain transcriptomes and genome-wide genetic effects of cigarettes per day (CPD) to investigate the neurogenetic mechanisms of nicotine misuse. We constructed whole-brain and intramodular region-specific coexpression networks using BrainSpan's developmental transcriptomes and the GWAS-identified risk variants of CPD derived by the U.K. Biobank. Eight brain-region-specific coexpression subnetworks were identified in association with CPD (p-values<0.01): amygdala, hippocampus, medial prefrontal cortex (MPFC), orbitofrontal cortex (OPFC), dorsolateral prefrontal cortex, striatum, mediodorsal nucleus of the thalamus (MDTHAL), and primary motor cortex (M1C). Using an independent cohort, we confirmed that the genes in the eight subnetworks were collectively associated with CPD. Based on network topology to prioritizing proteins, we identified three hub proteins encoded by *GRIN2A* (glutamate-receptor-ionotropic-NMDA-subunit-2A) in the amygdala, *PMCA2* (plasma-membrane-Ca^{2+}-ATPase-2) in the hippocampus, MPFC, OPFC, striatum, and MDTHAL, and *SV2B* (synaptic-vesicle-glycoprotein-2B) in M1C, which have been implicated in stress response, drug memory, calcium homeostasis, and inhibitory control. We also observed that the pancreatic secretion pathway appeared in all of the significant subnetworks of protein interactions, suggesting pleiotropic effects between pancreatic diseases and cigarette smoking. To our knowledge, we present the first study linking developmental brain transcriptomes and GWAS risk variants to identify brain-region-specific networks enriched for CPD. The findings provide new evidence of the neurogenetic underpinnings of smoking severity in relation to emotional distress, ingrained drug memory, decision-making, reward processing, and inhibitory control dysfunction.