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Modeling nicotine and smoking exposures in the developing brain

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Tobacco use is the leading cause of preventable morbidity in the US. While some consequences of prenatal tobacco exposure have been characterized in brain, very little is known about the substance-specific effects. Therefore, we administered nicotine or cigarette smoke to pregnant mice and performed RNA sequencing on frontal cortices of the P0 pups and frontal cortices and blood from adults, totaling 208 samples. 354 and 2,201 genes were differentially expressed (DEGs) for the nicotine- and smoking-exposed pups, respectively (FDR <1%; 19 nicotine-exposed vs 23 controls; 46 smoking-exposed vs 49 controls). In KEGG enrichment analysis, nicotine exposure was related to dopaminergic synapses and the oxytocin signaling pathway, while smoking exposure was associated with DNA instability. By comparing nicotine to smoking directly in the developing frontal cortex, we found 539 DEGs (FDR <1%), only 9 of which were shared among the nicotine and smoking results. 6 of the 14 known DEGs (FDR <10%) from frontal cortices of smoke-exposed human fetuses replicated in our exposed pups. Lastly, we found no DEGs at FDR <1% in adult mouse frontal cortices or blood (8 pregnant vs 4 nonpregnant smoking-exposed; 7 pregnant vs 5 nonpregnant controls), and only 2.4% of $p < 0.05$ DEGs in brain were blood biomarkers. We found largely orthogonal substance effects on fetal development: nicotine, not smoking, altered reward pathways and neural development in the developing brain. These results have important implications for the applicability of mouse models for nicotine addiction and the relevance of blood biomarkers for brain traits.