

Smoking and alcohol interaction effects on postmortem human brain DNA methylation and RNA expression

Despite public health efforts to reduce smoking and drinking, cigarette smoking (CS) and alcohol use disorder (AUD) frequently co-occur, with worse health and treatment outcomes among individuals with comorbid use. While several genome-wide studies, including our own, have identified differential DNA methylation (DNAm) and RNA expression (RNAexp) associated with CS or AUD in postmortem human brain, effects of CS in the context of AUD have not been examined in appreciably sized studies, which limits our understanding of gene regulation amid comorbid addiction. Here, we set the stage for such investigations by conducting a preliminary investigation of CS×AUD interaction effects on DNAm and RNAexp in the dorsolateral prefrontal cortex (DLPFC) and nucleus accumbens (NAc) from 117 decedents of European ancestry (non-AUD/non-CS = 31; non-AUD/CS = 30; AUD/non-CS = 25; AUD/CS = 31). Using EPIC methylation array data, we tested CS×AUD interactions at 226 CpG sites previously associated with either substance in methylome-wide association studies. Parallel analyses were conducted for RNAexp in the same individuals at 508 previously implicated genes. No interaction effects survived false discovery rate (FDR) correction in either brain region; however, 20 CpGs in DLPFC and 11 in NAc showed nominal interaction evidence ($p < 0.05$). Similarly, RNAexp analyses identified 25 nominally significant genes in each region, with no FDR-significant findings. These results suggest that CS×AUD interaction effects may be modest, though these pilot analyses are still likely underpowered. To address this limitation, we are assembling the largest postmortem human brain dataset characterized for smoking and alcohol to date ($N \sim 800$), which will substantially improve power to detect interaction effects and help refine our understanding of molecular mechanisms underlying comorbid AUD and CS.

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