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Differential Gene Expression of Opioid Overdose Death Across Human Brain Regions

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Opioid addiction and overdose deaths (OOD) are public health crises. However, our understanding of the genetics and neurobiological mechanisms associated with these conditions remain limited which constrains development of new treatments. The nucleus accumbens (NAc) and prefrontal cortex (PFC) are two key brain regions in the reward pathway. Here, we conducted differential gene expression (DGE) analyses for a new dataset of NAc RNAseq samples from post-mortem human brains (N=92) and meta-analyzed these results with DGE summary statistics from an existing cohort (Seney et al., N=40) using a random-effects model to account for inter-dataset variability. Cases were defined by OOD among opioid misusers, and controls had negative toxicology for opioids and no history of opioid misuse at time of death. Of the 16,183 meta-analyzed genes, 192 differentially expressed genes (DEGs) were identified (FDR < 0.1). We compared the NAc DEGs to those from a similar random-effects DGE meta-analysis for OOD in the PFC across three published datasets (Seney et al., Sosnowski et al., Mendez et al.) and a newly processed dataset (N=325). When testing whether the 191 available NAc DEGs extended to the PFC meta-analysis, 16 genes showed significant replication ($p < 0.05/191$), indicating predominantly region-specific but some cross-region DGE by OOD status. Overrepresentation analyses of cross-region OOD DEGs with Reactome database gene set terms identified several signal transduction pathways (e.g., RAF-independent MAPK1/3 activation and Signaling by NTRK1 (TRKA)) and NPAS4 regulation pathways (e.g., Regulation of NPAS4 gene expression) enriched for DEGs at FDR < 0.05.
Hyperlink to relevant publication