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The Hippocampus and Nucleus Accumbens Show Unique and Shared Gene Expression Patterns in a Selectively Bred Rat Model of Contrasting Temperaments that Impact Drug Use

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Examining gene regulation in hippocampus (HPC) and nucleus accumbens (NAcc)--two brain areas involved in temperament, stress reactivity, reward processing, and substance use disorders (SUD)--in a selectively-bred rat model of temperament will help elucidate molecular correlates of individual differences in vulnerability to addictive behaviors. Divergent behaviors of our bred High Responders (bHRs) and Low Responders (bLRs) map onto temperamental extremes predictive of externalizing and internalizing psychiatric disorders and model two paths to drug abuse. We performed RNAseq/ATACseq in NAcc (N=40) and RNAseq in HPC (N=24) from two bHR/bLR generations. Selective breeding produced a robust molecular phenotype, showing greater differential gene expression (DGE) associated with bHR/bLR lineage than with sex. This DGE was more pronounced in NAcc (N=1,820 genes, FDR<0.05) obtained from a later generation than HPC (N=144 genes, FDR<0.05). Gene set enrichment analysis revealed both unique and common gene sets between brain areas when comparing bHRs to bLRs. Among bHRs, neurons were enriched in HPC, while oligodendrocytes were enriched in NAcc; growth/proliferation pathways were upregulated in HPC, while phospholipid metabolic processes were upregulated in NAcc. Among bLRs, microglia were enriched in both brain areas, plus energy regulation, mitochondria, and immune-related pathways. In contrast, metabolism pathways were upregulated in HPC, while secretory pathways were upregulated in NAcc of bLRs. Regions of differentially accessible chromatin between bHRs and bLRs are being identified in NAcc. Our findings elucidate common and unique gene expression patterns in two brain areas involved in shaping temperament differences contributing to externalizing and internalizing behaviors inherent in SUD.