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Adolescent Stress Results in Sex-Specific Reprogramming of the Reward Circuitry Transcriptome in Adulthood

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Background: Adolescence is a time of heightened sensitivity to rewarding stimuli and increased vulnerability to psychiatric disorders. Male rodents that experience adolescent social isolation stress (SI) form stronger preferences for drugs of abuse. However, little is known about how females respond to SI. Our findings suggest that SI reverses sex differences in adult reward-associated behaviors. Given these behavioral alterations, we tested the hypothesis that SI alters the transcriptome in a persistent and sex-specific manner in nucleus accumbens (NAc), ventral tegmental area (VTA), and prefrontal cortex (PFC).
Methods: Male and female mice were isolated or group housed (GH) from P22 - P42, then GH until ~P90. Transcriptome-wide changes in NAc, VTA, and PFC were investigated by RNA-seq after acute/chronic cocaine administration.
Results: SI reduces sexually dimorphic gene expression across all three brain regions. Further analysis revealed that SI results in expression profiles in males that more closely resemble GH females, suggesting that SI “feminizes” the male transcriptome. Importantly, when SI females are exposed to the first dose of cocaine, their transcriptional profiles resembled GH males suggesting that SI “masculinizes” the female transcriptional response to acute cocaine. Gene co-expression network analysis revealed that SI alters global co-expression in NAc and VTA, but not PFC. Keydrivers identified using co-expression analysis are being investigated for their sex-specific therapeutic potential.
Conclusions: These data suggest that SI has region-specific effects on sex-specific transcriptional responses to cocaine. Additionally, SI disrupts sex-specific adolescent development of transcription throughout the reward circuitry and reprograms an individual’s responses to acute/chronic cocaine.