Serotonergic hyperinnervation modifies cocaine responses in mice expressing the psychiatric disorder-associated DAT Val559 variant

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Individuals with psychiatric conditions including attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BPD), which are characterized by disruptions in dopamine neurotransmission, are more likely to abuse illicit drugs. In order to identify genetic changes in dopamine signaling that drive ADHD risk and generate improved animal models of ADHD, the Blakely lab screened for rare coding variation in the dopamine transporter (DAT, *SLC6A3*) in ADHD subjects. They identified the Ala559Val substitution, a mutation previously identified in an individual with BPD that triggers anomalous dopamine efflux and alters dopamine clearance, levels, and behavior in mice. These mice show a lack of locomotor stimulation from cocaine, but still display cocaine conditioned place preference (CPP) and sex-dependent CPP extinction, indicating that the rewarding effects of the drug remain intact. Introduction of the cocaine-insensitive serotonin (5-HT) transporter (SERT) Met172 mutation led to a complete rescue of cocaine-induced hyperactivity in DAT Val559 mice leading us to postulate that the dopaminergic dysfunction may trigger a compensatory neuroplasticity in the serotonin system. Indeed, 3D analysis of 5-HT axons revealed increased serotonergic innervation in the dorsal striatum of DAT Val559 male mice and medial prefrontal cortex of female DAT Val559 mice. In the dorsal raphe nucleus, mRNA expression of 5-HT neurons markers including *SERT*, *Tph2*, and *ePet1* was also greater in DAT Val559 mice with the fold change higher in DAT Val559 females. These data suggest that a critical interplay between the 5-HT and DA systems may contribute to altered risk for substance abuse in individuals with neuropsychiatric disorders.