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Polygenic risk for extreme cocaine intake associates with larger dopaminergic responses to cocaine in the nucleus accumbens of BXD inbred mice

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Cocaine use disorder is significantly influenced by genetics, yet the specific neural pathways through which genetic susceptibility affects cocaine self-administration remain unclear. Our prior studies characterized cocaine intravenous self-administration across 84 inbred mouse strains, revealing heritable variation in behavior. The present research utilized inbred strains prone to extremely high or low cocaine consumption, providing a framework for modeling polygenic risk and isolating neurobiological mechanisms linked to genetic susceptibility. Dopamine neurotransmission in the nucleus accumbens is a major determinant of cocaine reinforcement and a likely pathway by which addiction risk is impacted. Therefore, we investigated the dopaminergic response to cocaine in the nucleus accumbens in three BXD strains prone to high cocaine consumption and compared them to three BXD strains prone to low consumption. Dopamine levels were measured using fiber photometry with the GRABDA dopamine sensor, providing a real-time measure of dopamine dynamics in the nucleus accumbens. Results showed that strains with high cocaine intake exhibited amplified dopamine responses at all doses (5, 10, 15 mg/kg, IP), a pattern not replicated with saline. This suggests a link between genetic propensity for excessive cocaine self-administration and heightened dopaminergic responses, implying that genetic risk may influence self-administration by modulating dopamine reactions to cocaine. Future investigations will measure dopamine while mice self-administer cocaine, to further elucidate the genetic effects on cocaine-dopamine interactions under reinforcement testing. Collectively, this research may reveal the impact of genetic risk on cocaine-dopamine dynamics and pave the way for a better understanding of addiction neurogenetic pathways.