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Cannabinoid exposure in adolescence dysregulates genes that orchestrate dopamine development and alters cocaine-motivated behavior

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Cannabis is the most commonly abused illicit drug among adolescents, and excessive use in this population is associated with the development of psychiatric conditions, including drug addiction. Adolescence is a critical period for the refinement and organization of neuronal connectivity, especially within the mesocorticolimbic dopamine circuity. In particular, dysregulation of the guidance cue receptor, Dcc, in ventral tegmental area (VTA) dopamine neurons disrupts spatiotemporal targeting of dopamine axons to the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC). We have previously demonstrated that exposure to amphetamine in early adolescence (PND21-32) disrupts the development of dopamine circuitry development, leading to alterations in cognitive processing and drug seeking in adulthood. Here, we examine whether exposure to the synthetic cannabinoid-1/2 receptor agonist WIN-55,212-2 (WIN) in early adolescence regulates *Dcc* mRNA expression in the VTA and induces alterations in drug-motivated behaviors and in dopamine function in adulthood. Preliminary findings demonstrate that adolescent exposure to WIN downregulates the *Dcc* receptor in the VTA and its ligand, Netrin-1, in the NAc and mPFC, suggesting disruption of pre- and postsynaptic components of mesocorticolimbic dopamine circuitry. Additionally, WIN-treated mice display aberrant responding for cocaine as well as potentiated cocaine-mediated anxiety. Ongoing experiments will elucidate functional changes in cocaine-evoked phasic dopamine release in the NAc and mPFC. Overall, these findings support that repeated exposure to a cannabinoid-1/2 receptor agonist in adolescence impacts mesocorticolimbic dopamine system maturation and may have important implications for dopamine-mediated learning and psychostimulant-motivated behavior later in life.