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## **Prenatal Stress and THC Exposure Impact Maternal and Adolescent Behaviors**

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Cannabis is the most commonly used illicit substance worldwide, with pregnant women among vulnerable populations. Reported use for cannabis during pregnancy is to manage nausea or stress/anxiety. Its main psychoactive component, delta-9-tetrahydrocannabinol (THC), readily cross the placenta barrier and is secreted in maternal milk. Chronic prenatal cannabis exposure has been linked to behavioral teratogenic effects, but little is known about the combined impact of prenatal THC and stress on adolescent behavior and cognition.

In this study, pregnant dams underwent 10 days of stress with concurrent THC exposure until birth. Anxiety-like behaviors were assessed in dams post-stress exposure, while their adolescent offspring were tested for anxiety-like and motivated behaviors. Additionally, we explored the transcriptome of exposed offspring to identify molecular alterations.

In dams, stress alone heightened anxiety-like behaviors, while THC exposure alone had no significant effect. However, combined prenatal THC and stress significantly increased anxiety-like behaviors. In adolescent offspring, we observed sex-specific anxiety-like behaviors. Effort-related motivated test revealed an interaction effect between prenatal THC and stress, but no main effects of THC or stress alone. Transcriptomic analysis revealed altered gene expression in synaptic, mitochondrial, and extracellular matrix processes in the medial prefrontal cortex and nucleus accumbens of exposed adolescents.

These findings highlight the compounded behavioral and molecular effects of prenatal THC and stress exposure, with implications for adolescent neurodevelopment.