**Prenatal THC exposure produces a hyperdopaminergic phenotype rescued by pregnenolone**

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[*Nature Neuroscience*](https://www.nature.com/neuro) (2019) | [Download Citation](https://www.nature.com/articles/s41593-019-0512-2.ris)

**Abstract**

The increased legal availability of cannabis has led to a common misconception that it is a safe natural remedy for, among others, pregnancy-related ailments such as morning sickness. Emerging clinical evidence, however, indicates that prenatal cannabis exposure (PCE) predisposes offspring to various neuropsychiatric disorders linked to aberrant dopaminergic function. Yet, our knowledge of how cannabis exposure affects the maturation of this neuromodulatory system remains limited. Here, we show that male, but not female, offspring of Δ9-tetrahydrocannabinol (THC)-exposed dams, a rat PCE model, exhibit extensive molecular and synaptic changes in dopaminergic neurons of the ventral tegmental area, including altered excitatory-to-inhibitory balance and switched polarity of long-term synaptic plasticity. The resulting hyperdopaminergic state leads to increased behavioral sensitivity to acute THC exposure during pre-adolescence. The neurosteroid pregnenolone, a US Food and Drug Administration (FDA) approved drug, rescues synaptic defects and normalizes dopaminergic activity and behavior in PCE offspring, thus suggesting a therapeutic approach for offspring exposed to cannabis during pregnancy.