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Analysis of single nuclei RNA-seq from the nucleus accumbens of heterozygous reeler mice exposed to THC during adolescence suggests a link between THC exposure, Reelin signaling, and vulnerability to human psychiatric disorders

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Cannabis use is widespread during adolescence when developing brains are especially susceptible to the harmful effects of its psychoactive component, tetrahydrocannabinol (THC). Adolescent cannabis use is associated with increased risks of drug addiction and schizophrenia later in life.

However, the molecular underpinnings that explain the effects of THC exposure on cell type-specific developmental trajectories are unknown. Here, we investigate for the first time the impact of THC adolescent exposure on gene expression networks (modules) in distinct cell types of the nucleus accumbens (NAc) of mice using single nuclei (sn)RNA-seq. We compared wild-type and heterozygous reeler mice, which express a lower level of *Reln*, a gene that influences the behavioral phenotypes altered by adolescent exposure to THC. While the majority of modules were correlated with either treatment or genotype across different cell types, we identified three modules that significantly correlated with both THC exposure and *Reln* haploinsufficiency. These modules were related to addiction, axon guidance, cell junction assembly, and chromatin remodeling. The integration of these modules with human genetic data from GWAS of substance use disorders and schizophrenia identified one module from *Drd1*+ medium spiny neuron and one from interneurons that might underlie converging mechanisms explaining the interaction between *Reln* haploinsufficiency, adolescent cannabis exposure, and risks of drug addiction and schizophrenia later in life. These results shed light on the cell type-specific mechanism bridging neurodevelopment disturbance and chronic cannabis exposure and open up avenues for further investigations.