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## **Transcriptional alterations in opioid use disorder reveal the interplay between neuroinflammation and synaptic remodeling across corticostriatal circuits**

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Prevalence rates of opioid use disorder (OUD) have increased dramatically, accompanied by a surge of overdose deaths. While opioid dependence has been extensively studied in preclinical models, we still have a very limited understanding of the biological changes that occur in the brains of people who chronically use opioids and who are diagnosed with OUD. To address this, we conducted the largest transcriptomics study to date using postmortem brains from subjects with OUD. We focused on the dorsolateral prefrontal cortex (DLPFC) and nucleus accumbens (NAc), two regions heavily implicated in OUD. We discovered a high degree of overlap in transcripts between DLPFC and NAc in OUD, primarily associated with neuroinflammation. Moreover, additional transcripts were enriched for factors that control pro-inflammatory cytokine-mediated signaling and remodeling of the extracellular matrix. Our results also implicate a role for microglia as a critical driver for opioid-induced neuroplasticity. Overall, our findings reveal new connections between the brain's immune system and opioid dependence in the human brain.