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**Single Nucleus Transcriptomic Profiling of Human Ventral Midbrain
Reveals Widespread Activation of Multiple Glial Subtype**

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Ventral midbrain (VM), including the ventral tegmental area (VTA) and substantia nigra (SN) is important for mediating habitual behaviors and salience of cues associated with drug use, as well as withdrawal-related anhedonia and dysphoria. These and other functions related to drug addiction and dependence heavily rely on the non-neuronal cellular constituents, including their interactions with VTA/SN dopaminergic and non-dopaminergic (incl. gabaergic) neurons.

However, the functional and clinical significance of VM glial populations in (human) cases of drug abuse and dependence remains unexplored, including for opioid use disorder (OUD), with opioid overdose as the leading cause of accidental deaths in the United States.

Here, we present our initial findings from an ongoing transcriptomic study at single nuclei resolution in the ventral midbrain from N=94 OUD/overdose cases and controls. Initial findings point to a profound activation of multiple glial subpopulations in the VM from opioid-related deaths, with neuroinflammation and activation of cytokine signaling and other immune pathways in microglia and astrocytes, together with alterations in the oligodendrocyte-specific transcriptome. Our dataset will provide a much-needed neurogenomics resource at single cell resolution for the wider field of drug abuse research.

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