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## **Identifying and characterizing neuron subtypes and circuits regulating SUD**

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Substance use disorder (SUD) has become an urgent social and economic problem with limited intervention methods due to the lack of understanding of the underlying mechanisms. Previous studies have linked SUD to maladaptation of the brain reward system, which includes the prefrontal cortex (PFC), nucleus accumbens (NAc), and ventral tegmental area (VTA). Since each of these brain regions is composed of multiple molecular and anatomically distinct neuron subtypes, a mechanistic understanding of SUD requires identification of the relevant neuron subtypes followed by molecular and circuit characterization with a functional readout. Using single cell spatial transcriptomics approaches, we have comprehensively classified the neuron subtypes in the PFC and NAc. We then generated and characterized several Cre-lines implicated in SUD. By monitoring the neuronal activity of specific neuron subtypes during drug-associated behavior paradigms such as conditional place preference (CPP) and/or intravenous self-administration (IVSA), or conversely by analyzing the effect of neuronal inhibition or activation during CPP and IVSA, we demonstrate the involvement of certain PFC and NAc neuron subtypes in addiction-related behaviors. We further characterized the circuit and molecular mechanisms. Thus, our study not only revealed distinct neuron subtypes mediating SUD, but also revealed the underlying molecular and circuit mechanisms, which are the basis for potential therapeutic intervention.