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A molecularly and spatially defined prefrontal cortical circuit regulating drug relapse

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Relapse is a major challenge in rehabilitation from drug addiction. The prefrontal cortex (PFC) is believed to play a prominent role in relapse. However, it has been difficult to understand the mechanisms in PFC owing to its molecular/cellular complexity and the involvement of this region in diverse behavioral functions. Using single cell sequencing and spatial transcriptomics, we mapped the molecular composition, spatial organization and subcortical projections of all neuronal subtypes in PFC. We identified a distinct, molecularly defined, L5 pyramidal neuron subtype that potently regulates addictive behavior. These neurons project predominantly to the ventral tegmental area and periaqueductal gray in midbrain. Chemogenetic activation of these neurons in a Cre mouse line prevented sensitization to cocaine, while retaining the normal locomotor response. Activation in an intravenous drug self-administration model did not impair drug learning/taking, however, dramatically reduced relapse or drug seeking behavior, when allowed access after two weeks of abstinence. RNA-seq of nuclei purified by Cre-mediated nuclear tagging revealed molecular signatures of hypoexcitability in these neurons upon chronic drug administration, which is consistent with prior reports of PFC hypofunction. Cumulatively, identification of a spatially and molecularly defined PFC circuit regulating drug relapse will not only promote better understanding of mechanisms underlying relapse, but also facilitate potential therapeutic approaches that can help manage the rapidly escalating pandemic of addiction.