Single-cell transcriptomics reveals a "master regulator" of opioid reward located in the ventromedial prefrontal cortex.

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Oxycodone is one of the most prescribed analgesics and has physiochemical properties that allow it to accumulate in the brain at rates higher than other opioids (Bostrom et al., 2006, 2008), perhaps explaining its considerable abuse potential. We used the iDISCO+ tissue clearing method to identify a the Dorsal Peduncular Cortex (DPC) as a novel opioid-responsive component of the ventromedial prefrontal cortex, and single-nuclei sequencing to molecularly characterize this region for the first time. This identified a population of deep-layer pyramidal neurons that co-express *Oprm1* and *Slc17a6* (vGluT2), a highly unique cell population within the cortex. Using optogenetic stimulation in C57 and vGluT2-Cre mice, we show that stimulation of these neurons induces a real-time place aversion in opioid-naïve mice, and augments symptoms of naloxone-precipitated withdrawal in opioid-dependent mice. Furthermore, selectively knocking down μ receptor expression in the DPC via AAV-Cre injection into *Oprm1*$^{flox/flox}$ mice reverses the hedonic valence of oxycodone, such that these mice form a conditioned place aversion in response to a 5mg/kg oxycodone dose that results in a conditioned place preference in AAV-GFP injected control mice. Together these data indicate that the DPC is a highly novel opioid-responsive component of the vmPFC, and that *Oprm1/vGluT2* expressing neurons in this region regulate the rewarding and aversive properties of opioid exposure and withdrawal.

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