Dorsal Peduncular Prefrontal Cortex contains cells uniquely sensitive to opioids: Relevance to opioid reward and addiction.

Alexander C.W. Smith¹, Samuel W. Centanni², Soham Ghoshal¹, Sohail Khan¹, Clementine Fillinger¹, Kristin Beaumont², Danny G. Winder³, Paul J. Kenny¹

¹Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, 10029
²Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, 10029
³Department of Molecular Physiology & Biophysics, Vanderbilt University, Nashville, TN, 27235

Background: The US is in the midst of an opioid abuse and overdose epidemic, with over 115 people dying each day from opioid overdose; this has been declared a public health emergency. Rationale: The vast majority of research on opioid addiction has focused on a small number of circuits, primarily the mesocorticolimbic circuit. We used iDISCO+ tissue clearing and c-Fos staining to create a whole-brain map of transcriptionally responsive neurons following acute oxycodone (5 mg/kg) or saline injection. Results: This revealed 39 regions with significant oxycodone-induced alterations in c-Fos expression. We chose to further examine the dorsal peduncular area (DP), the ventral-most component of the medial prefrontal cortex (mPFC). Single-cell RNA-sequencing, qPCR, and RNAscope revealed unique properties of opioid-responsive DP neurons relative to surrounding mPFC. The DP is enriched in Oprm1 (µ opioid receptor) and Slc17a6 (vGlut2) relative to neighboring infralimbic cortex. Surprisingly, Oprm1 and Slc17a6 are co-expressed in DP neurons in layer 5 that show robust transcriptional responses to oxycodone. Using FosTRAP mice, we ‘tagged’ opioid-responsive neurons DP, and optogenetic stimulation of this DP ensemble produced aversion-related behaviors that were blocked by oxycodone. Further, optical stimulation of DP in opioid-dependent mice enhanced naloxone-precipitated withdrawal symptoms. Whole-brain projection mapping revealed opioid-responsive DP neurons project to several mid- and hindbrain sites with known involvement in aversive behaviors, including the parabrachial nucleus (PBN). Optical stimulation of DP-PBN circuit recapitulated the aversive phenotype seen during DP somatic stimulation. Discussion: The DP is a major prefrontal site that regulates opioids reward and dependence.