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A Single-Cell Connectomic Map Identifies Sexually Dimorphic Circuits in Opioid Use Disorder

Background:

Opioid use disorder (OUD) affects over 2.1 million people in the United States. Females have a higher susceptibility to comorbid mood disorders than males, suggesting sex-specific remodeling of affective circuitry. The interpeduncular nucleus (IPN) is a primary target of the dorsal diencephalic conduction system (DDCS), one of the two major pathways connecting the limbic forebrain and the brainstem. The IPN contains some of the highest densities of mu opioid receptors in the brain, and emerging evidence implies the IPN and its efferent in regulating negative affective states associated with withdrawal. Furthermore, the IPN is sensitive to ovarian hormones and has been implicated in female-specific reproductive behaviors. Despite these findings, the IPN remains remarkably understudied, hindering our ability to harness the therapeutic potential of the DDCS to address sex-dependent vulnerabilities in addiction.

Method:

We investigated the role of the IPN in regulating sex-specific physiological and behavioral responses to opioids. To map its complex efferent architecture, we employed Multiplexed Analysis of Projections by Sequencing (MAPseq), profiling the efferent connections of IPN neurons in males and females at single-cell resolution. Our connectomic analysis revealed that the majority of IPN neurons innervate the median raphe nucleus (MnR), a critical serotonergic hub for emotional processing. Follow-up electrophysiological recordings identified robust sex differences in connectivity strength within the IPN-MnR circuit. Using transgenic mouse models to dissociate chromosomal and gonadal effects, we demonstrated that this dimorphism is bidirectionally regulated by gonadal hormones, independent of sex chromosome complement.

Conclusion:

In summary, our high-throughput, single-cell connectomic analyses reveal striking sex-dependent differences in IPN neurons and their efferent connectivity. By elucidating the hormonal mechanisms that shape this circuit's connectivity, these insights establish a structural basis for female-specific vulnerabilities in addiction and highlight the DDCS as a promising, under-explored therapeutic target.

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