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NPAS4-Expressing Ensemble in the Nucleus Accumbens Facilitates Reward-Related Behavior

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Expression of Neuronal PAS Domain Protein 4 (Npas4), an activity-regulated transcription factor, is induced in a select ensemble of cells within the nucleus accumbens (NAc) during cocaine conditioning. Our previous work has shown that Gi-DREADD-mediated inhibition of this ensemble decreases cocaine conditioned place preference (CPP), that the ensemble is composed primarily of medium spiny neurons (MSNs; ~75%), and that NPAS4 itself functions in MSNs expressing D2 dopamine receptors (D2-MSNs) to regulate the cell type-specific activation balance in the NAc following cocaine exposure. To better define the non-MSN cells included in this ensemble, we conducted single nuclei RNA sequencing with NAc tissue collected from adult male and female wildtype C57BL/6J mice. We find significant upregulation of Npas4 in Drd1, Drd2, and Grm8 positive MSNs after cocaine conditioning compared to naïve controls and identify other “highly” expressing (top 25%) non-MSN Npas4+ cells, including Pnoc, Pvalb, Sst, or Th positive interneurons. We hypothesize that Npas4+ ensembles encode information about cue-reward associations and, in support of this, find that activity in the ensemble expressing Npas4 during the final acquisition sessions of sucrose self-administration is required for the later cue-induced reinstatement of sucrose seeking. We expect this will be true for the cue-induced reinstatement of cocaine seeking as well and experiments to test this hypothesis are ongoing. We are also working to investigate how the calcium dynamics of cells recruited to this ensemble may differ from those excluded over the multi-phase self-administration paradigm, and how these ensemble dynamics may differ between sucrose and drug self-administration.