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Modulating levels of ΔFOSB alters nucleus accumbens medium spiny neurons activity to salient stimuli

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ΔFOSB is a key transcription factor that mediates gene expression changes in the nucleus accumbens (NAc) following chronic exposure to stimuli. The NAc is composed of GABAergic medium spiny neurons (MSNs) that express either dopamine receptor 1 (D1) or dopamine receptor 2 (D2). Previous work indicates that chronic stimuli induce ΔFOSB in a cell-specific manner, with cocaine mainly inducing ΔFOSB in D1 MSNs. This regulation correlates with differential effects of the ΔFOSB on synaptic properties of MSNs: ΔFOSB decreases excitatory synaptic strength and increases silent synapses onto D1 MSNs, with opposite effects seen for D2 MSNs. However, no studies have investigated how changes in ΔFOSB expression levels in the NAc alter the in vivo activity of MSNs. Utilizing fiber photometry and epigenome-editing tools that either induce or repress endogenous ΔFOSB in the NAc. we recorded in vivo neuronal activity of D1 and D2 MSNs in response to aversive and rewarding stimuli. We found that manipulation of ΔFOSB primarily altered MSNs responses to salient stimuli such as foot shock and cocaine conditioned place preference (CPP). In fact, decreasing ΔFOSB in D1 MSNs attenuated foot shock-induced calcium transients, while decreasing ΔFOSB in D2 MSNs enhanced them. In addition, decreasing ΔFOSB in D1 MSNs only blocks cocaine CPP and attenuates neuronal activity aligned with entrance to cocaine paired side. These findings of opposite in vivo modulation of D1 vs. D2 MSN activity by ΔFOSB demonstrate how ΔFOSB influences circuit activity and shed light on cell-autonomous mechanisms controlling behavioral responses.