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The extracellular matrix protein Reelin is enriched in cocaine-activated D1-MSNs and modulates transcriptional responses to dopamine

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Reelin is a large, secreted extracellular matrix protein encoded by the *Reln* gene, which is conserved across vertebrate evolution and plays a critical role in cortical and hippocampal development and experience-dependent plasticity. In the adult brain, mRNA for *Reln* is enriched in the nucleus accumbens (NAc) and dorsal striatum, and is required for psychostimulant response. However, despite genetic links to human psychostimulant abuse, almost nothing is known about the molecular and cellular functions of *Reln* in the NAc. To characterize the cellular distribution of *Reln* in the rat NAc, we used a recently generated transcriptional atlas in which single-nucleus RNA-seq was performed with NAc tissue following acute cocaine experience. This comprehensive dataset yielded the unexpected discovery that mRNA for *Reln* was enriched in *Drd1*+ medium spiny neurons (MSNs), and was among the top markers of a Drd1-MSN subcluster that was robustly activated by cocaine. These observations were extended to the postmortem human NAc using multiplexed single-molecule fluorescent in situ hybridization, confirming that *RELN* mRNA is enriched in *DRD1*+ MSNs. To manipulate *Reln* expression in striatal neurons, we designed and validated a CRISPR sgRNA targeting the *Reln* promoter, enabling robust bidirectional regulation of *Reln* expression using CRISPR activation or CRISPR interference strategies. Notably, CRISPR activation of *Reln* in rat primary striatal neuron cultures enhanced stimulus-dependent transcription of immediate early genes following dopamine stimulation. Likewise, knockdown of *Reln* blunted the dopamine-induced increases in MSN firing rate. These results suggest that Reelin may contribute to dopamine-dependent transcriptional and physiological changes caused by cocaine.