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Neuron Navigator 1 (Nav1) Regulates Learning, Memory and the Response to Multiple Drugs of Abuse (DOA)

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Consistent with the effect that genetic factors have on addiction susceptibility, inbred mouse strains exhibit substantial differences in the extent of voluntary cocaine self-administration (CSA). Computational genetic analysis identified *Nav1,* which is a member of the neuron navigator family that regulates neurite formation and axonal guidance, as a candidate gene affecting CSA. To test this genetic hypothesis, CRISPR engineering was used to produce a *Nav1* KO in C57BL/6 embryos. Proteomic and smRNA-FISH analyses confirmed that *Nav1* protein and mRNA were absent in *Nav1* KO mice. *Nav1* KO mice exhibited a reduced sensitivity to the psychomotor activating effects of cocaine and reduced tendency to be become opiate dependent. While *Nav1* KO mice exhibited normal motor coordination, they had impaired spatial learning and recognition. At the cellular level, preliminary electrophysiology results indicated that neurons in the nucleus accumbens of *Nav1* KO mice respond differently to morphine than those of C57BL/6 controls. Immunohistochemical staining indicated that inhibitory synapse formation was significantly reduced in the cortex of *Nav1* KO mice. Transcriptomic analysis identified an increase in layer 5 pyramidal cortical neurons, which are excitatory neurons that express a set of amphetamine-addiction related genes. Collectively, our results indicate that *Nav1* alleles regulate learning, memory, and the response to multiple DOA.