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

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Genetics has a major effect on addiction susceptibility and on learning and memory capability. 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,* a member of the neuron navigator family that regulates dendrite formation and axonal guidance, as a candidate gene affecting CSA. The *Nav1* mRNA expression level in striatum is cis-regulated and inversely correlated with striatal *Drd2* mRNA expression. We hypothesized that *Nav1* alleles affect memory, learning, and DOA responses. To test this hypothesis, CRISPR engineering was used to produce a *Nav1* KO in C57BL/6 embryos. *Nav1* KO mice exhibited a reduced sensitivity to the psychomotor activating effects of cocaine and reduced susceptibility to opiate dependence. They also exhibited normal motor coordination but impaired spatial learning and recognition. On the cellular level, our preliminary data indicates that inhibitory synaptic transmission in the *Nav1* KO cortex was reduced. Collectively, our results suggest that *Nav1* alleles regulate learning, memory and the response to multiple DOA. We are now using scRNA-Seq to molecularly characterize Nav1 effects on DOA responses, and are investigating whether a Nav1-associated protein complex provides a new therapeutic target for prevention of drug addiction.