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Neuron navigator 1 regulates the self-administration of cocaine

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Genetic variation accounts for a substantial proportion of an individual's risk for developing a cocaine use disorder. Inbred mouse strains also exhibit substantial and heritable differences in the extent of voluntary cocaine intravenous self-administration (IVSA) and can be utilized to discover genes that regulate addiction-relevant phenotypes, including self-administration of cocaine. Computational genetic analysis of IVSA data obtained from an inbred strain panel identified neuron navigator 1 (Nav1), a member of the neuron navigator family that regulates dendrite formation and axonal guidance, as a candidate gene. To test this hypothesis, we generated and characterized Nav1 knockout (KO) mice for cocaine IVSA (fixed ratio 1, 10 daily 2-hr sessions) in a between-subjects dose-response test (0.1, 0.5, and 1.0 mg/kg body weight/infusion). Nav1 KO mice exhibited increased cocaine intake during IVSA testing relative to heterozygous and wild-type mice, across all doses of the dose-response test. An additional cohort of mice were tested for self-administration of a palatable food and we found the Nav1 KO increased intake of food, similar to the effect on cocaine self-administration, suggesting that the impact of Nav1 generalizes across drug and non-drug reinforcers. As cocaine and food reinforcement are, in part, mediated by common neurobiological mechanisms, these data suggest that Nav1 may impact reinforcement circuits. Collectively, these results indicate that Nav1 may have a role in moderating risk of problematic cocaine intake and should be further investigated as a candidate gene for addiction neurogenetics. Future work will investigate how Nav1 may regulate brain function to cause these behavioral effects.