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Enhanced cognitive flexibility and phasic dopamine dynamics in Norepinephrine transporter knockout mice

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The catecholamine neuromodulators dopamine and norepinephrine are implicated in locomotion, motivation, and cognition. Although roles for striatal dopamine in these aspects of behavior are well established, the specific roles for cortical catecholamines in regulating striatal dopamine dynamics and behavior are less clear. We recently showed that cortical dopamine but not norepinephrine inhibits hyperactivity in dopamine transporter knockout mice, which have elevated striatal dopamine levels. Microdialysis studies show that norepinephrine transporter knockout (NET KO) mice have a distinct phenotype as they show elevated extracellular cortical catecholamines but reduced striatal dopamine levels. Here we evaluated the consequences of altered catecholamine levels in NET KO mice on cognition and behavior. In a probabilistic reversal learning task, NET KO mice showed enhanced reversal learning, which was consistent with larger phasic dopamine transients (dLight) in the dorsomedial striatum (DMS) during reward delivery and omission in NET KO mice compared to WT controls. Selective depletion of prefrontal cortex (PFC) norepinephrine in WT mice did not alter performance on the reversal learning task; however, NE levels were important for goal-directed behavior in a nestlet shredding task, suggesting that PFC norepinephrine might predominantly regulate arousal and negative reinforcement, but not positive reinforcement learning. During instrumental responding on a variable interval schedule, NET KO mice maintained sensitivity to devaluation at a timepoint at which WT mice exhibited habit-like behavior. Finally, NET KO mice did not show altered breakpoints in a progressive ratio task, suggesting intact food motivation. Collectively, these studies show novel contributions of cortical catecholamines to different aspects of goal-directed behavior, motivation, and phasic dopamine signaling, which could lead to better understanding of dopamine neurotransmission and help develop novel therapeutic strategies to counter multiple CNS disorders.

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