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Septal inputs to habenula regulate nicotine craving

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Relapse rates are remarkably high in tobacco smokers attempting to quit, particularly during early stages of withdrawal when craving is most intense, yet mechanisms of nicotine craving and relapse remain poorly understood. The septum is a core component of the limbic system strategically positioned between the hippocampus, basal forebrain and basal ganglia to regulate memory, mood and motivation. Abstinent smokers show deficits in these same processes, suggesting that septal dysfunction could contribute to relapse vulnerability. Using *in vivo* electrophysiological recordings, we found that neurons in the triangular nucleus of the septum (TNS) oscillate at theta frequency and that this pattern of activity optimally enhances TNS-derived excitatory signaling in the habenula. Nicotine profoundly decreased the activity of TNS neurons, the power of theta oscillations in TNS, and TNS-derived excitatory transmission in the habenula. Doses of nicotine sufficient to disrupt TNS-habenula communication, as measured by excitatory post-synaptic currents in the habenula optically evoked from TNS terminals, triggered intense craving-like nicotine-seeking responses during the early stages of withdrawal in rats and mice. Chemogenetic stimulation of TNS neurons that project to the habenula attenuated withdrawal-induced nicotine-seeking, whereas selective lesion or chemogenetic inhibition of habenula-projecting septal neurons exacerbated this craving response. Using single-cell sequencing, we found that nicotine markedly altered patterns of gene expression in neuronal and non-neuronal cells in the TNS. Currently, we are exploring the role for nicotine-responsive genes in non-neuronal TNS cells in regulating nicotine craving. Our findings suggest that perturbations in septal communication with the habenula contributes nicotine craving and relapse.