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Title: Abnormal striatal cholinergic signaling and compulsive behaviors

Project Summary:

The striatum is central to a broad range of motor and neuropsychiatric disorders. Compulsive motor behaviors – repetitive, stereotyped, insuppressible behaviors – are a common comorbid motor symptom associated with striatum-based disorders. Treatments are limited, due to insufficient understanding of the underlying brain circuit dysfunctions. The dorsal striatum contains two types of projection neurons (SPNs): “direct-pathway” SPNs *promote* action initiation and “indirect-pathway” SPNs *suppress* it. Evidence suggests that compulsive motor behaviors result from imbalanced striatal output that favors the direct pathway. The basis for this imbalance is unclear. Based on novel preliminary data, our central hypothesis is that impaired striatal *cholinergic signaling* promotes pathway imbalance that underlies compulsive motor behaviors. We will test this using *two* genetic mouse models of compulsive motor behavior. Aim #1 will address how striatal acetylcholine (ACh) release is pathologically elevated. Aim #2 will address *pathway-specific* effects of ACh on SPN function. Aim #3 will test if pathological striatal ACh release causally drives compulsive motor behaviors and underlying striatal circuit adaptations. We will utilize cutting-edge imaging and electrophysiological techniques, molecular manipulations and behavioral tests. Successful completion of this study will identify the striatal cholinergic system as a driver of compulsive motor behaviors, revealing novel targets for therapeutic intervention.