Striatopallidal dysfunction underlies repetitive behavior in Shank3 model of autism

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Abstract: Objective SHANK3 is a postsynaptic scaffolding protein critical for the development and function of glutamatergic synapses. Disruption of the Shank3 gene has been strongly implicated as a monogenic cause of autism and Shank3 mutant mice show repetitive grooming and social interaction deficits. Although dysfunction of basal ganglia has been proposed to play a key role in repetitive behaviors, few studies have provided direct evidence supporting this notion and the exact cellular mechanisms are still largely unknown. Methods We investigated how mutation of Shank3 may differentially affect striatonigral (direct pathway) and striatopallidal (indirect pathway) medium spiny neurons (MSNs) and its relevance to repetitive grooming behavior in the Shank3B mutant mouse model of autism with behavior,
Results We found that Shank3 deletion preferentially affected synapses onto striatopallidal MSNs. Striatopallidal MSNs showed profound defects including synaptic transmission, synaptic plasticity and spine density. Importantly, the repetitive grooming behavior was rescued by selectively enhancing the striatopallidal MSN activity using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs- hM3Dq) technology. Conclusion Our findings provide direct evidence demonstrating the existence of distinct changes between two striatal pathways in a mouse model of autism, and highlight that the indirect striatal pathway disruption might play a causative role in repetitive behavior of Shank3B mutant mice.

Keywords: Shank3, striatum, autism, striatonigral, striatopallidal, repetitive behavior