**Forebrain knock-out of torsinA reduces striatal free-water and impairs whole-brain functional connectivity in a symptomatic mouse model of DYT1 dystonia**

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**Introduction**

Convergent evidence from human and animal studies establishes the striatum as a key region in dystonia pathophysiology. It remains unclear how striatal dysfunction affects network-level changes in functional connectivity (FC) across cortical, subcortical, and cerebellar networks. Understanding how striatal pathology affects network-level FC in pre-clinical models is important for dissecting pathophysiology and providing readouts for disease modifying interventions. We acquired in vivo diffusion MRI and resting-state functional MRI in a mouse model characterized by conditional knockout (cKO) of torsinA from forebrain (i.e., striatum, cortex, globus pallidus, basal forebrain, and reticular thalamic nucleus) cholinergic and GABAergic neurons. We test the hypothesis that torsinA loss-of-function in cKO mice causes abnormal microstructural changes in free-water (FW). Further, we examine how microstructural changes in the striatum influence whole-brain functional connectivity patterns.

**Experimental**

The study utilized diffusion MRI and a bi-tensor diffusion analysis pipeline [1] to examine microstructural changes in FW as a consequence of torsinA eradication in the forebrain of cKO mice. Functional MRI and a seed-based computational approach was then performed to examine how microstructural changes in the forebrain of cKO mice influences functional connectivity [2] between the striatum and other cortical, subcortical and cerebellar regions. Imaging data was collected on the high field 11T Magnex Scientific magnet at the McKnight Brain Institute at the University of Florida.

**Results and Discussion**

The striatum in cKO mice was the only region to exhibit an abnormality in free-water, indicating selective microstructural deficit of that region. Free-water values in cKO mice, but not controls, were inversely related to mean diffusivity. The striatum of cKO mice exhibited widespread increases in functional connectivity with the somatosensory cortex, thalamus, vermis, cerebellar cortex, and brainstem (Fig. 1)



**Fig.1** shows increased whole-brain functional connectivity with the striatum in cKO mice compared to controls

**Conclusions**

The current study provides the first in vivo support that direct pathological insult to forebrain torsinA in a symptomatic mouse model of DYT1 dystonia can engage genetically normal hindbrain regions into an aberrant connectivity network. These findings have important implications for the assignment of a causative region in CNS disease.

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**References**

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