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)

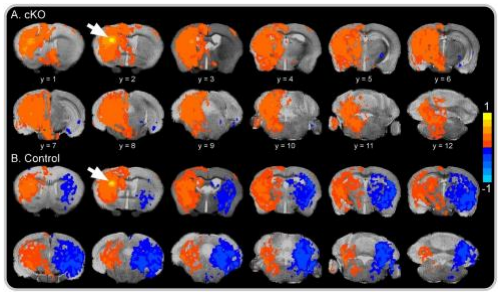

Fig.1 shows increased whole-brain functional connectivity with the striatum in cKO mice compared to controls

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.

Acknowledgements

A portion of this work was performed at the National High Magnetic Field Laboratory, which is supported by National Science Foundation Cooperative Agreement No. DMR-1157490 and the State of Florida. This study was funded by the National Institutes of Health (RO1 NS52318, ROI NS75012, T32 NS082169).

References

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