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Editorial: Models, mechanisms, and maturation in developmental dystonia

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Editorial on the Special Issue
Models, mechanisms, and maturation in developmental dystonia

In this Special Issue, a comprehensive examination of dystonia pathogenesis is undertaken through four original research papers. These studies use manipulations at various sites in the cerebello-thalamo-striatal dystonia network using both genetic and functional network analyses. Furthermore, the papers presented here offer a fine-grain dissection of the pathophysiology of one of the most well studied genetic dystonias, DYT1 (and the associated mouse Dyt1), and shed light on possible therapeutic interventions that could be valuable.

The dissection of Dyt1 dystonia pathophysiology includes the work of Xing et al., in which a neurophysiological analysis of a knock-in mouse model of human Dyt1 dystonia reveals alterations in cholinergic tone and dopamine signaling in striatal interneuron populations. This study offers insight into the functional network alterations underlying this genetic dystonia, an important step in understanding this enigmatic disorder. Yellajoshyula et al. delve further into the network effects of Dyt1 dystonia while also taking advantage of the sophisticated manipulations offered by mouse genetics. Using conditional knock-out technology and laser microdissection, Yellajoshyula et al. look at the morphology of striatal cholinergic interneuron-enriched populations and compare them to GABAergic-enriched populations, finding unique differences in dendritic morphology in these neuronal populations that are relevant to dystonia. Furthermore, using high throughput -omics methodologies, they provide a database for understanding downstream gene expression changes that will open up avenues for further exploration, potentially of broader dystonia etiologies. Rounding out the issue's dissection of Dyt1 dystonia, King et al. develop and exploit a translationally-driven approach towards the development of a biomarker platform with validation through application of a candidate therapeutic intervention. Using mouse

embryonic fibroblasts derived from the Dyt1 knock-in mouse model, King et al. isolate and characterize extracellular vesicles (referred to as EVs) from culture, which is a proof of concept for human blood based EVs, and importantly show that application of a candidate therapy, ritonavir, that is known to act on the previously implicated integrated stress response pathway, may correct some of the abnormal changes in the affected Dyt1 EVs.

Finally, Van Der Heijden et al. take a different approach, focusing on functional network manipulations and developmental dystonia. They use targeted and cell-type specific genetic manipulations to functionally silence neurotransmission from inferior olivary neurons onto their target Purkinje cells, a model previously shown to induce severe dystonia in mice, and use a suite of behavioral tools to characterize early onset dystonia in postnatal mice. Given the paucity of studies and tools looking at early onset dystonia, and its importance in clinical pediatric neurology, this is a powerful step towards addressing a gap in the field of dystonia research.

Together, the research perspectives assembled in this Special Issue illuminate both novel technical approaches for better understanding dystonia, covering analytic techniques from laser microdissection to extracellular vesicle analysis, as well as deep analysis of existing models, from the conditional approach used in Yellajoshyula et al. to the novel biomarker platform developed by King et al. Indeed, a key difficulty in understanding dystonia has been the functional component, which manifests both in the incomplete penetrance of genetic dystonias such as Dyt1 but also in the idiopathic dystonias. Van Der Heijden et al. tackle this difficult issue by using an anatomically-driven brain network manipulation and the application of behavioral assays that conveniently characterize motor dysfunction in mouse pups. Through a close reading of the papers in this Special Issue, readers will gain not only an understanding of one of the most important genetic dystonias, Dyt1, but come away with an analytic toolkit to further their own explorations towards untangling the problems in dystonia.

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Conflict of interest

AS and RS are Editors in Chief of Dystonia.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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