DYSTONIA

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Editorial: Exploring dystonia symptoms through animal models and patient studies

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Editorial on the Special Issue
Motor circuits and motor symptoms in dystonia: translational approaches from animal models to patients

Fine control of postural tone and complex limb coordination are generated at multiple levels in the brain, primarily through the integration of information from the basal ganglia (BG) and cerebellum (CB) in conjunction with the cerebral cortex. In dystonia, these motor abilities are lost due to impaired integration of information between and within these brain nodes, leading to abnormal postures and/or movements. Symptom expression can be isolated, or in combination with other motor disorders or neurological diseases, including Parkinson's disease. Importantly, the penetrance of genetic forms of dystonia is variable and the symptoms vary in severity, age of onset, focal or generalized localization and progression, even in patients carrying identical mutations [1]. This intrinsic variability in dystonia suggests the involvement of interacting mechanisms that either synergize or counteract at different levels of central motor centers, ultimately influencing the onset of symptoms.

The present Special Issue brings together researchers working on animal models and patients, as well as experts in physiology of the cerebral cortex, basal ganglia and cerebellum. Some consider a global view on different nodes of this network (Gray et al., Kasiri et al., Zeuner et al.), while others focus on single nodes to understand the functional underpinning of this particular structure in dystonia (Gray et al., Huber et al., Salazar-Leon and Sillitoe). These complementary approaches are crucial for understanding the pathophysiological processes of this complex disease.

The primary sensorimotor area has refined somatotopic representation of body parts, particularly those involved in precise movements (hands, lips, tongue). Dystonia is associated with a loss of inhibition, increased excitability, and somatotopic disorganization (see Zeuner et al.). Investigating cortical activity in patients with writer's cramp, Huber et al. take advantage of advanced MRI to improve our knowledge of cortical organization in focal hand dystonia. Their findings reveal that disorganization of cortical activity of the hand representation occurs at different levels of

cortical layers, i.e., at the level of interneurons receiving cortico-cortical interactions and at the level of cortico-spinal neurons controlling the motor output. Being the main origin of the cortico-spinal connections, the primary motor cortex also represents the main output pathway of the voluntary motor command [2], and possibly involuntary dystonic signals. Gray and collaborators investigate the cortical mechanisms underlying dystonic attack using multimodal electrophysiological and calcium imaging approaches in mice model of episodic ataxia type 2. They demonstrate that M1 activity is not at the origin of the dystonic attacks. Combining results from both human and mouse studies, it appears that the primary sensorimotor cortex exhibits abnormal integration of information coming from multiple sources and seem to propagate (rather than initiate) certain dystonic features into the motor command.

The BG are a hierarchically organized set of interconnected subcortical nuclei, including the striatum, the globus pallidum (GP), subthalamic nucleus (STN) and the thalamus (TH). Classical models of dystonia suggest that involuntary muscle contractions result from reduced activity in GP internus (GPi) leading to inadequate inhibition of thalamic inputs to cortex during the movement. Here, Kasiri et al. perform deep electrophysiological recordings of multiple BG nodes in three children with genetic dystonia. In contrast with the classical model of opposite activity patterns of GPi and TH, activity was elevated in both GPi and TH during movement. In a refinement of the classical model, the authors propose that the cerebral cortex primarily excites the thalamus. The role of the GPi would be to selectively inhibit the cortical excitatory afferent at the thalamic level, effectively shaping the thalamo-cortical loop. This precise mechanism would be impaired in dystonia.

Within the BG, the striatum contributes to learning. Zeuner et al. review striatal dysfunction during learning of finger sequences in focal hand dystonia. In particular, striatal dysfunction could be associated with alteration in the subcortical dopaminergic network important for learning. For instance, dystonia symptoms occur in Parkinson's disease, which primarily affects dopaminergic pathways. In this Special Issue, Norris et al. investigate common mechanisms and the temporal interplay between dystonia and Parkinson symptoms by combining behavioral scoring, post-mortem counting of striatal and nigral dopaminergic neurons in MPTP monkeys. Their findings indicate that the severity of dystonic symptoms predicted the severity of Parkinsonism, but the relationship between striatal dopamine and dystonic symptom was complex and depended on the severity of nigral dopaminergic cell loss. This suggests that the sequential order of node dysfunction is significant. It gives additional evidence that dopaminergic system is a vulnerable point of network dysfunction in dystonia [3, 4].

Traditionally, the CB was considered a crucial node for motor execution and learning. However, in patients with focal dystonia, cerebellar activity and connectivity are altered during both the execution and imagination of movements in absence of motor output (see Zeuner et al. in the present Special Issue). Recent work suggest that the cerebellum can contribute to sleep regulation [5, 6]. In the present issue, Salazar-Leon and Sillitoe use two different mice lines with disrupted afferents to the CB, each with different coverage over climbing fibers only or over both climbing and mossy fibers, inducing different motor severities. Despite the differences in dystonia-related motor severities, the mutant mice exhibited similarly impaired sleep physiology and disrupted circadian rhythms, mirroring patterns observed in human pathology [7, 8]. This work indicates that aberrant cerebellar activity not only disrupts motor function but also impacts sleep.

By considering results in both human patients and animal models, we progress in our understanding of dystonia pathophysiology. Collectively, the findings in this Special Issue indicate that dystonia is a circuit disorder in which abnormalities in one system may well lead to dysfunction of the other because of their reciprocal connections in the brain. Data obtained from dystonic patients and animal models allows identifying common pathophysiological mechanisms on a robust foundation, that inhibiting the thalamic region could potentially block dystonia. Animal models can recreate the circuit-wide defects through different connections. This Special Issue also introduces innovative therapeutic approaches focused on retraining to achieve enduring improvements in motor symptoms. The ongoing research involving animal models and patients is paving the way for improved future therapeutics that have the potential to simultaneously address both motor and non-motor dysfunctions in the context of motor diseases.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The 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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