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# Oligodendrocyte and ECM contributions to CNS motor function: implication in dystonia

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**Abstract**
The quest to elucidate nervous system function and dysfunction in disease has focused largely on neurons and neural circuits. However, fundamental aspects of nervous system development, function and plasticity are regulated by non-neuronal elements, including glial cells and the extracellular matrix (ECM). The rapid rise of genomics and neuroimaging techniques in recent decades has highlighted neuronal-glial interactions and ECM as a key component of nervous system development, plasticity and function. Abnormalities of neuronal-glial interactions have been understudied but are increasingly recognized to play a key role in many neurodevelopmental disorders. Here, we consider the role of myelination and the ECM in the development and function of CNS motor circuits and the neurodevelopmental disease dystonia.

**Introduction**
Dystonia manifests as prolonged involuntary twisting movements that occurs either in isolation or combination with other neurological symptoms [1, 2]. The pathophysiology of dystonia is complex with cellular and circuit dysfunctions from multiple regions implicated thus far [3]. Functional and molecular deficiencies observed in animal models and in multiple inherited forms of dystonia include cholinergic dysfunction [4-10], impaired inhibition [11-15], abnormal connectivity [16-22] and deficits in plasticity [23-25]. These core features highlight the varied mechanisms contributing to dystonia pathophysiology, which lead to remarkably similar motor deficits. Many of these phenotypes emerge during CNS maturation, which is supported by recent studies using animal models manipulating TorsinA (*Tor1A* or DYT1) expression demonstrating its importance during a "critical period" of neurodevelopment [23, 26-28]. These findings and the recent identification of several monogenic variants with high diagnostic value in early onset dystonias [29-31] offer strong support to the premise that dysregulation of neurodevelopmental mechanisms is a key feature of dystonia pathophysiology.

Advances in sequencing technologies have expanded our understanding of the genes associated with dystonia [2, 32, 33]. Genetic mutations causing isolated (*TOR1A, THAP1, GNAL, ANO3, PRKRA, KMT2B, GCH1* and *HPCA*) and combined dystonia (*ATP1A3, SGCE, TAF1, SLC2A1/GLUT1, PNKD, PRRT2, VPS16, VPS41, KCTD17)* are all ubiquitously expressed in the CNS (Figure 1; single cell portal, BROAD Institute; *https://singlecell.broadinstitute.org/single_cell)*. Most dystonia associated genes are expressed in both neuronal and glial cells (Fig. 1), with only ATP1A3 expression exhibiting neuronal restricted expression (confirmed in single cell portal, BROAD Institute and https://www.brainrnaseq.org). These observations are consistent with the possibility that dystonia etiology is not limited to mechanisms originating from neuronal cells. Here, we examine emerging evidence implicating abnormalities of the extracellular matrix, myelination, and axon-glia interactions in motor function and dystonia pathogenesis.

**White matter and oligodendrogenesis in motor learning and plasticity**

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Generation of white matter (WM) in the brain is a gradual postnatal process as observed in humans and rodents whereby oligodendrocyte cells (referred to as OLs) wrap axons with a myelin sheath that supports rapid neurotransmission [34]. These myelinating glial cells differentiate from oligodendrocyte progenitor cells (OPCs). Peak myelination in the developing brain occurs concomitant with peak synaptogenesis, with the bulk of it occurring in the first 2 years in humans and first 3 weeks in rodents [35-37]. However, myelination continues through puberty in both animals and humans [37], including changes in myelinated white matter volumes in frontal brain regions that can be detected in humans up to 40 years of age [38, 39]. Thus, critical periods during the emergence of sensory and motor function coincide with the differentiation of OPCs into myelinating OLs.

Studies in mice have established that motor learning promotes key aspects of oligodendrogenesis, including increased OPC proliferation, generation of mature myelin-producing OLs [40, 41], and myelin sheath remodeling [42]. Increased oligodendrogenesis from motor learning is a critical aspect of “adaptive myelination”, whereby neural activity promotes the generation of myelinating OLs [43, 44]. In an elegant approach, Gibson et al. demonstrated that optogenetic stimulation of layer V projection neurons in the premotor cortex promotes oligodendrogenesis, increases myelin thickness and altered motor function [45].

While changes in myelination in animal models can be quantitatively assessed though many techniques and reagents post-mortem, in humans and live animal studies, WM tracts are commonly assessed using the MRI technique diffusion tensor imaging (DTI). This techniques measures water diffusion as a proxy for the integrity and organization of axonal tracts [46, 47]. Fraction anisotropy (FA), a measure of the orientation-dependence of water diffusion, is a DTI parameter that is commonly used to assess tract integrity [46, 47]. FA values are higher in WM tracts compared to grey matter due to the highly organized axonal bundles that restrict water diffusion along defined paths [47, 48]. While higher FA values positively correlate with axonal myelination [48] and low FA values are observed in demyelinating disorders [46], WM integrity is also dependent on axon density, caliber, and the presence of other glial cells. Thus FA is a biomarker of microstructural architecture [47], but is not exclusive to changes in myelination.

Several DTI studies indicate that motor skill learning causes WM structural changes. For example, corticospinal tract FA values increase with extensive piano practicing [49], while juggling training increases FA in the intraparietal sulcus [50]. Interestingly, the whole-body movement paradigm Quadrato Motor Training (QMT) induces FA increases across multiple WM regions, including the corticospinal tract, anterior thalamic radiations, and uncinate fasciculi [51]. Motor learning also induces WM changes in laboratory models. Learning a highly skilled reaching task increased FA in the WM of sensorimotor cortex contralateral to the trained limb compared with untrained control rats, and ex vivo myelin staining density correlated with learning rate [52].

A critical question is whether the activity-induced myelination and oligodendrogenesis is necessary for motor learning and skill. This question was addressed directly by

disrupting the generation of new OLs in animals learning the skill of running on a wheel with unequally placed rungs [40, 41]. These investigators conditionally deleted from OPCs *Myrf*, a factor critical for differentiation of OPC to OL. This perturbation impaired the generation of myelinating OLs and caused deficits in the wheel task, particularly in the early stages of motor learning [40, 41]. Similar motor learning deficits were observed in studies using cuprizone induced demyelination in mice performing skilled reaching, where demyelination is followed by incomplete OL replacement and motor learning defects [42].

**Genetic links between white matter, oligodendrocyte dysfunction and dystonia**

Parallel to the work linking white matter and motor learning are clinical and laboratory studies implicating alterations of white matter in the pathophysiology of dystonia. Changes in WM microstructure have been reported in patients with twelve different forms of inherited dystonia - either in isolation or combination with other neurological symptoms (Table 1). Eight of the mutated genes implicated in primary (Table 1: *THAP1,YY1, TUBB4A*)*) and secondary dystonia* (Table 1: *SLC2A1/GLUT1, BAP31, FA2H, SLC16A2/MCT8* and *POLR3*) have an established role in myelination. Several additional studies have reported microstructural WM changes in idiopathic dystonias [53]. For example, significant changes in FA values have been reported in subjects with cervical dystonia in the putamen, corpus callosum [54] and internal globus pallidus [55, 56]. Similar findings have been reported in patients with "writer's cramp" (a form of task specific dystonia) and spasmodic dysphonia (47-49).

Studies of THAP1 function are first direct demonstration of a primary dystonia gene functioning in the oligodendrocyte lineage [57, 58]. DYT-THAP1 (DYT6 dystonia) is caused by loss of function mutations in THAP1 [59], a transcription factor with an atypical zinc-dependent DNA-binding domain [60, 61]. More than 100 mutations have been reported in the protein coding region of this gene [62]. We reported that, despite its ubiquitous expression (Fig.1) [57], THAP1-regulated pathways are highly enriched within the OL lineage [57]. Mice conditionally deficient for *Thap1* in the entire CNS (using Nestin-cre) or conditionally deficient for *Thap1* in the OL lineage (using Olig2-Cre) exhibit severe myelination defects during the first month of life [57]. Ultrastructural studies demonstrate a reduced density of myelinated axons in the WM despite normal axon number [57].

Of the eight dystonia genes with a role in myelination, six genes (Table 1; *THAP1, SLC2A1/GLUT1, FA2H, YY1, SLC16A2/MCT8* and *TUBB4A*) have an established function within the oligodendrocyte lineage of which five (Table 1: *THAP1, FA2H, YY1, SLC16A2/MCT8* and *TUBB4A*) have a regulatory role in the generation of mature OL. Thus far, mutations for *THAP1, FA2H, YY1* and *SLC16A2/MCT8* have been established to result in loss-of-function [63-68]. Studies using mouse models have demonstrated that both *THAP1* and *YY1* regulate the generation of mature OLs from OPCs [57, 69]. Interestingly, THAP1 and YY1 are co-bound transcription factors that share a large number of target genes, and YY1 binding is functionally dependent on THAP1 binding [57, 64]. The THAP1 null CNS has normal numbers of OPC and immature OLs, but a clear defect in the progression to mature myelinating OLs both *in vitro and in vivo* [57]. While the mechanism of actions of these six genes implicated in dystonia may vary, their loss

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of function would commonly affect myelination resulting from their actions within the OL lineage.

**ECM-mediated plasticity in motor learning and function**

CNS axon-glia interactions are profoundly influenced by the ECM, a complex three-dimensional milieu composed of fibrous proteins (e.g., collagen, elastin), glycosaminoglycans (GAGs, a class of long unbranched mucopolysaccharides), and GAG-modified proteins (proteoglycans "GAG-PG") [70]. The brain ECM is estimated to occupy ~20% of the adult brain [71] acting both as a physical scaffold and a signal organizing center affecting growth, synaptic activity and neural plasticity [72-74]. Consequently, the ECM has a broad influence on both the development and plasticity of the CNS, including motor learning and function.

Brain ECM exists in both diffuse and condensed forms [75]. The best characterized CNS ECM structure is the perineuronal net (PNN). PNNs are lattice-like structures composed of CSPGs (chondroitin sulfate proteoglycans) typically surrounding parvalbumin-positive (PV) GABAergic interneurons [74]. The appearance of the defined PNNs around interneurons in the striatal matrix occurs at the end of a critical developmental period (~ 3 weeks of age) that correlates with the appearance of adult-like gait from an immature, predominantly forelimb dependent 'crawl' [76]. Enzymatic ablation of these striatal CSPGs impedes the transition to a mature gait [77] suggesting an important role in motor function during development. PNNs also form around PV neurons during critical periods of postnatal development in the somatosensory cortex [78, 79]. Sensory deprivation leads to quantitative and qualitative changes in PNNs in the mouse barrel [78] and somatosensory cortex [80]. These observations establish a role for ECM composition and dynamics in establishing sensory and motor function during CNS development.

Despite their necessary role in establishing motor function during development, the effect of CSPGs on motor function is complex and not binary or unidirectional. For instance, injuries in the CNS lead to acute accumulation of CSPGs, which inhibit neural plasticity and oligodendrogenesis [72, 79, 81-87]. Motor learning deficits following focal motor cortex ischemia [88] or cervical spinal cord injuries [89] are ameliorated by enzymatic ablation of the accumulating CSPGs; these observations suggest that lesion-induced ECM accumulation inhibits motor recovery. Multiple GAG species, in their free forms and as proteoglycans, have been demonstrated to inhibit oligodendrocyte maturation *in vitro* and *in vivo* [72, 81-87, 90-93].

**Genetic links between ECM and dystonia**

Thus far three genetic causes of inherited dystonias have interactions with or contribute to ECM homeostasis (Table 1; *THAP1, SGCE* and *VPS16*). ε-sarcoglycan (SGCE) is a transmembrane glycoprotein interacting with extracellular ECM and the intracellular cytoskeleton [94]. Recent studies have identified that THAP1 is involved in the lysosomal regulation of ECM components [58]. THAP1 regulates catabolism of GAGs, the major ECM components in the OL lineage [58]. Loss of THAP1 in OPCs results in the accumulation and secretion excess GAGs, inhibiting OPC maturation through an auto-inhibitory mechanism [58]. THAP1 regulates GAG catabolism by binding to and regulating

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the *GusB (MPS7)* gene encoding the GAG-catabolizing enzyme β-glucuronidase [58], which resides in the lysosomes and whose loss of function is responsible for the lysosomal storage disorder, mucopolysaccharidosis type VII (MPS VII) or sly syndrome [95]. Interestingly, loss-of-function variants in the homotypic fusion and vacuole protein sorting (HOPS) complex genes *VPS16* and *VPS41* have been identified to cause early onset dystonia [96]. HOPS is a conserved protein complex known to mediate lysosomal (endosome-lysosome and autophagosome–lysosome) fusion events [97]. Two recent studies have identified patients with homozygous *VPS16* variants are associated with a novel disease, resembling mucopolysaccharidosis-plus syndrome that include developmental delay, delayed myelination, skeletal abnormalities and high-normal glycosaminoglycan excretion [94, 98].

## Concluding remarks

There is increasing evidence for the role of extra neuronal mechanisms in neurodevelopmental and neurodegenerative disorders. In this brief review we have curated and discussed a growing body of work linking abnormalities of myelination and ECM biology to dystonia pathogenesis and pathophysiology. The roles of other glial populations (e.g., astrocytes and microglia) in motor function are relatively well studied but have not been examined in the context of dystonia. This omission is especially pertinent given recent studies demonstrating microglial-astrocyte crosstalk with themselves and with oligodendrocytes. Similarly, astrocytes and microglia have established role in ECM generation and regulation. Given the wide range of cellular and physiological pathways implicated in dystonia pathogenesis, the roles of these extra neuronal mechanisms and neuronal-glial interactions are important future directions to pursue to unravel the cellular and molecular mechanisms of neurodevelopmental disease, including dystonia.

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D.Y., S.S.P and W.T.D - writing of the first draft, review and critique.

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## Figure legends

**Figure 1: CNS cell type specific expression of dystonia genes:** Dot plot showing the expression pattern of inherited dystonia genes (rows) derived from single nucleus RNA-seq of mouse cortex (single cell portal, BROAD Institute) [99]. The relative expression genes in various cell types of (columns) is scaled (0-1 = blue to red) relative to each gene's expression across all cells. The size of the dot represents the relative expression in the given cell type.

## Table legends

**Table 1:** Reference to prior studies for inherited dystonia genes and their relation to white matter, oligodendrocytes and ECM.

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**Table 1: White matter & ECM abnormalities associated with dystonia.**

| | | Evidence of white matter abnormalities | | | |
|---|---|---|---|---|---|
| Gene | Phenotype | Neuroimaging | Myelination | Functional role in oligodendrocyte lineage | Role in ECM |
| TOR1A | DYT-TOR1A | 18 | | | |
| THAP1 | DYT-THAP1 | 100 | 57, 101 | 57, 58 | 58, 102 |
| KMT2B | DYT- KMT2B | 103, 104 | | | |
| VPS16 | DYT-VPS16 and MPS-plus syndrome-like disease (Mucopolysaccharidoses) | 98 | 98 | | 94 |
| SGCE | DYT- SGCE | | | | 105 |
| SLC2A1/ GLUT1 | Paroxysmal dyskinesias dystonia | 106, 107 | 108 | 108 | |
| BAP31 | Deafness, dystonia, and cerebral hypomyelination | 109 | 109 | | |
| FA2H | Spastic Paraplegia; dystonia | 110 | 111-113 | 112, 113 | |
| SLC16A2 /MCT8 | Allan-Herndon-Dudley syndrome | 114-116 | 115-120 | 115-117, 120 | |
| YY1 | DYT-YY1 and Gabriele-de Vries syndrome | | 69 | 69 | |
| POLR3 | POLR3-related leukodystrophy | 121, 122 | 121, 122 | | |
| *TUBB4A* | DYT-TUBB4A and Leukodystrophy including Hypomyelination with Atrophy of Basal Ganglia and Cerebellum. | 123, 124 | 123 | 125, 126 | |

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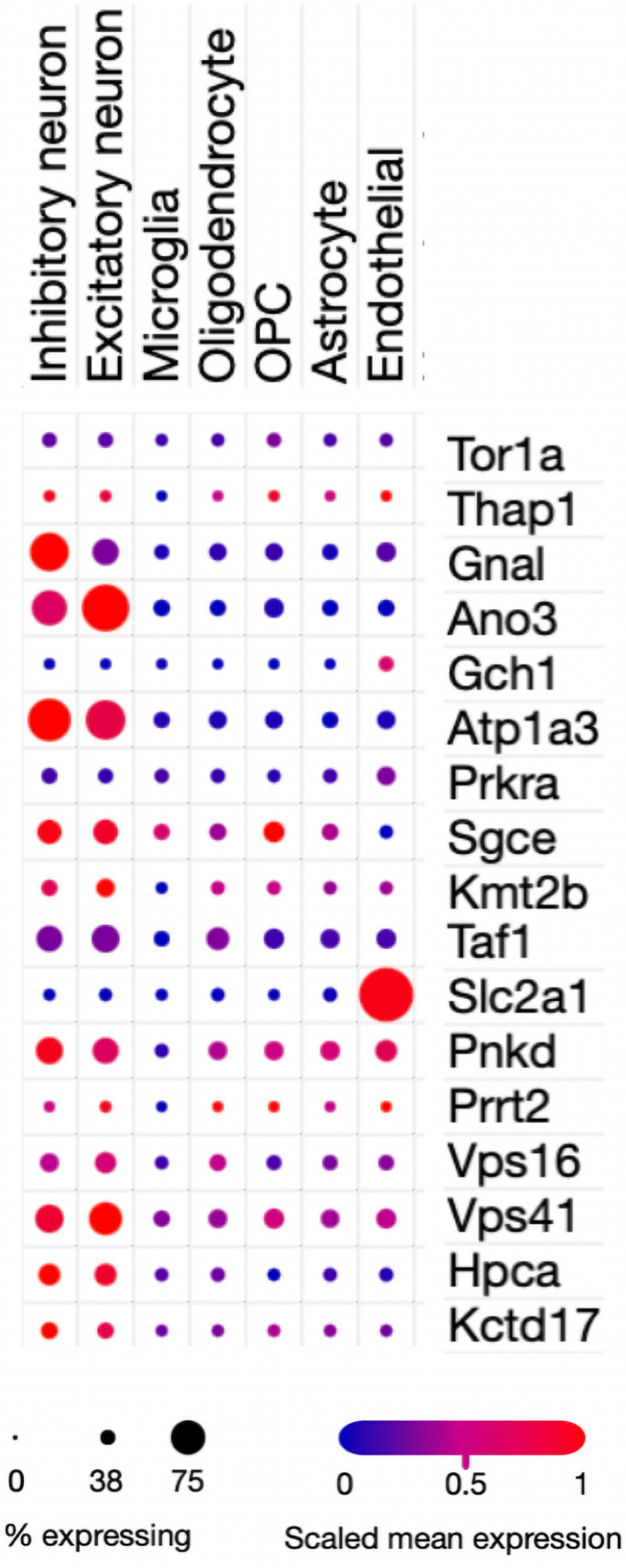


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