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CONSENSUS PAPER

Current Opinions and Areas of Consensus on the Role of the Cerebellum in Dystonia

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Abstract A role for the cerebellum in causing ataxia, a disorder characterized by uncoordinated movement, is widely accepted. Recent work has suggested that alterations in activity, connectivity, and structure of the cerebellum are also associated with dystonia, a neurological disorder characterized by abnormal and sustained muscle contractions often leading to abnormal maintained postures. In this manuscript, the authors discuss their views on how the cerebellum may play a role in dystonia. The following topics are discussed:

- The relationships between neuronal/network dysfunctions and motor abnormalities in rodent models of dystonia.
- Data about brain structure, cerebellar metabolism, cerebellar connections, and noninvasive cerebellar stimulation that support (or not) a role for the cerebellum in human dystonia.
- Connections between the cerebellum and motor cortical and sub-cortical structures that could support a role for the cerebellum in dystonia.

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Overall points of consensus include:

- Neuronal dysfunction originating in the cerebellum can drive dystonic movements in rodent model systems.
- Imaging and neurophysiological studies in humans suggest that the cerebellum plays a role in the pathophysiology of dystonia, but do not provide conclusive evidence that the cerebellum is the primary or sole neuroanatomical site of origin.

Keywords Cerebellum · Dystonia · Ataxia · DYT1 · Networks · Circuits

Introduction

Dystonia is a neurological disorder characterized by sustained involuntary muscle contractions, which distort the body into abnormal postures. These muscle contractions can also sometimes cause abnormal, repetitive movements, often initiated or worsened by voluntary action and associated with overflow muscle activation [1]. Dystonias may be classified based on clinical characteristics or etiology. Clinically, dystonia may affect only one body region or may be more generalized [1]. Spontaneous genetic mutations and pharmacological manipulations in animals can produce abnormal movements that resemble human dystonia. Although the mechanism for these movements in animals may sometimes be disparate from the human disorder, it is helpful to study these movements in animals to derive possible mechanistic information regarding the etiology of human dystonia. For the purpose of this review, dystonia in both humans and animals is defined by the characteristic phenotype of abnormal, repetitive movements which distort the body into abnormal postures.

Movement in mammals is a result of coordinated activity of multiple areas of the nervous system, ultimately converging on muscles that are under the control of motor neurons in the spinal cord and brainstem. Although all these systems are interconnected, abnormalities in distinct nodes or anatomical regions of the nervous system are likely responsible for distinct movement disorders such as dystonia.

The basal ganglia represent one such node; dystonia is traditionally viewed as a disorder of the basal ganglia [2], but recent evidence suggests that other nodes in the motor network may also contribute to dystonia [3]. These observations have led to speculation that dystonia may arise from different types of defects within the motor network [4]. It may arise from dysfunction of a single node in the network, simultaneous dysfunction of more than one node, or abnormal communication between the nodes. One such additional node that has recently been implicated in dystonia is the cerebellum.

In this manuscript, animal studies linking the cerebellum to dystonia are summarized. This is followed by a summary of the role of the cerebellum in human dystonia. A consensus opinion of the role of the cerebellum in dystonia is presented, in addition to areas for future research.

Motor Pathways Involved in Dystonia (H.A. Jinnah, Yoland Smith, Ellen Hess)

Some of the strongest evidence for involvement of nodes other than the basal ganglia in dystonia has come from animal studies and, particularly, rodents. This evidence must be interpreted in view of potential species differences.

Species Differences in Motor Behavior

The normal motor behavior of humans and rodents is quite different, so the first question to address is whether or not dystonia can occur in rodents. Dystonia is defined by the quality of abnormal movements, with excessive contraction of muscles that lead to twisting or repetitive movements or postures [1]. By definition, any abnormal movements with these qualities are "dystonic". Co-contraction of antagonistic muscle pairs is said to be characteristic of dystonia, but this phenomenon is not universal [5]. Electromyography can be helpful in confirming some of the electrophysiological correlates of these movements [6], but the results are not required for diagnosis because they are neither sensitive nor specific for dystonia.

The spontaneous occurrence of dystonic movements also has been reported in the veterinary literature for many other species including farm animals such as horses and chickens, other domestic animals such as dogs and cats, and wild birds. Dystonic movements have been reported following a variety of manipulations in different experimental animals including non-human primates [7], cats, and rodents [8, 9]. Many of these studies include careful descriptions of abnormal movements, often with accompanying video demonstrations that fulfill currently accepted clinical criteria for "dystonia" [8, 9]. Thus, dystonic movements are not unique to humans.

Some critics of animal models argue that the abnormal movements seen in rodents may be a "phenocopy" of dystonia and not "real" dystonia. Unfortunately, this argument is invalid because the concept of a "phenocopy" is meaningless when a disorder is defined by its phenotype. The more relevant concern is whether the biological mechanisms responsible for the same phenotype are similar in humans and rodents. Because these mechanisms are poorly understood, this question remains open.

Species Differences in Anatomical Pathways

The normal nervous system of rodents and humans is quite different, so one important question to address is whether the anatomical structures and pathways causing dystonia differ

across species. For the motor system, the most obvious species differences are at the gross structural level [10]. For example, the rodent brain is clearly much smaller. All three major motor control nodes are clearly recognizable in rodents, but within each region there are again some visible differences. However, beyond these superficial differences in gross appearance, there are many similarities across species at the synaptic, cellular, and molecular levels.

Motor Cortex Grossly, the rodent motor cortex is smooth, unlike humans where there are prominent sulci and gyri. The rodent "primary motor" cortex is made up of M1 and M2 subareas that are poorly demarcated from each other, whereas in humans, there are clear functional subdivisions into primary motor, ventral and dorsal pre-motor, supplementary motor, cingulate motor, and other related cortices. Cytoarchitechtonically, the laminar structure of the rodent motor cortex is simpler than in humans. However, the various neuronal subtypes and their general morphology are grossly similar between rodents and humans. Most notable are the large pyramidal neurons that project to motor neurons in the brainstem and spinal cord, and others that project to the basal ganglia or cerebellum. All of these pathways use the excitatory transmitter glutamate in both species, and post-synaptic signal transduction mechanisms are likely to be the same in rodents and humans. However, there are some significant differences in the extent of direct interactions between corticospinal axons and motoneurons. Although direct cortico-motoneuronal connections are a predominant feature in primate species including humans, they do not exist in rodents and carnivore species [11]. This evolutionary feature likely subserves new aspects of fine motor control, including manual dexterity in humans, an issue of importance in some forms of focal dystonia.

Basal Ganglia Like the motor cortex, the basal ganglia are less structurally demarcated in rodents compared to humans. For example, the caudate nucleus and putamen are separate in humans, but merged into a single structure called the caudoputamen in rodents. In addition, rodents do not have an internal globus pallidus like humans; the rodent homolog is the entopeduncular nucleus, which has some similarities, but also some differences in cell types and projections compared to the human internal pallidum. Further, the human basal ganglia are functionally and somatotopically organized from the input stage through thalamocortical outputs. This topography is less obvious in rodents.

Despite these gross anatomical differences between humans and rodents, the intrinsic circuitry of the basal ganglia is strikingly similar across species, with both direct, indirect and hyperdirect subcortical pathways. The major afferent and efferent pathways also are similar, although the relative importance of individual pathways may vary. Robust striatal afferents come from the cerebral cortex, thalamus, substantia nigra, and other areas. Key efferents exit through thalamocortical connections or descending brainstem projections. Histologically, the appearance and relative abundance of cell types in the striatum are strikingly similar in rodents and humans with medium spiny neurons projection neurons constituting 90 % of the neurons and a smaller number of interneurons. Functional properties of striatal neurons are also preserved across species as diverse as lampreys to mammals [12]. Finally, the chemical anatomy of the rodent and human basal ganglia is similar. The same neurotransmitter are used by all of the major basal ganglia afferents (glutamate, dopamine, acetylcholine, norepinephrine, and serotonin), intrinsic connections (glutamate, GABA, acetylcholine, and adenosine), and efferents (mostly GABA).

Cerebellum The gross anatomy of the rodent cerebellum is different from humans; it is smaller with relatively less prominent hemispheres. However, the major efferent and efferent connections are similar in rodents in humans, with entry and exit through three very similar peduncles. Once again, however, the relative contribution of afferent and efferent pathways differs between rodents and humans. The cytoarchitectonics are strikingly similar across species with a cerebellar cortex divided into 3 layers (molecular layer, Purkinje layer, and granule layer) and distinct cerebellar nuclei deep in the white matter (dentate, globose, fastigial, and emboliform). The intrinsic circuitry of the cerebellum also is identical across species, with a highly characteristic layout of climbing fibers, mossy fibers, parallel fibers, and Purkinje neuron output.

Are Species Differences Relevant for Dystonia?

With regard to both motor behavior and neuroanatomy, there are clear differences between rodents and humans that must be acknowledged. Regarding motor behavior, some subtypes of dystonia such as writer's cramp may not occur in rodents, but there is no reason to suspect that other types of dystonia do not occur. Regarding the neuroanatomy, species differences are obvious, but the similarities are more extensive. The critical issue is not whether there are differences between humans and rodents, but whether these differences are sufficiently critical to dismiss the rodent literature. The answer to this question is unknown. However, there is presently no clear evidence that dystonia in rodents and humans is mediated by different anatomical pathways. Instead, the more parsimonious working hypothesis is that these pathways are biologically similar.

The continuing debate regarding the potential relevance of species differences is not constructive to the future research mission because it promotes the view that we must be skeptical of results obtained from rodents until these differences can be conclusively resolved. These differences will never be

resolved. If this skepticism is allowed to guide future experimental strategy, then we must also begin to question results from *Drosophilia melanogaster*, *Caenorhabditis elegans*, and other common experimental models. For these models, species differences are even larger. A further extension of this line of thinking is that tissue culture models also are invalid. An experimental toolkit for dystonia that involves only in vivo studies of primates profoundly limits the types of studies that can be conducted. This overly restrictive philosophy is not applied to other neurological disorders such as Parkinson's disease, Alzheimer's disease, or epilepsy. It therefore should not be applied in dystonia research, unless there is evidence that rodent experiments lead to results that are misleading for human dystonia.

Rather than dismiss potentially valuable novel insights from these simpler experimental models, a more productive approach is to explore the relevance of any findings from these other models in humans (Fig. 1a), or at least non-human primates (Fig. 1b). The ultimate proof of the value of simpler experimental models is how effectively they can guide studies of human dystonia. In fact, studies in humans based on novel insights from these simpler models have already begun to emerge. The majority of these studies so far appear to confirm the concept originating from animal work that dystonia is a motor network disorder that is not due exclusively to defects in the basal ganglia [4, 13–17].

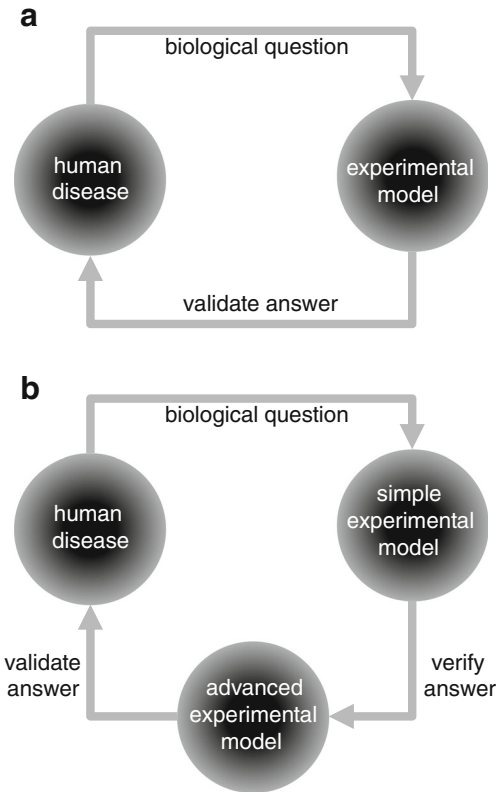

Fig. 1 The role of animal models in exploring the pathogenesis and treatment of human disorders. **a** An experimental question about the human disorder can be explored in animal models. The relevance of the result from the animal model must ultimately be confirmed in humans. **b** In some cases, an experimental question about a human disorder can be explored in a simple animal model, such as a rodent. Results from the simple model can be explored further in non-human primates before confirming in humans

The Cerebellum and Primary Dystonia: What Do Rodent Models Based on Human Dystonia Genes Tell Us? (William Dauer)

Modeling dystonia by recapitulating the disease in animal models is an important and appealing approach to understanding the neural basis of the disease, yet pitfalls and land mines abound. First, what behavior constitutes dystonia in a rodent? The difficulty in answering this question becomes apparent when one considers that the movement disorder community recently felt necessary to update the definition of dystonia *in humans* [1], and the frequent disagreements between clinicians as to whether or not the abnormal movements of certain patients constitute dystonia. There are examples of dystonic-appearing movements in rodents that arise from derangements of CNS regions not thought relevant to human dystonia [18], highlighting the danger of relying exclusively on a behavioral definition in an experimental model. Challenges in dystonia research arise to a considerable degree because there is no test that definitively identifies movements as dystonic; even if we accept a working definition of dystonia as any abnormal twisting movement (as done in this review), it remains uncertain which of these "dystonias" in rodents is consequent to mechanisms causing human dystonia. Co-contraction of agonists and antagonists is frequently used as an electrophysiological definition, but this feature is non-specific, occurring in several movement disorders, and in normal people (try making a tight fist, and you will quickly appreciate the co-contraction of the forearm flexors and extensors).

One way to potentially circumvent these difficulties is to begin with an etiological insult that causes dystonia in humans—mutant genes for primary dystonia. However, because the organization of the rodent and human CNS differs—including the organization of the basal ganglia and related pathways—a *molecular* lesion that causes dystonia in humans could, in principal, produce a distinct behavioral abnormality in rodents. For example, lesions of the subthalamic nucleus cause hemiballism in humans, but not in rodents. This issue is eloquently discussed in detail in an opinion article by Tim Schallert and colleagues [19] where they state, "The first question to ask is not whether a rat would show a given neurological symptom, but rather, how that neurological symptom would manifest itself in a rat."

Based on these considerations, I will review published data that implicate the cerebellum in the genesis of *any* motor abnormalities caused by the manipulation of human primary dystonia genes. All such data come from studies of the DYT1 mutation ("ΔE") in the dystonia gene *TOR1A* that encodes the protein torsinA.

Establishing the involvement of a brain structure (or cell type) in a behavior requires careful analysis of the *necessity* and *sufficiency* of that structure for the behavior. In the context of primary dystonia, this means demonstrating that the genetic insult (torsinA loss of function) selectively within the cerebellum disrupts motor function (sufficiency), and that torsinA-related cerebellar dysfunction is *necessary* to disrupt motor behavior. There are data demonstrating that some cerebellar cell types are sensitive to torsinA loss of function. However, no data exists that establish a role for these cells, or the cerebellum generally, in torsinA-related motor dysfunction.

Tor1a$^{\Delta E/+}$ mice, the genetic phenocopy of the human disease, exhibit little [20] or no [21] motor phenotype, but show abnormalities of cerebellar metabolism [22]; the role, if any, of these areas in creating motor dysfunction was not addressed. A broad neuropathological assessment of these animals, including the cerebellum, identified only subtle microstructure abnormalities of striatal projection neurons [23]. Several models exhibit overtly abnormal twisting behaviors, including conditional deletion of *Tor1a* from the CNS or midbrain/hindbrain, or selective expression of ΔE-torsinA in these two patterns [24]. These models also show striking degeneration of deep cerebellar nuclear (DCN) neurons, but no morphological abnormalities of other cerebellar cell types. Selective expression of the *Tor1a*$^{\Delta E/+}$ genotype in the midbrain/hindbrain region similarly does not disrupt motor behavior in any overt way [25]. These data demonstrate that within the cerebellum, DCN neurons are uniquely sensitive to torsinA loss of function, but do not establish the necessity or sufficiency of these cells for the abnormal behavior.

In contrast to these data, conditional deletion of *Tor1a* from forebrain cholinergic and GABAergic neurons [26], or from striatum or cortex [27, 28] all cause motor dysfunction. These models suggest that torsinA-related cerebellar abnormalities are not *necessary* for torsinA-related motor dysfunction.

There are several caveats and qualifications to the above analysis, which cannot be addressed in this short format. Perhaps most important is the question of whether focusing on a single structure as a dystonia "cause" is the right approach for a phenomenon that appears to be a network disorder that can be provoked by insults to several motor areas [29] or when the function of a structure is altered: Does the resulting behavior derive from that structure or compensation from other brain regions? Developing an improved conceptual construct of what constitutes dystonic behavior, and the CNS circuit abnormalities that are likely to drive such behavior, seems essential.

Anatomical Pathways for Cerebellar Contributions to Dystonia (Andreea Bostan and Peter Strick)

Here, we discuss the substantial anatomical connections in nonhuman primates that identify potential routes for interactions between the cerebellum and basal ganglia in the manifestation of dystonia.

The cerebellum and basal ganglia have long been recognized for contributions to the control of movement through influence on the primary motor cortex (M1). More recently, experiments using neurotropic viruses as transneuronal tracers in nonhuman primates have demonstrated that cerebellar and basal ganglia outputs reach not only M1, but also premotor, prefrontal, and parietal areas [30]. Cerebellar output channels to M1 and premotor areas cluster in dorsal regions of the cerebellar dentate, identifying a motor domain within this nucleus [31]. A motor domain has also been identified in the internal segment of the globus pallidus (GPi), a major output nucleus of the basal ganglia [32]. In general, the ratio of basal ganglia to cerebellar input to a motor area is 1:1, i.e., a cortical motor area is the target of output from equal numbers of basal ganglia and cerebellar output neurons. The one exception to this pattern is the supplementary motor area, in which the ratio of basal ganglia to cerebellar output is approximately 3:1 [32]. Clearly, the motor domains of the cerebellum and basal ganglia provide substantial input to each of the cortical motor areas and, thus, can have a significant influence over their function.

As the outputs from the cerebellum and basal ganglia to the cerebral cortex are relayed through separate thalamic nuclei, any interactions between cerebellar and basal ganglia loops with the cerebral cortex were thought to occur at the level of the cerebral cortex [33]. Results from recent anatomical experiments in nonhuman primates challenge this perspective and provide evidence for disynaptic pathways that link the cerebellum with the basal ganglia more directly (Fig. 2). Transneuronal transport of rabies virus demonstrated that the dentate nucleus projects, via the intralaminar thalamic nuclei, to the striatum and then to the external segment of the globus pallidus (GPe) [34]. Projections originate from both motor and nonmotor domains of the dentate and may influence both motor and nonmotor functions within the basal ganglia. Remarkably, the number of dentate neurons that target localized portions of the GPe is comparable to the number of dentate neurons that reach areas of cerebral cortex [34], emphasizing the functional relevance of cerebellar influences on basal ganglia activity. Indeed, studies in mice found that cerebellar stimulation alters activity in about half of striatal neurons and can affect cortico-striatal plasticity, via the disynaptic cerebello-thalamo-striatal pathway. Furthermore, under pathological conditions, this pathway can transmit abnormal cerebellar activity to the basal ganglia, resulting in dystonic movements [35].

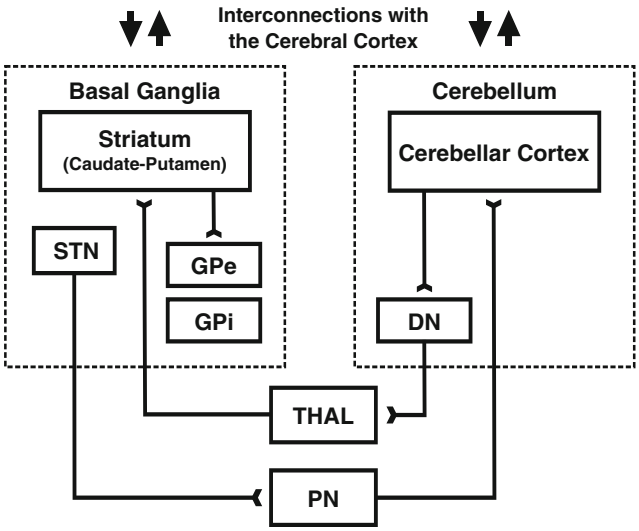

Fig. 2 Cerebellar connections with the basal ganglia. Schematic representation of the anatomical connections between the cerebellum and basal ganglia in non-human primates. Based on [34] and [36]. *DN* dentate nucleus, *GPe* external segment of the globus pallidus, *GPi* internal segment of the globus pallidus, *PN* pons, *STN* subthalamic nucleus

In a different series of anatomical experiments, virus transport demonstrated that the subthalamic nucleus (STN) projects disynaptically to the cerebellar cortex (Fig. 2) [36]. Projections to the cerebellar cortex originate from motor and nonmotor domains within the STN [36].These inputs terminate in motor and nonmotor regions of the cerebellar cortex and, thus, enable basal ganglia activity to affect multiple functional domains of the cerebellum. The numbers of STN neurons that target a specific site within the cerebellar cortex are comparable to the numbers of STN neurons that influence areas of the cerebral cortex (e.g., M1; see [37]). This result emphasizes the functional relevance of the STN influence on cerebellar activity. Indeed, deep brain stimulation of the STN in rats can alter activity of cerebellar neurons [38].

Overall, the results from neuroanatomical studies in non-human primates indicate that basal ganglia and cerebellar outputs converge at the level of the cortical motor areas. In addition, our new results demonstrate that basal ganglia and cerebellar circuits with the cerebral cortex are massively interconnected at the subcortical level. In an output stage of cerebellar processing, the dentate nucleus is disynaptically linked to the input stage of basal ganglia processing, the striatum. Similarly, an output stage of basal ganglia processing, the STN, is disynaptically linked to the input stage of cerebellar processing, the cerebellar cortex. These interconnections suggest that the cerebellum and basal ganglia are more functionally interdependent than previously suspected. Furthermore, these interconnections allow for abnormal activity in the cerebellum to alter basal ganglia function and vice versa. This new perspective suggests that disorders typically associated with the basal ganglia, such as dystonia, are best understood as disorders of an integrated network that includes the basal ganglia, cerebellum, and the motor cortical areas.

How Does the Cerebellum Fit into the Functional Neuroanatomy of Dystonia in Mouse Models? (Robert Raike, H.A. Jinnah, and Ellen Hess)

Although imaging studies in humans have proven invaluable for providing evidence of abnormalities in patients, the results are often correlative, so it is difficult to distinguish cause from consequence. Therefore, animal models, oftentimes mouse models, have been used to facilitate our understanding of the role of the cerebellum in dystonia. Abnormal cerebellar activity is observed in many different mouse models of generalized dystonia. Genetically engineered mouse models of *Dyt1* dystonia exhibit an increase in metabolic activity within the cerebellum and expression of the immediate early gene c-fos, a reliable reporter of changes in neuronal activity is observed in the cerebellum of *tottering* mice, which exhibit episodes of generalized dystonia caused by a defect in the Cav2.1 calcium channel [39] [22, 40]. Further, abnormal Purkinje cell firing rates are associated with generalized dystonia in tottering mice, mouse models of rapid-onset dystonia parkinsonism (RDP), and IPCR1 (inositol 1,4,5-triphosphate receptor type 1) deficit mice. In all of these models, the abnormal Purkinje cell activity correlates with the abnormal body movements [41–44].

Eliminating cerebellar output abolishes the generalized dystonia in mouse models of dystonia, suggesting that the cerebellum is a critical node in the pathway leading to the expression of dystonia [45, 46]. Surgical removal of the cerebellum eliminates generalized dystonia in tottering mice, lesioning the deep cerebellar nuclei reduces the dystonic movements in RDP mice, and the progressive cerebellar degeneration observed in leaner mice, another calcium channel mouse mutant, is associated with a significant amelioration in their severe generalized dystonia [47] [48, 49]. Similarly, pharmacological inactivation of the cerebellum ameliorates the dystonia in RDP mice and IPCR1 deficit mice [44, 47]. Further, genetic deletion of Purkinje cells, the only efferents of the cerebellar cortex, using toxic transgenes or mutations abolishes dystonia in the *tottering* mutant and IPCR1 deficit mice [44, 45, 50]. While these cerebellar lesion and inactivation experiments suggest that cerebellar signaling is necessary for the expression of dystonia in these models, such experiments cannot determine whether the cerebellum actually causes the dystonia.

Mouse models have been used to establish a causal relationship between cerebellar dysfunction and dystonia by experimentally disrupting cerebellar signaling to instigate dystonia. Pharmacological induction of abnormal cerebellar signaling through the intracerebellar administration of AMPA receptor

agonists or ouabain, an inhibitor of the Na^+/K^+ ATPase ion pump, induces generalized dystonia in normal mice, but mice that lack Purkinje cells do not respond to similar challenges [51–53]. Like pharmacologic challenge with ouabain, knockdown of the α3 isoform of the Na^+/K^+ ATPase within the cerebellum also causes dystonia in normal mice; loss of function mutations in the α3 isoform of the Na^+/K^+ ATPase cause RDP in human. Finally, conditional expression of a dystonia-causing genotype in only Purkinje cells also induces generalized dystonia in mice [50], suggesting that a single cell type may mediate the abnormal movements. Importantly, isolating the expression of a dystonia-causing genotype to only a small region of the cerebellum in mice induces focal dystonia, suggesting that focal and generalized dystonia may arise through shared underlying cerebellar defects [50]. Thus, work in animals has extended the studies in humans by demonstrating that the cerebellum can actually instigate dystonic movements.

Despite the evidence demonstrating that cerebellar dysfunction can induce dystonia, studies using mouse models suggest that the cerebellum does not act alone. Indeed, some studies suggest that combined dysfunction in the cerebellum and the basal ganglia contributes to the expression of dystonic movements. Striatal insults in either pharmacologically induced or genetic models of "cerebellar" dystonia exaggerate the dystonia [47, 48]. Further, lesions of the centrolateral nucleus of the thalamus, which links the cerebellum with the basal ganglia, ameliorate the cerebellar-induced dystonia [47], providing additional evidence that communication within the motor network is critical for the expression of dystonic movements. However, depending on the type of dystonia, the cerebellum may not be involved at all. For example, the basal ganglia and dopamine neurotransmission are associated with many dystonic disorders, such as L-DOPA-responsive dystonia, which is caused by defects in enzymes necessary for the synthesis of catecholamines and ameliorated by L-DOPA treatment. In a knock-in mouse model of L-DOPA-responsive dystonia, restoration of catecholamine synthesis in the striatum via striatal L-DOPA administration ameliorates the dystonic movements, but administration of L-DOPA directly to the cerebellum is ineffective [54], demonstrating that the cerebellum is not always central to or even involved in the expression of dystonia. Thus, the many forms and etiologies of dystonia likely reflect the diversity of brain regions and biochemical defects underlying this heterogeneous disorder.

The Relationship Between Cerebellar Neuronal Dysfunction and Dystonia (Rachel Fremont and Kamran Khodakhah)

Since the 1970s, it has been appreciated that certain dystonic patients refractory to other treatments could benefit from surgical interventions involving the cerebellum [55]. Recent work corroborates this finding with studies this year showing that transcranial magnetic stimulation of the cerebellum and deep anterior cerebellar stimulation can improve dystonic symptoms [56, 57]. Therefore, while dystonia is canonically thought to be a disorder of the basal ganglia, there is reason to believe that in some cases the cerebellum is likely involved as well [58, 59]. For this reason, there has been a push to understand the neural substrates of cerebellar dystonia in tractable animal models.

Studies have demonstrated that electrical stimulation of the cerebellum in species from rodents to humans can elicit movement [60–62]. One elegant study published recently used optogenetics to show that the coordinated silencing of Purkinje cells was sufficient to cause activation of DCN neurons and elicited discrete movements in the mouse [63]. Additionally, the application of a number of pharmacologic agents that alter the firing of cerebellar neurons can elicit abnormal dystonic-like movements in rodents [47, 52]. Therefore, there is good evidence that under experimental conditions, the cerebellum can be driven to cause abnormal movements similar to dystonia in many species.

Some of the first animal studies specifically linking the cerebellum to dystonia were done in the DT rat, a naturally occurring autosomal recessive mutation characterized by the development of a progressive axial and appendicular generalized dystonia [64, 65]. Surprisingly, early experiments demonstrated that cerebellectomy was sufficient to completely alleviate dystonia in these animals whereas interventions involving the basal ganglia showed no benefits. Further studies demonstrated that in DT rats, both cerebellar Purkinje cells and projection neurons within the deep cerebellar nuclei (DCN) exhibited erratic and abnormal burst firing. In fact, the extent of burst firing appeared to correlate with severity of the symptoms.

Interestingly, the DT rat is not the only animal model of dystonia in which abnormal burst firing of cerebellar neurons has been implicated. It was recently shown that in both genetic and pharmacologic models of rapid-onset dystonia parkinsonism (RDP), abnormal bursting cerebellar output underlies dystonia [43, 47, 66]. Studies have shown that acute knockdown or pharmacologic inhibition of the α3 isoform of the sodium pump, the protein mutated in human RDP, converts the normally regular activity of Purkinje cells to burst firing [43, 66]. This erratic Purkinje cell activity in turn modifies the activity of DCN neurons, resulting in highly irregular cerebellar output.

A role for cerebellum in dystonia has also been established in the tottering mice, a model of the human disorder episodic ataxia type 2 which, in some patients, is associated with dystonia in addition to ataxia [67, 68]. As noted in the prior section, studies on tottering have repeatedly implicated the cerebellum in the episodes of ataxia and dystonia [42, 45, 69], and pharmacologically normalizing the activity of

cerebellar neurons can alleviate dystonic symptoms in these animals [70, 71]. In addition to episodic attacks of dystonia/severe ataxia, tottering mice also exhibit a baseline ataxia which can also be improved by medications that normalize the activity of cerebellar neurons [42]. Therefore, it appears that ataxia may be caused by irregular cerebellar output similar to what is found in cerebellar dystonia. In fact, in the pharmacologic model of RDP, it was shown that infusing lower concentrations of ouabain to the cerebellum resulted in ataxia while higher concentrations caused dystonia [47]. These findings suggest that ataxia and dystonia may exist on a continuum where modest changes in the regularity of cerebellar output may underlie ataxia while highly irregular firing (erratic bursting) of cerebellar output neurons underlies dystonia. Irregularity of cerebellar output can be quantified as the coefficient of variation of the interspike intervals (CV ISI) recorded from deep cerebellar nuclei (DCN) neurons. Unpublished studies from our lab on a large number of mouse models of ataxia and dystonia suggest that this is indeed the case and that the severity of motor disability increases from ataxia to dystonia as the irregularity of cerebellar output neurons increases (Fig. 3). Taken together, these studies suggest that erratic bursting of cerebellar output neurons may be a common mechanism by which dystonia is induced and that the degree of spiking irregularity from the cerebellum may dictate whether animals present with ataxia or dystonia (Fig. 3).

A recent study has provided a possible mechanism by which erratic cerebellar output may lead to dystonia. Chen et al. (2014) found that there is a powerful di-synaptic pathway from the cerebellum to the striatum via the thalamus that enables the cerebellum to rapidly modulate the activity of the basal ganglia. Transmission of aberrant cerebellar output to the basal ganglia through this di-synaptic pathway was found to be necessary for cerebellar-induced dystonia and caused burst firing in the basal ganglia [35] similar to that seen in dystonic patients [72]. Selective disruption of this communication alleviated dystonic symptoms providing a potential therapeutic target for DBS [35, 47].

Overall, studies in rodents strongly suggest that highly erratic cerebellar output is likely a common substrate for a number of dystonias. Importantly, there is evidence from both imaging and lesion studies in patients that also suggest that abnormal cerebellar output is involved in some dystonic patients. Already, these findings have been making their way back to the clinic where deep brain stimulation of the cerebellum is again being considered for some dystonic patients. Further work addressing the prevalence of cerebellar dystonia and the presence of abnormal cerebellar output in patients with dystonia will be vital and will help guide more targeted treatment for patients with this devastating disorder.

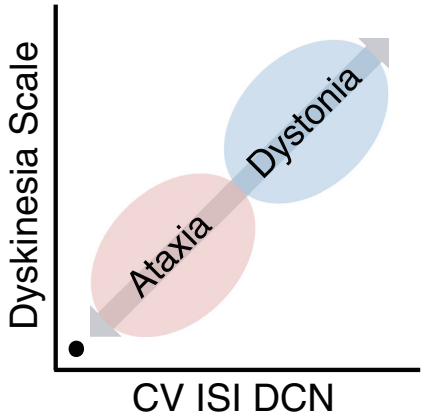

Fig. 3 Schematic of the proposed relationship between locomotor disability and irregularity of cerebellar output in mouse models. A proposed relationship between locomotor disability and irregularity of cerebellar output in mouse models described as having ataxia and/or dystonia. Here, locomotor disability is quantified based on a previously published dyskinesia scale that incorporates symptoms consistent with ataxia and dystonia. As the severity on the dyskinesia scale increases, the motor phenotype transitions from ataxia to dystonia. Irregularity of cerebellar output can be quantified as the coefficient of variation of the interspike intervals (CV ISI) recorded from deep cerebellar nuclei (DCN) neurons. This value takes into account both the standard deviation of the interspike intervals and the average firing rate of the cell. Under normal conditions, the dyskinesia score is low as is the CV ISI for DCN cells (*black dot*). We propose that there may be a monotonic relationship between disability and irregular cerebellar output such that as cerebellar output becomes more erratic, the disability of the animal increases (*gray line*). In this scenario, mice exhibiting only mildly irregular DCN output would have symptoms consistent with ataxia (*red oval*) while mice with more erratic bursting activity would have symptoms more consistent with dystonia (*blue oval*)

Relationship Between Cerebellar Neuronal Dysfunction in Animal Models and Human Dystonia (Mark S. LeDoux)

As noted in prior sections, isolated dystonia may be a network disorder of the CNS due to dysfunction at one or more nodes of the highly interconnected motor subsystem that includes the cerebellum and basal ganglia [3, 15]. Alternatively, dystonia may be driven by a single population of dysfunctional neurons and network alterations are simply downstream manifestations of aberrant efferent signals [64, 22]. Consensus regarding site of origin is lacking given that cerebellar cortex, striatum, and sensorimotor cortex have been proposed as loci of critical functional pathology [64, 73, 74].

To date, study of well-characterized genetic forms of dystonia has not provided convincing evidence in support of a cerebellar or basal ganglia origin of dystonia. Although a high percentage of DYT1 patients with the classic ΔGAG mutation in *TOR1A* respond to deep brain stimulation (DBS) of the internal segment of the globus pallidus (GPi), many patients with dystonia show little or no benefit from DBS [75–77]. Moreover, high-resolution metabolic maps of DYT1 dystonia in a transgenic mouse model suggest that the DYT1 carrier

state increases energy demand in the olivocerebellar network and the inferior olive may be a pivotal node for abnormal basal ganglia-cerebellar interactions [22]. Among the three main genetic causes of isolated dystonia (*TOR1A*, *THAP1*, and *GNAL*) [78–80], only *GNAL* shows relatively circumscribed transcription in the CNS with concentrated expression of its encoded protein Gα(olf) in the olfactory bulb, striatum, and cerebellar Purkinje cells [80–82]. Although modestly enriched in cerebellum, *TOR1A* and *THAP1* are broadly expressed throughout the brain [81, 82].

Functional imaging in humans with primary dystonia and clinical-pathological correlations in secondary dystonia have provided evidence that dystonia may be a disorder of olivocerebellar pathways [82, 83]. A critical role for the cerebellum in the pathophysiology of dystonia [84, 85] is supported by data from a variety of clinical fronts including the lesion localization in secondary dystonia [86, 87], the syndrome of dystonia with cerebellar atrophy (DYTCA) [59], the postmortem pathology in cervical dystonia [88], and the well-known finding that dystonia may be a presenting or prominent feature in several of the hereditary ataxias (SCA1, SCA2, SCA3, SCA6, etc.), although it should be noted that these are multisystemic diseases with degeneration that is not confined to the cerebellum.

Data from animal models also implicates olivocerebellar pathways, particularly Purkinje cells and cerebellar nuclear neurons, in the pathophysiology of dystonia [43, 66, 89]. For instance, morphologically/physiologically defective Purkinje cells or Purkinje cell loss has been described in tottering mice, DYT1 knock-in mice, waddles mice and dt rats [89–92]. In addition, virtually, all genes associated with dystonia in spontaneous mutants (*tottering*, *stargazer*, *ophisthotonus*, *ducky*, *lethargic*, *waddles*, and *wriggle*) are involved in Purkinje cell Ca^{2+} signaling (*Canca1a, Cacng2, Itpr1, Cacna2d2, Cacnb4*, and *Pmca2*). Moreover, the genetically dystonic rat, which exhibits a defect at the climbing fiber-Purkinje cell synapse, shows up-regulation of plasma membrane calcium-dependent ATPase 4 (PMCA4) in parallel fibers [93]. In humans, autosomal-recessive mutations in *HPCA* cause childhood-onset dystonia and the encoded protein, hippocalcin, is robustly expressed in Purkinje cells and serves as a Ca^{2+} sensor [94, 95].

As noted in prior sections, Raike and colleagues have shown that the manifestation of dystonia in response to stress, caffeine, and ethanol in *Canca1a* mutant *tottering* mice can be isolated to abnormal Purkinje cells [96]. At high concentrations, caffeine acts at ryanodine receptors (RyR) to facilitate the mobilization of calcium from intracellular stores. In tottering mice, intracerebellar injections of ryanodine prevented paroxysms of dystonia. Purkinje cell dysfunction can also be presynaptic in origin given that *quirky* mice, in which *Cacna1a* loss is limited to cerebellar granule cells, exhibit dystonia [97]. In final analysis, abnormal signaling in cerebellar cortex due to dysfunction of Purkinje cells or their afferents (parallel and/or climbing fibers) will manifest as abnormal firing patterns of cerebellar nuclear neurons [64, 89, 98]. Compatible with this model, abnormalities of cerebellar outflow have been reported in humans and animal models of primary or isolated dystonia [40, 43, 66, 74, 99].

What Do Studies of Cerebellar Metabolism and Connections in Humans Tell Us about a Role for the Cerebellum in Dystonia? (Christian Dresel, Martin Niethammer, and David Eidelberg)

Studies in human subjects with dystonia suggest a role for the cerebellum in this disorder. Here, we review metabolic changes in the cerebellum as well as structural and functional connections between the cerebellum and the rest of the central nervous system in patients with generalized and focal dystonia.

Cerebral Metabolism and Blood Flow

[^{18}F]-Fluorodeoxyglucose (FDG) PET studies have found increased glucose metabolism at rest in the cerebellum of patients with sporadic and genetic dystonias [58, 100–103]. Spatial covariance approaches based on principal component analysis identified a disease-specific pattern of regional metabolic activity, termed torsion dystonia-related pattern (TDRP) [104]. This pattern is characterized by relative metabolic increases in the putamen/globus pallidus, supplementary motor area, and cerebellum. Increased expression of TDRP appears unrelated to somatotopic distribution of clinical manifestations or penetrance in gene carriers of DYT1, though it should be noted that non-manifesting carriers of the DYT6 mutation do not exhibit such an increased expression pattern [105, 106].

Studies of blood flow changes with [^{15}O]-H_2O PET, which measures alterations in brain activity, have demonstrated abnormal activation in numerous brain regions in dystonia, including the cerebral cortex, basal ganglia, thalamus, and the cerebellum [107–110]. Moreover, non-manifesting DYT1 carriers showed compensatory cerebellar activation during motor sequence learning [109]. Abnormal activation of cerebellar structures has also been measured with functional magnetic resonance imaging (fMRI) using blood oxygenation level-dependent (BOLD) contrast in a number of focal dystonias [17].

Structural and Functional Cerebellar Connectivity

Using diffusion tensor imaging (DTI) and voxel-based morphometry, MRI demonstrated reduced fractional anisotropy (a marker of impaired axonal integrity) and decreased gray matter volume in the cerebellum of patients with generalized and

focal dystonia [111, 112]. Applying probabilistic tractography, Argyelan and colleagues identified genotype-specific fiber tract differences between manifesting and non-manifesting DYT1 and DYT6 mutation carriers [99]. Manifesting and non-manifesting carriers were found to have reduced integrity in their cerebellothalamic fiber tracts irrespective of clinical status, in line with earlier results in primary torsion dystonia [112]. Non-manifesting carriers had an additional connectivity abnormality in the thalamocortical segment of the cerebello-thalamo-cortical projections, suggesting a penetrance model in dystonia, whereby cerebellothalamic pathway disruptions lead to dystonia, unless counterbalanced by a second lesion downstream [99]. Indeed, these findings were supported by a genetic mouse model of DYT1 [40]. In a follow-up human study, DYT1 and DYT6 mutation carriers showed microstructural changes in the form of reduced fractional anisotropy in the paravermian cerebellar white matter [113]. When this area was used for subsequent DTI fiber tracking, patients with both inherited and sporadic forms of dystonia showed a 60–70 % reduction of white matter tracts passing through the thalamus to the leg representation in the primary sensorimotor cortex as compared to healthy subjects. Functionally, cerebellar pathway integrity is linked to motor activation responses. In manifesting and non-manifesting DYT1 and DYT6 carriers, reductions in cerebellothalamic connectivity correlated with reduced motor activation in the cerebellum and increased activation in cortical motor areas, consistent with loss of inhibition at the cortical level [99].

DYT1, but not DYT6 carriers, exhibited significant increases in motor sequence learning-related activation in the left lateral cerebellar cortex and in the right premotor and inferior parietal regions. In these DYT1 carriers, learning-induced increases in premotor cortical activation correlated with reductions in cerebellar pathway integrity [108]. Genotype-specific reductions in cerebellothalamic connectivity appeared to be smaller in carriers of the DYT6 relative to the DYT1 mutation [99]. We therefore hypothesized that the magnitude and spatial extent of this microstructural abnormality is greater in DYT1 carriers, perhaps accounting for learning deficits with this genotype, but not with the (clinically more localized) DYT6 mutation [105].

In this vein, affected DYT1 carriers were recently found to exhibit abnormal fMRI activation in response to the visual perception of motor [114]. In healthy individuals, the perceptual distinction between "natural" vs. "unnatural" motion is mediated through the right cerebellar, superior parietal, and temporo-occipital cortical association areas. However, the pattern of task-related activation was abnormal in the DYT1 subjects in association with microstructural changes involving ponto-cerebellar pathways. Subsequent preliminary work from our group has demonstrated analogous changes in affected DYT6 carriers and in individuals with sporadic dystonia. Irrespective of inherited trait or genotype, motion perception-related activation correlated with loss of microstructural integrity involving cerebellar outflow pathways.

The mechanistic basis underlying these changes is not clear. Using resting-state fMRI, Dresel et al. found increased negative functional connectivity (FC) between several seed regions-of-interest of the motor cerebellum (namely crus I and II) to primary and secondary cortical sensorimotor areas in patients with sporadic writer's cramp [115]. The (absolute) magnitude of FC was inversely correlated with duration and severity of disease. This finding was unexpected and raised the question if stronger cerebellocortical coupling in affected patients could be a compensatory mechanism as suggested by the studies of metabolism and motor learning. A decline of this increased FC might then be interpreted as progressive failure of such compensation in patients with longer or more severe disease.

In summary, imaging studies in human dystonia subjects have revealed changes in resting cerebellar metabolism, as well as reduced microstructural integrity and functional connectivity in cerebello-thalamo-cortical projection pathways. It is unclear whether these changes reflect underlying cerebellar pathology, a compensatory mechanism, or a combination of the two effects. Quantitative measures of structural connectivity suggest that hereditary dystonias may have a neurodevelopmental origin, whereby disruptions in cerebellothalamic fiber tracts lead to the development of symptoms unless associated with a second downstream lesion in thalamocortical pathways.

What Do fMRI and VBM Studies Tell Us about a Role for the Cerebellum in Dystonia? (Traian Popa, Cécile Gallea, and Stéphane Lehericy)

Imaging studies, whether structural using voxel-based morphometry (VBM) and diffusion imaging or functional using fMRI and PET, have repeatedly reported evidence of cerebellar abnormalities in human primary dystonia. Structural changes within the brain are present at various levels of the sensorimotor network. Using structural neuroimaging techniques, such as VBM and diffusion tensor imaging, grey matter increase or decrease and white matter changes were observed in primary dystonias in the sensorimotor, premotor, and parietal cortex, the basal ganglia, the thalamus, and the cerebellum. Cerebellar changes were reported in sporadic forms including non-task specific cervical dystonia and blepharospasm [116–118], task-specific laryngeal dystonia, and writer's cramp [118], as well as inherited forms [99, 119]. Using diffusion imaging, white matter changes were also observed in the cerebellum of sporadic dystonia [118]and the cerebello-thalamo-cortical fiber tract in DYT1-6 dystonia [99, 113]. Changes varied between studies and types of dystonia, and so far, it is not precisely known whether these

variations are due to the type of dystonia or to technical differences between studies. However, as noted in the previous section, changes in the cerebello-thalamic fiber tract may be common to patients with inherited and sporadic dystonias, whereas changes in the thalamo-cortical fiber tract may only be observed in non-manifesting carriers or in non-affected regions of patients with sporadic dystonia [113].

Functional MRI has shown changes that mirrored the structural changes at the level of the basal ganglia, the motor-related cortical regions as well as the cerebellum [118, 120]. In the cerebellum, abnormal activation during performance of various sensorimotor tasks has been reported using fMRI in blepharospasm [121–123] and writer's cramp [124, 125] and using $^{15}H_20$ PET in patients with DYT1 and DYT6 mutations [108]. Abnormal cerebellar involvement related to proprioceptive drift during the rubber hand illusion was also observed in focal hand dystonia [126]. In patients with focal hand dystonia, reduced interactions between the striato-cortical and cerebello-cortical networks have also been reported with reduced communication between the striatum and the cerebellum [125, 127].

Using fMRI at rest, a functional connectivity decrease is frequently found among many motor regions of patients with focal hand dystonia. This decrease was found between the parietal and dorsal premotor areas [128], in the left postcentral areas [129], and between the affected sensorimotor cortex and the basal ganglia and premotor cortex and prefrontal cortex, which correlated with disease severity [115]. In the cerebellum, a stronger negative functional connectivity of cerebellar structures to primary and secondary sensorimotor areas was found in some [115] but not all studies [128].

Imaging studies are limited in some ways because often they do not allow determining whether the observed structural changes are the cause or the consequence of the disease and because knowledge of the pathological correlates of imaging data is poor [130]. In spite of these limitations, imaging results provide overall converging evidence from structural and functional techniques that the cerebellum is implicated in the pathophysiology of various types of dystonia. They also suggest that not only nodes (i.e., brain regions) in the sensorimotor network but also communications between them are abnormal, in line with the view that dystonia is a network disorder. Indeed, the cerebellum and the basal ganglia are able to interact at various levels of the sensorimotor network as described above. In the cortex, physiological studies have shown that the cerebellum was able to dynamically modulate sensorimotor plasticity in healthy subjects by gating peripheral inputs [131]. This gating does not exist anymore in dystonic patients [132]. Impairment of the cerebellar outflow to the cortex is supported by neuroimaging studies of fiber integrity in dystonic patients [99, 105, 114]. Anatomically, the existence of a disynaptic connection between the basal ganglia and the cerebellum is another route where the two networks may interact [34, 133, 134]. It is possible that disturbance in any part of the cortico-striatal and cortico-cerebellar circuits would lead to functional imbalances and also trigger compensatory activity in the remaining circuits. Abnormal communication between the nodes would result in a lack of control of the motor output.

Changes in specific nodes and abnormal functional interactions between these nodes may contribute differently to the various forms of dystonia. In task-specific dystonia such as writer's cramp which is associated with intensive practice and overuse of a particular group of synergistic muscles, the loss of interaction between the cerebellar and striatal networks during learning [125, 127] might contribute to impaired information transfer and thus to the acquisition of an abnormal sensorimotor representations. In contrast, in genetic dystonia, cerebellar activation during motor sequence learning may be compensatory [108]. The cerebellum could play a role in sensory deficits in focal hand dystonia [135], as suggested by the abnormal cerebellar involvement reported during sensory processing in these patients [126]. This hypothesis is further supported by the fact that the cerebellum exerts powerful influences over the somatosensory system and receives direct somatosensory input from the spinal cord [136, 137]. Further studies will determine whether there is a pathophysiological substrate common to all forms of dystonias or whether changes in specific nodes and circuits, and abnormal functional interactions between these nodes contribute differently to the various forms of dystonia.

What Does Brain Structure in Human Dystonia Tell Us about a Role for the Cerebellum? (Amit Batla, Kailash P Bhatia)

We examine here, the clues from the understanding of brain structure and its abnormalities and what this tell us about a role for the cerebellum in human dystonia.

a. *Evidence from cerebellar changes observed in clinical practice and using clinical neuroimaging*

   i. *Cerebellar atrophy* with or without cerebellar signs has been recognized on routine neuroimaging in patients with dystonia [59, 86]. In one study, 9 % of patients with segmental and cervical dystonia were found to have cerebellar atrophy [138]. The spinocerebellar ataxias (SCA) are known to have structural atrophy and degeneration of the cerebellum. Dystonia may be a presenting clinical feature of SCA [138] with up to 9 % of SCA2 patients reported to have dystonia at presentation [139, 140]. SCA17,

SCA3, and other SCAs [141] are also commonly associated with dystonia . Two clinical case series [142, 143] have been reported under the rubric "the syndrome of (predominantly cervical) dystonia and cerebellar ataxia (DYTCA)" [142, 143].

ii. *Lesions of cerebellum in patients with dystonia.* Some case reports [144] and small series [86] have reported cerebellar lesions in patients with dystonia. More recently, a clinical study of 188 patients described clinically overt lesions of cerebellum in 5 % of cases with cervical/segmental dystonia [138].

The clinical association of dystonia with cerebellar lesions, atrophy, and inherited ataxias supports the role of cerebellum and its connections in a small proportion of patient with dystonia; however, such evidence needs to be interpreted carefully and causality cannot be assumed from these results [130].

b. *Evidence from structural changes observed using advanced neuroimaging*

As noted in the prior section, imaging in primary dystonia (DYT-1) using voxel-based morphometry (VBM) has demonstrated abnormalities in cerebellum and its connections with lenticular nucleus and supplementary motor area [117]. In cases with focal dystonia, VBM studies have shown structural grey matter abnormalities in the cerebellum in patients with upper limb dystonia [111], cervical dystonia [116, 117], and blepharospasm [117]. In cases with primary generalized dystonia, diffusion tensor imaging (DTI) has been used to study microstructural changes deduced through fractional anisotropy (FA) [112]. In DYT 11 patients and carriers, microstructural abnormalities have been demonstrated using DTI in the vicinity of cerebellar peduncles. Similarly in patients with DYT-1 and DYT-6 genetic mutations, diffusion tractography showed reduced connectivity of the cerebellum with the thalamus [99]. These changes are however not exclusive to the cerebellum but also affect the basal ganglia, thalamus, and frontal lobes [130]. Based on these observations, it has been suggested that loss of inhibition at the cortical level consistent with a loss of cerebellar inhibitory outflow may be present in patients with dystonia [99, 130].

c. *Evidence of structural involvement of cerebellum derived from neurophysiology*

Physiologically, dystonia has been suggested as a result of changes to defects in neural inhibitory processes, sensorimotor integration, or neural plasticity. The cerebellum and more specifically the connections between inferior olive and the deep cerebellar nuclei can be studied using eyeblink conditioning (EBC). Abnormalities in EBC have been shown in primary focal dystonia [145], but not in patients with DYT1 and DYT6 dystonia [15]. Patients with basal ganglia dysfunction such as Parkinson's disease are expected to have normal EBC [146]. Thus, abnormalities in this paradigm support the idea that other structures such as cerebellar nuclei may be involved.

d. *Directly observed structural abnormalities of the cerebellum on pathology.* Patchy loss of Purkinje cells, areas of focal gliosis, and torpedo bodies have been seen in the cerebellum in patients with cervical dystonia [88, 111]. A bilateral increase in the gray matter volume of cerebellar flocculus was seen in patients with cervical dystonia [116], and bilateral structural abnormalities in the sensorimotor territory of the cerebellum were observed in patients with focal hand dystonia [111]. In primary generalized dystonia, Purkinje cell loss has been seen in DYT1 patients [147]. Mild to moderate cell loss in dentate nucleus has been seen in a case with Meige's syndrome [148] but not in DYT6, and other cases with pure primary dystonia [149]. It is however interesting to note that TorsinA (the protein product affected in DYT 1 mutations) is widely distributed throughout the central nervous system in humans including cerebellar Purkinje cells and Dentate nucleus [149].

In summary, evidence supports that cerebellar atrophy, cerebellar degenerative disease, cerebellar lesions, and microstructural changes in cerebellum can be associated with dystonia. This is further confirmed by pathological studies demonstrating cerebellar changes in dystonia. Neurophysiological changes in dystonia support the role of a "network model" that accommodates neuropathological and neuroimaging evidence that dystonia may be associated with abnormalities in multiple brain regions including cerebellum [3]. From the current understanding, it seems plausible that dystonia may result from a disorder that affects the basal ganglia, cerebellum, or their connections through the thalamus or directly with the motor or premotor cortex. The evidence however needs to be examined critically, and although cerebellum may contribute significantly to the subcortical network abnormality leading to dystonia, causal association is far from established [130] and further studies are needed.

Noninvasive (Transcranial Magnetic (TMS) and Transcranial Direct Current (tDCS)) Stimulation Studies of the Cerebellum in Dystonia (Sabine Meunier and Mark Hallett)

Noninvasive modulation of cerebellar activity in humans can help understand a role for the cerebellum in motor control. Here, we examine what cerebellar stimulation studies tell us about a role for the cerebellum in dystonia.

Instantaneous Change: Dual Site Single Pulse TMS: the CBI Paradigm

In healthy subjects, a single TMS shock to the posterior cerebellum on one side inhibits the test MEP evoked by a single TMS shock to the contralateral primary motor cortex (M1). Inhibition occurs when the test shock follows the cerebellar shock by 5 to 7 ms [150]. The MEP inhibition is referred to as "cerebellar-brain-inhibition" (CBI). The cerebellar shock likely activates the Purkinje cells inducing an inhibition of the dentate nucleus and a de-facilitation of the excitatory dentato-thalamo-cortical pathway. CBI was decreased on both affected and non-affected side of patients with focal hand dystonia compared to healthy volunteers [151]. The bilateral distribution despite unilateral symptoms suggested a bilateral involvement of the cerebellar cortex and/or the efferent cerebellar pathways that maybe an endophenotype of the disease. This finding has not been replicated so far; the CBI was found normal in groups of cervical dystonia patients [152] and focal hand dystonia patients. In this latter group, despite normal mean CBI level, greater CBI was associated with worse hand function [56].

Enduring Change of Cerebellar Excitability

Plasticity-inducing protocols using TMS (1 Hz or theta burst rTMS) or tDCS can be used to induce lasting (in the range of the hour) changes of excitability of the cerebellar cortex.

Cerebellum Modulation of M1 Plasticity

In healthy subjects, excitation of the cerebellar cortex by intermittent theta burst rTMS (iTBS) prevents the development of a subsequent associative plasticity (induced by paired associative stimulation, PAS) in M1. Inhibition of the cerebellar cortex by continuous theta burst rTMS (cTBS) enhances subsequent M1 plasticity, along with spread to the motor representations of adjacent muscles in M1 [131]. Both anodal and cathodal tDCS to the cerebellum prevent the development of a concurrent PAS-induced plasticity in M1 [153]. Converging arguments indicate that modulation of associative cortical plasticity is not exerted through a direct effect on the cerebello-cortical output, but instead through local changes of cerebellar excitability that impact the cerebellar processing of afferent volleys involved in the PAS-induced effects [131, 153].

In patients with writer's cramp, iTBS and cTBS to the cerebellum both failed to influence the subsequent development of PAS-induced plasticity [132]. This suggests that the inability of the cerebellum to adequately process the incoming sensory afferent volleys may lead it to send an erroneous message to M1 and de facto causes a cerebellum-M1 functional decoupling. These group results have been questioned (1) as the high variability in the individual responses to PAS may cause an overlap between the plastic responses of patients and healthy volunteers and (2) because anodal cerebellar stimulation was found to retain its ability to reduce the PAS-induced plasticity in a sub group of writer's cramp patients selected for having significant plastic responses after PAS [154].

More studies with a detailed screening of the distribution of the PAS responses in the control and patient groups are needed to reach the conclusion that the lack of cerebellar control onto the development of sensorimotor plasticity in M1 is a physiological hallmark of dystonia.

Cerebellar Modulation of Motor Adaptation Tasks

At the behavioral level, the use of cerebellar stimulation has confirmed that the cerebellum plays a role in the abnormal sensorimotor adaptation documented in dystonia [145, 155]. The capacity for online adjustment to a visuo-motor conflict (that involves the cerebellum) and the capacity for washing out an earlier adaptation were predictors of the extent of cerebellum-induced changes of M1 plasticity, but not of the extent of the plastic responsiveness of M1 by itself [132].

Acquisition of eye blink classical conditioning (EBCC), a cerebellar-dependent form of associative motor learning that depends on the integrity of the olivo-cerbellar circuit, was impaired in patients with writer's cramp or cervical dystonia [145]. Cerebellar cTBS normalized the EBCC in patients with cervical dystonia [156] while it disrupted it in healthy volunteers [157].

The results of the behavioral and EBCC studies confirm that abnormal encoding of motor memories in dystonia relies on phenomena occurring upstream from M1, likely, at least in part, in the cerebellum. They also raise the possibility that disruption of the cerebellum in dystonia may be reversible.

Therapeutics of Focal Dystonia by Cerebellum Stimulation

A blind randomized controlled study has shown a modest beneficial effect of 2 weeks sessions of cTBS to cerebellum in cervical dystonia patients [152]. Indeed, 2 weeks of stimulation led to a transient (less than 2 weeks) decrease of 15 % of the TWSTRS scale. This clinical effect was paralleled by neurophysiological effects including effects on the PAS-induced plasticity and the CBI that both showed a trend to be back to the normal pattern as observed in controls.

One session of cTBS to cerebellum failed to improve the writing performances of writer's cramp patients [158]. One session of anodal tDCS was reported to improve the kinematics of handwriting (reduced mean stroke frequency and average pen pressure and increased writing speed) in 8 people with focal hand dystonia [56] while there was no effect on the WCRS and investigator or self-rated assessment of handwriting speed [154]. No study so far has looked at the effects of

repeated sessions of TBS to cerebellum in focal hand dystonia.

Taken together, the data showing various abnormalities in different types of dystonia in response to various paradigms involving the cerebellum are strong. Moreover, the possible improvement in dystonic symptoms with cerebellar modulation raises a possible new approach to therapy of these patients.

Consensus Summary

Rodent Studies

- Abnormal motor activity resembling human dystonia can be produced in rodents.
- In many rodent models, dystonia results from abnormalities in cerebellar cortical activity and subsequent abnormalities in cerebellar output.
- In rodent dystonia models, an alteration in cerebellar output correlates with abnormal and sustained muscle contraction.
- Eliminating cerebellar output abolishes the generalized dystonia in some rodent models of dystonia, suggesting that the cerebellum is a critical node in the pathway leading to the expression of dystonia.

Human Studies

- Healthy human subjects exhibit the phenomenon of "cerebellar-brain-inhibition" (CBI) in response to TMS shock to the posterior cerebellum. Excitation of the cerebellar cortex by iTBS prevents the development of a subsequent associative plasticity in the motor cortex, while inhibition of the cerebellar cortex by continuous theta burst cTBS enhances subsequent motor cortex plasticity. These data suggest that under these conditions, the cerebellum is capable of directly modulating motor activity. These physiological mechanisms appear to be abnormal in patients with dystonia revealing cerebellar abnormality in the pathophysiology.
- In subjects with some forms of dystonia acquisition of eye blink classical conditioning (EBCC), a cerebellar-cortex dependent form of associative motor learning is impaired.
- Diffusion tensor imaging (DTI) and voxel-based morphometry demonstrate reduced fractional anisotropy (a marker of impaired axonal integrity) and decreased gray matter volume in the cerebellum of some patients with generalized and focal dystonia.
- In subjects with some inherited forms of generalized dystonia, manifesting and non-manifesting carriers have reduced fiber tract integrity in their cerebellothalamic tract as assessed by DTI. Non-manifesting carriers had an additional abnormality in thalamocortical connectivity.
- In some studies, using fMRI, increased resting state functional connectivity was found between the cerebellum and sensorimotor areas.
- PET imaging demonstrates abnormal cerebellar activity and metabolism in several different forms of dystonia.
- Structural defects of the cerebellum including atrophy, and lesions are associated with dystonia.

Consensus Opinions for Future Research

- Abnormal cerebellar activity in rodents causes sustained muscle contractions producing maintained postures similar to human dystonia.
- The cerebellum can act as a primary node for the causation of dystonia in rodent models.
- Data from human studies demonstrate an association between cerebellar abnormalities and dystonia. However, it is not yet clear whether the role of the cerebellum is causal, contributory, or compensatory.
- Future studies should be designed to differentiate a primary causal role for the cerebellum in dystonia from compensatory and contributory effects. Studies needed to prove causation of the cerebellum in dystonia in humans will likely be difficult.
- The identification of the cerebellum as a potential node in dystonia is important in order to determine whether interventions directed towards the cerebellum may be a treatment modality for dystonia. Future studies continuing to explore the role for the cerebellum in dystonia are therefore important.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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