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Tremor and Other Hyperkinetic Movements

Reviews

The Anatomical Basis for Dystonia: The Motor Network Model

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Abstract

Background: The dystonias include a clinically and etiologically very diverse group of disorders. There are both degenerative and non-degenerative subtypes resulting from genetic or acquired causes. Traditionally, all dystonias have been viewed as disorders of the basal ganglia. However, there has been increasing appreciation for involvement of other brain regions including the cerebellum, thalamus, midbrain, and cortex. Much of the early evidence for these other brain regions has come from studies of animals, but multiple recent studies have been done with humans, in an effort to confirm or refute involvement of these other regions. The purpose of this article is to review the new evidence from animals and humans regarding the motor network model, and to address the issues important to translational neuroscience.

Methods: The English literature was reviewed for articles relating to the neuroanatomical basis for various types of dystonia in both animals and humans.

Results: There is evidence from both animals and humans that multiple brain regions play an important role in various types of dystonia. The most direct evidence for specific brain regions comes from animal studies using pharmacological, lesion, or genetic methods. In these studies, experimental manipulations of specific brain regions provide direct evidence for involvement of the basal ganglia, cerebellum, thalamus and other regions. Additional evidence also comes from human studies using neuropathological, neuroimaging, non-invasive brain stimulation, and surgical interventions. In these studies, the evidence is less conclusive, because discriminating the regions that cause dystonia from those that reflect secondary responses to abnormal movements is more challenging.

Discussion: Overall, the evidence from both animals and humans suggests that different regions may play important roles in different subtypes of dystonia. The evidence so far provides strong support for the motor network model. There are obvious challenges, but also advantages, of attempting to translate knowledge gained from animals into a more complete understanding of human dystonia and novel therapeutic strategies.

Keywords: Dystonia, cervical dystonia, torticollis, blepharospasm, focal hand dystonia, laryngeal dystonia, spasmodic dysphonia, neuroanatomy, neuroimaging

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Introduction

The dystonias include a group of disorders with diverse clinical manifestations.[1] They may first emerge in infants, or in older adults. They may affect virtually any region of the body, alone or in various combinations. Their evolution over time also varies, with subtypes that are acute onset and static, others that are slowly progressive, and some that progress in stepwise fashion or appear episodic. Etiologically, the dystonias are also quite diverse.[2,3] Genetic and acquired causes are recognized, but many cases are idiopathic. Some subtypes are associated with static focal lesions of the brain, others show degenerative changes, and many have no apparent brain pathology. This clinical and etiological heterogeneity is important when considering their biological underpinnings.

Although the dystonias are grouped together on the basis of their motor manifestations, pathogenesis may differ among the subtypes. For example, it is likely that the biological processes responsible for

causing early-onset childhood generalized dystonias differ from those that cause late-onset focal dystonias. Clear differences in pathogenesis have been identified among certain early-onset dystonias,[4] late-onset focal dystonias,[5] and inherited versus acquired dystonias.[6] The similarities and differences in the pathogenesis of different subtypes of dystonia are important when considering the development of new therapies.[7,8]

Traditionally, the dystonias were viewed as disorders of the basal ganglia, but there has been increasing appreciation for involvement of other brain regions. Considering the etiological heterogeneity, the involvement of different brain regions is not surprising. The evidence suggesting involvement of different regions was first summarized in a comprehensive review in 2011 that encompassed the historical context, basic neuroanatomy, clinical observations, and experimental results from animals and humans.[9] Collectively, the evidence suggested a motor network model in which different types of dystonia might be caused by defects in different brain regions. Since then, numerous additional studies evaluating the motor network model have been published, along with multiple reviews and commentaries.[10–17]

The purpose of the current review is to summarize some of the more recent evidence regarding the neuroanatomical basis for the dystonias. Additional evidence from animal studies has now provided unequivocal evidence that the basal ganglia or cerebellum can independently play a causal role for specific types of dystonia. Additional evidence has been obtained from human studies also, but a causal role for specific brain regions has been more challenging to establish. A major reason for the limitations of the human studies is that studies required to prove causation usually cannot be conducted. This review addresses the challenge of translating results from basic sciences involving animal studies into a more complete understanding of human dystonia, and to consider how this translation might impact therapeutic strategies.

Methods

The PubMed database was reviewed to find English language articles relevant to the neuroanatomical basis for dystonia. Various terms commonly used to describe dystonia (dystonic, torticollis, blepharospasm, Meige, writer's cramp) were combined with anatomical terms (basal ganglia, putamen, caudate, globus pallidus, pallidum, cerebellum, dentate, thalamus, cortex, midbrain, brainstem, magnetic resonance imaging [MRI], pathology, histopathology). The citations provided in these articles were also reviewed. More than 200 articles were reviewed. Because a comprehensive review of this topic has been published,[9] the emphasis here was on the more recent articles, and especially those that addressed the neuroanatomical basis.

The anatomical basis for dystonia: evidence from rodents

Historical perspective. Animal studies have provided the most direct evidence regarding specific brain regions responsible for dystonia. The earliest studies were summarized previously,[9] and those that are most relevant to neuroanatomical localization are listed in Table 1. For example, a role for the basal ganglia has been established by showing that selective lesions of the striatum with the neurotoxin 3-nitropropionic acid can cause dystonia in rodents.[18,19] A role for the cerebellum has been established by genetic models of dystonia such as the *dt* rat[20,21] or the *tottering* mouse,[22,23] and by pharmacological studies showing activation of cerebellar glutamate receptors can cause dystonia in normal mice.[24] Other animal studies have pointed to abnormal interactions among different motor control centers.[25,26]

Since then, additional studies have provided further evidence that dystonia may arise from selective dysfunction of the basal ganglia or cerebellum, or combined dysfunction of multiple regions. These new studies are divided below into pharmacological and genetic models, focusing on those that are most directly relevant to anatomical localization.

Pharmacological rodent models. Animal models that involve microinjection of specific drugs into selected brain regions are valuable because they can pinpoint neurochemical processes in specific brain regions that may be responsible for their effect.[27] Because the basal ganglia are accepted as a source for dystonia, most of the newer studies have focused on other regions. Early studies showing that direct pharmacological activation of cerebellar glutamate receptors can cause dystonia in mice[24] have now been replicated by independent laboratories.[28–30] The phenomenon appears to be partly topographically organized, such that injection of glutamate agonists into the cerebellar midline cause axial dystonia, while injections into the hemispheres are more likely to cause limb dystonia. The effect is mediated by sustained activation of the α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) subtype of glutamate receptors in the cerebellum and does not appear to require the basal ganglia.[25]

Another study showed that silencing olivocerebellar glutamatergic synapses via genetic methods can cause dystonia in mice.[31] In this model, dystonia is associated with abnormal physiological activity of cerebellar Purkinje neurons and their target neurons in the deep cerebellar nuclei. Deep brain stimulation (DBS) directed to the deep cerebellar nuclei blocks dystonia, providing strong evidence for involvement of cerebellar pathways in this model.

Other studies have used a pharmacological approach to model rapid-onset dystonia–parkinsonism, which in humans is caused by mutations in the sodium–potassium pump encoded by the *ATP1A3* gene (DYT12). This pump is widely expressed in the brain, but pharmacological inhibition with ouabain injections directly into the cerebellum can cause dystonia in normal mice.[32] This effect results from the drug's ability to induce abnormally persistent high-frequency burst-firing of cerebellar Purkinje neurons.[33] Dystonic movements are thought to arise because the abnormal output from these cerebellar Purkinje neurons disrupts signaling in the basal ganglia.[34] In a related study, dystonia also emerged after knocking down expression of the same pump directly in the cerebellum with short hairpin RNAs.[35] This model supports a mechanism in which a defect beginning in the cerebellum can produce dystonia by disrupting the function of the basal ganglia.

Genetic rodent models. Genetic rodent models are attractive because they can provide information on the functions of a gene associated with dystonia in humans.[36] One recently described model is a

Table 1. **Rodent Models with Dystonic Motor Phenotype**

Genetic models	**Gene**	**Gene Product**	**Phenotype**	**Biological Basis for Dystonia**
Tottering mouse	*Cacna1a*	α1a subunit of P/Q-type calcium channel	Paroxysmal generalized dystonia with mild ataxia	Abnormal cerebellar Purkinje neuron activity
Leaner mouse	*Cacna1a*	α1a subunit of P/Q-type calcium channel	Severe generalized dystonia and ataxia	Abnormal cerebellar Purkinje neuron activity and degeneration
dt rat	*Atcay*	Caytaxin	Severe generalized dystonia	Abnormal cerebellar Purkinje neuron activity
DRD mouse	*TH*	Tyrosine hydroxylase	Diurnal dystonia	Reduced striatal dopamine
Gunn rat	*Ugt1A1*	Uridine diphosphate glucuronyltransferase	Bilirubin encephalopathy (kernicterus) with dystonia	Abnormal striatal neuron activity
Ip3r1 mouse	*Ip3r1*	Inositol trisphosphate receptor	Severe generalized dystonia	Abnormal cerebellar Purkinje neuron activity
Pharmacological models	**Pharmacological agent (s)**	**Mode of Induction**	**Phenotype**	**CNS Alterations**
Blepharospasm rat	6-OHDA	Lesion of nigral neurons combined with partial injury of the facial nerve	Sustained partial eyelid closure with increased blink rate	Abnormal basal ganglia function
Rapid-onset dystonia parkinsonism mouse	Oubain	Inhibition of cerebellar sodium/potassium pump by local microinjection	Generalized dystonia	Abnormal cerebellar Purkinje neuron activity
Cerebellar glutamate receptor activation (mouse or rat)	Kainic acid or AMPA agonists	Activation of cerebellar glutamate receptors by local microinjection	Generalized dystonia	Abnormal cerebellar Purkinje neuron activity
Levodopa-induced dyskinesia (mouse or rat)	6-OHDA Levodopa	Levodopa-induced dyskinesias following nigral neuron lesion	Trunk and limb dystonia	Abnormal striatal neuron activity
3-nitroproionic acid lesions (mouse or rat)	3-Nitroproionic acid	Lesions of striatum by local or systemic injections	Trunk and limb dystonia	Abnormal striatal neuron activity
sigma receptor ligand rat	1,3-di-o-Tolylguanidine	Microinjection into the red nucleus	Generalized dystonia	Abnormal rubral neuron activity

This table selectively includes rodent models where the anatomical origin of dystonia has been well studied. It does not include many models where the anatomical source for dystonia has not been clearly established, or genetic models with no apparent dystonic motor phenotype.
Abbreviations: 6-OHDA, 6-Hydroxydopamine; AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid.

genetically engineered mouse for dopa-responsive dystonia.[37] In this model, a point mutation affecting tyrosine hydroxylase that causes dopa-responsive dystonia in humans was introduced into mice. In mice carrying this mutation, the mutation caused a diurnal pattern of abnormal movements with clinical and electrophysiological hallmarks of human dystonia. The abnormal movements could be reduced with either peripheral or direct intrastriatal administration of levodopa, directly implicating basal ganglia dopamine signaling.

The Gunn rat model of kernicterus also displays early-onset generalized dystonia that has been linked with dysfunction of the basal

ganglia.[38] In this model, electrophysiological recordings have revealed abnormal output from the basal ganglia, and focal lesions of the basal ganglia cause dystonic movements.

Other genetic models have implicated the cerebellum. The *CACNA1A* gene encodes a calcium channel that is widely expressed in the human brain and associated with numerous different clinical phenotypes including episodic or progressive ataxia, migraine with or without hemiplegia, epilepsy, dystonia, and others.[39] Several mouse mutants harbor different mutations in the same gene, and they have equally varied phenotypes. Different mutations cause paroxysmal dystonia in the *tottering* and *rocker* mutants,[23,40] or generalized dystonia in *leaner*, *wobbly*, and knockout mutants.[41,42] In the *tottering* mutants, selective expression of the mutant gene in only Purkinje neurons is sufficient to cause paroxysmal dystonia. The severity of dystonia is related to the percentage of abnormal Purkinje neurons. In the *leaner* mutants, age-related degeneration of Purkinje cells is accompanied by transformation of a dystonic phenotype into an ataxic phenotype. Additionally, mutations of the *Ip3r1* gene that disrupt intracellular calcium signaling are also associated with dystonia that originates from the cerebellum.[43] The results from these studies imply that dystonia results from abnormal signaling by cerebellar Purkinje neurons, not loss of these neurons.

One of the best-studied genetic animal models is based on the *TOR1A* gene that is responsible for DYT1 dystonia in humans. Although the brain appears grossly normal in the majority of the transgenic and knock-in mice, careful histological studies have revealed microstructural defects in both the striatum[44] and the cerebellum.[45–47] MRI studies have similarly implied microstructural defects in both areas.[48–50] Physiological studies have revealed functional abnormalities in striatal cholinergic neuron signaling,[51–57] and neurochemical studies have revealed striking defects in striatal dopamine release.[58–61] On the other hand, metabolic studies implicate prominent functional disturbances of cerebellar pathways,[62] and conditional knockout of the *TOR1A* gene revealed relatively selective degeneration of cerebellar pathways.[63] The hippocampus also appears to be abnormal.[64,65] Because the anatomical and functional studies of the DYT1 models have revealed abnormalities in multiple brain regions, it has been challenging to know which areas might be most responsible for causing dystonia. However, one study showed that regional knockdown of the *Tor1a* gene only in the cerebellum, but not in the basal ganglia, was sufficient to cause dystonic movements.[66]

Summary of recent animal studies. Some of the recent animal studies imply that dystonia arises from selective dysfunction of the basal ganglia (e.g., the genetic model for dopa-responsive dystonia or the Gunn rat model of kernicterus). Other animal models imply that dystonia arises from dysfunction of the cerebellum (e.g., models involving *Ip3r1* mutations or pharmacologic or genetic manipulations of cerebellar circuits). Some models imply abnormal interactions among the basal ganglia and cerebellum (e.g., models of rapid-onset dystonia–parkinsonism). Together, the results suggest different underlying anatomical substrates may be responsible for different types of dystonia in animals.

The anatomical basis for dystonia: evidence from non-human primates

Although dystonia also has been described in non-human primates, published studies are less abundant than those for rodents due to the technical challenges and costs associated with primate studies.[67] Several early studies revealed that toxic lesions[68,69] or local pharmacological manipulations of the putamen or its connections[70,71] could induce dystonia in normal primates. To date, there are no publications describing dystonia following manipulations of the cerebellum in primates.

However, several studies have implicated other brain regions. For example, one study described abnormal head movements resembling human cervical dystonia following manipulations of the superior colliculus in macaques.[72] In another series of studies, abnormal head movements resembling human cervical dystonia were induced following selective manipulations of the midbrain interstitial nucleus of Cajal in macaques.[73–76] This region is interconnected with both the basal ganglia and the cerebellum, placing it at a location where it can interface with both regions.[16] Interestingly, the interstitial nucleus of Cajal is the same region that served as a target for stereotactic surgical treatments for cervical dystonia more than 30 years ago.[77]

The anatomical basis for dystonia: evidence from humans

Historical perspective and lesion studies. Historically, dystonia was viewed as a psychiatric disorder. An organic basis was not widely accepted until the publication of a series of papers linking it with focal lesions of the nervous system, particularly the basal ganglia.[78] Subsequent studies described focal lesions in many regions of the nervous system. A summary of individual case reports can be found in prior reviews,[9,17] and the largest series are summarized in Table 2. The earliest of these series focused on hemidystonia.[79,80] In hemidystonia, the majority of lesions affected the basal ganglia, and particularly the putamen. Since then, multiple other studies have addressed cervical dystonia,[81] craniofacial dystonia,[82] limb dystonia,[83] and series with mixed populations.[84,85] A summary these studies indicates that the basal ganglia are not the only regions to be affected (Table 2). The thalamus, cerebral cortex, cerebellum, and brainstem are frequently involved in other types of dystonia.

Although studies of focal lesions have traditionally played a very important role in clinical neurology, a well-known limitation is that it is very difficult to prove a causal relationship between the lesion and the clinical disorder. Another caveat is that the earliest studies from the 1980s relied mostly on CT, which has poor sensitivity for small lesions (e.g. thalamus) and those in the posterior fossa (e.g. cerebellum and brainstem). As a result, the early studies likely underestimated the contributions from certain types of lesions in some regions.

Modern imaging studies. In routine clinical imaging studies, the vast majority of patients with dystonia lack overt lesions. However, experimental imaging methods involving positron emission tomography or MRI have revealed subtle quantitative abnormalities for many types of dystonia. Multiple MRI-based studies have been reported

Table 2. **Focal Lesion Studies in Dystonia**

Type of Dystonia	Study	Source of Cases		Focal lesions					
		Literature Review	Chart Review	Basal Ganglia	Cortex	Thalamus	Brainstem	Cerebellum	Other
Hemidystonia	Marsden et al.[79]	13	28	45	1	7	0	0	Internal capsule=13
Hemidystonia	Pettigrew et al.[80]	0	22	11	0	1	0	0	Internal capsule=1
Mixed	Obeso and Gimenez-Roldan[85]	32	39	68	8	16	1	6	0
Cervical	LeDoux and Brady[81]	21	4	6	0	0	0	11	Spinal cord=6
Mixed	Strader et al.[84]	0	16	4	12	1	0	0	0
Blepharospasm	Khooshnoodi et al.[82]	30	18	9	1	12	11	9	Midbrain=7
Upper limb	Liuzzi et al.[83]	72	4	17	4	39	4	1	Spinal cord=7

This table lists the locations of brain lesions in series of cases with presumed secondary dystonia. Because some cases had lesions that overlapped more than one region, the numbers of lesions may differ from the total number of cases. In cases where lesions overlapped regions, the reports sometimes listed the regions separately and sometimes combined. Several studies included a literature review, so some cases may be reported more than once.

including voxel-based morphometry (VBM), diffusion tensor imaging (DTI), resting state (rsMRI), or functional MRI (fMRI). These imaging studies have been reviewed several times,[9,13,86,87] including one meta-analysis for VBM.[88] Several conclusions have emerged. First, abnormalities can be detected in multiple brain regions including the basal ganglia, cerebellum, cortex, and others. Second, connectivity between these regions is often abnormal. Third, the regions affected across these studies are similar, but not always consistent. Fourth, it is challenging to discriminate regions that cause dystonia from regions that may show secondary changes.

To illustrate these points, the results from VBM are summarized in Table 3. This method has revealed abnormalities in several brain regions. However, the results are not consistent across studies, even when evaluated according to different types of dystonia. For example, the sub-regions affected within the basal ganglia or the cerebellum are not always the same. In some cases, the direction of changes (increased or decreased volume) is different even within the same brain region. The reasons for these discrepancies are not clear, but they may reflect different patient populations studied, different procedures for data acquisition, or different methods for data analysis. Whatever the reasons, the inconsistencies have led to concerns regarding the generalizability of conclusions from individual studies, especially those with relatively small numbers of cases.

Another challenge has been the discrimination of brain abnormalities that cause dystonia from those that are compensatory or a consequence of dystonia. Even for normal individuals, suppression of movements (e.g., immobilization restraint) or augmentation of movements (e.g., training) both alter brain microstructure, and the changes can be measured via VBM.[89,90] For example, professional musicians and golfers both have subtle changes in regional brain volumes that can be detected via VBM.[91,92] In addition, brain abnormalities reported for dystonia change dynamically following botulinum toxin treatment.[93–96] One study revealed significant abnormalities by fMRI among patients with psychogenic dystonia.[97] Taken together, these studies imply that at least some of the abnormalities detected via these methods are a consequence of dystonia, not a cause for it.

Overall, the human imaging studies are provocative because they reveal changes in the brains of patients with dystonia. The results can be interpreted in support of the concept that dystonia is a network disorder, because they have revealed changes in several nodes of the network, or in the functional connectivity between the nodes. However, the results do not provide conclusive evidence for a causal role for any specific brain region because it is impossible to establish whether the changes reflect a cause or consequence of abnormal movements.

Behavioral studies. The motor network model has also stimulated multiple behavioral studies of dystonia. These studies are driven by the concept of association; if dystonia results from abnormalities of the basal ganglia or cerebellum, then it should be possible to find other evidence that these regions are abnormal. For example, dystonia and parkinsonism frequently occur together. Dystonia in Parkinson's disease may be a presenting feature, a late feature, or a complication

Table 3. **Voxel-based Morphometry Studies of Dystonia**

Type of Dystonia	Study	Cases/Controls	Regions Affected			
			BG	CRB	CTX	Other
BSP	Etgen et al.[148]	16/16	Put (↑)		IPL (↓)	
BSP	Obermann et al.[149]	11/14	Caud (↑) Put (↓)	Hem (↑)		Thal (↓)
BSP	Martino et al.[150]	25/24			PreF (↑) SMC (↓) STL (↓)	
BSP	Suzuki et al.[151]	32/48			SMC (↑) Cing (↑)	
CCD	Piccinin et al.[152]	35/35		Verm (↑) Hem (↓)		
CCD	Piccinin et al.[153]	27/54		Verm (↓) Hem (↓)	IPD (↓) OCC (↓) PMC (↓) SMA (↓) SMC (↓)	HPC (↓)
CD	Draganski et al.[154]	10/10	GP (↑)	Floc (↑)	PM (↑) SMA (↓) DLPFC (↓) OCC (↓)	
CD	Egger et al.[155]	11/31				
CD	Obermann et al.[149]	9/14	Caud (↑) Put (↓)	Hem (↑)	STL (↑)	Thal (↑)
CD	Draganski et al.[156]	29/28	Put (↑) GP (↑)			
CD	Pantano et al.[157]	19/28	Caud (↓) Put (↓)		PM (↓) SMC (↓)	
CD	Prell et al.[158]	24/24	GP/Put (↑)		PM (↓) SMA (↓) SMC (↓) PreF (↑) OCC (↑)	

Table 3. Continued

Type of Dystonia	Study	Cases/Controls	Regions Affected			
			BG	CRB	CTX	Other
CD	Bono et al.[159]	19/25			PM (↓)	
					PMC (↓)	
CD	Waugh et al.[160]	17/17				
CD	Filip et al.[161]	25/25		Verm (↑)	PMC (↑)	
				Hem (↑)		
DYT1	Draganski et al.[156]	11/11	Put (↓)			
FHD	Garraux et al.[162]	36/36			SMC (↑)	
FHD	Egger et al.[155]	11/31	GP (↑)			
FHD	Delmaire et al.[163]	30/30		Hem (↓)	SMC (↓)	Thal (↓)
FHD	Granert et al.[89]	14/14			PM (↑)	
FHD	Granert et al.[164]	11/12	Put (↑)			
FHD	Zeuner et al.[165]	22/28	GP (↑)			
			Put (↑)			
GEN	Egger et al.[155]	9/31	GP (↑)			
LD	Simonyan et al.[166]	40/40	Put (↑)	Hem (↑)	SMC (↑)	
					PreF (↑)	
LD	Waugh et al.[160]	7/7				

Arrows show increased (↑) or decreased (↓) volumes. Studies involving multiple types of dystonia are separated according to type of dystonia rather than as a mixed group.
Abbreviations: Caud, Caudate; CCD, Craniocervical Dystonia (a mixed population of cranial dystonia, cervical dystonia and both combined); Cing, Cingulate Gyrus; DLPFC, Dorsolateral Prefrontal Cortex; Floc, Cerebellar Flocculus; GEN, Generalized Dystonia; GP, Globus Pallidus; Hem, Cerebellar Hemisphere; HPC, Hippocampus; IPL, Inferior Parietal Lobule; Pref, Prefrontal Cortex; NA, Nucleus Accumbens; OFC, Orbitofrontal Cortex; OCC, Occipital Cortex; PM, Primary Motor Cortex; Put, Putamen; SMC, Sensorimotor Cortex; STL, Superior Temporal Lobe; SMA, Supplementary Motor Area.

of levodopa treatment.[98–100] Dystonia and parkinsonism are also combined in a number of inherited disorders associated with damage or dysfunction of the basal ganglia including dopa-responsive dystonia, neurodegeneration with brain iron accumulation, Wilson's disease, and others.[2,101] These clinical observations highlight connections between dystonia and the basal ganglia dysfunction.

Dystonia also frequently occurs in association with disorders of the cerebellum. It can be a presenting feature, the only feature, or the predominant feature for several of the spinocerebellar ataxias[9,102] and several other inherited disorders that primarily affect the cerebellum.[2,103] Although most patients with idiopathic adult-onset dystonia do not have overt ataxia,[14] many have a tremor that resembles essential tremor,[104,105] which has been linked with dysfunction of cerebellar circuits. In a recent retrospective review of 188 patients with cervical dystonia, 26 had abnormalities of the cerebellum on routine clinical imaging studies, and 10 were thought to have had cerebellar signs on examination.[106] Quantitative studies of the gait have also revealed subclinical problems with balance and stepping.[107,108] These clinical observations highlight connections between dystonia and the cerebellar dysfunction.

Collectively, these observations are useful because they show that various types of dystonia may be linked with additional clinical features typically associated with the basal ganglia or cerebellum. However, they do not provide causal evidence regarding anatomical localization of dystonia.

Other experimental paradigms have been explored to reveal abnormalities of brain regions associated with various subtypes of dystonia.

Because the contributions of the basal ganglia in dystonia have been accepted for many years, most of the recent studies have focused instead on the cerebellum. One paradigm is the classical conditioned eye blink reflex, which is dependent on cerebellar circuits.[109,110] In this paradigm, an apparatus is used to deliver a gentle puff of air to the cornea to stimulate an eye blink. If the puff is repeatedly preceded by a sound, normal people begin to blink following the sound, even with no air puff. This reflex is abnormal among patients with adult-onset cervical or limb dystonia,[111,112] a phenomenon that may be predicted by co-existing tremor.[113] This reflex is also abnormal in patients with isolated segmental dystonia or DYT11 dystonia.[6,114] It is not abnormal among those with DYT1 or DYT6 dystonia, or dystonia acquired from brain injury.[6,115,116]

The cerebellum also plays a key role in other forms of motor adaptation (motor learning). Tasks that involve adaptation of saccades are abnormal in patients with DYT11,[114] but not adult-onset cervical dystonia.[117] Adaptation of hand tasks is abnormal in patients with writer's cramp,[118] but not cervical dystonia.[117,119] Tasks that require adaptation of the gait are abnormal in blepharospasm and hand dystonia, but not cervical dystonia.[120]

These behavioral studies are provocative because they imply that cerebellum-dependent motor learning may be abnormal in some types of dystonia but not others. Some investigators have interpreted the results in support of the concept that cerebellar dysfunction contributes to dystonia. Others favor the interpretation that these "cerebellar" abnormalities reflect indirect consequences of basal ganglia dysfunction. All of these studies must be interpreted with caution, because results vary according to subtype of dystonia and task, and most were conducted with very small numbers of cases. It is not feasible to extrapolate findings from one task in one type of dystonia to make generalizations regarding all types of dystonia, because the underlying anatomical mechanisms may be different for different subtypes of dystonia.[6] A more important limitation is that these types of studies are based on the concept of "guilt by association" and do not provide unequivocal evidence for a causal role for any brain region in dystonia.

Interventional studies. In principle, interventional studies have greater potential for establishing causal links between specific brain regions and dystonia. Observations that pallidotomy or DBS of the internal segmental of the globus pallidus (GPi) are effective in treating many forms of dystonia have been cited as evidence for involvement of abnormal basal ganglia signaling for many years. An important caveat is that some types of dystonia respond very well, while others do not.[121–124] These observations reinforce the concept that different anatomical substrates are important different types of dystonia.

Before DBS was widely used for dystonia, it was common for surgeons to explore the effects of lesions in different brain regions.[125–127] The cerebellum and thalamus were frequent targets, but fell out of favor because results were inconsistent. Some patients responded very well, while others derived no benefit. The motor network model has encouraged a re-evaluation of these older studies, based on the idea that some subtypes of patients may respond best to interventions involving the basal ganglia while others may respond to interventions involving the cerebellum. For example, there has been increasing interest in thalamotomy or DBS of the thalamus. Some of these studies have targeted the ventral intermediate nucleus of the thalamus (which receives cerebellar afferents) or the ventral oralis anterior nucleus (which receives pallidal afferents), or both combined.[128–133] Some dystonia patients seem to respond best to procedures targeting one region over another region.

Another example is that stimulation of the anterior lobe of the cerebellum or stereotactic lesions of the deep cerebellar nuclei have been used for many years in cerebral palsy to reduce excessive muscle tone and abnormal movements, which often reflect a combination of spasticity and dystonia. Recent studies have attempted to dissect whether the benefits of these procedures are related to reductions in spasticity or dystonia.[134,135] The observations imply that interrupting abnormal basal ganglia or cerebellar signaling may provide effective therapy for dystonia. However, larger and more methodical studies are needed to determine optimal surgical targets for different subtypes of dystonia.

Another intervention that has proven useful in exploring the anatomical substrates for dystonia is transcranial magnetic stimulation (TMS). Because the magnetic stimuli penetrate only the most superficial parts of the brain and do not reach the basal ganglia, TMS has been used to address contributions of the cerebral cortex and cerebellum. Numerous studies have been conducted, and they have been the focus of several recent reviews.[10,17,136–138] Here we summarize only the interventional studies reporting TMS effects on dystonic movements.

A randomized sham-controlled study involving 1 Hz repetitive TMS (theta burst stimulation) over the cerebellum for 2 weeks produced a small but significant decrease (–15%) in Toronto Wester Spasmodic Torticollis Rating Scale (TWSTRS) motor scores in 20 patients with cervical dystonia.[139] Another sham-controlled study involving a similar cerebellar TMS paradigm for 10 weeks combined with physical therapy also produced small but significant decreases (–10%) in TWSTRS motor scores and improvements in quality of life measures in 16 patients with cervical dystonia.[140] These studies are provocative because they imply that interventions involving the cerebellum may influence dystonic movements. On the other hand, a randomized sham-controlled study revealed no benefits after a single session of 1 Hz repetitive TMS over the cerebellum in 10 patients with writer's cramp.[141] A related study using a similar single-session paradigm showed no changes in the kinematics of abnormal movements for 13 patients with cervical dystonia and 13 with hand dystonia.[142] It remains to be determined whether the different outcomes reflect differences in the dystonia populations studied or other factors in study design such as duration of TMS.

Translational neuroscience and dystonia

Translational science. "Translational neuroscience" refers to the strategy of applying knowledge learned from simpler experimental conditions to more complex ones. For translational medicine, this often

means conducting experiments first in animals, and subsequently evaluating relevance for humans. The major benefits of starting with animals include the ability to conduct studies rapidly and efficiently in tightly controlled experimental settings, and the opportunity to perform direct experimental manipulations that cannot be done in human subjects.

Rodents have emerged as one of the most popular species in biomedical research, because they are inexpensive, easy to work with, and have sufficient biological similarities to humans for many experimental goals. A major attraction of rodents is that efficient methods have been developed to precisely manipulate specific biological targets, in ways that can be limited to specific brain regions or neuronal subtypes.[27,36,143] An important limitation is that species differences may limit applicability to humans. As a result, these species limitations must be carefully considered.

Species differences in motor behavior. An obvious difference between rodents and humans is their normal motor behavior. These differences lead to a fundamental question regarding whether or not specific movement disorders, such as dystonia, can occur in rodents. Dystonia is defined by its characteristic movements,[1] most notably excessive involuntary muscle contractions leading to movements that are excessively forceful or repetitive. Muscle contractions in dystonia often spread to nearby muscles, leading to twisting movements, abnormal postures, and sometimes co-contraction of antagonist muscles. By definition, any movements with these clinical characteristic qualities can be called "dystonic". Electromyography (EMG) can be used to verify the electrophysiological characteristics of dystonic movements,[144] but these characteristics are not considered diagnostic.

Abnormal movements fitting the clinical and EMG criteria used to define dystonia occur in several species. They have been reported in the veterinary literature for rodents, cats, dogs, horses, birds, and other species. Dystonic movements also have been reported in the biomedical research literature for rodents,[27,143] cats,[145,146] and non-human primates.[67] Several of these studies included video recordings demonstrating the abnormal movements, sometimes with EMG verification of the characteristic hallmarks of dystonia. Of course, some types of dystonia, such as writer's cramp, are very unlikely to be reproducible in species such as rodents.

Skeptics of animal models sometimes question whether dystonic movements reported for rodents reflect "real" dystonia. The implication of this question is that some types of dystonia are real and some are not. However, dystonia is defined by the nature of abnormal movements, so the more relevant question is not whether dystonic movements are "real", but whether the mechanisms responsible for dystonia are shared across species. In other words, is there any evidence that biological mechanisms causing dystonia differ among species?

Species differences in anatomical pathways. The brains of rodents and humans are obviously quite different. The rodent brain is much smaller and simpler than the human brain.[147] The most obvious differences are at the macroscopic level. The corticospinal motor pathways in rodents are simpler than those of humans. In rodents, the cortex is less clearly subdivided into specific functional domains, and the laminar organization of the cortex is simpler than in humans. For basal ganglia pathways, the rodent brain is again simpler than the human brain. For example, the caudate and putamen are separate structures in humans but combined into a single structure (caudoputamen) in rodents. Further, the basal ganglia in humans are functionally and somatotopically organized into multiple discrete but partially overlapping parallel pathways, which are absent in rodents. For cerebellar pathways, the main differences between rodents and humans again exist at the macroscopic level with differences in size and relative proportions of different subregions.

Despite these differences, there are numerous similarities. Histologically, for all three major motor pathways, the major neuronal subtypes and their morphologies are very similar across rodents and humans. Their neurotransmitter phenotypes and post-synaptic signal transduction pathways are similar too. Intrinsic connectivity is quite similar across species too. For example, for both species, cerebellar circuitry is remarkably stereotyped with a very ordered arrangement of climbing fibers, mossy fibers, parallel fibers, and Purkinje neuron output. The major afferents and efferents to each region are similar too, although they differ in proportions.

The goal of translational neuroscience. Skeptics uncomfortable with translational sciences are often quick to emphasize the behavioral and anatomical differences between rodents and humans. On the other hand, there are many similarities. For translational neuroscience, cataloging the similarities and differences is less relevant than whether these anatomical differences preclude the use of rodents for dystonia research. Rodents have been used very successfully for studying other neurological disorders such as Parkinson's disease, tremor, Huntington's disease, and spinocerebellar ataxias. A research toolkit that is limited to humans or primates would severely restrict progress in dystonia.

The value of rodent models is not related to how closely they resemble humans. Instead, their value lies in how effectively they can point to novel insights and guide studies in humans. Findings from rodents can be re-evaluated in humans, or at least in non-human primates, and either discarded as irrelevant, or exploited to generate novel insights. The strong evidence regarding the role of the cerebellum in rodents with dystonia has already stimulated numerous recent human studies looking at the cerebellum. Judging from the number of recent human studies that so far appear to validate the motor network model developed via studies of animals, the process of translation is well under way. The human studies are often inconclusive because of the nature of experimental interventions that can be applied in humans. The most valuable aspect of translational neuroscience may be the development of novel treatments that take the new evidence into account. Some investigators have already called for more methodical studies of direct interventions of cerebellar circuits, based on rodent studies showing that deep brain stimulation of cerebellar circuits can reduce dystonia.[77] The motor network model provides the biological framework in which the results of these studies can be interpreted.

Conclusions

The motor network model posits that all subtypes of dystonia are not the result of dysfunction of a single brain region. Instead, different brain regions are involved in a motor network that includes the basal ganglia, cerebellum, thalamus, and cortex. For different types of dystonia, the starting point may be different.

The motor network model has received strong support from numerous animal studies, which have provided unequivocal evidence that certain subtypes of dystonia may originate from dysfunction in the basal ganglia, cerebellum, or both combined. Similar evidence has begun to emerge from human studies, although the results are not conclusive because of the limits of the types of experimental interventions that can be applied in humans.

The anatomical heterogeneity underlying dystonia has only recently been appreciated. Until this heterogeneity is better understood, it is important to avoid making overly generalized conclusions about all forms of dystonia from studies of a single subtype. Considering the remarkable clinical heterogeneity of dystonia, a related heterogeneity of the underlying anatomical substrates is not surprising. A better understanding of this heterogeneity may be used to guide developing novel treatment strategies.

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