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The cerebellum in dystonia – Help or hindrance?

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HIGHLIGHTS

- There are intimate structural and functional connections between cerebellum and basal ganglia that appear to be involved in patients with dystonia.
- The data summarised in this review suggest that in most forms of dystonia the cerebellum has abnormal, probably compensatory activity, secondary to pathology elsewhere within the sensori-motor network which is yet to be fully characterised.
- It is likely that in some types of dystonia cerebellar dysfunction plays a primary role in the pathophysiology.

ABSTRACT

Dystonia has historically been considered a disorder of the basal ganglia. This review aims to critically examine the evidence for a role of the cerebellum in the pathophysiology of dystonia. We compare and attempt to link the information available from both clinical and experimental studies; work detailing cerebellar connectivity in primates; data that suggests a role for the cerebellum in the genesis of dystonia in murine models; clinical observation in humans with structural lesions and heredodegenerative disorders of the cerebellum; and imaging studies of patients with dystonia. The typical electrophysiological findings in dystonia are the converse to those found in cerebellar lesions. However, certain subtypes of dystonia mirror cerebellar patterns of increased cortical inhibition. Furthermore, altered cerebellar function can be demonstrated in adult onset focal dystonia with impaired cerebellar inhibition of motor cortex and abnormal eyeblink classical conditioning. We propose that abnormal, likely compensatory activity of the cerebellum is an important factor within pathophysiological models of dystonia. Work in this exciting area has only just begun but it is likely that the cerebellum will have a key place within future models of dystonia.

Contents

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1. Introduction

Dystonia has long been considered to be a manifestation of basal ganglia dysfunction, similar to other movement disorders. However, there is accumulating evidence from a wide variety of sources that the cerebellum may have a role to play in the pathophysiology of dystonia. Here we review this evidence, and demonstrate how the intimate structural and functional connections between cerebellum and basal ganglia appear to be involved in patients with dystonia.

1.1. Anatomy

The cerebellum and the basal ganglia receive input from multiple cortical areas and have been traditionally been thought to modulate motor control via distinct thalamic nuclei that project to the primary motor cortex (Alexander et al., 1986). However studies using viral tracers in primates reveal the macro-architecture of an increasing number of cerebellar and basal ganglia projections. Multisynaptic circuits link the cerebellum and basal ganglia with the primary motor cortex, supplementary motor area (SMA), pre-SMA, oculomotor, prefrontal, and posterior parietal cortex (Lynch et al., 1994; Middleton and Strick, 2001; Akkal et al., 2007; Prevosto et al., 2010). Many cortical areas project topographically to specific cerebellar and basal ganglia territories that reciprocally innervate these same cortical areas (Bostan and Strick, 2010). There is also a substantial direct communication between the basal ganglia and the cerebellum: a disynaptic projection linking the dentate nucleus (output stage of cerebellar processing) to the striatum (input stage of basal ganglia processing) (Hoshi et al., 2005), and a forward connection from the subthalamic nucleus of the basal ganglia to the cerebellar cortex (Bostan et al., 2010). The reciprocal communication between these two major subcortical structures suggests that they directly modulate each other. Brainstem nuclei provide another junction for the cerebellum and basal ganglia to interact, for example in cats the red nucleus receives input from both the basal ganglia and cerebellar nuclei which then project directly to motor nuclei (Pong et al., 2008). These neuronal circuits provide an anatomical substrate for the cerebellum and basal ganglia to have wide ranging functions in motor and non-motor domains. Dysfunction in either structure could induce either compensatory activity or disruption in the other.

To date, there is a paucity of information regarding the neuropathology of dystonia, and there has not been specific exploration of cerebellar pathology or cerebellar-basal ganglia projections in brains of dystonia patients. Reported autopsy studies in sporadic primary dystonia and DYT 1 dystonia have not shown an overt neurodegenerative process or clear patterns of cell loss (Holton et al., 2008; Standaert, 2011).

1.2. Animal models

Pharmacological and mutant mouse models of dystonia provide further data supporting a role of the cerebellum in the genesis of dystonia (Neychev et al., 2008; Ledoux, 2011). For example, tottering mice mutants exhibit paroxysmal dystonia due to a point mutation in a gene that codes for a calcium channel (Wakamori et al., 1998). Clinically and electrophysiologically these episodes have characteristics similar to human dystonia (Jinnah et al., 2005). Surgical removal of the cerebellum abolishes dystonic attacks in these mice (Neychev et al., 2008). Elimination of dystonic movements following cerebellectomy has also been found in other murine models of dystonia (LeDoux et al., 1993; Devanagondi et al., 2007). Similarly, dystonia is abolished if the tottering mouse is bred with an additional genetic mutation that causes Purkinje cell degeneration (Campbell et al., 1999). In a pharmacological mouse model for dystonia, microinjection of low doses of kainic acid into the cerebellar vermis of mice generates dystonia of a severity proportional to kainite dose (Pizoli et al., 2002). Microdialysis of the striatum reveals dystonic attacks to be associated with reductions in striatal dopamine in both tottering mice and the kainic acid pharmacological model, which suggests that that cerebellar activity can directly influence the dynamics of striatal dopamine (Neychev et al., 2008). Recently, a pharmacological model of rapid onset dystonia parkinsonism (DYT12) has been created (Calderon et al., 2011) by selective blockade of the sodium–potassium ATPase pump (which is mutated in the disorder). Both cerebellar and basal ganglia blockade of the sodium pump were needed to cause dystonic symptoms, and lesioning of cerebellar output nuclei or the disynaptic cerebellar-basal ganglia link caused significant resolution of symptoms (Calderon et al., 2011).

1.3. Clinical data

There are a substantial number of case reports linking dystonia to structural lesions of the cerebellum. However, there is considerable heterogeneity amongst cases with variable lesion location, aetiology and extent, type of dystonia produced, time interval between initial insult to onset of dystonia, and quality of clinical data. It has long been recognised in both adult and paediatric neurology that posterior fossa tumours can present with cervical dystonia (Grey, 1916; Extremera et al., 2008). A review of 25 cases of secondary cervical dystonia with a range of aetiologies in adults revealed that structural lesions of the brainstem and cerebellum were the most frequent cause of cervical dystonia (44%), with basal ganglia lesions accounting for less (24%) of cases (LeDoux and Brady, 2003). In two cases of cerebellopontine angle tumours, the cervical dystonia improved following successful removal of the tumour (Krauss et al., 1997). Focal limb dystonia has also been associated with cerebellar lesions. In an intriguing case, successful treatment of an isolated tuberculoma of the left cerebellar hemisphere led to parallel resolution of left arm dystonia (Alarcon et al., 2001). Other cases document the emergence of late-onset oromandibular dystonia after bilateral cerebellar infarction, blepharospasm/torticollis after bilateral cerebellar infarction, and left hemidystonia following ipsilateral vertebral artery occlusion (Rumbach et al., 1995; O'Rourke et al., 2006; Waln and LeDoux, 2010).

Patients with genetic degenerative cerebellar disorders (for example spinocerebellar ataxia type 3, SCA3) commonly demonstrate dystonia as part of their clinical phenotype, and sometimes dystonia may be the predominant presentation (Münchau et al., 1999). The neurodegeneration in such patients is widespread however, and the dystonia is usually assumed to be the result of basal ganglia rather than cerebellar degeneration. Pathological studies have indeed confirmed involvement of other motor system structures such as the pallidum and substantia nigra (Van Gaalen et al., 2011). We have reported two separate series of patients with a syndrome of cervical dystonia and mild cerebellar ataxia (DYTCA) of undetermined etiology (Kuoppamaki et al., 2003; van de Warrenburg et al., 2007). Dystonia is the more prominent and disabling symptom in this disorder, with the cerebellar ataxia being relatively mild and slowly progressive. Imaging findings vary between patients from cerebellar and brainstem atrophy to normality. Twelve further patients have been described in a separate series; although in these patients marked cerebellar atrophy (albeit with mild cerebellar signs) was the norm (LeBer et al., 2006). We have speculated whether the cerebellar pathology in our DYTCA patients contributes to (or perhaps is even wholly responsible for) the development of

their dystonia. The electrophysiological studies that lend some support for this hypothesis are detailed below.

It is worth noting that in primary dystonia there is an absence of clear cerebellar signs on clinical examination, even when there is neurophysiological evidence to support cerebellar dysfunction (Teo et al., 2009). This might be taken to support a more compensatory role for the cerebellum in some forms of primary dystonia, and at the very least tells us that the role of the cerebellum in dystonia is more complicated than simply a loss or gain of cerebellar function.

1.4. Functional and structural imaging data in dystonia

In vivo functional and structural imaging studies in dystonia can broadly be divided into studies of (i) grey and white matter structure and integrity (ii) neurotransmitters and (iii) brain metabolism at rest and during learning and motor tasks. The hereditary dystonias are particularly interesting as the incomplete penetrance of clinical manifestation in patients with mutations of DYT 1 or DYT 6 allow one to make distinctions between patterns of abnormality related to genotype and phenotype.

Voxel-based morphometry applied to high resolution MRI has demonstrated subtle changes in grey matter, with increases in putamal, internal globus pallidus and prefrontal cortex as a common pattern across different types of primary dystonia (Egger et al., 2007). Both increases and decreases of cerebellar grey matter volume have been found with this technique in different types of dystonia and thus further studies are required to elucidate the significance of these observed changes (Draganski et al., 2006; Delmaire et al., 2007; Obermann et al., 2007). Diffusion tensor imaging (DTI-MRI) can be used to assess microstructural white matter integrity with fractional anisotropy (FA) as a measure of axonal coherence (Sen and Basser, 2005). Axonal integrity is reduced in the subgyral white matter of the sensorimotor area in both manifesting and non-manifesting DYT1 carriers, with additional FA reductions in the dorsal pons at its juncture with the superior cerebellar peduncle in manifesting subjects (Carbon et al., 2004, 2008b) Additionally, DTI-MRI combined with probabilistic tractography techniques in DYT1 and DYT6 have demonstrated reduced connectivity of the cerebello-thalamic pathway near the dentate nucleus (Argyelan et al., 2009). This was most pronounced in clinically affected mutation carriers compared with clinically unaffected mutation carriers. DTI-MRI in non-hereditary primary dystonias has also demonstrated white matter integrity abnormalities but as yet cerebellar connectivity has not been specifically studied (Colosimo et al., 2005; Bonilha et al., 2007; Fabbrini et al., 2008; Delmaire et al., 2009).

As dystonia has traditionally been conceptualised as a basal ganglia disorder, abnormalities of dopaminergic neurotransmission have been investigated using radioligand binding. Decreased striatal D2 radioligand uptake has been demonstrated in various forms of primary dystonia including hand, cervical and cranial dystonia and patients with DYT1, DYT6 and DYT11 mutations regardless of clincial manifestation (Perlmutter et al., 1997; Naumann et al., 1998; Beukers et al., 2009; Carbon et al., 2009). However, a recent study suggests that D3 rather D2 receptor affinity is reduced in focal dystonia, thus further work with increasingly specific radioligands is needed to investigate whether this pattern is seen across other types of primary dystonia (Karimi et al., 2011). This work provides an interesting link with work presented above in animal models that cerebellar activity may directly modulate striatal dopamine (see above).

Alterations in regional brain function at rest can be measured using positron emission tomography (PET) with selective radioligands. Patients with sporadic and genetic forms of dystonia demonstrate relative increases in regional metabolic activity in the posterior putamen/globus pallidus, supplementary motor area (SMA) and cerebellum (Eidelberg et al., 1995; Eidelberg et al., 1998; Niethammer et al., 2011). Elevated network activity persists during sleep in manifesting DYT1 carriers and is also present in non-manifesting DYT1 carriers (Eidelberg et al., 1998). Contrasting findings with regard to cerebellar metabolism have been found in DYT6 carriers, but all clinically affected DYT1 and DYT6 patients show relative metabolic increases in the pre-SMA and parietal association regions (Carbon et al., 2010).

Sequence learning is a task that requires cerebellar processing (Molinari et al., 2008). Sequence learning ability and task-related brain activation is abnormal in non-manifesting carriers of the DTY1 deletion (Ghilardi et al., 2003). Sequence learning in conjuction with an equiperformance study design in this patient group resulted in overactivation of the lateral cerebellum, perhaps as a compensation for lack of recruitment of pre-frontal regions in order to achieve normal motor performance (Carbon et al., 2008a).

A normal motor-related activation pattern (NMRP) has been proposed by combining PET activation data with multivariate network modelling in control subjects (Niethammer et al., 2011). The NMRP is characterised by contributions from the cortico-striato-pallidal-thalamocortical and cerebello-thalamo-cortical motor circuits. Groups of dystonic patients that have been studied to date (sporadic cervical dystonia and manifesting DYT1 and DYT6) demonstrate increased activity of the NMRP (Niethammer et al., 2011). Furthermore, the increased activity of the NMRP correlated with severity of dystonia and also microstructural changes observed by fractional anisotropy in cerebellar outflow as described above (Niethammer et al., 2011).

A large number of fMRI-BOLD studies have been conducted in patients with idiopathic primary dystonia and cerebellar abnormalities have repeatedly been described. Patients with musician's dystonia and focal hand dystonia show abnormal cerebellar activation during different tapping tasks (Kadota et al., 2010; Wu et al., 2010) and abnormal cerebellar activation is observed during writing in writer's cramp (Preibisch et al., 2001; Hu et al., 2006). Task-related activity in the cerebellar nuclei, posterior vermis, right paramedian cerebellar hemisphere and dorsal pons was however inversely related with the severity of hand dystonia and proposed to reflect secondary compensatory reorganization. Abnormal cerebellar activation in spasmodic dysphonia (Simoyan and Ludlow, 2010) during voice production and essential blepharospasm during eyeblinking (Baker et al., 2003) is also reported. Patients with cervical dystonia show BOLD signal increase in a number of brain regions including the cerebellum during passive movement (Obermann et al., 2010).

1.5. Electrophysiological studies

Electrophysiological studies in dystonia have revealed a distorted balance between the excitatory and inhibitory circuitry of the sensori-motor system at various levels and there are abnormal responses to protocols inducing plasticity-like effects (Deuschl et al., 1992; Chen et al., 1995; Edwards et al., 2003; Quartarone and Pisani, 2011). Investigation into the role of the cerebellum in these observed changes in dystonia is at an early stage. Firstly we compare the contrasting neurophysiological profiles seen in dystonia and cerebellar disorders. We then discuss eyeblink classical conditioning (EBCC), a paradigm that is heavily cerebellar dependent that is abnormal in dystonia. Finally we summarise recent work examining cerebellar inhibition in dystonia and areas for future investigation.

Studies investigating cortical excitability profile in primary dystonia using transcranial magnetic stimulation (TMS) have reported reduced cortical inhibition, observable as a relatively greater

increase in motor evoked potentials (MEPs) with increasing stimulus intensities (Ikoma et al., 1996), shortening of the cortical silent period (CSP) (Chen et al., 1997) and reductions in short intracortical inhibition (SICI) (Ridding et al., 1995; Chen et al., 1997; Siebner et al., 1999). A more limited number of studies have assessed the cortical excitability profile of patients with cerebellar lesions. The balance between cortical excitatory and inhibitory circuitry appears disturbed, but the shift is opposite to that seen in primary dystonia, with increases in motor cortical thresholds (Schwenkreis et al., 2002), abnormal prolongation of the CSP (Wessel et al., 1996; Oechsner and Zangemeister, 1999; Tamburin et al., 2004), reduced intracortical facilitation (ICF) (Liepert et al., 1998, 2004) and an increase in SICI (Liepert et al., 2004). We have compared measures of cortical excitability in five patients with DYTCA and found SICI to be increased (Talelli et al., 2011), in contrast to typical primary dystonia, but similar to patients with cerebellar lesions (Liepert et al., 2004). Of interest, in myoclonus dystonia (DYT 11) the expected decrease in SICI seen in primary dystonia is absent (Meunier et al., 2008). Thus, cortical excitability profiles in dystonia are different with certain types (DYTCA, myoclonus dystonia) having patterns that more closely resemble patients with cerebellar disorders rather than typical primary dystonia. More work is clearly needed in this area, including testing response to plasticity protocols in these disorders to see if they are different from typical primary dystonia. Little is known about the role of the cerebellum in response to plasticity protocols, but preliminary work suggests that in cerebellar degeneration electrophysiological responses to plasticity inducing paradigms are normal (Teo et al., 2008).

Perhaps the most compelling electrophysilogical evidence for cerebellar involvement in dystonia is seen when studying EBCC. This is a paradigm of associative motor learning in which paired presentation of a conditioned (CS) and unconditioned stimulus (US) leads to the production of a conditioned eyeblink response (CR). Eyeblink classical conditioning has extensively been studied in humans and animals and is critically dependent on the cerebellum (Gerwig et al., 2007). Patients with Parkinson's disease perform as well as healthy controls on EBCC (Sommer et al., 1999), indicating that basal ganglia dysfunction does not necessarily impact significantly on this learning paradigm. In contrast, patients with adult onset focal dystonia have abnormal eyeblink classical conditioning (Teo et al., 2009). Previous studies in animals and humans has revealed a cerebellar circuitry underlying EBCC in which the cerebellar cortical Purkinje cell (PC) receives convergent afferent information about the CS and US via two separate pathways with an additional potential convergence upon the underlying interpositus nucleus (IN) (Yeo and Hesslow, 1998). It is noteworthy that structural imaging studies in dystonia identify grey matter abnormalities in the area of the cerebellar cortex that is involved in this circuit (Draganski et al., 2006).

Purkinje cells in the cerebellar cortex have an inhibitory connection with the underlying dendate nucleus, which in turn displays a disynaptic excitatory connection through the ventral thalamus to the contralateral M1 (Middleton and Strick, 1998). Paired pulse transcranial magnetic stimulation (TMS) protocols can be used to study this pathway. In healthy subjects, a conditioning pulse delivered over the cerebellar cortex 5–7 ms prior to a test pulse over the contralateral M1 will result in reduction of the MEP amplitude relative to a test pulse given alone over this cortical area: "cerebellar brain inhibition" (CBI). This inhibitory effect is thought to arise from activation of Purkinje cells that will consequently inhibit the dentate nucleus and thus reduce the disynaptic excitatory drive from cerebellum to motor cortex (Saito et al., 1995; Ugawa et al., 1995). In eight patients with idiopathic focal limb dystonia, a cerebellar conditioning pulse had no effect on the test pulse MEP amplitude, SICI or ICF (Brighina et al., 2009). The authors hypothesized that the reduced cerebellar modulation of motor cortex excitability could arise through hyperactive purkinje cells in dystonia, that may be compensating for basal ganglia dysfunction. Another possibility is a reduced integrity of the cerebello-thalamo-cortical pathway in idiopathic primary dystonia, as has been described for hereditary primary dystonia (Argyelan et al., 2009).

It is possible that aberrant CBI in dystonia might interact with another phenomenon commonly reported in dystonia: abnormal surround inhibition. This is a muscle-specific modification of the excitability of the corticospinal pathway where just prior to and in the early phase of movement, muscles not involved in the planned movement but surrounding the active muscles show a decreased excitability due to active inhibition (Sohn and Hallett, 2004b). Surround inhibition (SI) has repeatedly been reported to be disrupted in patients with primary dystonia and could account for the overflow of muscle activation seen in this movement disorder (Sohn and Hallett, 2004a; Beck et al., 2009). The mechanism through which this inhibition is regulated has repeatedly been investigated but remains unknown and we have recently explored in healthy subjects whether there is a relationship between SI and CBI (Kassavetis et al., 2011). We did not observe a muscle specific modulation of CBI in parallel with SI, as CBI was reduced in both active and surround muscles at the onset of movement. However, the cerebellum has been proposed to be involved in the movement initiation processes and the observed change of the cerebellar inhibitory drive to the motor cortex at onset of movement is consistent with this. Although yet to be explored, it is possible that the abnormal CBI known to be present in dystonia could interfere with this process.

Regional cerebral blood flow in the ipsilateral cerebellum is negatively correlated with reaction time (Horwitz et al., 2000) and an increased reaction time is observed in patients with cerebellar dysfunction (Grill et al., 1997) as well as a decreased premovement corticospinal excitability (Battaglia et al., 2006). It is intriguing that this increase in reaction time also applies to patients with primary dystonia (Jahanshahi et al., 2001) as well as the lack of MEP facilitation normally present before movement (Gilio et al., 2003). This altered release of motor programs in dystonia has been attributed to basal ganglia dysfunction, but a role for the cerebellum in these abnormalities is also conceivable.

2. Conclusions

Here we have outlined current evidence that explores a possible role for the cerebellum in dystonia. This field of exploration is still at an early stage and there are many unanswered questions. There is certainly *a priori* evidence from the important reciprocal anatomical connections between the cerebellum and basal ganglia to support the hypothesis that dysfunction in either structure might cause dysfunction or elicit a compensatory response in the other. Compensatory responses can also have their cost for the integrity of neural systems, seen for example in increases in activity of motor areas in the non-stroke hemisphere after stroke which may have an unwanted inhibitory effect on the stroke hemisphere and impair recovery (Murase et al., 2004). This increases the complexity of interpreting abnormalities in the cerebellum revealed by experimental studies in dystonia patients.

In certain types of dystonia cerebellar dysfunction may play a primary role in the pathology of the disorder. Here the data from clinical cases with cerebellar lesions and dystonia, and from patients with DYTCA or myoclonus dystonia who have the electrophysiological "profile" of patients with cerebellar degeneration rather than typical primary dystonia are noteworthy.

However, the lack of traditional ''cerebellar signs'' in most patients with dystonia points more strongly to a compensatory role for the cerebellum in most forms of primary dystonia. This is in line with functional imaging data showing increased cerebellar dependence for sequence learning in dystonic patients (Carbon et al., 2008a). Even the finding of abnormal eye blink conditioning in primary dystonia might be explained by a disruption of cerebellar function induced by compensatory changes in this structure that are induced by primary basal ganglia dysfunction.

Work in this exciting area has only just begun, but already it is clear that the historical reputation of dystonia as a mysterious and constantly changing concept is likely to continue. In the future, the cerebellum is likely to have a key place within pathophysiological models of this enigmatic disorder.

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References

Akkal D, Dum RP, Strick PL. Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. J Neurosci 2007;27:10659–73.
Alarcon F, Tolosa E, Munoz E. Focal limb dystonia in a patient with a cerebellar mass. Arch Neurol 2001;58:1125–7.
Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–81.
Argyelan M, Carbon M, Niethammer M, Ulug AM, Voss HU, Bressman SB, et al. Cerebellothalamocortical connectivity regulates penetrance in dystonia. J Neurosci 2009;29:9740–7.
Baker RS, Andersen AH, Morecraft RJ, Smith CD. A functional magnetic resonance imaging study in patients with benign essential blepharospasm. J Neuroophthalmol 2003;23:11–5.
Battaglia F, Quartarone A, Ghilardi MF, Dattola R, Bagnato S, Rizzo V, et al. Unilateral cerebellar stroke disrupts movement preparation and motor imagery. Clin Neurophysiol 2006;117:1009–16.
Beck S, Schubert M, Richardson SP, Hallett M. Surround inhibition depends on the force exerted and is abnormal in focal hand dystonia. J Appl Physiol 2009;107:1513–8.
Beukers RJ, Booij J, Weisscher N, Zijlstra F, van Amelsvoort TA, Tijssen MA. Reduced striatal D2 receptor binding in myoclonus-dystonia. Eur J Nucl Med Mol Imaging 2009;36:269–74.
Bonilha L, de Vries PM, Vincent DJ, Rorden C, Morgan PS, Hurd MW, et al. Structural white matter abnormalities in patients with idiopathic dystonia. Mov Disord 2007;22:1110–6.
Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. Proc Natl Acad Sci USA 2010;107:8452–6.
Bostan AC, Strick PL. The cerebellum and basal ganglia are interconnected. Neuropsychol Rev 2010;20:261–70.
Brighina F, Romano M, Giglia G, Saia V, Puma A, Giglia F, et al. Effects of cerebellar TMS on motor cortex of patients with focal dystonia: a preliminary report. Exp Brain Res 2009;192:651–6.
Calderon DP, Fremont R, Kraenzlin F, Khodakhah K. The neural substrates of rapid-onset Dystonia Parkinsonism. Nat Neurosci 2011;14:357–65.
Campbell DB, North JB, Hess EJ. Tottering mouse motor dysfunction is abolished on the Purkinje cell degeneration (pcd) mutant background. Exp Neurol 1999;160:268–78.
Carbon M, Kingsley PB, Su S, Smith GS, Spetsieris P, Bressman S, et al. Microstructural white matter changes in carriers of the DYT1 gene mutation. Ann Neurol 2004;56:283–6.
Carbon M, Ghilardi MF, Argyelan M, Dhawan V, Bressman SB, Eidelberg D. Increased cerebellar activation during sequence learning in DYT1 carriers: an equiperformance study. Brain 2008a;131:146–54.
Carbon M, Kingsley PB, Tang C, Bressman S, Eidelberg D. Microstructural white matter changes in primary torsion dystonia. Mov Disord 2008b;23:234–9.
Carbon M, Niethammer M, Peng S, Raymond D, Dhawan V, Chaly T, et al. Abnormal striatal and thalamic dopamine neurotransmission: Genotype-related features of dystonia. Neurology 2009;72:2097–103.
Carbon M, Argyelan M, Eidelberg D. Functional imaging in hereditary dystonia. Eur J Neurol 2010;17:58–64.
Chen R, Wassermann EM, Canos M, Hallett M. Impaired inhibition in writer's cramp during voluntary muscle activation. Neurology 1997;49:1054–9.
Chen RS, Tsai CH, Lu CS. Reciprocal inhibition in writer's cramp. Mov Disord 1995;10:556–61.
Colosimo C, Pantano P, Calistri V, Totaro P, Fabbrini G, Berardelli A. Diffusion tensor imaging in primary cervical dystonia. J Neurol Neurosurg Psychiatry 2005;76:1591–3.
Delmaire C, Vidailhet M, Elbaz A, Bourdain F, Bleton J-P, Sangla S, et al. Structural abnormalities in the cerebellum and sensorimotor circuit in writer's cramp. Neurology 2007;69:376–80.
Delmaire C, Vidailhet M, Wassermann D, Descoteaux M, Valabregue R, Bourdain F, et al. Diffusion abnormalities in the primary sensorimotor pathways in writer's cramp. Arch Neurol 2009;66:502–8.
Deuschl G, Seifert C, Heinen F, Illert M, Lucking CH. Reciprocal inhibition of forearm flexor muscles in spasmodic torticollis. J Neurol Sci 1992;113:85–90.
Devanagondi R, Egami K, LeDoux MS, Hess EJ, Jinnah HA. Neuroanatomical substrates for paroxysmal dyskinesia in lethargic mice. Neurobiol Dis 2007;27:249–57.
Draganski B, Thun-Hohenstein C, Bogdahn MD, Winkler J, May A. ''Motor circuit'' gray matter changes in idiopathic cervical dystonia. Neurology 2006;61:1228–31.
Edwards MJ, Huang YZ, Wood NW, Rothwell JC, Bhatia KP. Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the DYT1 gene mutation. Brain 2003;126:2074–80.
Egger K, Mueller J, Schocke M, Brenneis C, Rinnerthaler M, Seppi K, et al. Voxel based morphometry reveals specific gray matter chagnes in primary dystonia.. Neurology 2007;22:1538–42.
Eidelberg D, Moeller JR, Ishikawa T, Dhawan V, Spetsieris P, Przedborski S, et al. The metabolic topography of idiopathic torsion dystonia. Brain 1995;118:1473–84.
Eidelberg D, Moeller JR, Antonini A, Kazumata K, Nakamura T, Dhawan V, et al. Functional brain networks in DYT1 dystonia. Ann Neurol 1998;44:303–12.
Extremera VC, Alvarez-Coca J, Rodriguez GA, Perez JM, de Villanueva JL, Diaz CP. Torticollis is a usual symptom in posterior fossa tumors. Eur J Pediatr 2008;167:249–50.
Fabbrini G, Pantano P, Totaro P, Calistri V, Colosimo C, Carmellini M, et al. Diffusion tensor imaging in patients with primary cervical dystonia and in patients with blepharospasm. Eur J Neurol 2008;15:185–9.
Gerwig M, Kolb FP, Timmann D. The involvement of the human cerebellum in eyeblink conditioning. Cerebellum 2007;6:38–57.
Ghilardi MF, Carbon M, Silvestri G, Dhawan V, Tagliati M, Bressman S, et al. Impaired sequence learning in carriers of the DYT1 dystonia mutation. Ann Neurol 2003;54:102–9.
Gilio F, Curra A, Inghilleri M, Lorenzano C, Suppa A, Manfredi M, et al. Abnormalities of motor cortex excitability preceding movement in patients with dystonia. Brain 2003;126:1745–54.
Grey EG. Studies on the localization of cerebellar tumors: the position of the head and suboccipital discomforts. Ann Surg 1916;63:129–39.
Grill SE, Hallett M, McShane LM. Timing of onset of afferent responses and of use of kinesthetic information for control of movement in normal and cerebellar-impaired subjects. Exp Brain Res 1997;113:33–47.
Holton JL, Schneider SA, Ganesharajah T, Gandhi S, Strand C, Shashidharan P, et al. Neuropathology of primary adult-onset dystonia. Neurology 2008;70:695–9.
Horwitz B, Deiber MP, Ibanez V, Sadato N, Hallett M. Correlations between reaction time and cerebral blood flow during motor preparation. Neuroimage 2000;12:434–41.
Hoshi E, Tremblay L, Feger J, Carras PL, Strick PL. The cerebellum communicates with the basal ganglia. Nat Neurosci 2005;8:1491–3.
Hu XY, Wang L, Lui H, Zhang SZ. Functional magnetic resonance imaging study of writer's cramp. Chin Med J 2006;119:1263–71.
Ikoma K, Samii A, Mercuri B, Wassermann EM, Hallett M. Abnormal cortical motor excitability in dystonia. Neurology 1996;46:1371–6.
Jahanshahi M, Rowe J, Fuller R. Impairment of movement initiation and execution but not preparation in idiopathic dystonia. Exp Brain Res 2001;140:460–8.
Jinnah HA, Hess EJ, Ledoux MS, Sharma N, Baxter MG, Delong MR. Rodent models for dystonia research: characteristics, evaluation, and utility. Mov Disord 2005;20:283–92.
Kadota H, Nakajima Y, Miyazaki M, Sekiguchi H, Kohno Y, Amako M, et al. An fMARI study of musicians with focal dystonia during tapping tasks. J Neurol 2010;257:1092–8.
Karimi M, Moerlein SM, Videen TO, Luedtke RR, Taylor M, Mach RH, et al. Decreased striatal dopamine receptor binding in primary focal dystonia: A D2 or D3 defect? Mov Disord 2011;26:100–6.
Kassavetis P, Hoffland BS, Saifee TA, Bhatia KP, van de Warrenburg BP, Rothwell JC, et al. Cerebellar brain inhibition is decreased in active and surround muscles at the onset of voluntary movement. Exp Brain Res 2011. doi:10.1007/s00221-011-2575-5.
Krauss JK, Toups EG, Jankovic J, Grossman RG. Symptomatic and functional outcome of surgical treatment of cervical dystonia. J Neurol Neurosurg Psychiatry 1997;63:642–8.
Kuoppamaki M, Giunti P, Quinn N, Wood NW, Bhatia KP. Slowly progressive cerebellar ataxia and cervical dystonia: clinical presentation of a new form of spinocerebellar ataxia? Mov Disord 2003;18:200–6.
LeBer I, Clot F, Vercueil L, Camuzat A, Viemont M, Benamar N, et al. Predominant dystonia with marked cerebellar atrophy. Neurology 2006;67:1769.
LeDoux MS, Lorden JF, Ervin JM. Cerebellectomy eliminates the motor syndrome of the genetically dystonic rat. Exp Neurol 1993;120:302–10.

LeDoux MS, Brady KA. Secondary cervical dystonia associated with structural lesions of the central nervous system. Mov Disord 2003;18:60–9.
Ledoux MS. Animal models of dystonia: lessons from a mutant rat. Neurobiol Dis 2011. doi:10.1016/j.nbd.2010.11.00.
Liepert J, Kucinski T, Tuscher O, Pawlas F, Baumer T, Weiller C. Motor cortex excitability after cerebellar infarction. Stroke 2004;35:2484–8.
Liepert J, Wessel K, Schwenkreis P, Trillenberg P, Otto V, Vorgerd M, et al. Reduced intracortical facilitation in patients with cerebellar degeneration. Acta Neurol Scand 1998;98:318–23.
Lynch JC, Hoover JE, Strick PL. Input to the primate frontal eye field from the substantia nigra, superior colliculus, and dentate nucleus demonstrated by transneuronal transport. Exp Brain Res 1994;100:181–6.
Meunier S, Lourenco G, Roze E, Apartis E, Trocello JM, Vidailhet M. Cortical excitability in DYT-11 positive myoclonus dystonia. Mov Disord 2008;23:761–4.
Middleton FA, Strick PL. Cerebellar projections to the prefrontal cortex of the primate. J Neurosci 2001;21:700–12.
Middleton FA, Strick PL. The cerebellum: an overview. Trends Cogn Sci 1998;2:305–6.
Molinari M, Chiricozzi FR, Clausi S, Tedesco AM, De Lisa M, Leggio MG. Cerebellum and detection of sequences, from perception to cognition. Cerebellum 2008;7:611–5.
Münchau A, Dressler D, Bhatia KP, Vogel P, Zühlke C. Machado-Joseph disease presenting as severe generalised dystonia in a German patient. J Neurol 1999;246:840–2.
Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol 2004;55:400–9.
Naumann M, Pirker W, Reiners K, Lange KW, Becker G, Brucke T. Imaging the pre- and postsynaptic side of striatal dopaminergic synapses in idiopathic cervical dystonia: a SPECT study using [123I] epidepride and [123I] beta-CIT. Mov Disord 1998;13:319–23.
Neychev VK, Fan X, Mitev VI, Hess EJ, Jinnah HA. The basal ganglia and cerebellum interact in the expression of dystonic movement. Brain 2008;131:2499–509.
Niethammer M, Carbon M, Argyelan M, Eidelberg D. Hereditary dystonia as a neurodevelopmental circuit disorder: Evidence from neuroimaging. Neurobiol Dis 2011. doi:10.1016/j.nbd.2010.10.01.
Obermann M, Yaldizli O, De Greiff A, Lachenmayer ML, Buhl AR, Tumcczak F, et al. Morphometric changes of sensorimotor structures in focal dystonia. Mov Disord 2007;22:1117–23.
Obermann M, Vollrath C, de Greiff A, Gizewski ER, Diner HC, Hallett M, et al. Sensory disinhibition on passive movement in cervical dystonia. Mov Disord 2010;25:2627–33.
Oechsner M, Zangemeister WH. Prolonged postexcitatory inhibition after transcranial magnetic stimulation of the motor cortex in patients with cerebellar ataxia. J Neurol Sci 1999;168:107–11.
O'Rourke K, O'Riordan S, Gallagher J, Hutchinson M. Paroxysmal torticollis and blepharospasm following bilateral cerebellar infarction. J Neurol 2006;253:1644–5.
Perlmutter JS, Stambuk MK, Markham J, Black KJ, McGee-Minnich L, Jankovic J, et al. Decreased [18F]spiperone binding in putamen in idiopathic focal dystonia. J Neurosci 1997;17:843–50.
Pizoli CE, Jinnah HA, Billingsley ML, Hess EJ. Abnormal cerebellar signaling induces dystonia in mice. J Neurosci 2002;22:7825–33.
Pong M, Horn KM, Gibson AR. Pathways for control of face and neck musculature by the basal ganglia and cerebellum. Brain Res Rev 2008;58:249–64.
Preibisch C, Berg D, Hofmann E, Solymosi L, Naumann M. Cerebral activation patterns in patients with writer's cramp: a functional magnetic resonance imaging study. J Neurol 2001;248:10–7.
Prevosto V, Graf W, Ugolini G. Cerebellar inputs to intraparietal cortex areas LIP and MIP: functional frameworks for adaptive control of eye movements, reaching, and arm/eye/head movement coordination. Cereb Cortex 2010;20:214–28.
Pisani Quartarone A. Abnormal plasticity in dystonia: disruption of synaptic homeostasis. Neurobiol Dis 2011. doi:10.1016/j.nbd.2010.12.01.
Ridding MC, Sheean G, Rothwell JC, Inzelberg R, Kujirai T. Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. J Neurol Neurosurg Psychiatry 1995;59:493–8.
Rumbach L, Barth P, Costaz A, Mas J. Hemidystonia consequent upon ipsilateral vertebral artery occlusion and cerebellar infarction. Mov Disord 1995;10:522–5.
Saito Y, Yokota T, Yuasa T. Suppression of motor cortical excitability by magnetic stimulation of the cerebellum. Brain Res 1995;694:200–6.
Schwenkreis P, Tegenthoff M, Witscher K, Bornke C, Przuntek H, Malin JP, et al. Motor cortex activation by transcranial magnetic stimulation in ataxia patients depends on the genetic defect. Brain 2002;125:301–9.
Sen PN, Basser PJ. Modeling diffusion in white matter in the brain: a composite porous medium. Magn Reson Imaging 2005;23:215–20.
Siebner HR, Tormos JM, Ceballos-Baumann AO, Auer C, Catala MD, Conrad B, et al. Low-frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. Neurology 1999;52:529–37.
Simonyan K, Ludlow CL. Abnormal activation for the primary somatosensory cortex in spasmodic dysphonia: an fMRI study. Cereb Cortex 2010;20:2749–59.
Sohn YH, Hallett M. Disturbed surround inhibition in focal hand dystonia. Ann Neurol 2004a;56:595–9.
Sohn YH, Hallett M. Surround inhibition in human motor system. Exp Brain Res 2004b;158:397–404.
Sommer M, Grafman J, Clark K, Hallett M. Learning in Parkinson's disease: eyeblink conditioning, declarative learning, and procedural learning. J Neurol Neurosurg Psychiatry 1999;67:27–34.
Standaert DG. Update on the pathology of dystonia. Neurobiol Dis. 2011. doi:10.1016/j.nbd.2011.01.01.
Talelli P, Hoffland BS, Edwards MJ, Bhatia KP, et al. A distinctive pattern of cortical excitability in patients with the syndrome of Dystonia and Cerebellar Ataxia. Clin Neurophysiol 2011. doi:10.1016/j.clinph.2011.02.02.
Tamburin S, Fiaschi A, Marani S, Andreoli A, Manganotti P, Zanette G. Enhanced intracortical inhibition in cerebellar patients. J Neurol Sci 2004;217:205–10.
Teo JT, Schneider SA, Cheeran BJ, Fernandez-del-Olmo M, Giunti P, Rothwell JC, et al. Prolonged cortical silent period but normal sensorimotor plasticity in spinocerebellar ataxia 6. Mov Disord 2008;23:378–85.
Teo JT, van de Warrenburg BP, Schneider SA, Rothwell JC, Bhatia KP. Neurophysiological evidence for cerebellar dysfunction in primary focal dystonia. J Neurol Neurosurg Psychiatry 2009;80:80–3.
Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum in humans. Ann Neurol 1995;37:703–13.
van de Warrenburg BP, Giunti P, Schneider SA, Quinn NP, Wood NW, Bhatia KP. The syndrome of (predominantly cervical) dystonia and cerebellar ataxia: new cases indicate a distinct but heterogeneous entity. J Neurol Neurosurg Psychiatry 2007;78:774–5.
Van Gaalen J, Giunti P, van de Warrenburg BP. Movement disorders in spinocerebellar ataxias. Mov Disord 2011. doi:10.1002/mds.23584.
Wakamori M, Yamazaki K, Matsunodaira H, Teramoto T, Tanaka I, Niidome T, et al. Single tottering mutations responsible for the neuropathic phenotype of the P-type calcium channel. J Biol Chem 1998;273:34857–67.
Waln O, LeDoux MS. Delayed-onset oromandibular dystonia after a cerebellar hemorrhagic stroke. Parkinsonism Relat Disord 2010;16:623–5.
Wessel K, Tegenthoff M, Vorgerd M, Otto V, Nitschke MF, Malin JP. Enhancement of inhibitory mechanisms in the motor cortex of patients with cerebellar degeneration: a study with transcranial magnetic brain stimulation. Electroencephalogr Clin Neurophysiol 1996;101:273–80.
Wu CC, Fairhall SL, McNair NA, Hamm JP, Kirk IJ, Cunnington R, et al. Impaired sensorimotor integration in focal hand dystonia patients in the absence of symptoms. J Neurol Neurosurg Psychiatry 2010;81:659–65.
Yeo CH, Hesslow G. Cerebellum and conditioned reflexes. Trends Cogn Sci 1998;2:322–30.