Unmasking the true pathophysiology of dystonia

Is the basal ganglia really all to blame?

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For a long time, scientists have perceived the basal ganglia to be the perpetrator in dystonia. However, evidence is emerging from animal models, clinical observations of patients and imaging studies to suggest that the cerebellum may play an important role. Unmasking the pathogenesis & pathophysiology of dystonia is vital if we are to develop better treatments and potentially a cure for this neurological disorder. This essay endeavors to discuss some of the evidence base postulating a role for the cerebellum in dystonia and ultimately determine whether it is more to blame than the basal ganglia!

Unmasking the true pathophysiology of dystonia….is the basal ganglia really all to blame?

Introduction

Imagine having painful muscular contractions in your neck which swing your head backwards and forwards or being a concert pianist who cannot control their fingers…dystonia is a distressing and disabling condition. It has been estimated that over 70,000 people in the UK alone suffer from some form of dystonia[1], 8,000 of whom are children or young adults[2]. In the recent past, much work has been carried out but sadly, despite the huge leaps and bounds made, a definitive cure for dystonia is yet to be elucidated. Dystonia is believed to be primarily a disease of the basal ganglia and existing treatments target these nuclei buried deep within the cerebrum. However, there is a growing body of evidence to suggest that other structures may be implicated, including the cerebellum. The following account aims to delineate the cerebellum's role in dystonia and prove that the basal ganglia is not all to blame!

What is dystonia?

Dystonia is an umbrella term used to describe a range of movement disorders characterised by involuntary spasms and muscular contractions. These result in abnormal postures or repetitive twisting motions (athetosis). Tremor is also a common feature. Symptoms are often triggered by particular tasks, such as writing or playing a musical instrument, or certain positions and intriguingly resolve on the application of a sensory, usually tactile, stimulus to the affected area. This phenomenon is known as 'geste antagoniste' or 'sensory trick'[9].

Dystonia disorders can be classified as either focal, if they affect a single body part or generalised, if the distribution is more widespread. These disorders can also be grouped

according to their aetiology. Idiopathic disease has no distinguishable cause, which is the case for most. Some forms of dystonia are inherited – 12 different gene mutations have been identified believed to be responsible for the primary dystonias such as primary torsion dystonia (DYT-1) and dopa-responsive dystonia. Drugs, infections, neurological disorders including stroke and Parkinson's disease and head injury have all been implicated in secondary acquired disease[10, 11].

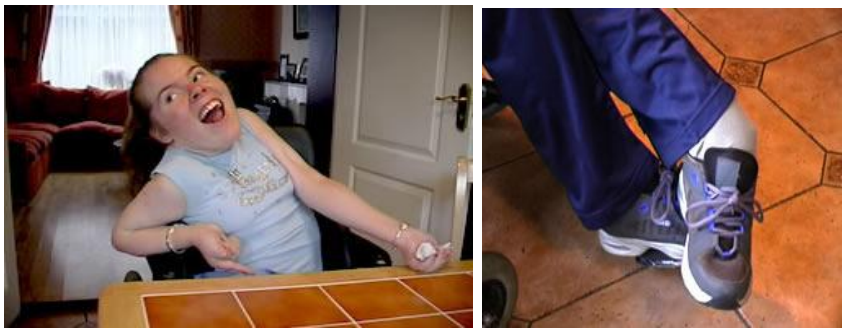

Figure 1: Young woman with early onset generalised dystonia. Note the twisting contraction of her left foot. Taken from http://www.dystonia.ie/page.asp?Page=36&Menu=32

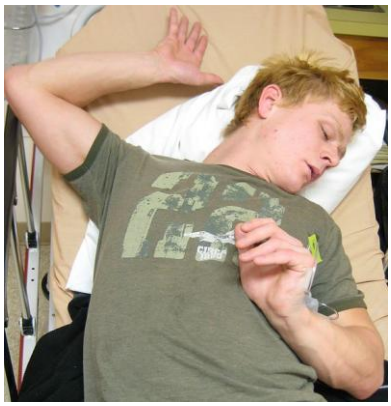

Figure 2: Young man exhibiting symptoms of dystonia in neck & upper limb muscles following administration of a drug. Taken from http://upload.wikimedia.org/wikipedia/commons/thumb/3/35/Dystonia2010.JPG/230px-Dystonia2010.JPG

Diagnosis of dystonia is largely clinical, though blood and urine tests, electromyography (EMG), electroencephalography (EEG) and genetic screening tests may help in some instances[12]. At present, there is no cure for dystonia - most sufferers suffice with analgesia and using 'sensory tricks'; muscle relaxants and botulism injections have also been shown to provide symptomatic relief. Medications such as levodopa and anticholinergics target the basal ganglia and may be of some benefit in certain individuals. Recently, there has also been an interest in surgical interventions such as deep brain stimulation and selective peripheral denervation in treating dystonia[13].

What are the current beliefs surrounding dystonia?

Historically, dystonia was considered a disease of the basal ganglia. Dysfunction in this collection of nuclei has long been the accepted underlying mechanism. In 1989, Robertson et *al.* showed that injecting a conscious monkey with kynurenic acid, a potent inhibitor of excitatory amino acid neurotransmission, deactivated its basal ganglia and produced dystonia-esque symptoms[3,4]. Later, Inase et *al.* showed that as little as 0.25 micrograms of muscimol, a $GABA_A$ receptor agonist, disrupted basal ganglia output in normal, healthy primates and interfered with the control of arm position and movement[5].

However, it was Chiken et *al*'s. novel work with transgenic mice that really sealed the deal. Chiken and his team discovered that murine models of early-onset DYT1 dystonia had abnormally reduced basal ganglia output. In health, the basal ganglia acts via the thalamus, and its connections with the motor cortex, to either facilitate or impede voluntary movement. The pallidal segments of the basal ganglia are tonically active and release GABA to inhibit the thalamus and motor cortex, preventing unwanted movements. Inhibition of the globus pallidus causes so-called disinhibition of the thalamus and expedition of movement[6].

Chiken et *al.* found that in 'dystonic' mouse models, the cortex induced somatotopic disarray and long-lasting inhibition of the pallidal segments. Neuronal activity in the globus pallidus pars externa and pars interna was reduced significantly with abnormal bursts and pauses[7]. Chiken et *al.* concluded that this internal derangement was responsible for the abnormal involuntary movements and self-clasping of limbs seen in these mice[8].

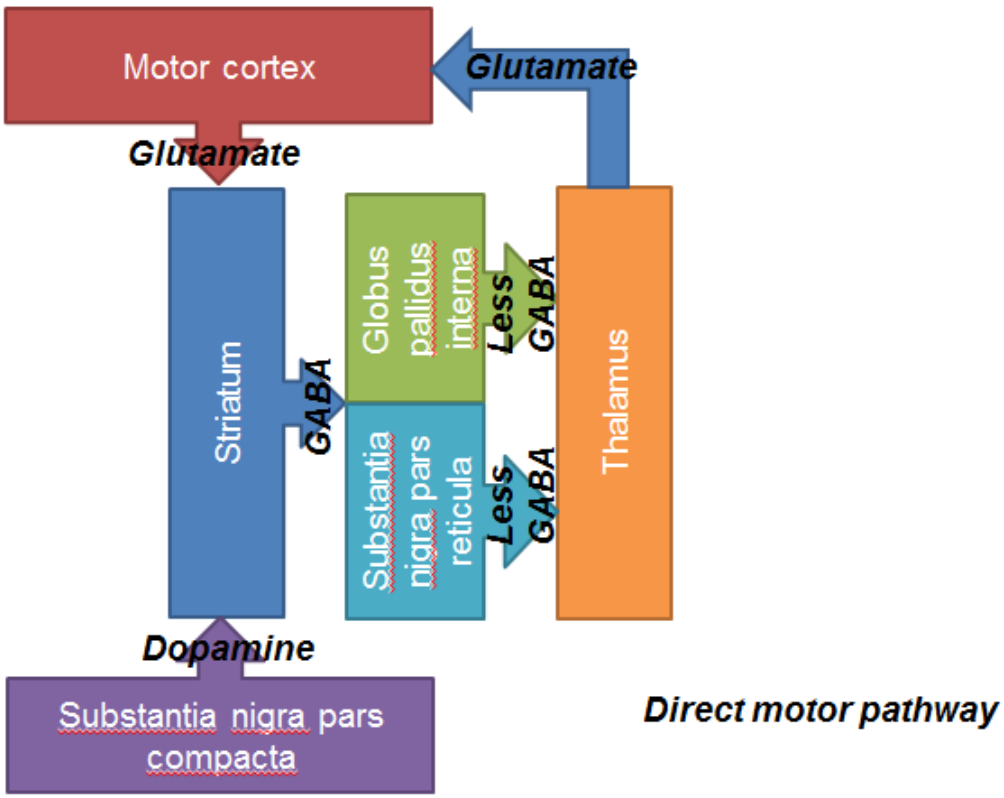

Figure 3 – The direct motor pathway. Substantia nigra pars compacta & motor cortex excite the striatum. In turn, the striatum releases GABA which inhibits the substantia nigra pars reticula & globus pallidus interna. Subsequently, they release less GABA and the thalamus is 'disinhibited' so it releases glutamate to stimulate the motor cortex & promote movement.

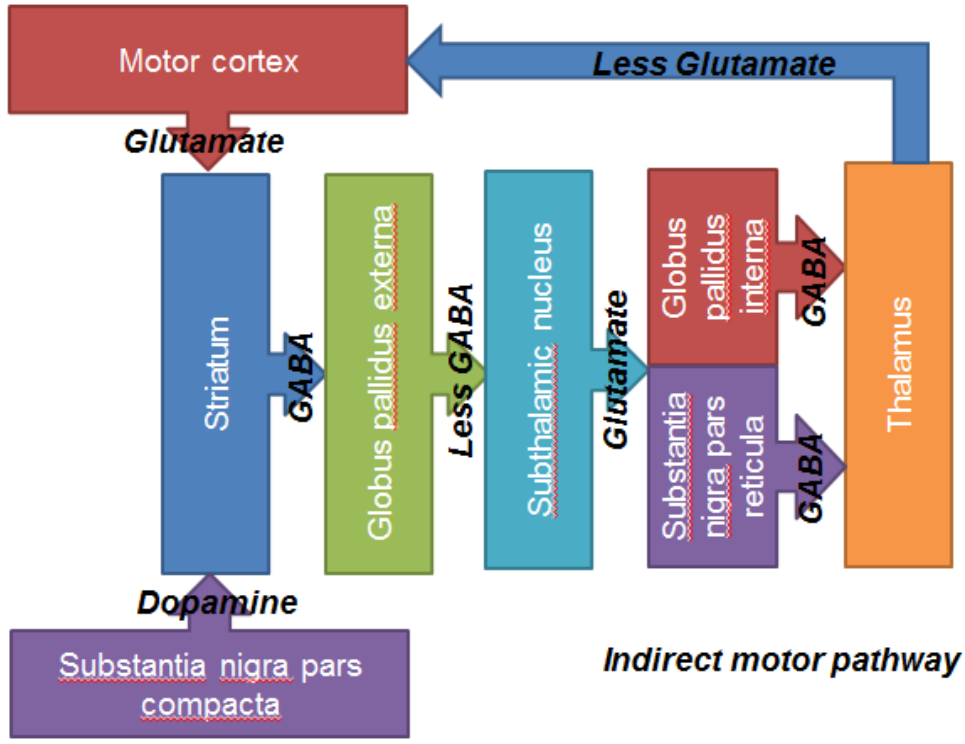

Figure 4 – The indirect motor pathway. Substantia nigra pars compacta & motor cortex excite the striatum. In turn, the striatum releases GABA which inhibits the globus pallidus externa. Subsequently, this releases less GABA so the subthalamic nucleus is relatively excited & releases glutamate. The glutamate excites the substantia nigra pars reticula & globus pallidus interna causing them to release more GABA. The GABA inhibits the thalamus so it does not stimulate the motor cortex & movement is suppressed.

Clearly there is reason to believe that the basal ganglia has some role to play in the pathophysiological mechanisms underlying dystonia. However, there is emerging evidence to suggest that the cerebellum has some part too. This evidence is derived from a variety of sources including animal models, clinical observations and imaging studies. The remainder of this essay will endeavour to review these studies and determine whether or not the cerebellum is as innocent as it seems.

What can animal models tell us about the pathophysiology of dystonia?

Animal models of dystonia have been crucial in our understanding of its pathophysiology. Since the first model was developed in 1976, our knowledge of this condition has grown immensely. In the past decade, copious models have been developed ranging from invertebrates such as Drosophilia melanogaster to nonhuman primates[14]. Work from these models, murine especially, has provided a lot of evidence to suggest the cerebellum may contribute to the pathogenesis of dystonia. This segment will outline some of these animal models – both genetic and pharmacological and what we can glean from them.

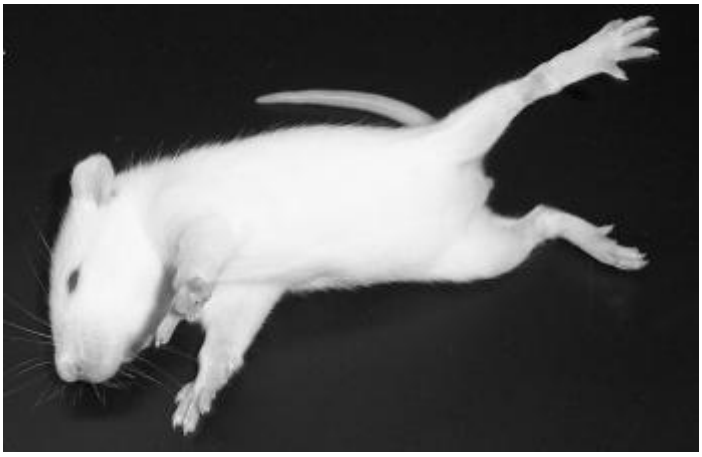

Figure 5 - Photograph of a tottering mouse. Taken from Raike RS, Jinnah HA, Hess EJ. Animal models of generalised dystonia. NeuroRx. 2005 July; 2(3): 504-512

The photograph above depicts a 'tottering mouse', first bred by Wakamori et *al.* in 1998. These mice possess a mutation in the gene encoding the $Ca_v2.1$ (P/Q-type) Ca^{2+} channel needed for normal cerebellar function[15]. As such, these mice experience periods of cerebellar disturbance and, interestingly, suffer from signs and symptoms not dissimilar to those seen in human dystonia. Neychev et *al.* found cerebellectomy significantly improved symptoms and hence, proposed a role for the cerebellum in dystonia. The figure below, taken from Neychev's study, shows motor disability ratings for 5 control mice and 5 mice whose

cerebellums had been removed. Those without a cerebellum had consistently lower scores[16].

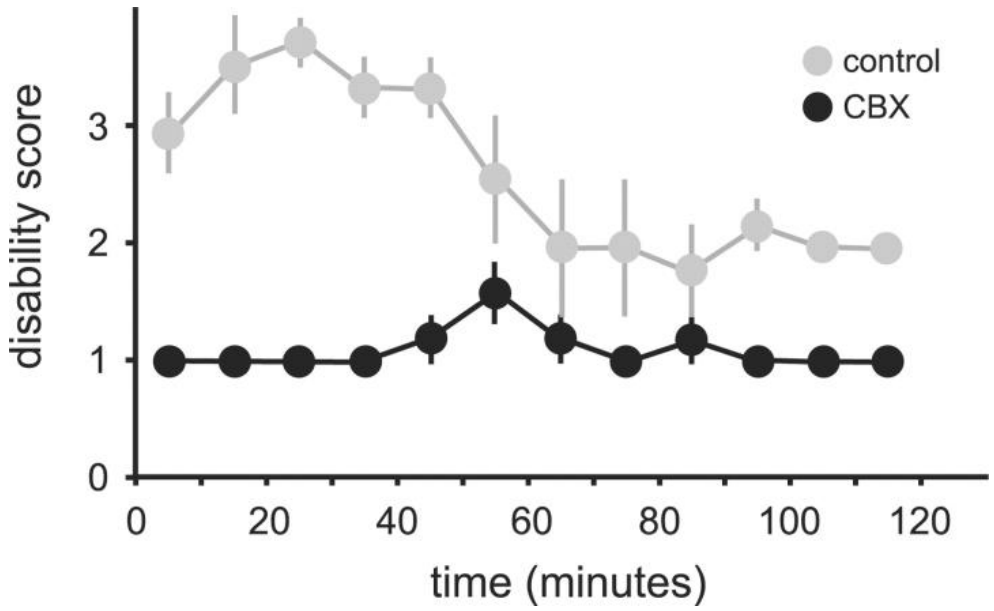

Figure 6 – Graph showing motor disability scores for tottering mice and tottering mice who had their cerebellums excised. Taken from Neychev VK. The basal ganglia and cerebellum interact in the expression of dystonic movement. Brain. 2008 September; 131(9): 2499–2509.

Devanagondi et *al.* at John Hopkins Hospital in Baltimore reported similar findings. Devanagondi and his team studied lethargic mice – a murine model of paroxysmal dyskinesia, a condition characterised by transient attacks of involuntary muscle spasm and contractions. Caffeine was used to induce attacks in these mice before and after cerebellectomy. Post-surgery, as evident in the graphs below, mice exhibited fewer abnormal movements and posturing following treatment with caffeine[17].

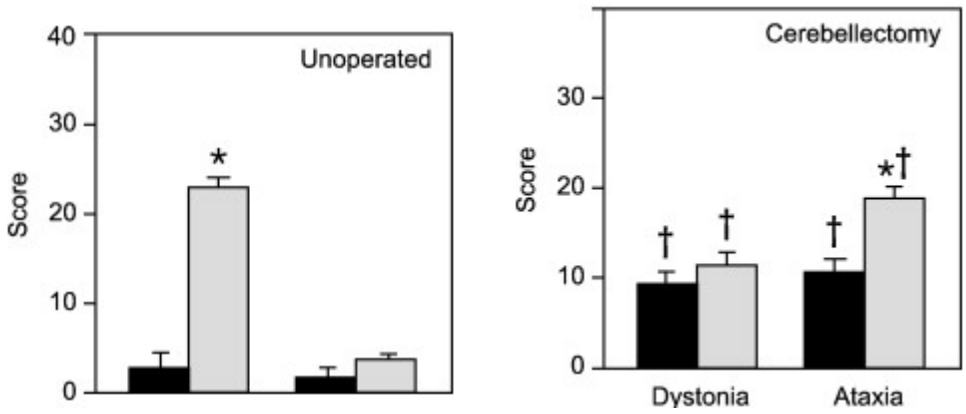

Figure 7 – The grey bars on the graphs above illustrate the incidence of caffeine induced - dystonia symptoms in lethargic mice before and after cerebellectomy. Taken from Devanagondi R, Egami K, LeDoux MS, Hess EJ, Jinnah HA. Neuroanatomical substrates for paroxysmal dyskinesia in lethargic mice. Neurobiol Dis. 2007 Sept; 27(3): 249-57

Devanagondi & Neychev are 2 of many works with murine models in this field. Campbell et *al.* discovered transferring Purkinje cell degeneration (*pcd*) genes into tottering mice completely eradicated their cerebellar Purkinje cell population and also their dystonia[18]. Yokoi et *al.* earlier this year also reported improved motor performance in cerebellar Purkinje-cell knock-out mice[19]. Pharmacological models also point fingers at the cerebellum. Pizoli et *al.* injected kainic acid, a neuroexcitatory amino acid, into the cerebellar vermis of healthy mice and evoked dystonic postures. The results showed a strong positive correlation between the dose of kainic acid and the severity of symptoms with doses of 100 μg/ml and more causing immobilisation[20].

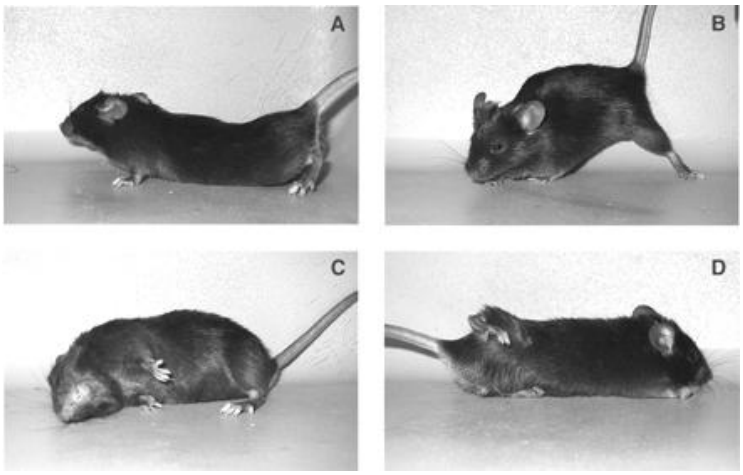

Figure 8 – Kainic acid induced dystonia symptoms in wild type mice. Taken from Pizoli CE, Jinnah HA, Billingsley ML, Hess EJ. Abnormal cerebellar signalling induces dystonia in mice

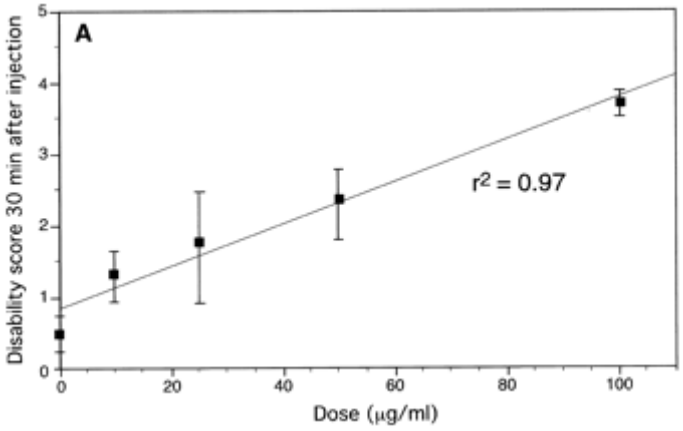

Figure 9 – Graph showing the strong positive correlation between kainic acid dose and motor disability score in wild type mice. Taken from Pizoli CE, Jinnah HA, Billingsley ML, Hess EJ. Abnormal cerebellar signalling induces dystonia in mice

Needless, the literature is littered with animal models supporting a role for the cerebellum in dystonia. Despite sharing 99% of our genes, there are species more closely related to us than mice. More work is needed with these models and advances such as developing the first pig model of dystonia will move us a step closer[22]. Another issue of concern is that findings in animal models may not correlate in humans. It is therefore important to study humans with dystonia. This next section will discuss the evidence in clinical models of disease and what inferences these have.

What have we observed in clinical practice?

Patients can teach us a lot about diseases including dystonia. As well as educating us about the signs and symptoms, they can also teach us about its pathogenesis. Analysis of clinical data provides us with a lot of information regarding the cerebellum's involvement.

Case reports dating right back to the previous century indicate that patients with cerebellar lesions often present with dystonia-like symptoms. Machado-Joseph disease (MJD) is a rare, autosomal dominantly inherited disorder characterised by progressive cerebellar degeneration[22]. It presents with the usual cerebellar signs such as ataxia, nystagmus and dysarthria but Münchau et *al.* discovered that 'dystonia can be part of the clinical spectrum' also. Münchau described a 20 year old MJD sufferer with involuntary twisting and cramping in her extremities and abnormal posturing[23]. Usmani et *al.* postulated a link between cerebellar infarction, and subsequent dysfunction, with late onset focal dystonia, after observing a 37-year old gentleman who developed cervical dystonia 15 months following a cerebellar haemorrhage[24]. Other studies found that cerebellar infarction was also associated with acquired blepharospasm and oromandibular dystonia[25].

Interesting observations have been noted in patients with intracranial neoplasms. There are

numerous types of brain tumour but they all have the potential to compress and/or infiltrate underlying structures. This can result in abnormal function. Posterior fossa tumours can compress the cerebellum, and a 2003 review found were responsible for 44% of acquired cervical dystonia. Compare this to the 24% of cases attributed to the basal ganglia[26]! Resection of these tumours has been shown to improve dystonia symptoms. Krauss et *al.* at the Department of Neurosurgery in Freiburg, Germany discussed the curious case of 3 patients with posterior fossa tumours, who all presented with cervical dystonia. Following removal, symptoms improved in two of the patients – completely remitting in one. However, in the 3rd patient involuntary contractions of the neck muscles persisted [27]. This illustrates that the link between cerebellar dysfunction and dystonia is not simple and there is much to learn. However, there is lots of strong evidence to suggest there is a relationship and we should continue to search.

There are very few clinicopathological studies on dystonic human autopsy tissue and even fewer which examine the cerebellum[28, 29]. With the growing evidence that the cerebellum has an important role in dystonia, such studies may be invaluable. What evidence exists, however, shows significant changes. Examination of the cerebellum of a 3-year-old girl with dystonic limb movements revealed 'inferior olive atrophy, dentate nucleus fragmentation, and thinning of the cerebellar cortex'[30]. A study published earlier this year reported structural abnormalities in cerebellar specimens of 4 subjects with primary cervical dystonia. Neuropathologists documented a 'patchy loss of Purkinje cells, areas of focal gliosis and torpedo bodies' such as those pictured below[31]. Studies such as these and the pioneering analysis by Ma et *al.* endeavouring to quantify these abnormalities, as well as describing them[32], are exciting and provide new insight into dystonia and the cerebellum.

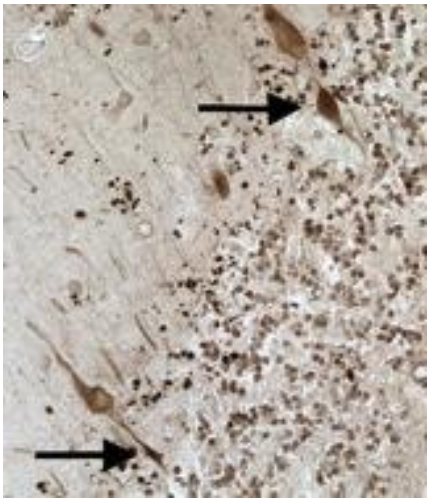

Figure 10 – Torpedo bodies. Dendritic swellings of Purkinje cells in the cerebellum. Taken from Louis ED, Ma K, Babij R, Cortes E, Liem RK, Vonsattel JPG, Faust PL. Neurofilament protein levels: quantitative analysis in essential tremor cerebellar cortex. Neuroscience letters 2012 (518) 1: 49-54

What can imaging show us?

Neuroimaging has been an invaluable resource in our search for knowledge. Being able to look inside the brain has allowed us to make sense of many neurological and psychiatric disorders, dystonia included. Less than a century ago, the only way of peering into the central nervous system was with ventriculography. This method developed by Walter Dandy, celebrated American neurosurgeon, involved injecting filtered air into the ventricles of the brain and using X-rays to create images of the brain and spinal cord[33]. Since then numerous modalities have cropped up including computerised tomography (CT), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI)[34]. Imaging studies have provided a lot of evidence for the cerebellum's role in dystonia. The following section will analyse some of these studies.

Neuroimaging techniques can be broadly classified into those that look at brain function and

those that look at brain structure[34]. Functional imaging data especially, such as those collated using fMRI has been pivotal in our understanding of dystonia. fMRI can measure blood flow to different brain regions in subjects whilst carrying out various tasks. Kadota et *al.* studied musicians with focal hand dystonia during a 'tapping' task. Subjects were asked to touch each of their fingers to their thumb in a sequential order and their brains were monitored using fMRI. The scans revealed abnormal activation of the left cerebellum[35]. Wu et *al.* reported similar findings in their paper in 2010[36]. Wu found significantly reduced blood flow to various brain regions, including the cerebellum, in focal hand dystonia patients asked to perform various hand movements. Abnormal cerebellar activation is also seen in patients with writer's cramp[37] whilst writing and in patients with essential blepharospasm during eyeblinking[38].

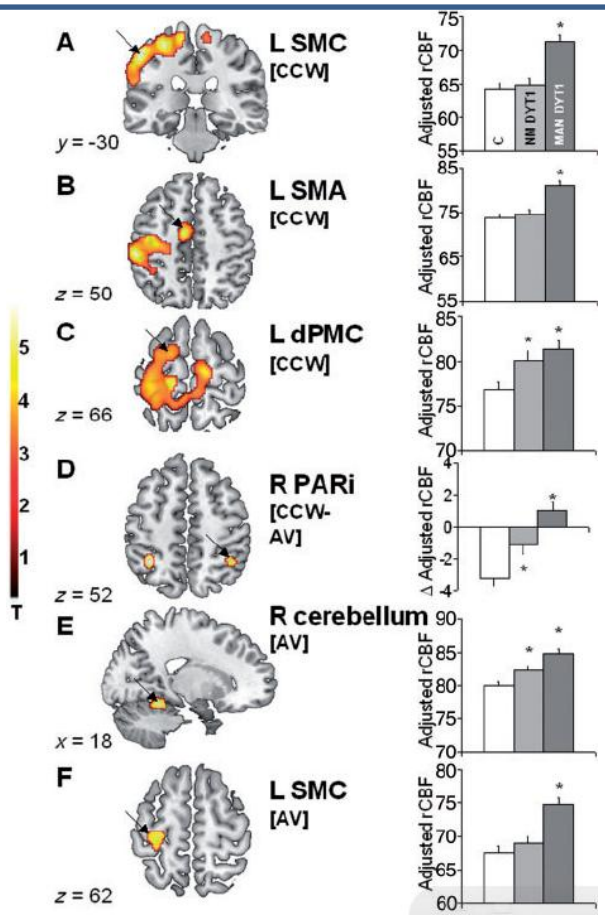

Figure 11 – fMRI images of DYT1 & DYT6 mutation carriers showing abnormal activation in various brain regions including the cerebellum. Taken from Carbon M, Argyelan M, Habeck C, Ghilardi MF, Fitzpatrick T, Dhawan V et *al.* Increased sensorimotor network activity in DYT1 dystonia: a functional imaging study. Brain 133 (2010) 690-700

Inappropriate cerebellar activation is not only seen during movement in dystonia, but at rest too. The figure above was taken from a study by Carbon et *al.* in 2010. Carbon and his team used fMRI to study DYT1 and DYT6 mutation carriers and subjects with sporadic adult-onset cervical dystonia. Carbon reported baseline abnormalities in the cerebellar vermis and hemispheres of dystonic subjects, compared to healthy controls[39]. Eidelberg et *al.* used positron emission tomography (PET), a different form of functional neuroimaging, to

determine the difference in brain activity at rest between DYT1 dystonia patients and healthy controls. He scanned 10 patients and 14 normal volunteers and discovered impaired metabolic activity in the cerebella of the dystonia patients at rest. He also observed that the dystonia patients showed a similar pattern during sleep[46].

Imaging studies have taught us a lot about the pathophysiology of dystonia. In conjunction with animal models and clinical data from patients, we have a wealth of evidence to put the cerebellum behind bars. The next step is determining exactly how the cerebellum is involved in dystonia.

So…we have the evidence but how does the cerebellum actually cause dystonia?

Ikoma et *al.* demonstrated a hyperexcitable motor cortex in patients with dystonia due to an imbalance in excitatory and inhibitory inputs[47]. Till now this imbalance has been credited to the basal ganglia but there is now evidence that the cerebellum is to blame. The final section of this essay will discuss how the cerebellum causes this cortical hyperexcitability.

In health, the cerebellum's main role is ensuring fluid body movements. It tweaks signals traversing the corticospinal tract and coordinates their timing and strength. This makes sure the correct muscle group contracts at the correct time with the correct power, so limb movements are smooth and precise. The cerebellum receives inputs from the ascending sensory pathways and various parts of the brain. Nuclei embedded deep within its substance integrate these inputs and signal to the motor cortex via the thalamus[40].

So what goes wrong in dystonia? The most popular theory at present is failure of the cerebellum to effectively dampen cortical activity as it should (so called cerebellar brain inhibition or CBI). Indeed, Brighina et *al.* demonstrated diminished cerebellar suppression of corticomotor excitability[42]. Furthermore, insufficient corticomotor modulation is only

otherwise seen in patients with cerebellar lesions and hemicerebellectomy[43].

Exact mechanisms underlying insufficient CBI are yet to be elucidated but many theories have been proposed. Argyelan et *al.* found there was reduced cerebellothalamocortical connectivity in dystonia gene carriers. The figure below taken from their study shows poor cerebellar outflow in dystonia gene carriers [both symptomatic (NM) and asymptomatic (MAN)] compared with healthy controls (NL). This poor outflow was associated with over activation of the motor cortex and subsequent dysfunction of muscle groups[41].

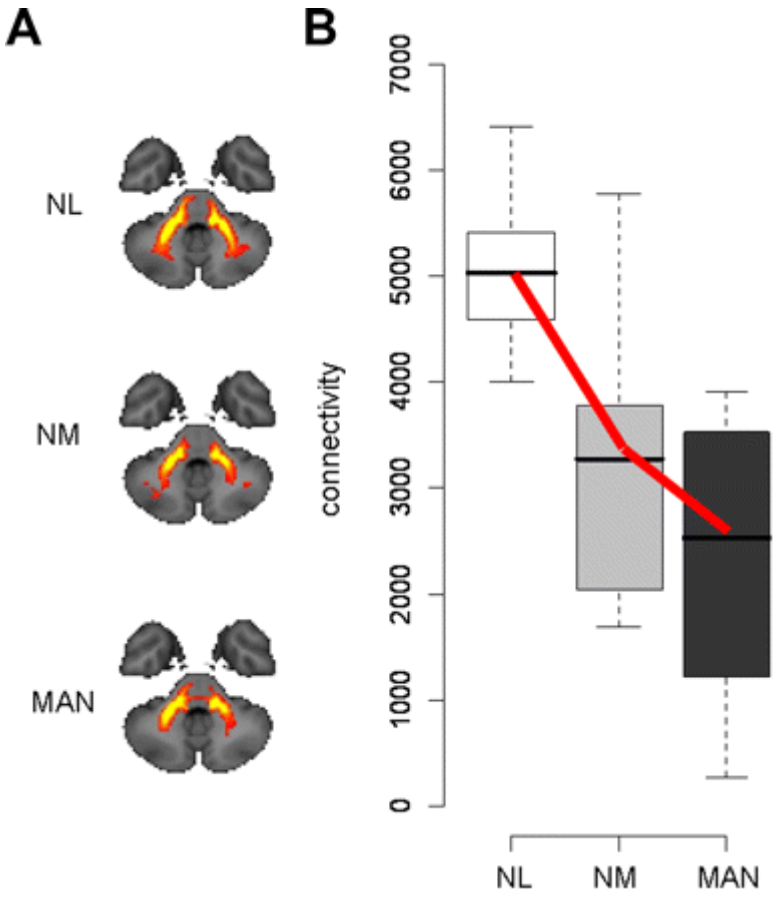

Figure 12 – fMRI images illustrating cerebellothalamocortical connectivity in dystonia gene carriers. Taken from Argyelan M, Carbon M, Niethammer M, Ulug AM, Voss HU, Bressman SB et *al.* Cerebellothalamocortical connectivity regulates penetrance in dystonia. J Neurosci 29 (2009) 9740-9747

Different groups have also put forward different reasons for this 'cortical hyperexcitability'. Argyelan attributes the inadequate cerebellothalamic connectivity[42]. Other studies suggest Purkinje cells in the cerebellum are the problem. Purkinje cells are a major component of the cerebellum. Their job is to tonically inhibit the deep cerebellar nuclei that communicate with the thalamus. Saito et *al.* and Ugawa et *al.* propose that Purkinje cells are hyperactive in dystonia[44, 45]. This results in inappropriate inhibition of the cerebellar nuclei and ultimately reduced cerebellar outflow.

As we have seen from imaging studies, there is abnormal activation of the cerebellum during movement. Hallet et *al.* conducted PET scans on patients with dystonia and discovered their cerebella were only weakly roused by vibration and other tactile stimuli compared with healthy controls. Hallet and his coworkers concluded that was due to diminished cerebellar input from sources such as the spinocerebellar pathway. This seems like a logical explanation but current studies have failed to replicate Hallet's results. More data is needed if we are to accept this theory[48].

One final hypothesis to mention was proposed by Kassavetis et *al.* in 2011. Kassavetis proposed that in dystonia, the cerebellum fails to tightly regulate surround inhibition. Efferent neurones can act on neighbouring neurones to depress activity in the latter and prevent subsequent muscle stimulation. This is known as surround inhibition and accounts for muscle groups working independently of one another[50]. Breakdown of this results in adjacent neurones being simultaneously activated and cocontraction of agonist & antagonist muscle groups. Kassaveti evaluated motor evoked potentials (MEPs) in the first dorsal interosseous (FDI) and abductor digiti minimi (ADM) muscles during a simple motor task where FDI was supposed to be active and ADM was quiescent. Kassaveti demonstrated reduced CBI and surround inhibition on initiation of movement in patients with dystonia but as with many of

the hypotheses described reproduction of results is very much needed to determine its viability[49].

Cortical hyperexcitability appears to be responsible for the signs and symptoms seen in dystonia. How the cerebellum contributes to this remains a mystery, though many scientists have offered their views. The diagram below summarises the hypotheses discussed above.

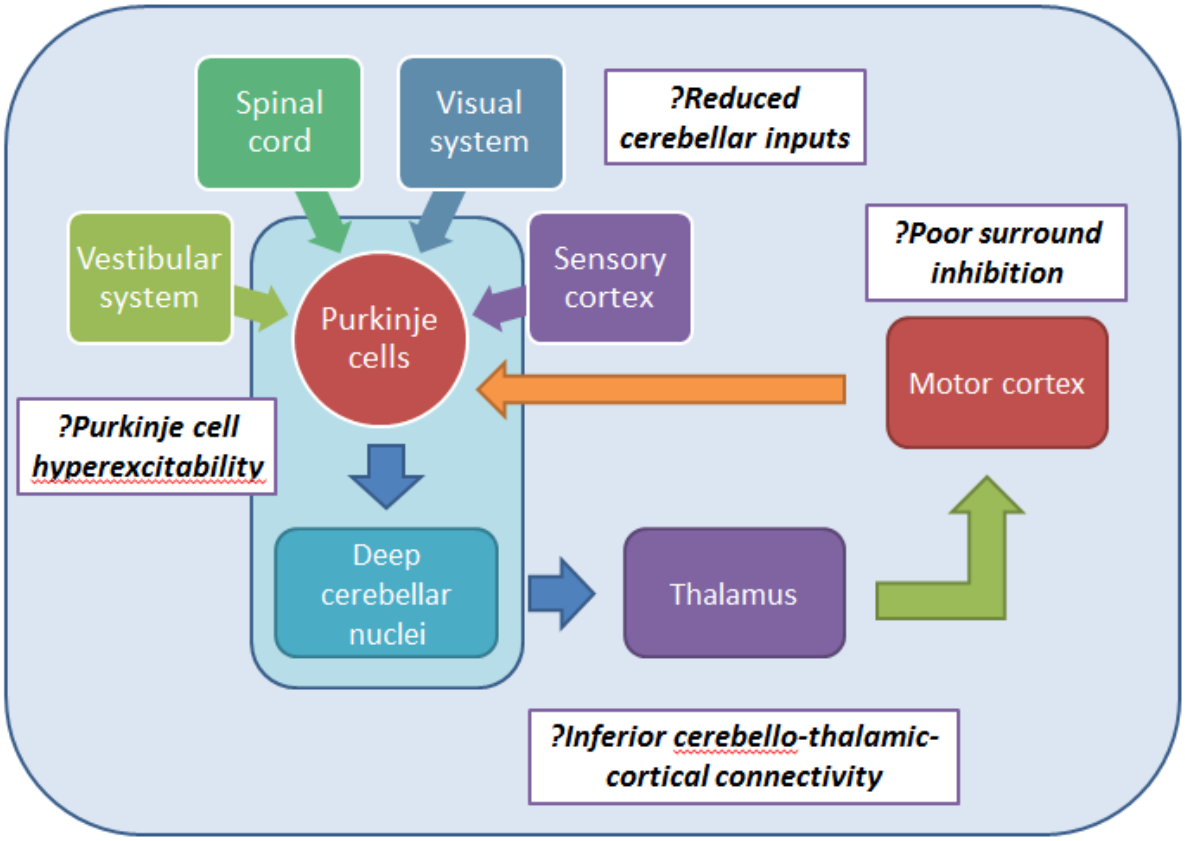

Figure 13 – Schematic illustrating possible cerebellar mechanisms underlying the pathophysiology of dystonia

Conclusion

Dystonia is a surprisingly common disorder, affecting a considerable proportion of the UK population. Despite many advances, we are yet to understand the mechanisms underlying this distressing neurological condition. For a long time, the basal ganglia was deemed to be the perpetrator but thanks to new evidence from animal models, clinical data and imaging studies we now know it is not the only structure to blame. There is a lot of proof to suggest that the cerebellum is implicated, though we are far from deciphering exactly what role it plays. Given that unmasking the true pathophysiology of dystonia will undoubtedly help us improve the management and lives of patients, this is a role definitely worth deciphering.

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