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Basic and Translational Applications of the Network Theory for Dystonia

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Preface

Dystonia is a highly disabling disorder of human movement and postural control. Clinical and scientific data suggest that dystonia can be caused by dysfunction across a range of different brain regions leading to the network theory of dystonia. However, the causal rules of network dysfunction across the subtypes of dystonia are poorly defined. This volume, features work from key researchers in the field that use multimodal methods to explore this fundamental research topic. Chapters focus on both animal models of dystonia and subtypes of dystonia in humans. Edited by Sadnicka and Shaikh, this comprehensive volume is a valuable resource, overviewing contemporary concepts of the pathophysiology of dystonia.

Cleveland, OH, USA — Aasef Shaikh
London, UK — Anna Sadnicka

Editorial

The term dystonia was first introduced by Oppenheim in 1911 and, in combination with other descriptions in the literature, a grouping of a particular type of movement abnormality emerged [1–3]. Patients with dysregulation (-dys) of muscular tone (-tonia) came to be labelled with the disorder dystonia and we now recognize dystonia as one of our core hyperkinetic movement disorders [4].

However, the term dystonia has always been synonymous with complexity and uncertainty. Other early descriptions such as 'tonic cramps in hysterical symptoms' introduced ambiguity as to whether dystonia was a disorder of psychiatric or neurological origins [3]. Furthermore, multiple different loci within the brain have been proposed to play a role. For example, in the 1930s, the vestibular apparatus was considered causative and attempts were made to treat cervical dystonia by sectioning the vestibular nerve [5]. By the 1970s, researchers started appreciating the role of subcortical nuclei in dystonia. The association of focal lesions in the putamen, globus pallidus, and thalamus with dystonia, and favorable response to surgical treatments that modulate or ablate these nuclei, consolidated a role of the basal ganglia and thalamus [6]. The sensory influences over dystonia also became better delineated and the successful treatment of dystonia peripherally with botulinum toxin injections to affected muscles broadened the domain of dystonia even further [7, 8]. More recently, the renewed interest in the prevalence of dystonia in primary cerebellar disorders brought in a new, cerebellar-centric concept of dystonia [9]. However, this in turn also heralded much debate. Some authorities proposed the basal ganglia were the sole cause of dystonia while others emphasized the role of the cerebellum [10]. The challenging and interesting aspect was why those who have basal ganglia involvement or cerebellar involvement present with the shared motor phenotype, dystonia.

Subsequently, the idea of dystonia as a network disorder has emerged [11, 12]. The sensory-motor control network is thought to have multiple nodes and abnormality in any of the nodes can lead to perturbation of the dynamic function of the entire network. The network theory for dystonia helps to explain the diverse physiology of dystonia justifying multiple brain regions as a cause of the same clinical phenomenology. The common resulting abnormal motor outflow is dystonia. Yet it

also offers many challenges as gaining insight into causal mechanisms at each level of description of the nervous system has remained elusive. At which levels are mechanistic substrates shared and where do mechanistic substrates diverge? Such knowledge is key to providing specific treatment tailored to every individual's dystonia.

This book is a collection of chapters from some of the world's experts who have focused their careers on understanding network dysfunction in dystonia. Multimodal research tools such as genetics, animal models, imaging, electrophysiology, and behavioral paradigms have been deployed to probe network function. We are very excited to have been involved in collating these chapters, each of which brings different voices and perspectives to our understanding of dystonia. It is only through the integration of such knowledge that we will start to approach a deeper understanding of the dystonic network. There remains much future promise that we can build on these principles to design better treatments for dystonia.

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Dystonia in Childhood: How Insights from Paediatric Research Enrich the Network Theory of Dystonia

Verity M. McClelland and Jean-Pierre Lin

Abstract Dystonia is now widely accepted as a network disorder, with multiple brain regions and their interconnections playing a potential role in the pathophysiology. This model reconciles what could previously have been viewed as conflicting findings regarding the neuroanatomical and neurophysiological characteristics of the disorder, but there are still significant gaps in scientific understanding of the underlying pathophysiology. One of the greatest unmet challenges is to understand the network model of dystonia in the context of the developing brain. This article outlines how research in childhood dystonia supports and contributes to the network theory and highlights aspects where data from paediatric studies has revealed novel and unique physiological insights, with important implications for understanding dystonia across the lifespan.

Keywords Dystonia · Children · Brain networks · Dystonic cerebral palsy · Sensorimotor integration · Plasticity · EEG · EMG · Neurodevelopment · Neuromodulation

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Abbreviations

CMC	Corticomuscular coherence
CP	Cerebral palsy
DBS	Deep brain stimulation
EEG	Electroencephalogram
EMG	Electromyogram
ERD	Event-related desynchronisation
ERS	Event-related synchronisation
GPi	Globus pallidus internus
HIE	Hypoxic ischaemic encephalopathy
IMC	Intermuscular coherence
MRI	Magnetic resonance imaging
NBIA	Neurodegeneration with brain iron accumulation
PANK2	Pantothenate kinase 2
PET	Positron emission tomography
SEPs	Somatosensory-evoked potentials

Introduction

Dystonia is now widely accepted as a network disorder: rather than a single brain region being responsible, there is strong evidence that sub-types of dystonia may arise from dysfunction within various parts of the sensorimotor network, including the basal ganglia, thalamus, sensorimotor cortex and cerebellum [1–3]. The network model reconciles observations from anatomical studies demonstrating that patients with lesions in multiple brain regions share similar phenotypic features with each other and with dystonia patients who show no evidence of structural abnormalities on cranial MR imaging [1, 4].

The model also accommodates the multiple physiological abnormalities that have been observed in patients with dystonia, including impaired inhibitory function across many parts of the nervous system [5], abnormal sensorimotor processing [6], exaggerated cortical plasticity [7, 8] and pathologically enhanced low-frequency (4–7 Hz) neuronal oscillatory activity within the basal ganglia [9–11], which is coherent with oscillatory activity in the cortex and cerebellum [12].

Dystonias in childhood are relatively under-researched [13–15], and most of the evidence on which the network concept is based originates from adult humans or animal studies. However, research in childhood dystonias not only provides support for the network theory but also has the potential to provide further mechanistic insights, by considering the origins of dystonia from the perspective of the developing brain and a stratum of early expressed and subsequently archived movements and postures capable of re-emerging involuntarily through a variety of pathophysiological mechanisms [13–15]. To fully understand the sensorimotor network

implicated in dystonia requires an understanding of how these circuits first become established in early life.

In this chapter, we initially discuss some of the advantages and difficulties related to research in paediatric dystonia and then review how paediatric research findings in this field support the network theory of dystonia. In particular we focus on those aspects where data from paediatric studies has revealed novel and unique physiological insights, with important implications for understanding dystonia across the lifespan. Finally we highlight the critical need for an expansion of research in paediatric dystonia and suggest future directions needed to inform clinical practice.

Why Study Dystonia in Childhood?

Movement disorders in childhood are a neglected field. There is a considerable body of work in children with cerebral palsy (CP) of predominant spastic phenotype, especially early spastic hemiparesis. The motor disorder in these children includes weakness, hemi-atrophy, reflex excitability and a restricted motor repertoire [16–18]. In contrast, dystonia in childhood, including dystonic/dyskinetic CP, characterised by an over-abundance or overspilling of involuntary movements is sparsely studied [13, 15]. There may be several reasons for this, as follows:

1. Dystonia in childhood is considered to be relatively uncommon compared with spastic CP (although dystonic/dyskinetic CP is under-recognised). This has an adverse effect on opportunities for research, funding and participant recruitment.
2. Dystonia in childhood is usually generalised and severe, affecting the whole body, whereas a larger proportion of dystonia in adults is focal or segmental: Acquiring robust neurophysiological data in any participant with a movement disorder is challenging, but this is even more so when the dystonia is generalised.
3. Assumptions are made that the findings from adult studies can be extrapolated to children.
4. Assumptions are also made that findings can be extrapolated across different types of dystonia (neglecting the different distribution of disorders seen in adults and children).
5. The regulatory approval process for research in children is even more stringent than for adults.

This lack of research in childhood dystonia needs to change for a number of reasons (Table 1) including to improve our understanding of the *complexity* as well as the possible *simplicity* of the 'dystonias' [19]. Children deserve to have an opportunity to participate in research and for research to be pertinent to their specific disorders. Extrapolating from adult studies can be helpful where no other data is available but can also be misleading as the underlying neurophysiology and neurobiological context is different. In addition, research in children can provide valuable mechanistic

Table 1 Importance and value of studying dystonia in childhood

1	The brain is continuing to develop and mature through childhood – one cannot assume that findings in adults can be extrapolated to children
2	Acquired dystonias are more common in childhood, so studying children with dystonia ensures these otherwise under-researched disorders are included in research and, in sufficient numbers, give adequate statistical power to demonstrate or exclude a difference between groups
3	Developmental mechanisms can be investigated – several genetic dystonias have onset in mid-childhood, and many acquired dystonias have onset in the perinatal period
4	Plasticity is generally greater in childhood. This is associated with critical developmental windows for normal development which are also potentially relevant for early intervention
5	Research in childhood is essential for understanding disorders across the lifespan – studying the origins of disease in early life, even in the prenatal and perinatal periods, can provide important insights into mechanisms of what are traditionally considered adult-onset disease

insights which are relevant to patients of all ages and which cannot be gleaned from adult studies alone.

Difference in Sub-type

There are many different sub-types of dystonia and a plethora of different aetiologies [20]. In contrast to adult populations, in which idiopathic or isolated genetic, focal and segmental dystonias are common, acquired dystonias or heredodegenerative diseases are the most frequent aetiology of childhood-onset dystonias [21]. Figure 1 shows the now historically known distribution of aetiology in a cohort of 279 children with dystonia referred to a tertiary paediatric movement disorder service. It is clear that the profile is dominated by acquired dystonias, with 53% of the group having dystonic CP (dystonia due to hypoxic ischaemic encephalopathy [HIE], prematurity, kernicterus or other brain injury before the 1st year of life) [22].

In the field of dystonia research, much *neuropathological* information has been derived from acquired dystonias [23], which have implicated a wide range of brain regions in the pathogenesis of dystonia. In contrast, most *neurophysiological* studies have focussed on adults with ‘primary’ (i.e. idiopathic or isolated genetic) dystonias, in which no structural lesions are visible on conventional brain imaging and which usually show a focal or segmental distribution. Corresponding neurophysiological studies in acquired dystonia are sparse, leading to a mismatch or gap in our knowledge of the relationship between structure and function within the context of dystonia pathophysiology [24].

This is important because some neurophysiological abnormalities that are considered ‘characteristic’ of dystonia are not observed in all patients, and several studies have reported differences in physiological findings between patients with acquired dystonias and those with idiopathic or isolated genetic dystonias [25–27] or between patients with acquired dystonias in which the anatomical site of the lesion is different [28]. The latter study used transcranial magnetic stimulation to investigate measures of corticospinal excitability in 10 adults with various lesions of the basal ganglia. The authors measured the threshold, amplitude and latency of the motor-evoked potential, as well as two measures of inhibition (the silent period and

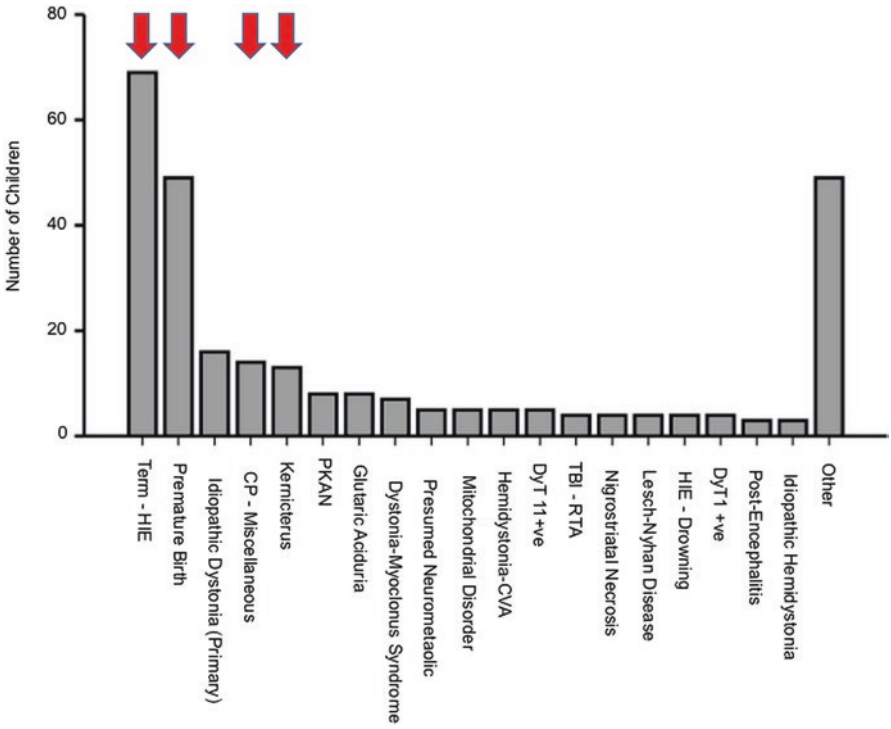

Fig. 1 Aetiology of dystonia in childhood. Diagnostic cause of dystonia across cohort of 279 children referred to a tertiary paediatric movement disorder service. Categories were thresholded at 1% of the total number of children in the cohort. All diagnoses comprising <1% of the total cohort were combined in the 'other' group. Vertical arrows indicate those cases that would collectively meet a diagnosis of cerebral palsy. These have been further subdivided into cerebral palsy caused by hypoxic ischaemic encephalopathy (HIE) at term, as a consequence of premature delivery, as a consequence of kernicterus and miscellaneous other causes. *HIE* hypoxic ischaemic encephalopathy, *CP* cerebral palsy, *PKAN* pantothenate kinase-associated neurodegeneration, *CVA* cerebrovascular accident, *TBI* traumatic brain injury, *RTA* road traffic accident. (Figure reproduced from Lin et al. [22])

short latency intracortical inhibition), and found a correlation between the site of lesion and the neurophysiological findings [28]. Given the greater prevalence of acquired dystonias in childhood, neurophysiological research in paediatric dystonia can provide an opportunity to understand the physiological abnormalities in acquired dystonias, ideally matched to typically developing children, as will be discussed later.

Developmental Insights, Plasticity and Dystonia Across the Lifespan

Another advantage of research in children is the ability to study sensorimotor development, both in typically developing children and in those with movement disorders. Several genetic dystonias have clinical onset in mid-childhood (e.g. DYT1, DYT6), and many acquired dystonias arise from brain injury in the perinatal period

(dystonic cerebral palsy due to extreme prematurity or neonatal encephalopathy/HIE) [29]. These conditions have clear implications for the development of the sensorimotor network and its function.

Developmental Neuroplasticity

Neuroplasticity is generally greatly heightened in childhood compared with adulthood due to the necessity of emerging developing functions of the embryo and in infancy, childhood and adolescence [30]. Several studies have demonstrated lower levels of intracortical inhibition in children than in adults [31–33], which is suggested to facilitate this greater plasticity and motor learning during development [31, 34]. As well as neuroplasticity being generally enhanced during development, the extent to which various plasticity mechanisms are active varies across different parts of the brain and changes during maturation [35]. Thus neurophysiological studies in children with dystonia can provide mechanistic insights that are highly relevant to adults. Although DYT1 and DYT6 dystonia and dystonic cerebral palsy are lifelong conditions, their clinical onset occurs in mid-childhood or the perinatal period, and understanding the pathophysiology in early life is likely to be key to developing and applying relevant therapies and to planning the timing of these early interventions to capture critical windows for neuroplasticity [15, 30].

It is also possible that dystonic disorders with clinical onset in adulthood may have their origins in early life. For example, although mutations in the TOR1A gene were originally identified in DYT1 dystonia, recent studies have demonstrated an association between variant TOR1A mutations and focal dystonias, including writer's cramp [36]. Thus neurophysiological studies in early life, even in prenatal and perinatal periods, may provide important insights into the mechanisms of what are traditionally considered adult-onset disorders.

How Does Research in Childhood Dystonia Support and Enhance the Network Theory?

Although studies investigating the pathophysiology of dystonia in childhood are sparse, the findings from these studies exemplify the network theory by providing evidence for abnormalities within different nodes of the sensorimotor network or their interconnections and also demonstrating that the function of a given node may be impaired in a different way depending on the underlying aetiology.

Basal Ganglia

The involvement of the basal ganglia as one of the key nodes in the pathology of dystonia is well established [1]. Imaging and pathology studies have demonstrated abnormalities of the basal ganglia in acquired dystonias, whilst functional imaging studies including fMRI and PET have provided evidence for involvement of the basal ganglia in 'primary' dystonias (idiopathic or isolated genetic dystonias). Microelectrode recordings obtained from the basal ganglia at the time of surgery

(either for pallidotomy or for implantation of deep brain stimulation [DBS]) have demonstrated abnormal rates and patterns of neuronal firing in dystonia, with lower firing frequencies compared with the non-human primate or patients with Parkinson's disease and a tendency to more irregular, bursting activity [37–40]. Local field potential recordings have revealed exaggerated low-frequency neuronal oscillations in the globus pallidus and subthalamic nucleus in dystonia [9, 11, 12, 41, 42].

A study of microelectrode recordings from the basal ganglia in a cohort of 44 children undergoing deep brain stimulation for dystonia confirmed abnormal neuronal firing rates and patterns in the globus pallidus in this age group (age 3–18 years) [26]. This study also revealed clear differences in globus pallidus neuronal firing patterns between different aetiological groups of dystonia patients, both between primary and acquired dystonia and between sub-types of acquired dystonia [26]. Earlier studies had suggested that abnormalities of basal ganglia neuronal firing were similar between patients with primary and secondary dystonia [43, 44], but this may have been a reflection of small numbers of acquired dystonia patients in these studies ($n = 9$ and $n = 3$, respectively), whereas the paediatric study included 30 patients with acquired dystonia, giving adequate power to detect a difference and the ability to compare sub-groups of acquired dystonia [26]. For example, findings from a sub-group of eight patients with neurodegeneration with brain iron accumulation (NBIA) due to pantothenate kinase 2 (PANK2) deficiency differed from those with other acquired dystonias, with higher firing rates, more in keeping with those seen in Parkinson's disease [26], and a greater proportion of regularly firing pallidal neurons, which tended to be associated with more fixed/tonic dystonia phenotypes [26, 45]. A study reporting local field potentials in six young patients with NBIA (age 8–24 years) shows concordant findings and supports a relationship between pallidal neuronal activity and dystonia phenotype [42]. In contrast, the lowest pallidal firing rates were seen in those with acquired dystonia due to perinatal brain injury (dystonic cerebral palsy) [26]. Similarly low pallidal firing rates have been reported in a more recent study of young people with acquired dystonia [46], indicating reproducibility of these findings.

Sensory Pathways

Somatosensory-evoked potentials (SEPs) are a standard neurophysiological tool used to test the integrity of the sensory pathway from peripheral nerve to sensory cortex. In adults with idiopathic or isolated genetic dystonias, the primary early components of standard cortical SEPs are normal [47–49]. However, in a large cohort ($n = 103$) of young people with dystonia being investigated as possible candidates for DBS, almost half (47%) of the children had an abnormal SEP from at least one limb [50] – see Fig. 2. In contrast, the integrity of the corticospinal tract, as assessed using transcranial magnetic stimulation to measure central motor conduction time, was normal in approximately 80% of the cohort [50–52]. These findings are concordant with diffusion tensor imaging studies showing a higher proportion of abnormalities in thalamocortical sensory rather than motor pathways in children with CP and periventricular leukomalacia [53, 54].

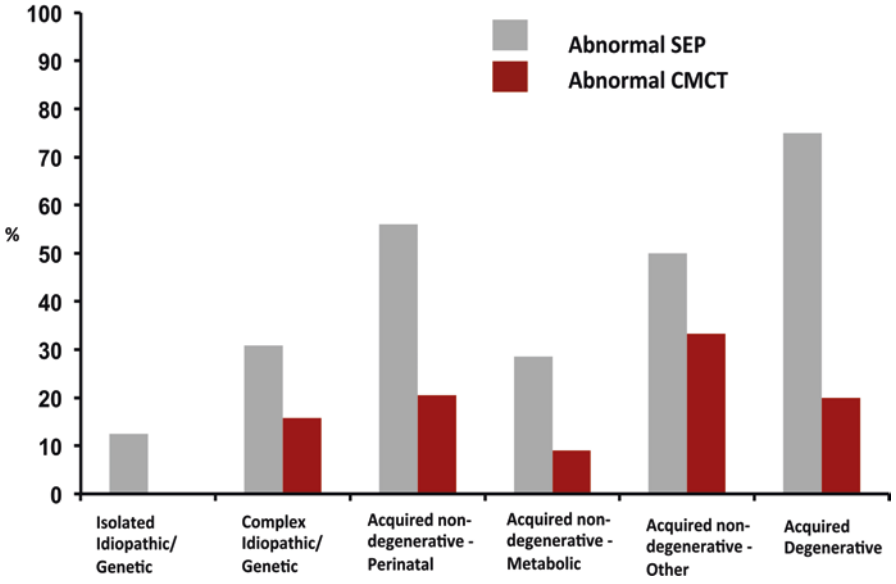

Fig. 2 Proportion of children with dystonia showing evidence of abnormal sensory or motor pathway integrity. Bar chart shows results of neurophysiological tests in a cohort of children with medically refractory dystonia, reported in McClelland et al. 2018. The proportion of children in each aetiological group with one or more abnormal somatosensory-evoked potentials (SEP – grey) or abnormal central motor conduction time (CMCT- red) is shown. Note different denominators since SEP recordings were commenced more recently than CMCT recordings: CMCT abnormal in 0/14 genetic/idiopathic isolated, 3/19 idiopathic complex, 14/68 acquired perinatal (dystonic-dyskinetic cerebral palsy), 1/11 acquired metabolic, 8/24 acquired non-degenerative 'other' and 2/10 acquired degenerative. SEP abnormal in 1/8 genetic/idiopathic isolated, 4/13 idiopathic complex, 28/50 acquired perinatal (CP), 2/7 acquired metabolic, 9/18 acquired non-degenerative 'other' and 3/4 acquired degenerative patients. (Figure reproduced from McClelland et al. [50])

The abnormal SEPs were observed predominantly in the acquired dystonia group, particularly those with dystonic/dyskinetic CP and those with degenerative dystonia due to neurodegeneration with brain iron accumulation or mitochondrial disease. When compared with cranial imaging findings, the abnormal SEPs were seen most frequently in those children with evidence of periventricular white matter damage on MRI [50]. However, abnormal SEPs were seen also in a third (8/25) of those with normal brain MRI scans, suggesting a functional rather than a structural abnormality of the sensory pathway in these cases and emphasising that imaging and neurophysiological techniques both provide important and complementary information [50].

The observed abnormalities of sensory pathway integrity are readily interpreted within the network model of dystonia: whilst adults with isolated idiopathic/genetic dystonia demonstrate abnormal *processin*g of sensory inputs, the abnormal cortical SEPs in a proportion of children with acquired dystonias, particularly dystonic cerebral palsy, provide evidence of an abnormality earlier in the pathway, such that even

the arrival (and/or very earliest processing) of afferent information at the sensory cortex is disrupted [50], i.e. a different node in the sensorimotor network is affected. The brain regions involved in different aetiologies of dystonic CP are clearly in keeping with those implicated in the 'dystonia network'. In particular, it is striking that the brain regions typically affected by a term hypoxic ischaemic insult, i.e. the thalamus, basal ganglia (particularly the posterior putamen), perirolandic sensorimotor cortex and sometimes the cerebellum [55–58], overlap entirely with the main regions implicated in the dystonia network. In extreme prematurity, periventricular leukomalacia or the sequelae of intraventricular haemorrhage are often seen, potentially disrupting thalamocortical pathways, although structural MRI is reported as 'normal' in up to 50% prematurely born children with dystonic/dyskinetic CP [59]. In kernicterus, the injury on MRI is localised to the globus pallidus internus and subthalamic nuclei. It should also be noted that many individuals with dystonic/dyskinetic CP may have had a double or multiple 'hit', with injury to multiple parts of the dystonia network and their interconnections. Moreover, the presence of dysfunction within the sensorimotor network in the perinatal and early postnatal period is likely to have adversely affected the experience-dependent refinement of sensorimotor circuits that is normally ongoing during this critical developmental window [14, 30]. Thus these children add a different perspective to the network concept: they may demonstrate abnormalities at multiple nodes in the network but also illustrate the importance of both the timing and nature of an insult in the developing brain.

Sensorimotor Cortex

Whilst a large proportion of children with acquired dystonia showed an abnormality of sensory pathway function, SEPs were normal in approximately 53% of the children studied, indicating intact primary sensory pathways. The primary components of SEPs are also normal in adults with isolated idiopathic/genetic dystonias, whereas several abnormalities of sensory processing have been demonstrated. For example, abnormal pre-movement gating of SEPs has been shown in adults with writer's cramp [48] or action-type autosomal dominant dopa-responsive dystonia [60], whilst adults with idiopathic/genetic isolated dystonia have impaired central integration of dual somatosensory inputs [49]. The question therefore follows: is sensory processing abnormal in children with dystonia? How can this be investigated?

The studies outlined above assess gating of sensory information using paired pulse SEP studies, which can be difficult to perform reliably in children with movement disorders. However, a more recent study demonstrated abnormal sensory processing in children with dystonia, by investigating changes in spectral EEG activity over sensorimotor cortex in relation to a proprioceptive stimulus [61]. The classical mu rhythm, an 8–12 Hz EEG rhythm recorded over the central regions, is typically suppressed by movement or somatosensory stimulation of the contralateral upper limb [62, 63]. This event-related desynchronisation (ERD) is usually followed by a rebound increase in mu activity, known as an event-related synchronisation (ERS). The mu ERD reflects an activation of the underlying cortical network, triggered by movement preparation or processing of sensory information, whilst the mu ERS reflects a resetting of the sensorimotor system ready for subsequent activity [62–64].

McClelland et al. [61] used a robotic wrist interface to deliver controlled wrist extension movements, thus providing brief stretches of the wrist flexors, in young people with dystonia aged 5–19 years. A clear stretch-evoked potential was seen with comparable amplitude between patients and controls, confirming intact primary sensory pathways and arrival of the afferent information at the sensory cortex in the group studied. However, the typical mu ERD seen in controls was reduced in individuals with dystonia, in keeping with impaired processing of sensory information relating to the stretch stimulus (Fig. 3). Importantly, this finding was observed

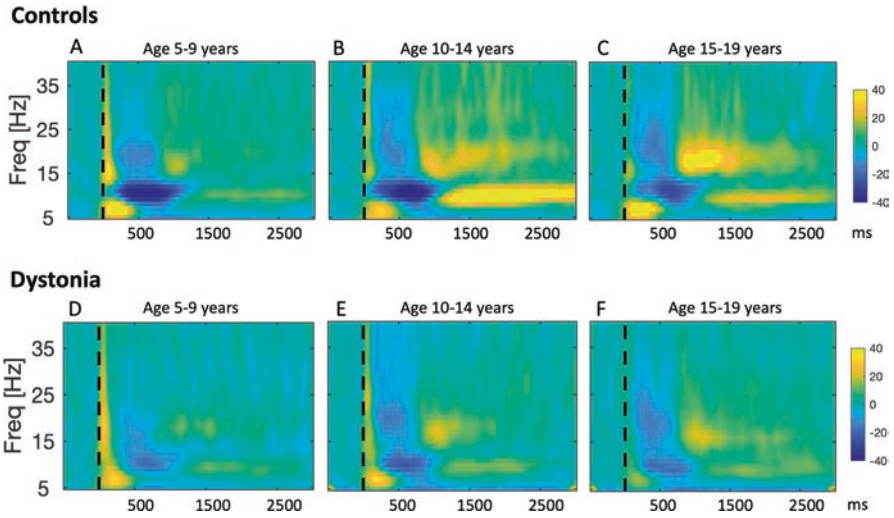

Fig. 3 Developmental sequence of event-related changes in EEG power in relation to a proprioceptive stimulus in typically developing children and children with dystonia, illustrating that children with dystonia show abnormal patterns of oscillatory brain activity compared with controls, in response to passive wrist movement. Changes in sensorimotor cortex EEG were recorded in response to proprioceptive stimuli in 30 young people with dystonia and 22 controls (McClelland et al. 2021). A robotic wrist interface delivered controlled passive wrist extension movements, resulting in brief stretches of the wrist flexors (12° from neutral). Up to 160 wrist extension movements were recorded for each hand. Scalp EEG was recorded using a BrainVision system, and stimulus timing was synchronised with the EEG recordings. Offline, data were segmented into epochs comprising 1 s pre- and 3.5 s post-stimulus. After artefact rejection, EEG power was calculated using continuous Morlet wavelet transform. Relative changes in post-stimulus EEG power with respect to the pre-stimulus period were calculated. The figure shows pooled time-frequency plots across subjects showing the response over the contralateral hemisphere to stretch of the dominant hand wrist flexors, i.e. right cortex for left hand movement, left cortex for right hand movement for controls (**a**–**c**) and dystonia (**d**–**f**), grouped by age. Left column: 5–9 years, $n = 10$ and $n = 7$ respectively; middle column: 10–14 years, $n = 6$ and $n = 11$ respectively; right column: 15–19 years, $n = 6$ and $n = 12$ respectively. x-axis shows time in ms after the stimulus (dashed vertical line), y-axis shows frequency, colour scale shows relative power at each frequency with respect to the pre-stimulus period, such that dark blue indicates event-related desynchronisation (ERD) and yellow-orange indicates event-related synchronisation (ERS). Note that the dark blue ERD in the mu range (8–12 Hz) present in controls around time 500 ms is largely absent in patients, and the yellow mu-range ERS present in controls from 1200 to 2500 ms is also diminished in patients. (Figure reproduced from McClelland and Lin [15])

both in children with isolated genetic or idiopathic dystonia and in those with dystonic CP, indicating a common abnormality of cortical oscillatory activity relating to sensory processing in these groups [61]. Furthermore, the impaired mu modulation was present even in the youngest children tested (age 5–9 years) [61]. To our knowledge this was the first ever study to investigate sensorimotor processing in young children with dystonia and paves the way for future studies investigating how the *development* of sensorimotor processing is impaired in this population.

Reduced mu ERD in response to somatosensory stimuli has been associated with a decline in sensory gating seen in healthy aging [65], so the impaired mu modulation in children with dystonia reported by McClelland et al. [61] may be a parallel finding to the impaired gating of sensory inputs shown in adults with idiopathic or genetic dystonias using paired pulse paradigms [47–49, 60]. The mu ERS was also reduced in patients with dystonia compared with controls (Fig. 3), particularly for the dominant hand, suggesting that the cortical inhibitory processes involved in 'resetting' the sensorimotor network following activation are also impaired [61].

Interestingly, another recent study found that several electrophysiological measures of somatosensory inhibition and sensory cortical plasticity were normal in a group of ten adults with acquired hemidystonia [27]. However, there are several reasons why that study may have observed different findings, including use of different methodologies, which may reflect different aspects of sensorimotor processing, and a more heterogeneous population comprising three perinatal-onset and seven adult-onset brain lesions. The timing of a brain injury will have a significant influence on the effect that a brain lesion exerts on the sensorimotor network [15, 66, 67].

Cerebellum

The cerebellum plays an important role in sensorimotor integration and motor adaptation, i.e. responding to afferent feedback and overcoming perturbations during a motor task, and several studies have provided evidence for a role of the cerebellum and the cerebello-thalamo-cortical pathways in the pathophysiology of dystonia [2, 7, 68–70], although the precise role remains to be defined [71]. A large number of genetic dystonia-ataxia syndromes also exist, consistent with an overlap in pathophysiological mechanisms [72–74]. These include ataxia telangiectasia, in which dystonia may be a presenting or prominent feature [75]. As yet, there are no neurophysiological studies specifically investigating the role of the cerebellum in children with dystonia. However, a recent genetic study of early-onset ataxia with comorbid dystonia has revealed some shared molecular pathways between ataxia and dystonia, in particular relating to cellular energy metabolism and signal transduction [76].

Network Connectivity

Event-related dynamic neuronal connectivity was also found to be abnormal in 16 young people with dystonia [77]. This study used EEG data from across the whole cortex, recorded during the same experimental paradigm as in the mu modulation study discussed above, in which controlled brief wrist extension movements were delivered by a robotic interface [61].

Time-frequency coupling between cortical regions was estimated using the imaginary part of the wavelet transform coherency [78] to assess event-related changes in neuronal connectivity triggered by the proprioceptive stimulus [77]. Individual dynamic connectivity maps showed a strong band of event-related connectivity in the 4–8 Hz (theta) range in young people with dystonia, which was not seen in controls. This is illustrated by the striking yellow patches seen throughout the EEG connectivity matrix in the dystonia patient (A2) in Fig. 4, reflecting excessive neuronal synchronisation in the theta frequency band, engaging many cortical regions (Fig. 4). The overall engagement of cortical areas into short-lived theta-band networks related to the stretch stimulus was calculated for each subject as the global microscale nodal strength and was significantly elevated in the dystonia group compared with controls [77]. Individuals with dystonia also tended to show more widespread engagement of different cortical regions in the activated network [77].

Although structural brain imaging is usually normal in isolated genetic/idiopathic dystonias, previous functional imaging studies have demonstrated clear abnormalities in network activity: in writer's cramp, both functional ('resting state') and effective (during a motor task) fMRI connectivity are abnormal in the

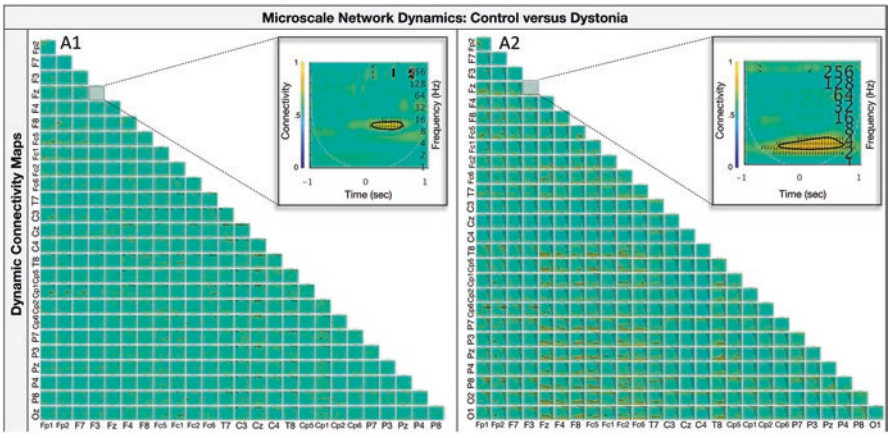

Fig. 4 Dynamic EEG-based neuronal connectivity maps show a striking difference between controls and dystonia with strong stimulus-evoked theta (4–8 Hz)-band dynamic connectivity in dystonia. Connectivity was assessed in response to a proprioceptive stimulus, comprising brief passive wrist extension movements delivered by a robotic wrist interface. Maps show synchronisation values between all possible pairs of EEG electrodes for a typical control (A1) and child with dystonia (A2). Electrodes are shown in X–Y axes with connection strength between pairs as cold (low) and warm (high) colours. Connectivity for each pair is estimated over time and frequency domains (x- and y-axis of subgraphs, respectively) to show the microscale network dynamics around the stretch stimulus (time zero). Upward and downward directions of arrows indicate flow of information from the Y-axis electrode to the X-axis electrode and vice versa. The striking yellow patches throughout the EEG connectivity matrix in the dystonia patient (A2) reflect excessive neuronal synchronisation in the 4–7 Hz (theta) frequency band, engaging many cortical regions. (Figure reproduced from Sakellariou et al. [77])

cortico-basal ganglia and cortico-cerebellar networks [79, 80]; in cervical dystonia, a lesion network mapping study found abnormal functional connectivity, with the cerebellum and somatosensory cortex as the key regions in both idiopathic and acquired cervical dystonia groups [4]; and in DYT1 dystonia, resting-state functional connectivity is increased in the sensorimotor network compared with controls [81]. Animal models are concordant, with a mouse model of DYT1 dystonia showing increased resting-state functional connectivity across the striatum, thalamus and somatosensory cortex but reduced resting-state functional connectivity in the motor cortex and cerebellum [82].

EEG-based connectivity studies have also shown evidence of abnormal cortical oscillatory coupling between regions of the sensorimotor network in dystonia, particularly in the beta- and gamma-bands [83, 84], and reduced gamma-band coupling between primary motor and primary sensory cortices during movement [85]. As noted above, exaggerated 4–12 Hz oscillatory activity has also been demonstrated within the basal ganglia-cortical network in dystonia, indicating excessive neuronal synchronisation in this low-frequency band [11, 12] which is coherent with dystonic EMG [86]. However, our study of dynamic, event-related connectivity in young people with dystonia is the first to demonstrate a theta-band hyper-synchronisation of neuronal activity across multiple cortical regions, *triggered specifically by the proprioceptive stimulus*. The finding was observed in patients with genetic/idiopathic dystonia ($n = 12$) and in acquired dystonia (dystonic CP, $n = 4$) and emphasises that abnormal network activity does not only comprise *reduced* connectivity or coupling but that *increased* connectivity or synchronisation may also be pathological.

Miocinovic et al. [10] found that inter-hemispheric coherence of alpha-range (8–10 Hz) oscillatory activity both at rest and during movement was increased in patients with dystonia when their DBS was turned off and was reduced again when DBS was turned on, suggesting that one of the mechanisms of DBS in dystonia is to reduce network hyper-synchronisation in this frequency range [10].

Motor Command

Understanding the abnormalities within the sensorimotor cortex-basal ganglia-thalamo-cerebellar network underlying dystonia is critical, but it is also important to understand how this abnormal network activity is translated into the motor command.

EMG studies in adults with dystonia reveal abnormal motor unit synchronisation between muscles, showing that co-contraction in dystonia is neurophysiologically distinct from physiological co-contraction [87]. Frequency analysis of the EMG and intermuscular coherence studies reveal a low-frequency (approx. 4–7 Hz) synchronisation between muscles in cervical dystonia [88, 89], myoclonus dystonia [90], and DYT1 dystonia [91]. Although 4–7 Hz intermuscular coherence can also be identified in some healthy controls [92], its prominence in dystonia is striking. Overall, the findings suggest an abnormal low-frequency descending drive to muscles in dystonia, although this may not necessarily be cortical in origin, as discussed below. The level of low-frequency intermuscular coherence in dystonia is reduced

by pallidal DBS and correlates in part with dystonia severity and improvement [93]. Low-frequency pallidal oscillations are coherent with dystonic EMG, with evidence of a bidirectional communication, but with a greater drive from GPi to muscle than in the opposite direction [86], supporting the notion that exaggerated pallidal low-frequency oscillatory activity is not simply a reflection of abnormal afferent feedback.

What do paediatric studies add? A strong band of low-frequency intermuscular coherence has also been demonstrated in children with dystonia [94]. Importantly this low-frequency intermuscular coherence was present not only in isolated genetic or idiopathic dystonias but also in those with acquired dystonias, demonstrating that this is a common feature across multiple aetiologies [94] (Fig. 5).

So what is the origin of this low-frequency drive observed in dystonic muscles and how does it relate to abnormalities within the cortico-basal ganglia-thalamo-cerebellar network? Intermuscular coherence is often used as a surrogate for corticomuscular coherence, with inferences about cortical drive being made based on the pattern of intermuscular coherence. However, it cannot be assumed that the two represent the same physiological phenomenon. Intermuscular coherence may be mediated in part by sub-cortical processes. Interestingly, the same group of individuals with dystonia who demonstrated a strong low-frequency band of *inter*muscular coherence did not show a corresponding band of significant low-frequency coherence between cortex and muscle. Moreover there are differences in the patterns of intermuscular and corticomuscular coherence during the same task: even within the beta-range, patterns of intermuscular and corticomuscular coherence show differences within a given individual [94]. These observations suggest that other, sub-cortical, descending pathways such as the reticulospinal or rubrospinal tract may play a role in this abnormal descending drive in dystonia. It is notable that reticular circuits play a role in sensorimotor integration and in the acoustic startle reflex [95, 96].

Beta-range corticomuscular coherence is also abnormal in dystonia. Beta-corticomuscular coherence represents a bidirectional communication between sensorimotor cortex and muscle and is typically increased by a sensory stimulus relevant to the task [97]. However, young people (age 12–18 years) with isolated genetic or idiopathic dystonia did not modulate their beta-corticomuscular coherence in response to the sensory stimulus [94]. This provides another example of abnormal sensorimotor integration in dystonia as illustrated in a paediatric population, with patients apparently unable to integrate this sensory information into the motor command. In contrast, some of the children studied who had *acquired* dystonia demonstrated a more normal pattern of corticomuscular coherence modulation, indicating a difference in this aspect of sensorimotor network function between individuals with dystonia of different aetiologies [94].

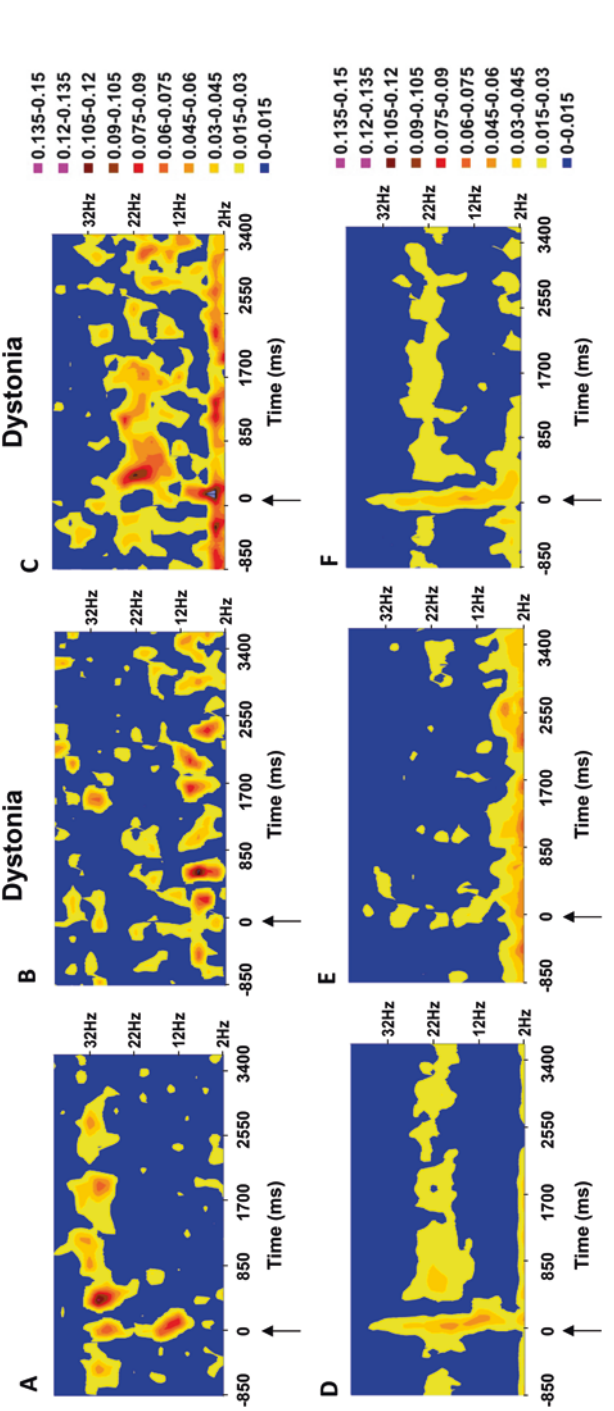

Fig. 5 Intermuscular coherence in children with dystonia versus healthy controls. Plots show spectrograms of intermuscular coherence (IMC) between forearm extensors and first dorsal interosseous during a motor task in which the participant performed a grasp task with the dominant hand. The task involved holding a plastic ruler against the stylus of an electromechanical tapper. Defined tap pulses were delivered to the ruler at time zero, and the pattern of coherence between the two muscles was calculated over time with respect to the stimulus (shown by the vertical arrow). Top row: example spectrograms from individual subjects from (**a**) control, (**b**) idiopathic/genetic dystonia and (**c**) acquired dystonia groups, showing IMC (colour scale) at each frequency (y-axis) over time (x-axis) with respect to the stimulus (arrow). Blue represents non-significant coherence values. IMC is estimated in overlapping 500 ms windows plotted for each 50 ms step. Specified time always refers to the mid-point of the 500 ms time windows. Bottom row: pooled spectrograms for (**d**) controls, (**e**) idiopathic/genetic and (**f**) acquired dystonia. Beta-range IMC is seen in both the control and acquired dystonia groups but is less apparent in the idiopathic/genetic dystonia group. Note the prominent band of 4–12 Hz IMC seen in both dystonia groups, but absent in controls. (Figure reproduced from McClelland et al. [94])

Development of Brain Networks and Directions for Future Research

Understanding network connectivity is likely to prove important for guiding clinical decisions, as illustrated by specific connectivity profiles predicting clinical outcomes from subthalamic nucleus DBS in Parkinson's disease [98]. It is important to recognise that whilst the majority of patients receiving DBS for Parkinson's disease are adults, a substantial proportion of patients being considered for DBS for dystonia are children, and it is clear that the organisation of these networks is still developing even during mid-late childhood [99], as are many processes involved in sensorimotor function [32, 34, 61, 100–104]. This needs to be taken into consideration when investigating the possible use of such measures to guide clinical decision-making such as selection or stratification of patients for neuromodulation or other therapeutic approaches. In addition to patterns of neuronal connectivity changing with age/maturation, these patterns will also be influenced by both the nature and, critically, the timing of a brain insult in early life. For example, preterm birth (one of the causes of dystonic cerebral palsy) is associated with extensive alterations in functional connectivity, due to the associated disruption to early neurodevelopment [105, 106].

Greater understanding of normal sensorimotor network development and how this is disrupted in children with dystonia is therefore critical if we are to move toward a precision medicine approach and optimise therapy on an individual basis. Dystonia is considered a high priority for biomedical research [23, 107] and comprehensive research priorities have been presented, but consideration of age/developmental status as a specific factor is often overlooked in such discussions [107].

Given the greater plasticity in the developing brain [30], the enduring, lifelong impacts of abnormal neuronal activity in early life during critical windows of neurodevelopment [108, 109], and the potential to exploit these windows of opportunity for early intervention to bring greater benefit to patients [15, 110], we argue that further research priorities should include a comprehensive study of the development of sensorimotor networks in typically developing infants/children and in those with early-onset dystonia or at risk of developing dystonia due to perinatal brain injury [15]. The use of common methodologies for clinical, neurophysiological and neuroimaging characterisation of dystonias, including in children, many of which we have reviewed above, has recently been supported in a position paper on dystonia indicating the need for more networked activity to gather bigger datasets and refine understanding and decision-making [111]. Without addressing these significant knowledge gaps, opportunities to harness neuroplasticity within the sensorimotor network to improve the lives of individuals with, or at risk of developing, dystonia will continue to be missed.

Conclusion

Neurophysiological findings in childhood dystonia both support and enhance the network model of dystonia. The inevitable different focus of research in childhood dystonia, with an emphasis on acquired dystonia/dystonic CP, has provided insights that expand and complement scientific knowledge gained from adult studies. Practical and ethical considerations limit some of the work that can be conducted in children, but families are keen to participate, and carefully designed studies can provide valuable opportunities to study the brain during critical periods of development, when brain networks are undergoing rapid change/maturation, when there is prominent experience-dependent refinement of synaptic connectivity and greater neuroplasticity in sensorimotor circuits. Decades of research have led to the unifying theory of the network model of dystonia – the next challenge is to understand this network in the developing brain.

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Focal Dystonia and the Stress Network: The Role of Stress Vulnerability and Adverse Childhood Experiences in the Development of Musician's Dystonia

Stine Alpheis, Eckart Altenmüller, and Daniel S. Scholz

Abstract Musician's dystonia is often described as a neurological disorder, resulting from reduced inhibition in the basal ganglia and the cerebellum and dysfunctional cortical plasticity. However, several studies over the last decades support the hypothesis that psychological factors play an important role in the aetiology of dystonia, contradicting its classification as "purely neurological". Especially adverse childhood experiences (ACEs) such as neglect, maltreatment, or household dysfunction may influence the sensorimotor system, additionally to the impact they have on psychological traits. They are known to alter limbic networks, such as the amygdala, the hippocampus, and the stress response via the hypothalamus-pituitary-adrenal (HPA) axis and might also affect the cortico-striatal-thalamo-cortical loop that is vital for correct motor movement learning. Especially a higher activity of the basolateral amygdala could be important by increasing the consolidation of dysfunctional motor memories in stressful situations.

Therefore, this chapter explores how musician's dystonia might be a result of dysfunctional stress-coping mechanisms, additionally to the already established neurological alterations.

Keywords Musician's dystonia · Adverse childhood experiences · Stress · Limbic network · HPA axis · Amygdala · Dysfunctional brain plasticity

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Abbreviations

ACC	anterior cingulate cortex
ACEs	adverse childhood experiences
ACTH	adrenocorticotropic hormone
AVP	arginine vasopressin
BDNF	brain-derived neurotrophic factor
BLA	basolateral amygdala
BOLD	blood oxygenation-level dependent
CBT	cognitive behavioural therapy
CRH	corticotropin-releasing hormone
CSA	childhood sexual abuse
DBT	dialectical behaviour therapy
EMDR	eye movement desensitisation and reprocessing
fMRI	functional magnetic resonance imaging
GPi	globus pallidus internus
HPA axis	hypothalamus-pituitary-adrenal axis
HPE	high psychological effect
LPE	low psychological effect
MD	musician's dystonia
MIST	Montreal Imaging Stress Task
PFC	prefrontal cortex
PTSD	post-traumatic stress disorder
RNA	ribonucleic acid
SMA	supplementary motor area

Introduction

Professional classical musicians are very much at risk for mental and physical disorders. This is mostly attributed to extremely stressful work conditions with high mental and physical demands and relatively low control options [1, 2]. Playing a musical instrument at a professional level requires years of extensive training of fine motor movements and constant practice throughout a lifetime, while simultaneously being exposed to the unyielding control and scrutiny of colleagues, critiques, the audience, and – above all – oneself.

The great impact that stress has on mental and physical health is well-researched and generally known. It is associated with changes in health risk behaviour and numerous non-communicable diseases such as heart disease, stroke, or cancer and furthermore plays a key role in the development of psychological disorders by influencing a person's psychological dispositions, as well as their neurological functioning. But apart from putting musicians at risk for "conventional" stress-related disorders, we are convinced that stress also affects the key element of any

musician's success: the correct function of sensorimotor movement programs, including their planning, anticipation, and evaluation.

The following chapter therefore offers an overview of current theories centring around the causes and the role of stress in the development of movement disorders in professional musicians, putting a focus on the pathogenesis of musician's dystonia and its involved central nervous networks.

The Psychological Perspective on the Aetiology of Musician's Dystonia

Most professional musicians start playing their instrument in early childhood and have an accumulated practice time of about 10,000 h when they reach the age of 18 [3]. Because of the self-rewarding and emotional aspect of making music, the limbic system is also activated [4], which makes musicians the perfect subject for researchers investigating the mechanisms of movement learning [5–7]. The prolonged training and behavioural shaping of movements with the highest temporal and spatial precision are accompanied by a series of neuroplastic changes, which enable musicians to perform highly complex and quick movement patterns that non-musicians are not able to reproduce. On the downside, under specific circumstances, these neuroplastic mechanisms can also be maladaptive or dysfunctional, leading to a deterioration of motor control [8].

Musician's dystonia (see also contribution by Doll-Lee et al. in this volume), also known as "musician's cramp", has often been described to be a result of dysfunctional neuroplasticity, mostly in sensorimotor cortices [6, 9, 10]. This form of dystonia is to be differentiated from other forms of focal dystonia, such as blepharospasm or cervical dystonia. It is task-specific, which means it is characterised by co-contractions of antagonistic muscle groups, muscular incoordination, and a decrease of voluntary motor control during the specific task of playing a musical instrument. Other fine motor actions (e.g., tying a shoelace or writing) are usually not affected. At instruments such as the piano or the violin, musician's dystonia presents itself as involuntary curling or flexion of limbs/fingers. But it might also occur in the embouchure muscles of wind players, leading to reduced sound quality and loss of articulation and breath control. The highly trained ear and motoric system of professional musicians are sensitive to the slightest of changes. Therefore, even minor impairments of motor control may cause a significant loss of playing ability, and the disorder often ends a performing career. Without appropriate treatment, musician's dystonia may progress into a "dystonic cramp" which as of now can be successfully treated (e.g., with retraining, anticholinergics, or botulinum toxin injections) but not completely healed.

However, maladaptive neuroplastic changes in cortical networks are not the only aetiological factor accompanying musician's dystonia. The involvement of additional brain structures is constantly discussed. Apart from cortical reorganisation,

several findings suggest reduction of inhibition causing the typical co-contractions of antagonistic muscles in focal dystonia patients. This is usually attributed to alterations in the basal ganglia circuitry (for review, see [11]). In the cortico-striatal-thalamo-cortical circuit, one of the many roles of the basal ganglia is facilitating desired movements and inhibiting undesired movements based on the information they receive from the cortex [12]. Recent studies further suggest that the cerebellum, which is important in the accuracy and timing of precise movements, might play a role in cortical excitability and the development of dystonic movements [13, 14]. Therefore, several studies suggest focal dystonia to be the result of alterations in the functional connectivity of networks that include the basal ganglia, the cerebellum, and the thalamus [15, 16]. However, looking at recent findings in musician's dystonia research, this cerebello-basal ganglia network might not be the only network involved, as shall be discussed in the following.

When investigating the pathomechanisms of musician's dystonia, it is to be considered that it is not a nosological entity and comprises different phenotypes. Besides the "classical" task-specific cramping, other motor disturbances in musicians exist that may appear similar to musician's dystonia but present themselves more flexible and better treatable. To describe this condition, Altenmüller and colleagues [17] introduced the term "dynamic stereotype" (DS). It originates from Pavlov (1951; as portrayed by Windholz [18]) and describes conditioned reflexes generated by the influence of numerous outer and inner environmental stimuli on the cerebral cortex. For musicians, a stimulus could, for example, be a performance under highly stressful circumstances where muscular tension is enhanced and dysfunctional motor movements are induced. Dysfunctional motor performance thereby becomes a conditioned reaction to performing under stress. Simultaneously, this conditioned reflex might also be linked to the expectations and even strong emotions associated with certain pieces of music. Some patients show almost no symptoms when performing new music, while at the same time struggling with childhood tunes they have known for a long time. Results of studies investigating psychological profiles and the severity of dystonia in musicians furthermore indicate that a less severe form of dystonia is often associated with stress and perfectionism [19, 20].

If we consider dynamic stereotype as a preliminary stage of musician's dystonia, so to say a "pre-dystonic syndrome", this leads to the question of what role stress and stress vulnerability play for the development of musician's dystonia and movement disorders in musicians in general, both on a neurological and a psychological level. Furthermore, it is still unclear whether musician's dystonia can be differentiated from a dynamic stereotype or if both disorders simply are different degrees of severity on a continuum and both can be considered as the extremes of a "spectrum disorder".

Trauma, Stress, and Anxiety

Apart from established risk factors for musician's dystonia (e.g. male sex, a genetic disposition, and a late start of playing the instrument [21–23]), there has been an ongoing discussion throughout the last decades to what extent trauma and psychological trigger factors play a role in the development of musician's dystonia. With respect to bodily trauma, we fortunately have an animal model, clarifying some of the aetiological mechanisms. In animal experiments it was demonstrated by Ip and colleagues [24] that peripheral nerve lesions of the sciatic nerve induced limb dystonia far more frequently in genetically modified mice expressing only 50% of Torsin1a, as compared to wild-type mice. This was accompanied by complex alterations of striatal dopamine homeostasis. When considering bodily trauma as a trigger of focal dystonia in adult humans, the situation becomes more complex. It has been known for many years that peripheral injuries and trauma may trigger focal dystonia. This has been demonstrated very convincingly in patients suffering from complex regional pain syndrome (for review, see [25]) and has been verified in a huge database on more than 65.000 dystonia patients for other physical trauma [26]. However, the situation is not as straightforward when considering the location of the trauma and the phenotype of focal dystonia. Defazio and colleagues [27] analysed data from the Italian Dystonia Registry regarding the occurrence of acute peripheral trauma severe enough to require medical attention in 1382 patients with adult-onset idiopathic dystonia and 200 patients with acquired adult-onset dystonia. They found in idiopathic and acquired dystonia a similar burden of peripheral trauma in terms of the number of patients who experienced trauma (115/1382 vs. 12/200) and the overall number of injuries (145 for the 1382 idiopathic patients and 14 for the 200 patients with secondary dystonia). Most traumata occurred before the onset of idiopathic or secondary dystonia. However, only in about 10% of such injuries, dystonia developed in the same body part as that affected by dystonia. Therefore, it seems that an underlying independent factor, such as stress, linked to the bodily trauma, may be causally involved.

In several studies, certain psychological predispositions and personality characteristics have been identified to occur more frequently in task-specific dystonia patients. Jabusch and colleagues [28] found higher perfectionism scores in musicians with dystonia, compared to healthy controls and musicians with chronic pain. Musician's dystonia patients stated no differences in their perceived perfectionism before and after the onset of dystonia, meaning the perfectionistic tendencies may have contributed to the pathogenesis of dystonia. Dystonia patients also show more often anxiety disorders and stronger emotionality, as well as higher scores in internal control [28]. Studies researching anxiety in musician's dystonia patients found especially social phobias and specific phobias to co-occur more often [29]. In a related study, significantly higher state and trait anxiety as well as neuroticism were observed in musicians with dystonia compared to healthy controls [30]. Whether these characteristics are psycho-reactive phenomena or are pre-existing to the disorder, thereby promoting its pathogenesis, cannot easily be determined. Since most

musician's dystonia patients seem to report these psychological characteristics as pre-existent to the onset of their dystonic symptoms, Jabusch and Altenmüller [31] suggested anxiety and perfectionism to be aggravating factors, possibly rendering the sensorimotor system more susceptible to dysfunctional procedural sensorimotor memory traces and movement habits. Alternatively, already in this paper, Jabusch and Altenmüller discussed whether anxiety and perfectionism influenced practice behaviours in a way that would predispose for maladaptive plasticity in sensorimotor networks.

Musicians have furthermore reported to often have been confronted with psychological and/or social stressors (e.g. increased practice time due to an important audition or concert) prior to their first dystonic symptoms [5, 32]. Under circumstances with increased social pressure, small disturbances in motor performance are perceived as even more stressful and threatening, especially for musicians who already show tendencies towards perfectionism and anxiety. A low stress resilience in the highly stressful work environment of a professional musician therefore might pose an additional risk factor for musician's dystonia.

When exploring psychological characteristics of musician's dystonia patients, Ioannou and Altenmüller [33] differentiate between a "high psychological effect" (HPE) and a "low psychological effect" (LPE) cluster in their study. The HPE group was characterised by elevated levels of anxiety, stress, and perfectionistic behaviour. It was observed that musicians with focal dystonia were six times more likely to belong to the HPE group than healthy musicians, but about half of the musician's dystonia patients could also be characterised by LPE. In a further study, [20] investigated stress reactivity in musician's dystonia patients using the Trier Social Stress Test [34]. In this study, they found proportionately more focal dystonia patients than healthy musicians to belong to the "stress responder" group, meaning an increased neurobiological reaction to the presented stressors. These stress responders were additionally found to have developed dystonia about 10 years earlier than the stress non-responders.

Recent studies and numerous individual reports of dystonia patients have now led to the hypothesis that adverse childhood experiences (ACEs) might also play a role in the aetiology of musician's dystonia [35, 36]. In a qualitative multiple case study by Schneider and colleagues [36], six musicians suffering from dystonia reported high levels of perceived stress in childhood through traumatic experiences, such as emotional neglect, violence from a parent, divorce, or extreme pressure from teachers. Through follow-up questions and grounded theory methodology, patients and researchers alike associated these experiences to the movement disorder in later life. In a further comparison between musician's dystonia patients and healthy musicians [19], emotional neglect from parents was experienced more often by the patients and identified as a relevant influencing factor for musician's dystonia. Musicians with more severe adverse childhood experiences were also found to experience more severe subjective disability due to their disorder. The results of the study made it clear, however, that psychological traumata are highly individual and not easily measured by standardised questionnaires. Many participants reported additional single traumatic events that were not assessed in the questionnaires

applied, which is why further investigations are needed. Developing musician's dystonia after having experienced adverse events in childhood, however, would not be all together surprising; early trauma such as abuse or neglect are known to foster perfectionism [37] and anxiety [38], which are both associated with musician's dystonia. But adverse childhood experiences also alter stress regulation on a neurobiological level [39]. We therefore hypothesise that adverse childhood experiences increase the risk of suffering from movement disorders by inducing lower levels of stress resilience and contributing to more vulnerable sensorimotor programs [40, 41]. The precise neurobiological network disbalance, however, remains to be determined.

Proposed Model of Interplay Between Psychological Stresses and Development of Musician's Dystonia

Even though psychological components are clearly involved in the aetiology of musician's dystonia, their role seems to be different from the role psychological factors play in the aetiology of what is clinically often referred to as "psychogenic" or "functional" movement disorders. The most recent version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) uses the terms conversion disorder and functional neurological symptoms disorder to describe disorders with somatic symptoms that are not compatible with "recognised neurological and medical conditions" [42]. These symptoms might range from weakness, paralysis, and abnormal movements to abnormal sensory sensations. Functional neurological symptoms disorder is often associated with stress and trauma (physical and/or mental) and co-occurs with additional diagnoses such as anxiety, depression, or chronic fatigue [43, 44].

Interestingly, according to a recent review [45], functional movement disorders in children seem to be related to physical, emotional, and sexual child abuse or to neglect. However, another study [46] found no significant correlations between perfectionism, adverse childhood experiences, and functional movement disorder phenotypes (20% of which were dystonia). Due to the unique neural mechanisms behind playing a musical instrument (see section "The neurobiological effects of stress on movement learning and motor memories in musicians"), it is unclear if these findings are transferable to the aetiology of musician's dystonia. In dystonia patients, depression and anxiety sometimes appear as psycho-reactive phenomena, given that the disorder usually threatens the professional position and entire livelihood. However, additional psychological diagnoses and cognitive symptoms are not usually documented as a cause or at the onset of dystonia. But since anxiety – just as stress and traumatic experiences – lies at the base of many mental and physical disorders, cause and effect are very difficult to differentiate in this context. Shill and Gerber [47] evaluated diagnostic criteria for psychogenic movement disorders and worked out four main criteria besides psychological comorbidity. These criteria can

be nicely used to compare similarities and differences in functional movement disorders and dystonia: (1) sudden onset of symptoms – musician's dystonia usually is a slowly oncoming process, with the symptoms intensifying with time and with more practising; (2) inconsistent symptom presentation – most dystonia patients experience consistent symptoms with very specific tasks or with very specific musical pieces; (3) clear response to placebo interventions – in some patients, termination of the dystonia minutes after application of botulinum toxin injections has been observed [48]. If this is the case, the dystonic symptoms are believed to be more of a functional movement disorder, since botulinum toxin only develops its full effect after 2–3 days and its effect should not be noticeable directly [49]. (4) Improvement of symptoms when directing attention to an external focus, as has been reported in several studies – some patients show short-time improvement when the sensory input at the affected limb is altered, for example, by wearing a latex glove [50]. An external focus, e.g. focus on the musical output, which is actively practised when making music, does not seem to affect the symptoms. As becomes apparent in this direct comparison, there are common elements, but also clear differences, between musician's dystonia and functional movement disorders. We suggest that musician's dystonia is a manifestation of dysfunctional stress regulation on a network level, which sets dystonia on a continuum between neurological and psychogenic movement disorders. Adverse childhood experiences could contribute to the genesis of musician's dystonia by affecting psychological dispositions and stress regulation, making musicians more susceptible to perfectionism and anxiety, and increasing muscular tension in "threatening" situations. But – as described in Fig. 1 – the effects of experiencing stress are never purely psychological but always connected to alterations in neurobiological structures and their functioning. Furthermore, stressors and psychological states and traits are interconnected via numerous feedback loops. For example, a traumatised child might display behaviours which then may lead to alterations in parental bonding resulting in emotional neglect as consequence of prior traumatisation. Additionally, many of the psychological conditions displayed in Fig. 1 may be interrelated, for example, anxiety disorders and perfectionism. The association of perfectionism with numerous forms of psychopathology was impressively displayed in a meta-analysis by Limburg and colleagues [49], while a study on young musicians [50] further confirmed an association of dysfunctional perfectionism with anxiety.

Regarding the classification of musician's dystonia, an involvement of adverse childhood experiences in the aetiology supports the theory that musician's dystonia may differ from other forms of focal dystonia, such as torticollis or blepharospasm. Obviously, it is not only the result of motor circuit dysfunctions of the basal ganglia and the cerebellum but also a manifestation of dysfunctional stress-coping mechanisms involving limbic structures. Different degrees of involvement of emotional-memory pathways through the limbic system and frontal cortical areas could offer an explanation for the differences in symptom severity and symptom expression observed in musician's dystonia patients [33].

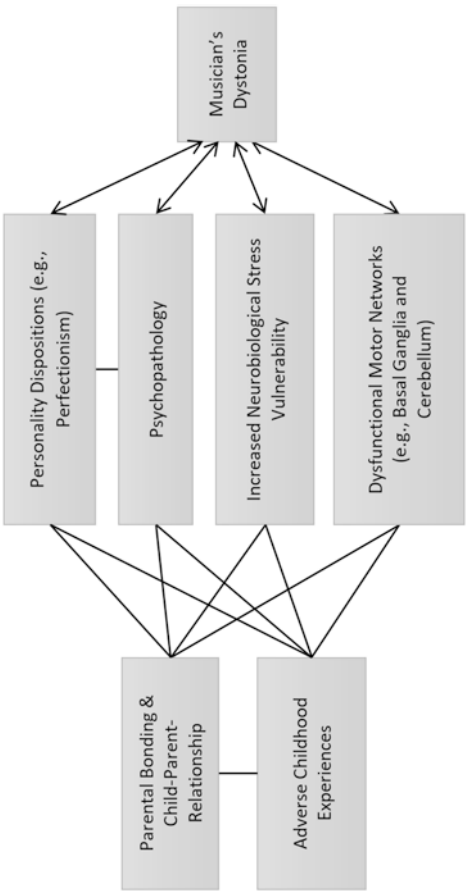

Fig. 1 Potential pathogenic influences of adverse childhood experiences and their psychological and neurological correlates on musician's dystonia

The following section describes a hypothetical causality of how stress might be central to the pathogenesis of movement disorders such as dystonia by affecting different neural networks.

The Impact of Stress on Neural Networks and the Development of Musician's Dystonia

The stress network includes several structures and functions that are active in perceivably stressful and threatening situations. Mainly associated with stress are the limbic system, including the amygdala, hippocampus, and orbitofrontal cortex, and the hypothalamus-pituitary-adrenal (HPA) axis (for review, see [51]). The HPA axis, responsible for coping or fighting external stressors ("fight or flight" [52]), is activated in threatening situations and responds by releasing different neuroactive hormones. When confronted with a potential threat, the corticotropin-releasing hormone (CRH) and vasopressin (AVP) are released in the hypothalamus. This leads to the secretion of the adrenocorticotropic hormone (ACTH) in the pituitary gland, which is in turn responsible for the release of glucocorticoids (e.g., cortisol) in the adrenal gland. Glucocorticoids help to increase attentiveness and alertness in a situation of threat and release energy to better be able to face the stressor [53, 54]. In these situations, stress responses are clearly functional and have adaptational value. In contrast, chronic stress, especially during sensitive periods in childhood and adolescence, has severe consequences on learning and memory formation and impacts neuronal networks via direct neuroplastic and indirect epigenetic mechanisms not only in the limbic system and the hippocampus but also in the prefrontal cortex (for a review on the detailed respective mechanisms, see [55]). Since the prefrontal cortex is crucially involved in sensorimotor planning and multisensory integration, here we have a hypothetical link between chronic stresses during sensitive periods such as adverse childhood experiences and susceptibility for network dysfunction.

In the investigation of the aetiology of musician's dystonia, alterations in the cerebral cortex, the basal ganglia, and cerebellum are often discussed together with a loss of inhibition on a neural and spinal level. The basal ganglia are essential in the cortico-striatal-thalamo-cortical circuit for facilitating desired movements and inhibiting undesired movements based on the information they receive from the cortex [12]. Studies have amongst others found overactivity in the globus pallidus and the substantia nigra pars reticulata of the basal ganglia [56, 57], as well as increased activation of the thalamus [58] in dystonia patients. The resulting decrease of inhibitory mechanisms in the motor cortex is believed to possibly lead to the often-observed unwanted movements and co-contractions of antagonist muscle groups in musicians with dystonia, while also affecting further planning and execution of motor movements [59, 60].

We shall explore now in detail how both these networks, the limbic and the sensorimotor network, are affected by adverse childhood experiences and stress and how these factors may induce susceptibility for musician's dystonia.

How Stress and Adverse Childhood Experiences May Cause Dysfunctional Procedural Movement-Memories in Adulthood

Both postnatal and early childhood experiences are especially important in forming a healthy stress response, since adverse childhood experiences seem to lead to a dysregulation of the sympathetic nervous system and influence stress regulation from an early age [39]. Even though researchers agree that adverse childhood experiences do have an influence on the HPA axis, findings are contradictory as to whether this influence results in hyper- or hypoactivity of the HPA axis, correspondingly leading to an increased or decreased level of cortisol (for full review, see [61]). In some studies [62, 63], increased activity of the HPA axis in stressful situations has been reported as a result of long-term elevated release of cortisol (e.g., due to regular parental maltreatment). Correspondingly, affected individuals would sooner assess a situation as threatening, would feel attacked more quickly, and often react aggressively [53]. Other studies [64] reported lower levels of cortisol in victims of adverse childhood experiences compared to non-traumatised adolescents. According to De Bellis and Zisk [61], neurobiological long-term consequences of childhood trauma seem to depend on genetic predispositions, the type of trauma, and other promoting environmental factors (e.g., secure attachment to the not-mistreating parent). As described above, musicians are constantly exposed to stressful situations in their work environment, while they are performing and playing concerts but also while they are practising and learning new movements. There is furthermore evidence that musicians in general have experienced adverse events more often in their childhood, compared to a control group of non-musicians [65], which might be received as surprising. A possible explanation for this could be that those individuals with a history of negative childhood events use music to either escape reality or else to regulate their emotional state [66] and therefore decide to pursue this profession more often.

As already mentioned above, adverse childhood experiences and chronic stress are known to alter the limbic system on different levels. As excellently reviewed by McEwen and colleagues [55], on a biomolecular level, chronic stress induces dendritic remodelling in both the hippocampus and the basolateral amygdala, probably via brain-derived neurotrophic factor (BDNF) over- or under-expressing [67]. Additionally, excitatory amino acids and reduced endocannabinoid receptors seem to play a major role in the long-term consequences of chronic stress. Finally, the role of epigenetics, specifically in the hippocampus, is about to be clarified. Obviously chronic stress can lead to reduction of the coding and non-coding ribonucleic acid (RNA) in the dentate gyrus of the latter structure (for review, see [55]).

On a structural level, several reviews and meta-analyses have been conducted investigating the associations of experiencing childhood trauma with stress-relevant neural structures such as the hippocampus, the amygdala, and the anterior cingulate cortex (ACC; [68, 69]). These areas might be especially relevant to the stress respondence due to their high number of glucocorticoid receptors [70]. Several studies observed a reduction in hippocampal volume in victims of childhood maltreatment. However, this effect seems to be strongly dependent on gender, psychopathology, and type of maltreatment [68]. Contrary to the hippocampus, the amygdala has most often been found to be increased in volume. Early life stress in the form of long-term institutional rearing, for example, has been associated with greater amygdala volume, as well as difficulties in regulating emotions [71]. There is furthermore some evidence that experiencing a specific type of trauma affects especially those brain regions that were also involved in perceiving the trauma; witnessing domestic violence, for example, has been associated with alterations in the connection between the limbic and the visual system [72]. Whether this might also hold true for physical trauma and corresponding alterations in the motor regions involved in musician's dystonia remains unclear. Cortical thinning of amongst others the somatosensory representation of the genital areas and the ACC was found in victims of childhood sexual abuse (CSA; [73]). A smaller volume of the ACC and the caudate nucleus of the basal ganglia was also observed by Cohen and colleagues [74], but it has not been investigated how such findings relate to movement disorders in the upper extremities. Furthermore, Anderson et al. [75] noted a decreased blood flow in the cerebellar vermis of CSA survivors, and a decrease in volume of the cerebellum was found in previously maltreated children and adults [76]. Network alterations in this region may affect movement organisation [77], especially if the abuse occurred early. As is shown in several studies, including a chapter in this volume, the cerebellum is involved in a network relevant for musicians' dystonia (see Doll-Lee et al. in this volume).

In a meta-analysis, Stark et al. [78] explored activation patterns in the basal ganglia in patients with history of trauma with or without post-traumatic stress disorders (PTSD) compared to a trauma-naïve control group. There were no significant differences found in the activation between these two, but there were differences in the basal ganglia involvement when comparing PTSD patients and trauma-exposed individuals without PTSD. This leads to the suggestion that basal ganglia-limbic interactions play a role in the development of PTSD, due to their involvement in memory and emotion.

Regarding the association between stress, traumatic experiences, and dystonia, the HPA axis and the limbic system have not yet been investigated concerning their role in the pathogenesis of musician's dystonia but have very recently been explored in some studies concerning other forms of idiopathic focal dystonia. Apart from an increased volume of the basal ganglia and the thalamus, Tomić and colleagues [79] also found increased volume of the amygdala in a sample of task-specific dystonia patients, compared to healthy controls. They furthermore detected increased grey matter volume of the left amygdala, as well as in several motor regions, and increased cortical thickness of sensorimotor areas and prefrontal regions. Rafee

et al. [80] also focused on cognitive and attentional networks surrounding the prefrontal cortex and the amygdala. They hypothesise that collicular-pulvinar-amygdala network is involved in adult-onset dystonia, which is involved in processing aversive and threatening stimuli, as well as sensorimotor information. They base their hypothesis inter alia on the often-present comorbidities of depression and anxiety dystonia and argue that correct cognitive functioning needs to be further explored in dystonia patients.

When summarising the results in this paragraph, there are several pathways and mechanisms from a molecular to a neuro-system level of how adverse childhood events and early trauma could increase the susceptibility for the development of a dystonic movement disorder in musicians. Apart from dysfunctional plasticity in the hippocampus, the cerebellum, or the temporal lobe, the mechanisms behind movement learning may also be affected, as will be shown in the next paragraph.

The Neurobiological Effects of Stress on Movement Learning and Motor Memories in Musicians

A unique aspect of making music and acquiring new skills at the instrument is the involvement of emotions, especially of reward and motivational systems. Music has been found to affect almost all limbic and paralimbic structures, such as the amygdala, the hippocampus, the auditory cortex, the cingulate cortex, and the supplementary motor area (SMA), to name only a few [4, 81, 82]. The amygdala as centre for the processing of fear and emotional memories is of course especially relevant when discussing the effects of stress and trauma in musicians. Interestingly, the basolateral amygdala (BLA) that is responsible for guiding goal-directed behaviour based on differently evaluated stimuli seems to receive projections directly from the auditory cortex, thereby giving emotional valence to the auditory stimulus [81], while it is furthermore involved in dysplastic brain adaptations following trauma [55].

There is evidence that sensorimotor regions are more activated under stress when learning a new motor task, while the hippocampal-cortical areas were progressively less engaged throughout the learning of the task [83]. This could hint towards the hypothesis that correct motor movement learning is disrupted or at least altered by stress.

As explained above, alterations of the HPA axis resulting from childhood stress can lead to a quicker assessment of stressful situations as threatening. The release of the stress hormone norepinephrine in a threatening situation activates the basolateral amygdala, which promotes emotion-induced memory consolidation [84]. For musicians especially susceptible to stress, practising or performing in stressful situations or under high pressure could therefore lead to enhanced memory consolidation of the practised motor movements, as studies found movements to be acquired better under BLA activation [85]. Simultaneously, stress-induced muscle hypertonia could foster the onset of muscle cramps at the instrument, which might explain

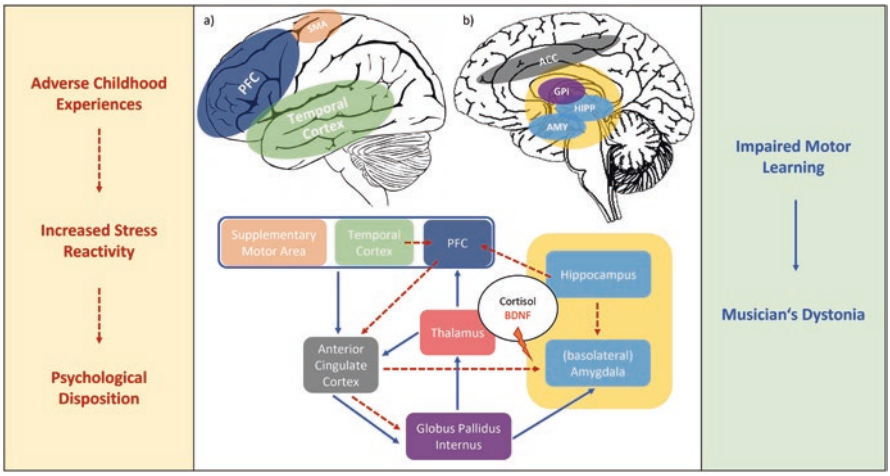

Fig. 2 Network interactions of the limbic network (red, dotted arrows) and the cortico-basal ganglia-thalamo-cortical circuitry (blue, continuous arrows) in musician's dystonia patients with elevated stress reactivity. (**a**) Relevant areas of the cerebral cortex; (**b**) sagittal section revealing the ACC, GPi, and the limbic system. *ACC* anterior cingulate cortex, *AMY* amygdala, *GPi* globus pallidus internus, *HIPP* hippocampus, *PFC* prefrontal cortex, *SMA* supplementary motor area, *BDNF* brain-derived neurotrophic factor

why the newly acquired movement patterns for these musicians are dysfunctional. Individuals with high levels of perfectionism and anxiety tend to shift their attentional focus to the internal motor task rather than to the external result, which has been found to have repercussions for motor learning and the development of dystonia [86–88].

The information portrayed in sections "How stress and adverse childhood experiences may cause dysfunctional procedural movement-memories in adulthood" and "The neurobiological effects of stress on movement learning and motor memories in musicians" is combined in Fig. 2, which proposes a schematic model of the neural circuits involved in musician's dystonia.

Current Research on Stress, Trauma, and Musician's Dystonia

More research is needed to better understand the involved networks in the pathogenesis of musician's dystonia and to investigate the associations proposed in Fig. 2. A currently ongoing project will therefore investigate the link between childhood experience, psychological dispositions, and neurological structures and functioning, by comparing musician's dystonia patients and healthy musicians. One goal of this project is to generate a comprehensive personality diagnosis of dystonia patients since results of past studies have sometimes been contradictory. The main psychological focus lies on the exploration of childhood experiences. This includes adverse

experiences such as physical, sexual, and emotional abuse or physical and emotional neglect, as well as family dysfunctions such as divorce or the illness of a parent. But it also includes exploration of the parent-child relationship since a secure attachment to at least one primary caregiver is vital for healthy child development. Parental emotional neglect is associated with increased odds of developing mood disorders such as major depression and dysthymia [89, 90]. As previous research has shown that traumatic events in childhood may be highly individual and subjective, participants will get the opportunity to report these events, additionally to the experiences described in the standardised questionnaires. The psychometric diagnosis will further include questionnaires concerning personality traits, depression, anxiety, and resilience. This will offer information as to whether certain personality traits act as mediator between adverse childhood events and musician's dystonia. But the information will also be used to construct models of personality profiles especially at risk for developing dystonia, using data-driven analysing methods.

In the same study, functional magnetic resonance imaging (fMRI) is used to determine structural differences between the musicians, as well as differences in resting-state functional connectivity and stress reactivity. The latter is assessed using the Montreal Imaging Stress Task (MIST). This paradigm was developed by Dedovic et al. [91] for specific use in an fMRI setting and induces stress by asking participants to solve mental arithmetic tasks while being subjected to socially evaluative pressure. The MIST consists of three conditions: a rest condition, a control condition, and an experimental condition. In the control condition, participants solve the arithmetic task presented on the screen without time constraints, selecting the answer on a rotary dial. In the experimental condition, however, a time bar is displayed and a bar showing the participants that they are performing below average (which is set artificially). Between the runs of the different conditions, the investigators give negative feedback about the performance and tell the participants that more effort is required from them. Cortisol levels are measured before, throughout, and after the task. This paradigm has been shown to successfully raise cortisol levels and lead to alterations in blood oxygenation-level-dependent (BOLD) activity, especially in subjects with a history of childhood maltreatment [91, 92].

The brain images gathered in this study will be analysed with a focus on sensorimotor networks, the basal ganglia, and the limbic network, especially the amygdala. Observing how musicians with and without dystonia react to stress, and whether this affects the activity of sensorimotor areas, might help to better understand the pathomechanisms of dystonia.

The concluding goal of this research project is to combine the information about the neurological and psychological differences between healthy musicians and musician's dystonia patients. Furthermore, the project should offer deeper insights into the individual chain of effects in the pathogenesis of musician's dystonia; how do childhood experiences and individual psychological differences alter neurological structures and functioning in musicians? Are these alterations responsible for making the motor system more vulnerable to developing a movement disorder? These are the questions the project hopes to answer.

Implications for Treatment and Prevention

Even though the previous sections focus mostly on alterations and dysfunctions of neural networks in dystonia patients, we are convinced that the cause for the alterations of these networks is (at least to some extend) based in psychological dispositions and experiences. Therefore, psychotherapy or at least psychological exploration should be more firmly implemented into the treatment of dystonia.

In a recent study [19], it became apparent in the Childhood Trauma Questionnaire [93] and from individual answers of the participants that many musician's dystonia patients seem to have experienced "lesser" traumatic events in the form of emotional neglect and rejection in their childhood and adolescence. These experiences were not only made in their relationships with parents but also in their relationships with instrumental teachers, which are sometimes very intense throughout early musical education (for review, see [94]). A very important focus for future studies should therefore lie on the relationship quality between dystonia patients and their parents, as well as with early instrumental teachers, as was already done in a first approach by Detari and Egermann [35]. Another promising focus is psychological resilience of focal dystonia patients and its neural correlates. A high resilience is generally known to positively influence mental and physical health [95, 96] and has been found to work protectively against mood disorders and PTSD, for example, in victims of child maltreatment [97, 98]. Improving resilience has been found to improve patients' well-being and health status and can be addressed effectively in most therapy settings [99]. Yet resilience has not been investigated regarding the role it plays in the development of musician's dystonia. Improving individual resilience could be an important addition to conventional dystonia treatments. In psychological research, a high stress vulnerability is often viewed as the opposite of high resilience [100] which would accordingly mean that musicians with a history of emotional neglect and rejection are possibly more susceptible to stress and therefore at risk for the maladaptive neural mechanisms described above.

Educating parents and instrumental teachers about the importance of an emotionally secure environment and a supportive teaching and practising atmosphere remains one of the key elements in prevention, not only of dystonia but of negative mental and physical health outcomes in general. First instrumental teachers are especially important in building the foundation of how a student will perceive pressure and react to the general striving for perfectionism in the music world. It is the responsibility of music schools and conservatoires to move away from the negative error culture towards a supportive, healthy approach to practising and musical education. There should further be a stronger focus on strategies such as mental practising, relaxation, and breathing techniques that are known to reduce stress and anxiety and support healthy instrumental playing but are up to now barely used by musicians [101, 102].

For musicians who have experienced traumatising adverse childhood events and are suffering from severe long-term consequences, psychotherapy should be based on conventional psychotherapy for traumatised patients. Several techniques and

manuals from dialectical behaviour therapy (DBT; [103]), as well as from cognitive behavioural therapy can be applied and adapted. Individually tailored psychotherapy for musicians should focus on the many resources musicians bring into the therapeutic setting. By learning a musical instrument, they have acquired a tool to regulate and express emotions. Furthermore, they show strong determination and self-discipline, which are necessary traits while pursuing the long-term goal of becoming a professional musician. These skills can and should be used and implemented in a specific musician's psychotherapy. Regarding the effects of psychotherapy on the previously discussed neural structures, there is evidence from numerous studies that psychotherapy can affect structures such as the amygdala, the hippocampus, or the prefrontal cortex. Psychotherapy for depression, for example, has been found to lead to a normalisation of the amygdala activity (for full meta-analysis, see [104]), while eye movement desensitisation and reprocessing (EMDR) therapy which is used in the treatment of PTSD leads to a significant increase of the volume of the left amygdala [105]. This further underlines the close connection of psychological dispositions with neurological alterations and emphasises that psychological aspects of musician's dystonia should not be neglected, need to be further investigated, and implemented into successful dystonia treatment.

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Embouchure Dystonia as a Network Disease

Johanna Doll-Lee, André Lee, Tobias Mantel, Bernhard Haslinger, and Eckart Altenmüller

Abstract While the pathophysiology of embouchure dystonia, a sub-entity of musician's dystonia, is still not fully understood, recent research has shown that it involves alterations of several brain functions and networks. Maladaptive plasticity in sensorimotor integration, sensory perception, and deficient inhibitory mechanisms at cortical, subcortical, and spinal level seem to contribute to its pathophysiology. Furthermore, functional systems of the basal ganglia and the cerebellum are involved, clearly pointing toward a network disorder. We therefore propose a novel network model, based on electrophysiological and recent neuroimaging studies highlighting embouchure dystonia.

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Keywords Musician's dystonia · Embouchure dystonia · Task specificity · Network disorder · Movement disorder

Abbreviations

AFN	Auditory function network
BOLD	Blood oxygen-level dependent (signal)
CN	Cerebellar network
ED	Embouchure dystonia
fMRI	Functional magnetic resonance imaging
LMFN	Lateral motor function network
MD	Musician's dystonia
MRI	Magnetic resonance imaging
PVM	Primary visual network
SMFN	Sensorimotor function network

Introduction

Embouchure dystonia (ED) is a task-specific dystonia and sub-entity of musician's dystonia, which occurs mostly in highly trained brass musicians and less frequently in woodwind players. It is characterized by a deterioration or loss of control of skilled movements of muscle groups involved in playing a wind instrument. The effects of ED result in poor sound quality, lack of articulated playing (e.g., unclear "attack" of the sound), or reduction of range or stamina. Frequently it involves tremor of lips, jaw, or soft palate, which leads to instability of pitch. Clearly these symptoms may end a professional career. Compared with musician's hand dystonia (MHD), treatment options for ED are highly unsatisfactory. While in hand dystonia at least three effective therapy methods are available, namely, (a) local injections with botulinum toxin into the cramping muscles, (b) retraining, and (c) anticholinergic drugs, such as trihexyphenidyl [1, 28, 36, 78], these options do mostly not exist for ED as the involuntary cramping cannot be pinned down to single muscles but affects groups of facial muscles as well as laryngeal muscles and may spread even to the tongue and breathing muscles [23, 33]. Furthermore, anticholinergic drugs seem to be less efficient, and retraining needs to be scientifically evaluated [74]. Another obstacle toward progress in successful treatment of MHD and ED is that the pathophysiology of both phenotypes of dystonia is not fully understood. Especially in "embouchure dystonia", reduced muscular stamina as a consequence of aging and less well-developed technical skills seem to be quite frequent and may blur the diagnostic criteria of ED. According to a large survey in German professional brass instrumentalists, 59% reported having suffered from embouchure disorders and among them 30% from embouchure fatigue [72]. Furthermore, tongue

stopping, a difficulty in timing of articulation, especially in exposed brass entries, is not considered embouchure dystonia and more related to general stresses and anxiety disorders [23].

Diagnostic criteria for embouchure dystonias therefore exclude age-related weakness of muscular stamina and anxiety disorders. With respect to the "real" ED, recent research into brain network alterations has led to a better understanding of underlying mechanisms. These will be discussed in this chapter.

Pathophysiology

Briefly summarizing, most studies of MHD and ED reveal abnormalities in three main areas: a) reduced inhibition in the motor system at cortical, subcortical, and spinal levels, b) impaired sensorimotor integration, and c) altered sensory perception and integration. All of these changes are believed to primarily originate from dysfunctional brain plasticity.

A *lack of inhibition* is a common finding in studies of patients with all forms of dystonia (for a classic review, see [44]). Fine motor control in general requires a subtle balance in neural circuits between excitation and inhibition. This fact is particularly important in allowing precise and smooth movements required for making music. For example, rapid individuated finger movements in piano playing require selective and specific activation of muscles to move the intended finger in the desired manner and to inhibit movements of uninvolved fingers [25]. In patients suffering from hand dystonia, electromyographic recordings have revealed abnormally prolonged muscle firing with co-contraction of antagonistic muscles and overflow of activation to inappropriate muscles [24]. Lack of inhibition is found at multiple levels of the nervous system: in focal dystonia, it has been described at the cortical level [58], which is consistent with the finding of reduced intracortical GABA transmission in writer's cramp [42], as well as on the spinal level [48]. Moreover, a loss of surround inhibition, a mechanism that reduces neural excitability in an area surrounding active neurons, has been found [7, 69], leading to the phenomenon of overflow, which means an unintended activation of neighboring muscles in otherwise precise movement execution [29].

At the spinal level, lack of inhibition leads to reduced reciprocal inhibition of antagonistic muscle groups producing co-contraction, for example, of wrist flexors and extensor muscles [8]. This in turn produces a feeling of stiffness and immobility and frequently leads to abnormal postures with predominant flexion of the wrist due to the relative strength of the flexor muscles. At the cortical level, abnormal inhibition has been demonstrated by using noninvasive transcranial magnetic stimulation to measure intracortical inhibition [70]. Interestingly, at this level, abnormal inhibition is frequently seen in both hemispheres, despite unilateral symptoms. This points toward a more generalized form of inhibition deficit. Finally, lack of inhibition is also seen in more complex tasks, such as when movement preparation is required prior to scale playing and for sudden movement inhibition following a stop

signal in pianists [63]. This lack of inhibition is accompanied by increased cortical excitability, resulting in sensorimotor overactivity during movement preparation [63] and during actual playing in pianists with MHD [43]. Similarly, imaging studies in guitarists and patients with writer's cramp revealed an increase of sensorimotor activation during dystonic tasks [51, 54].

The ubiquitous demonstration of deficient inhibition is suggestive of a common underlying genetic cause. However, it has to be emphasized that none of these electrophysiological effects allow diagnosis on an individual level, since the variability in both healthy and dystonic musicians is extremely large.

Impaired *sensorimotor integration* also plays an important role in the pathophysiology of musician's dystonia. It is illustrated by the "sensory trick" phenomenon: some musicians suffering from dystonia show a marked improvement of fine motor control when playing a modified mouthpiece or, when suffering from hand dystonia, with a latex glove – thus changing the somatosensory input. In experimental settings, vibrating stimuli lead to a worsening of musician's dystonia. In one study, when transcranial magnetic stimulation was used in conjunction with muscle vibration, motor evoked potentials decreased in agonist muscles and increased in antagonist muscles [60, 61]. These data again suggest an altered central integration of sensory input in musician's dystonia, which might be due to the failure to link the proprioceptive input to the appropriate motor cortical area. Reversing these effects of sensorimotor disintegration is the approach of several retraining therapies. Sensory retraining in the form of tactile discrimination practice can ameliorate motor symptoms, suggesting that the abovementioned sensory abnormalities may drive the motor disorder. Interestingly, a positive response to the sensory trick phenomenon is linked to a better outcome in attempts to reeducate musicians with dystonia [52].

Altered *sensory perception* may also be a sign of maladaptive brain plasticity. Several researchers have demonstrated that the ability to perceive two stimuli as temporally or spatially separate is impaired in patients with musician's dystonia, whether sensation is via the fingertips in hand dystonia [12, 13] or the lips in embouchure dystonia [34]. This behavioral deficit is mirrored in findings of the cortical somatosensory representation of fingers or lips. It has been demonstrated with various functional brain imaging methods that in the somatosensory cortex the topographical location of sensory inputs from individual fingers overlaps more in patients with musician's cramp than in healthy controls [17]. Similar findings have been reported for writer's cramp [50] and various types of focal hand dystonia [6]. Maladaptive plasticity therefore seems to play a key role in the pathogenesis of dystonia [56, 57]. It should be mentioned, however, that findings are still controversial, and actual fMRI studies with high-resolution imaging and different analysis approaches did not replicate these findings [65].

Other abnormalities include elevated temporal discrimination thresholds, a marker of *basal ganglia dysfunction* found to be relevant to the pathogenesis of focal dystonia [76]. Since in healthy musicians an increase of the size of sensory finger representations has been interpreted as an adaptive plastic change to support the current needs and experiences of the individual (see above [17]), it could be

speculated that these changes overdevelop in musicians suffering from dystonia, shifting brain plasticity from being beneficial to maladaptive [61]. In this context it is worth recalling that local pain and intensified sensory input due to nerve entrapment, trauma, or muscle overuse have been described as potential triggers of dystonia [36]. There are clear parallels of abnormal cortical processing of sensory information and cortical reorganization between patients with chronic pain, specifically with complex regional pain syndromes and those with focal dystonia (e.g., [67]; for a review of this topic, see [49]). A classical and up to now the only ecologically valid animal model of focal hand dystonia established in overtrained monkeys supports this suggestion; repetitive movements induced both types of symptoms – pain syndromes as well as dystonic movements. In this experiment, mapping of neural receptive fields has demonstrated a distortion of cortical somatosensory representations [12], suggesting that overtraining and practice-induced alterations in cortical processing may play a role in focal hand dystonia. This finding not only highlights the role of somatotopic disorganization but also the effect of repetitive and stereotype movements in provoking dystonia. The latter is further underlined by an animal model study that induced blepharospasm in rats by inducing hyperexcitability of the trigeminal-mediated blink reflex after combining an injury of nigral neurons with weakening of the orbicularis oculi muscle of the eye [66].

These observations also have given rise to the assumption of a two-factor model with environmental factors such as overtraining and an intrinsic abnormal plasticity rendering individuals susceptible for the onset of dystonia [55].

Finally, the notion of *cerebellar involvement* has gained increasing support, given observations in recent dystonia animal models. A kainic acid model in rats proved that injections into the vermis of the cerebellum were seen to cause dystonia [4, 19, 22]. Interestingly and in favor of such a cerebellar involvement, the conditioned eye blink reflex, a circuit mediated by the cerebellum, is abnormal in patients with focal dystonia such as writer's cramp and cervical dystonia [75]. A recent study could show an ipsilateral cerebellar overactivity when pianists suffering from MHD exerted a task eliciting dystonic symptoms [37]. The same study as well as a study investigating writer's cramp patients [62] could furthermore show alterations in cortico-cerebellar pathways.

A Holistic Network Model of Musician's Dystonia

We have put together the available evidence for the pathogenesis of musician's dystonia into a *network model* (Fig. 1), inspired by work of the group of Reza Shadmer [5] and of Konczak and Abbruzzese [38]. This model seems most suitable for comprehensively accommodating all of the evidence pointing to various involved brain regions including the cerebral cortex, basal ganglia, cerebellum, thalamus, and the limbic system [2]. We have depicted parallel feedback and feedforward mechanisms (internal models) shaping the motor commands and adapting to changes in motor output. Furthermore, we have adjusted the model to the life conditions of

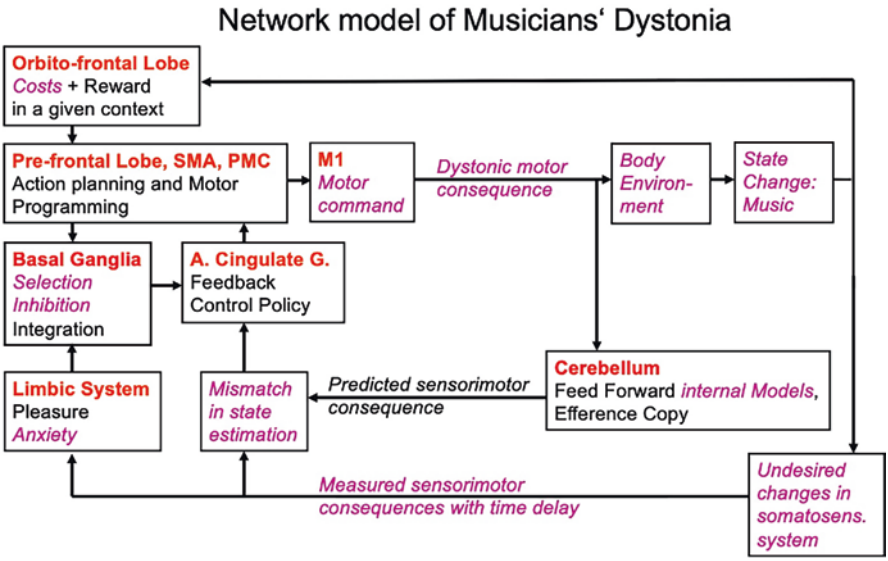

Fig. 1 A network model of musician's dystonia demonstrating the interaction of the cortex, basal ganglia, cerebellum, and limbic system in a framework of a dysfunctional feedforward-feedback model. Further detailed explanation in the text

performing musicians, characterized by high expectations, high social pressures, and high investments of time and energy leading to mostly unconscious "calculations" of costs and rewards of a concert. This is why we name this model a "holistic model." Finally, we have added the presumed anatomical regions, representing the networks involved in the complex situation of a performance. In short, a feedforward model generates predicted (expected) sensory feedback based on the specified motor commands. Predicted and afferent sensory feedback are compared (reafference vs. afference) resulting in an outgoing signal, frequently termed exafference. With respect to one's own movement, this signal indicates how well the movement was executed in relation to the plan. After a skill has been learnt, this mechanism can monitor the success of the execution, generating an error signal, if there is a discrepancy between desired and actual movement outcome. Such signal could be used to update the motor plan and/or to retrain the dystonic movements in musicians.

In the following we will guide the reader through Fig. 1: our starting point is the orbito-frontal lobe, programming long-term goals of the individuals' behavior and especially of social and individual consequences of actions in general (for a recent review on the role of the orbito-frontal cortex, see Boorman et al. [11]). In a hierarchical perspective of sensorimotor processing, the orbito-frontal lobe plays a higher-order role in embedding the individual actions into biographical and social contexts. In the figure, the "costs" of a performance are investment of time, including careful preparation of the performance, taking the ten thousands of hours into account which are linked to acquisition of professional expertise as musician [18]. This includes refinement of sensorimotor skills, memory skills, and

performative-expressive skills required by a performer. Further costs are the emotional impact of public performance, including risk-taking, performance anxiety, and the omnipresent Damocles sword of failure with eventual negative social consequences, such as disapproval and contempt. The latter is highly relevant in musicians suffering from dystonia, because they will anticipate possible consequences of dysfunctional movements and may have reduced self-confidence and increased anxiety [68]. On the other side, performing includes many rewards, joy, flow experience, self-efficacy, sense of meaning, social admiration, narcissistic feed, and money [71]. Positive balance sheets of costs and rewards will motivate to further advance sensorimotor skills, to invest more time and work even harder, and in case of musician's dystonia to invest in therapies, such as retraining or injection therapy with botulinum toxin [28].

In the situation of a musical performance, the sensorimotor hierarchical system will be initiated, including the prefrontal lobe for action planning and the supplementary and the premotor cortex for selection of appropriate sensorimotor programs [16, 59]. Motor planning includes the basal ganglia loop, which allows for selection, activation, and initiation of motor patterns, and at the same time constitutes the interface between goal-directed learned motor actions and emotional "coloring" of movements [20]. Efferences from the basal ganglia loop to the anterior cingulate gyrus, a part of the cingulate commonly subsumed under the limbic system, allow for control of planned movements. Here, feedback on the temporospatial accuracy of movement is provided, allowing to modify almost simultaneously generated motor commands. Evidence for such a feedback mechanism in highly trained professional pianists is provided by the electrophysiological marker of the pre-error negativity, arising from the anterior cingulate gyrus, reflecting erroneous movement plans, *before* an actual error is committed [63]. In musicians with dystonia, significantly larger error-related brain responses before and following errors were observed. Furthermore, phase synchronization between the SMA and the motor areas was altered. This indicated that degraded neural activity at all levels of the central nervous system is manifested in specific neural correlates of the executive functions that monitor an overlearned sensorimotor performance [64, 73].

Via the cerebral-cerebellar loop, the motor command will give rise to a feedforward model, which in professional musicians is established through prolonged learning processes and can be considered as a very precise efference copy. According to the feedforward model, the cerebellum predicts the sensory consequences of the motor commands and is involved in computing sensory prediction errors by comparing the predictors to the sensory feedback [53]. In case of musicians, the sensory feedback involves not only somatosensory, mostly proprioceptive feedback, but auditory feedback entailing not only timing but also sound quality, pitch, and timbre. In musician's dystonia, these parameters are at least during some instances of the performance altered and will give rise to a mismatch between the intended movement/sound and the actual movement effect which can elicit an alteration of auditory-somatosensory integration involving the anterior cingulate gyrus [14].

Following motor execution and coordinated programming of the body environment, music will sound. This is the desired state change, and in case of a satisfying

quality of sound, timing, and emotional apperception, this will motivate the interpreter to continue (arrow to the orbito-frontal lobe). However, the motor consequences in symptomatic dystonia will be different. “Involuntary” movements may occur; undesired changes in the somatosensory system will produce cramping and tension, and the consequences, namely, lack of sound quality, wrong notes, and unprecise timing, will not only create a time-delayed mismatch in state estimation but also negative emotions, anxiety, shame, anger, and frustration. This in turn will lead to activation of the stress system and most probably provide further memory stabilization of dysfunctional movement patterns in musician’s dystonia [35, 39]. Thus, dysfunctional connectivity in networks involving frontal cortices, sensorimotor cortices, basal ganglia, cerebellum, and the limbic systems is reinforced, this way stabilizing the undesired behavioral consequences of musician’s hand or embouchure dystonia.

Embouchure Dystonia as an Example for the Network Model

In embouchure dystonia, especially in the last decade, high-quality neuroimaging studies have been conducted. These studies constitute the basis together with findings from work on other focal dystonias, to propose a more refined and specific network model with precise neuroanatomical correlates.

In a first functional MRI imaging study on ED patients, local increases in blood oxygen level as correlate of *increased neuronal activity* (i.e., increased functional activation) compared to healthy brass players was demonstrated during a dystonic task (“buzzing” into a MRI-compatible mouthpiece) in several brain areas. These comprised the pre- and primary motor cortex, the primary and secondary somatosensory cortex, and the basal ganglia. Interestingly, this functional overactivity was in part also present during a task that did not provoke dystonic movement (blowing into a tube) [31]. Investigating somatosensory processing further, a subsequent functional MRI study applied tactile stimuli to ED patients and healthy controls onto body parts that were affected (i.e., upper lip) or not affected (i.e., forehead and hands) by dystonia. This likewise revealed functional overactivity in the primary and secondary somatosensory cortex and interestingly also in the cerebellum [45]. The findings of increased functional sensorimotor activation using functional neuroimaging are in line with the electrophysiological findings of reduced inhibition in other focal dystonias. Observation of abnormal somatosensory cortex activation both during motor and non-motor tasks as well as tactile stimulation of affected and non-affected body parts was an intriguing finding that may constitute a correlate of abnormalities in somatosensory processing as an underlying predisposition for the development of dystonia [31]. Further, the observation of increased cerebellar functional activation during somatosensory processing in dystonia underlines the cerebellar role in sensory processing. This is particularly interesting as the cerebellum is essential for the storage and retrieval of internal models [10], which are involved in the feedforward control and motor preparation of automated movements as well as

sensorimotor integration [30, 79]. As we exemplified above, two types of internal models have been described: forward models that predict the sensory consequences of motor actions and inverse models that predict the motor command for a desired sensory or motor outcome. Interestingly, in focal hand dystonia, an alteration of internal forward model prediction of sensory consequences of motor action [40] and an impairment in updating the internal inverse model [26] have been observed. In the latter study, pianists with MD showed difficulties in adapting to (i.e., predicting) altered piano-key dynamic properties that were induced by changing the weight of a piano key. This not only corroborates the cerebellar role in MD but also the notion that MD is not purely a motor disorder.

Beyond activation changes, tactile stimulation of affected and non-affected body areas revealed shifts in primary somatosensory functional topographic representations of these body areas, together with a reduced variability of areas activated in left-sided stimulation of the upper lip as an area involved in embouchure dystonia [45]. This is in line with an earlier electrophysiological study that found disorganization of the somatosensory representations with smaller distances between finger and lip representations in ED patients [34]. These findings were amended by a functional MRI study by Uehara et al. [77] that congruently showed somatotopic alterations of primary somatosensory cortex regarding areas representing mouth and hands when applying a dystonia-provoking task ("buzzing" into a plastic mouthpiece) as previously implemented by Haslinger et al. [31].

A further study focusing on changes in gray matter structure showed an increased gray matter volume of the primary somatosensory and motor cortex in areas representing face and lips in ED patients compared to healthy professional brass players. Interestingly, the respective gray matter volume of sensorimotor cortices in healthy brass players was between that of dystonia patients and healthy nonmusicians [46], suggesting that adaptive neuroplastic changes necessary for gaining musical expertise may deteriorate to ED due to maladaptive plasticity [61] as described in previous animal models [12].

Deepening the understanding of functional alterations in ED, a relatively new imaging method has emerged lately that assesses functional connectivity. It is based on the finding that networks of different brain regions temporarily correlate in their activity by low-frequency fluctuations of the blood oxygen-level-dependent (BOLD) signals in the absence of tasks [9, 15, 21]. The observed networks resemble the task-specific activation patterns seen in experimental tasks, suggesting that the task-specific activity is a superposition of different spontaneous BOLD signals at rest [21]. Studying the resting-state connectivity might therefore allow to identify underlying phenotypical changes of the disease.

Such an fMRI resting-state study revealed alterations of functional connectivity of different brain regions in ED patients. These included not only functional connections of primary sensorimotor representations of the mouth but also of the hands, as well as of secondary somatosensory, premotor, and parietal areas, again mirroring abnormal sensorimotor integration processes in focal dystonias. Furthermore, functional connectivity of the cerebellar network and the lateral motor function network (containing the sensorimotor mouth representation in addition to parts of the

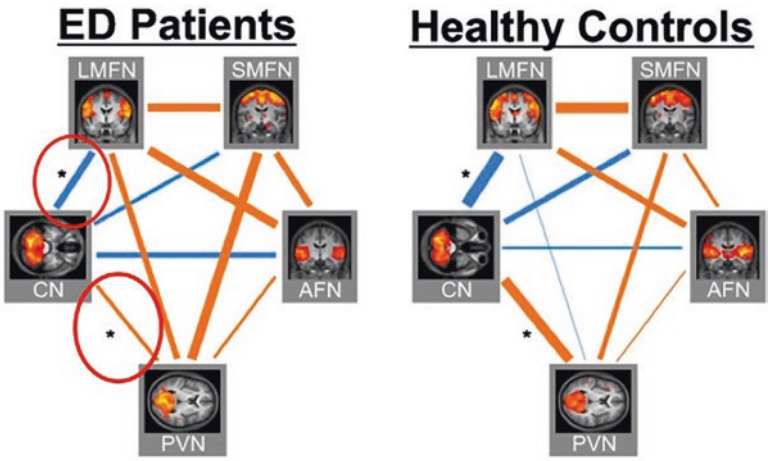

Fig. 2 Altered resting-state connectivity of the cerebellum with motor and visual networks in ED compared to healthy musicians. *AFN* auditory function network, *CN* cerebellar network, *LMFN* lateral motor function network, *PVN* primary visual network, *SMFN* sensorimotor function network. [Courtesy of Haslinger et al. [32]]

sensorimotor and premotor cortex as well as parts of the cerebellum) differed in ED patients compared to healthy controls as well as functional connectivity between cerebellar networks and primary visual networks (Fig. 2), emphasizing once more the importance of the cerebellum in the pathogenesis of dystonia [32].

A recent multimodal analysis applied functional MRI and diffusion tensor imaging to combine the analysis of functional connectivity with an evaluation of structural integrity within the probable trajectories of white matter tracts between distinct brain areas involved in the disease. This revealed evidence for structural alterations accompanying functional connectivity change in projections between the primary somatosensory cortex and the putamen in ED patients. Moreover, there were alterations in the white matter integrity of trajectories within the superior longitudinal fascicle linking the supplementary motor area and the superior parietal lobe, which plays a key role for the integration of multimodal sensory and spatial information with motor function. Altogether, these findings were consistent with a network model comprising alterations in basal ganglia functions as well as in cortex-level sensorimotor integration [47].

Correlating findings from brain imagery studies with clinical scales assessing symptom severity has been challenging in ED for several reasons: the identification of the affected muscles is difficult because the dystonic movement is not as obvious as in MD of the upper extremities, where it manifests usually as a flexion of one or more fingers [3]. Moreover, the rating scales rely on a subjective assessment of the sound quality by the clinician. However, in a study by Lee et al. [41], a method to objectively assess the severity of ED was established. It could be shown that patients who were asked to play a sustained note had a larger fluctuation of the fundamental frequency F0 (i.e., less stable sound production) compared to healthy controls [41].

A study by Uehara et al. [77] correlated F0 fluctuation as measure of the severity of dystonic symptoms with brain activation data generated during a dystonia-inducing task. A multiple regression analysis was able to predict the observed F0 fluctuation depending on the brain activity and revealed that regions accounting for F0 fluctuation included the primary somatosensory primary motor cortices as well as the cerebellum and the putamen [77]. This finding fits similar observations of objective clinical measures with brain imaging data in focal hand dystonia, where in pianists with MD a correlation between temporal variability of a scale played on a piano and gray matter volume of the putamen was found [27]. It furthermore corroborates the notion of an underlying network problem in ED.

In summary, there is growing evidence of altered functional networks comprising the basal ganglia, the cerebellum, and the somatosensory, motor, and premotor cortices and their in-between networks that form a pathophysiological correlate of focal dystonias such as embouchure dystonias. While alterations of activity and connectivity of these regions in resting stage as well as in asymptomatic tasks may hint at underlying predisposing traits of sensorimotor processing, it is still difficult to differentiate between cause and effect in terms of possible compensatory mechanisms. Nevertheless, assuming network alterations leading to focal dystonia, a therapeutic approach to this disorder needs to encompass multimodal interventions. Further studies are needed to identify and compose optimal treatment regimens to best enable affected musicians to get back to their high professional performance level and enable them to pursue their respective careers.

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Sensorimotor Incoordination in Musicians' Dystonia

Shinichi Furuya and Takanori Oku

Abstract To acquire and maintain outstanding sensorimotor skills for playing musical instruments inevitably requires extensive training from childhood. However, on the way toward musical excellence, musicians sometimes develop serious disorders, such as tendinitis, carpal tunnel syndrome, and task-specific focal dystonia. Particularly, task-specific focal dystonia in musicians, which is referred to as musician's dystonia (MD), has no perfect cure and therefore often terminates professional careers of musicians. To better understand its pathological and pathophysiological mechanisms, the present article focuses on malfunctions of the sensorimotor system at the behavioral and neurophysiological levels. Based on emerging empirical evidence, we propose that the aberrant sensorimotor integration, possibly which occurs in both cortical and subcortical systems, underlies not only movement incoordination between the fingers (i.e., maladaptive synergy) but also failure of long-term retention of intervention effects in the patients with MD.

Keywords Plasticity · Focal dystonia · Dexterity · Maladaptation · Synergy

Introduction

Musicians' dystonia (MD) is a form of task-specific focal dystonia that accompanies involuntary movements mostly in musical performance [1–3]. The prevalence rate is approximately 1–2% among musicians, which is higher compared with the other forms of task-specific focal dystonia such as writer's cramp [1]. Several studies also reported etiological and pathophysiological differences between MD and writer's cramp [4–6], which suggests uniqueness of MD. However, a key issue that remains unsolved is a lack of a comprehensive understanding of behavioral abnormalities

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such as deficits of sensorimotor skills and its task specificity in MD, which has limited not only unveiling malfunctions of the nervous system subserving fine motor control but also performing accurate diagnosis and evaluation of prognosis. In this article, we introduce aberrant sensorimotor skills specific to MD, particularly focusing on incoordination of movements between the fingers (i.e., maladaptive synergy). Then, based on evidences of the behavioral and pathophysiological abnormalities of the sensorimotor system, we propose the aberrant sensorimotor integration as a putative mechanism underlying task-specific manifestation of symptoms in MD.

Phenomenology of Musicians' Dystonia

In general, MD is associated with sensorimotor abnormalities at a particular body portion that has undergone repetitions of precise movement production for the prolonged period, such as the fingers of pianists and string players [7–9], mouth and tongue of brass players (i.e., embouchure dystonia) [10–15], and foot of drummers and organists [16]. The primary symptom of MD is loss of fine motor control particularly when performing some trained tasks (i.e., task-specific manifestation) [17]. For example, focal hand dystonia among musical instrumentalists such as pianists and string players typically involves imprecision of timing and/or force control and loss of quickness in the sequential finger movements during playing the instrument [9, 18, 19]. Similarly, embouchure dystonia of brass players accompanies instability of pitch control in tone production [15, 16]. Accordingly, the symptom of MD severely impairs musical performance that requires high spatiotemporal precision. The other tasks that can trigger task-specific focal dystonia such as writing cramp requires no temporal precision, which may underlie differences in pathophysiology between MD and the other forms of focal dystonia.

To quantitatively characterize abnormalities of movements in MD, several studies using movement analyses and electromyography have been performed. For example, in piano performance, patterns of the finger movements are characterized by covariation of motions across multiple fingers and joints, which is called "synergy" [20–24]. Originally, synergy is defined according to the modality, such as "kinematic synergy" that represents coordinated movement patterns between multiple joints [25, 26] and "muscle synergy" that represents synchronized activation across different muscles [27, 28]. However, the kinematic synergy and muscle synergy are likely to be altered maladaptively in patients with MD (Fig. 1). For pianists suffering from hand MD, the kinematic synergy of the finger movements was abnormally altered, in which the finger depressing the key moved in the same direction with the adjacent finger in pianists with MD, in contrast to the healthy pianists who moved these fingers in the opposite movement direction [18]. A further analysis using a regression model identified that the patients with larger alteration of the kinematic synergy displayed larger degradation of timing control in the piano performance, which suggests that the abnormal pattern of the movement covariation in pianists with MD is associated with MD-related impairment of the performance. An

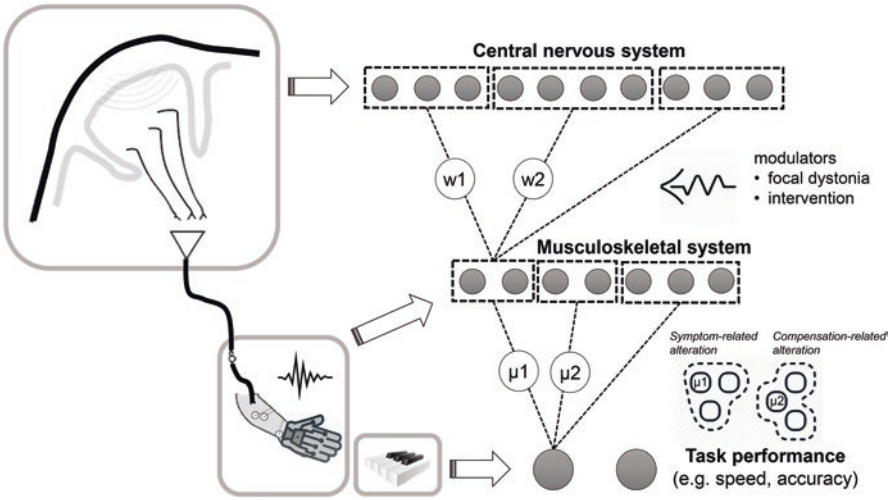

Fig. 1 A schematic drawing of the concept of synergy and its maladaptation through the development of musicians' dystonia. In this framework, patterned movements (kinematic synergy) and/or muscular activities (muscle synergy) are encoded in the nervous system. However, the encoded synergy changes plastically not only through musical training but also through the development of musicians' dystonia. The maladaptive change in synergy due to MD is at least classified into two groups according to whether it impairs task performance (e.g., fine motor control) or compensates for the performance deterioration. To identify maladaptive changes in synergy in association with the dystonic symptom is therefore essential for accurate diagnosis and effective intervention (e.g., constraint-induced therapy, sensorimotor retraining)

electromyographic recording of activities of the intrinsic and extrinsic finger muscles during playing the piano further provided evidence of maladaptive changes in the muscle synergy [29]. In this study, muscular activities were analyzed by a combination of the nonnegative matrix factorization and unsupervised classification analysis, and the extracted covariation patterns of activities across the muscles were compared between healthy expert pianists, healthy recreational piano players, and pianists with MD. The results identified six covariation patterns of the activities across the muscles (i.e., muscle synergies), and some of these patterns were altered specifically in pianists with MD, but not in the healthy players with different skill levels. This indicates that the altered muscle synergy does not merely reflect motor proficiency but rather represents MD-related abnormality. A further analysis with the regression model segregated the abnormal muscle synergies, according to whether the alteration specific to MD was associated with degradation of fine motor control (i.e., symptom) or decrease of the movement variability (i.e., compensation). The findings therefore highlight two distinct roles of adaptation of muscle synergies through the development of MD in musical performance, which requires carefully defining the target muscle of interventions (e.g., botulinum toxin injection). Interestingly, although several studies have reported abnormal elevation of simultaneous activities of the antagonistic pair of finger muscles (i.e., co-contraction)

in focal hand dystonia and other forms of dystonia [30–34], this study did not provide any quantitative evidence supporting the aberrant co-contraction in pianists with MD. This raises questions firstly whether MD is categorized into the same entity with the other forms of task-specific focal dystonia and secondly whether the term "musicians' cramp" is the right words to describe this disorder even though it has been frequently used in many situations.

The kinematic analysis of movement patterns in MD is not limited to the hand dystonia. A recent study developed a novel technology that enabled to capture the tongue movements while brass players with embouchure dystonia were playing the instrument by using a real-time MRI [35–37]. The real-time MRI captured abnormal and imprecise tongue movements (i.e., "tongue stop") in the patients, which is likely to represent incoordination of movements between the lip and tongue during blowing of breath to produce a musical sound.

In addition to the motor abnormalities, sensorimotor malfunctions in association with MD have been also reported in studies using psychophysics experiments. The sensorimotor abnormalities include aberrant transformation between sensory afferent inputs and motor efferent outputs (i.e., internal model). When producing a target loudness level of sound through depressing a piano key, accurate estimation of the force level necessary for eliciting the target loudness is inevitable. The computational process responsible for this estimation of the motor output based on the target sensory goal is referred to as the internal inverse model [38], in which a relationship between the keypress force and elicited loudness of a tone is represented. One established experimental paradigm to probe this process is the sensorimotor adaptation (i.e., the well-known "force field" paradigm originally established by Shadmehr and Mussa-Ivaldi [39]). In a study that extended this paradigm to piano playing, pianists produced the designated loudness level of piano tone through depressing a key that was artificially weighted using a miniature robot attached on the piano key. While healthy pianists successfully elicited the target loudness level after striking the weighted key several times (i.e., adaptation), pianists with MD failed to adapt completely following a number of repetitive strikes, even though they did not show any deficit of the muscular strength [40]. The failure to adapt to the weighted key in the sequential piano keystrokes may reflect malfunctions of the internal inverse model of the MD patients, because the adaptation requires newly estimating the target force necessary for eliciting the target loudness through updating internal representation of dynamics of the piano key. It is intriguing to address whether such a learning failure serves as a predictor of the development of MD in future studies. In contrast to the internal inverse model, the process of estimating sensory outcomes based on motor commands to be issued is referred to as the internal forward model [41, 42]. Similar to the inverse model, a psychophysics experiment demonstrated that a difference in perceived intensity between self- and externally applied tactile stimuli to the finger differed between the patients with MD and healthy musicians, which suggests malfunctions of the forward model [43]. Together, these findings suggest maladaptive changes in the sensorimotor transformation process through the development of MD.

Finally, effects of MD on perceptual functions remain controversial. MD patients demonstrated deficient perception of timing anomalies in sequential stimuli in both the auditory and somatosensory domains [44]. By contrast, visual temporal discrimination ability was intact in patients with MD, although the sensorimotor neural system may compensate for the perceptual malfunction [45]. Another study also reported that basic timing abilities stayed intact in patients with MD [46]. These findings, together with the aforementioned sensorimotor malfunctions, provide evidence that at least active perception during movements but not necessarily passive perception is affected by MD.

Pathophysiology of Musicians' Dystonia

An intriguing question is how the behavioral abnormalities of sensorimotor skills in MD are associated with functional maladaptation of the nervous system. This has been a challenging issue in MD, since many of the behavioral tasks do not map neatly to a particular brain region and activate network. Of specific interest is an impact of the development of MD on the sensorimotor system subserving the movement coordination (i.e., synergy). One putative neural substrate of the synergy has been considered as the motor cortex, which encodes information on the coordinated movements [25] and changes the encoded motor skills through extensive training with the musical instrument [23, 24]. A study using the paired pulse transcranial magnetic stimulation showed that pianists with MD displayed both reduced inhibition and exaggerated facilitation of the excitability of the motor cortex that innervates the fingers [19]. A further analysis using machine learning to the neurophysiological and behavioral datasets demonstrated that the abnormally reduced inhibition and elevated facilitation were associated with increased timing variability and decreased quickness of the sequential finger movements during playing the piano in pianists with MD, respectively. These findings suggest aberrant motor cortical functions as the pathophysiology underlying loss of fine motor control in MD. With respect to production of the coordinated movements between the fingers, somatosensory input into a finger plays a role in inhibiting the motor cortical excitability of the nonadjacent finger in healthy pianists (i.e., surround inhibition) [5, 47, 48]. However, the surround inhibition of pianists with MD was abnormally reduced [49], which can be considered as a mechanism of aberrant movement coordination between the fingers in the MD patients, possibly due to failed suppression of involuntary movement production at a finger relevant to the task performance. In addition, at the somatosensory domain, the somatotopy of the individual fingers are altered in musicians with MD at the hand [50]. These observations let us postulate that malfunctions of the somatosensory-motor system play vital a role in loss of the finger dexterity in MD. If somatosensory inputs derived from a mechanical interaction between the body and the musical instrument are abnormally integrated into a process responsible for the movement production via

the aberrant sensorimotor integration due to MD, it makes sense that the motor incoordination of MD manifests in a task-specific manner.

A further supporting evidence for this claim is cerebellar malfunctions in focal task-specific dystonia. A recent neuroimaging study using a functional magnetic resonance imaging demonstrated abnormal hyperactivities of the cerebellum when pianists with MD were playing a nonmagnetic piano keyboard in the scanner [51]. It is well-known that the cerebellum is a neural substrate responsible for the sensorimotor transformation based on internal representation of dynamics of the tool to be manipulated [52]. The cerebellar malfunction may therefore implicate that the malfunctioned sensorimotor integration, which is likely to emerge at both cortical and subcortical levels, underlies emergence of the symptom specifically during musical performance in patients with MD.

With respect to a causal relationship between the sensorimotor malfunction and emergence of dystonic movements, several studies demonstrated restoration of loss of fine motor control through sensorimotor retraining, such as constrained induced therapy [53, 54], muscle vibration [49], and bi-hemispheric transcranial direct current stimulation with motor retraining [55]. However, a common issue among these interventions is failure of stabilizing the restoration effect over the prolonged period (i.e., long-lasting retention). This indicates that the aberrant neural state underlying production of the dystonic movements is stable and robust, possibly due to maladaptation of neuroplasticity due to MD. In other words, MD is likely to distinctly alter control and learning of skillful sensorimotor performance. To make this pathological state unstable in order to enhance the transition to a non-dystonic state, one postulation is to augment variability of movements such as through differential learning [56]. Indeed, differential learning in piano practicing (i.e., practicing with a variety of rhythms) reorganized muscle synergy so as to reduce activation unnecessary for the task performance in healthy pianists [57], which implicates a potential of this training for rehabilitation of MD.

Conclusion

To play musical instruments requires a time-varying mechanical interaction between the body and instrument. This dynamic process successfully works firstly when efference motor commands that accurately elicit the desired sensory outputs (e.g., production of the target loudness level) can be programmed in the nervous system through taking into account mechanical characteristics of the instrument to be played and secondly when afferent sensory inputs accurately can update the motor programming process so as to reduce upcoming spatiotemporal error of movements. An accumulated number of behavioral and neurophysiological evidence of aberrant sensorimotor integration in patients with MD therefore suggests that emergence of the dystonic movements specifically during playing a musical instrument in MD is associated with malfunctions of this sensory-motor loop. Intriguingly, this sensorimotor transformation may involve organizing coordinated patterns of joint

movements and muscular activities, as exemplified by the surround inhibition [47, 48, 58], which further suggests that normalizing the maladaptive synergy in MD requires multimodal interventions targeting both sensory and motor systems, such as functional connectivity-based neurofeedback [59].

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Electromyography as a Method for Distinguishing Dystonia in Mice

Amanda M. Brown, Elizabeth P. Lackey, Luis E. Salazar Leon, Alejandro G. Rey Hipolito, Jaclyn Beckinghausen, Tao Lin, and Roy V. Sillitoe

Abstract Electromyography (EMG) methods allow quantitative analyses of motor function. The techniques include intramuscular recordings that are performed in vivo. However, recording muscle activity in freely moving mice, particularly in models of motor disease, often creates challenges that prevent the acquisition of clean signals. Recording preparations must be stable enough for the experimenter to collect an adequate number of signals for statistical analyses. Instability results in a low signal-to-noise ratio that prohibits proper isolation of EMG signals from the target muscle during the behavior of interest. Such insufficient isolation prevents the analysis of full electrical potential waveforms. In this case, resolving the shape of a waveform to differentiate individual spikes and bursts of muscle activity can be difficult. A common source of instability is an inadequate surgery. Poor surgical techniques cause blood loss, tissue damage, poor healing, encumbered movement, and

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unstable implantation of the electrodes. Here, we describe an optimized surgical procedure that ensures electrode stability for in vivo muscle recordings. We implement our technique to obtain recordings from agonist and antagonist muscle pairs in the hindlimbs of freely moving adult mice. We validate the stability of our method by holding EMG recordings during dystonic behavior. Our approach is ideal for studying normal and abnormal motor function in actively behaving mice and valuable for recording intramuscular activity when considerable motion is expected.

Keywords Electromyography · Mouse · Dystonia · In vivo physiology · Motor behavior

Introduction

As our understanding of movement disorders continues to grow, the contribution of a network of motor-processing regions to the presentation of abnormal motor phenotypes, including dystonia, has become increasingly apparent. The movement disorder dystonia, defined by involuntary postures, twisting, and repetitive movements caused by abnormal muscle contractions [1], has primarily been associated with defects in the basal ganglia. However, the cerebellum, brain stem, thalamus, and cortex are now known to contribute to this devastating disease [2]. In addition to multiple loci of dysfunction in the nervous system, dystonia has many potential etiologies that can be either inherited or acquired [3]. Dystonia can also appear in combination with other abnormal motor phenotypes, further complicating the presentation of the disorder and possibly indicating a greater network contribution [4]. While there have been notable advancements in our understanding of this disorder across model systems and methodologies, incongruences have emerged between the pathogenesis of human disease and phenotype presentation in experimental models [5]. One strategy to resolve these differences in model systems and the many potential contributors to the disease is to study the final output of the motor system: the electrical activity at the level of the muscle. As dystonia is primarily defined by the abnormal muscle contractions rather than the underlying pathogenesis of the contractions [1, 4, 6], studying the electrophysiological output of the motor system can provide a standard to determine whether dystonia is present, differentiate dystonia from other movement disorders, detect if dystonia is concurrent with other movement disorders, and classify the various involuntary muscle contractions of dystonia.

Many behavioral and electrophysiological methods are now available for assessing motor function in humans and animal models of movement disorders. These methods include approaches for recording electrical potentials from the muscles in vivo, known as electromyography (EMG) [7–9]. EMG utilizes electrodes placed either within or overlying the target muscle. One can also record with relatively noninvasive surface electrodes or with intramuscular needle electrodes, but

instability often limits the utility of these techniques, and the signals collected may not be adequate for the specific questions being asked. In all cases, the preparation must be stable enough that the experimenter can collect an adequate number of clean electrical potentials for statistical analyses. However, collecting clean electrical potentials is a challenge because noise can increase during the animal's movements. In awake, freely moving animal models of severe motor disorders, the overt, high-amplitude movements increase the risk of signal disturbances, which makes overcoming signal instability especially difficult. To capture the natural movement, one must therefore overcome the sources of instability. A common source of instability in animal model preparations is an inadequate surgery. Poor surgical techniques can cause blood loss, tissue damage, poor wound healing, hypothermia, infection, encumbered movement, and ultimately, unreliable implantation of the electrodes. In EMG analyses, the experimenter often wishes to resolve the shape of a muscle-derived waveform to differentiate individual spikes and bursts of muscle activity accurately. Proper implantation of the electrodes is key to achieving the low signal-to-noise ratio necessary for successful isolation of EMG signals during the behavior of interest. Without this clarity, the experimenter is unable to discriminate electrical potentials from those of neighboring muscles or from the noise inherent to in vivo electrophysiology.

Models of motor disorders present a significant challenge for EMG recordings. Severely aberrant muscle activity results in abnormal motions of the limbs and body that can cause considerable noise in unstable EMG implantations. Moreover, if one attempts to study disease-like motions in an unstable preparation involving multiple channels, the functional relationship between muscles could be hard to parse, and interpretations may be compromised. Stable EMG recordings are especially critical in animal models of dystonia because investigators can use co-activation or overcontraction of agonist/antagonistic muscles as a key phenotyping criterion [6]. Here, we describe an optimized surgical approach with recommendations for the experimenter to optimize stability. We implement our technique in mice, a powerful animal model of choice due to the genetic tools available for experimental manipulation. In the following protocol, we delineate a step-by-step procedure for reliably fabricating and implanting in vivo electrodes and securing a connector to acquire stable intramuscular recordings in freely moving mice. We implement our technique to obtain recordings from the tibialis anterior (TA) and gastrocnemius (GC) muscles and validate the stability of our approach by holding recordings during dystonic behavior as well as tremor, which is often present with dystonia [10–12]. Despite the severe shaking and twisting of the animal's limbs, we were able to isolate stable EMG signals. To demonstrate the successful isolation, we resolved the electrical potential waveforms and describe statistical analyses of spikes and bursts of activity, waveform correlations, and power spectra that are all useful for quantitative interpretations. We confirm that the chronic EMG implant does not affect the normal gross movements of the animal and report minimal muscle tissue damage through anatomical observation using histological staining of the muscle tissue at the site of electrode implantation.

Materials and Methods

Animals

All experiments were performed in accordance with a protocol approved by the institutional animal care and use committee (IACUC) at Baylor College of Medicine and within the National Institutes of Health guidelines. Mice were housed on a 14 h/10 h light/dark cycle and bred using standard timed pregnancies. Noon on the day a vaginal plug was detected was designated as embryonic day (E) 0.5 and the date of birth as postnatal day (P) 0. Male and female mice between 2 and 6 months old were used in all experiments. Control mice of mixed background were ultimately maintained on a C57BL/6 J background and used in the footprinting, histology, and EMG experiments. *Ptf1a*^{Cre}*; Vglut2*$^{flox/flox}$ mutant mice with genetically induced dystonia [10] were used for the EMG experiments. Dr. Christopher Wright (Vanderbilt University School of Medicine) kindly provided the *Ptf1a*^{Cre} driver allele. The *Vglut2*$^{flox/flox}$ mice were purchased from JAX (the Jackson Laboratory; #012898). Genotyping of the *Ptf1a*^{Cre}*; Vglut2*$^{flox/flox}$ mice was performed using previously described *Cre* [13] and *Vglut2* [10] primers.

EMG Electrode Fabrication

A completed EMG implant has two twisted bipolar recording electrodes [8] and one ground electrode soldered onto a six-pin connector and isolated in epoxy (Fig. 1a–f). Perfluoroalkoxy-coated silver wire (A-M Systems, Carlsborg, WA, US; #785500) is used to make all electrodes due to its small diameter, excellent flexibility, and conductive properties. First, a wire segment that is double the length needed to reach from the skull to the target muscle with additional length for slack during movement is cut from the spool. For example, the length necessary is ~30 cm for the forelimb and ~35 cm for the hindlimb of an adult mouse. Next, the wire is folded in half. The top of the resulting half-loop is taped to a work surface. The wire is twisted tightly for ~1 cm and then loosely until the twist is ~5 cm from the tips. The strands are tied into a knot at this location to hold the loose twist in place. The initial loop is freed from the work surface and cut open to create two forking wires followed by a tightly twisted region, a loosely twisted region, the knot, and finally two separate ends of wire. Approximately 5 mm of coating at the tips of the forked region is removed either by heating with a small flame or stripping it away (described below). The region including the knot and subsequent separate wire ends is taped down in the field of view of a dissection microscope with the wire ends pulled tightly into a "Y" shape. A small segment of the silver wire is then exposed on each of the separated wires. The length of exposed wire depends on the length of the target muscle. For example, 1 mm of coating should be removed if targeting shorter muscles such as those in the forelimb, and 2 mm of coating should be removed if targeting longer

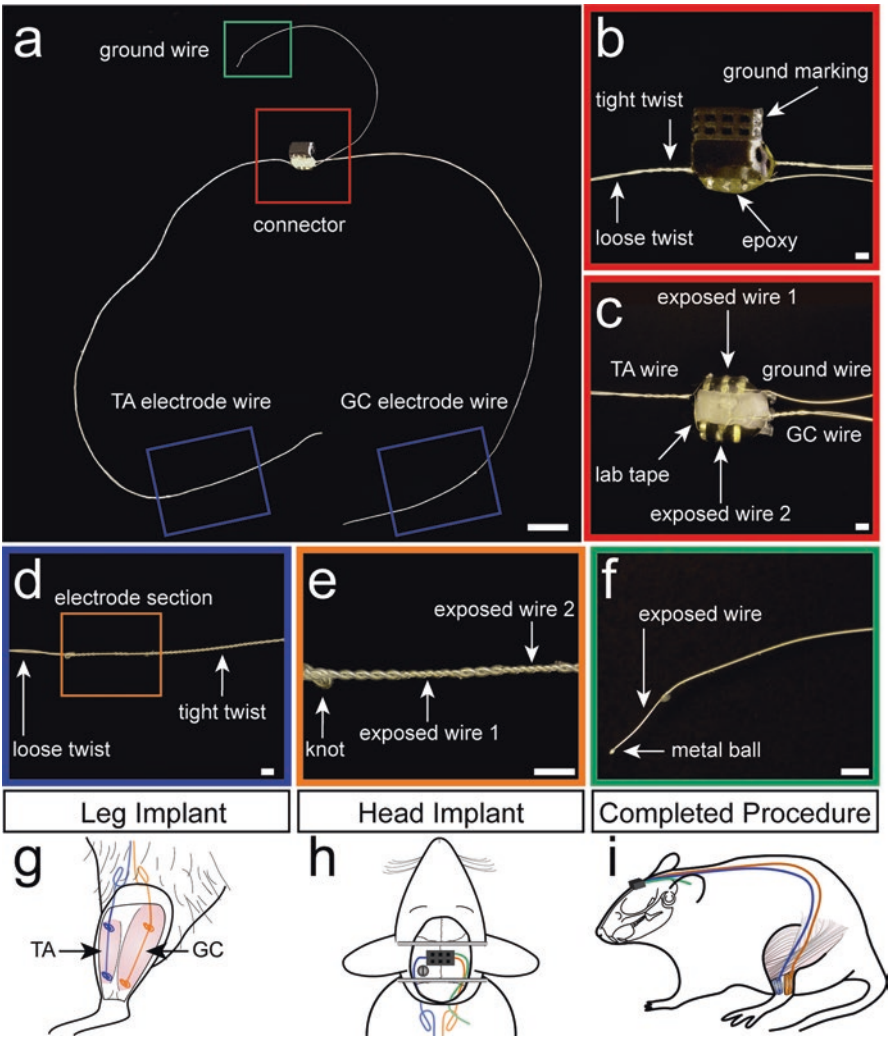

Fig. 1 A technique for chronic implantation of EMG wire electrodes into an agonist and antagonist muscle pair. (**a**) Image of a completed implant for chronic implantation of EMG wires into an antagonistic muscle pair. A connector (red inset) is the only portion of the implant that is exposed on the animal and interfaces with the external recording setup via a preamplifier. In the pictured setup, a six-pin connector is used. This allows for two bipolar recording electrodes (blue insets) and a ground wire (green inset). Scale = 1 cm. (**b**, **c**) Higher-power image of the connector. Scale = 1 mm. (**b**) Top and side view of the connector. (**c**) Underside of the connector. (**d**) Higher-power image of the bipolar electrode section on the wire. Scale = 1 mm. (**e**) Inset from **d** with enhanced view of the knot and exposed sections of the wires. Scale = 1 mm. (**f**) Higher-power image of the ground wire highlighting the exposed section of wire with the spherical tip that results from melting. Scale = 1 mm. (**g**) Schematic of the leg portion of the surgical procedure directly before suturing the leg closed. *TA* tibialis anterior. *GC* gastrocnemius. (**h**) Schematic of the head portion of the surgical procedure directly before sealing with Metabond and dental cement. (**i**) Schematic of the completed procedure with the connector cemented to the skull and the wires implanted into the tibialis anterior and the gastrocnemius muscles

muscles such as those in the hindlimb. If the length of the electrode section (Fig. 1d) is too long, then it will exceed the length of the target muscle belly and record off-target signals. If the length is too short, it will record from a limited area of the muscle. The first exposed wire segment is made 1–2 mm below the knot on one loose end. Exposing the wire can be achieved in multiple ways. For example, a 23-gauge needle can be used to nick the coating on either side of the enclosed wire, allowing the experimenter to peel the coating away from the silver using forceps (Fine Science Tools, Foster City, CA, US; either #11210-10 or #11254-20). Alternatively, the coating can be sliced off the enclosed wire using a needle or a fine blade (McKesson Medical-Surgical Inc., Richmond, VA, USA; #16-63815). No matter the method chosen, the experimenter must take care not to damage the enclosed wire to ensure a quality EMG signal. The second exposed segment is made on the opposite loose end, 1 mm below the bare section of the first wire. After one section is exposed on each wire, the two loose ends of the wire are tightly twisted together (Fig. 1d). A dissection microscope is then used to confirm that the bare wires do not contact each other (Fig. 1e). This process is repeated to make the second bipolar electrode for the opposing muscle. To fabricate a ground electrode, a ~7 cm wire segment is cut from the spool, and a small flame is used to melt ~2 mm of the coating on one end. This should create a small metal ball of melted wire at the tip of the exposed section but should not otherwise melt the wire. Approximately 5 mm of coating is then removed from the opposite end either by burning or stripping, as described above.

The wires can now be connected to a disposable six-pin connector (Pinnacle Technology, Lawrence, KS, US; #8235). To prepare the connector for the wires, the connector is first painted white on one side to distinguish the side that will connect to the ground electrode (Fig. 1b). This will allow the experimenter to see that the preamplifier is plugged into the connector in the correct orientation. Because epoxy will eventually be applied to the bottom of the connector, a piece of lab tape is applied between the pins on the underside of the connector to prevent the epoxy from flowing into the sockets (Fig. 1c). Then, forceps are used to wrap each bare wire of the forked region around two opposite pins on the connector corresponding to an EMG channel (Fig. 1c). The bare wires must not contact any other pins. This is repeated for the second EMG channel and the ground wire. Orienting the electrode wires to opposite ends of the connector and being consistent with the muscle to which each wire is targeted is important, as it allows the experimenter to distinguish the wires from each other during surgery and implant them into the correct muscles. A small amount of stainless-steel flux solution is then applied to the pins with a cotton swab. Each pin is then soldered, with special care taken to prevent the solder on the pins from touching any other pin. A multimeter (Fluke, Everett, WA, USA; #115) is then used to test the connection of each exposed wire to each pin and confirm that all of the connections are isolated properly. Three layers of light-curing epoxy (Bondic, Niagara Falls, NY, USA) are applied over and around the pins to insulate them and the connector (Fig. 1b). Each layer of epoxy is solidified with ultraviolet (UV) light before adding the next. The entire connector is then placed under a UV lamp until the epoxy is fully solidified.

Surgery

The surgical procedure is performed using sterile techniques and equipment under a surgical microscope (Zeiss, Oberkochen, DE; Stemi DV4) and a fiber optic light source (Schott, Southbridge, MA, USA; ACE 1). Preemptive analgesics are administered at least 30 min before the start of the procedure. These consist of a 1 mg/kg dose of sustained-release buprenorphine and a 5 mg/kg dose of meloxicam by subcutaneous injections. Anesthesia is induced in a small box chamber with 3% isoflurane vaporized in oxygen before transferring the animal to a sterile diaper pad overlying a DC current rechargeable heating pad (Kent Scientific, Torrington, CT, USA; #DCT-15). The animal is then head-fixed in the prone position on a stereotaxic platform with a ventilator mask, tooth holder, and metal ear bars (David Kopf Instruments, Tujunga, CA, USA; Model 940). Next, we reduce the isoflurane level to 2% and monitor anesthesia by testing the withdrawal reflex to a toe pinch at least every 30 min. Ophthalmic ointment is applied to prevent the eyes from drying during surgery (Henry Schein, Melville, NY, USA; #1296576). The fur on the skin dorsal to the skull and neck is removed using an electric trimmer (Conair, Stamford, CT, USA; #PG2RN) and depilatory cream (Church & Dwight Co., Ewing Township, NJ, USA; Nair). However, only a trimmer, clipper, and/or shaver should be used on the leg or other parts of the body with sensitive skin. Once the fur is removed from the skin at the head and EMG site, the skin is cleaned with three alternating applications of betadine scrub and 70% ethanol pads. A skin incision is made from the frontal bone to the caudal aspect of the occipital bone using forceps and dissection scissors (Fine Science Tools; #14082-09). The fascia is then teased away, and all plates of the skull are scraped with a scalpel blade and dried with sterile cotton swabs to create an ideal surface for bonding agents. A skull screw is placed in a thick portion of the skull lateral to the midline and anterior to lambda (Fig. 1h) to provide a strong anchor for the implant. To place the screw, an Ideal Micro-Drill surgical drill (Harvard Apparatus, Holliston, MA, USA; #726065) is used to drill a hole slightly smaller than the diameter of the 1/16 screw (00-90 × 1/16 flat point stainless-steel machine screws; #B002SG89QQ). A drill hole diameter that is too large will result in a skull screw that is too loose to serve as an anchor. To prevent this, test the size of the hole with a screw and drill more as needed. The experimenter should not drill down too quickly, as this can cause blood loss and increases the risk of drilling into the underlying brain tissue. Even slight contact can cause loss of cerebral spinal fluid, tissue damage, internal brain bleeding, and/or infection. Any bleeding that occurs during surgery should be stopped with sterile cotton swabs before proceeding with the next steps. The sterilized 1/16 screw is placed into the drill hole with forceps and very slowly advanced with a screwdriver (Wiha, Monticello, MN, USA; #26015) until secure, with extreme care taken to prevent penetrating the brain.

At this point, the focus of the surgery moves to the target muscles (Fig. 1g). We describe and show data using the hindlimb as a primary example, although below we also briefly describe the procedure for targeting the forelimb. An incision in the

skin overlying the muscles is made using forceps and dissection scissors. Care must be taken to avoid damaging vasculature near the ankle when targeting the gastrocnemius and tibialis anterior muscles. The gastrocnemius and tibialis anterior are located on either side of intermuscular fascia that appears as a pearly white streak. Approximately 1 cm of both of the recoding electrode tips is passed through a small eyelet at the end of a long custom-made rod and folded over to ensure that the tips will remain in place even with a light tug. The rod and recording electrodes are passed subcutaneously from the cranial incision at the top of the neck to exit at the limb incision. If resistance is met when passing the rod, adjustments are made to the path of the rod to avoid penetrating the body wall. The electrode wires are pulled out from under the skin until the knots are visible, and the bent portion of the electrode wires are cut to free them from the rod. A gentle tug is applied to each electrode wire while the experimenter observes their contact points on the connector to identify which ports correspond to each electrode. This allows the experimenter to identify the muscle target of each wire. Once the muscle target is identified, the corresponding recording electrode is threaded into the shaft of a sterile 23-gauge needle until the tip of the wire is visible at the heel of the bevel. The needle is then passed through the muscle belly parallel to the muscle fibers starting at the proximal end of the muscle and exiting at distal end of the belly. Adjusting the angle of entry based on the size and depth of the targeted muscle is important. For example, the gastrocnemius is a much larger and deeper muscle than the tibialis anterior, and therefore the angle of entry is more acute for the tibialis anterior than the gastrocnemius. The needle is then removed from the wire. The wire is gently pulled at the distal end until the proximal knot in the wire is just adjacent to the muscle. Two overlapping knots are tied in the wire where the distal end emerges from the muscle with the leg at full extension. The length of wire between the knots must be sufficient to allow the full range of motion of the leg. Therefore, we recommend maintaining the leg at full extension for this and the remaining steps. Once this is done, the excess wire at the distal end is cut, and the remaining nub is folded over the knot. The knot is then flattened with forceps or a hemostat. Mitigating rough edges within the implant that can cause damage to the surrounding tissue or prompt the awake animal to disturb the surgery sites is important. The steps are repeated for the remaining muscle. Finally, the skin incision is sutured beginning at the distal end using a 13 mm 3/8 circle cutting needle with nonabsorbable 4-0 silk braided suture (Henry Schein, Melville, NY; #101-2590). Interrupted sutures are used so that if a single suture knot fails, the incision remains closed. At the point that half of the incision is closed, forceps are used to pull a small amount of additional slack in the wire at the proximal end of the incision and tuck it underneath the skin of the thigh before completing the sutures. The goal is to provide enough slack that there is no resistance to the animal's natural movements, but not so much that the wire becomes bulky under the skin.

A similar procedure is used when targeting the long head of the biceps brachii (Bic L) and the long head of the triceps brachii (Tri L) muscles in the forelimb. One important difference is that separate skin incisions are made for each muscle. To target the Bic L, an incision along the medial proximal forelimb is made where the

muscle is visible proximal to the elbow joint. The experimenter may prefer to access the Bic L with the animal in the prone position or may choose to rotate the animal to the supine position to access the medial forelimb. To limit the time the surgical sites are open, we recommend implanting an electrode into one forelimb muscle and closing the incision before making the second skin incision to implant an electrode into the other forelimb muscle. To target the Tri L, a separate skin incision is made along the lateral proximal forelimb where the large muscle belly is visible proximal to the elbow joint. The forelimb is gently extended when suturing to prevent skin tension at the surgery site during movement. Again, care must be taken to ensure normal range of motion is preserved.

Finally, the experimenter can complete the implant at the head (Fig. 1h). The connector is attached to the skull posterior to bregma either with light-curing epoxy or a small amount of C and B Metabond Adhesive Luting Cement (Parkell, Edgewood, NY, USA; #S380). The ground port of the connector is consistently oriented to the same side of the skull between animals for easy identification in case the white paint cannot be visualized later. The ground electrode is then threaded into the shaft of a 23-gauge needle until the exposed tip of the wire is visible at the heel of the bevel. The needle is used to penetrate the surface of the skin at the edge of the skull skin incision and thread the ground wire through the skin. The needle is removed from the wire, and the wire is folded underneath the skin until it is secure. This provides an anchor to the ground wire to ensure it remains in place under the skin. The remaining loosely twisted portions of all of the wires are tucked under the skin of the nape of the neck to provide additional slack for the animal's movements. The wires protruding from the connector should not extend past the borders of the open cranial incision. Metabond is applied around the connector, over the skull screw and the skull, and extending over the edges of the skin incision. While the Metabond is still wet, we place a ~1.5 cm segment of 0.81 mm diameter stainless-steel wire (Wire and Cable Specialties Inc., Coatesville, PA, USA; #MC0320-5#S) to both the anterior and posterior side of the connector and cover the centers with more Metabond. The wires will be used to hold the head of the awake animal in place when plugging in the preamplifier. While one wire would be sufficient to hold the head, concurrently holding two provides additional stability when working with the animal. Once the Metabond has completely hardened, methyl methacrylate dental cement (A-M Systems, Sequim, WA, USA; powder #525000, solvent #526000) is placed around the connector and over the wires, the skull and skull screw, the skin incision, and the center of the steel tubing to cover all Metabond present. Dental cement must not enter or block the sockets. Once the dental cement is solidified, the ear bars are removed from the animal. The isoflurane level is reduced to 0% for at least 30 s before the animal is transferred from the stereotaxic frame to a warming box (Peco Services, Brough, UK; #V500). The animal's postoperative recovery is monitored at least every 15 min for 2 h. Postoperative analgesics are provided for at least 72 h as needed. Animals are allowed to recover for at least 72 h before recordings are made. The result of this procedure is a mouse with chronically implanted EMG wires in an agonist/antagonist muscle pair, a ground wire under the skin of the

neck, and a connector and bracing wires anchored to the skull with a skull screw, allowing for freely moving EMG recordings to be performed.

Recording

Ring forceps (Fine Science Tools; #11106-09) are used to grasp the steel wire on either side of the head mount. This stabilizes the head while plugging in the preamplifier (Pinnacle Technology Inc., Lawrence, KS, US; #8406 series customized with 2 EMG channels) into the connector. The preamplifier applies both a 50× gain and 10 Hz high-pass filter to the recording electrodes. The preamplifier is then connected to a swivel commutator (Pinnacle Technology, #8408) that is bolted to a mounting plate (Pinnacle Technology; #8426) above the cage to allow unencumbered movement during the recording session. The swivel commutator delivers the signals to an analog adapter (Pinnacle Technology; #8442-K). Secondary amplification is applied with a 10x gain and 5 kHz low-pass filter (Brownlee Precision, Santa Clara, CA, US; Model 410). The signals are digitized at 5000 Hz (Cambridge Electronic Design, Cambridge, UK; Power1401) and recorded using Spike2 software (Cambridge Electronic Design). Synchronized video and/or keyboard strokes can be used to identify time points with specific behaviors of interest.

EMG Analysis

Burst duration, burst frequency, the presence of co-contractions, and oscillatory activity of raw EMG signal can be used to discern the resultant motor phenotype. For burst duration and frequency, Spike2 software is used to center the trace on zero using an averaging function (DC Remove). A threshold is then placed on the trace in order to sort raw EMG activity into isolated events that comprise bursts of muscle activity. Because the EMG activity is raw, each event represents the spike activity of a varying number of synchronously active muscle units. The Spike2 script bursts.s2s is used to group these sorted events into bursts based on user-defined maximum initial inter-event interval of burst onset, maximum inter-event interval within a burst, and minimum events per burst. These defined bursts can then be analyzed within Spike2 or exported to other softwares such as Matlab or Excel to determine mean burst duration and frequency. We recommend analyzing multiple periods/instances of the movement of interest, particularly if they vary in duration, and averaging across the analyzed movements. To evaluate the level of co-activation between muscles, we center the EMG traces on zero and then rectify the two signals. We use the waveform correlation function in Spike2 to measure the extent of signal correlation. The gastrocnemius trace is shifted in time relative to that of the tibialis anterior. A trough when the traces are aligned at time = 0 indicates reduced correlation between the muscle signals, suggesting the expected suppression of the

gastrocnemius when the tibialis is active. However, a peak at zero suggests co-contraction of muscle activity, which is indicative of dystonia. Dystonic animals do not always exhibit co-contractions, however; we show here a milder case, which can be distinguished by the reduced trough at zero. Tremor can also be distinguished using this method, appearing as a rhythmic oscillation of correlation values. Here, we used a 2.5 s offset and width of 5 s on EMG traces lasting 60 s. We recommend analyzing signals during behaviors of interest, such as locomotion, and analyzing at least 30 s of activity from each trace using the same sampling frequency across traces. Spike2 software is also used to evaluate oscillatory muscle activity. We use the power spectrum function in Spike2 to perform a fast Fourier transform (FFT) on the signal and display its frequency components. Here we used a 4096 FFT block size and applied a Hanning window.

Gait Analysis

A straightforward analysis of gait can be performed by collecting the footprints of mice as they voluntarily ambulate across a flat surface. First, a walkway is prepared by placing a sheet of white paper inside a custom-made plexiglass tunnel measuring 10 cm wide by 51 cm long. The end of the tunnel is placed inside a dark rigid bag or box to provide motivation for the mice to traverse the length of the tunnel. Second, the soles of the paws of each mouse are painted with nontoxic paint (Crayola, Easton, PA, USA; #54-1204). Performing this step smoothly and quickly is important to minimize stress on the animal. Either the front, hind, or both sets of paws may be painted. Choose different colors for the front and hindpaws and be consistent with the paw/color pairing to avoid confusion during analysis. Once the paws are painted, gently place the mouse in the entrance of the prepared tunnel. The mouse will then traverse the tunnel and enter the dark container at the end of the tunnel where it can be collected by the experimenter and returned to the home cage. Allow the mouse to rest for at least 5 min before repeating the process. A trial is considered successful if there are at least three consecutive steps in which (1) sufficient paint transferred onto the paper to determine where the paws landed, (2) the steps occurred in a straight line (the animal was not turning), and (3) the animal maintained a consistent walking speed, neither stopping nor running. Three successful trials are collected from each animal per day. Analysis is performed by measuring the "stride," "sway," and "stance" length. Stride is defined as the distance between two consecutive footprints from the same paw (e.g., left hind to left hind). Sway is defined as the lateral distance between two consecutive footprints. Stance is defined as the diagonal distance between two consecutive footprints. For examples, please refer to our previous work [14, 15].

Perfusion and Tissue Preparation

To perform transcardial perfusion, mice are first anesthetized by intraperitoneal injection with Avertin (2,2,2-tribromoethanol; Sigma-Aldrich, St. Louis, MO, USA; #T48402). They are then perfused with ice-cold 1X PBS followed by ice-cold 4% paraformaldehyde (4% PFA) diluted in 1X PBS. The left hindlimb is then dissected away, the skin removed, and post-fixed in 4% PFA at 4 °C for at least 48 h.

To prepare the tissue for paraffin embedding, the gastrocnemius and tibialis anterior are dissected from the leg, cut in half, and placed in a plastic holding chamber. The muscles are then dehydrated in a series of ethanol solutions consisting of three stages: 70% ethanol overnight, 95% ethanol for 8 h, and 100% ethanol overnight. Then they are placed in xylene for at least 2 hours before immersing them in 2 baths of 65 °C liquid paraffin in series. They are immersed in the first paraffin bath for 1 hour and the second overnight. These paraffin baths are the same, and the two-step process is performed to get rid of any residual chemicals before solidifying the paraffin. The muscles can then be placed on a Tissue-Tek TEC 4 cryo console (Sakura, Torrance, CA, USA; #4709) set at −1 °C for ~1 h or at room temperature until the paraffin solidifies. To embed the muscles in paraffin using a Tissue-Tek TEC 4 embedding console (Sakura, Torrance, CA, USA; #4710), metal molds are first filled with a thin layer of 65 °C paraffin that is allowed to solidify over the Tissue-Tek cold spot set at 15 °C. Using this thin layer like an adhesive substrate, the muscles are then carefully placed upright on the layer using forceps before filling the mold to the top with paraffin. The filled molds are then placed over the Tissue-Tek cryo console until the paraffin block fully solidifies for sectioning. Sections are cut at 6 μm thickness on a microtome, floated in a warm water bath (set at 50 °C), and then carefully collected on electrostatically coated slides with a soft paintbrush.

Histology

Visualization of the electrode implant site in the muscle tissue is achieved using standard hematoxylin/eosin staining. Muscle tissue is prepared as described above. Tissue sections are dried on electrostatically coated slides and then placed in xylene for 5 min. The tissue is then rehydrated in a series of ethanol solutions consisting of three stages of 100% ethanol followed by 95% ethanol and 70% ethanol, with 2 min per stage. Next, the tissue is rinsed under warm tap water 1 to 3 times for about 10 s each. The tissue is then placed in hematoxylin (22-220-100, Fisher Scientific, Hampton, NH, USA) for 45–60 s before being transferred to warm tap water for 5 min. The staining should look dark blue/violet. The tissue is then placed in a bath of lithium for about 1–5 s before being transferred back into tap water for ~10 s. The tissue is then incubated in eosin (23-314-631, Fisher Scientific, Hampton, NH, USA) for 15–30 s, resulting in a pink stain. The tissue is washed in warm tap water a third time for ~10 s and then dehydrated via reversing the previous ethanol series

at 2 min per solution. The tissue is then placed in two xylene baths in series for 2 min each. Finally, the tissue sections are coated with Cytoseal permanent mounting media (8312-4, Thermo Fisher Scientific, Waltham, MA, USA) and coverslipped while still wet with xylene. The glass slides should be allowed to dry overnight before any further handling and imaging occurs.

Imaging

Photomicrographs of stained tissue were obtained using a Leica DMC2900 camera mounted on a Leica DM4000 B LED microscope using Leica Application Suite X software (Leica Microsystems, Wetzlar, Germany). Images of the electrodes and connector setup were collected using a Zeiss AxioCam MRc5 camera mounted on a Zeiss Axio Zoom.V16 microscope with Zeiss AxioVision software (Zeiss, Oberkochen, Germany). Images were adjusted for brightness and contrast using Adobe Photoshop CC (Adobe Systems, San Jose, CA, USA). Schematics and figures were made in Adobe Illustrator CC (Adobe Systems, San Jose, CA, USA) and then imported into Adobe Photoshop CC to assemble the final figures.

Results

Chronic EMG Implantation Causes Minimal Disruption of Muscle Tissue

The muscle tissue must remain healthy during the process of observing the dystonic phenotype through EMG. However, some limited tissue disruption is unavoidable when chronically implanting wires into the muscle belly (Fig. 2). Despite some localized tissue disruption, H&E histology demonstrates that muscle integrity is well-preserved even after the EMG implants have been in place for a week (Fig. 2).

Chronic EMG Does Not Disrupt Overall Movement

The method of measuring EMG must not impact the animal's movements. The impact of EMG electrodes targeted to the limbs on the animal's movements can be observed using gait analysis. Here, we performed a gait analysis on control animals by painting their front and hindpaws in contrasting colors and measuring the stride, sway, and stance apparent in the locations of their footfalls (Fig. 3a). We measured these gait parameters before surgery on the same day as the procedure (day 0), four days after the procedure (day 4), and eight days after the procedure (day 8)

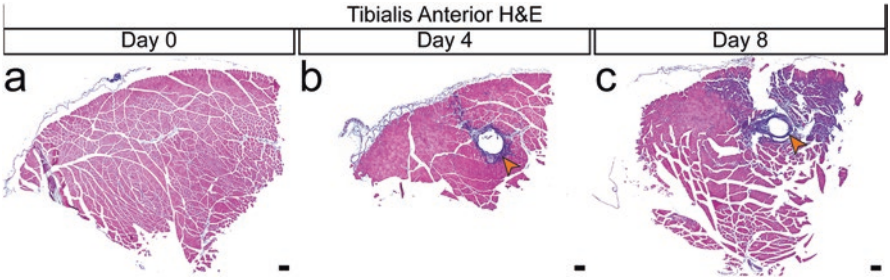

Fig. 2 Minimal tissue damage is caused by chronically implanted EMG electrodes. (**a-c**) Representative images of tibialis anterior muscle sections with H&E stain (**a**) without surgery, (**b**) 4 days post-surgery, and (**c**) 8 days post-surgery. Arrowhead = implantation site. Scale = 100 μm

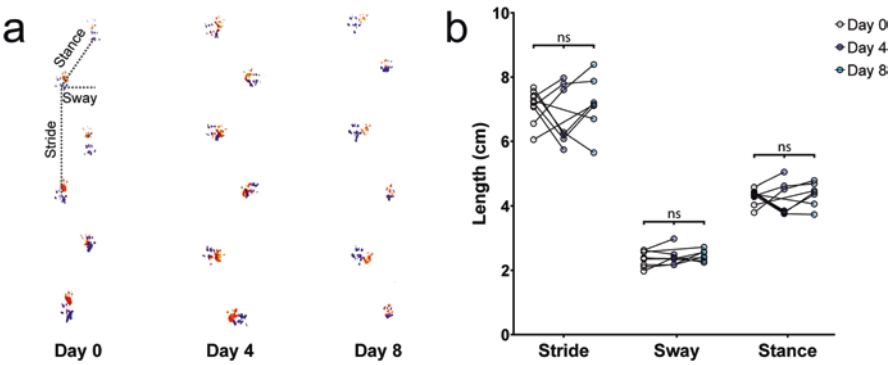

Fig. 3 Chronically implanted EMG wire electrodes in the hindlimb do not impact the basic features of normal gait. (**a**) Representative images of hindpaw (purple) and forepaw (orange) footprints recorded before surgery (day 0), four days post-surgery (day 4), and eight days post-surgery (day 8). Schematic of the three gait parameter measurements – stride, stance, and sway – is overlaid. (**b**) Population statistics for the three gait parameters on days 0, 4, and 8. Each circle represents one animal on one day of measurement. Mice with repeated measures are connected by a line. No significant effect was found in any of the measures assayed for the different number of days with EMG wires implanted

(Fig. 3b). No difference was found in any of the gait parameters (mixed effects model. Stride, day 0 mean = 7.13 cm, SD = 0.488; day 4 mean = 6.814 cm, SD = 0.9368; day 8 mean = 7.155 cm, SD = 0.8694. Day 0 vs. day 4 $p = 0.7144$. Day 0 vs. day 8 $p = 0.9982$. Day 4 vs. day 8 $p = 0.4949$. Sway, day 0 mean = 2.336 cm, SD = 0.2283; day 4 mean = 2.423 cm, SD = 0.2737; day 8 mean = 2.46 cm, SD = 0.1706. Day 0 vs. day 4 $p = 0.4938$. Day 0 vs. day 8 $p = 0.2493$. Day 4 vs. day 8 $p = 0.9219$. Stance, day 0 mean = 4.296 cm, SD = 0.2239; day 4 mean = 4.201 cm, SD = 0.5208; day 8 mean = 4.364 cm, SD = 0.3621. Day 0 vs. day 4 $p = 0.8936$. Day 0 vs. day 8 $p = 0.9298$. Day 4 vs. day 8 $p = 0.4577$). This suggests that the described method of chronic EMG electrode implant does not impact the animals' basic movements, even after a long duration with the implant in place. This preservation

of innate movement is essential to have confidence that abnormal disease-related movements, such as those observed in dystonia, are measured accurately and that the abnormal movements are not arising from the implant itself.

EMG Can Distinguish the Dystonic Motor Phenotype Based on Muscle Burst Timing and Duration

Distinct and reproducible patterns of EMG activity can be recorded in the tibialis anterior and gastrocnemius of control, dystonic, and tremoring mice (Fig. 4). These muscles are useful for quantifying motor phenotypes because they act as an agonist and antagonist muscle pair, are large and therefore easy to target, are frequently involved in the presentation of abnormal movements in mice, and can be easily examined in typical movements such as walking. The tibialis anterior and gastrocnemius act as an extensor and flexor on the ankle joint, respectively. Therefore, the tibialis anterior and gastrocnemius should not be active concurrently during normal movement of the leg. Indeed, in control animals, suppression of gastrocnemius activity is observed when the tibialis anterior produces a burst of activity (Fig. 4a, b, g). However, bursts of tibialis anterior activity are frequently observed concurrent with bursts of gastrocnemius activity in mice with genetically induced dystonia (Fig. 4c–d, h). Importantly, this abnormal co-contraction phenotype can be distinguished from tremor, another hyperkinetic movement disorder that can be present with dystonia. The relative timing of contraction and suppression appears largely similar to control mice in the context of harmaline tremor (Fig. 4e–f, i), although the contractions are much more rhythmic than in controls. The comparison of relative contraction timing can be made using a cross-correlogram, which will have a trough centered on zero when muscle activity is anti-correlated and a peak centered on zero when co-contractions are predominant (Fig. 5a–d). Burst duration is another useful quantitative measure for identifying a dystonic phenotype. We recommend using the tibialis anterior for this analysis, as it typically has better defined bursts of activity than the gastrocnemius. This is because the gastrocnemius also plays a large role in postural control and therefore frequently has long periods of elevated activity. Dystonic mice tend to have a longer average burst duration of the tibialis anterior compared to both the control and tremoring mice (Fig. 4g–i). This feature is suggestive of an over-contraction. Finally, the presence of rhythmic bursts of muscle activity are indicative of the frequency and severity of tremor in mice [16]. Power spectrum analysis can be used to elucidate underlying oscillatory activity in EMG traces, which would be a predominant feature of EMG activity when tremor is present but less so in control and dystonic animals (specifically if dystonic tremor is not pronounced) (Fig. 5e). These techniques can be combined to define motor phenotypes such as dystonia and tremor and can be employed for more complex neurological cases such as dystonic tremor.

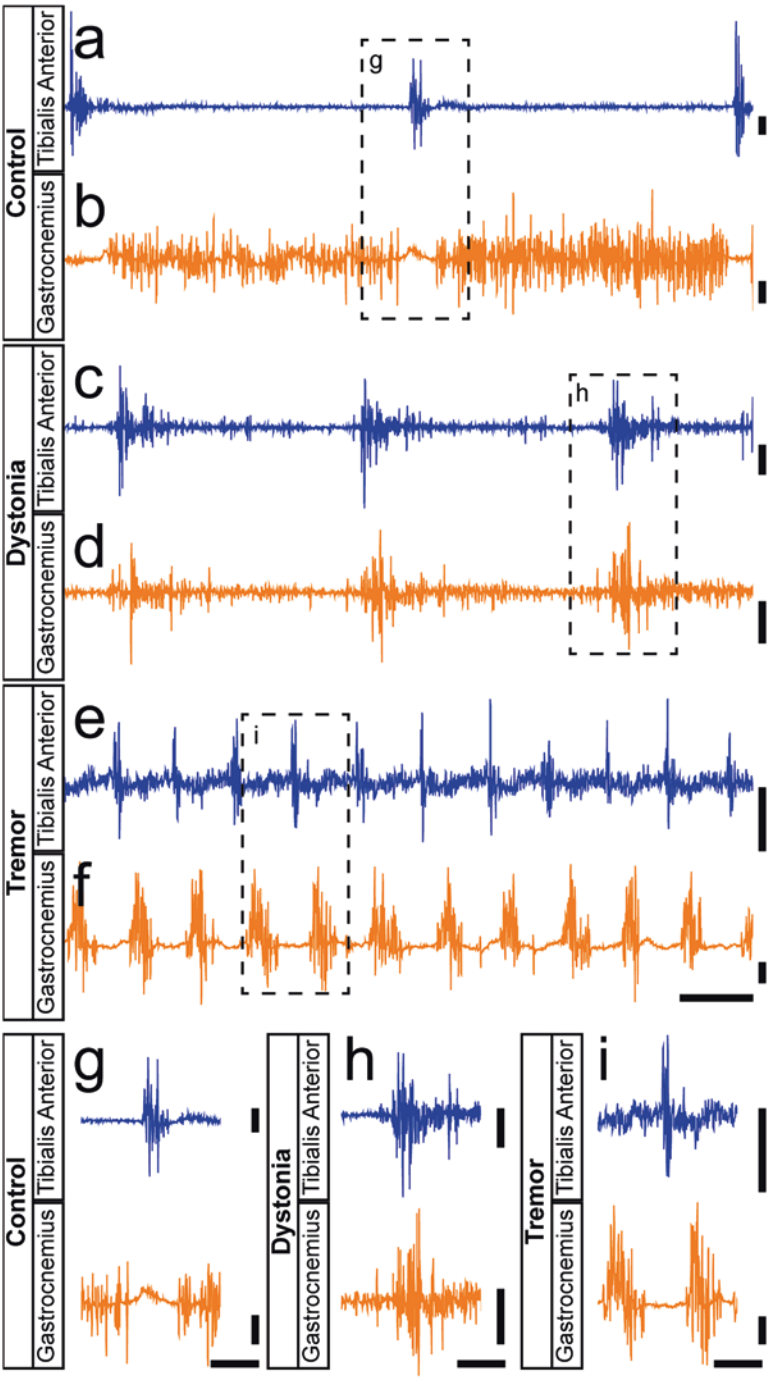

Fig. 4 EMG from dystonic animals can be distinguished from activity recoded in control and other hyperkinetic movement conditions. (**a**, **b**) Representative traces from (**a**) the tibialis anterior

Discussion

The range of motor symptoms and phenotypes characteristic of motor disorders is diverse and complex. In this study, we focused on dystonia to examine electrophysiological methods of reliably defining the behaviors that may be used to diagnose the key properties of a motor condition. Dystonia is the third most common motor disorder. Dystonia has hereditary and genetic forms, and onset can occur during childhood or adulthood, depending on the form of the disease. The presentation of the disease is heterogeneous, owing in part to the targeting of the disease to different body parts and to muscles in the limbs or torso. As such, dystonia can be generalized, as in the genetic *DYT1* condition [17], or focal, as in blepharospasm [18]. Although the disease is thought to arise because of abnormal connectivity and function in the cerebellum, thalamus, and basal ganglia [19], the end result is that muscle function is compromised, which ultimately causes the twisting postures and dystonic tremor associated with the disease. The muscles typically exhibit sustained or intermittent contractions that can occur as prolonged over-contraction or co-contractions of agonist and antagonist muscle pairs [20]. In recent years, a major effort has been made to develop model systems to mimic these behavioral features of the disease [10, 21–26]. However, these efforts have increased the need for quantitative measurements that accurately report dystonia in animals [10]. Here, we described the use of rodent EMG [9, 27] as a powerful measure for examining and quantifying dystonic movements in freely moving mice.

We presented a surgical procedure for targeting the tibialis anterior and gastrocnemius muscles. However, one can apply the same procedure to target other muscles for examining muscle responses in different disease models. Using EMG as a method of defining dystonia in mice had several benefits. First, the bursts of EMG could be used to track co-contractions of the tibialis and the gastrocnemius. The *Ptf1a*^{Cre}*; Vglut2*$^{flox/flox}$ mice are not always in a severe dystonic attack. However, when they are, the attack is reflected in the abnormal muscle responses with co-contractions occurring. This provided a second benefit: we could record periods where prolonged contraction of a muscle was occurring, with and without periods of co-contractions. Third, in humans, dystonia is often comorbid with other neurological conditions such as tremor [12]. In our mice, tremor also coexists with the twisting postures [10]. However, in addition to testing for the presence of tremor using EMG, using the EMG signals to distinguish the dystonic defects from isolated tremor [16], or even from the muscle defects that occur in ataxia [28], may be beneficial. Thus, EMG signal correlations and burst analysis are powerful quantitative measures for phenotyping different disease signals in mutant mice.

Fig. 4 (continued) and (**b**) the gastrocnemius in a control animal. (**c**, **d**) Representative traces from (**c**) the tibialis anterior and (**d**) the gastrocnemius in a dystonic animal. (**e**, **f**) Representative traces from (**e**) the tibialis anterior and (**f**) the gastrocnemius in an animal with harmaline tremor. (**a-f**) Vertical scale = 150 mV. Horizontal scale = 100 ms. (**g**) Inset of a single tibialis anterior burst from **a-b**. (**h**) Inset of a single tibialis anterior burst from **c-d**. (**i**) Inset of a single tibialis anterior burst from **e-f**. (**g-i**) Vertical scale = 150 mV. Horizontal scale = 50 ms

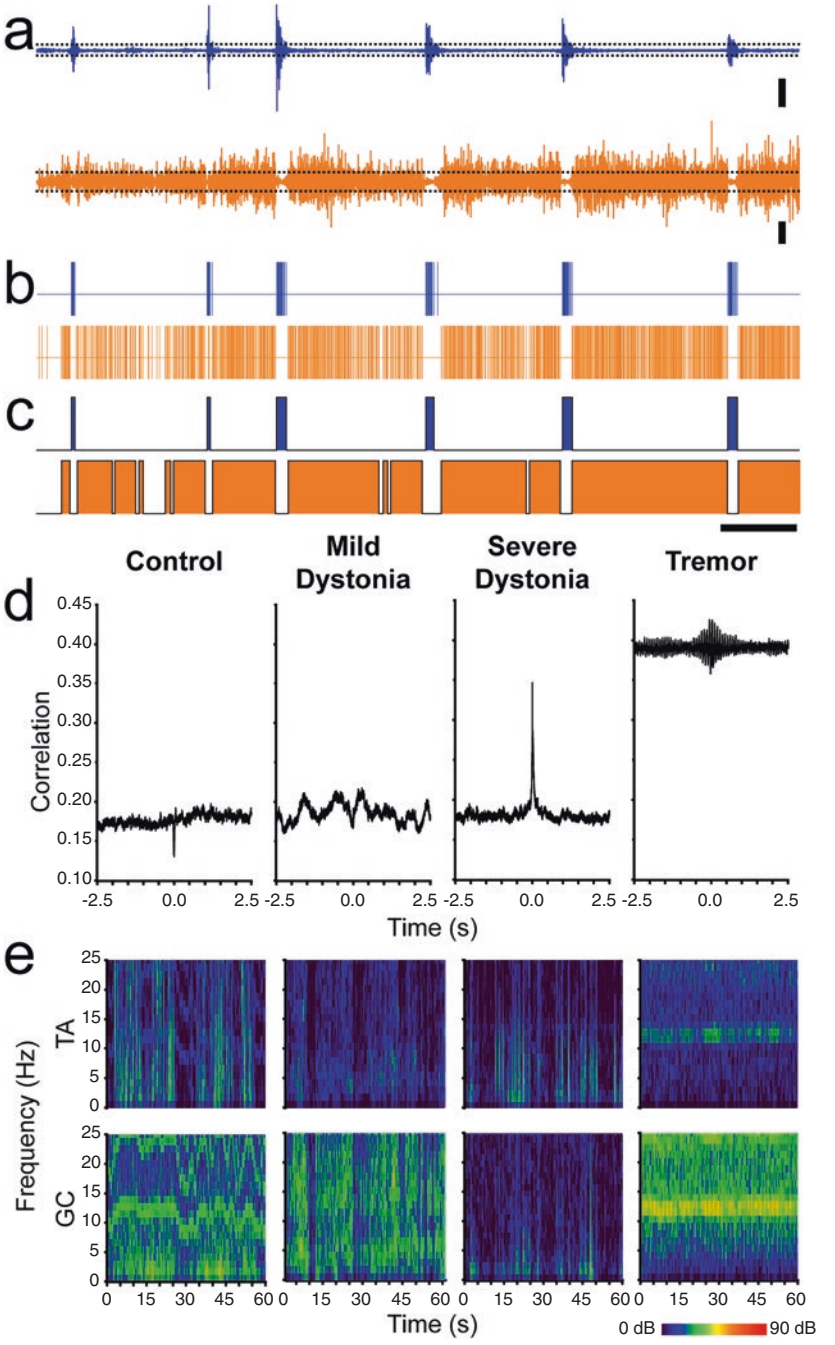

Fig. 5 Representation of a battery of analyses of EMG signals for the definition of motor phenotypes. (**a**–**c**) Representation of burst analysis pipeline. Horizontal scale = 0.5 s. (**a**) First, a threshold is placed on EMG signals to separate burst activity from moments of quiescence. *Top:* tibialis

One major hurdle to using EMG analysis in mice is the surgical skill required to generate clean signals. We have attempted to help overcome this hurdle by providing a step-by-step protocol for generating high-quality electrodes and implanting the electrodes so that they remain stable within the muscle, as well as recommendations for basic analyses of the recorded muscle signals. Because the implants are invasive, some muscle fibers may be damaged, causing inadvertent alterations to motor function. However, we also show that with careful technique, the implants induce limited muscle disturbances and the basic properties of normal gait can be preserved (Figs. 2 and 3).

In vivo EMG is a flexible and powerful tool for quantitatively defining the core features of muscle activity to characterize the neurological phenotype of mouse mutants. EMG is also ideal because it can be paired with other electrophysiological techniques such as in vivo brain recordings or optogenetics, which can be used to control neuronal activity on demand and induce immediate muscle responses [16]. The generation of additional mouse models with complex neurological phenotypes will likely require the use of EMG as a standard technique for characterizing the phenotypes. This technique allows millisecond precision in the monitoring of ongoing muscle activity to be linked to other experimental manipulations employed in the pursuit of greater understanding and treatment of motor disorders.

In summary, dystonia is a complex disorder of many possible etiologies. Abnormal muscle activity represents the final output of a network of motor regions. Each of the nodes of this network may be producing or compensating for abnormal activity within the network of disease. Electrophysiological recordings from these nodes can only capture a piece of the underlying origin of the abnormal muscle contractions of dystonia. Similarly, manipulations targeted to any one of these nodes may affect the other nodes of the disease circuit in unexpected ways. However, our goal of studying this complicated motor phenotype is to understand why these abnormal muscle contractions begin and how to stop them from occurring. Therefore, reliably quantifying and classifying the electrical activity that produces these abnormal movements at the level of the muscle is of paramount importance. Quantifying how abnormal muscle activity occurs in relation to ongoing computations within the central nervous system or therapeutic manipulations provides a view of dystonia that can be generalized across etiologies, species, and experimental models. Chronically implanted EMG electrodes, as we have described here, provide the means to stably and reliably distinguish dystonic muscle activity for the purposes of these advancements.

Fig. 5 (continued) anterior raw signal (blue). Scale = 500 mV. *Bottom*: gastrocnemius raw signal (orange). Scale = 200 mV. Thresholds (black dotted lines). (**b**) Events that cross the set thresholds are isolated. *Top:* tibialis anterior detected events (blue). *Bottom*: gastrocnemius detected events (orange). (**c**) Bursts are defined based on desired maximum initial inter-event interval of burst onset, maximum inter-event interval within a burst, and minimum events per burst. *Top:* tibialis anterior bursts (blue). *Bottom*: gastrocnemius bursts (orange). (**d**) Representation of cross-correlations of individual traces from a control, mildly dystonic, severely dystonic, and tremoring mouse. (**e**) Representation of power spectrum analysis performed over time as a sonogram trace. The same traces analyzed in **d** are used for these analyses. Scale = 0 dB – 90 dB

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Conflicts of Interests We have nothing to disclose.

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Deep Brain Stimulation of the Interposed Cerebellar Nuclei in a Conditional Genetic Mouse Model with Dystonia

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Abstract Dystonia is a neurological disease that is currently ranked as the third most common motor disorder. Patients exhibit repetitive and sometimes sustained muscle contractions that cause limb and body twisting and abnormal postures that impair movement. Deep brain stimulation (DBS) of the basal ganglia and thalamus can be used to improve motor function when other treatment options fail. Recently,

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the cerebellum has garnered interest as a DBS target for treating dystonia and other motor disorders. Here, we describe a procedure for targeting DBS electrodes to the interposed cerebellar nuclei to correct motor dysfunction in a mouse model with dystonia. Targeting cerebellar outflow pathways with neuromodulation opens new possibilities for using the expansive connectivity of the cerebellum to treat motor and non-motor diseases.

Keywords Dystonia · Neuromodulation · Cerebellum · Deep nuclei · Movement · Circuits

Highlights

- We describe how to target DBS electrodes to the interposed cerebellar nuclei for reducing dystonic behaviors in mice.
- The reliability of the approach allows for modulating different neural circuits with DBS.
- The flexibility of the approach is compatible with long-term behavioral analyses.
- The overall setup is versatile enough for stimulating the interposed cerebellar nuclei of mice with severe motor deficits.

Introduction

As the third most common movement disorder behind essential tremor and Parkinson's disease, dystonia is not only debilitating to everyday tasks, but it can also be painful [1]. Dystonia is characterized by over- or co-contractions of agonist and antagonist muscles and causes twisting postures, face and neck spasms, and rigidity [2]. In cases of focal dystonia, in which abnormal contractions affect single muscles or restricted parts of the body, medications or injections of botulinum toxin can relieve symptoms [1]. However, patients affected by body-wide generalized dystonia or hemidystonia are typically not suitable for such treatments. For patients with these severe forms of the disorder, the overt symptoms are frequently intractable. Within the last four decades, deep brain stimulation (DBS) has become a more promising and successful surgical intervention for motor disease patients who are not suitable for certain treatments or are unresponsive to medication [3]. However, exploring the efficacy of DBS parameters as well as the possibility of targeting different brain regions is a crucial step for maximizing the beneficial outcomes and reducing the potential for side effects [4]. The cerebellum is one such region that has showed significant therapeutic promise in dystonia, but it requires further research to optimize the targeting and assess its utility in different diseases [5].

DBS is primarily used in drug-resistant hyperkinetic and hypokinetic motor disorders [6]. Today, it is also being tested for use in neuropsychiatric disorders such as obsessive-compulsive disorder, depression, and schizophrenia [7]. The efficacy of DBS has dramatically improved as target locations and stimulation parameters

have been refined and optimized [8–10]. However, more studies on its utility and mechanism of action are necessary to allow for its use in additional disorders, reduce its side effects, improve the electrode targeting, and discover new areas for better long-term treatment. Besides the documented surgical risks such as hemorrhaging and infection [10], psychiatric side effects have also been reported for DBS; these include risk-seeking and aggressive behavior, hallucinations, hypomania, and suicidal ideation [4, 11–13]. Not all patients experience neuropsychiatric changes, but for those that do, improvements in motor dysfunction may not outweigh the burden of the non-motor effects [4]. In addition, the mechanisms by which DBS exerts its therapeutic benefits are still largely unknown. Some theories hypothesize that DBS disrupts pathological activity within brain circuits, primarily within the basal ganglia-thalamo-cortical circuits [14–16]. However, at the cellular level, the mechanism is debated [17–22]. Similarities in the outcomes between lesioning and high-frequency stimulation suggest an inhibitory effect, which is supported by recordings of the stimulated region in various animals [23–26]. Paradoxically, recordings from regions downstream of the stimulated sites indicate the opposite: that output function at these DBS-receiving regions is increased [27–30]. While these hypotheses of inhibition and excitation appear contradictory, other investigators have attempted to reconcile these opposing findings by proposing "disruption" hypotheses involving a dissociation of the target's inputs and ouptuts [31]. Overall, however, the details of how DBS exerts its therapeutic benefits at the cellular level remain elusive [32]. Therefore, dissecting how circuits respond to DBS is imperative if we are to continue advancing its use as a therapy. To do so, having a reliable, consistent procedure for implantation of DBS electrodes into animal models [33] is ideal to minimize confounding differences between labs and experiments. Even minor differences in procedures and supplies may induce disparities in results, perhaps due to subtle differences after tissue damage, inaccurate electrode targeting, instability or drift of electrodes, or variance in data collection. Mechanistic links between models of DBS for numerous diseases will advance our understanding of treatments as we seek to restore neural function and behavior.

Four brain regions are typically targeted with DBS: the ventral intermediate nucleus of the thalamus, the subthalamic nucleus (STN), the globus pallidus interna (GPi), and the anterior limb of the internal capsule [34]. The GPi is the preferred target for drug-refractory dystonia. While many patients benefit from pallidal DBS, improvements are often seen after an extended period of time [35, 36]. This is in contrast to the faster recovery of movement seen in Parkinson's disease and tremor [37, 38]. In low-efficacy cases, the graded and gradual response in dystonia following GPi DBS may be due to suboptimal targeting within the dystonia circuit. Originally, this region was targeted because of the primary role of the basal ganglia in dystonia [39–44]. However, the role of the cerebellum in dystonia pathophysiology is becoming well accepted, and the cerebellum may even serve as a source of basal ganglia dysfunction by propagating pathophysiological output [45, 46]. In humans and mouse models, DBS targeted to the cerebellar nuclei reduces the motor phenotypes of dystonia [5, 47]. Therefore, the cerebellar nuclei may be an ideal alternate DBS target for the treatment of dystonia.

Here, we provide a comprehensive description of how to target DBS electrodes to the interposed nucleus of the cerebellum in mice. Although we suggest the cerebellum as a promising target for DBS, our procedure can be adapted to target any area of the brain. Therefore, use of our procedure is beneficial for labs planning to investigate DBS mechanisms that restore function in different disease models. We provide a platform that will inspire further studies that may give patients greater degrees of improvement with DBS treatment, while also minimizing the unwanted side effects.

Materials and Methods

Animals

We purchased and maintained animal colonies of C57BL6/J and *Vglut2*$^{fx/fx}$ mice (#012898) from the Jackson Laboratory (Bar Harbor, ME). Dr. Chris Wright (Vanderbilt University School of Medicine) kindly provided the *Ptf1a*^{Cre} mice. Adult animals of both sexes aged 8 weeks to 1 year were used for surgical DBS implants and subsequent behavior studies. To test the efficacy of the DBS implants, we generated crosses of *Ptf1a*^{Cre}*;Vglut2*$^{fx/fx}$ mutant mice, a conditional genetic line that we use to delete the vesicular glutamate transporter, VGLUT2, in a class of neurons that projects afferent terminals to the cerebellum. VGLUT2 protein is required for loading glutamate into vesicles in presynaptic terminals during neurotransmission. Homozygous mice with the *Cre* and floxed alleles exhibit dystonia due to genetic silencing of climbing fiber input onto Purkinje cells. This is accomplished by deletion of VGLUT2 specifically in inferior olive neurons [5] (Fig. 1a). *Cre*-negative littermates that had the *Vglut2* floxed allele (*Vglut2*$^{fx/fx}$) and C57BL6/J mice from unrelated litters were used as controls. For breeding, the day a vaginal plug was detected was considered embryonic day 0.5 and the day of birth was considered postnatal day 1. All animal studies were carried out under an approved IACUC animal protocol according to the institutional guidelines at Baylor College of Medicine (BCM).

Fig. 1 (continued) Sillitoe, 2017 [5]. (**b**) Final constructed bilateral DBS electrodes targeted for the interposed cerebellar nuclei. (**c**, **d**) Surgical setup in which regions to be targeted for DBS (interposed nuclei) are marked Fig. 1 (continued) on the skull (red arrows) and checked for accuracy with the DBS electrodes before drilling. (**e**) Top-down view of implanted electrodes after surgery, secured with pink dental cement and two cannulas to later grasp in order to attach DBS wires. (**f**) Side view of a mouse post-surgery connected to the DBS electrodes. This setup allows animals to move freely during stimulation

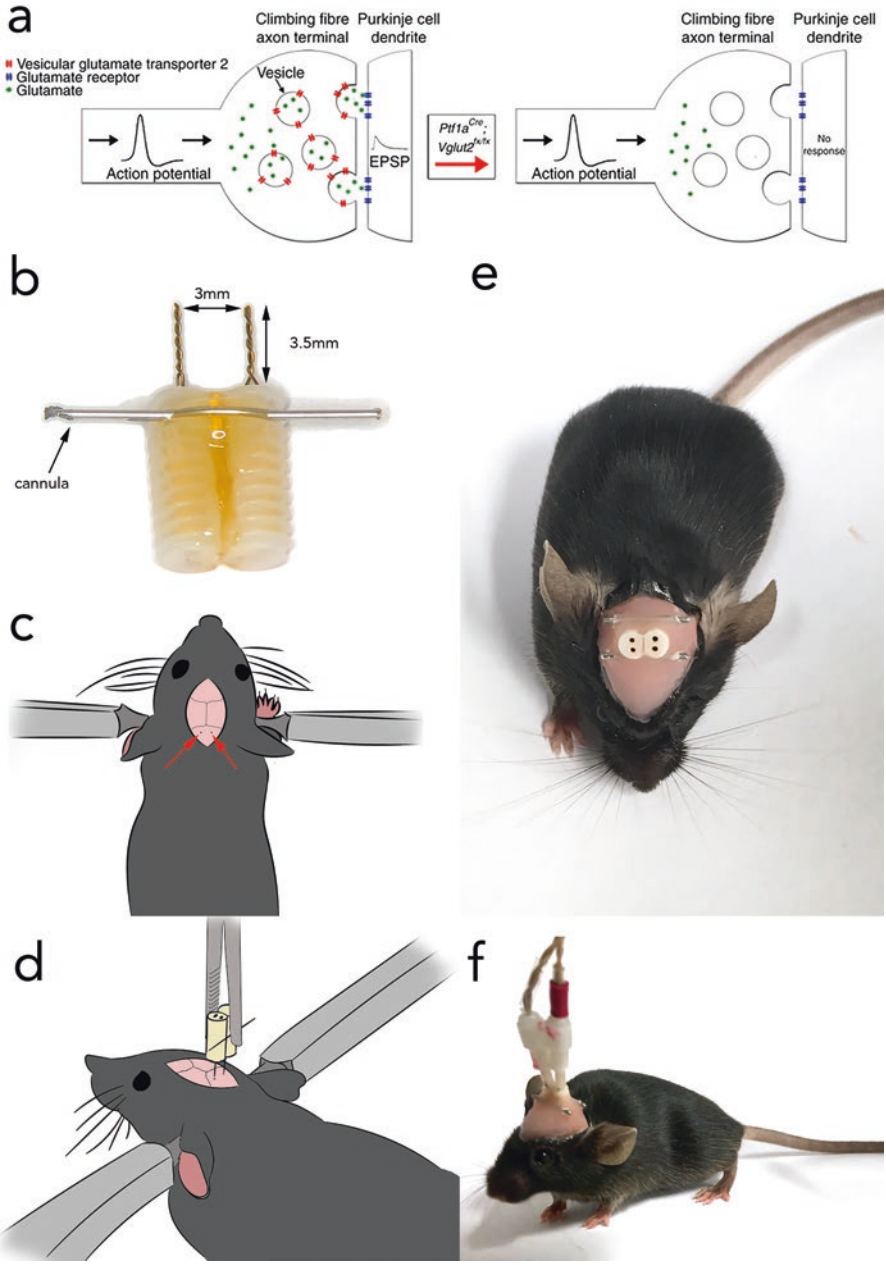

Fig. 1 DBS construction and implant in the *Ptf1a*^{Cre}*;Vglut2*$^{fx/fx}$ mouse model of dystonia. (**a**) Schematic depicting normal neural transmission between the inferior olive and Purkinje cells (left) and a genetic manipulation in which vesicular glutamate transporter 2 (VGLUT2) is deleted from inferior olive neurons in the brain stem, thereby functionally silencing their climbing fiber output to Purkinje cells in *Ptf1a*^{Cre}*;Vglut2*$^{fx/fx}$ mice (right). Schematic was adapted from White and

Making Bilateral DBS Electrodes for Mouse Cerebellar Stimulation

To make electrodes at the bench from standard materials, two ~3 mm sections are cut from a hollow stainless steel tube (Stainless Steel 304 Hypodermic Tubing, 20 gauge, 0.0355″ OD, 0.0235″ ID, 0.006″ Wall, part number: h0035006t304 3′) using a Dremel 4000 rotary tool. These tubes will eventually serve as sockets for the DBS stimulator, thereby connecting the head-mounted DBS implant with the external source of electrical stimulation. Both tubes will be needed for a unilateral bipolar electrode; if a bilateral bipolar electrode is desired, repeat all steps separately until the end. Next, Teflon-coated tungsten wire (0.004″ diameter, A&M system, cat 795500) is soldered into one end of each socket. Ensure that the wires are in physical contact with the inside of the tube wall. To bond these two sockets together, use epoxy (Bondic 1586809), but be careful not to coat too much of the exposed tungsten wires. The epoxy will serve as the electrode casing. Gently twist the two tungsten wires together to create a single bipolar electrode, and cut this electrode slightly larger than the desired length using sharp scissors (for the interposed nucleus, cut at 3.5 mm). When the electrode is later lowered to the correct depth, there should be a slight gap between the skull and the electrode's epoxy casing. This will be necessary to fully cement and stabilize the electrode in the correct position. After cutting, compare the end of this electrode with a Plastics One premade electrode for quality, if desired. For our purposes, we do not peel any coating from the ends of our electrodes; instead, because the wire is very thin, we use sharp scissors to cut the tip of the electrode so that only the terminal end of the wire is cleanly exposed for delivering stimulation.

Alternatively, commercially premade 50 mm twisted tungsten bipolar electrodes mounted in ribbed plastic casing (#8IMS303T3B01, cut 3.5MM below pedestal) can be ordered from Plastics One (Roanoke, VA). Whether made within the lab or ordered from Plastics One (or other sources), two encased electrodes are carefully placed side by side, temporarily secured in position by double-sided tape on the benchtop, and adjusted to an appropriate distance apart based on the brain target desired (for the interposed nuclei, electrodes were placed 3 mm apart). For very short bilateral distances, the diameter of the casings around the electrodes may prevent achievement of the correct electrode-to-electrode distance. In these cases, a hot soldering iron is used to carefully melt one side of each casing, which allows the electrodes to be placed closer together. Once the appropriate distance between electrodes is obtained, we glue the electrode casings together and secure them in place using UV light epoxy (Bondic 1586809). Keep in mind that the ends of both electrodes must fall at the same position. The distance between electrodes is again checked for accuracy after gluing using an electronic caliper. Also, each electrode is examined by eye to ensure that both are straight and parallel to one another. Electrodes that appear to bend at a slight angle are straightened out gently using blunt forceps. Any obvious deflections in the electrodes or their positioning will result in off-target stimulation and can potentially damage adjacent brain structures.

After the two bipolar electrodes are securely mounted together, a small cannula (stainless steel 304 hypodermic tubing, B000FMUP3U*)* is cut to approximately 1 cm in length and glued to the ribbed casings perpendicular to the protruding electrodes. This cannula is secured with the UV light epoxy (Fig. 1b). This junction must be properly secured, as we will later grasp the cannula on the awake mouse to allow for plugging and unplugging of the DBS power source to the mounted electrodes, which often requires a firm hold to adequately stabilize the mouse's head.

Surgical Procedure for Implanting the DBS Electrodes

Prior to surgery, all surgical tools and supplies (dissector scissors FST #14082-09, #55 forceps FST #11255-20, Dumont AA forceps FST #11210-10, drill head for Ideal Micro-Drill™ Surgical Drills #726065, drill bit FST #19007-05) are sterilized in a dry glass bead sterilizer (FST Steri 250) at 250 °C for at least 2 min and allowed to cool on a sterile surface. A small anchoring screw (#303 00-90 × 1/16 flat point stainless steel machine screw, B002SG89QQ) and the bipolar electrodes described above are sterilized using 70% EtOH and allowed to dry on a sterile 100% EtOH pad. Where required, specific tools and supplies are autoclaved beforehand.

Mice are anesthetized by initially delivering 1.5% isoflurane gas to a small box chamber (Parkland Scientific, Coral Springs, FL, USA). Every 2 min, the isoflurane level is increased by 0.5% until a maximal level of 3% is obtained. When no longer responsive to a toe pinch reflex test, the mouse is transferred to a stereotaxic frame (stereotaxic apparatus from David Kopf Instruments, Tujunga, CA, USA) equipped with a DC current rechargeable heating pad (Kent Scientific, Torrington, CT, USA; #DCT-15) to maintain body temperature during surgery. The heating pad is draped with a sterile diaper pad to maintain a clean surgical area. To stabilize the mouse's head and maintain its anesthetic plane, the front teeth are secured in a tooth holder, and a gas mask/nose piece is drawn snugly over the mouse's nose. Care is taken to ensure the tongue is pulled to the side of the mouth to prevent blockage of the throat so proper gas exchange can occur. The isoflurane delivery is switched from the small box chamber to the gas mask of the stereotaxic frame and lowered to a level of 2% for the remainder of the surgery. However, the mouse's breathing rate and toe pinch reflex is monitored throughout the surgery, and isoflurane level is adjusted as required, as mouse-to-mouse variation is typical. The head is then leveled by adjusting the position of the nosepiece. Ear bars are used to secure the mouse's head in the correct position.

Before performing the surgical procedures, the mouse is injected with 1 mg/kg sustained-release buprenorphine and 5 mg/kg meloxicam subcutaneously as preoperative analgesics. Following the surgery, the mouse is supplemented with 5 mg/kg meloxicam subcutaneously once a day for 3 days to prevent any postoperative pain. Furthermore, for the remainder of the operative procedure, personal protective equipment is used to maintain sterility of the area. This includes a sterile gown,

gloves, mask, and hair net. Sterile surgical draping is also used throughout the procedure.

Eye drops are applied to both eyes to prevent drying out (Celluvisc; NDC 0023-4554-30). Fur is then removed from the top of the mouse's head and neck using depilatory cream (Nair lotion with body oil). The area is sanitized using a 70% EtOH pad followed by application of povidone-iodine (Betadine solution swab aids, Purdue Pharma, Stamford, CT, USA; #67618-152-01). Two more rounds of EtOH/Betadine wipes are used to ensure sterility of the area. Using a scalpel blade (Harvard apparatus #728360), a small incision is made at the midline from just behind the eyes to the most posterior part of the occipital bone. Sterile cotton swabs are used to push apart the skin, remove subcutaneous fascia, and thoroughly dry the surface of the skull. Bregma is identified and lightly marked with a pencil. Using the stereotaxic frame and a Vernier scale, the target locations in relation to Bregma (interposed nucleus, −6.4 mm AP, +/− 1.5 mm ML) are also marked (Fig. 1c). To check the position of these bilateral target marks with the distance between the electrodes made previously, we create a stable holder for the DBS electrodes using forceps, a small clamp, and a probe holder. To do so, we use the forceps to hold the glued electrode pair by the casing and use the clamp to secure the forceps (still holding the electrodes) to the probe holder. This homemade apparatus is then secured to the stereotaxic frame and guided to the appropriate position above the bilateral craniotomies. We then carefully lower the electrodes to just above our pencil markings to ensure proper alignment (Fig. 1d). Care must be taken not to touch the electrodes to the skull surface, as this may cause the delicate wires to bend or collect debris before they are placed into the brain. This process allows any adjustments to be made prior to drilling the skull.

Assuming accurate alignment of the target markings on the skull with the electrodes, we gently swing the electrodes out of the work area to allow for unobstructed drilling. We initially drill a small hole on the left side of the cortical skull, slightly anterior and lateral to our target marks, using a Micro-Drill™ surgical drill (#726065). The diameter of the hole should be approximately 1 mm (slightly smaller than the diameter of the screw prepared earlier). Using a small screwdriver and sterile forceps, we carefully screw a sterile anchoring screw a few turns in the craniotomy. The screw head should not be flush with the skull; instead, a few ribs should remain above the skull. The purpose of this step is to provide a sturdy mount for the dental cement, applied at the last step, such that the entire DBS apparatus is stable atop the mouse's head. We have found that a screw length of 1/16″ is ideal for this purpose. An increase in the length may cause penetration or disruption by putting pressure on the brain surface, whereas a shorter screw may be insufficient to adequately take hold in the skull. In addition, we have found that one screw is sufficient for proper anchoring of the apparatus. Though more screws in additional locations can be used, we find that the risk of damage to the brain makes this unfavorable. Different experiments may require adjustments.

Next, we drill small craniotomies on the target marks. Because of the small diameter of the electrodes, a single penetration of a 0.5 mm drill bit through the skull is sufficient. If any bleeding occurs, cotton-tipped applicators are applied with

pressure until the bleeding stops. The electrodes, still mounted to the homemade stereotaxic holder, are then returned to the work area and centered above the craniotomies. The electrodes are slowly lowered until they contact the brain surface, which is judged by eye through the lens of a surgical microscope. From there, they are carefully and slowly lowered to the appropriate target depth (interposed nucleus, ~2.5 mm below brain surface). If any bleeding occurs, cotton-tipped applicators are once again used to absorb blood and stop bleeding.

Before releasing the electrodes from the homemade holder, cement is used to secure their position. Metabond (4 drops of B Quick Base for C&B METABOND® mixed with 1 drop of "C" Universal TBB Catalyst, then mix Metabond with Clear L-Powder) is liberally applied around the anchoring screw and between the skull and the electrode casings at the target location. The cement is allowed to dry for approximately 10 min until rock hard by touch. The ear bars are then loosened to allow for movement of the head in parallel with any accidental movement of the electrodes while releasing the clamp. This step is critical, as movement of the forceps during the next step could move the electrodes or harm the mouse if its head is forcibly restrained. After gently unscrewing and removing the holder's clamp while maintaining a firm hold on the forceps, the forceps can be released from their grip on the electrode casings. Dental cement is then applied to the entire exposed skull and liberally applied around the DBS mount (Fig. 1e). Again, the cement is allowed to dry for about 10 min. Finally, 3 M Vetbond (#NC0304169) is applied around the edges of the dental cement and the mouse's skin to secure the apparatus in place. The nosepiece is then gently removed and the isoflurane gas shut off. The mouse is placed in a 37 °C warmed incubator (V500, Peco Services Ltd., Cumbria, UK) during recovery to prevent hypothermia and is monitored until able to self-right and move freely. Only once the mouse is fully awake and mobile is it returned to its home cage. From this point on, the mouse is singly housed to prevent harm to itself and cage mates due to the head-mounted DBS apparatus. As previously stated, the mouse is supplemented with 5 mg/kg meloxicam subcutaneously once a day for 3 days to prevent postoperative pain. Furthermore, the mouse is allowed to recover in its home cage for 4 days prior to behavioral or stimulation studies. With experience, the surgical procedure can be completed in approximately 1 h. Help from an assistant surgeon is advantageous and recommended.

Programming the Pulse Generator and Connecting to the Stimulus Isolators

The Master-8 pulse generator (AMPI, Jerusalem, Israel) can be programmed with up to 8 DBS paradigms. To program DBS frequencies into the Master-8, parameters such as duration (DURA, D), delay (DELAY, L), and interval (INTER, I) must be set. The duration defines the start-to-end time of an individual pulse, while the delay defines the time between the start of an input trigger and the start of the output

pulse. The interval defines the time from the start of one pulse to the start of the next pulse. In the case of high-frequency stimulation (130 Hz), one channel is programmed with the following parameters: the duration (D) equals 60 μs, the interval (I) equals 7.692×10^{-3} s, and the delay (L) is left blank, unless the channel is receiving a trigger. The interval is calculated using the following equation: $I = \frac{1}{f(Hz)}$. An internal trigger is applied to connect channels. For instance, if channel 1 triggers channel 2 and channel 3 triggers channel 4, then channels 1 and 3 are the internal triggers and are programmed accordingly with the desired channel using the CONNECT button on the Master-8. Experimenters can use any equivalent pulse generator.

Once the DBS paradigm is programmed into the Master-8, it can be checked (CHECK, CH → Channel Number → Enter) and selected to run (ALL → Channel Number → Enter). We recommend that an oscilloscope be used to confirm the output frequency of the Master-8. When connecting a BNC cable from the Master-8 to the oscilloscope, one end is plugged into a Master-8 port that combines two channels (e.g., "channels 2 + 3," a channel pair that feeds into two ISO-Flex stimulus isolators, AMPI, Jerusalem, Israel) and the other end into "channel 1" or "channel 2" of the oscilloscope. After selecting the DBS program to run on the Master-8, the oscilloscope provides a digital readout of the received frequency. We suggest recording the values for later reference.

Perfusion and Tissue Preparation

After behavior tests and DBS stimulation are completed, mice are deeply anesthetized with 2,2,2-tribromoethanol (commonly known as Avertin). Once unresponsive to a firm toe pinch, they are perfused through the heart with 0.1 M phosphate-buffered saline (PBS; pH 7.4) followed by 4% paraformaldehyde (4% PFA) diluted in PBS. The DBS apparatus is carefully, but firmly, removed from each mouse's head by steadily lifting the base of dental cement perpendicular to the head surface. Great care must be taken to avoid removing the electrodes at an angle, which can cause tissue damage and prevent the accurate verification of the DBS electrode's target location. Dissected brains are then post-fixed for 24 to 48 h in 4% PFA and cryoprotected stepwise in buffered sucrose solutions (15% and 30% diluted in PBS). After embedding, positioning, and freezing in optimal cutting temperature solution (OCT) for at least 1 h at −80 °C, the prepared brains are cut into serial 40-μm-thick coronal or sagittal sections on a cryostat. Each slice is carefully collected, typically in 24-well plates, as free-floating tissue sections in PBS. Some brains are embedded in paraffin instead and cut on a microtome at 10 μm.

Conformation of Electrode Targeting Through Histology and Imaging

All tissue slices are examined for proper cellular architecture and integrity at the site of the electrodes with H&E staining. We use a Zeiss AxioCam MRc 5 camera mounted on a Zeiss Axio Imager M2 microscope for imaging. Target confirmation of the DBS electrodes is achieved by examining the electrode tracks in the tissue, and during this anatomical examination, the experimenter can also observe the extent of tissue damage throughout the sections. The tissue preparation described above will also work with immunohistochemistry analyses for cell type-specific or cell death markers and histology for checking for white matter degeneration.

Results

We targeted DBS to the interposed nuclei for several reasons. First, the interposed nuclei project to other brain regions involved in ongoing movement, such as the red nucleus, and to the thalamus, which interacts with several key motor regions [5]. Second, previous work from our laboratory has shown that DBS of the interposed nuclei can resolve dystonia [5], tremor [48], and ataxia [49]. The functional connectivity of these nuclei and the efficacy of their stimulation in treating motor dysfunction underscores their potential as a therapeutic target.

Four days after surgery, mice can be subjected to behavioral paradigms to test the efficacy of DBS stimulation (Fig. 1f, 2). Because of the reliable and strong motor phenotype of our *Ptf1a*^{Cre}*;Vglut2*$^{fx/fx}$ dystonic mice, a dystonic rating scale [50–52] can be used to score the improvement upon stimulation (Table 1). To ensure our experimental paradigm does not induce unwanted motor deficits when applied to healthy controls, we use non-*Cre*-expressing littermates that undergo the same surgical procedures and stimulation parameters. Furthermore, we control for the DBS-induced improvements by including a sham condition, in which a cohort of the dystonic *Ptf1a*^{Cre}*;Vglut2*$^{fx/fx}$ mutant mice receive all surgical and handling procedures, but not the actual stimulation paradigm, meaning no current passes through the implanted electrodes.

We place a mouse with the interposed nucleus DBS implant (either untreated control, treated control, sham with the genotype for dystonia that will not receive stimulation, or dystonia genotype that will receive DBS) in a transparent glass vase large enough to allow the mouse to walk around. After connecting the DBS electrodes to the stimulation source (Master-8 pulse generator and an ISO-Flex stimulus isolator, Fig. 2, Table 2), we deliver a 130 Hz, 60 ms pulse at 30 mA for 1 h. Unstimulated dystonia (sham) littermates and stimulated littermate controls that underwent the same implantation surgery are valuable for ensuring that any improvements are due to the stimulation itself rather than the surgical procedure. The entire process before, during, and after stimulation is recorded with high-quality video for

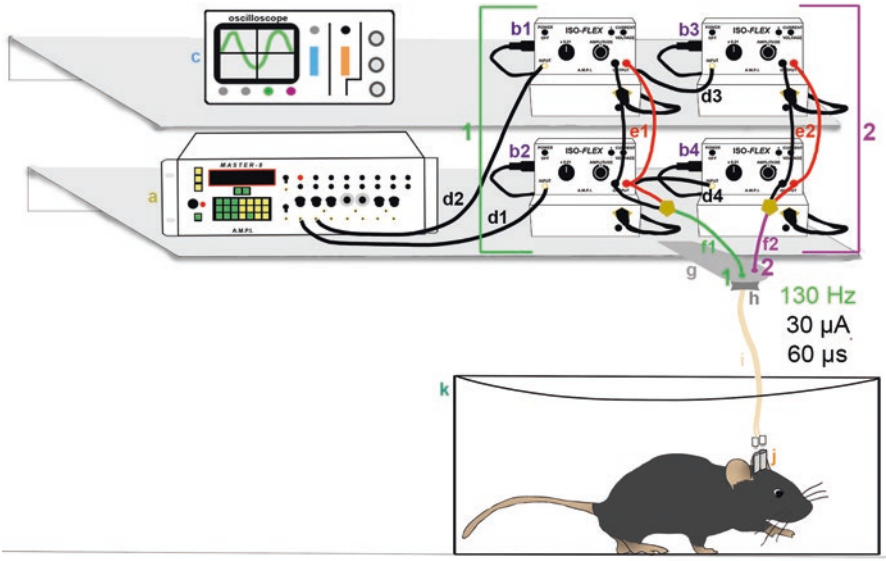

Fig. 2 Deep brain stimulation setup. DBS requires various pieces of equipment, connected as depicted. See Table 2 for equipment information as referenced by figure letters

Table 1 Scoring scale for mouse models of dystonia

Score	Behavioral readout
0	Normal motor behavior, normal posture
1a	No impairment, but slightly slowed movements
1b	Normal motor behavior, but some abnormal postures
2	Mild impairment: Occasional abnormal postures and movements
3	Moderate impairment: Frequent abnormal postures and movements with limited ambulation
4	Severe impairment: Sustained abnormal postures without any ambulation or upright position

Modified from Jinnah et al. [50]
Behavioral evaluation of dystonia improvements can be numerically scored based on posture and different features of motor behavior. Control/wild-type mice exhibit a score of 0, whereas severely dystonic mice that cannot engage in normal locomotor behavior and have generalized muscle co-contractions exhibit a score of 5.

later analysis. This procedure is repeated once a day for 5 days or as dictated by the paradigm. The video is analyzed, and mice are assessed according to the dystonia rating scale. The scale has rankings from 0 to 5, and the behaviors that are assessed for each rank are described as follows:

0 – no motor abnormalities
1 – slightly slowed or abnormal motor behavior, no dystonia

Table 2 Suggested equipment to perform cerebellar deep brain stimulation (DBS) in mice

Figure 2 labels	Equipment piece	Company	Quantity	Function
a	Master-8 pulse stimulator	A.M.P.I.	1	Generate stimulus
b	ISO-Flex- the stimulus isolator	A.M.P.I.	4 per animal	Isolate stimulus
c	Digital oscilloscope	Tektronix	1	Confirm frequency
d	BNC cables	–	4	Connects ISO-Flex systems to Master-8
e	Red/black double-sided Banana connectors (stackable)	Plastics one	2 sets	Connects ISO-Flex systems together
f	Custom mesh banana connectors (1 side split with 2 banana jacks, 1 side with electrode jacks)	Plastics one	2	Connects ISO-Flex systems to electrode commutator
g&h	Custom electrode commutator mount (g) and commutator (h)	Plastics one	1 per animal	Serves as an interface between the stimulation equipment and the mouse brain
i	DBS wire (50 cm–100 cm)	Plastics one	1 per animal	Connects the commutator to the DBS electrodes
j	DBS tungsten electrodes (0.127 mm diameter; cut 3.5 mm below pedestal)	Plastics one	2 per animal for bilateral stimulation	Delivers stimulus to mouse cerebellum
k	Clear glass cylinder vase	Amazon	1 per animal	Holds the animal(s) during stimulation

To standardize both the surgical procedure for DBS implantation and the postsurgical data collection process, we provide a comprehensive list of all equipment necessary for bilateral DBS stimulation. This table accompanies Fig. 2, which depicts the setup in a schematic.

2 – mild impairment, sometimes limited ambulation, dystonic postures when disturbed
3 – moderate impairment, frequent spontaneous dystonic postures
4 – severe impairment, sustained dystonic postures and limited ambulation
5 – prolonged immobility in dystonic postures.

At baseline, our dystonic mice score approximately 3.7–4.0 on the dystonia rating scale [5]. They exhibit obvious twisting movements and abnormal muscle contractions in addition to limb stiffness while walking, particularly on the smooth glass surface. During DBS stimulation, these phenotypes are immediately improved. The mice walk around their environment normally, perch on their hind legs to groom, and score an average of ~2 on the dystonia rating scale [5] (Fig. 3, Table 1). The level of improvement continues over time, as daily bouts of DBS are provided to the mutant mice.

Although the overt phenotype of dystonia in our *Ptf1a*^{Cre}*;Vglut2*$^{fx/fx}$ mice makes for straightforward visualization of improvements in a "glass jar" behavioral test, other quantifiable measures can be examined to test particular motor functions. For example, an accelerating rotarod [5, 53] can be used to test balance and

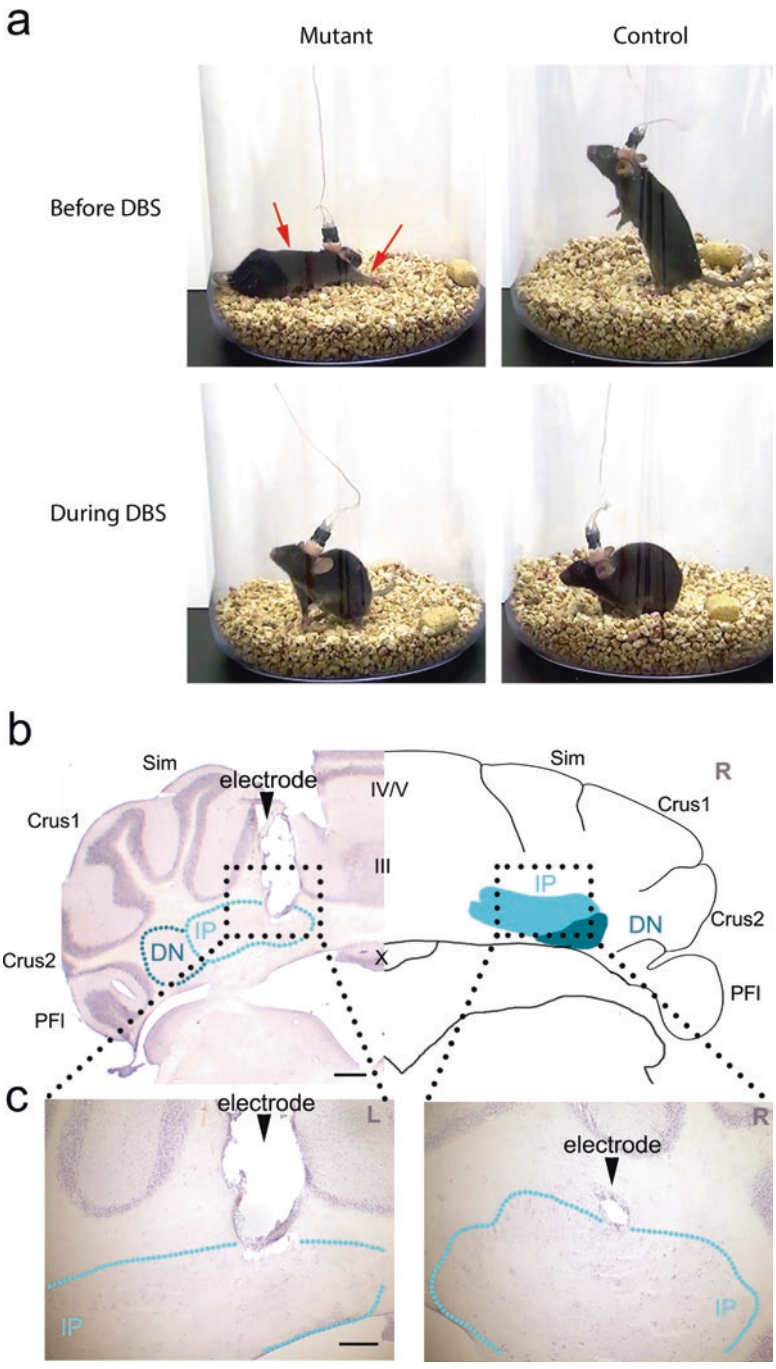

Fig. 3 DBS to the interposed cerebellar nuclei rescues normal movement in mice with dystonia. (**a**) Example of a dystonic Ptf1a^{Cre};Vglut2$^{fx/fx}$ mouse prior to stimulation (top left), with red arrows indicating co-contracting muscles leading to extended limbs and abnormal back posture.

coordination, and basic footprint analysis can be used to examine changes in stance, swing, and stride during locomotion [54–56]. Using a combination of such behavioral tests, we recently showed that mice with dystonia, ataxia, and tremor show significant improvement upon DBS stimulation, indicating that the cerebellum may be an important therapeutic target for the equivalent human conditions [3, 5, 48]. In these studies, we also assessed improvements using highly quantitative measures such as in vivo electrophysiology, electromyography (EMG), tremor monitor recordings, and cell type-specific marker analyses. In summary, because cerebellar DBS improves movement in dystonia [5], tremor [48], and ataxia [49], we propose that other motor and perhaps even non-motor cerebellar-dependent diseases could potentially be treated by targeting specific cerebellar circuits.

Discussion

Although the preferred brain targets for DBS include the subthalamic nuclei and the GPi region of the basal ganglia [57, 58], animal model studies focusing on additional target regions should be explored. Locations with beneficial outcomes could then be used to improve opportunities for restoring movement in patients. Toward this goal, we have described how to target the interposed nucleus of the cerebellum in a mouse model with dystonia, and we demonstrate example strategies for assessing the poststimulation recovery and utility in restoring motor behavior.

The anatomy of the cerebellum is well understood, and the functions of each of its major cell types have been the subject of intense scrutiny. The overall architecture of the cerebellum is organized into three primary layers: the granule cell layer, the Purkinje cell layer, and the molecular layer (Fig. 4). With the cell bodies typically contained within their respective layers and their dendritic and axonal processes spanning multiple layers, each cell type can communicate across layers and contribute to the cerebellum's computational power. Ultimately, the Purkinje cell integrates the key signals and serves as the sole output of the cerebellar cortex. This powerful cell then sends its output into the inner core of the cerebellum, to three pairs of cerebellar nuclei. The cerebellar nuclei subsequently transmit motor and non-motor information to a large number of circuits throughout the brain and spinal cord, which contain multiple closed-loop circuits.

Cerebellar Heterogeneity as a Tool for Uncovering DBS Mechanisms

The simplicity of the cerebellum's laminar organization belies a more complicated patterning of parasagittal stripes and transverse zones [59–67]. This topographical organization divides cerebellar circuitry into functional modules that help define the

Fig. 3 (continued) Bottom left panel shows complete rescue of posture and motor behavior during 130 Hz DBS. Right panels demonstrate the lack of adverse effects of DBS on a control mouse. Still images were adapted from videos in White and Sillitoe, 2017 [5]. (**b**) Coronal-cut, H&E-stained tissue section of the cerebellum used to anatomically confirm the targeting of DBS electrodes as identified by disruption of the tissue due to electrode penetration. Hemisphere lobules are denoted as Crus1, Crus2, PFl (paraflocculus), and Sim (lobulus simplex) and the vermis lobules as IV/V, III, and X. (**c**) High-resolution bright field images of electrode targeting in an area dorsal to the interposed nuclei

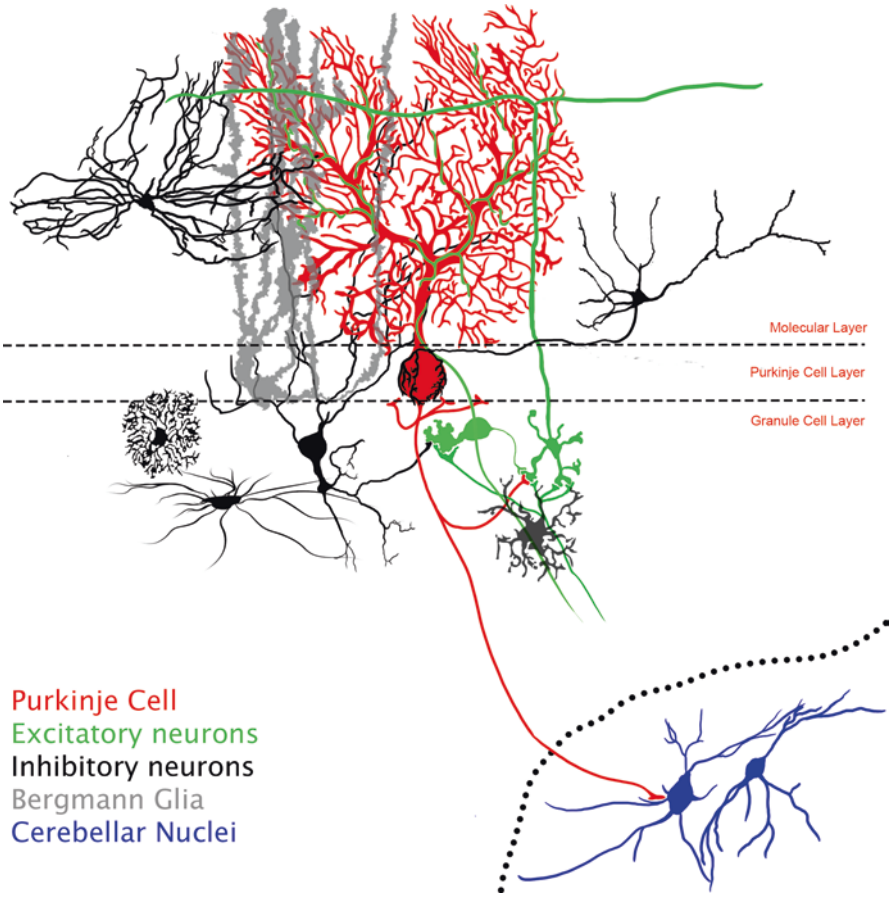

Fig. 4 The Purkinje cell to cerebellar nuclei connection is central to the cerebellar circuit function. The cerebellar circuit consists of inhibitory neurons (gray) and excitatory neurons (green) that converge onto the inhibitory Purkinje cells (red), which integrate and transmit these combined inputs to the cerebellar nuclei (blue). The cerebellar nuclei are the major output of the cerebellum, communicating information to extra-cerebellar brain regions and the spinal cord. This organization makes the cerebellar nuclei an ideal target for influencing the activity of numerous circuits in the brain and spinal cord

distribution of excitatory and inhibitory neurons [68]. Though necessary for proper function [53, 69–71], these stripes and zones add an extra level of complexity when using the cerebellar cortex as a target for treatment. When the cerebellum was originally examined as a DBS target for cerebral palsy and epilepsy, the majority of patients exhibited significant clinical improvements [72]. Nevertheless, some patients and animal models either did not improve or experienced worsening of symptoms. For this reason, cerebellar targeting was temporarily abandoned. However, the primary reason for variations in the outcome of cerebellar cortex-targeted DBS was likely due to the inadvertent targeting of different zones in the

cerebellar cortex [69, 73]. With a much more advanced understanding of cerebellar organization, this brain region could now serve as a unique tool for uncovering the genetic, cellular, molecular, and circuit mechanisms of DBS, which are still largely unclear.

After retrograde tracing and related studies have demonstrated connectivity of different muscle groups to distinct Purkinje cell stripes of the cerebellar cortex [71], we now understand that these Purkinje cells are central to unique modules based on their protein expression and individual connectivity [74]. In support of these tracing studies, electrical stimulation of neighboring zones has been shown to cause different behavioral outcomes in patients with cerebral palsy [75]. This finding, combined with the knowledge that Purkinje cell output converges on the cerebellar nuclei, suggests that DBS at the level of the nuclei could have different effects depending on which zones are activated [3]. Therefore, most stimulation paradigms now bypass this complex cortical map by directly targeting the downstream cerebellar nuclei where parasagittal zones and stripes converge. Considering these individual nuclei as potential DBS targets, they could allow for specific and reliable control of downstream neural circuits by modulating a single cerebellar site. Moreover, combination paradigms involving the stimulation of multiple cerebellar nuclei locations, perhaps each with different stimulation features, could be considered. Such paradigms could be useful in cases with a complex phenotype that involves distinct deficits. In disease, one could imagine using a combination stimulation approach to treat patients that exhibit ataxia plus tremor or dystonia plus tremor.

The cerebellum also provides a unique inroad for DBS in a wide range of motor and non-motor functions, including motor planning, adaptive motor learning, language, and cognition [3]. Even within a single cerebellar nucleus, connectivity and function have relevant distinctions. For example, the dentate nucleus can be divided into motor and non-motor regions [76], and the fastigial nucleus is comprised of distinct cell types, each of which has distinct projections to regions associated with motor and non-motor functions [77]. In addition, as explained previously, subregions of the interposed nuclei have unique projection targets [78] and may be involved in encoding different aspects of movement [79]. Therefore, different sites of stimulation, even within the same cerebellar nucleus, could have vastly diverse effects. Because many motor diseases have psychiatric comorbidities and motor treatments often exert psychiatric side effects, harnessing the complex organization of the cerebellum could lead to new insights into the mechanisms of DBS.

Each Cerebellar Nucleus May Serve as a Unique Therapeutic Target

With cerebellar output separated into three functionally distinct nuclei (the dentate nucleus, the interposed nucleus, and the fastigial nucleus), a great degree of precision in targeting a specific function may be achievable. In fact, DBS of the cerebellar nuclei already shows great promise. In a 2009 study from the group of Andre Machado, rats with limited motor function after cerebral ischemia recover significant motor abilities following contralateral stimulation of the cerebellar dentate nucleus [80]. Stimulation of the dentate nucleus promotes persistent recovery of motor function after stroke, facilitating improvement at the rotating beam test even

two weeks after the cessation of stimulations [81]. Dentate stimulation has also been shown to significantly improve gait ataxia in the *shaker* rat [82]. Furthermore, in 2016, Machado and colleagues targeted DBS to the dentate nucleus in a post-stroke hemiparesis patient [83]. In this patient, motor function improved, demonstrating promise for using the cerebellum to treat this condition [3]. Cerebellar DBS of the dentate nuclei has also been shown to improve symptoms in the long term. After two thalamotomies failed to resolve a patient's dystonia, stimulation of the cerebellar nuclei resulted in improvement for two years after implantation [47]. Recent studies have explored all three cerebellar nuclei as treatment areas for epilepsy. In mouse models of seizures, millisecond stimulation of fastigial neurons via optogenetics is sufficient to completely disrupt abnormal brain activity during seizures, thereby aborting the disease state [84–86]. Other studies show similar inhibition of seizures when targeting the dentate and interposed nuclei [87, 88]. Overall, these data suggest that each cerebellar nucleus may serve unique and overlapping roles in disease pathology and perhaps can serve to treat distinct but complex symptoms of disease.

Besides the location of stimulation, the outcome of a given DBS paradigm may also depend on the stimulation frequency. Upon testing stimulation of the dentate nuclei at a range of frequencies, Anderson et al. have found that 30 Hz stimulation is most effective at treating ataxia in the *shaker* rat, while higher or lower frequencies worsen other symptoms [81]. The group proposes that high-frequency stimulation reduces information transmission, while low-frequency stimulation may enhance network output [81]. Therefore, the ideal frequency for treating a given motor disorder may depend on whether the symptoms are caused by increased or decreased neural activity. Anderson et al. have found that higher frequencies of stimulation worsen incoordination caused by Purkinje cell degeneration, while lower frequencies worsen tremor, possibly by inducing oscillations at tremor frequencies [81]. These results support the idea that DBS frequency can differentially affect motor symptoms based on the neural circuit affected. Examining how different frequencies of cerebellar stimulation impact different motor symptoms could shed light on the mechanisms of DBS. In addition, other features of the DBS paradigm such as pulse duration should be tested in detail.

The Functional Impact of the Cerebellum Extends Beyond Motor Functions

Although many of the cerebellar circuits are well studied, ongoing research continues to reveal additional targets of cerebellar output. For example, though the cerebellum was previously thought to communicate with the basal ganglia mainly through the cortex, studies now demonstrate that the cerebellum and basal ganglia also interact at the level of the thalamus [89]. Furthermore, the cerebellum contributes significantly to non-motor functions such as cognition, language, aggression, emotion, and addiction [90–92]. Interestingly, many of these deficits are also seen in patients with motor diseases. Beyond correlation with human behavior, these observations are supported experimentally by additional studies of cerebellar circuitry. For example, the cerebellum interacts functionally and anatomically with various non-motor brain regions, including the hypothalamus [93] and amygdala

[94]. Therefore, stimulation of the cerebellum to treat motor dysfunction may simultaneously engage specific non-motor abnormalities.

Connectivity of the Interposed Cerebellar Nuclei

Here, we specifically chose to stimulate the interposed cerebellar nucleus. We demonstrate that DBS to the interposed nuclei in a mouse model of dystonia results in improved mobility and decreased twisting and limb stiffness [5]. Previous studies from our lab have also shown that DBS applied to the interposed nucleus reduces the severity of harmaline-induced tremor [48]. These findings suggest that DBS of the interposed nucleus could be used to treat various movement disorders. Among the many targets of the interposed nucleus are the red nucleus, which controls ongoing movement, and the thalamus, which communicates with the rest of the motor circuit [5]. Interestingly, the interposed nucleus can be subdivided into the anterior interposed nuclei (AIN) and posterior interposed nuclei (PIN) [95]. While these subnuclei both target the red nucleus, thalamus, and inferior olive, the AIN and PIN each have additional distinct targets throughout the brain [78]. Furthermore, each region of the interposed nucleus may preferentially encode different aspects of movement. For example, when firing neurons in the interposed nucleus of the rat are recorded during forelimb movement, most of the active neurons in the AIN are sensitive to movement direction and velocity, whereas as a larger proportion of the neurons in the PIN are modulated by movement speed [79]. Therefore, stimulating different parts of the interposed nucleus may have different effects on motor behavior based on connectivity and function. Dynamic temporal functional features should also be considered.

The Interposed Cerebellar Nucleus in Rodents Compared to Human

Many of the primary anatomical characteristics of the cerebellum are conserved between humans and rodents. For example, both humans and rodents possess a foliated cortex with three cell layers, as well as three sets of cerebellar nuclei nestled in the core of the white matter. In humans, the interposed nuclei consist of the emboliform and globose nuclei, which are completely separated, while in mice, the subnuclei are referred to as the aforementioned AIN and PIN [95]. In contrast to their human counterparts, in rodents, the AIN and PIN are nearly impossible to distinguish based purely on gross anatomy [95]. Despite these distinctions, the major components of the interposed nuclei are conserved. In both humans and rodents, the interposed nuclei contain a combination of glutamatergic and GABAergic cells [95], and single-nucleus RNA sequencing across species has revealed that all cerebellar nuclei are composed of a conserved pattern of cell types [96]. Although the human lateral nucleus has a greater proportion of one cell class compared to other species, mice and humans share the same archetypal cellular pattern for the medial and interposed nuclei [96]. Overall, the anatomical and molecular conservation between humans and rodents make the interposed nucleus, along with the other cerebellar nuclei, a promising target for testing translational therapies. Nevertheless, the complexities of the human cerebellum, including human-specific cellular and molecular features, should be considered, as the translational jump from model to patient must be made with caution [97].

Although we have focused on the interposed cerebellar nucleus for the treatment of severe dystonia, stimulating the dentate and fastigial nuclei independently or cooperatively with the interposed would be interesting to test whether additional improvements in motor and social behavior can be elicited. Although great progress has been made in thalamic and basal ganglia DBS in humans [98–101], we must explore new targets such as the cerebellum in animal models to eventually provide a complete correction of dysfunction in critically affected patients. With a standardized protocol for DBS implantation in mice, we now have the tools to make great strides in the treatment of motor and non-motor deficits in neurological and neuropsychiatric disorders.

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Conflicts of Interest We have nothing to disclose.

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Applications of Transcranial Magnetic Stimulation for Understanding and Treating Dystonia

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Abstract Transcranial magnetic stimulation (TMS)-based studies have led to an advanced understanding of the pathophysiology of dystonia. This narrative review summarizes the TMS data contributed to the literature so far. Many studies have shown that increased motor cortex excitability, excessive sensorimotor plasticity, and abnormal sensorimotor integration are the core pathophysiological substrates for dystonia. However, an increasing body of evidence supports a more widespread network dysfunction involving many other brain regions. Repetitive TMS pulses (rTMS) in dystonia have therapeutic potential as they can induce local and network-wide effects through modulation of excitability and plasticity. The bulk of rTMS studies has targeted the premotor cortex with some promising results in focal hand dystonia. Some studies have targeted the cerebellum for cervical dystonia and the anterior cingulate cortex for blepharospasm. We believe that therapeutic potential could be leveraged better when rTMS is implemented in conjunction with standard-of-care pharmacological treatments. However, due to several limitations in the studies conducted to date, including small samples, heterogeneous populations, variability in the target sites, and inconsistencies in the study design and control arm, it is hard to draw a definite conclusion. Further studies are warranted to determine optimal targets and protocols yielding the most beneficial outcomes that will translate into meaningful clinical changes.

Keywords Transcranial magnetic stimulation · rTMS · Dystonia · Focal hand dystonia · Blepharospasm · Cervical dystonia

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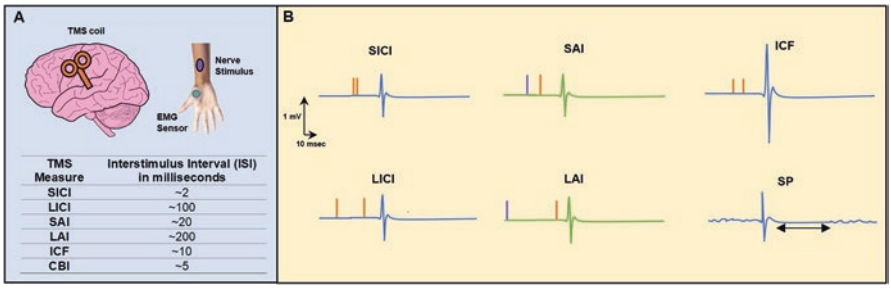
Introduction

Dystonia is a debilitating movement disorder characterized by involuntary muscle contractions with abnormal and repetitive movements, postures, or both [1]. Transcranial magnetic stimulation (TMS) is a painless, noninvasive brain stimulation technique that has shed insights into the pathophysiology of dystonia involving multiple brain regions. Treatment of dystonia can be challenging as the current oral pharmacological therapies have modest benefits and dose-limiting side effects. Botulinum toxin injections, first-line therapy for focal or segmental dystonia, are painful and complicated by side effects such as dysphagia and neck muscle weakness, and benefits often wear off before the next set of injections are due [2]. Deep brain stimulation (DBS) of the globus pallidus internus or subthalamic nucleus is effective for managing some instances of medication-refractory dystonia. However, the procedure is invasive and expensive. Not all patients are appropriate candidates for this surgery [3, 4]. TMS has also shown promise as a therapeutic tool for mitigating dystonia symptoms through modulation of excitability and plasticity of the pathogenic brain regions. Additionally, clinical outcomes are difficult to predict for many patients since we do not fully understand the pathophysiology. In this narrative review, we will discuss the role of TMS in understanding the circuit-based and network-based theories for dystonia and the potential of applying rTMS as a potent therapy.

Basic TMS Paradigms

TMS uses a magnetic field to induce an electric field directed at specific brain targets for stimulation (Fig. 1a). TMS can be employed as single-pulse, paired-pulse, and repetitive-pulse paradigms. Single-pulse TMS targeted over the primary motor cortex (M1) leads to the generation of a motor evoked potential (MEP), captured on EMG recordings from the peripheral limb muscles. The resting motor threshold (RMT) is defined as the lowest stimulation intensity required to cause a twitch in a target muscle for half of the applied pulses. Single-pulse TMS delivered during voluntary muscle contraction leads to a period of EMG suppression known as the silent period (SP) [5].

Paired-pulse TMS paradigms involve the pairing of a subthreshold conditioning pulse with a test pulse at specific interstimulus intervals (ISI). The MEP response is inhibited when the ISI is short (1–4 ms), known as the short-interval intracortical inhibition (SICI), or long (50–200 ms) known as long-interval intracortical inhibition (LICI), but the MEP response is facilitated when the ISI is intermediate (10–15 ms) known as the intracortical facilitation (ICF) [6]. These measures reflect organization of the motor cortex circuitries. Paired-pulse paradigms examining sensorimotor integration involve sensory stimulation of a peripheral nerve (such as the median nerve) paired with a TMS pulse to the motor cortex. The ISI between the



TMS Measure	Interstimulus Interval (ISI) in milliseconds
SICI	~2
LICI	~100
SAI	~20
LAI	~200
ICF	~10
CBI	~5

Fig. 1 (**a**) Example of an experimental setup in which the TMS coil is positioned at the left hemisphere, and the peripheral nerve stimulus (on the median nerve) and EMG sensor (on abductor pollicis brevis) are placed on the contralateral extremity. The table summarizes the different interstimulus intervals for various TMS measures **(b)** Representative EMG recordings for the following TMS measures: ISI of 1–4 msec between two TMS pulses (orange lines) results in SICI; ISI of 50–200 msec between two TMS pulses (orange lines) results in LICI; ISI of 20–50 msec between a peripheral nerve stimulus (purple line) and TMS pulse (orange line) results in SAI; ISI of 200–1000 msec between a peripheral nerve stimulus (purple line) and TMS pulse (orange arrow) results in LAI; ISI of 10–15 msec leads to facilitation of the motor evoked potential (ICF), and the period of silence on the EMG following the motor evoked potential is known as the silent period (SP) (black arrow)

sensory pulse and TMS pulse can be short (20 ms) known as short-latency afferent inhibition (SAI) or long (200 ms) known as long-latency afferent inhibition (LAI) [6]. Paired associative stimulation (PAS) combines electrical pulses delivered to a peripheral nerve (such as the median nerve) with TMS pulses delivered to the motor cortex [6]. When repeated at specific ISI, these paired pulses evoke plasticity changes in the sensorimotor cortex [6]. A particular type of paired-pulse paradigm examining the cerebello-thalamo-cortical pathway pairs a conditioning pulse to the cerebellum at an ISI of 5–7 ms with a test pulse to the motor cortex leading to inhibition of the test MEP known as cerebellar brain inhibition (CBI) [7] (Fig. 1B). These TMS paradigms can be used to understand the pathogenic brain circuitries in dystonia involving the sensorimotor cortex and the cerebellum.

Repetitive TMS (rTMS) refers to the repeated application of magnetic pulses to specific brain targets for modulation of brain excitability (Fig. 2). An rTMS paradigm delivered at low frequency (≤1 Hz) mimics long-term depression, resulting in cortical inhibitory effects. In contrast, rTMS paradigms delivered at high frequency (>5 Hz) mimic long-term potentiation, resulting in excitatory cortical changes [6]. Theta-burst stimulation (TBS) employing triplet bursts of stimulation allows more pulses to be delivered in a shorter amount of time. Continuous delivery of triplet bursts (cTBS) exerts an inhibitory effect similar to low-frequency rTMS, whereas intermittent delivery (iTBS) exerts an excitatory impact similar to high-frequency rTMS [8]. These changes in excitability and plasticity have been leveraged to derive therapeutic benefits. We will discuss TMS paradigms used in patients with dystonia in the following sections.

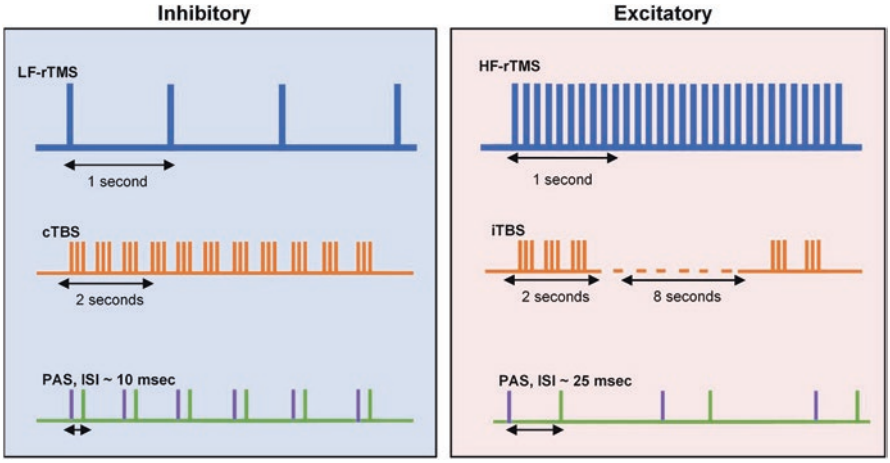


Fig. 2 Schematic representations of various TMS paradigms, classified by their resultant effect on cortical excitation. Inhibitory paradigms (left) include the following: low-frequency rTMS in which pulses are delivered at a rate $\leq$ 1 Hz, continuous theta-burst stimulation in which triplet bursts of stimulation are delivered continuously, and paired associative stimulation in which peripheral nerve stimulation (purple) is delivered followed by a pulse of TMS (green) with an interstimulus interval around 10 milliseconds. Excitatory paradigms (right) include the following: high-frequency rTMS in which pulses are delivered at a rate > 5 Hz, intermittent theta-burst stimulation in which triplet bursts of stimulation are delivered for 2 seconds followed by an 8-second period without stimulation, and paired associative stimulation in which peripheral nerve stimulation (purple) is delivered followed by a pulse of TMS (green) with an interstimulus interval around 25 milliseconds

Pathophysiological Insights with TMS

The pathophysiology of dystonia is complex and still not fully understood. In general, the pathophysiology involves loss of inhibition in the motor cortex, leading to hyperactivity and overflow of excessive muscle contractions [9], maladaptive sensorimotor plasticity, and altered sensorimotor integration [2]. TMS studies have shown that cerebellar circuits also contribute to the pathogenesis [7, 10], which supports the theory that dystonia is a network disorder involving multiple brain regions [11]. These pathophysiological insights, summarized in Table 1, will be individually discussed below.

Abnormalities of Inhibitory Circuits Involving Primarily the Motor Cortex

A variety of TMS studies have demonstrated abnormalities within the inhibitory circuits of the motor cortex region. One of the earliest studies found that SICI was decreased in patients with focal hand dystonia, and changes were detected in the

Table 1 Summary of TMS studies evaluating underlying pathophysiology of dystonia

	Study	Study design	Main findings
Inhibitory dysfunction	Ridding 1995	Paired-pulse TMS delivered to 15 FHD and 8 HC	Reduced SICI in FHD patients
	Mavroudakis 1995	TMS was delivered at 120% RMT and 25% of maximal contraction in 13 dystonia patients and 15 HC	Patients with focal dystonia had significantly higher MEPs compared to healthy controls; prolonged SP
	Ikoma 1996	Paired-pulse TMS	Increased MEPs in patients with dystonia; no difference in SP
	Chen 1997	Paired-pulse TMS at 110% RMT in 8 WC compared to HC	Shorter SP and reduced inhibition of MEP with voluntary contraction in WC
	Filipovic 1997	TMS was delivered at 120% RMT under induced dystonic conditions as well as voluntary contraction	Shorter duration of SP during dystonic contraction compared to voluntary contraction
	Rona 1998	Paired-pulse TMS delivered to 10 patients with right arm dystonia compared to HC	Longer interstimulus intervals led to more inhibition of test response and shortened SP in dystonic patients
	Siebner 1999	10 trains of 1 Hz rTMS over L M1 at 105% RMT in 14 WC and 10 HC	Increased MEP in WC compared to HC
	Gilio 2003	5 Hz rTMS at 120% RMT over M1 plus ulnar nerve stimulation in FHD vs. HC	Significantly longer-lasting increased MEP in patients with dystonia compared to HC
	Stinear and Byblow 2004	Single- and paired-pulse TMS following 4 blocks of 1 Hz stimuli in 5 FHD	No change in MEP, SP, or ICI following rTMS
Loss of surround inhibition	Beck 2009	10 FHD vs. 10 HC underwent single- and paired-pulse TMS	Loss of surround inhibition and increased premotor-motor inhibition in FHD but not HC following stimulation
	Veugen 2013	15 WC vs. 10 HC underwent 50 Hz cTBS at 70% RMT for 40 sec (600 pulses) at the dPMC	Loss of surround inhibition in WC; improvement in writing speed but no restoration of surround inhibition following stimulation of dPMC
	Pirio Richardson 2014	9 WC vs. 9 HC underwent rTMS at dPMC at 70% RMT	Enhanced dPMI at rest and with tasks in WC; improved error rate in WC following rTMS
	Kassavetis 2018	11 CD vs. 12 HFD vs. 31 HC underwent single-pulse TMS	No significant difference in surround inhibition between groups
Cerebellar brain inhibition	Brighina 2009	8 FHD vs. 8 HC underwent paired-pulse rTMS over the cerebellar hemisphere	There was decreased MEP, increased ICF, and decreased SICI in HC but no changes in FHD following cerebellar stimulation
	Hubsch 2013	21 WC vs. 25 HC underwent either cTBS or iTBS over the cerebellar cortex followed by PAS protocol	In HC, iTBS led to reduced plasticity, and cTBS led to enhanced plasticity; in WC, no effect on plasticity following iTBS or cTBS

(continued)

Table 1 (continued)

	Study	Study design	Main findings
Enhanced cortical plasticity	Quartarone 2003	10 WC vs. 10 HC underwent PAS protocol of the median nerve followed by TMS over M1	WC had stronger increase in corticospinal excitability and attenuated facilitation of intracortical inhibitory circuits following PAS compared to HC
	Weise 2006	10 WC vs. 10 HC underwent PAS with mixed median or ulnar nerve stimulation followed by TMS of the M1	Abnormal amplitude and spatial plasticity following PAS
	Baumer 2007	7WC vs. 8 HC underwent 1 Hz rTMS over the M1 and S1 paired with electrical stimulation over the index finger	Reduction in SAI following rTMS to the S1 but not M1 in WC but not HC patients
	Quartarone 2008	10 CCD vs. 9 HF vs. 10 HC underwent PAS of the median vs. ulnar nerve with TMS over M1	Prolonged SP in HC and HFS but no effect on SP in CCD; loss of topographic specificity with facilitation in CCD
	Quartarone 2009	10 organic dystonia vs. 10 psychogenic dystonia vs. 10 HC underwent PAS of the median nerve in combination with TMS over M1	Abnormal plasticity in organic dystonia but not in psychogenic dystonia or HC
	Tamura 2009	10 FHD vs. 10 HC underwent PAS of the median nerve followed by TMS over S1	Abnormal plasticity in patients with FHD but not HC
	Kang 2011	10 WC vs. 10 HC underwent PAS of the median nerve followed by TMS	There was no change in MEP following PAS in either group, but there was suppression of plasticity in HC but not WC following PAS25
	Meunier 2012	17 FHD vs. 19 HC underwent PAS	In FHD, LAI was increased, and LICI was unchanged following PAS indicating maladaptive plasticity
	Kojovic 2013	11 secondary dystonia vs. 10 primary segmental dystonia vs. 10 HC underwent PAS at the median nerve with TMS of the M1	Secondary dystonia showed reduced SICI on affected side but normal on unaffected side; normal plasticity response in secondary but enhanced plasticity response in primary dystonia
	Sadnicka 2014a	15 WC underwent PAS of the median nerve followed by TMS of the M1	No evidence of change in motor cortex excitability following PAS protocol
	Sadnicka 2014b	10 WC underwent PAS25 protocol using median nerve and TMS of M1 comparing active and sham cerebellar stimulation using	No significant clinical improvement following active cerebellar stimulation; variable responses of plasticity changes

(continued)

Table 1 (continued)

	Study	Study design	Main findings
Abnormal sensorimotor integration	Abruzzese 2001	12 FHD, 9 CD, and 16 HC had peripheral nerve stimulation followed by induction of MEPs with TMS	FHD patients did not have the expected cortical motor suppression following peripheral nerve stimulation
	Rosenkranz 2005	Paired-pulse TMS applied to 7 MD, 6 WC, 8 healthy musicians, and 8 HC	Reduced SICI in musician's dystonia compared to writer's cramp
	Simonetta-Moreau 2006	18 WC and 14 HC received paired-pulse TMS as well as median nerve and digital nerve stimulation	No difference in SICI; reduction in SAI in WC compared to HC
	Baumer 2007	7 WC and 8 HC received 1 Hz rTMS targeted to the S1 and M1	No difference in SAI at baseline; S1 rTMS but not M1 rTMS led to reduction in SAI in WC
	Zittell 2015	20-min 1 Hz rTMS over the M1 or S1 at 90% RMT (1200 pulses) in 12 CD vs. 8 HC	In CD patients, increased corticospinal excitability following S1 stimulation, and normalization of SAI following stimulation of both S1 and M1
Network dysfunction	Siebner 2003	7 FHD received 30-min 1 Hz rTMS at 90% RMT over the dPMC followed by PET	Reduced CBF in lateral and medial premotor areas, putamen, thalamus, and PMC and increased CBF in cerebellum
	De Vries 2012	7 CD vs. 10 HC underwent 1 Hz TMS-fMRI while completing imagined and physical wrist movements	Following TMS, similar but weaker activation pattern in the bilateral prefrontal and posterior parietal regions on fMRI in CD compared to HC and no activation in right angular gyrus in CD compared to HC
	Bharath 2015	19 WC vs. 20 HC underwent fMRI before and after 1 Hz rTMS	Increased resting-state connectivity of the left thalamus-right globus pallidus-right thalamus-right prefrontal lobe network following rTMS
	Bharath 2017	14 WC underwent EEG-fMRI before and after 15-min 1 Hz rTMS at 90% RMT at the PMC	Modulation of frontoparietal regions on EEG and the cerebellum, insula, and medial frontal lobe on fMRI following rTMS

Key: *CBF* cerebral blood flow, *CCD* craniocervical dystonia, *CD* cervical dystonia, *cTBS* continuous theta-burst stimulation, *dPMC* dorsal premotor cortex, *dPMI* dorsal premotor-motor inhibition, *EEG* electroencephalogram, *FHD* focal hand dystonia, *fMRI* functional magnetic resonance imaging, *HC* healthy control, *HFS* hemifacial spasm, *ICI* intracortical inhibition, *LAI* latency afferent inhibition, *LICI* long-interval cortical inhibition, *M1* primary motor cortex, *MD* musician's dystonia, *MEP* motor evoked potential, *PAS* paired associative stimulation, *PMC* premotor cortex, *RMT* resting motor threshold, *rTMS* repetitive transcranial magnetic stimulation, *S1* primary sensory cortex, *SAI* short-latency afferent inhibition, *SP* silent period, *SICI* short-interval intracortical inhibition, *TMS* transcranial magnetic stimulation, *WC* writer's cramp

Note: The primary findings of each study are highlighted in the above table; additional secondary outcomes for each study can be found through consultation of the references

bilateral motor cortex even though the clinical symptoms were unilateral [12]. Some found that MEP is increased and SP is reduced in dystonia, signifying an inhibitory dysfunction that contributes to clinical manifestations [13–22]. Additional evidence for inhibitory dysfunction was obtained with an assessment of surround inhibition in dystonia. As the term implies, surround inhibition refers to the active inhibition of surrounding muscles not involved in a specific muscle movement, thereby facilitating selective or intentional muscle movements [23]. The surround inhibition process is enhanced with task difficulty, indicating that it may be an essential mechanism for the performance of individual finger movements. Although one study found no difference in surround inhibition between healthy controls and patients with focal hand dystonia [24], several other studies found surround inhibition in patients with focal hand dystonia was deficient during movement initiation, leading to involuntary overactivation of muscles [25–27]. An abnormal surround inhibition in dystonia has been attributed to abnormalities within the motor cortex as reflected by reduced SICI. [26] Another consideration is abnormal functioning of the dorsal premotor cortex (dPMC); [26, 28] however theta-burst stimulation did not reveal restoration of normal values indicating a partial contributory role [27].

There is growing recognition for the cerebellum as a pathogenic contributor to dystonia [29, 30]. A recent study found CBI was reduced in writer's cramp patients presenting with dystonic hand tremor further supporting the role of the cerebello-thalamo-cortical pathway in dystonia pathophysiology [32]. In one study, theta-burst stimulation of the cerebellum led to significant changes in SICI and ICF recorded from the motor cortex [31]. Interestingly, these modulatory effects were seen in cervical dystonia patients but not seen in focal hand dystonia [31].

Abnormalities in Sensorimotor Plasticity

Many studies found increased MEP with PAS paradigms, indicating abnormal sensorimotor plasticity in dystonia [33–37]. Enhanced cortical plasticity is likely a maladaptive trait that predisposes individuals to develop the clinical symptoms of dystonia as these changes are seen even though the muscles are clinically uninvolved [34, 38]. In fact, one study suggested that the abnormal plasticity response may not be restricted to the circuits involving dystonia but may be more generalized in these patients [39]. Some studies found M1 [33–35, 37] and primary sensory cortex (S1) [36, 40] excitability could be modulated with the application of the PAS paradigm.

Some groups investigated the effects of cerebellar stimulation on motor cortex excitability and sensorimotor plasticity. They found that conditioning pulses or repetitive pulses did not exhibit modulatory effects [41–43]. Simultaneous application of TMS pulses to the cerebellum with the PAS paradigm also did not affect the plasticity response [44–46]. One study reported that the abnormalities in PAS were selectively spared in functional dystonia [34]. These findings were viewed with particular interest as previous studies had found TMS abnormalities as reflected by reduced SICI and SP in patients with functional dystonia [47, 48]. Abnormalities in

PAS are also less in dystonia secondary to brain lesions [49]. PAS can be utilized as a marker to track treatment outcomes for dystonia. For example, in one study, PAS was found to normalize in patients with cervical dystonia treated with physical therapy in conjunction with botulinum toxin treatments. In another study PAS was restored toward normal in response to DBS therapy targeted to the subthalamic nucleus [50, 51].

Abnormalities in Sensorimotor Integration

Sensory feedback plays a critical role in the manifestation of dystonia, which can be observed in many patients who report a "sensory trick" to overcome their symptoms [52]. Indeed, the cortical processing of sensory information is known to be abnormal in dystonia [53, 54]. In one study, the effects of sensory feedback were more notable in patients with musician's dystonia than writer's cramp [55]. While some studies found no difference compared to healthy controls [40, 42, 56], others found reduced SAI [57, 58] or reduced LAI in patients with dystonia [37, 56]. One study also found normalization of SAI following low-frequency stimulation of the sensory and the motor cortex in patients with cervical dystonia [59]. These results confirm that abnormal sensorimotor integration is one of the key pathophysiological substrates underlying dystonia.

Abnormalities in the Network Functions

TMS studies are increasingly combined with imaging as there is a growing recognition that a more widespread network dysfunction is involved in the pathophysiology of dystonia. In one study, TMS to the sensory parietal cortex was interleaved with fMRI during motor task performance [60]. Compared to healthy controls, patients with cervical dystonia had lesser activation of the specific brain regions remote from the site of stimulation, which indicated that impairment of sensory feedback networks contributed to pathogenesis [60]. Subsequent studies combining TMS with imaging also demonstrated activation changes remote from the stimulation site, thus supporting the idea that dystonia is related to a network dysfunction and TMS can potentially modulate the functions of those networks [60–64].

Limitations

Although a considerable number of studies have investigated the pathophysiology of dystonia, some limitations such as small samples involving focal hand dystonia or cervical dystonia warrant attention. Some TMS measures such as SICI and SP

lack specificity as these can be seen in other hyperkinetic disorders [23]. Recently, concerns were raised whether some TMS measures such as the SP could be regarded as "canonical" as the abnormalities are not consistently recorded across studies. It is unclear whether TMS abnormalities are a cause or a response to having dystonia. Many studies with cross-sectional designs have not probed the effects of pharmacological or surgical treatments on these measures. These concerns could be mitigated by employing more reliable measures with minimum interindividual biological variability in carefully selected large homogenous samples that is followed longitudinally [65].

Therapeutic Role of rTMS

As the pathophysiological studies have elucidated an increased excitability of the motor system, the vast majority of studies have employed an inhibitory low-frequency rTMS protocol to attain an increased inhibition. Most studies have focused on isolated dystonia, mainly focal hand dystonia (writer's cramp), cervical dystonia, and blepharospasm. Only a few studies have involved patients with generalized dystonia and dystonia secondary to other structural brain changes. Several different brain regions have been targeted for alleviating the clinical symptoms (Fig. 3). These studies will be discussed below (summarized in Table 2).

Focal Hand Dystonia

The target cohort for rTMS studies have thus far included patients with task-specific dystonia such as writer's cramp and musician's dystonia. Siebner et al. found subjective writing improvements in 6/16 participants and a significant reduction in mean writing pressure during a digitized task with low-frequency rTMS to the M1, but the motor cortex excitability as reflected by MEP, SICI, and SP was not observed to significantly change [66]. [22] Another study included the premotor cortex (PMC) and supplementary motor area (SMA) besides M1 as potential treatment sites. Low-frequency rTMS to all three sites led to improvements in subjective ratings, writing pressure, and tracking errors in the computer-aided ratings [20]. PMC stimulation appeared to be more promising, as there was a prolongation of SP and restoration of the inhibitory dysfunction [20]. In another study, when low-frequency rTMS to the PMC was delivered for five consecutive days, a significant increase in pen velocity was seen in the active but not the sham group [21]. The clinical benefits were observed to last for at least 10 days following the stimulation sessions [21]. The study also found an increase in SP following active stimulation [21]. Extended clinical benefits with longer therapies were also reported by various case reports involving focal hand dystonia [67, 68] and task-specific leg dystonia [69]. Although more stimulation sessions could potentially increase the duration of benefits [21],

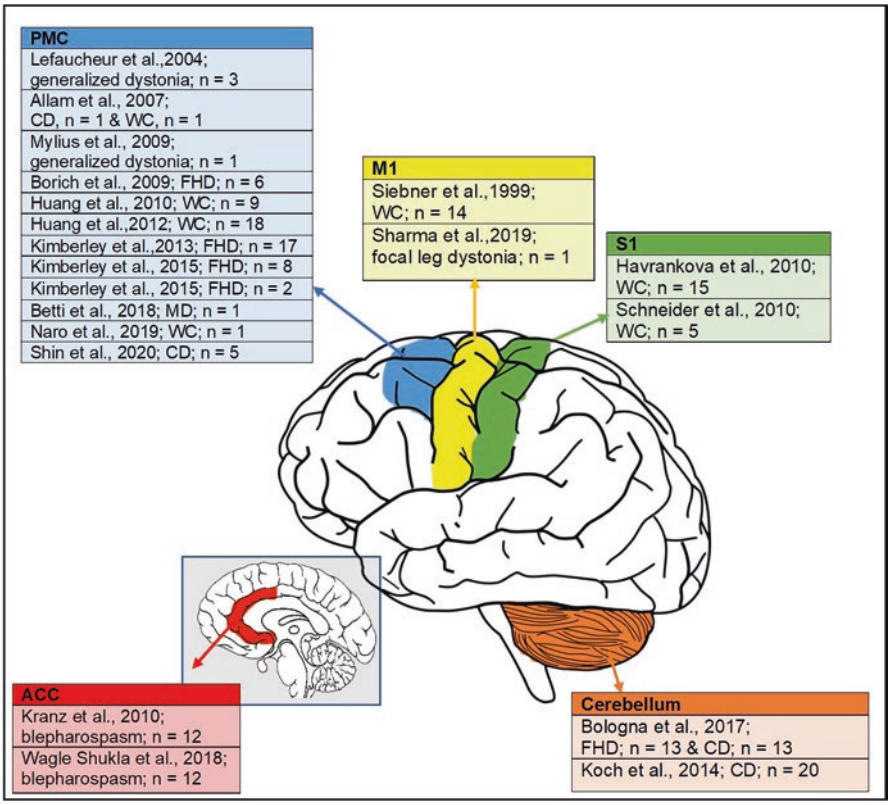


Fig. 3 Therapeutic rTMS studies as well as number and type of enrolled dystonia patients in each study, organized by stimulation target location. ACC, anterior cingulate gyrus; CD, cervical dystonia; FHD, focal hand dystonia; M1, primary motor cortex; PMC, premotor cortex; S1, primary sensory cortex; WC, writer's cramp

5 days of stimulation have not been found to be adequate for clinical improvements [70–72]. One study attempted to distinguish if the extent of cortical excitability abnormalities at baseline could be used to choose the most appropriate rTMS protocol [73]. They found that the patient who exhibited impaired inhibition responded well, whereas the patient with normal findings at baseline was unaffected by the rTMS [73]. These findings suggest that baseline markers could guide rTMS therapy, although larger studies are needed for further confirmation.

Similar to stimulating the PMC, a few studies targeting the S1 found inconclusive results. In a sham-controlled writer's cramp study, five daily sessions of 1 Hz rTMS applied to the S1 led to subjective improvements in handwriting in most patients, but objective changes were not seen [62]. Another study found an increase in tactile discrimination abilities seen in healthy controls but not in patients with writer's cramp in response to 5 Hz rTMS to S1 [74]. This same study used fMRI to demonstrate that the healthy controls had significant changes in the basal ganglia

Table 2 Summary of studies using TMS for clinical benefit in patients with different types of dystonia

Type of dystonia	Study	Patient population	TMS paradigm	Target	Number of sessions	Main findings
Focal: Focal hand dystonia	Siebner 1999	14 WC vs. 11 HC	30-min 1 Hz rTMS at 90% RMT (1800 pulses)	M1	1	Significant reduction in mean writing pressure in WC patients following stimulation
	Murase 2005	9 WC vs. 7 HC	20-min 0.2 Hz rTMS at 85% RMT (250 pulses)	MC, PMC, SMA, or sham over PMC	1 per target site (4 sessions total) 1-week washout	Improvement at PMC (78%), SMA (56%), MC (37%), and sham (11%); prolonged CSP over PMC
	Borich 2009	6 FHD vs. 9 HC	15-min 1 Hz rTMS at 90% RMT (900 pulses)	PMC	5	Significant increase in pen velocity following active rTMS; no change in pen pressure, tracing error, or fluency; increased CSP following active rTMS
	Havrankova 2010	15 WC	30-min 1 Hz rTMS at 90% AMT (1800 pulses)	S1	5	Significant subjective clinical improvement following active but not sham rTMS; no change in BFMDRS or 2MWT; increased activity on fMRI in the bilateral S1, PPC, and SMA following rTMS
	Schneider 2010	5 WC vs. 5 HC	25 trains of 5 Hz rTMS at 90% RMT	S1	1	No improvement in tactile discrimination and lack of connectivity between S1 and basal ganglia in patients with dystonia
	Huang 2010	9 WC vs. 9 HC	50 Hz cTBS at 80% AMT for 40 sec (300 or 600 pulses)	dPMC	1	Significant increase in speed of writing and maze completion in WC patients; improved SICI
	Huang 2012	18 WC vs. 8 HC	50 Hz cTBS at 80% AMT for 40 sec (300 or 600 pulses)	dPMC	1	Subjective improvement in writing; no difference in writing speed or maze spirals between active or sham stimulation
	Kimberley 2013	17 FHD	30-min 1 Hz rTMS at 90% RMT (1800 pulses)	dPMC	5 per active or sham (10 sessions total)	No significant differences between active and sham stimulation; reduced pen force at day 5; increased CSP at day 3
	Kimberley 2015	8 FHD	20-min 1 Hz rTMS at 80% RMT (1200 pulses)	dPMC	5 per active or sham (10 sessions total)	Improvement in self-rated changes but no additional benefit from sensorimotor retraining
	Kimberley 2015	2 FHD	20-min 1 Hz rTMS at 90% or 110% RMT (1200 pulses)	PMC or dPMC	1 day per week for 6 weeks	
	Bologna 2016	13 FHD, 13 CD, 13 HC	50 Hz cTBS at 80% AMT for 40 sec (300 or 600 pulses)	Cerebellar hemisphere	1 per active or sham (2 sessions total)	No changes in clinical scores; reduced M1 excitability following cTBS in CD and HC but not FHD
	Betti 2018	1 MD	30-min 1 Hz rTMS at 90% RMT (1800 pulses)	PMC	5	Significant improvement in motor coordination task following rTMS
	Naro 2019	1 WC	20-min 1 Hz rTMS at 90% AMT (1200 pulses)	PMC	5 blocks of 15 sessions over 8 months (75 sessions total)	Significant improvements in WCRS and 1MWT lasting up to 1 year following initial treatment

Focal: Cervical	Koch 2014	20 CD	50 Hz cTBS at 80% AMT for 40 sec (600 pulses)	Bilateral cerebellum (2 trains over left and 2 trains over right)	10	15% improvement in TWSTRS score in cTBS group; no significant change in BFMDRS
	Pirio Richardson 2015	8 CD	15-min 0.2 Hz rTMS at 85% RMT (180 pulses)	Left ACC, dPMC, MC, SMA, or sham over dPMC	1 session per target site (5 sessions total)	Trend in improved TWSTRS score for the dPM and MC sites
	Shin 2020	5 CD	1 Hz rTMS at 90% RMT for 10 min (600 pulses)	dPMC	5	No change in BFMDRS or TWSTRS
Focal: Blepharospasm	Kranz 2009	7 blepharospasm	rTMS: 15 min 0.2 Hz (180 pulses) cTBS: 50 Hz (600 pulses)	rTMS: 90% RMT at MC, PMC, and ACC; 100% AMT at SMA; cTBS: 80% AMT for MC, PMC, ACC, and SMA	1 session per target (10 sessions total)	Significant improvement in blink reflex recovery, physician rating, and patient rating of symptoms with rTMS only
	Kranz 2010	12 blepharospasm	15-min 0.2 Hz rTMS at 100% AMT (180 pulses)	ACC	1 session per coil type (3 sessions total)	Significant improvement in blink reflex recovery, physician rating, and patient rating of symptoms for regular and H-coil only
	Wagle Shukla 2018	12 blepharospasm	15-min 0.2 Hz rTMS at 100% AMT (180 pulses) in combination with botulinum toxin injections	ACC	10	Significant improvement in Jankovic rating scale, quality of life, and blepharospasm frequency and severity compared to botulinum toxin plus sham rTMS
Focal: Leg dystonia	Sharma 2019	1 running dystonia	44-min 1 Hz rTMS at 90% AMT (2600 pulses)	M1	10	No improvement following rTMS
Segmental	Allam 2007	1 CD and WC	20-min 1 Hz rTMS at 90% RMT (1200 pulses)	PMC	5	50% reduction in neck portion of BFMDRS which persisted for 4 months; no change in WC symptoms
Generalized	Lefaucheur 2004	3 secondary generalized dystonia	20-min 1 Hz rTMS at 90% RMT (1200 pulses)	PMC	5	No significant change in BFMDRS; subjective improvement in dystonic spasms
	Mylius 2009	1 secondary generalized dystonia	20-min 1 Hz rTMS at 95% RMT (1200 pulses)	PMC	5	Decreased number of dystonic attacks following active but not sham stimulation

Key: 1MWT/2MWRT, 1 or 2 min writing test; *ACC* anterior cingulate cortex, *AMT* active motor threshold, *BFMDRS* Burke-Fahn-Marsden Dystonia Rating Scale, *cTBS* continuous theta-burst stimulation, *CSP* cortical silent period, *CD* cervical dystonia, *dPMC* dorsal premotor cortex, *HC* healthy control, *FHD* focal hand dystonia, *MC* motor cortex, *MD* musician's dystonia, *PMC* premotor cortex, *PPC* posterior parietal cortex, *RMT* resting motor threshold, *rTMS* repetitive transcranial magnetic stimulation, *S1* primary sensory cortex, *SMA* supplementary motor area, *TWSTRS* Toronto Western Spasmodic Torticollis Rating Scale, *WC* writer's cramp, *WCRS* writer's cramp rating scale

activation pattern following rTMS, but these effects were not seen in patients with dystonia, indicating an impairment of basal ganglia-S1 processing and sensorimotor integration [74]. As normal sensory processing is critical for dystonia, one study found combining multiple rTMS sessions with sensorimotor retraining therapy led to significant improvements in subjective ratings, supporting greater therapeutic potential with an integrated approach [71].

The use of inhibitory theta-burst protocols were also associated with mixed results. An initial study found significant improvements in writing speed and spiral maze completion with cTBS to the dorsal PMC in patients with writer's cramp [75]. However, a follow-up study using a similar protocol found no significant differences in objective measures between active and sham stimulation [76]. Another study targeting the cerebellum found that even though the motor cortex excitability in response to cTBS did not change in focal hand dystonia, there were notable changes in cervical dystonia, thereby supporting a greater contributory role of the cerebellum in specific forms of focal dystonia [31].

Cervical Dystonia

Koch et al. targeted bilateral cerebellar cortex with inhibitory theta-burst stimulation in a cohort comprising patients with predominant cervical dystonia symptoms [7]. Following 2 weeks of stimulation, there was a significant improvement in neck symptoms, but dystonia in other body parts did not improve [7]. Another study tested the clinical applicability of four different cortical sites, including the M1, supplementary motor area (SMA), dorsal PMC, and anterior cingulate cortex (ACC), with a single session of low-frequency rTMS [77]. The study included a sham arm targeting the dorsal PMC. Stimulation to each site was separated by at least 2 days to allow for a "washout" period. Although dorsal PMC emerged as one of the promising targets [77], a follow-up study did not find notable improvements with rTMS extended to 5 days [78].

Blepharospasm

Only a few studies have examined the role of rTMS in blepharospasm. In one study, Kranz et al. found that inhibitory rTMS over the ACC led to promising results, which were not seen with M1, PMC, and SMA stimulation [79]. The same group conducted a follow-up study using three different stimulation coils: regular coil, H-coil, or sham coil applied to the ACC [80]. The purpose of using the H-coil was to determine if penetration to deeper tissues yielded more beneficial results. This study found that the regular figure-of-eight coil and H-coil led to similar clinical improvements [80]. While these studies included single sessions, Wagle Shukla

et al. applied low-frequency rTMS to the ACC for 2 weeks [81]. Their study included blepharospasm patients reporting suboptimal benefits with the standard-of-care botulinum toxin injections. They found ACC stimulation for an extended period led to partial improvements in frequency and severity of symptoms, activities of daily living, and the social quality of life [81].

Generalized Dystonia

Generalized dystonia symptoms are challenging to treat. Medications are commonly limited by side effects or only partial or limited benefit. While certain forms of genetic dystonia have had a successful therapeutic response to more invasive DBS therapy, other forms of secondary generalized dystonia have not shown the same success rates [82]. Thus, novel treatment strategies are well justified in these patients. In one open-label study involving severe generalized dystonia secondary to brain injuries, low-frequency rTMS to PMC for 5 consecutive days led to a reduction in painful spasms that lasted for several days even after treatment sessions were over [82]. However, the study was small, and there were no significant differences in the scales used to measure disability related to dystonia. A case report found a reduction of dystonic spasms in a child with severe generalized dystonia secondary to pantothenate kinase-associated neurodegenerative disease employed with five daily rTMS sessions [83]. These findings indicate rTMS could be a potential avenue for treating challenging cases, although more studies are needed to determine optimal stimulation parameters and whether longer treatment sessions would lead to more extended benefits.

Limitations

While a growing number of studies are examining rTMS for dystonia, most evidence is available from small sample sizes, many of which are case reports or small case series with varying etiologies [7, 75]. The protocol design across studies has also been heterogeneous. Some studies included healthy populations as controls [20, 21, 31, 61, 74–76], some used a crossover design [7, 62, 70, 71, 77, 79, 80], and some included sham rTMS as a control group that creates a loud noise and a tapping sensation on the patient's head similar to real rTMS. There have been many inconsistencies in the use of sham rTMS techniques. Some used tilting of the coil at 90 degrees [21, 62, 70, 74], some applied coil flipping at 180 degrees from the target site [76], some turned the coil and stimulated at a lower motor threshold [7], or some included a separate sham coil [77, 79, 80]. The orthogonal positioning of the coil can potentially induce stimulation, which is entirely avoidable using a true sham coil. In addition, the "washout" period between stimulation conditions was

variable. Some studies waited 2 days to a week [31, 75, 79, 80], while others waited for several weeks or months before stimulating again [62, 71]. It is unclear if shorter washout periods would affect results. Additional logistical limitations of rTMS as a therapeutic tool include affordability, duration of therapy, and access to TMS within a reasonable distance from the patient.

Another difference between the studies was related to the total number of pulses delivered to patients. There is evidence which suggests that more pulses could lead to more pronounced clinical effects [21] and longer-lasting changes [68]. Finally, a significant limitation pertains to the outcome measures since the existing scales for assessing dystonia symptoms may not be sensitive or specific enough to detect rTMS-related changes. Indeed, many studies found subjective improvements without a corresponding difference in objective measures. Thus, further studies are warranted to determine optimal targets and protocols yielding the most beneficial outcomes that will translate into meaningful clinical changes.

Conclusion

In summary, TMS has advanced our understanding of dystonia pathophysiology. Reduced functions of the inhibitory circuits within the motor cortex and the cerebello-thalamo-cortical pathway enhanced sensorimotor plasticity, and abnormal sensorimotor integration contributes to the pathogenesis. There is increasing data to indicate that dystonia pathophysiology involves a widespread dysfunction of brain regions. Multimodal studies applying TMS with fMRI or TMS with EEG are warranted to better understand the network properties of dystonia. The bulk of the clinical studies so far targeted the PMC with promising results to some extent in focal hand dystonia, but additional target sites such as the cerebellum for cervical dystonia and the ACC for blepharospasm may also be promising. Finally, the neuromodulation benefits of rTMS can be leveraged better when applied as an adjunct therapy combined with standard-of-care medical treatments.

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Brain Connectivity in Dystonia: Evidence from Magnetoencephalography

MEG and Dystonia

Deepal Shah-Zamora, Susan Bowyer, Andrew Zillgitt, Christos Sidiropoulos, and Abhimanyu Mahajan

Abstract Magnetoencephalography (MEG) detects synchronized activity within a neuronal network by measuring the magnetic field changes generated by intracellular current flow. Using MEG data, we can quantify brain region networks with similar frequency, phase, or amplitude of activity and thereby identify patterns of functional connectivity seen with specific disorders or disease states. In this review, we examine and summarize MEG-based literature on functional networks in dystonias. Specifically, we inspect literature evaluating the pathogenesis of focal hand dystonia, cervical dystonia, embouchure dystonia, the effects of sensory tricks, treatment with botulinum toxin and deep brain stimulation, and rehabilitation approaches. This review additionally highlights how MEG has potential for application to clinical care of patients with dystonia.

Keywords Connectivity · MEG · Imaging · Coherence · Dystonia

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Introduction to MEG

Magnetoencephalography (MEG) is a functional neuroimaging tool that detects synchronized activity within a neuronal network by measuring magnetic field changes generated by intracellular current flow (Fig. 1). The current is derived from the net contributions of excitatory and inhibitory postsynaptic potentials [1, 2]. Since the magnetic fields produced from the brain are very weak, highly sensitive superconducting quantum interference devices (SQUIDs) are used to acquire and amplify the signals generated by the simultaneous activation of several thousand spatially aligned neurons [3]. MEG data can be displayed in sensor space as a waveform (data are recorded across the two-dimensional distribution of sensors) or in source space as a location on the MRI (data are reconstructed to a three-dimensional brain model); the latter is preferred as it can localize with more precision [2]. MEG sensors detect the large electromagnetic oscillations generated by synchronized activity within a neuronal network with millisecond temporal resolution.

Fig. 1 MEG detects synchronized activity within a neuronal network by measuring magnetic field changes generated by intracellular current flow

Oscillatory activity within a neuronal network occurs at various frequencies, which can be classified into several frequency bands with higher-frequency bands indicating smaller networks and lower-frequency bands reflecting large networks. Additionally, frequency bands show changes in synchronization over time and form the basis of measurements of connectivity [4]. Connectivity is based on how two brain regions are networked together to send or receive information. There are three categories of brain connectivity. The first is structural connectivity that is based on tracts that physically connect regions of the brain. These connectivity images are diffusion tensor images (DTIs) from magnetic resonance Imaging (MRI). Functional connectivity, extracted from MEG data, describes brain regions with similar frequency, phase, and/or amplitude of correlated activity. Finally, effective connectivity builds on the concept of functional connectivity and determines the influence of one neural system over another [1]. MEG functional connectivity quantifies the frequency and amplitude of synchronicity of neuronal oscillatory activity using Fourier transformations and phase synchrony, which measures how a phase difference between oscillations varies over a short period of time [1]. Spatial data, thus collected, can be superimposed onto the subject's brain MRI to map out neuronal networks and provide information on the flow of communication between brain regions (Fig. 2).

Here we review published studies using MEG for the assessment of dystonia. Frequency bands mentioned in the review are classified as follows: delta (0.5–4 Hz), theta (4–8 Hz), alpha (alpha low, 8–10 Hz; alpha high, 10–13 Hz), beta (13–30 Hz), and gamma (30–48 Hz) [5].

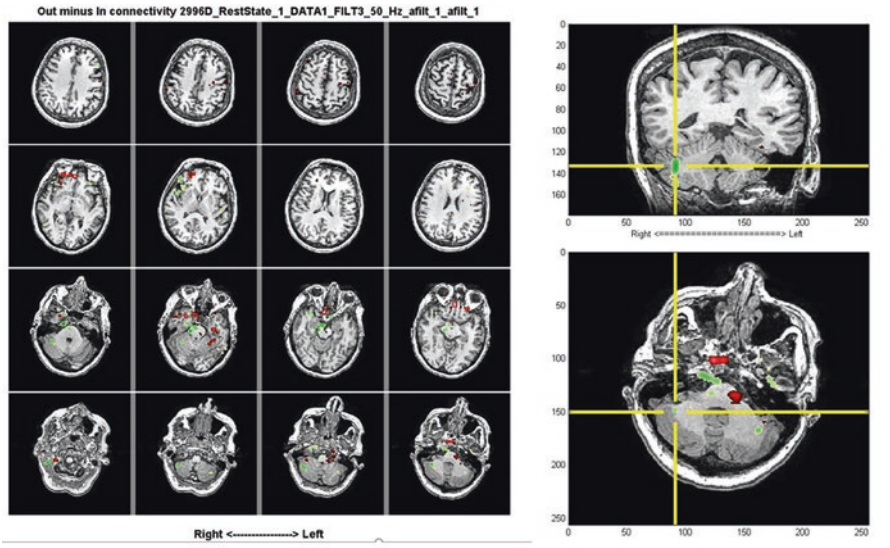

Fig. 2 Sample image of subject with dystonia. MEG allows for superimposition of subject neuronal oscillatory activity onto the subject's brain MRI to map out neuronal networks

MEG in Dystonia (Table 1)

Task-Specific Focal Hand Dystonia

Writer's Cramp

Writer's cramp is a task-specific focal dystonia, which manifests itself as abnormal postures and muscle spasms that interfere with the task of writing [6]. It usually manifests between the ages of 30 and 50 years and is treated with botulinum toxin [7].

Neurophysiological studies showed no difference between writer's cramp patients and healthy controls in their peak in EMG during physiological and dystonic writing at a frequency that mirrored writing frequency, theta (3–7 Hz) [8]. Cerebro-muscular coherence between the extensor digitorum communis muscle (EDC) and contralateral sensorimotor cortex (SMC1) was at this writing frequency or at first harmonic (10 Hz). Stronger co-contraction of agonist and antagonist muscles was associated with stronger cerebro-muscular coherence and weaker coherence with ipsilateral SMC1. The oscillatory network for both physiological and dystonic writing contained the same components: contralateral and ipsilateral SMC1, ipsilateral cerebellum, premotor cortex, posterior parietal cortex, and thalamus. However, cerebro-cerebral coherence between both SMC1 was greater in writer's cramp patients than healthy controls, with less frequent coupling noted between ipsilateral cerebellum and posterior parietal cortex [8]. The abnormal coherence between hemispheres is consistent with previously described bilateral pathophysiology of writer's cramp and reduced cerebello-parietal coupling points toward impaired sensorimotor integration in this task-induced dystonia.

In both patients with writer's cramp and healthy controls, cortical coherence between primary somatosensory cortex (S1) and the contralateral secondary somatosensory cortex (S2) was greater in all frequency bands than coherence between S1 and ipsilateral S2. Cortical coherence between S1 and contralateral S2 was also greater in all frequency bands than coherence between bilateral S2 [9]. Notably, patients with writer's cramp demonstrated reduced alpha and theta frequency coherence between S1 and ipsilateral S2. Alpha and beta frequency coherence between bilateral S2 was also decreased in writer's cramp patients compared to healthy controls. Additionally, there was no correlation between coherence and disease duration. These findings suggest that abnormal cortico-cortical coupling is related to widespread sensorimotor impairments in writer's cramp patients. Another study evaluating the effect of movement in those with task-specific focal hand dystonia (FHD), including writer's cramp and musician's dystonia, found reduction in gamma band coherence between the contralateral primary motor cortex (M1) and S1 during movement of both affected and unaffected hands, instead of a normal increase [10]. There was also increased alpha activity within sensorimotor areas but no difference in task-related beta power in FHD patients compared to controls. The

Table 1 Brain connectivity in dystonia

Condition	State	Frequency	Synchronicity	Location
Task-specific focal hand dystonia	**Writer's cramp**	Alpha, theta	↓	Primary somatosensory cortex and ipsilateral secondary somatosensory cortex [1]
		Alpha, beta	↓	Bilateral secondary somatosensory cortices [1]
	Before movement of affected hand	Gamma	↓	Ipsilateral postcentral gyrus [2] Contralateral primary motor and primary sensory cortices [3]
	After movement of affected hand	Beta	↓	Cuneus of occipital lobe Secondary somatosensory cortex [2]
Embouchure dystonia	**Resting**	Alpha	↑	Bilateral parietal cortices Bilateral inferior frontal cortices [4]
	During dystonic movement	Alpha, beta, gamma	↑	Bilateral sensorimotor cortices [4]
	After dystonic movement	Alpha, beta	↓	Bilateral parietal and frontal regions [4]
		Gamma	↑	Bilateral parietal and frontal regions [4]
Cervical dystonia	**Resting**	Alpha	↑	Left cingulate gyrus and putamen, left putamen and right inferior frontal gyrus, left putamen and right inferior occipital gyrus [5]
	After botulinum toxin treatment	Alpha	↑	Left cingulate gyrus and putamen, left putamen and right inferior frontal gyrus, left putamen and right inferior occipital gyrus, and left putamen and right superior parietal gyrus [5]
	Sensory trick	Gamma	↑	Cerebellum, temporal, and parietal cortex [6]
		Alpha	↓	Cerebellum, temporal and parietal cortex [6]
Deep brain stimulation	**Globus pallidus interna**	Theta	↑	Inferior temporal gyrus [7]
		Alpha	↑	Central cerebellum Peripheral brain stem [7]
		Beta	↑	Sensorimotor areas [7]

Frequency bands are classified as follows: delta (0.5–4 Hz), theta (4–8 Hz), alpha (alpha1, 8–10 Hz; alpha2, 10–13 Hz), beta (13–30 Hz), and gamma (30–48 Hz) – per systematic review Boon
Increased synchronicity ↑, decreased synchronicity ↓

authors concluded that bilateral hemispheric sensorimotor integration abnormalities may suggest that an endophenotypic trait increases disease susceptibility.

Comparison of somatosensory evoked field potentials (SEF) between writer's cramp patients and healthy controls showed that the response was the same to electrical stimulation between the two groups, and the source of the SEF was located in the posterior wall of the central sulcus [11]. There was no difference between groups in evoked gamma oscillations, peak frequency, or latency in the S1 with electrically induced beta frequency event-related synchronization (ERS) or movement [9, 11]. However, beta ERS was significantly lower in the contralateral motor area in patients with writer's cramp a half-second after termination of movement. There was no abnormality in sensory processing in writer's cramp patients, but there was evidence of reduced inhibition and motor cortex dysfunction.

High-frequency oscillations (HFOs) are field potentials reflecting short-term neuronal synchronization. While frequency alone is an insufficient predictor of pathology, HFOs in the range of 80–200 Hz ("ripples") are thought to represent normal physiology, and those in the range of 250–600 Hz ("fast ripples") are thought to be pathologic [12]. Other studies have identified them as frequency bursts (with low amplitude) higher than 400 Hz using EEG and MEG [13]. With peripheral nerve stimulation, HFOs demonstrate somatotopic organization within S1. Comparison of HFO patterns in patients with writer's cramp and healthy controls revealed no difference in baseline values with median nerve stimulation, suggesting normal conduction of the peripheral stimulation to the S1 cortex. Patients with writer's cramp showed no correlation between global HFO and N20 latencies on evoked potentials, whereas in healthy controls there was a strong correlation. Overall, there was decreased global HFO energy and altered somatotopic organization in patients compared to controls, due to desynchronized bursting of cortical neuronal networks. These data suggest that the HFO generating network is abnormal in patients with writer's cramp. The reduced HFO energy may be due to lesser activation of bursting neurons or that they were activated equally but the bursts themselves were not synchronized [13]. Additionally, healthy controls demonstrated two HFO subcomponents with distinct frequency bands. The HFO subcomponents in dystonic patients had reduced power suggesting impaired bursting synchronization, and the subcomponents had a weaker correlation over time indicating impaired temporal coordination. Taken together, the HFO patterns in dystonic patients show spatiotemporal desynchronization at the cortical level in response to sensory processing. However, the results must be interpreted with caution since our knowledge of HFO generators is limited.

Cortical Representation

At rest, writer's cramp patients had reduced distance between thumb and little finger in cortical representation bilaterally [14]. While with writing or brushing movements, this distance was increased compared to rest, it was still lesser in patients compared to controls. In addition, while there was subjective cramping during

writing only, there were no cortical organizational differences between writing and brushing tasks. There was also decreased dipole strength for somatosensory evoked responses during all conditions in patients but more so with executing movements after tactile stimulation, compared to rest. These findings are consistent with a previous study of cortical representation of digits in musicians with FHD [15]. Cortical representation in S1 of both hands was smaller in musicians with dystonia compared to musicians without dystonia and nonmusician controls. There were also equal amounts of fusion of digit representation in bilateral hemispheres in patients with task-specific FHD. The reduced distance between cortical S1 representation of digits in patients with dystonia may suggest that activation of the thumb or little finger can cause co-activation of cortical representation of neighboring fingers [14]. A clear causal relationship between abnormal cortical representation and development of dystonia is not established, however. The cortical fusion abnormalities may contribute to dystonia, or the dystonia, due to other factors, may create cortical abnormalities over time [15]. The bilateral abnormalities noted in some patients with task-specific FHD do suggest an underlying neural predisposition for dystonia.

In patients with task-specific FHD, a detailed assessment of somatosensory organization and digital representation found similar results with reduced amplitude of SEF responses for digits involved on the affected hand in the early response phase [16]. On the unaffected hand, the corresponding digits to those affected on the dystonic hand had higher amplitude in the late phase compared to the uninvolved digits. The spread of source localization was greater in the FHD patients for both hands compared to controls. The area of digital representation was larger for the unaffected side in FHD patients, but the volume was the same on the affected side for both patients and matched controls. They also found altered organization of digits along S1 of both hands for FHD patients. Cortical location of digits in those with FHD was more anterior, lateral, and superior compared to controls. These findings suggest that impaired cortical sensory processing can interrupt the sensorimotor feedback loops and subsequently impair motor control, explaining why FHD often occurs with repetitive tasks.

Mapping of the sensory representation for each digit was found on the postcentral gyrus. In healthy controls, this mapping revealed the location of digits one through five organized from inferior lateral to superior medial pattern [17]. Finger representation in FHD patients was not normally sequenced on S1 for either the affected or unaffected side compared to controls, but the order was more variable in the dominant rather than nondominant hemisphere [17, 18]. When there was an aberrancy, usually there was superimposition or inversion of digit cortical organization. These abnormalities were primarily noted in the nondominant hemisphere, controlling the non-dystonic side, where there was atypical topographic organization of the digits, which the authors hypothesized to be endophenotypic traits of dystonia [15]. The abnormal topographic organization of the nondominant hemisphere suggests that each hemisphere may have its own course of progression, and the nondominant hemisphere may be affected first. The level of disorganization of the nondominant sensory cortex also correlated with the severity of clinical impairment [17]. In the dominant hemisphere, which controlled the dystonic hand, the

topographic organization of digits was more abnormal in severely affected patients compared to mild FHD patients [15, 18]. In those with mild dystonia, the area of hand representation was larger than those with severe dystonia. The size of the area of representation of the affected hand was not significantly different from controls, but the size of the area of representation of the unaffected hand was larger for FHD participants compared to controls. These findings support the sensorimotor hypothesis of aberrant learning, based on the principles of neuroplasticity, for the development of FHD [18].

Several studies evaluated task-specific FHD and included patients with writer's cramp, musician's hand dystonia, and other task-specific hand dystonias. Changes in amplitude and latency of activity in bilateral S1 and its projection to the S2/parietal ventral area (PV) were noted in patients in response to somatosensory stimuli presented at low and high rates [19, 20]. Low-rate and novel stimuli delivered to the unaffected hand resulted in increased response latency in the contralateral S1, while high-rate stimuli to the affected hand increased response latency in the ipsilateral S1 and decreased latency in ipsilateral S2/PV. Low-rate stimuli presented to the affected hand increased latency in the ipsilateral S2/PV. Additionally, the response amplitude was increased in the bilateral S2/PV when high-rate stimuli was delivered to the affected hand and in the contralateral S2/PV only when high-rate stimuli was presented to the unaffected hand. The increases in latency and amplitude in the ipsilateral hemisphere to the affected hand directly correlated with clinical measures of sensorimotor impairment. These findings demonstrate that there is abnormal physiology in contralateral S1 and bilateral S2/PV. The bilateral S2/PV amplitude changes for affected and unaffected hands imply the S2/PV area's role in high-level sensory processing. Increased response latencies in ipsilateral S1 and S2/PV, associated with good clinical performance on sensorimotor tasks, may indicate inhibition and selectivity of sensory processing in these regions [19]. Abnormalities in the bilateral S2/PV and ipsilateral regions relative to both affected and unaffected hands suggest that sensorimotor retraining for rehabilitative purposes may also need to be bilateral and simultaneous and include cortical sensory processing [19].

The effects of self-initiated movement of a digit was compared between patients with various forms of task-specific FHD and controls [21]. Just prior to a button push with the affected right hand, there was a significant reduction in high gamma band (65–90 Hz) over the right postcentral gyrus. After the button push, there was a subsequent decrease in high gamma over this region in FHD patients. There was also reduction in the beta power band over the cuneus of the occipital lobe during movements with the affected hand and over S2 during movements with the unaffected hand in patients with FHD. The increased activity in the visual cortex with movement suggests reliance of other sensory signals to improve motor control. Thus, biofeedback which uses both auditory and visual information may be considered as an aid in retraining abnormal movements [21]. Disrupted proprioceptive feedback in the affected hand in FHD may increase reliance on the visual and auditory system.

To further discriminate between sensory and motor counterparts in the cortex involved in task-specific FHD, participants were asked to perform isometric contraction and relaxation of each hand in response to a beeping tone [22]. All

abnormalities were found in bilateral hemispheres but were more pronounced contralateral to the dystonic hand. Cortico-muscular coherence in the beta range was higher in FHD patients compared to controls, but it became slightly reduced in patients with maintenance of muscle contraction. Cortico-muscular coherence was unchanged by an experimental sensory stimulus, but patients with FHD demonstrated decreased sensory area responsiveness, reduced excitability in M1, and weaker activation of the parietal cortices. This suggested that there was a stronger movement-induced sensory gating mechanism. In addition, the authors also hypothesized FHD was partly due to reduced parietal projections, which contributed to relative frontal area hyperactivity and affected M1 sensory processing.

In summary, abnormal coherence patterns at multiple frequencies detected by MEG reveal issues with sensorimotor integration and bilateral hemispheric involvement, with disorganized cortical somatotopy in task-specific FHD. Studies assessing cortical response to sensorimotor stimuli are consistent with prior knowledge that cortical sensory processing is impaired, particularly in motor cortex response.

Embouchure Dystonia

Embouchure dystonia is a task-specific incoordination of the lower face, jaw, and tongue and can include lip tremor and pulling [23]. A case study evaluated a professional flautist with a dystonic upper lip tremor when lower lip was touched. Compared to controls, in this patient at rest, there was increased coherence diffusely in bilateral parietal cortices and bilateral inferior frontal cortices, right greater than left. Prior to the dystonia, there was increased alpha activity. The cingulate and insular regions received information, and the right inferior frontal region relayed output. During the dystonic movement, alpha, beta, and gamma frequencies increased, and coherent networks became more localized to the bilateral sensorimotor cortices. After the dystonic movement, alpha and beta activities were reduced, and gamma activity increased with persistently increased coherence in the bilateral parietal and frontal regions. The right inferior frontal region was no longer active, and the cingulate and insular regions provided output during the dystonic movement and afterward. While this is a study of only one patient, the patterns of coherence suggest decreased intracortical inhibition impairing sensorimotor processing in embouchure dystonia [24].

Analysis of face and lip representation in embouchure dystonia revealed a shorter distance between lip and first digit cortical representations [25]. The reduced distance was not due to smaller lip cortical representation. Instead, the representation in the somatosensory cortex of the hand and mouth appeared abnormal and was reported to be associated with embouchure dystonia. The shorter distance between cortical representation of the hand and mouth in embouchure dystonia is similar to that of finger representation distances in FHD. There was also an increased sensory threshold of the upper lip compared to the lower lip of patients with embouchure dystonia. The upper lip is primarily involved in vibration and sound production. Additionally, techniques used by musicians may create increased pressure and

compression of the upper lip. This results in minor sensory nerve damage and decreased sensitivity in the upper lips. Furthermore, upper lip repetitive movements were positively correlated with occurrence of uncontrollable muscle contraction around the lips. Together, these studies highlight the bilateral involvement in coherence patterns in embouchure dystonia and the association between task-specific dystonias and abnormal somatotopic cortical organization.

Cervical Dystonia

Resting State

The effects of botulinum toxin injections on functional connectivity were evaluated in four patients with cervical dystonia (CD) [26]. Compared to controls, CD patients showed increased coherence in the fronto-striatal pathways and in the occipito-striatal, parieto-striatal, and temporo-striatal networks, demonstrating the involvement of the frontal and occipital pathways in dystonia. During maximal benefit around 2 to 3 weeks post-botulinum toxin treatment, patients had increased coherence especially in the frontal-frontal, frontal-parietal, frontal-temporal, and cingulate-occipital pathways, from pre-botulinum toxin state. Statistical correction for false positivity revealed a significant difference in patients compared to controls in the left putamen and right superior parietal gyrus (which integrates multiple sensory inputs into a single spatial frame) after botulinum toxin. Thus, the clinical benefit of botulinum toxin in cervical dystonia may be related to improved sensorimotor integration. However, while MEG data were captured approximately at the time of best possible clinical benefit, the duration of coherence changes from botulinum toxin injections and differences between muscle contractions and connectivity patterns were not studied. These can be future areas of research.

Executive Function

A subsequent study evaluating executive function in CD patients using a continuous performance task revealed a change in coherence in the frontal networks in response to botulinum toxin injections. Two to three weeks post-injection, cervical dystonia patients showed diffusely increased coherence especially in frontal networks [27].

Sensory Trick

MEG evaluation prior to botulinum toxin injections in a cervical dystonia patient with a sensory trick revealed that prior to the sensory trick, there was increased alpha range coherence between the right and left inferior frontal lobes and left

temporal regions [28]. There was also increased activity in the inferior frontal, left cerebellum, and left parietal regions. After the sensory trick, there was increased gamma coherence between the right and left temporal lobes as well as increased activity in the occipital and left temporal region. Gamma activity correlates with GABA [29, 30], so these findings support the hypothesis that low intracortical inhibition is involved in the generation of dystonia and/or in the effect of sensory trick on dystonia. The sensory trick also reduced alpha activity. After botulinum toxin injections in this patient, there was increased coherence in the left temporal and parietal areas and right and left cerebellum, and there was increased activity in the occipital region, right cerebellum, and right temporal areas. Alpha activity increased and gamma activity was unchanged. These findings from a single dystonic patient may indicate common sensory mechanisms between effective sensory tricks and botulinum toxin injections, but larger studies must be conducted to better understand these associations [28].

Deep Brain Stimulation (DBS) for Dystonia

Power spectral analysis of cortico-subthalamic networks in a patient with bilateral subthalamic nucleus (STN) DBS for dystonia induced by chorea-acanthocytosis revealed significant subthalamo-cortical coherence in the high beta band bilaterally and in the mesial-sensorimotor areas, consistent with what has been previously reported for Parkinson's disease (PD). The authors reported increased power in alpha-theta spectrum and decreased power in low beta spectrum in the STN in dystonia compared to a previous PD cohort [31].

Cortico-pallidal beta coherence in sensorimotor areas, particularly premotor and motor cortices, was noted in several types of dystonic patients with bilateral GPi DBS [32]. Theta coherence extended from subcortical areas to the temporal region and was maximal in the inferior temporal gyrus. Alpha band coherence was noted over the central cerebellum and overlapped peripherally with the brain stem. Clinically, there was a negative correlation between dystonia symptom severity and pallido-cerebellar alpha range connectivity, especially in those with segmental or cervical dystonia, indicating alpha network's role in pathophysiology of dystonia. In a patient with hemidystonia and unilateral GPi DBS, unilateral cerebellar involvement and increase in whole brain beta and gamma coherence that extended to bilateral cerebellum were noted. There were further increases in coherence with treatment with anticholinergic medication [33]. The findings from these studies highlight that multimodal neuroimaging techniques can potentially direct choices for developing therapeutics.

Rehabilitation Detected by MEG

Using a targeted repetitive peripheral sensory stimulation device during performance of skilled manual tasks for rehabilitation, Euclidean distance measurements were similar in those who improved with rehabilitation and controls and larger in those with non-rehabilitated writer's cramp [34]. The normalization of MEG abnormalities controlling the dystonic hand, including size of hand representation, in writer's cramp patients adequately treated with rehabilitation suggests that long-term plasticity develops and may persist over time.

In sensorimotor retuning, a custom device was used to splint fingers in such a way that dystonic movements were avoided while playing an instrument [35]. Before retuning, the somatosensory organization of individual fingers differed between affected and unaffected hands. After treatment with retuning, cortical finger representations became similar between the affected and unaffected hands and were more organized, following the motor homunculus. Following treatment, there was also a decrease in the Euclidean distances between cortical representations of the digits 1, 2, and 5 and little change in distances of the cortical representation of the non-dystonic hand [36]. This suggests that cortical organization can be modified with context-specific treatment. Since the movement limitation during retuning altered cortical sensory organization, there appears to be a strong relationship between the sensory and motor systems [35]. The changes noted before and after rehabilitative exercises are consistent with abnormalities seen at rest and with various sensorimotor stimuli described earlier.

Potential of MEG Use in Dystonia

MEG has helped uncover the pathogenesis of FHD and replicate the findings of previous cervical dystonia studies as well as highlight several aspects of dystonia pathophysiology and possible mechanisms for the benefit of symptomatic treatment. MEG can also be used to identify altered sensory processing that interrupts the sensorimotor feedback loops in FHD, as well as to detect ipsilateral areas that can become active to support sensorimotor activity during writer's cramp. The most significant finding shows that MEG can detect decreased gamma activity which has been shown to represent GABA, the inhibitory neurotransmitter; low intracortical inhibition may be one of the underlying generators of dystonia. However, MEG's utility remains inadequately explored both in research and in clinical care [37]. With the advent of more MEG system installations across the country, there may be more utilization of this noninvasive neuroimaging technique to investigate the effect of treatments on dystonia to help define therapies. Recent concerns regarding functional MRI's inability to infer actual neuronal activity from the secondary BOLD flow response [38] put MEG in a unique place to answer the same questions using a direct measure of neuronal function [1]. Leveraging MEG's noninvasive technology

to target cortical network dysfunction with therapeutic interventions will facilitate the translation to clinical use. Combining this with multicenter collaborations will provide exciting advances in curing or alleviating movement disorders in the future [39].

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Dysfunctional Networks in Functional Dystonia

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Abstract Functional dystonia, the second most common functional movement disorder, is characterized by acute or subacute onset of fixed limb, truncal, or facial posturing, incongruent with the action-induced, position-sensitive, and task-specific manifestations of dystonia. We review neurophysiological and neuroimaging data as the basis for a dysfunctional networks in functional dystonia. Reduced intracortical and spinal inhibition contributes to abnormal muscle activation, which may be perpetuated by abnormal sensorimotor processing, impaired selection of movements, and hypoactive sense of agency in the setting of normal movement preparation but abnormal connectivity between the limbic and motor networks. Phenotypic variability may be related to as-yet undefined interactions between abnormal top-down motor regulation and overactivation of areas implicated in self-awareness, self-monitoring, and active motor inhibition such as the cingulate and insular cortices. While there remain many gaps in knowledge, further combined neurophysiological and neuroimaging assessments stand to inform the neurobiological subtypes of functional dystonia and the potential therapeutic applications.

Keywords Functional dystonia · Fixed dystonia · Networks · Neurophysiology · Cortical inhibition · Sensorimotor processing

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Abbreviations

CSP	cortical silent period
CRPS-1	complex regional pain syndrome type I
EBCC	Eyeblink classical conditioning;
EMG	electromyographic
FD	Functional dystonia
FMD	functional movement disorder
ICF	intracortical facilitation
LAI	long-afferent inhibition;
LICI	long-interval intracortical inhibition
M1	primary motor cortex
MRI	Magnetic resonance imaging;
SAI	short-afferent inhibition
PAS	paired associative stimulation
PET	Positron emission tomography
SICI	short-interval intracortical inhibition
TDT	temporal discrimination threshold
TENS	transcutaneous electrical nerve stimulation

Introduction

Functional dystonia (FD) is the second most common functional movement disorder (FMD) and one of the most challenging to diagnose and treat [24, 28, 65]. FD affects young women in approximately 80% of the cases, with symptoms often developing after a physical injury of minor/moderate degree of severity or an emotional triggering event [49, 50].

FD has been the subject of considerable controversy, partially due to the overlapping clinical features and comorbidities with other types of dystonia [2, 16, 56]. The criteria for the definite diagnosis of FMD have rested on the documentation of incongruence and inconsistency in the neurological examination, and the identification of positive signs supporting a diagnosis of inclusion, not exclusion [71]. Less diagnostic value has been placed on associated historical or psychological features [16]. They can "suggest" a functional disorder, but only incongruent/inconsistent features elicited at the bedside during the neurological examination can confirm the diagnosis of FMD [16]. However, FD provides the single exception to the no-history rule to a phenotype-specific diagnostic approach as it requires ascertaining a *rapid onset* [16].

The first official diagnostic criteria for FD were established by Fahn and Williams in 1988, and included four diagnostic categories: documented, clinically established, probable, and possible FD [20]. The documented and clinically established categories were subsequently unified as "clinically definite" FMD. The 2009 Gupta and Lang's revised FMD criteria eliminated the *possible* and *probable* diagnostic

categories and introduced a laboratory-supported diagnostic category (i.e., neurophysiology) [26].

Core Clinical Features

FD is recognized by the rapid onset of fixed posturing of a body part (most often a limb) suggesting dystonia. The *incongruence* with (organic) dystonia is demonstrated by a phenotype that violates key phenotypic features [16, 18, 19, 46]. The posturing or tremor associated with FD is not action-induced, position-sensitive, task-specific, or associated with motor overflow or a *geste antagoniste*, namely the trick whereby attenuation of the phenotype occurs upon application of a closed-loop sensory feedback [16]. Several phenotypes can be topographically recognized: in the feet, fixed plantar flexion with ankle inversion or the "toe sign" [15]; in the hands, fixed flexion of digits 3–5 with extension of thumb and index fingers, sparing the pincer function [66]; in the cervical region, posttraumatic painful *torticollis*, with fixed *laterocollis*, ipsilateral shoulder elevation, and contralateral shoulder depression [61]; and in the face, tonic lateral deviation of the lips or jaw with variable ipsilateral platysma involvement [21, 22, 33]. Other manifestations affecting the face include alternating spasms from one side of the face to the other and absence of ipsilateral eyebrow elevation (the "other" Babinski sign) [73].

The *inconsistence* component of FD relates the variability of the phenomenology over time [46]. The acute or subacute onset of FD may be maximal at onset but followed by fluctuating severity or rapid progression alternating with unexplained periods of improvement [26]. Over time, the fixed posturing of a limb can compromise the underlying joints and microvasculature, giving rise in many of these patients to contractures and features suggestive of complex regional pain syndrome type I (CRPS-I), previously known as reflex sympathetic dystrophy [77]. Most patients diagnosed in the past with CRPS-I met criteria for clinically definite FD [16].

Associated Features

Predisposing, precipitating, and perpetuating factors may be associated the development and maintenance of FD [49, 50]. Patients with FD are often impacted by psychological/psychiatric comorbidities and pain [16]. Compared to organic dystonia, patients with FD are more likely to have psychiatric comorbidities, particularly anxiety, depression, apathy, and posttraumatic stress disorder (Tomic et al. 2017; [51]). Moreover, FD patients are more likely to have high levels of alexithymia and deficits of interoception and emotional processing [12, 18, 19, 57]. These patients also exhibit higher prevalence of other functional somatic disorders such as, fibromyalgia, irritable bowel syndrome, chronic pain disorders, and chronic fatigue [69].

Finally, it has been suggested that a risk factor for the development and maintenance of FD might be the joint hypermobility syndrome [34].

Prognosis

The prognosis for patients with FD is generally poor. The worst outcome has been documented in those with chronic pain, diagnosis of CRPS-I, depression and presence of other somatic functional symptoms [30]. These patients also represent a heavy financial burden on their families and healthcare systems [70]. The costs are in part due to delayed FD diagnosis or to misdiagnoses, which lead to unnecessary investigations and inappropriate treatments with iatrogenic harm [13, 14, 46].

For the purposes of this review, we have eliminated the use of "primary" dystonia, often used in the literature as the main comparator in FD studies. *Primary* has evolved into *isolated or idiopathic*, according to the clinical of etiological axis of the latest diagnostic guidelines [2]. We have also limited the use of "organic" dystonia as comparison to "functional" since, as it will become apparent, it is becoming increasingly apparent that FD is an organic disorder, with better defined neurobiology than in the past.

Neurophysiology and Neuroimaging

To date, several neurophysiological and neuroimaging studies have been conducted on patients with FD. Several issues remain unresolved, among them the extent to which the abnormalities observed are specific for FD and the cause-versus-consequence relationship between the experimental data and the clinical manifestations. Clarifying these issues would help clarify the pathophysiological underpinning of FD. We here will review the main neurophysiological and neuroimaging studies investigating the pathophysiology of FD, highlighting the pathophysiological relevance of the abnormalities detected contrasting FD with organic dystonia (Table 1). We will propose a model based on the theory of network dysfunction, as proposed for organic dystonia, discussing its potential clinical implications.

Neurophysiology

Transcranial Magnetic Stimulation (TMS) Studies

TMS is one of the most used widely neurophysiological tools for the assessment of cortical motor areas in healthy and diseased populations [11, 60]. TMS, delivered using different paradigms of stimulation, allows the measurements of corticospinal

Table 1 Neurophysiological studies in functional dystonia

Author, year	Number of patients, condition(s)	Technique(s)	Main findings in FD
[17]	10, FD 8, OD 12, HS	TMS parameters: SICI, ICF, LICI, CSP, BP	CSP, SICI, and LICI reduced, ICF unchanged in FD and OD; BP increased in OD
[4]	12, FD 10, OD 11, HS	TMS parameters: CSP, SICI, SAI, LAI	CSP and SICI reduced in FD; SAI and LAI did not vary between the three groups
[54]	10, FD 10, OD 10, HS	TMS parameters: SICI, SAI, LAI, PAS	SICI reduced in FD and OD; SAI and LAI unchanged; PAS increased only in OD
[44]	10, fixed dystonia 10, HS	TMS parameters: CSP, SICI, ICF, SAI, LAI	SAI and LAI reduced, ICF increased in patients; CSP unchanged; PAS was comparable in patients and HS
[55]	6, FD 7, OD 6, HC	TMS parameters: PAS	No differences across the three groups
[68]	9, AB 10, BEB 9, HS	R2 blink reflex recovery cycle	R2 did not differ between AB and HS, whereas it was altered in BEB
[31]	11, fixed dystonia 7, HS	EBCC	No differences between patients and controls
[35]	11, fixed dystonia 11, OD 10, HS	Mental rotation of body parts and sensory temporal discrimination	Only mental rotation was impaired in fixed dystonia
[43]	10, FD 10, OD 16, HS	TDT	TDT was higher in FD and OD compared to HS
[45]	12, FD 10, OD 16, HS	Tactile, pain thresholds, and pain tolerance	No differences in tactile and pain thresholds; pain tolerance was increased in all body regions only in FD
Metha et al., 2013	4, fixed dystonia 5, OD 6, HS	EMG analysis	Coactivation of ipsilateral and contralateral muscles of the affected limb in the movement preparation phase in fixed dystonia
[38]	9, FD 9, OD	EMG analysis	Reduced cocontraction during voluntary movements in FD when compared to OD; Normal reaction time in FD
[48]	1 FD	Wireless-EMG analysis of gait	Cocontraction in the muscles of the affected limb, while the unaffected limb showed regular EMG bursts

FD functional dystonia, *OD* organic dystonia, *HS* healthy subjects, *TMS* transcranial magnetic stimulation, *SICI* short-interval intracortical inhibition, *LICI* long-interval intracortical inhibition, *CSP* cortical silent period, *BP* Bereitschaftspotential, *SAI* short-afferent inhibition, *LAI* long-afferent inhibition, *PAS* paired associative stimulation, *AB* atypical blepharospasm (presumed functional), *BEB* benign essential blepharospasm, *EBCC* eyeblink classical conditioning, *TDT* temporal discrimination threshold, *EMG* electromyography

excitability, intracortical inhibition (e.g., cortical silent period – CSP, short-interval intracortical inhibition – SICI, and long-interval intracortical inhibition – LICI) and facilitation (ICF), cortical plasticity, and other parameters.

The first examination of intracortical excitability was undertaken in a relatively small and clinically heterogeneous sample of 10 patients with FD [17]. A reduction in cortical inhibition was observed in the affected muscles: CSP, SICI and LICI were abnormally lower in patients with FD, as in patients with organic dystonia, while ICF was normal [17]. These findings demonstrated that the altered patterns of cortical inhibition in patients with FD were shared with those of organic dystonia [27, 53]. However, given the cross-sectional design of the study (median duration of symptoms of 4 years), the authors could not conclude whether the abnormalities of cortical inhibition predated or followed the onset of FD; as such, impaired cortical inhibition could be a consequence of the dystonic posture rather an abnormality predisposing to dystonia, as has been observed in organic dystonia [27, 53]. Avanzino et al. [4] have examined CSP, SICI, and short- and long-afferent inhibition (SAI and LAI, respectively) in three groups of subjects: patients with FD (mainly fixed dystonia patients), patients with organic dystonia with predominantly unilateral dystonic postures, and healthy volunteers. The authors found that CSP and SICI were significantly altered in patients with FD, indicating impaired inhibition in both hemispheres. Conversely, SAI and LAI did not vary between the three groups. The authors considered it unlikely that bilateral cortical excitability changes reflected unilateral symptoms and concluded that they more likely reflected a dystonia susceptibility trait, that is, a predisposing endophenotype [4]. Loss of cortical inhibition, as assessed by shortened SICI, but normal SAI and LAI in FD have been confirmed in subsequent investigations [54]. Thus, impaired cortical inhibition seems to be a consistent neurophysiological change in patients with FD. Separately, Quartarone et al. [54] using a paired associative stimulation (PAS) paradigm documented no significant abnormal sensorimotor plasticity in FD in contrast to its impairment in patients with organic dystonia. Similar results with PAS paradigms were obtained by Ramos et al. [55] in a smaller group of participants. Finally, Morgante et al. [44] tested cortical excitability and sensorimotor plasticity in patients who developed a fixed posture of the hand in the context of a CRPS-I observing a reduction in SICI and LAI in the affected hand of patients compared with control subjects while sensorimotor plasticity was comparable to normal subjects.

Brainstem and Spinal Reflexes

The trigeminal blink reflex allows the neurophysiological assessment of brainstem and the testing of reciprocal inhibition in forearm muscles and the cutaneous silent period allows the neurophysiological assessment of spinal circuits. These techniques also permit indirect inferences on the state of suprasegmental areas, namely the basal ganglia, and the regulation by these structures of brainstem and spinal cord inhibitory interneuronal mechanisms [6, 76].

Trigeminal blink reflex. Schwingenschuh et al. [68] tested the recovery cycle of the R2 component of the trigeminal blink reflex as a measure of excitability of human brainstem interneurons in patients with functional blepharospasm. The authors found that R2 recovery cycle was not significantly altered in patients compared to controls, suggesting normal brainstem interneuron excitability in these patients and a useful *laboratory-supported* tool to distinguish functional blepharospasm from essential blepharospasm [68].

Forearm reciprocal inhibition and cutaneous silent period. Espay et al. [17] documented reduced spinal inhibition in FD as in isolated dystonia. Also, the authors found an increase in the CSP in FD as in isolated dystonia [17]. Hence, impairment in spinal inhibition is indistinguishable between FD and isolated dystonia, suggesting that it may be a consequence of the abnormal posturing rather than its cause.

Cerebellar Function

Eyeblink classical conditioning (EBCC) is a paradigm of associative motor learning relying upon olivo-cerebellar and ponto-cerebellar pathways in which an abnormality is considered a neurophysiological indicator of cerebellar dysfunction [25, 29].

Janssen et al. [31] used the EBCC to investigate cerebellar functioning in patients with fixed dystonia and healthy controls. While previous studies have demonstrated abnormal EBCC in organic dystonia [29, 74], Jannsen et al. [31] have shown normal cerebellar function in un-medicated patients with FD (fixed dystonia patients), although a slower learning rate was observed in patients compared to healthy controls. In this regard, it has been observed that cerebellar impairment, as assessed by the EBCC, reflects the presence of tremor in patients with dystonia [3]. With these limited data, further studies will be needed to examine whether the cerebellar function in FD differ from that of idiopathic dystonia. Recent data suggest that any cerebellar impairment may vary considerably within patients with isolated dystonia.

Sensory Processing

Although dystonia is a motor disorder, it is now increasingly recognized that it is characterized by sensory processing abnormalities [53]. In FD, studies on sensory processing have revealed some inconsistencies, possibly due, at least in part, to subtle different clinical features of the patients enrolled in the various studies. For example, Katschnig et al. [35] first documented normal temporal discrimination in patients with fixed dystonia when compared to patients with isolated dystonia. Conversely, Morgante et al. [43] showed impaired processing of somatosensory inputs in both FD and isolated dystonia, compared to healthy subjects, as assessed by testing of the temporal discrimination threshold (TDT). Moreover, TDT did not correlate with disease duration, and it did not differ between the affected and the unaffected side in both groups. Hence the authors suggested that in FD impaired

processing of somatosensory inputs could represent a neurophysiological trait predisposing to dystonia, possibly being triggered by psychological stimuli [43].

Elevated TDT in patients with mixed types of FMD were confirmed in a recent study [64]. The authors used the drift diffusion model to reveal that the mechanism behind this shift in performance was an impairment in the quality of the information that drives decision processes.

Morgante et al. [45] also documented normal tactile and pain thresholds in FD, isolated dystonia, and healthy subjects, while they found increased pain tolerance in all body regions in FD when compared to isolated dystonia and healthy subjects [45]. These results further suggest abnormal sensory processing in FD, which involve both the somatosensory stimuli integration and the dissociation between the discriminative and affective dimensions of pain in this condition.

Moreover, Pareés and colleagues [49, 50] explored the sensory attenuation phenomenon, defined as a measure of the sense of action for a given movement, through a force-matching task, in FD patients and age-matched healthy subjects. They found a significant loss of sensory attenuation in patients. These findings provide further evidence of altered sensory processing as a possible explanation of why patients report that they do not perceive the abnormal movement as voluntary. Finally, Katschnig et al. [35] explored higher order sensory processing using a task of mental rotation of body parts in patients with fixed dystonia, isolated dystonia, and healthy subjects. They found that patients with FD were impaired exclusively in the mental rotation task, while patients with isolated dystonia showed both abnormal mental rotation and TDT. They concluded that altered body image is a common pathophysiology for FD and isolated dystonia, possibly contributing to the development of dystonic posturing [35].

Movement Studies

Only few neurophysiological studies have investigated possible abnormalities of movement performance in FD. Concerning the movement preparation phase, the amplitude of the premovement *Bereitschaftspotential* was normal in FD, thus indicating that the preparation phase of voluntary movements in FD is not compromised as it may be in isolated dystonia [17]. Mehta et al. [42] have described an altered neurophysiological pattern in patients with fixed lower limb dystonia through electromyographic (EMG) techniques. The authors reported a sustained muscle coactivation of ipsilateral and contralateral muscles of the affected limb in the movement preparation phase [42]. However, using EMG, Macerollo et al. [38] found that patients with fixed dystonia showed lower levels of cocontraction during voluntary movements, when compared to those with secondary dystonia; moreover, the reaction time (RT) was normal [38]. In a single-case study, Oh et al. [48] used wireless EMG for gait analysis. When analyzing EMG signals from limb muscles during the gait, the authors found cocontraction in the muscles of the affected limb, while the EMG analysis of the contralateral, unaffected limb, showed regular EMG bursts

[48]. Pending the clarification of some limitations and inconsistencies in the literature, the abnormal coactivation EMG and/or the double-contraction signs have the potential of becoming useful laboratory-supported tools for diagnosing and monitoring response to treatment in FD.

Neuroimaging

Although several studies have investigated the neuroimaging correlates of functional disorders [58], to date, only a few studies have specifically investigated brain abnormalities in FD using neuroimaging techniques, including studies on functional and molecular imaging (Table 2). Comparisons between FD and isolated dystonia are scarce.

Table 2 Neuroimaging studies in functional dystonia

Author, year	Groups	Technique(s)	Main findings in FD
[75]	13, fixed dystonia 31, mobile dystonia 43, HS	3D T1-weighted and DT MRI	Severe disruption of WM architecture in the corpus callous, corticospinal tract, anterior thalamic radiations, and major long-range tracts bilaterally.
[40]	48, FMD (35% FD) 55, HC	T1-weighted MRI	Increased volume of the left amygdala, left striatum, left cerebellum, left fusiform gyrus, and bilateral thalamus, and decreased volume of the left sensorimotor cortex
[18]	12, FD 12, OD 25, HC	4 T fMRI: Finger-tapping task, basic emotion-recognition task, intense-emotion stimuli task	Basic-emotion tasks: Hyperactivation in the right middle temporal gyrus and bilateral precuneus; intense-emotion task: Hypoactivation in the left insular and left motor cortices and hyperactivation in the left fusiform gyrus.
[39]	35, FMD (43% FD) 35, HS	Resting-state fMRI	Decreased FC between the right TPJ and right sensorimotor cortex, cerebellar vermis, bilateral supplementary motor area, and right insula.
[8]	40, FD 43, HS	Resting-state fMRI	Reduced FC between fronto-subcortical and limbic circuits; enhanced FC between the right affective-cognitive part of the cerebellum and bilateral associative parietal cortex; and between the bilateral amygdala and the posterior cortical brain regions
[67]	6, FD 5, OD 6, HC	PET	Increased blood flow in the cerebellum and basal ganglia, and reduced flow in M1.

FD functional dystonia, *OD* organic dystonia, *HS* healthy subjects, *DT* diffusion tensor, *MRI* magnetic resonance imaging, *WM* white matter, *FMD* functional movement disorders, 4*T* 4 Tesla, *fMRI* functional magnetic resonance imaging, *TPJ* temporoparietal junction, *FC* functional connectivity, *PET* positron emission tomography, *M1* primary motor cortex

Magnetic Resonance Imaging (MRI)

Tomic and colleagues [75] used diffusion tensor (DT) MRI to investigate brain structural alterations in two diverse phenotypes of FD, the fixed dystonia and the mobile dystonia, compared to healthy subjects. They showed different patterns of cortical thinning and volume of cerebral areas between fixed and mobile dystonias, when compared to healthy subjects. Additionally, fixed dystonia patients showed a disruption of white matter structure in multiple brain areas. This MRI study showed the structural neural underpinnings of two different FD phenotypes, fixed and mobile FD. Patients with mobile dystonia had significant alterations in gray matter areas essential for sensorimotor control, cognition, and emotional processes. Patients with fixed dystonia showed white matter abnormalities in the sensorimotor and emotional networks [75].

Again, Maurer et al. [40] studied the gray matter volume alterations, through voxel-based morphometry MRI techniques, in 48 patients with FMD (35% FD) and healthy subjects. They found that FMD patients showed structural gray matter abnormalities in critical components of the limbic and sensorimotor circuitry (e.g., left amygdala, left striatum, left cerebellum, left fusiform gyrus, bilateral thalamus, left sensorimotor cortex). Taken together, these data suggest that FD is associated with certain structural and functional brain network abnormalities, although it is not clear whether these changes are related to the disease per se, or rather compensatory, or even due to other comorbidities [40].

In a task-based functional MRI (fMRI) study, Maurer et al. [39] have investigated the possible mechanisms underlying altered self-agency in a heterogeneous group of 35 patients with several FMD (including 43% with abnormal posturing) using resting-state fMRI. They found that, compared to the healthy controls, patients with FMD showed reduced functional connectivity between the right temporoparietal junction and the right sensorimotor cortex, cerebellar vermis, bilateral supplementary motor area, and right insula. They concluded that the reduced connectivity between the right temporoparietal junction and sensorimotor regions observed in these patients may support a pathophysiological model in which the impaired motor feed-forward together with the abnormal sensory feedback from sensorimotor areas to the right temporoparietal junction explains the impaired sense of self-agency reported from patients with FMD [39].

Espay and colleagues [18, 19] examined motor and emotional circuits in patients with FD, with isolated dystonia, and in healthy subjects. They found that FD subjects exhibited stimulus-dependent abnormal activation of motor preparation-related and execution-related networks, in spatial cognition, and attention control [18, 19]. These results support the concept of a network dysfunction in FD.

In a resting-state fMRI study, Canu et al. [8] examined the role of the affective-cognitive network in the two different FD phenotypes, fixed and mobile dystonia, compared to healthy subjects. Patients with fixed dystonia, showed a reduced functional connectivity in the cerebellar network, and between several sensorimotor and cognitive areas [8]. In conclusion, brain functional connectivity in the

affective-cognitive network is abnormal in patients with FD with differences between FD phenotypes.

Positron Emission Tomography (PET)

Schrag et al. [67] have investigated the role of the prefrontal cortex with PET functional neuroimaging of patients with FD and genetically determined dystonia (DYT1). Patients with FD showed excessive increase of blood flow in the cerebellum and basal ganglia, with reduction in the primary motor cortex (M1). Differently, isolated dystonia patients showed increase blood flow in M1 and thalamus, and decreases in the cerebellum, when compared with healthy subjects. When comparing FD with isolated dystonia patients, the former group showed increased blood flow in in the cerebellum and basal ganglia, whereas the latter group had increased blood flow in M1. Interestingly, the dorsolateral prefrontal cortex showed increased blood flow during movement execution in both FD and isolated dystonia, when compared to resting conditions. In sum, these data documented a cortical–subcortical demarcation between FD and isolated dystonia regarding regional blood flow, at resting states and during motor tasks. Also, abnormal prefrontal cortical activation was found in FD, although not specific for this condition. These results suggest that FD and isolated dystonia may share mechanisms of altered motor attention, but with different underlining pathophysiology [67].

Discussion

We have summarized the results of neurophysiological and neuroimaging data from studies on patients with FD as compared with isolated dystonia, highlighting both similarities and differences between FD and isolated dystonia. We will discuss how these abnormalities may modulate the expression of dystonic movements in FD, propose a network interpretation of FD pathophysiology, and discuss the current limits and research gaps in FD pathophysiology.

Neurophysiological Similarities and Differences between FD and Isolated Dystonia

Neurophysiologic studies demonstrated that patients with FD and with isolated dystonia share similar inhibitory abnormalities at the motor cortical and spinal levels as well as defective somatosensory processing. The neurophysiological similarities between FD and idiopathic dystonia support the hypothesis that the two conditions, share some common pathophysiological background or converge into a motor

system in overdrive, despite their differences in clinical phenomenology [23, 65]. Notably, as in isolated dystonia, impaired cortical and spinal inhibition and sensory processing abnormalities are often independent of dystonic symptoms, i.e., they are detected in the unaffected hemisphere, pointing to an endophenotypic predisposition. Hence, the above abnormalities of motor and sensory processing might represent traits, which needs other physiological, environmental, or psychological factors (e.g., stressful events and minor trauma) to produce the dystonic symptoms [32]. Alternatively, the pathophysiological similarities observed in FD and isolated dystonia may be interpreted because of dystonic posturing. It is well established that changes in sensory input cause both short- and long-term changes in the central nervous system [43]. A third possibility is that findings in both FD and isolated dystonia represent compensatory mechanisms.

One major neurophysiological difference between FD and isolated dystonia includes both excitability and plasticity mechanisms of M1. For example, SAI and LAI were the same in FD, isolated dystonia, and controls [4, 17, 54], whereas other studies suggested that there might be LAI abnormalities in patients with writer's cramp, but not in patients with cervical dystonia (CD) [1, 36]. Again, the abnormally enhanced M1-related plasticity in organic dystonia differs from the normal M1 plasticity in FD [54]. Finally, cerebellar involvement, as assessed by EBCC examination is another abnormality present in dystonia but not in FD [29, 31, 74]. These observations imply a selective involvement of specific pathophysiological features in FD and dystonia.

In summary, impaired cortical and spinal inhibition and altered somatosensory processing, possibly when combined with other psychological features, may either predispose individuals to develop FD or represent a consequence of the abnormal posturing. This statement is based on an assumption of reliability of neurophysiological measurements. However, it must be acknowledged that neurophysiological measurements are highly variable both under physiological conditions and in patients with movement disorders [37]. The causality is equally unclear in isolated dystonia, in which reduced cortical and spinal inhibition is associated with other excitability changes, such as LAI abnormalities and enhanced plasticity to manifest.

Relationship Between the Neurophysiological Abnormalities and the Clinical Manifestations of FD

There may be complex interactions between changes in the central nervous systems and dystonic posturing in FD. In the hypothesis of pre-existing endophenotypes, these changes may also play a role in producing the dystonic symptoms. Alternatively, dystonic posturing itself may induce changes in the central nervous system. Once developed, the central changes could participate in maintaining the pathologic process [18, 19].

Reduced inhibition at cortical level and in downstream motor effectors at the spinal cord may represent a basic pathophysiological alteration contributing to

abnormal muscle activation and cocontraction, possibly through the generation of abnormal sensorimotor connections [18, 19].

Altered sensory processing in FD possibly contributes to the development of dystonic posturing through altered body representation in patients with FD. For example, in the clinical setting, it has been described how patients with fixed dystonia report a normal ankle position with their eyes closed, whereas when their ankle was straightened, a feeling of "strange" position (sometimes even associated with disgust) appeared [72].

Dysfunctional Networks

Dystonia is increasingly considered as a disorder of distributed brain networks, that is, a motor disorder arising from the dysfunction of multiple connected brain areas, including but not limited to the connections of the basal ganglia to cortical areas, thalamus and the cerebellum resulting in abnormal neural motor programs [7, 23, 52, 62]. Despite the relatively lower number of pathophysiological studies in FD compared to isolated dystonia, it is plausible to hypothesize the presence of dysfunctional brain networks in FD (Fig. 1). Indeed, FD and isolated dystonia share, at least in part, the same clinical and physiological characteristics, and it is therefore reasonable to assume that these two conditions could also be underpinned, in part, by similar pathophysiological mechanisms and interpreted in the same motor control framework used for isolated dystonia [65].

For movement control, one dysfunctional network in FD is undoubtedly centered on M1, which encodes small movement fragments or "motor synergies" [63]. Reduced inhibition at the M1 level and in downstream motor effectors in the spinal cord, as well as altered sensorimotor processing, can be conceived as a basic pathophysiological alteration that may contribute to abnormal muscle activation and cocontraction, possibly perpetuated by abnormal sensorimotor connections. It should be noted, however, that these alterations have also been observed in patients in the cerebral hemisphere not directly affected by the dystonic phenomenon. This observation shows that they represent predisposing alterations for FD and that additional mechanism should be involved.

At the level of movement preparation, the mechanisms underlying conscious motor synergies appear to be unaltered in FD, as demonstrated by a normal *Bereitschaftspotential* [17]. However, there might be abnormalities at the selection of action control [63] possibly involving less explicit aspects of motor control. This would include altered connectivity between the limbic and motor networks [18, 19]. Additionally, there likely is an altered top-down regulation of motor activities and increased activation of areas implicated in self-awareness, self-monitoring, and active motor inhibition such as the cingulate and insular cortex. These possible abnormalities include the altered sense of agency. Indeed, a deficit in the sense of agency for movements is an appealing explanation for how movements that appear voluntary in nature (because they are altered by distraction) are experienced as

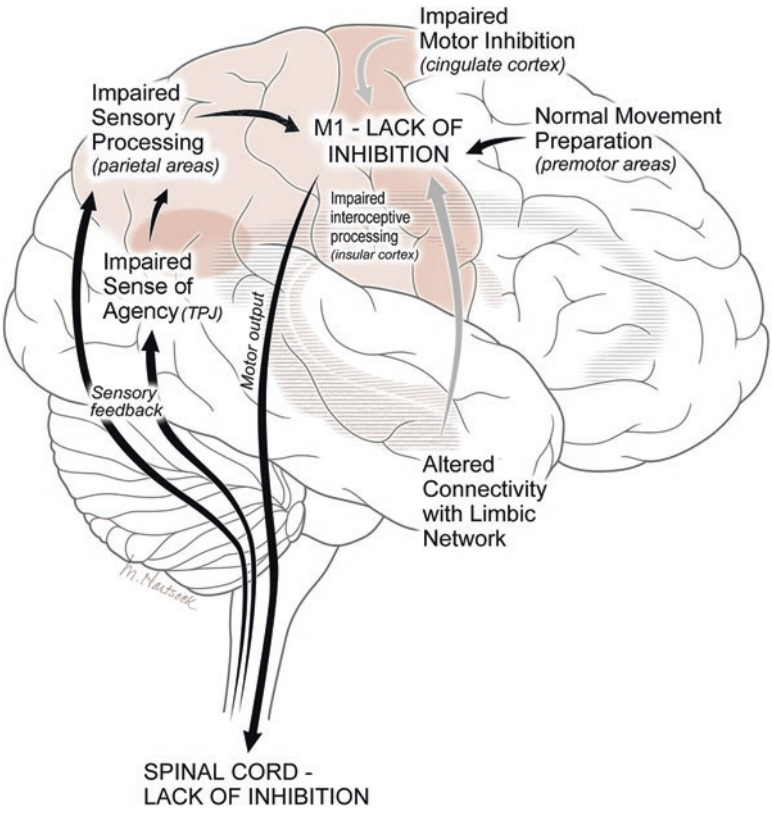

Fig. 1 Proposed dysfunctional brain networks in functional dystonia**.** Reduced inhibition at the primary motor cortex and spinal cord may contribute to abnormal muscle activation, possibly perpetuated by abnormal sensorimotor processing. Abnormalities in the selection of movements and sense of agency contribute to an altered connectivity between the limbic and motor networks. Additionally, there might be an abnormal top-down regulation of motor activities and increased activation of areas implicated in self-awareness, self-monitoring, and active motor inhibition such as the cingulate and insular cortices. M1, primary motor cortex; TPJ, temporoparietal junction

involuntary [5, 18, 19]. Supporting the role of impaired sense of agency in FD, in these patients, it has been observed hypoactivation of the temporoparietal junction [18, 19]. In this regard, the right temporoparietal junction is believed to serve as a general comparator of internal predictions/motor intentions with actual motor events resulting in disturbances in self-agency [23].

Implications for Treatment Options

The literature on possible therapeutic approaches specifically designed for FD remains scant. The use of physiotherapy for motor retraining has been shown to be effective in reducing motor symptoms in patients with FD and other FMD. The

physiotherapies are built on the rationale that abnormal movement patterns that develop outside of a patient's control, together with an increased level of self-directed attention, can be retrained [47]. These therapies can be delivered in an outpatient clinic setting or as an inpatient program in more severe cases where comorbidities complicate the clinical scenario requiring a multi/interdisciplinary team intervention (Lafaver & Ricciardi 2022).

Other treatment options that have been described are medications or other treatments that are well-established for movement disorders but which have their effect in FD via a placebo effect and not via the anticipated pharmacological effect of the drug. For example, the immediate response of patients with FD to botulinum toxin injections [13, 14]. In these cases, expectations and prior beliefs alter the sensory experience, becoming the basis for the placebo effect.

There is also scant evidence on the effect of motor cortex stimulation for FMD, and particularly for FD. Romito et al. [59] described a patient with fixed dystonia responsive to unilateral epidural motor cortex stimulation. The authors found a significant reduction of PET cerebellar glucose metabolism after cortical stimulation, suggesting a modulation of cerebellar function and, possibly, plastic reorganization of the cortical motor areas due to the modified cerebellar outflow to the motor cortex [59]. Other techniques as TMS and transcutaneous electrical nerve stimulation (TENS) have been employed in FMD [41]. As an example, Chastan and Parain [9] used TMS to treat patients with functional limb weakness with significant improvement. However, a placebo effect cannot be ruled out in these cases given the open-label, uncontrolled nature of these evaluations. A major problem with experimental approaches for therapeutic purposes in FMD and FD is that these are often not grounded on pathophysiological reasoning. This is nowadays unavoidable, as we do not yet have a thorough understanding of the FD pathophysiology. It is hoped that future scientific findings will provide the necessary basis for pathophysiology-guided therapeutic approaches. If we accept that FD and dystonia have, at least in part, a common pathophysiological background, therapeutic strategies in organic dystonia, such as sensory or motor training, could potentially be applied to those with FD.

Limitations

Apart from the methodological limitations inherent to the various experimental methods applied in FD, there are several specific factors that may have influenced the results of prior investigations. One critical issue concerns the diagnostic criteria for FD. In most studies, only a proportion of the patients were clinically definite cases, whereas the remainders were classified as probable, thus implying a possible recruitment bias. Because FD is relatively rare condition, most studies are based on limited samples, and therefore, it is not possible to draw firm conclusions because of such small numbers. Equally important, due to limited samples it is difficult to fully account the intersubject variability as well as heterogeneity of symptoms and

coexisting comorbidities. For example, FD patients generally do not present with isolated focal dystonia, making it difficult to adequately match the phenotypes of FD and organic dystonia. Moreover, many studies tested a mixed group of arm, neck and leg dystonia, possibly explaining the lack of specific deficits in FD, e.g., LAI. Moreover, the pathophysiological interpretation of experimental findings in FD is limited given the cross-sectional design of most studies and relatively long duration of symptoms in patients (usually, years). Thus, it is not possible to establish whether the neurophysiological abnormalities developed before, during, or as a consequence of the disease. Although theoretically possible, it is difficult to test FD patients shortly after symptom onset (days or weeks). To the best of our knowledge, there have been no longitudinal experimental studies in FD. Finally, it is worth noting that the similarities and differences between FD and isolated dystonia have only been reported at a group level; hence, their potential usefulness as an individualized diagnostic tool is not established [10, 18, 19, 54, 68].

Conclusions

The growing body of experimental studies in FD has revealed neurophysiological abnormalities at multiple levels in the central nervous system, including motor cortical and limbic areas and the spinal cord. FD shares some abnormalities with isolated dystonia, indicating a common pathophysiological or endophenotypic substrate. Abnormally enhanced cortical plasticity and altered EBCC may be tentatively useful to distinguish isolated dystonia from FD, in which these tests are normal, but these cannot yet be used reliably. Based on the available data, a unifying network model is difficult to draw; however, it can be hypothesized that dystonic symptoms in both FD and organic dystonia might rise from a combination of factors such as reduced intracortical and spinal inhibition contributing to abnormal muscle activation, possibly perpetuated by abnormal sensorimotor processing, impaired selection of movements, and hypoactive sense of agency in the setting of normal movement preparation but abnormal connectivity between the limbic and motor networks. Future studies, however, will be needed to delineate the reliability and the specificity of neurophysiological and neuroimaging abnormalities in FD as well as their relationship with clinical features, also in comparison to isolated dystonia, which are still largely unclear. In this regard, neurophysiological and neuroimaging assessments stand to provide further insights into the pathophysiological subtypes of FD and potential therapeutic implications.

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Neuromodulation in Dystonia – Harnessing the Network

Owen Killian, Michael Hutchinson, and Richard Reilly

Abstract Adult-onset isolated focal dystonia (AOIFD) is a network disorder characterised by abnormalities of sensory processing and motor control. These network abnormalities give rise to both the phenomenology of dystonia and the epiphenomena of altered plasticity and loss of intracortical inhibition. Existing modalities of deep brain stimulation effectively modulate parts of this network but are limited both in terms of targets and invasiveness. Novel approaches using a variety of non-invasive neuromodulation techniques including transcranial stimulation and peripheral stimulation present an interesting alternative approach and may, in conjunction with rehabilitative strategies, have a role in tailored therapies targeting the underlying network abnormality behind AOIFD.

Keywords Neuromodulation · Task-specific dystonia · Adult-onset isolated focal dystonia · Deep brain stimulation · Transcranial magnetic stimulation · Transcranial direct current stimulation · Peripheral stimulation

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Introduction

Adult-onset isolated focal dystonia (AOIFD), the third most common movement disorder, is a condition characterised by muscle contractions and abnormal posturing. It encompasses a range of different phenotypes of which cervical dystonia is the most common [2]. Although the pathogenesis of AOIFD remains poorly understood, several hypotheses exist. Waddy et al. [102] have suggested that there is a genetic basis, and further studies have supported a shared genetic component across AOIFD phenotypes [14, 20, 93] with a reduced penetrance, that is to say, a majority of carriers do not manifest the condition. A model of polygenic factors interacting with environmental and other determinants giving rise to specific phenotypes has thus been developed. This is borne out by observations of dystonic phenotypes being differentially expressed across a range of ages of onset [70], geographies [104], and sexes [15, 104]. Evidence of reduced intracortical inhibition [45] and altered (excessive) plasticity [74, 84] in Dystonia abounds and represents one of the earliest models of AOIFD. It is unclear however about the directionality of the causation seen between the dystonic phenotype and these changes in neuroplasticity. More recently, it has been suggested that these phenomena may in fact be an epiphenomenal secondary endophenotype of an underlying network disorder [38].

More recent work has attempted to understand the elements of this network as they relate to different subtypes of Focal Dystonia which has helped us to understand the deficits underpinning Dystonia as distinct from signals which are not causal and common to other movement disorders. Of these, two particular models bear particular consideration: the motor control model in task-specific Dystonias, abnormalities of temporal discrimination threshold underpinning a subcortical-basal ganglia network.

Given that Dystonia is a painful and disabling disorder, neuromodulation through the use of deep brain stimulation (DBS) is an intervention typically reserved for severe and drug-refractory cases [22, 65]. A recent Cochrane Systematic Review [79] demonstrated that DBS of the internal globus pallidus nucleus may reduce symptom severity and improve functional capacity in adults with cervical, segmental, or generalised moderate to severe Dystonia and may improve quality of life in adults with generalised or segmental Dystonia. However, neuromodulation (whether invasive with DBS or non-invasive) presents an opportunity to target the subcortical-basal ganglia network with a view to further elucidating the nodes involved and how they interact, and, moreover, to develop novel therapeutic strategies to modulate these network abnormalities with a view to treating the process underlying AOIFD rather than palliating the symptoms thereof. This chapter will provide an overview and pose questions on the use of neuromodulation as a means to probe networks implicated in AOIFD but also to open opportunities to harness the network as part of neurorehabilitation strategies.

Dystonia as a Disorder of Motor Control

Task-specific Dystonias such as Writer's Cramp and Musician's Dystonia (among others) represent a subtype of Dystonia in current classification systems [2]. However, the distinct phenomenology of task specificity gives rise to dystonic posturing in the context of specific patterned and characteristically highly-rehearsed movements (as with scalic passages in pianist's Focal Hand Dystonia or holding a pen in Writer's Cramp) leaving other patterned fine motor movements unaffected at least early in the disease course [35]. This subgroup of Dystonia poorly correlates with markers of enhanced plasticity or abnormal sensorimotor integration as noted in Kassavetis et al. [45] with respect to intracortical inhibition and in Bradley et al. [12] with respect to abnormal sensory processing. While further analysis with larger sample sizes of this clinically heterogeneous group has identified enhanced sensory processing in control musicians as a potential confounder [46, 62], this does not answer the question of pathomechanism. Sadnicka et al. [90] describe a model for understanding task-specific Dystonia based on our understanding of motor skill learning.

In health, motor learning allows us to become more accurate and faster (more effective) at a given task through the 'chunking' of fragments and elementary motor components that comprise a learned movement sequence into a single representational unit within a hierarchical neuronal network; this further allows the task to be completed more economically. While this is ideal for a highly rehearsed movement that is required to be executed accurately and rapidly, the 'chunking' that achieves this efficiency by obviating the need to individually select each fragment in sequence also carries specific disadvantages: more automatic movement sequences that lack flexibility and cannot respond effectively to changes in the capacity of peripheral systems to execute them. Further, these more automatic movements cannot error-correct and, should an aberrant dystonic movement arise, are likely to integrate and encode that movement as part of the motor programme. Sadnicka et al. [90] argue that the highly rehearsed movements of classically trained musicians for example develop over the course of rigorous, demanding practice of long, complex and stereotyped motor sequences. While in early practice phases, movements are selected and executed at high computational cost in a 1:1 fashion from the top to the bottom of the motor control network, as practice progresses, increasingly longer 'chunks' of a motor sequence are selected and executed with a greater degree of automaticity through intermediary levels within the hierarchy, thus achieving a lower computational cost [21]. Advanced levels of highly specific practice result in longer and longer chunks which are both increasingly efficient and context-specific [76]. The narrower the practice repertoire, the less readily these rehearsed efficiency gains are translated to other tasks [10]. This correlates well with the psychological and ecological characteristics of musician's suffering from task-specific Dystonia whose practice prior to the development of Dystonia is typically highly intensive and restricted [82].

Critically, the factors driving the development of Dystonia can be central, peripheral, task-, and tool-specific. A precipitating event such as injury or a change in technique is often noted prior to the development of task-specific Dystonias. This precipitating event gives rise to a mismatch in motor control between the highly rehearsed movement selected and the actual motor response required. This can readily be compensated for if alternative motor fragments can be recruited but if this cannot be attained, novel motor control strategies must be deployed which are inherently less practised and cannot be executed to the same standard of the highly rehearsed movements [91]. This is attentionally draining and computationally inefficient. When combined with psychological factors such as anxiety, perfectionism, and 'choking under pressure', this can interfere with planned movements in a manner that gives rise to Dystonia [23]. Sadnicka et al. [91] speak to the relevance of this model in the process of prevention and rehabilitation of task-specific Dystonias as by avoiding maladaptive practice techniques and through techniques such as Sensory Motor Retuning which attempts not to 'solve' the dystonic movements but rather to introduce continuous variations in practice technique (neither focusing on variations which are technically relevant or on the quality of the sound produced) specifically to facilitate motor reorganisation [80, 91].

This model of motor control coheres well with the existing literature relating to task-specific Dystonias; however, the relevance of abnormalities in motor control and learning is less clear in the case of other Dystonia phenotypes. Jinnah and Hess [42] provide a concise overview of the existing evidence supporting the model that dysfunction at one or more points in the motor control network give rise to a variety of primary and secondary Dystonias. They observe that it remains unclear whether Dystonia arises from one or other of dysfunction in one or more nodes or from abnormal communication between nodes. Evidence exists from both animal models and specific Dystonia syndromes for single and multi-focal lesions in the midbrain [36], thalamus, cerebellum [72], and basal ganglia [55] giving rise to Dystonia. Blepharospasm too can be considered an overuse phenomenon in a manner somewhat similar to the task-specific Dystonias whereby (as the environmental component of a two-hit process) sun exposure represents a risk factor for the development of Blepharospasm [67]. This is clearly not a phenomenon related to maladaptive highly-rehearsed motor skill learning but nevertheless links motor control to the development of another phenotype of focal Dystonia. The cerebellum too appears to have a role in mediating motor learning and control in the context of Dystonia as in Hoffland et al. [34] who looked at cerebellar sensorimotor adaptation and found it to be abnormal in both Writer's Cramp and Blepharospasm but not Cervical Dystonia. However, while evidence of abnormal cerebellar associative motor learning (as tested by eye-blink classical conditioning) seems to be seen across all tested phenotypes including Cervical Dystonia [33, 96], Sadnicka et al. [87] cast further doubts on the mediational role of the cerebellum in Cervical Dystonia and indeed cerebellar dysfunction may in fact even be compensatory in the context of primary Dystonia [85]. What role if any the cerebellum has in mediating or responding to abnormalities of motor control in Dystonia remains unclear.

While abnormalities in the brain networks underpinning motor control and learning appear central to the pathophysiology of AOIFD, beyond the purely task-specific Dystonias (which must additionally be mediated by psychological, environmental and peripheral sensory factors), abnormalities of sensory processing have also been noted in both task-specific and other AOIFD phenotypes. These may contribute to the evolution of the disorder, potentially through maladaptive sensori-motor integration.

Dystonia as a Disorder of Sensory Processing

The sensory aspects of primary focal Dystonia have long been understood. The *geste antagoniste* (sensory trick) represented an early target for treatment [26] and a feature pathognomonic for Dystonia [73] but further speaks to the sensory element of Dystonia. Distortion of the cortical sensory representation of the hand has been found in Focal Hand Dystonia where a loss of GABA-mediated surround inhibition of cortical neurons reduce the regional specificity of the cortex with adjacent fingers blurring into each other [71]. This has been considered as contributing to the poorer spatial discrimination seen in many with Focal Dystonia [66]; however, subsequent attempts to evaluate sensorimotor cortical representations of fingers in Musician's dystonia have not demonstrated these findings [91].

Metrics of sensory processing such as Spatial Discrimination Threshold (SDT; the shortest distance interval at which two stimuli can be recognised as spatially separate) and Temporal Discrimination Threshold (TDT; the minimum interstimulus interval at which subjects can recognise a pair of stimuli as separate) have been observed to be abnormal in primary focal Dystonia [11, 12, 48, 103].

The TDT score is known to increase with age; this increase exhibits sexually dimorphic differences with young women having lower TDTs than young men and older women having higher TDTs than older men [15, 103]. The male-predominant Dystonia phenotypes (such as Focal Hand Dystonias) are also noted to occur at younger onset ages than the female predominant forms (such as Cervical Dystonia) which predominate at older age [15, 103].

Abnormal TDT is a sensitive marker for AOIFD (86%, rising to 97% in Cervical Dystonia), and there exists a clear pattern of autosomal dominant inheritance of abnormal TDTs in families with more than one Dystonia sufferer, lending credence to the mediational endophenotype model [12, 48]. Voxel-based morphometry (VBM) studies have demonstrated increased putaminal volume which correlates with abnormal TDT in AOIFD patients [11]. Cervical dystonia patients and their relatives with abnormal TDTs demonstrated significantly reduced activations in their superior colliculi on functional MRI [64].

Abnormal TDT can be considered a mediational endophenotype: its presence being necessary for the development of AOIFD and being part of a genetically-mediated network abnormality which can result in disease manifestation, with age and environmental interactions such as trauma, overuse, stress, and other factors

influencing manifestation risk [38]. Mechanistically, abnormal TDT seems to stem from a deficit in a neural network incorporating the superior colliculus and basal ganglia which responds to novel environmental stimuli [38].

Another study of TDT which used alternative methods to distinguish sensory processing and cognitive tasks the effect of which are combined in more traditional procedures for testing TDT failed to find a difference in temporal processing between patients with AOIFD and controls [88, 89]. This study raised the possibility of altered decision-making underpinning the findings observed in prior studies of TDT in Dystonia [87]. This finding certainly merits further exploration in order to better elucidate the nature of the underlying abnormality giving rise to abnormal TDTs in AOIFD patients and their relatives and how this relates to the abnormalities found in the putamen and midbrain which correlate with abnormal TDT.

Taken together, the evidence discussed represents a strong case for AOIFD being a network disorder with abnormal sensory processing, motor control, and sensorimotor integration being central to this [89]. The key to more effective targeted therapies lies in leveraging these networks, an approach which is best achieved through neuromodulation [98].

Neuromodulation – Interfacing with the Network

Electrical stimulation of the nervous system has a history dating back to antiquity with the use of the torpedo fish applied externally to treat pain [29]. In the nineteenth century, faradisation was employed with peripheral stimulation of the affected muscle and its antagonist with varied success [26]; however, distinction between true cases of dystonia and cases of functional neurology among reports treated with peripheral electrotherapy is challenging. In contemporary practice, neuromodulation can be divided into invasive and non-invasive methodologies; deep brain stimulation, transcranial neuromodulation, and peripheral stimulation will be discussed here.

Deep Brain Stimulation: The Primacy of the Basal Ganglia

Deep Brain Stimulation (DBS) in Dystonia developed from pallidotomies initially carried out for Parkinson's disease (PD) which demonstrated efficacy in reducing rigidity, dyskinesias, and freezing phenomena [56, 94]. On this basis, pallidotomies were trialled in generalised Dystonias with positive outcomes [39]. While practice has favoured DBS over pallidotomy in PD due in part to the inherent adjustability and reversibility of DBS, no such randomised controlled trial has compared lesioning with DBS in Dystonia [3, 99].

DYT-*TOR1A*-related Dystonia responds very well to DBS of the internal segment of the globus pallidus [51, 52, 54, 59] whereas in AOIFD outcomes are more variable but generally favour those with younger ages of onset [105] and durations of symptoms [59, 60]. Of note, secondary and neurodegenerative Dystonias in particular those associated with cerebral palsy tend to respond less well to GPi DBS [25] with Tardive Dystonia being a notable exception to this [19, 101]. Indeed, combined Dystonias with associated non-dystonic neurological features tend to respond less well to GPi DBS [24, 77].

The efficacy of GPi DBS in the management of both TOR1A Dystonia and AOIFD allowed insight to be gleaned into the mechanism of this effect using Transcranial Magnetic Stimulation (TMS). An early study on this by Tisch et al. [97] demonstrated that a paired associative stimulation protocol, which in Dystonia typically demonstrates increased motor cortex plasticity versus healthy controls [75], caused a switch to increased cortical inhibition versus healthy controls with GPi stimulation ON. This effect disappeared with GPi OFF, resulting in equivalent levels of cortical plasticity in both healthy controls and they Dystonia patients.

This was subsequently looked at longitudinally pre- and post-DBS by the same group who found that as expected where were reductions in short latency intracortical inhibition and increases in motor cortex plasticity in Dystonia patients prior to DBS. Shortly after DBS, plasticity was abolished and intracortical inhibition had somewhat increased but by 3 and 6 months there was still further improvement in intracortical inhibition and an increase to normal levels of cortical plasticity [83]. These findings correlate nicely with the reported gradual improvement in clinical symptoms of Dystonia patients post-DBS over time [100]. One possible mechanism to account for this clinical improvement is the reduction in pre-motor cortical activation seen (likely through potentiation of thalamocortical inhibition) in subjects with GPi DBS [53].

It is worth noting that a study of temporal processing in a cohort of Cervical Dystonia patients with implanted GPi DBS demonstrated no improvements in TDT despite good clinical outcomes [86]. This has been hypothesised to be due to the fact that GPi DBS exerts its therapeutic effect downstream of these temporal processing abnormalities. Thus, while GPi DBS can modulate cortical plasticity, it does not remediate the network abnormalities underpinning the Dystonia itself.

There is much to commend the DBS approach and other stimulation targets of significance for dystonic tremor and Focal Hand Dystonia. DBS carries with it the risks of invasive neurosurgical procedures in addition to the potential for hardware-associated complications [40, 62]. There are abiding questions regarding patient selection for lesioning versus stimulation depending on factors such as surgical fitness, prior complications, patient preference and reversibility [43, 69]. However, the development in recent years of non-invasive methods of electrical neuromodulation has opened up a new avenue for potential therapies in movement disorders which are flexible enough to target many nodes in the network without the need for surgical intervention.

Non-invasive Neuromodulation in Dystonia – Harnessing the Network

Non-invasive approaches to neuromodulation are an emerging field in the research and treatment of network disorders with repetitive transcranial magnetic stimulation (rTMS) by far the most established as a research tool with therapeutic applications. The relevance of these methods of neuromodulation to movement disorders in general and dystonia in particular has been thoroughly reviewed by Erro et al. [27], Latorre et al. [57], and most recently by Ganguly et al. [31]. The FDA has approved the use of transcranial magnetic stimulation (TMS) in drug-resistant major depressive disorder which is now well established as a network disorder [57]. See Table 1 for a summary of the studies discussed in this section.

rTMS mediates its effect through a variety of patterned trains of pulses of magnetic field generated by an induction coil placed on the scalp. The pulses are short and therefore likely act exclusively on cortical and superficial subcortical structures.

Table 1 Selected studies and review articles of non-invasive neuromodulation in dystonia

First author	Year	Type	Modality	Phenotype	Outcome
Erro	2017	Review	TMS, TCS, TENS	CD, FHD	See text
Latorre	2019	Review	TMS	Mixed	See text
Ganguly	2020	Review	tDCS, tACS	CD, FHD	See text
Siebner	1999	Open-label study	rTMS to M1	FHD	Reduced writing pressure
Kimberley	2015	Randomised sham controlled	rTMS to dPMC	FHD	No objective benefit
Borich	2009	Crossover	rTMS to PMC	FHD	Sustained objective improvement in handwriting
Koch	2014	Sham controlled	TMS to cerebellum	CD	Transient reduction in TWSTRS
Kranz	2010	Sham controlled	rTMS to cingulate	Blepharospasm	Transient clinical improvement
Marceglia	2017	Two cases	Bilateral cathodal tDCS to MC	MD	Self-reported improvement in symptoms
Bradnam	2015	Sham controlled	Anodal tDCS to cerebellum	FHD	No change
Angelakis	2013	Single case	tDCS-tACS combination to MC	CD	Reduction in TWSTRS and pain scores

CD Cervical Dystonia, *dPMC* dorsal premotor cortex, *FHD* Focal Hand Dystonia, *MC* Motor Cortex, *MD* Musician's Dystonia, *PMC* Premotor Cortex, *tACS* transcranial Alternating Current Stimulation, *TCS* Transcranial Stimulation, *tDCS* transcranial Direct Current Stimulation, *TENS* Transcutaneous Electrical Nerve Stimulation, *TMS* Transcranial Magnetic Stimulation, *TWSTRS* Toronto Western Spasmodic Torticollis Rating Scale

The repetitive train of pulses replicates the techniques of direct stimulation used to generate long-term potentiation (LTP) through high-frequency stimulation or long-term depression (LTD) through lower-frequency trains [7]. This impact on plasticity is typically transitory [37] but if repeated over multiple sessions results in a more permanent plastic change [1].

While deeper subcortical structures such as the basal ganglia cannot be directly stimulated through current modalities of non-invasive neuromodulation, the cortical nodes of the relevant networks can be targeted which in turn results in demonstrable changes in these deeper structures. TMS of the dorsal pre-motor cortex has been shown to increase BOLD signal on fMRI in the striatum [6]. Thus, TMS has a role in modulating networks with cortical nodes involved in a variety of neurological conditions.

However, to date, therapeutic trials of TMS have demonstrated short-lived and inconsistent improvements. Erro et al. [27] performed a systematic review of studies of TMS, Transcranial Current Stimulation (TCS), and Transcranial Electrical Nerve Stimulation (TENS) in both Focal Hand Dystonia and a mixed group of Blepharospasm and Cervical Dystonia subjects. In the former group, studies evaluating single sessions of low-frequency (inhibitory) rTMS over the contralateral M1 Motor Cortex and pre-motor cortex demonstrated heterogeneous clinical improvements such as reduction in writing pressure with intracortical inhibition normalising in parallel with this [92]. The clinical improvement was not sustained; however, single session studies and other studies evaluating pre-motor cortex stimulation gave conflicting results. Studies evaluating outcome after multiple sessions demonstrated in longer-lived clinical improvements but again conflicted with some demonstrating subjective improvements alone after pre-motor cortex stimulation [47] and others demonstrating objective handwriting improvements over 10 days [9].

The review by Erro et al. [27] also identified improvements in clinical outcome in Cervical Dystonia patients using cerebellar continuous theta burst TMS [49] and in blepharospasm with low-frequency rTMS of the cingulate cortex (where they targeted the point of maximal motor evoked potential of the orbicularis oculi muscle [50]. In the former, repeated sessions over 2 weeks were used, and the improvement did not persist at 2 week follow-up. In the latter, only a single session of TMS was utilised.

Erro et al. [27] observed that due in part to clinical heterogeneity of the subjects involved in these studies and limitations in the sensitivity of the objective scales used to evaluate improvement, some benefits being observed particularly as self-reported by patients may be overlooked. The preliminary studies reviewed, while contradictory, suggest there is further scope for exploring more long-term interventions with TMS. Given what we know about the mechanism of action of TMS and the delayed clinical improvement associated with GPi DBS, studies with a greater number of TMS sessions combined with more sensitive kinematic analysis may have merit.

Beyond TMS, there are four other techniques for non-invasive neuromodulation which are relevant to this discussion: transcranial Direct Current Stimulation(tDCS), transcranial Alternating Current Stimulation(tACS), transcranial Random Noise

Stimulation (tRNS), and transcranial Pulsed Current Stimulation (tPCS). In much the same manner that there is shift from inhibition to excitation with increasing frequencies of rTMS, the cortical sequelae of the stimulation in tDCS are dependent on which electrode is stimulating. Anodal tDCS increases excitability, whereas cathodal tDCS decreases excitability [18].

tACS and tPCS differ in that the former utilises sinusoidal alternating current waveforms to entrain oscillations whereas the latter utilises monophasic rectangular pulses. tRNS as the name suggests makes use of a signal which is random, with both frequency and amplitude varying constantly [18]. To date, tPCS and tRNS have not been evaluated in Dystonia.

In their recent review article, Ganguly et al. [31] report and evaluate the existing literature on tDCS and tACS in AOIFD. Of note, a small pilot study ($n = 2$) evaluating bilateral cathodal tDCS applied to both premotor cortices in Musician's dystonia demonstrated self-reported improvements in symptoms after 5 consecutive days of stimulation [63]. Anodal tDCS over the ipsilateral cerebellum improved kinematic measures of handwriting in a small cohort ($n = 8$) with Focal Hand Dystonia [13]. These were both small studies and there is conflicting evidence of nil effect from other studies as reviewed by Ganguly et al. [31].

tACS was evaluated by Angelakis et al. [4] in a single subject study which used a combined approach of first cathodal tDCS of the motor cortex for five days followed by tACS also for five days. This approach resulted in a 54% reduction in the Toronto Western Spasmodic Torticollis Rating Scale with improvements in reported pain also. The effect persisted for at least one month. This benefit likely relates to the observed tendency for tACS to decrease the amplitude of motor evoked potentials and exert an inhibitory influence on cortical networks.

Our own experience of tDCS focused on attempts to alter temporal processing in a cohort of healthy controls in order to assess the ability of this technique to modulate the network underpinning Dystonia upstream from the cortical and clinical manifestations. Previous research has demonstrated that neuromodulation of the Frontal Eye Field (FEF) modulated sensory processing [78] in the visual cortex and attentional orienting [68] via its connections to the superior colliculus. Primate studies involving reversible inactivation of either the FEF or the Superior Colliculus were also noted to result in similar declines in detection performance in covert attention tasks [8]. The application of an anodal transcranial current stimulus to the FEF has been shown to facilitate saccade generation and improve midbrain sensory processing contralaterally [44].

In a protocol adapted from Kanai et al. [44], we delivered anodal stimulation to the left Frontal Eye Field for 20 min. There was a tendency towards reduction in TDT from before stimulation to after stimulation which was not significant. Sham stimulation was also trialled in two subjects in order to discount the possibility of a practice effect but a further larger study would be required to effectively observe this as significance was not attained.

The bulk of research on non-invasive neuromodulation in Dystonia targets either the motor or pre-motor cortices or cerebellum. Given the presence of a mediational endophenotype in the form of abnormal temporal processing and the complexity of

the network affected in Dystonia, consideration ought be given to other targets which have the capacity to influence sensory processing in future studies.

Taken together, however, these studies make a compelling argument for further larger and more prolonged studies evaluating transcranial stimulation modalities in AOIFD; however, it is clear that sensitive scales perhaps with the aid of kinematics will be required to accurately quantify the effect of the intervention. Moreover, given the conflicting findings between studies which target the same brain regions, judicious selection and optimisation of stimulation parameters will also be required. Given the putative therapeutic mechanisms of these non-invasive stimulation approaches in modulating diffuse brain networks indirectly and directly targeting cortical plasticity, a combination approach may be best suited which pairs neuromodulation, to overcome the maladaptive plasticity of Dystonia, with a retraining or biofeedback approach.

Closing the Loop – Combining Neuromodulation Strategies with Rehabilitation

Quite apart from the sensory processing abnormalities which appear to underpin the Dystonia phenotype, there is emerging evidence of significant sensory components among the non-motor symptoms identified in Dystonia. Pro-dromal sensory symptoms preceding onset of Dystonia such as neck stiffness in Cervical Dystonia and dry eyes in blepharospasm have been reported [32] in addition to the sensory relevance of the *geste antagoniste*. Considering these features in addition to the aforementioned sensory processing abnormalities, the network abnormalities that typify Dystonia clearly manifest sensory symptoms and moreover, in the case of the *geste*, are capable of being modulated by sensory inputs [95].

Thus, while the model proposed by Sadnicka et al. [89, 90] for task-specific Dystonia as discussed earlier talks about central, peripheral, task, and tool-related factors influencing the Focal Hand Dystonia of pianists, for example, it is likely that there are at least central and peripheral factors at play in non-task-specific Focal Dystonia. It is also worth observing that both peripheral and central sensory lesions can give rise to secondary Dystonias as with thalamic lesions [58] and in cases of peripheral trauma [41]. Increasingly, therefore, researchers are evaluating methods to optimise neurorehabilitative approaches, already well-established in task-specific Dystonia such as Sensory Motor Retuning for Musician's dystonia as developed by Candia et al. [17], through adjuvant non-invasive neuromodulation techniques [80, 81].

Furuya et al. [30] trialled the use of bilateral tDCS to the motor cortices in pianists with Focal Hand Dystonia who were undergoing a programme of motor retraining. They observed an improvement in the rhythmic accuracy of sequential finger movements in subjects with Focal Hand Dystonia but not healthy controls. Critically, sham stimulation and reversed montage stimulation (where anodal rather

than cathodal stimulation was applied to the affected cortex) resulted in no improvement nor did the intended stimulation montage if it was performed without concurrent motor training. The combined approach was essential to the benefit which was sustained at least 4 days post-stimulation. This bilateral approach with cathodal inhibition of the affected cortex and anodal facilitation of the unaffected cortex promoting transcallosal inhibition appears optimised to prime the affected cortex for the benefits of retraining.

Buttkus et al. [16] evaluated tDCS to the contralateral motor cortex in combination with a retraining technique of slow controlled keyboard movements in pianists with Musician's Dystonia. No benefit was seen with anodal or cathodal stimulation but only a single session was utilised in this study as compared with repeated sessions in the previously discussed paper which may indicate the inadequacy of a single session of tDCS to meaningfully alter the maladaptive plasticity engrained in the brains of Musician's Dystonia patients whose highly rehearsed movements have given rise to a highly reinforced pathological motor programme.

Rosset-Llobet and Fàbregas-Molas [80] evaluated a 2-week programme of Sensory Motor Retuning and biparietal tDCS. The group undergoing active stimulation demonstrated a significant improvement in Dystonia severity score versus sham (although both groups were significantly improved from baseline).

Additional approaches to neurorehabilitation may offer even greater opportunity to leverage the potentiating effects of transcranial Electrical Stimulation. By way of example, Atashzar et al. [5] presented a haptic feedback device to reduce the received sensation of rigidity emanating from the writing surface. This device was trialled in a cohort of patients receiving botulinum neurotoxin injections for Writer's cramp. The use of this feedback device reduced the severity of Dystonia symptoms and grip pressure versus a regular pen and moreover enhanced the degree of improvement arising from Botulinum toxin alone. Such biofeedback approaches are prime candidates for incorporation with a neuromodulation-based approach.

While biofeedback and neuromodulation montages tailored to the Dystonia phenotype of an individual patient represents a key domain for future research, recent work by Erro et al. [28] reinforces the significance of attending to the peripheral nervous system when addressing the network pathology of AOIFD. Having noted that high-frequency patterned peripheral stimulation of a body part (such as the index finger) improves somatosensory TDT at the affected site while potentiating intracortical inhibition, they found that the same high-frequency stimulation caused reductions in intracortical inhibition in both the somatosensory and primary motor cortices and a worsening TDT. Given that low-frequency stimulation in healthy controls results in worsening spatial discrimination, they trialled a paradigm of low-frequency peripheral stimulation in a cohort of Cervical Dystonia patients which gave rise to a normalised somatosensory TDT and moreover enhanced intracortical inhibition in somatosensory and primary motor cortices. The fact that the effects of low-frequency peripheral stimulation extended to both sensory and motor areas gives further credence to the notion that abnormal sensory processing and sensorimotor integration may be a necessary precursor to give rise to the abnormal motor programmes which manifest as Dystonia. Moreover, that these changes arose from

peripheral stimulation of an unaffected body part (the index finger of Cervical Dystonia patients) suggests this processing abnormality to be an underlying network-wide phenomenon which precedes the development of Dystonia potentially after a 'second hit', environmental or otherwise. If the changes induced by such peripheral stimulation are found to persist, they may represent an alternative approach to targeting the maladaptive plasticity and potentially addressing motor symptoms.

Conclusions and Future Research Questions

To date, studies evaluating combined approach non-invasive neuromodulation and neurorehabilitative strategies have focused on tDCS and evaluated protocols for stimulation which are agnostic to the patient phenotype. Moreover, the focus on tDCS has neglected the relevance of other novel modalities of transcranial electrical stimulation. Clarifying the specifics of the network abnormalities and correlating them with Dystonia phenotype and the individual parameters of a particular patient may allow us to more accurately target the network abnormalities underpinning the clinical picture. If the observed benefits can be maintained and the effect size is adequate, a personalised treatment combining retraining methods (perhaps incorporating biofeedback) with priming of the cortex through novel modalities of transcranial stimulation that are specific to the Dystonia phenotype may allow us to directly treat the network disorder that is Isolated Focal Dystonia with techniques which are definitive, non-invasive, safe, and well-tolerated.

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The Collicular–Pulvinar–Amygdala Axis and Adult-Onset Idiopathic Focal Dystonias

Shameer Rafee, Michael Hutchinson, and Richard Reilly

Abstract Adult-onset idiopathic focal dystonias (AOIFD) are the most common type of dystonia. It has varied expression including multiple motor (depending on body part affected) and non-motor symptoms (psychiatric, cognitive and sensory). The motor symptoms are usually the main reason for presentation and are most often treated with botulinum toxin. However, non-motor symptoms are the main predictors of quality of life and should be addressed appropriately, as well as treating the motor disorder. Rather than considering AOIFD as a movement disorder, a syndromic approach should be taken, one that accommodates all the symptoms. Dysfunction of the collicular–pulvinar–amygdala axis, with the superior colliculus as a central node, can explain the diverse expression of this syndrome.

Keywords Focal dystonias · Collicular–pulvinar–amygdala axis · Superior colliculus · Non-motor · Mood disorders

Introduction

Dystonia results from involuntary, uncoordinated contractions of agonist and antagonist muscles with excess activity of surrounding muscles, causing abnormal posturing of the affected area. Dystonia can be associated with tremor. An expert consensus group definition in 2013 agreed that: '*Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically*

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patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation' [1].

Dystonic disorders are a rare, heterogeneous group of hyperkinetic motor disorders encompassing a range of relatively mild focal dystonias to severe, generalised, disabling forms. They are typically classified into idiopathic, genetic or secondary forms (e.g. medication induced dystonias) and can be divided by anatomical distribution (Table 1) [2].

Adult-onset idiopathic focal dystonia (AOIFD), with onset after the age of 20 years, is the most common form of dystonia, and can present as focal hand dystonia (FHD), cervical dystonia, blepharospasm, oromandibular dystonia, orofacial dystonia, laryngeal dystonia or limb dystonia. Abnormal posturing can also occur during specific voluntary activities and are known as task-specific dystonia, e.g., writer's cramp (also named FHD) and musician's dystonia [2].

AOIFD is a rare disorder with reported prevalence ranging from 17.8×10^5 in Ireland [3] to 29.5×10^5 in Minnesota, USA [4]. The genetic aetiology of AOIFD is complex, and specific contributory genes remain to be identified. A family study of patients with blepharospasm and craniocervical dystonia show a pattern of distribution that is autosomal dominant with reduced penetrance [5]. A larger study, including patients with writer's cramp (FHD), noted a similar, likely autosomal dominant inheritance with low penetrance [6]. The actual penetrance across the subtypes of AOIFD can be difficult to ascertain until genes resulting in the varied phenotypes are identified.

Disease penetrance and phenotypic expression probably depend on environmental influences (see below). Dystonic movements are aggravated by voluntary movements, fatigue and stress. The motor features disappear during sleep [7]. At onset, AOIFD typically affects one body part, but spread to other adjacent anatomical sites (segmental spread) over years can occur. Some types of AOIFD, like blepharospasm, have higher risk of spread, usually to the neck muscles. Risk is highest in the first few years of onset, and other factors like family history and alcohol responsiveness also increase risk [8].

AOIFD is poorly recognised by non-neurologists. To the neurologist, AOIFD presents primarily as a movement disorder. However, there is accumulating evidence that the syndrome of AOIFD, when fully expressed, consists of (a) the movement disorder, (b) psychiatric symptoms, (c) cognitive changes as well as (d) sensory and subclinical abnormalities. It is these non-motor features, in particular anxiety and depression, that are the main predictors of quality of life [9]. Here we suggest that a network model, specifically involving the collicular–

Table 1 Classification of dystonia distribution

Focal	One part of the body
Multifocal	Two or more non-contiguous parts
Segmental	Two or more contiguous parts
Generalised	Affects limb or limbs, trunk and one other region

pulvinar–amygdala axis, would provide an anatomical and functional explanation for the spectrum of this disorder.

Non-genetic Influences on AOIFD Phenotype Expression

It is hypothesised that asymptomatic gene carriers of gene mutations in AOIFD develop dystonia, triggered by certain environmental exposures. Risk factors like head and body trauma, respiratory tract infections, eye infections have all been implicated in both disease penetrance and disease expression in AOIFD. Scoliosis, road traffic collisions requiring hospital admissions and surgical procedures are significant risk factors for development for cervical dystonia [10]. Childhood measles and mumps has a strong connection with spasmodic dysphonia. Psychological stress may act as a trigger [11]. Sunlight exposure and anterior segment eye disease confers a risk of development of blepharospasm. Coffee consumption may be protective. Excessive blinking due to xerophthalmia is linked with blepharospasm and Meige syndrome. Chronic sunlight exposure may lead to persistent straining of the orbicularis oculi muscle. High insolation (exposure to solar rays) as a risk factor for blepharospasm may be related to an overuse phenomenon, similar to what is seen in task-specific dystonias, such as writer's cramp [12].

The Adult-Onset Idiopathic Focal Dystonias: The Motor Disorder

Cervical Dystonia (CD)

This is the most common form of AOIFD and is sometimes described as 'spasmodic torticollis'. However, this is a misnomer as it is not always associated with spasms. The symptoms are insidious in onset, with patients reporting 'pulling in the neck' resulting in abnormal posturing. Most patients have a degree of constant head deviation at rest. Torticollis is the most frequently seen abnormal posture, followed by laterocollis, retrocollis and anterocollis. Often, more than one of these abnormal positionings are present, creating complex head and neck posturing. Up to 30% of patients have associated head and neck tremor [13]. Palpation of the neck can reveal an expanded neck; muscle stiffness and hypertrophy is a useful tool in identifying dystonic muscles. Muscle weakness is rare and, if present, suggests an alternative cause. An exception to this would be weakness following botulinum toxin therapy. Flexion contractures can occur over the long term in untreated cervical dystonia but this is rarely seen due to the widespread use of botulinum toxin. Symptoms are often attenuated shortly after waking in the morning, a so-called 'honey moon period'. This can be misleading to patients who feel that the condition has gone into remission.

Distraction techniques with alternating hand movements, asking patients to close their eyes, relax and allow head deviation can provoke dystonic movements and

allow targeting of appropriate muscles. Table 2 shows muscles involved in cervical dystonia [14]. A thorough assessment detailing range of movements, deviation, speed of movement, latency, aggravating and relieving manoeuvres is needed to track evolution of the disease.

Blepharospasm (BSP)

BSP results from hyperactivity of orbicularis oculi and surrounding eye muscles. It is the second most common AOIFD phenotype, predominantly affecting women in the sixth decade. Orbicularis oculi spasms can induce narrowing or closure of eyelids and can be brief or persistent [15]. It can be physically and socially debilitating, limiting reading, shopping and driving ability [16]. Onset can be unilateral but most patients develop bilateral symptoms within 2 years. Increased blinking at rest and during conversation occurs in some and is often the first sign [17]. Apraxia of eyelid (AEO) can be associated with BSP resulting in transient inability to reopen the eyes. AEO occurs due to dystonic spasms of the pretarsal portion of orbicularis oculi [18]. Evaluation of BSP should include AEO, increased blinking and spasms to grade severity and to monitor progression and treatment effect.

Oromandibular Dystonia (OMD)

OMD affects masticatory, lingual, perioral muscles and the platysma. This condition can impair speaking, chewing and swallowing and cause cosmetic disfigurement. Stress, glaring light, television and driving can trigger OMD. In multilinguals, OMD can occur during one specific language but not others. [19] Diagnosis can be challenging; the differential diagnosis includes temporomandibular joint dysfunction, facial myokymia, hemifacial spasm and tics. The specific phenotype depends on the muscles affected: [20]

- Jaw opening (most common): Lateral pterygoids, digastric

Table 2 Postures seen in Cervical Dystonia

Head movement	Muscles involved
Torticollis (head turn) (Fig. 1)	Ipsilateral splenius capitis; contralateral sternocleidomastoid, levator scapulae, trapezius, semispinalis capitis
Laterocollis (head tilt) (Fig. 2)	Ipsilateral sternocleidomastoid; ipsilateral splenius capitis; scalenes; levator scapulae; trapezius; semispinalis capitis
Anterocollis (head flexion) (Fig. 3)	Sternocleidomastoid; anterior scalenes; digastric; longus colli
Retrocollis (head extension) (Fig. 3)	Semispinalis capitis; levator scapulae; splenius capitis; erector spinae; rectus capitis posterior, major, minor; trapezius

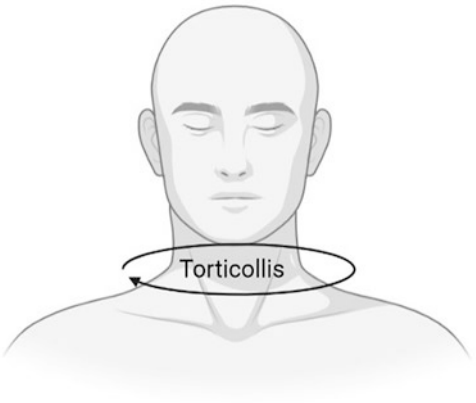

Fig. 1 Torticollis (head turn)

- Jaw closing: Masseters, temporalis, medial pterygoids
- Jaw deviation (least common): contralateral lateral pterygoid, ipsilateral temporalis

Dystonic spasms may result in nasal contractions, facial grimacing, lip pursing, lip sucking or smacking, chewing, tooth clenching and grinding and, tongue movements. Isolated OMD is uncommon. It can occur with BSP, with both forms presenting simultaneously in some patients. This is known as Meige syndrome [21].

Task-Specific Limb Dystonias

These are a group of AOIFD phenotypes that develop in body parts involved in skilled, rehearsed tasks, e.g., writing, typing, playing an instrument and occur only during performance of those tasks [22]. In writer's cramp (focal hand dystonia), muscle spasms appear immediately or within a few words as patients start to write. The hand may pronate with ulnar deviation of the wrist and elevation of the elbow. The thumb and index finger can flex leading to an excessive grip on the pen. Muscle strength and reflexes are usually normal. Increased muscle activity is seen in forearm flexors and extensors, biceps, triceps, deltoid and trapezius. The symptoms can disappear when writing shorthand. Fatigue during writing is often reported. Patients adapt to this condition by changing the way they hold their pen or using the other hand – even when using the other hand, some patients still display dystonic spasms on the affected side. If the symptoms are significant, a reduced arm swing can be observed when walking [23].

Musician's dystonia usually occurs in the hand that performs more demanding tasks, e.g., right hand in pianists, left hand in violinists. The excess muscle activity depends on the instrument, e.g., abnormal finger flexion is seen in pianists and finger extension in brass players due to lumbricals activation [24]. First reports described this condition as '*a hand that has forgotten it's cunning*'. The third finger

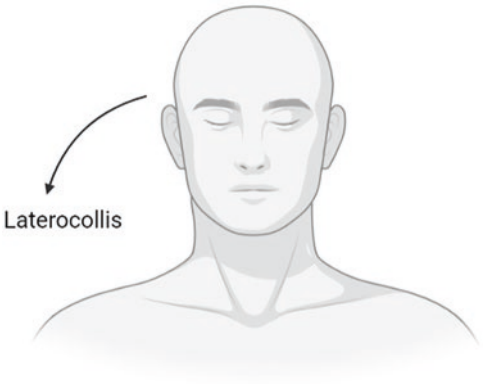

Fig. 2 Laterocollis (head tilt)

is most frequently involved and often only one finger is affected; finger flexion or extension can be observed [25]. Embouchure dystonia affects perioral and jaw muscles used to initiate and control amplitude and force of airflow into the mouthpiece of woodwind or brass instrument. The muscles involved are orbicularis oris, levator and depressor anguli oris, the levator and depressor labii superioris, risorius, mentalis, zygomatic major and minor and buccinator. Presenting complaints are loss of embouchure control, fatigue and lip tremor. Symptoms are specific – dystonia can develop within one octave, leaving everything else unaffected. Patients can adapt by retraining their embouchure [26].

Laryngeal Dystonia (LD)

Also known as spasmodic dysphonia, LD is a rare task-specific dystonia. The two main variants are adductor LD (82%) and abductor LD (17%), and a small number of patients have a mixed form. An irregular dystonic voice tremor is commonly seen. This type of dystonia occurs with speech whereas laughing, crying and whistling are not affected [27].

- Adductor LD: The primary abnormality is in the thyroarytenoid muscle and the lateral cricoarytenoid is also likely involved. Both these muscles act synchronously to adduct the vocal folds. Patients have a strained, rough voice with abrupt pauses [28]. Adductor spasms can occur during inspiration resulting in stridor and breathing difficulty. Laryngoscopy shows paradoxical laryngeal movement during inspiration leading to a narrow glottis [29].
- Abductor LD: This is due to reduced vocal fold adduction and may be due to abnormalities of posterior cricoarytenoid, thyroarytenoid and cricothyroid muscles. It is closely related to adductor LD. Patients suffer from breathy breaks and prolongation of voiceless consonants. The abnormalities can be unilateral or bilateral [30].

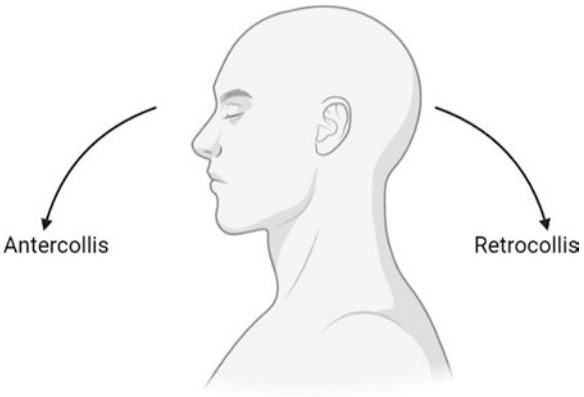

Fig. 3 Anterocollis (head flexion)

Laryngoscopy at rest reveals normal, symmetrical vocal folds. An understanding of anatomy is crucial to treating this condition. The thyroarytenoids lie parallel and lateral to the vocal fold. They arise in front from the lower half of the angle of the thyroid cartilage, and from the middle cricothyroid ligament and insert into the base and anterior surface of the arytenoid cartilage. Posterior cricoarytenoids are laryngeal abductors. They are paired muscles that extend from the posterior cricoid cartilage to the arytenoid cartilages in the larynx, and abduct the vocal folds by rotating the arytenoid cartilages laterally [31].

Adult-Onset Idiopathic Focal Dystonia: The Non-motor Disorder

As research over the last three decades has shown, the syndrome of AOIFD encompasses myriad motor features as well as several non-motor phenomena including psychiatric, cognitive, sensory dysfunction and subclinical symptoms. This is to be expected, given the numerous abnormalities noted in the non-motor regions of the brain in studies of patients with AOIFD. Indeed, other movements disorders like Parkinson's disease also have significant non-motor symptoms [32].

Psychiatric Abnormalities

A number of studies have assessed psychiatric disorders in AOIFD employing various validated instruments. Anxiety and depression are particularly prevalent in cervical dystonia [33]. Lifetime risk of depression has ranged from 15% to 53% and anxiety from 26% to 83%. The likelihood of meeting criteria for a psychiatric illness, of any type, is as high as 91%, compared with 35% in the general population

[34]. Perhaps unsurprisingly, more than 50% of patients with cervical dystonia also fulfil criteria for social phobia [35]. Obsessive compulsive disorder, a neuropsychiatric disease reflecting frontostriatal dysfunction, is more prevalent in blepharospasm and focal hand dystonia (FHD). Risk of major depression in FHD was 25% [36]. Although data in laryngeal dystonia is limited, there is evidence of higher prevalence of psychiatric disorder (up to 41%); this is much higher than in patients with vocal fold paralysis (a similar debilitating voice disorder) [37].

It is likely that mood disorders are an essential, independent feature of AOIFD, not secondary to the movement disorder, because:

- Mood symptoms often precede the onset of the motor symptoms of cervical dystonia, by many years [38].
- Mood disorder is more frequent in cervical dystonia when compared with other cosmetically disfiguring conditions, e.g., alopecia areata [39].
- The psychiatric symptoms are unrelated to the severity of the motor symptoms and persist despite effective treatment with botulinum toxin [40].
- There is an equal sex ratio in patients with AOIFD and depression. In the general population, anxiety and depression are more prevalent in women [41].
- Cervical dystonia patients with mood disorder prior to the onset of their dystonia (compared to others with no such history), have an earlier onset of their dystonia [33].

Anxiety and depression are major determinants of quality of life in CD. Studies have suggested that up to 50% of quality of life impairment is secondary to these mood disorders. This often goes unaddressed in botulinum toxin clinics. It is important that these factors are addressed equally with the motor symptoms [42].

Cognitive Dysfunction

The basal ganglia, implicated in the pathophysiology of movement disorders and AOIFD, plays a role in cognitive function. Although past studies have been contradictory, more recent evidence indicates subtle differences in patients with AOIFD. Screening using the Mini Mental State Exam (MMSE) and Addenbrooke's Cognitive Examination Revised (ACER) has indicated deficits in 32% of patients with BSP [43]. More detailed testing using the Cambridge Neuropsychological Test Automated Battery (CANTAB) demonstrated significant difficulties in extradimensional set shifting (test involving rule discovery and visual discrimination – an important marker of cognitive ability) [44].

In cervical dystonia, patients can have impaired attention and executive function, speed of information processing; these difficulties were independent of the presence of a mood disorder [45].

Prospective memory (PM) is the ability to carry out intended actions in the future, e.g., remembering an appointment at 3 pm, an important aspect of daily activity. Patients with BSP and CD showed deficits in time-based PM [46]. It has

been suggested previously that these disparate cognitive deficits may be motor symptom related. But as evidenced by patients with BSP, impaired cognitive flexibility (the ability to adapt to changing environments) was independent of symptom distraction, and likely reflects functional alterations in cortical-basal ganglia circuitry [47].

A component of our cognitive function, social cognition, allows us to interpret the behaviours and emotions of others and to predict behaviour. The network underlying this includes the posterior cortices, temporoparietal junction, superior temporal sulcus, posterior cingulate and precuneus. Assessing social cognition using the 'Faux Pas Recognition Test' in patients with CD indicated deficits in recognising social 'faux pas'. Patients also mistakenly perceived behaviour as being inappropriate more frequently than controls in situations where no 'faux pas' had occurred [48]. More specifically, cervical dystonia patients have difficulty with verbal and visual emotion recognition aspects of basic social cognition. Complex social cognition was normal [49].

Sensory Symptoms

Mild sensory symptoms can predate the onset of motor symptoms. Patients with BSP report preceding dry, gritty eyes or photophobia. Neck pain and stiffness can be present prior to the onset of cervical dystonia. Dry mouth or jaw discomfort can occur before OMD [50]. Kinaesthesia, an aspect of proprioceptive processing, can be impaired in AOIFD. It relies on intact sensory inputs from muscles spindles. Patients with BSP and CD had higher perceptual thresholds for detecting correct direction of finger displacements. This was seen in muscles affected by dystonia and in unaffected muscles [51]. Patients also showed evidence of impaired perception of vibratory stimuli [52].

Temporal discrimination thresholds (TDTs) are abnormal in AOIFD and can be considered a mediational *endophenotype.* The sensitivity and specificity of abnormal TDT is highest in CD and ranges from 97% to 100%. This *endophenotype* is highly penetrant, has uniform expression and is required to develop the phenotype. TDTs are considered a marker of an alerting system to environmental change. The superior colliculus, along with a subcortical network involving the basal ganglia is central to this function [53]. TDTs are an important research tool. This endophenotype is more penetrant than the phenotype and allows for identification of environmental exposures between clinically affected individuals and their unaffected siblings. It is also likely that AOIFD is genetically heterogeneous. A reliable endophenotype can facilitate exome sequencing and large linkage analyses [53].

A discussion of sensory AOIFD would not be complete without including one of its most fascinating phenomena. The *geste antagoniste* is a feature present in up to 70% of patients with cervical dystonia. Also known as a 'sensory trick', patients experience improvement in their symptoms by slightly touching the chin or cheek

ipsilateral to the dystonic posture. The complex mechanism underlying this is unclear, but probably relates to sensorimotor integration [54].

Functional Neuroanatomy: Linking the Motor and Non-motor Features

Collicular–pulvinar–amygdala (CPA) network dysfunction, due to loss of inhibition at the level of the superior colliculus, can explain the clinical syndrome (motor and non-motor symptoms) and subclinical manifestations. The superior colliculus acts as the central node in this network (Fig. 4).

Superior Colliculus (SC), the Substantia Nigra and Sensorimotor Processing

This structure forms the roof of the midbrain, caudal to the pineal gland. It is laminated, and can be subdivided into superficial and deep layers. The superficial layer is sensory and receives retinal inputs. The deep layers have sensorimotor functions, and neurons here respond to auditory, tactile and visual stimuli and have motor outputs [55]. Neurons in the SC control saccadic eye movements. Neurons in the

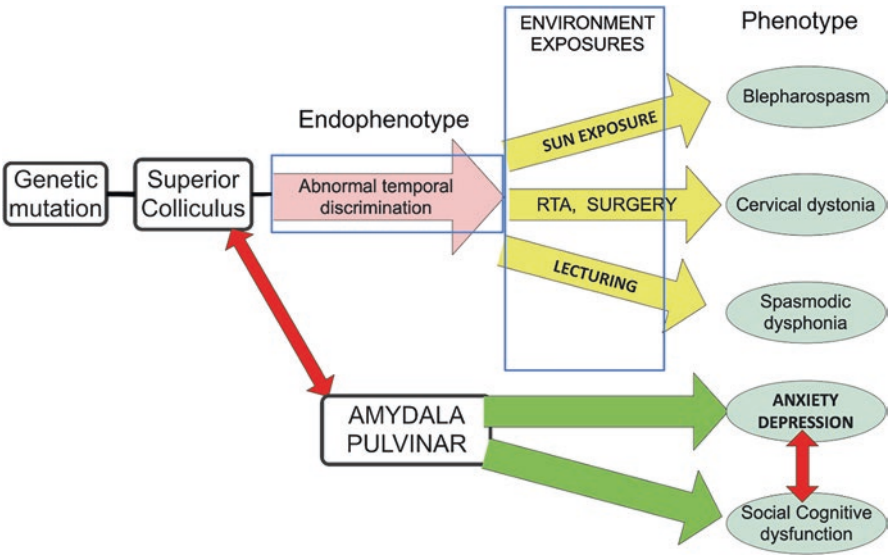

Fig. 4 The collicular–pulvinar–amygdala axis. Integrating the anatomical and environmental influence on the motor and non-motor expression of AOIFD

deep layer also discharge before head movements towards salient targets [56]. The detection of environmental changes is important for survival and implies accurate detection of approaching objects. The superficial layer of the superior colliculus mediates this process with 'looming sensitive' neurons. Functional MRI studies reveal reduced superficial layer activity and reduced putaminal activity to looming stimuli in patients with CD [57].

It is postulated that disordered GABAergic inhibition at the SC results in abnormal TDTs [58]. Although it is unclear how this arises, the substantia nigra pars reticularis has been shown to be one source of tonic GABAergic inhibition at the SC [59]. In primates, loss of inhibitory projections from the substantia nigra pars reticulata (SNpr) to the tectum evokes cervical dystonia. This was then attenuated by inhibition of the SC using muscimol. This indicates that the nigrotectal pathway is involved in the pathogenesis of CD [60].

The main motor function of the SC is to shift gaze to salient contralateral stimuli. The tecto-reticulospinal tract (predorsal bundle) can explain multiple motor manifestations in AOIFD. Originating in the intermediate and deep layers of the SC, the predorsal bundle terminates in the upper spinal cord, contacting in part, the motoneurons for the head extensor muscles. In primates and rats, this pathway has been shown to control shoulder and forelimb movements [61]. Coordinating gaze shifts and arm movements also involve the SC and the reticular formation. Neuronal populations, 'reach neurons', facilitate the control of arm movements. The most robust connections exist between the reticular formation and proximal arm muscles [62]. Further studies has shown the presence of two major output pathways from the SC to the brainstem: (1) a tectal 'orienting' pathway which crosses the midline in the ventral tegmental decussation and projects caudally, in the tectoreticulospinal tract, to the contralateral medial pontomedullary reticular formation (PMRF) and upper cervical spinal cord and (2) a tectal 'defence' pathway projecting from the medial SC caudally to the PMRF. The nomenclature reflects their predicted behaviours. Both pathways were involved in head orienting and body movements [63].

Psychiatric and Cognitive Features

Tractography has confirmed neural pathways exist between the SC, pulvinar nucleus and amygdala [64]. This subcortical pathway processes emotional facial recognition without conscious awareness. This pathway also mediates simple autonomic responses to aversive stimuli [65]. The amygdala has been classically linked to fear processing; more recent evidence suggests a larger role in emotion (positive and negative), memory and social cognition [66]. When measured by the strength and complexity of social networks, amygdala structure and connectivity seems intrinsic to social cognition [67]. Focal activation of the superior colliculus in animal studies resulted in emergence of defensive behaviours. Subsequent inactivation of the amygdala can attenuate this, highlighting the importance of both structures in social and emotional regulation [68].

Superior Colliculus and the Putamen

Structural changes within the putamen have been linked with abnormal TDTs. Patients with AOIFD (CD, BSP, FHD) and also their *unaffected relatives* with abnormal TDTs, have all been shown to have larger putaminal volumes by voxel-based morphometry [69]. Most cases of symptomatic or secondary dystonia are due to lesions of the putamen. In primary dystonias, dopamine D2 receptors have been shown to be deficient in the putamen [70]. A number of functional MRI studies have also noted abnormal connectivity in the putamen in cervical dystonia and focal hand dystonia [71–73]. Putaminal changes may then reflect temporal discrimination abnormalities and be an intrinsic factor in AOIFD. As both the SC and the putamen are involved in abnormal TDTs and are abnormal in studies on looming stimuli, it can be speculated that the putamen plays a role as the trigger for the loss of inhibition on the SC.

The CPA network remains to be confirmed as the active mediator in patients with AOIFD. Clinicians must be aware of the motor symptoms as well as the anxiety, depression and cognitive symptoms to effectively treat AOIFD. Similarly, any proposed pathogenesis for this rare disorder must explain both the motor and non-motor features. Loss of inhibition on the SC leading dysfunction in the amygdala and pulvinar nucleus, as part of a 'bottom-up' pathway, can provide an explanation for the mechanism underlying AOIFD. This area warrants further elaboration. One difficulty, due to the inherent heterogeneity of the AOIFD, and also the heterogeneity within AOIFD subtypes, is recruitment of large study populations. This problem can be addressed by increasing use of temporal discrimination to identify participants carrying similar subclinical changes.

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Does Pallidal Physiology Determine the Success of Unilateral Deep Brain Stimulation in Cervical Dystonia?

Alexey Sedov, Anna Gamaleya, Ulia Semenova, Rita Medvednik, Alexey Tomskiy, Hyder A. Jinnah, and Aasef Shaikh

Abstract Pallidal deep brain stimulation is a well-known surgical treatment for cervical dystonia. The resolution of dystonia typically requires bilateral pallidal stimulation, but in some instances, unilateral stimulation has been successful. In such instances, generally, the stimulated hemisphere was contralateral to the dystonic sternocleidomastoid, but rarely it was ipsilateral. We sought for the physiological features that determine the basis for success and laterality of deep brain stimulation for cervical dystonia with prominent torticollis. We found that pallidal physiology such as high burst to tonic ratio and significant interhemispheric differences in the neuronal firing rate and regularity are critical determinants of successful treatment with unilateral deep brain stimulation. We also found that higher lateralized differences in pallidal physiological parameters predict more robust improvement. In three out of four patients, the stimulation of the hemisphere ipsilateral to the dystonic sternocleidomastoid muscle was effective. These patients did not have any structural brain abnormalities on clinically available imaging studies. One patient responded to the unilateral deep brain stimulation in the hemisphere contralateral to the dystonic sternocleidomastoid. This patient had a structural puta-

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men lesion on brain MRI. These results provide objective parameters determining the success of pallidal deep brain stimulation for treatment of cervical dystonia. The results also depict differences in the pallidal physiology in patients where ipsilateral versus contralateral deep brain stimulation was effective.

Keywords Cervical dystonia · Single-unit activity · Globus pallidus · Deep brain stimulation

Introduction

Cervical dystonia (CD) is the most common form of isolated dystonia characterized by abnormal twisting and turning of the neck with or without head oscillations. Deep brain stimulation of globus pallidus internus (GPi-DBS) is a popular treatment for medically refractory CD. Traditionally, improvement in CD is described with bilateral GPi-DBS [1–3]; however, occasional literature reported improvement in CD with unilateral stimulation [4–8]. The unilateral GPi-DBS studies, mostly the case reports, focused on the treatment of torticollis due to dystonic sternocleidomastoid (SCM) contralateral to the stimulated hemisphere [4–6, 9]; but rarely ipsilateral stimulation was found effective [7, 8]. We asked what determines the efficacy of unilateral DBS in CD with prominent torticollis, and which factors determine the laterality of therapeutic DBS location. In order to address these overarching questions, our experiments examined:

1. The differences in the physiology of pallidal neurons in therapeutic versus control hemisphere.
2. How pallidal physiology differs in the patients that respond to therapeutic stimulation in the hemisphere contralateral to the dystonic SCM versus that ipsilateral to the dystonic SCM.
3. Whether physiology of pallidal neurons that are located in the therapeutic hemisphere but outside of the volume of activated tissue differ from the physiology of the pallidal neurons in the control hemisphere.

Methods

Clinical Data and Outcomes

We analyzed the effects of unilateral GPi-DBS in four CD patients with prominent torticollis. Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the Tsui torticollis rating scale scores were used to measure the clinical outcome. Unilateral stimulation tests were carried out on each pair of contacts, followed by an evaluation of the patient several hours later. Then we choose a final program of

unilateral stimulation for each patient (Table 1). Although in all patients the DBS electrodes were implanted in bilateral GPi, programming found effective treatment of their torticollis with only unilateral DBS stimulation; hence, only one hemisphere was stimulated. In three cases, the therapeutic DBS was ipsilateral to the dystonic SCM. In one patient, we found side contralateral to the dystonic SCM was effective. This patient characterized by putaminal stroke ipsilateral to the successfully stimulated hemisphere (Fig. 1).

Surgical Procedure and Physiological Data Collection

In each patient, two quadripolar DBS electrodes were implanted into bilateral GPi. The intervention was performed under local anesthesia. The Leksell stereotactic system was used, the intercommissural line and GPi coordinates were determined from the MR images. We recorded single-unit activity with tungsten microelectrodes (NeuroProbe, AlphaOmega) delineating the boundaries of the external and internal segments of the pallidum. To measure the motor evoked single-unit activity, the patients performed tasks such as shrugging shoulder or isometric contracting the SCM. The evoked activity was then recorded for off-line analysis. Once the ideal location of the electrode implantation was determined, we measured stimulation-induced side-effects using the current ranging from 1 to 5 mA. After implanting the DBS electrode, its location was radiologically confirmed. Subsequently, during an outpatient visit, the unilateral and bilateral stimulation tests were carried out on the different contacts with different parameters: duration, frequency, and amplitudes. The outcome was verified after 12 months of stimulation. Table 1 depicts the therapy parameters and DBS active electrode contact locations for all four patients.

Measuring the Volume of Tissue Activation

We used preoperative MRI and postoperative CT to determine the placement of electrodes by means of the Lead-DBS toolbox (https://www.lead-dbs.org/). We calculated the volume of activated tissue (VAT) and incorporated it in the patient's own MRI using a known approach [10]. Then we classified GPi cells that were within the boundaries of VAT, i.e., "responsive neurons" and those outside of the region, i.e., "nonresponsive neurons."

Data Analysis

We recorded spontaneous single-unit activity as the electrode advanced through GPe and GPi. Each cell was recorded for at least 20 s. Our inclusion criteria for additional offline analysis were that the neurons should have sufficiently long recordings containing at least 200 spikes. We used Spike 2 (CED, Cambridge, UK) for signal preprocessing and analysis. The signal was band-pass filtered between

Table 1 Clinical parameters for DBS in four CD patients

Cases	TWSTRS	TSUI	Improvement	DBS ipsilateral to active SCM			DBS contralateral to active SCM		
				Contact	Amplitude	Frequency	Contact	Amplitude	Frequency
Case 1	8	2	70%	3–4	3 mA	174 Hz	–	–	
Case 2	10	7	52%	10–11	2.2 V	90 Hz	–	–	
Case 3	16	11	45%	10	2.4 mA	130 Hz	–	–	
Case 4	10	6	59%	–	–	–	10	2.5 mA	130 Hz

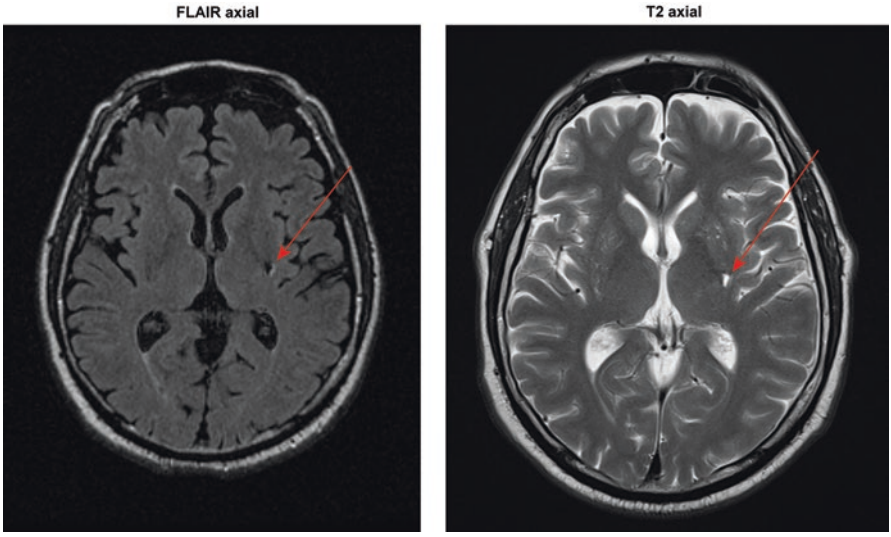

Fig. 1 FLAIR and T2 axial MRI brain slices of patient with putaminal stroke

300 Hz and 5000 Hz, and subsequently aligned for spike sorting. The amplitude threshold, at the value of 4-times standard deviation, was used to isolate spikes. Isolated single-units were then separated by K-means cluster selection in the principal component analysis (PCA) feature space based on several waveform parameters.

Statistical analysis with Mann–Whitney (MW), and Chi2 tests were performed with the Matlab Statistics toolbox and custom prepared algorithms. We computed instantaneous firing rate to measure the neuronal firing frequency. The coefficient of variance of interspike intervals (ISI) and asymmetry index (median ISI/mean ISI) measured the variability in the spike occurrence. The burst index, i.e., the number of ISI < 10 ms divided by the number of ISI > 10 ms, objectively characterized bursting behavior. The pause index, the number of ISI > 50 ms divided by the number of ISI < 50 ms, characterized pause behavior. We used the Poisson Surprise (PS) algorithm for burst detection. This algorithm assumes that the baseline firing rate follows the Poisson process with results equal to the mean firing rate of the sample spike train. The Poisson Surprise statistic is defined as $S = -\log(p)$, where p is the probability of more or the same number of N spikes occurring in the interval. Bursts are chosen to maximize the PS statistic with a surprise maximization algorithm [11]. Detected bursts for each isolated neuron were further used to determine the activity parameters such as burst percent (ratio of spikes in burst to the total number of spikes), inter- and preburst intervals, mean burst length, mean interspike interval within the burst, and mean value of spike-count within the burst. For grouping spike trains into specific patterns, we used hierarchical clustering [12].

Results

We asked how pallidal physiology differs in patients with CD (prominently torticollis) that respond to unilateral GPi-DBS. We also asked what determines the laterality of therapeutically successful side. The questions were addressed in four CD patients with unilateral GPi-DBS; three with DBS in GPi ipsilateral to the dystonic SCM; while in one with DBS in the GPi contralateral to the dystonic SCM. We measured the spontaneous activity of 265 pallidal neurons; 113 cells were localized in GPe while 152 cells were in GPi. Unsupervised machine learning separated the neuronal activity pattern into three types: burst, tonic, and pause (Fig. 2a). The hemisphere where DBS was therapeutic had relatively fewer GPi tonic neurons but more prevalent pause neurons (Fig. 2b, Chi2 = 7.51, $p = 0.024$). Such difference was not noteworthy in GPe (Fig. 2c, Chi2 = 5.8, $p = 0.055$).

Subsequent analysis compared the physiological parameters of pallidal neurons between two hemispheres (Table 2). The GPi neurons in the therapeutic hemisphere

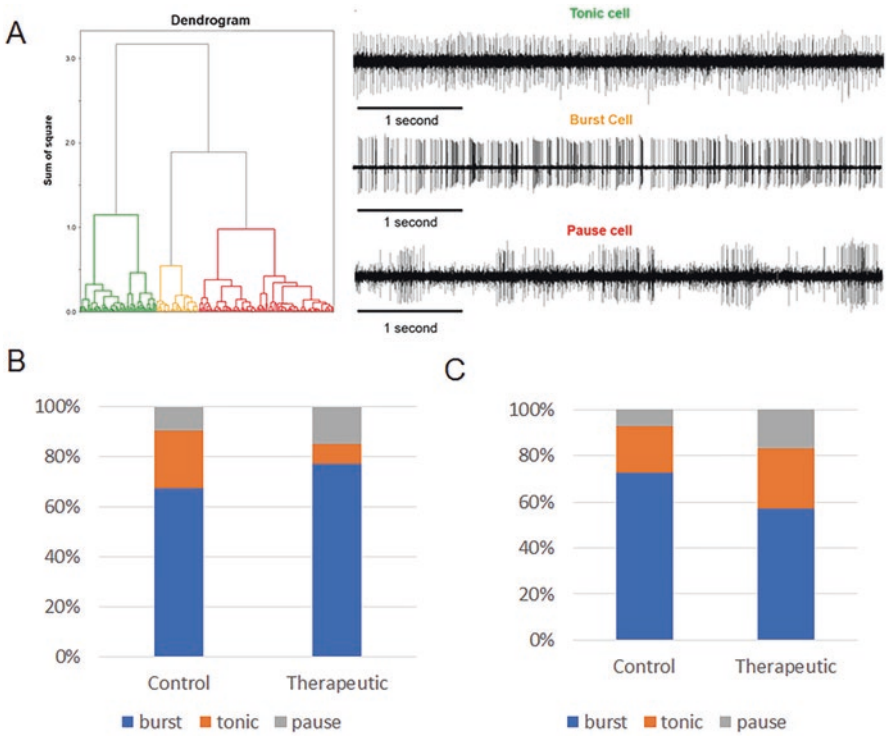

Fig. 2 (**a**) Hierarchical clustering algorithm to separate 265 pallidal cells into burst, tonic and pause neurons. The firing patterns in inset describe an example of the three neuron subtypes. In the inset, the neuronal spikes are plotted as a time-series signal (x-axis). The distribution of GPi neurons (**b**) and GPe neurons (**c**) into burst, tonic and pause subtypes. Comparison is done between control (nonstimulated) and therapeutic (stimulated) hemispheres

Table 2 Physiological parameters of pallidal neurons on therapeutic hemisphere versus control hemisphere – summary from all patients

	GPi			GPe		
Parameters\DBS side	Control	Rx	*p*	Control	Rx	*p*
Firing rate, spikes/sec	67	50	0.014	48	63	0.001
Coefficient of variance	0.99	1.06	0.025	1.12	1.10	0.631
Asymmetry index	0.68	0.63	0.003	0.68	0.65	0.652
Burst index	0.76	0.33	0.038	0.25	1.08	0.001
Pause index	0.03	0.09	0.003	0.09	0.04	0.001
Burst spike percent	0.22	0.24	0.011	0.26	0.23	0.825
Burst rate	1.53	1.46	0.385	0.95	1.27	0.030
Interburst interval, s	0.58	0.60	0.357	0.93	0.73	0.017
PreBurst interval, s	0.02	0.03	0.003	0.03	0.02	0.001
Mean burst length, ms	43	50	0.102	109	77	0.086
Mean ISI in burst, ms	6.2	6.5	0.025	8.4	6.7	0.001
Mean spikes in burst	8.2	8.6	0.927	10.8	11.8	0.114

had significantly lower median firing rate 50 (34–80) spikes/s compared to control hemisphere 67 (47–84) spikes/s (MW, $p = 0.01$). The GPi neurons on the therapeutic hemisphere were less regular, had more pause, and had less burst behavior compared to the control hemisphere. Less regularity was depicted by the smaller coefficient of variation (Table 2). The pause index measures the pause behavior, while the burst index and preburst interval is a gauge of burst behavior. The pause and burst indices of GPe and GPi neurons were notably different between therapeutic and control hemispheres. Such differences in GPe were however opposite compared to GPi. The GPe on the therapeutically effective side had less pause and more burst behavior compared to the control hemisphere (Table 2).

The analyzed group had three patients where the therapeutic side was ipsilateral to the dystonic SCM muscle. One patient had therapeutic response to the stimulation of the hemisphere that was contralateral to the dystonic SCM muscle. We compared the physiological differences in control and therapeutic hemisphere in those who had contralateral versus ipsilateral pallidal stimulation. The instantaneous firing rate was significantly lower in therapeutic GPi (Table 3) in three patients where the therapeutic hemisphere was ipsilateral to the dystonic SCM. In addition, the firing pattern was characterized by more pause-burst behavior in therapeutic GPi, that is significantly lower asymmetry index and higher pause index and preburst interval. At the same time, the firing rate was significantly higher in the therapeutic side GPe, while pause index and preburst interval were significantly lower.

The subsequent analysis separated GPi neurons that were within the volume of activated tissue (VAT), modeled according to the therapeutic DBS parameters. We found 28 GPi neurons within the boundary of therapeutic VAT, 53 GPi cells were outside of this region. There were significantly larger proportion of pause neurons and less prevalent tonic cells within the volume of activated tissue compared to outside of this region (Chi2 = 6.85, $p = 0.03$) (Fig. 3). There was no difference in the

Table 3 Physiological parameters of pallidal neurons on therapeutic hemisphere versus control hemisphere – differences between those with unilateral DBS contralateral versus ipsilateral to active SCM

	Therapeutic DBS ipsilateral to active SCM						Therapeutic DBS contralateral to active SCM					
	GPi			GPe			GPi			GPe		
Parameters\DBS side	Control	Rx	*p*-value	Control	Rx	*p*-value	Control	Rx	*p*-value	Control	Rx	*p*-value
Firing rate, spikes/sec	58.09	46.57	0.04	46.84	54.60	0.04	110.86	101.59	0.34	49.70	90.86	0.01
Coefficient of variance	1.01	1.08	0.08	1.13	1.11	0.86	0.84	0.90	0.37	0.97	1.09	0.16
Asymmetry index	0.67	0.62	0.01	0.63	0.65	0.75	0.72	0.73	0.44	0.72	0.64	0.08
Burst index	0.63	0.29	0.12	0.25	0.50	0.03	4.01	3.04	0.34	0.30	3.53	0.00
Pause index	0.04	0.11	0.01	0.09	0.05	0.02	0.00	0.01	0.16	0.08	0.02	0.01
Burst spike percent	0.23	0.26	0.05	0.26	0.23	0.71	0.11	0.15	0.15	0.16	0.20	0.18
Burst rate	1.61	1.46	0.65	1.00	1.15	0.18	1.31	1.50	0.37	0.83	1.39	0.04
Interburst interval, s	0.57	0.60	0.61	0.87	0.74	0.20	0.68	0.63	0.44	1.06	0.57	0.02
PreBurst interval, s	0.02	0.03	0.01	0.03	0.02	0.03	0.01	0.01	0.13	0.02	0.01	0.02
Mean burst length, ms	0.04	0.05	0.11	0.11	0.08	0.14	0.04	0.04	0.93	0.11	0.06	0.59
Mean ISI in burst, ms	0.01	0.01	0.05	0.01	0.01	0.06	0.00	0.00	0.98	0.01	0.00	0.00
Mean spikes in burst	7.73	8.36	0.68	11.38	11.65	0.70	10.89	9.17	0.88	9.65	18.67	0.02

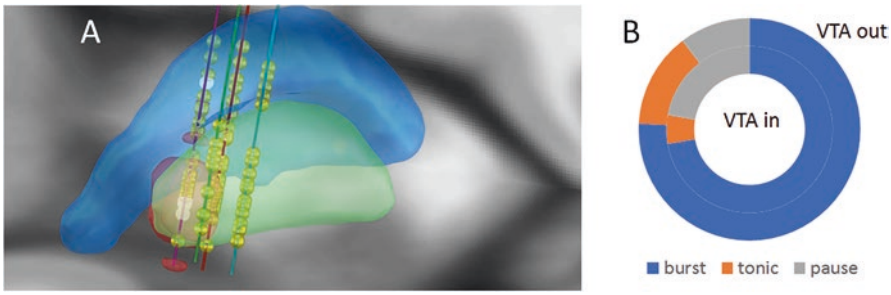

Fig. 3 (**a**) Example of neuronal coordinates plotted on the patient specific MR map. Each symbol depicts the location of the pallidal neuron, while sphere depicts the volume of activated tissue (VAT). (**b**) Distribution of burst, tonic and pause neurons in the region activated by electrical field (VAT in) and outside of the electrical field (VAT out)

firing rate of pallidal neurons inside [46 (32–59) spikes/s] versus outside [47 (34–79) spikes/s] the volume of activated GPi. However, the cells within the volume of activated tissue were more bursty (asymmetry index: inside = 0.61 (0.54–0.64); outside = 0.63 (0.58–0.71), burst spike percent: inside = 29% (20–41); outside = 24% (15–33)).

We also separately characterized the case with the most effective outcome (70%). The GPi neurons in the therapeutic hemisphere of this patient had significantly lower median firing rate 44 spikes/s compared to the control hemisphere 66 spikes/s (MW, $p = 0.006$), and a higher median pause index 0.12 compared to the control hemisphere 0.04 (MW, $p = 0.001$). The similar characteristics we observed in nine neck sensitive cells: median firing rate 45 spikes/s and median pause index 0.11. We did not find significant differences between therapeutic and control hemisphere single-unit activity in GPe.

We did not find any lateralized differences in the GPi single-unit physiology in one patient who had therapeutic improvement after stimulation of GPi on the side contralateral to the dystonic sternocleidomastoid. However, the differences were present in GPe, and they were comparable to the other cohort in which firing rate was higher on therapeutic hemisphere, and firing also had more irregularity (Table 3).

Discussion

Unilateral DBS was shown effective in selected cases of CD. Previous literature had reported that DBS on the side contralateral to the dystonic SCM (i.e., ipsilateral to the side of torticollis) is effective [4–6, 9]. On the contrary, a few reports suggested improvement after stimulating the GPi ipsilateral to the dystonic SCM [7, 8]. Physiological rationale for the choice of stimulated side remains unclear. The current study asks what determines the efficacy of unilateral DBS in CD and which

factors determine the laterality of therapeutic DBS location. The study addressed three questions.

1. The differences in the physiology of pallidal neurons in therapeutic versus control hemisphere.
2. How pallidal physiology differs in the patients that respond to therapeutic stimulation in the hemisphere contralateral to the dystonic SCM versus that ipsilateral to the dystonic SCM.
3. Whether physiology of pallidal neurons that are located in the therapeutic hemisphere but outside of the volume of activated tissue differ from the physiology of the pallidal neurons in the control hemisphere.

We recently showed that the pallidal activity featuring lower firing rate, burst index, and alpha oscillation score is associated with an excellent clinical outcome [13]. This study showed similar physiological trends when comparing the pallidal activity between two hemispheres, except for additional differences in the firing irregularity [14, 15]. The fundamental difference between our previous study and current data is that participants in the previous study required bilateral DBS for therapeutic response. In the current study, we found successful treatment with unilateral GPi DBS. The differences in cases where unilateral DBS was effective had much robust differences between two hemispheres; lower firing rate and burst index and frequent pause behavior of GPi cells in the contralateral side to the direction of torticollis.

Three parameters determined the therapeutic efficacy of unilateral DBS in patients with prominent torticollis – reduced firing rate, increased firing variability, higher proportions of pause, and less tonic neurons. These parameters are consistent with those thought to be the predictors of DBS efficacy within the pallidum [13]. The results depicted physiological characteristics alone do not determine whether stimulated location will be efficacious, but robust lateralized differences in the firing characteristics are also important. More polarized differences predict higher chances for unilateral DBS to succeed.

In the three CD cases, the effective DBS side was ipsilateral to the dystonic SCM. These patients did not have any imaging evidence of structural brain deficits. In contrast, the patient with putamen lesion responded to the DBS therapy in the hemisphere DBS in the opposite direction as dystonic SCM. In this patient, the activity of right and left GPi was comparable, but lateralization was found in the activity of GPe, again contralateral to the dystonic SCM. The interpretation of the efficacy of DBS on the unilateral side of the dystonic SCM is based on data from a single patient, such limitation must be viewed with caution. Nevertheless, the results provide important differences in the network dysregulation in those where focal lesions in the basal ganglia lead to dystonia, as opposed to those with no structural neurological deficits.

In summary, our study looked for the pallidal physiological features of patients with cervical dystonia that respond to unilateral DBS. We found that high burst to tonic ratio and interhemispheric differences in the neuronal firing rate and regularity are the critical determinants of the successful unilateral DBS therapy.

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Clinical Implications of Dystonia as a Neural Network Disorder

Giovanni Battistella and Kristina Simonyan

Abstract Isolated dystonia is a neurological disorder of diverse etiology, multifactorial pathophysiology, and wide spectrum of clinical presentations. We review the recent neuroimaging advances that led to the conceptualization of dystonia as a neural network disorder and discuss how current knowledge is shaping the identification of biomarkers of dystonia and the development of novel pharmacological therapies.

Keywords Network disorder · Functional connectivity · Structural networks · Connectome · Neurotransmission

Introduction

Isolated dystonia is a hyperkinetic movement disorder manifesting as involuntary sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both [2, 42]. It is the third most common movement disorder after Parkinson's disease and essential tremor. While the incidence of isolated dystonia is underestimated due to the clinical challenges in timely diagnosing the disorder [1], it is known to affect up to 35.1 per 100,000 cases [56], with a higher prevalence among white females [27, 50, 102]. The clinical presentations of dystonia are diverse. The topographic distribution of symptoms classifies dystonia into

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five main categories: (i) focal dystonia, affecting a single region (e.g., hand dystonia, cervical dystonia, blepharospasm, laryngeal dystonia, oromandibular dystonia); (ii) segmental dystonia, affecting two or more continuous regions; (iii) multifocal dystonia, affecting two or more nonadjacent regions; (iv) hemidystonia, dominantly affecting regions on one side of the body; and (v) generalized dystonia, affecting the trunk and at least two other sites [2, 105].

The pathophysiology of isolated dystonia is multifactorial. Diverging from the historical tenet that considered dystonia a basal ganglia disorder, the majority of current reports refer to dystonia as a neural network disorder. Various environmental stressors and underlying genetic factors interact with and influence abnormal reorganization of neural networks, further shaping the diversity of its clinical characteristics. However, despite the substantial progress in understanding the disorder pathophysiology, therapeutic approaches in dystonia are primarily geared toward symptom management. Botulinum toxin injections into the affected muscles are the "gold"-standard treatment for patients with focal dystonia. Pharmacological therapy (primarily, anticholinergics, dopaminergic, and GABAergic drugs) and deep brain stimulation (DBS) are available in severe cases of generalized or segmental dystonias. Treatment responses are known to be highly variable across patients, and their effectiveness may be limited due to side effects or other factor of therapeutic inefficiency [5, 86, 106]. Recent estimates suggest that nearly 40% of patients with focal dystonia do not receive any treatment [86]. To improve clinical management of patients with dystonia, a recent workshop organized by the National Institute of Neurological Disorders and Stroke (NINDS/NIH) on research priorities in dystonia stressed the urgent need to design effective therapeutic interventions based on the novel evidence of network-level dysfunction in dystonia [71].

In this chapter, we review the experimental evidence that led to the conceptualization of dystonia as a neural network disorder and discuss the impact of this current view of dystonia pathophysiology on the clinical management of patients affected by this disorder.

From the Historical Tenet of a Basal Ganglia Disorder to the Modern Consensus of Dystonia as a Neural Network Disorder

The understanding of the neural underpinnings of dystonia has considerably evolved in the past decade (Fig. 1). One of the first mentions of dystonia as a condition arising from a basal ganglia pathology due to mineral accumulations dates back to the 1949 case report of two patients [10]. Over the following decades, several other reports of patients with dystonia secondary to brain lesions provided further evidence for the involvement of the basal ganglia in symptom development (e.g., [82, 110]). These observations culminated in the landmark paper by Marsden and colleagues [77], which reviewed 28 patients with focal or hemidystonia secondary to

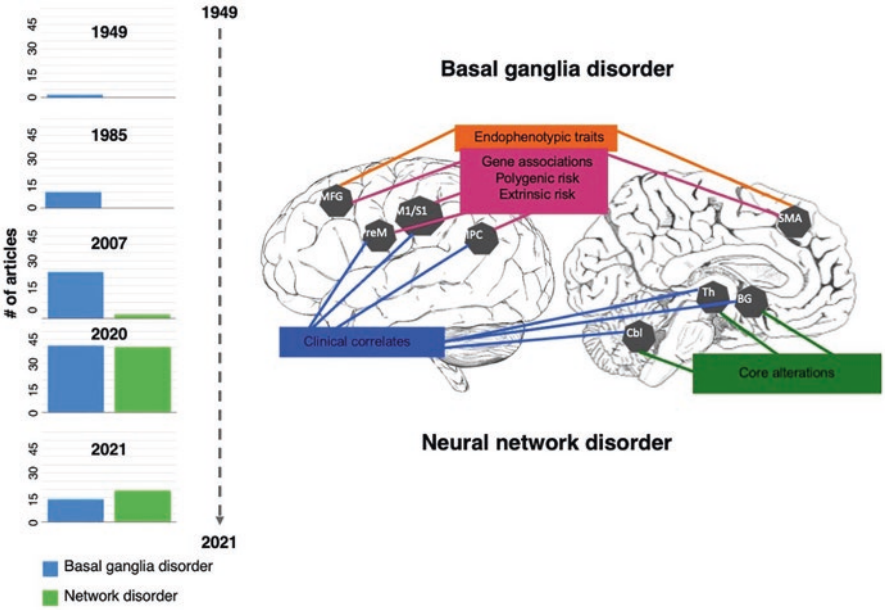

Fig. 1 Imaging signatures of dystonia and timeline of the basal ganglia vs. neural network disorder evolution. Schematic representation of the main regions of abnormal brain function, structure, and metabolism in dystonia and their associations with genes, endophenotypic traits, clinical features, and extrinsic/environmental risk (Adapted from Simonyan et al. [101]). The bar graphs of the timeline show how the view of the pathophysiology of dystonia changed over the years from a basal ganglia to a neural network disorder. Based on the literature search in PubMed, bars graphs show the number of articles published across the years considering dystonia a basal ganglia disorder, or a network disorder. The terms used for the search included: "idiopathic dystonia OR primary dystonia OR isolated dystonia AND brain AND basal ganglia disorder" and "idiopathic dystonia OR primary dystonia OR isolated dystonia AND brain AND network disorder." Abbreviations: *MGF* middle frontal gyrus, *PreM* premotor cortex, *M1/S1* primary sensorimotor cortex, *IPC* inferior parietal cortex, *SMA* supplementary motor area, *BG* basal ganglia, *Th* thalamus, *Cbl* cerebellum

brain lesions due to tumors, arteriovenous malformations, infarcts, or hemorrhages. The authors concluded that the "abnormal input from the thalamus to the premotor cortex, due to lesions either of the thalamus itself or the striatum projecting by way of the globus pallidus to the thalamus" may be causative in dystonia pathophysiology [77]. Despite the outlined prominence of the thalamus, the primary focus shifted to the basal ganglia and their presumed pathophysiological role in both secondary and primary (isolated) dystonias. This study thus cemented the notion that dystonia is a basal ganglia disorder and paved the way for decades of research to understand the role of this structure in the disorder pathophysiology. According to the basal ganglia model of dystonia, the imbalance of the direct and indirect pathways underlies bottom-up abnormal decreases of thalamic and intracortical inhibition and subsequently abnormal increases of motor cortical excitability, leading to the dystonic output of motor behaviors (e.g., [51, 53, 98]).

In the early 1990s, leveraging the breakthroughs in in-vivo investigations of human brain function, neuroimaging studies started unveiling more complex brain disorganization in patients with dystonia. Early studies, predominantly, in hereditary forms of dystonia caused by DYT1, DYT6, and DYT11 gene mutations relied heavily on the use of positron emission tomography (PET) with [^{15}O] H_2O and [^{18}F]-fluorodeoxyglucose (FDG) radiotracers to investigate cerebral blood flow and glucose metabolism, respectively, as a proxy of neuronal activity [19, 38–40, 58, 59, 66, 74]. These studies identified abnormalities not only in the basal ganglia and thalamus but also in the cerebellum and sensorimotor cortex, suggesting a wider range of regional alterations and their interactions. Collectively, these findings led to the formulation of the metabolic network model of dystonia.

In parallel, cerebellar dysfunction and atrophy were reported in heterogeneous cohorts of patients and animal models of dystonia [23, 37, 60, 70]. This line of research prompted the theory that cerebellar alterations, similar to those in the basal ganglia, may also be causative in the disorder pathophysiology, conceptualizing the cerebellar model of dystonia.

In the past decade, the further advancements of neuroimaging techniques and analytical tools permitted in-depth investigations of different properties of brain structure and function. Rather than focusing on a single structure or network as a primary contributor to dystonia pathophysiology, a new line of research took an unbiased, data-driven approach to examining brain alterations in patients with dystonia. Mapping large-scale brain organization in dystonia demonstrated the existence of shared and divergent patterns of alterations in multiple neural networks across various forms of dystonia (for review, [94]). While the basal ganglia, thalamus, and cerebellum were found to be at the core of neural network disorganization across all forms of dystonia, the distinct patterns of functional and structural alterations were determined in cortical and subcortical sensorimotor regions responsible for multisensory processing, sensorimotor integration, and motor execution dependent on a particular form of dystonia. Collectively, these findings provided an updated view on the pathophysiology of isolated dystonia, establishing the neural network model of the disorder.

A *PubMed* review of the literature[1] shows that most articles published until 2006 considered dystonia as a basal ganglia disorder (Fig. 1). Starting from 2007, the body of literature on the involvement of neural networks in dystonia pathophysiology steadily grew, balancing the articles referring to dystonia as a basal ganglia disorder by 2020 and surpassing these in 2021. The currently prevailing view is that dystonia is a functional and structural neural network disorder, not limited to the basal ganglia and cerebellar circuitries. This updated concept is crucial for identifying both shared and unique pathophysiological mechanisms in the various clinical manifestations of the disorder and informing the development of advanced diagnostics and the design of targeted therapeutics.

[1] The review conducted on 07/19/2021. The terms used for the search were: idiopathic dystonia OR primary dystonia OR isolated dystonia AND brain AND basal ganglia disorder & idiopathic dystonia OR primary dystonia OR isolated dystonia AND brain AND network disorder.

Clinical Implications of Dystonia as a Functional Neural Network Disorder

Among the most used functional neuroimaging methods in clinical research are task-based and resting-state functional magnetic resonance imaging (fMRI) paradigms. The former relies on changes in the blood oxygen level-dependent (BOLD) signal during the performance of a specific task or a behavior. The latter uses the measurement of low-frequency physiological fluctuations in the BOLD signal to examine regional correlations within intrinsic brain networks [16]. In the resting-state fMRI session, participants do not perform any cognitive tasks but are instead instructed to lay in the scanner, relax, and let their minds wander. This technique identifies multiple functional networks relevant to the salient states and behaviors in a single experimental session. In patients with dystonia, the use of resting-state fMRI circumvents the challenges associated with implementing a symptomatic (dystonic) task-based experimental design that needs to be customized according to muscles affected by the disorder, making direct comparisons between different forms of disorder not feasible. The independent component analysis (ICA) is one of the common techniques used to investigate the resting-state signal that defines functional networks by determining a set of statistically independent spatial maps and associated time courses.

Functional neuroimaging studies in dystonia demonstrate abnormal (typically increased) sensorimotor activity during the performance of symptomatic tasks and altered regional connectivity within sensorimotor and frontoparietal networks [7, 17, 18, 32, 33, 36, 55, 59, 64, 72, 76, 81, 95]. Task-specific dystonias, such as laryngeal, focal hand and musician's dystonias, are further characterized by significant alterations in cortical areas compared to prevalently subcortical changes in non-task-specific dystonias, such as cervical dystonia and blepharospasm [14, 89, 108]. External risk factors appear to specifically influence the altered function of the basal ganglia, premotor and parietal cortices [26], while subclinical features of dystonia, such as abnormal temporal discrimination, are associated with abnormalities in primary somatosensory and middle frontal cortices [106]. Vulnerable functional connectivity of premotor and parietal regions is linked to the polygenic risk of dystonia [88], whereas functional and structural abnormalities in prefrontal-parietal cortices, thalamus, and basal ganglia represent the intermediate endophenotype of dystonia penetrance, with additional alterations in the cerebellum contributing to the secondary endophenotype of dystonia manifestation [67]. Altered functional connectivity of the thalamus, basal ganglia, premotor, and parietal cortices correlates with clinical measures associated with disease severity and age of onset (e.g., [54, 96]).

Another powerful technique for delineating the architecture of brain networks is graph-theoretical analysis, which examines global and local features of large-scale functional and structural networks (connectomes) [91, 103]. Important properties of these connectomes are the integration and segregation of nodes in neural communities and the configuration of hubs necessary for the most efficient organization of the overall network. These essential nodes of information transfer may be

subdivided into provincial hubs that control within-community activity and connector hubs that control between-communities activity. Studies employing graph theoretical analysis provided the ultimate experimental evidence of dystonia as a neural network disorder. Specifically, an investigation of the large-scale architecture of the functional connectome in four different forms of focal dystonia (laryngeal dystonia, writer's cramp, cervical dystonia, and blepharospasm) compared to healthy individuals revealed the disorganization of neural communities, including a breakdown of the basal ganglia-thalamo-cerebellar community and abnormal loss or gain of network hubs that impacted the network hierarchy necessary for information processing [8]. The follow-up research showed that the functional network kernel and community structure associated with motor execution, sensorimotor processing, and motor planning are differentially affected in different forms of dystonia [45, 93]. Further experimental evidence exists that large-scale neural network alterations are shaped by the clinical subtypes of dystonia (e.g., adductor vs. abductor laryngeal dystonia, simple vs. complex writer's cramp), affected body part (e.g., hand vs. larynx), affected motor behavior (e.g., musician's dystonia vs. nonmusician's dystonia), and putative genotypes (e.g., familial vs. sporadic dystonia) [14, 15, 44, 93].

The current understanding of functional networks in dystonia presents a window of opportunity for developing novel interventions that selectively target and modulate the pathophysiologically abnormal functional neural network. One of such pathophysiologically based oral treatments showing promising potential is sodium oxybate, which is FDA-approved for cataplexy, excessive daytime sleepiness in narcolepsy, and idiopathic hypersomnia. Sodium oxybate is a centrally acting derivate of gamma-hydroxybutyric acid, which mimics the effects of alcohol. Notably, up to 55% of patients with dystonia report symptom improvement after alcohol intake [63, 68] (Fig. 2a). Alcohol modulates gamma-hydroxybutyric acid (GABA)-ergic function, which is decreased in dystonia contributing to the loss of inhibition within the dystonic network [52]. The recent open-label study in laryngeal dystonia (NCT01961297) showed that sodium oxybate modulates pathophysiological hyperactivity of brain regions associated with dystonic speech production, including the primary and secondary sensorimotor cortices, inferior frontal and superior temporal gyri, supplementary motor area, thalamus, and cerebellum [99] (Fig. 2a). This central effect translates into dystonic symptom improvement in 82.2% of alcohol-responsive patients [92]. The ongoing phase 2/3 double-blind, randomized, placebo-controlled, cross-over study of sodium oxybate in laryngeal dystonia (NCT03292458) is expected to provide concrete recommendations for its use in alcohol-responsive patients.

The existing knowledge of dystonia as a functional network disorder may also accelerate the development and implementation of new approaches for noninvasive therapeutic neuromodulation of brain networks in dystonia. As discussed above, ample evidence supports the role of premotor-parietal regions in dystonia, particularly in task-specific dystonias. Departing from the traditional view that dystonic symptoms are generated from pure motor cortical and/or basal ganglia dysfunction, a recent study using dynamic causal modeling in laryngeal dystonia demonstrated that abnormal functional connectivity is driven by the increased top-down influence

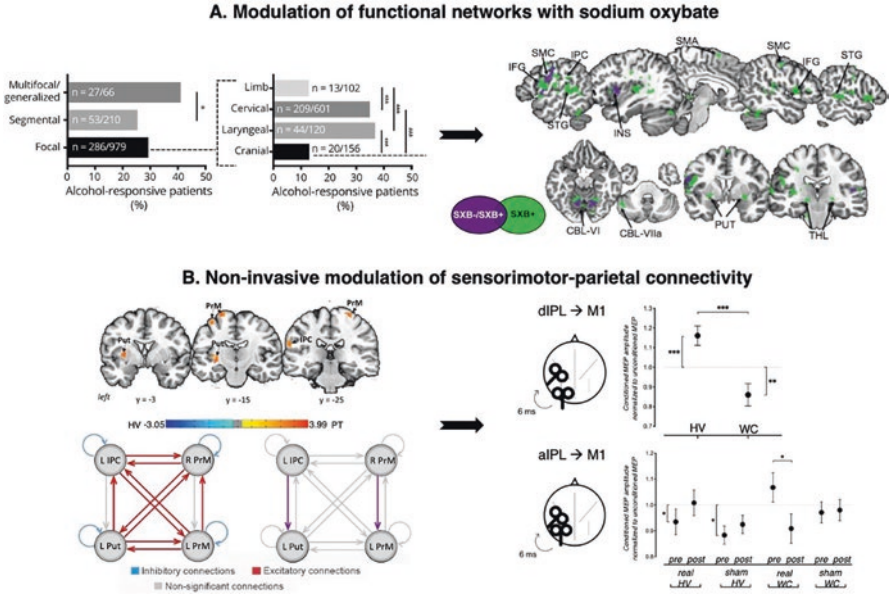

Fig. 2 Clinical implications of dystonia as a functional neural network disorder. (**a**) Alcohol responsiveness in dystonia and the effects of sodium oxybate on brain activity. The left panel shows the alcohol responsiveness across different forms of dystonia (in % of patients in the examined cohort). The black arrow indicates how the understanding of alcohol responsiveness in dystonia influenced the design of the open-label study in laryngeal dystonia using sodium oxybate, a gamma-hydroxybutyric acid that mimics the effects of alcohol. The right panel shows a series of sagittal and axial slices of regions of common (in purple) and distinct (in green) brain activity in drug responders vs. nonresponders during symptomatic speech production. (**b**) Modulation of sensorimotor-parietal connectivity in focal dystonia. The left panel shows series of coronal brain images with regional alterations in resting-state functional connectivity in patients with laryngeal dystonia compared to healthy subjects. The schematic representation of the results of dynamic causal modeling reveals the direction of abnormal information flow between these altered regions in patients. Excitatory connections (red), inhibitory connections (blue), nonsignificant connections (gray), differences between laryngeal dystonia patients and healthy subjects (purple). The black arrow shows how imaging studies of functional and effective connectivity in dystonia informed the design of noninvasive neuromodulation in these patients. The right panel summarizes the transcranial magnetic stimulation experiment in healthy subjects and patients with writer's cramp. The panel shows changes in sensorimotor-inferior parietal electrophysiological interaction introduced by real or sham continuous theta-burst stimulation. Abbreviations: *M1* motor cortex, *dIPL* dorsal inferior parietal lobule, *aIPL* anterior inferior parietal lobule. (Panel (**a**) adapted from Simonyan et al. [99]. Panel (**b**) adapted from Battistella G. and K. Simonyan [6] and Merchant et al. [80])

of the left inferior parietal cortex onto the putamen and increased interhemispheric right-to-left influence of the premotor cortex [6] (Fig. 2b). These findings indicated that the network disruption may be staged well before the primary motor cortex produces the dystonic behavior. In line with this, recent research in focal hand dystonia employed noninvasive neuromodulation to probe premotor and inferior parietal regions as candidate therapeutic targets. Improved dystonic symptoms were

observed following active vs. sham transcranial direct current stimulation (tDCS) of the parietal cortex coupled with behavioral retraining in patients with musician's dystonia [90]. Transcranial magnetic stimulation (TMS) with continuous theta-burst pulses over premotor and parietal regions was reported in another study to transiently decrease the parietal-premotor excitability and restore the motor cortical excitability in patients with writer's cramp [80] (Fig. 2b). In contrast, many prior studies on noninvasive stimulation of the primary motor cortex reported a range of clinical benefits but offered limited mechanistic explanations of these effects [24]. Building on this knowledge, the currently ongoing phase 1 clinical trial (NCT04421365) is using brain–computer interface (BCI) that specifically targets parietal-premotor alterations for rehabilitation of dystonic symptoms in patients with laryngeal dystonia.

Clinical Implications of Dystonia as a Structural Neural Network Disorder

It is well known that conventional brain MRI scans of patients with isolated dystonia do not show any gross structural abnormalities. However, advances in in-vivo high-resolution MRI-based neuroimaging techniques using measures of gray matter volume, cortical thickness, and white matter microstructural properties allowed the identification of fine-grained patterns of structural alterations across the clinical spectrum of dystonias. These studies reported predominantly increased gray matter volume and cortical thickness and decreased white matter integrity across different forms of dystonia [reviewed in [94]] (Fig. 3a). In parallel with research on functional abnormalities, studies focusing on the gray matter organization determined core alterations in the basal ganglia, thalamus, and cerebellum across different forms of dystonia [30, 34, 41, 83, 84, 96, 111]. The capability of neuroimaging techniques to investigate the whole brain in a data-driven fashion further allowed the identification of abnormalities in primary sensorimotor, supplementary motor, and frontoparietal areas associated with altered motor execution, sensorimotor processing, and integration [30, 48, 49, 57, 78, 84, 89, 96, 109, 111]. The specific location of sensorimotor changes was shown to vary according to the clinical phenotype. Increased gray matter volume in the hand area in focal hand dystonia [14, 30, 48] but the larynx area in laryngeal dystonia [15, 69, 96,] are examples of this differential involvement. Dystonia gene mutations also impact the extent of these abnormalities within the sensorimotor dystonic network. For instance, non-manifesting DYT1 mutation carriers and patients without the DTY1 genetic mutation have increased gray matter volume in the putamen compared to manifesting DYT1 carriers [35], and specific patterns of gray matter structural changes in the supplementary motor area and superior temporal gyrus are present in patients with a familial history of dystonia [15, 67].

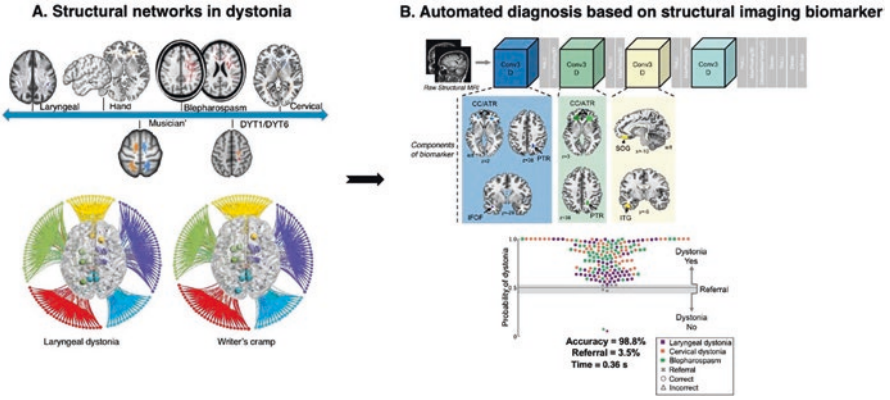

Fig. 3 Clinical implications of dystonia as a structural neural network disorder. (**a**) Structural abnormalities in dystonia: the top panel shows the major microstructural abnormalities across different forms of dystonia. The bottom panel shows the large-scale connectome in focal dystonias. (**b**) Automated diagnosis of dystonia using DystoniaNet. The automated algorithm identified gray and white matter regions classifying patients with different forms of focal dystonia. The scatterplot shows the accuracy of the algorithm. (Panel (**a**) adapted from Hanekamp and Simonyan [54]. Panel (**b**) adapted from Valeriani and Simonyan [109])

Investigations of white matter integrity across different forms of dystonia revealed a consistent pattern of shared and phenotype-specific abnormalities along fiber tracts connecting regions of altered functional connectivity and gray matter volume/cortical thickness responsible for motor control and sensorimotor processing [3, 15, 20, 21, 31, 75, 89, 100, 108]. More recently, the investigation of the large-scale structural connectome in focal dystonias using white matter tractography demonstrated large-scale alterations, involving the abnormal organization of neural communities and hubs. This study also determined abnormal prefrontal-parietal connectivity and altered hubs in the basal ganglia, prefrontal, parietal, and insular cortices influencing the whole-brain structural reorganization [54] (Fig. 3a). An earlier in-vivo diffusion MRI study combined with postmortem neuropathology in laryngeal dystonia revealed the potential cause of microstructural changes by showing focal axonal degeneration and demyelination within the corticospinal/corticobulbar tract and clusters of mineral precipitates in the parenchyma of putamen and cerebellum [100]. Mineral accumulations are known to lead to the generation of free radicals and lipid peroxidation, causing oxidative stress, cell membrane damage, ferroptosis, and a subsequent damage to neuronal function [9, 22, 43, 104]. Future studies are warranted to characterize abnormal processes leading to mineral accumulations, the results of which may be crucial for determining the biological signatures underlying structural and functional alterations in dystonia.

The findings of abnormal structural networks in dystonia have recently paved the way for identifying reliable neural network biomarkers of diagnostic potential. Despite being the third most common movement disorder, the diagnosis of isolated dystonia remains clinically challenging, with up to half of the cases misdiagnosed

at the first encounter and the final diagnosis extended up to 10 years [25, 26, 61, 62, 73, 87, 107]. The current diagnostic criteria are based purely on clinical syndrome characteristics, while the vast phenotypical variability of the disorder, the presence of conditions mimicking dystonia, and the experience and expertise of the clinician contribute to the misdiagnosis or delays in final diagnosis. Overall, this diagnostic approach is not reliable, as its specificity and sensitivity are not established, and the validity of the clinical diagnosis without a biomarker cannot be assessed [5, 28, 29, 56, 71, 86].

Based on the current knowledge of structural network abnormalities and motivated by the clinical need for an accurate and timely diagnosis of isolated dystonia, a deep learning algorithm, DystoniaNet, has been recently developed to objectively diagnose focal dystonia [109] (Fig. 3b). Using an automated, data-driven approach in a large cohort of 392 patients and 1770 healthy individuals, the DystoniaNet algorithm correctly identified gray and white matter regions frequently reported as microstructurally abnormal across the entire clinical spectrum of dystonia. Using this microstructural network biomarker, DystoniaNet achieved 98.8% accuracy in classifying patients with laryngeal dystonia, cervical dystonia, and blepharospasm while referring 3.5% of cases with an uncertain diagnosis for additional evaluations. Importantly, this algorithmic diagnostic decision was achieved in less than one second, significantly shortening the time from symptom evaluation to its diagnosis. Compared to the current diagnostic procedures, which often require various evaluations during multiple visits to multiple specialists, DystoniaNet-assisted diagnosis that is based on automatically determined pathophysiological neuroimaging signatures of the disorder may be critical in increasing the clinical accuracy and shortening the time to diagnosis.

Clinical Implications of Dystonia as a Neurotransmission Network Disorder

The last aspect of neuroimaging alterations in dystonia that may have widespread clinical implications relates to abnormal neurotransmission. The in vivo investigation of neurotransmission relies on PET neuroreceptor mapping with the use of specific radioligands to quantify dopamine, GABA, and other receptor bindings. Ample evidence demonstrates decreased striatal dopamine D_2/D_3 receptor binding during rest in focal and generalized forms of dystonia [4, 11, 12, 19, 85, 97]. Literature on focal dystonias also reports abnormally decreased phasic nigrostriatal dopamine release during symptomatic tasks and increased dopamine release during asymptomatic motor tasks [12, 98] (Fig. 4a). An earlier PET study including a patient cohort with different forms of focal dystonia reported no changes in striatal dopamine D_1 receptor binding [65]. However, a subsequent study that carefully stratified patients based on their clinical presentations identified increased striatal dopamine D_1 receptor [98]. Findings of D_1 receptor binding increases and D_2

receptor decreases are somatotopically distributed according to the affected body region in the sensorimotor and associative striatal subdivisions, pointing to highly specialized alterations of dopaminergic neurotransmission in the pathophysiology of dystonia. Reduced availability of striatal dopamine D_2/D_3 receptors decreases the inhibitory activity within the indirect basal ganglia pathway, while increased availability of striatal dopamine D_1 receptors increases the excitatory activity within the direct basal ganglia pathway. This imbalance between the direct and indirect basal ganglia pathways likely contributes to hyperexcitability of the thalamus and, subsequently, the bottom-up thalamo-cortical projections to sensorimotor and parietal areas [98].

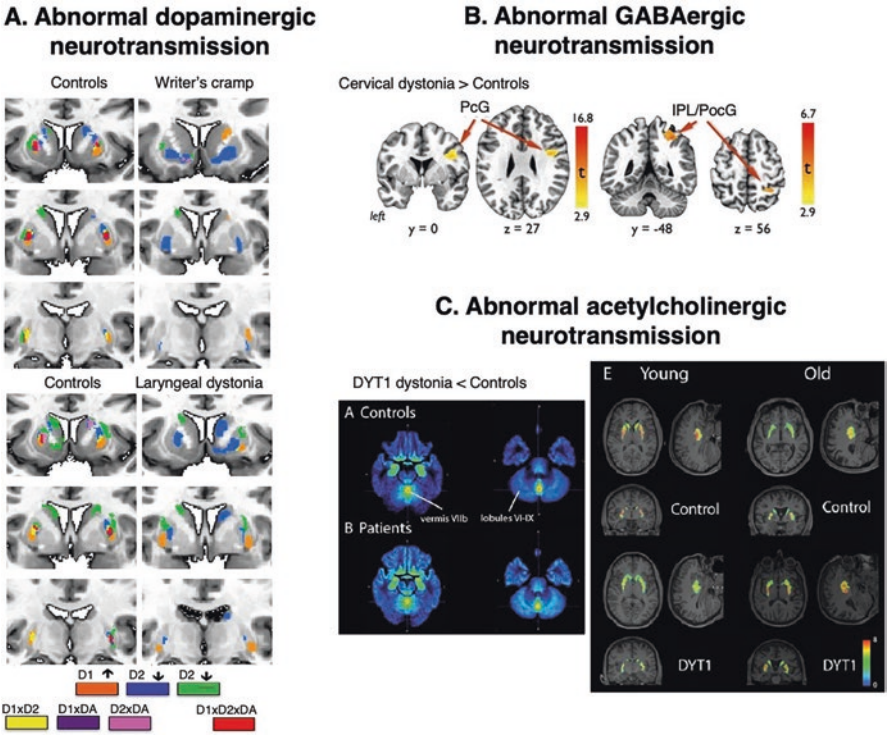

Fig. 4 Clinical implications of dystonia as a neurotransmission network disorder. (**a**) Topological distribution of phasic striatal dopamine in healthy subjects and patients with writer's cramp and laryngeal dystonia during finger tapping (for hand dystonia) and sentence production (for laryngeal dystonia). Different colors represent receptor-binding regions (D_1, D_2), dopamine release (DA), and their significant interactions. (**b**) Distribution of increased $GABA_A$ receptor binding in cervical dystonia compared to healthy subjects using [^{11}C] flumazenil radiotracer. (**c**) Parametric map of decreased vesicular acetylcholine transporter in patients with DYT1 dystonia compared to healthy subjects using ^{18}F-FEOBV-binding ratio and average binding in controls and patients stratified by age. (Panel (**a**) adapted from Simonyan et al. [98]. Panel (**b**) adapted from Berman et al. [13]. Panel (**c**) adapted from Mazere et al. [79])

In line with this, studies of GABAergic neurotransmission in different forms of dystonia showed decreased receptor binding within the dystonic network, including reduced $GABA_A$ receptor availability in premotor, primary sensorimotor, somatosensory, inferior parietal, insular cortices, caudate nucleus, and cerebellum [13, 46, 47, 98] (Fig. 4b). These abnormalities, albeit with minor variations across different clinical presentations of the disorder, are consistent across focal and generalized dystonias, including patients with the DYT1 gene mutation. Furthermore, reduced $GABA_A$ receptor binding correlates with increased gray matter volume and brain activity in the inferior parietal cortex [46, 98], reiterating the crucial role of this region in the pathophysiology of dystonia.

Adding to the landscape of abnormal neurotransmission in dystonia, a recent study in patients with DYT1 reported decreased vesicular acetylcholine transporter (VAChT) in the striatum and cerebellum, impacting the organization of functional connectivity within the motor network [79] (Fig. 4c). Interestingly, striatal VAChT expression was abnormal in young but not older patients, pointing to potential age-related compensatory changes. Collectively, these studies updated the basal ganglia model by including subtle alterations of the balance of major neurotransmitters within the basal ganglia-thalamo-cortical network.

The knowledge of abnormal neurotransmission in dystonia represents a powerful feature for designing novel pharmacological therapies. One such therapy includes the repurposing of sodium oxybate in laryngeal dystonia, which improves dystonic symptoms by normalizing the neural network activity via the modulation of GABAergic neurotransmission, as described above. Other well-designed randomized, blinded clinical trials of novel oral drugs in patients with different forms of dystonia should represent one of the primary research efforts in the field. These may include novel formulations and the repurposing of existing drugs that leverage the current knowledge of pathophysiologically altered neurotransmission.

Summary

The advancement of in vivo data acquisition protocols, neuroimaging techniques, and analytical tools permitted the investigation of different properties of brain microstructure and function that, collectively, transformed the understanding of dystonia pathophysiology over the past decade. These investigations were instrumental in identifying large-scale neural signatures of dystonia and defining the disorder as a network disorder, including alterations in brain function, structure, and neurotransmission. Both commonly shared and phenotype/genotype-specific changes are identified in different forms of dystonia. The basal ganglia with the thalamus and cerebellum are at the core of large-scale network disorganization in all forms of dystonia. In contrast, cortical abnormalities are characteristic of task-specific forms of dystonia in contrast to predominantly subcortical involvement in non-task-specific forms of dystonia. Cortical sensorimotor and parietal changes are linked to genetic predisposition and environmental triggers of dystonic symptoms.

Understanding the pathophysiology of dystonia through the lens of impaired neural networks paved the way for the development of novel strategies to diagnostics and therapy of these patients, including the targeting of dystonia-specific neuroimaging changes in brain function and neurotransmission with new oral drugs and non-invasive neuromodulation and using microstructural changes as an objective biomarker for dystonia diagnosis.

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