Dystonia

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Abstract | Dystonia is a neurological condition characterized by abnormal involuntary movements or postures owing to sustained or intermittent muscle contractions. Dystonia can be the manifesting neurological sign of many disorders, either in isolation (isolated dystonia) or with additional signs (combined dystonia). The main focus of this Primer is forms of isolated dystonia of idiopathic or genetic aetiology. These disorders differ in manifestations and severity but can affect all age groups and lead to substantial disability and impaired quality of life. The discovery of genes underlying the mendelian forms of isolated or combined dystonia has led to a better understanding of its pathophysiology. In some of the most common genetic dystonias, such as those caused by *TOR1A*, *THAP1*, *GCH1* and *KMT2B* mutations, and idiopathic dystonia, these mechanisms include abnormalities in transcriptional regulation, striatal dopaminergic signalling and synaptic plasticity and a loss of inhibition at neuronal circuits. The diagnosis of dystonia is largely based on clinical signs, and the diagnosis and aetiological definition of this disorder remain a challenge. Effective symptomatic treatments with pharmacological therapy (anticholinergics), intramuscular botulinum toxin injection and deep brain stimulation are available; however, future research will hopefully lead to reliable biomarkers, better treatments and cure of this disorder.

The term dystonia describes abnormal movements or postures that are caused by sustained or intermittent muscle contractions (Supplementary Video 1). Although the early reports of patients with dystonia date back to the 17th century, the concept of dystonia as an organic disease evolved only in the past few decades (FIG. 1). Dystonia can be used to refer to both a single sign or diseases in which dystonia is the sole or prominent clinical feature. The latter diseases encompass a range of acquired, inherited or idiopathic aetiologies (TABLE 1).

Previous classifications focused on aetiology and characterized dystonia as primary (whereby dystonia is the only clinical sign and includes idiopathic or genetic disorders with no neuropathological abnormalities) or secondary (dystonia arising from neurodegeneration, acquired causes (such as lesions within the brain) or genetic conditions with a progressive course)[1]. By contrast, the 2013 consensus update on the phenomenology and classification of dystonia focuses on clinical characteristics and classifies dystonia as isolated (whereby dystonia is the sole manifesting clinical feature with no other neurological or systemic signs) or combined (whereby dystonia is combined with other neurological or systemic signs)[2].

Most cases of isolated dystonia are caused by genetic alterations or are of unknown aetiology. Clinically, isolated dystonias can differ in their manifestation and severity but can affect all age groups and lead to substantial disability and impaired quality of life (QOL). Depending on the regions of the body affected, dystonia can be subclassified as focal (in which one region of the body is affected), segmental (in which adjacent regions of the body are affected) or generalized (in which several regions of the body are affected). Dystonia can be focal initially and then spread to affect other body parts or even become generalized. Clinically, dystonia can be described by age of onset, body distribution and temporal pattern, including its relation to voluntary actions or triggers[2] (BOX 1). The natural history of isolated (idiopathic or genetic) dystonia is that of an insidious onset with a stable disease course once the symptoms are fully established, which typically occurs over months to years. However, the clinical syndromes and aetiologies of dystonia overlap, which renders producing a unifying, clinical and pathophysiological conceptualization difficult. For example, one gene can underlie different dystonia phenotypes, and one phenotype of dystonia can be caused by several genetic alterations (FIG. 2).

In this Primer, we focus mainly on the isolated dystonias, as these pure forms are particularly informative regarding the essential clinical and pathophysiological features of dystonia. However, we touch upon some examples of combined dystonias, particularly those that are clinically or pathophysiologically relevant.

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Epidemiology

The true prevalence of dystonia remains unknown, but patients with dystonia represent ~20% of patients in movement disorder clinics[3,4]. Of the different forms of dystonia, isolated idiopathic and genetic forms are relatively more common[5]. The reported prevalence of dystonia subtypes differs, which is mostly due to the inherent methodological differences between epidemiological studies[4]. Different frequencies of isolated focal and generalized dystonia have been reported across regions, for example, Europe compared with Japan, although these effects are likely largely related to differences in ascertainment[4]. Clinic-based studies estimate a prevalence of ~16 per 100,000 individuals for adult-onset focal dystonias[4], whereas a rigorous population-based study reported 732 cases of this type of dystonia per 100,000 individuals, as most cases are undiagnosed[6]. Prevalence increases with age, and adult-onset focal dystonia is much more frequent than early-onset variants of dystonia, which have a prevalence of ~7.6 per 100,000 individuals[4,5]. The age at onset might be different in individuals of different ethnicities, for example, a later onset of focal or segmental dystonia in individuals of European ancestry than in first-generation immigrants from Asia and Africa has been suggested[4].

Isolated (idiopathic or genetic) dystonia follows a characteristic pattern with regard to age at onset, sex and anatomical distribution. Isolated generalized dystonia manifests in childhood or adolescence and has no sex predilection, although disease-causing *GCH1* mutations can have a reduced penetrance in males, which can give rise to a female preponderance[7]. Conversely, focal limb dystonias manifest typically in the fourth decade of life and have a balanced female to male ratio, except for musician's dystonia (BOX 1), which has a male preponderance and an earlier age at onset (mean age at onset 31.7 years)[8]. Cervical dystonia is the most common adult-onset dystonia, affects women earlier than and twice as often as men and has an onset typically in the fourth or fifth decade of life in both sexes[8,9]. Laryngeal dystonia (also called spasmodic dysphonia) has a slightly later age of onset (mean 50.1 years)[9] but a similar female preponderance as cervical dystonia (mean age at onset 41.7 years)[9,10]. Similarly, facial dystonia, which can present as blepharospasm (eye closing spasms), oromandibular dystonia or a combination of these (called Meige syndrome), is more common in women than in men, but onset usually occurs in the sixth or seventh decade of life[8].

Genetics

Autosomal dominant isolated dystonias. Studies investigating the genetic cause of isolated dystonia were initially hampered by the scarcity of families with multiple members with dystonia, the wide phenotypic variability of this disorder in terms of age and site at onset and the spreading of dystonia. Indeed, the first dystonia causative gene, *TOR1A*, was identified owing to the recurrence of a dominantly inherited ancient founder mutation (a GAG deletion) in the Ashkenazi Jewish population[11] (TABLE 2). In this population, this mutation is found in ~80% of patients with early-onset isolated dystonia, and *TOR1A*-related dystonia has an estimated prevalence of between 1 in 3,000 individuals and 1 in 9,000 individuals[12]. Subsequent studies demonstrated the same mutation in many individuals worldwide, owing to the same shared ancestry or owing to de novo mutations[13–17], with an estimated prevalence of 1 in 12,000 individuals in France[18]. Several years later, the study of a large Mennonite family with several family members with dystonia identified *THAP1* mutations as another cause of autosomal dominant isolated dystonia[19–21], and subsequently, over 100 distinct mutations in *THAP1* have been demonstrated in patients with familial and sporadic, mostly early-onset isolated dystonia[22,23].

With the advent of next-generation sequencing techniques, several candidate genes for autosomal dominant isolated dystonia have been reported. Mutations in some genes, such as *GNAL*[24,25] and *ANO3* (REFS[26,27]), were identified in several independent patients, and their causative roles have been conclusively established, allowing their use in diagnostic protocols. Conversely, although *CIZ1* mutations were also identified as a cause of autosomal dominant isolated dystonia[28], this finding has not been replicated and still requires validation[29,30].

Mutations causing autosomal dominant dystonia are often of incomplete penetrance, explaining the lack of positive family history in many individuals with this disorder. Penetrance varies among the distinct genetic forms, and for instance, is high (up to 90%) in *GNAL*-associated dystonia and is 20–30% in individuals with *TOR1A* GAG deletions[31,32]. In those with *TOR1A* GAG deletions, the presence of a *cis* or *trans* D216H polymorphism in *TOR1A* is a potential modifier of the penetrance, insofar as its presence in *trans* was found to be enriched in GAG deletion carriers without dystonia[33]. In addition, preliminary evidence suggests a role for extra-genetic factors, such as perinatal adversities[30] and developmental abnormalities in the cerebello-thalamocortical tracts[34], in modifying the penetrance of *TOR1A* mutations.

Autosomal recessive isolated dystonia. Autosomal recessive isolated dystonia is much rarer than autosomal dominant dystonia. Patients inherit two pathogenetic variants, one from each heterozygous healthy parent. This inheritance pattern would be suggested by the presence of multiple individuals in the same generation with dystonia or the presence of parental consanguinity. Biallelic mutations in *HPCA*[35], *VPS16* (REF.[36]) or *COL6A3* (REF.[37]) have been reported in single families, although

the clinical relevance of these mutations still awaits confirmation in larger cohorts. Replication studies failed to identify *HPCA* pathogenetic variants in 73 patients with early-onset isolated dystonia[38], which suggests that HPCA-related dystonia is rare, and questioned the validity of the association between *COL6A3* mutations and autosomal recessive dystonia[39].

Interestingly, mutations in *THAP1* or *GNAL* can also be inherited in a recessive manner, resulting in a clinical phenotype either indistinguishable from or more severe than the phenotype caused by dominantly inherited mutations[40–42]. Thus, a family history that is suggestive of recessive inheritance does not rule out autosomal dominant genetic causes of dystonia.

Combined dystonias. Several genetic disorders manifest with combined dystonia and have been reviewed elsewhere[43,44]. Overall, there are many (more than 100) different and very rare disorders, for which exact prevalence rates are unknown.

Mechanisms/pathophysiology

From anatomy to the network model

The anatomical basis for dystonia is still debated. Neuropathological studies of patients with isolated idiopathic or genetic dystonia have not generally revealed overt abnormalities at the macroscopic or microscopic level in the brain[45–47]. However, some microscopic abnormalities have been reported in specific forms of dystonia. For example, one study demonstrated perinuclear neuronal cytoplasmic inclusions containing torsin 1A, ubiquitin and lamin A/C in brainstem nuclei in individuals with *TOR1A*-related dystonia[48]; although these findings have not been replicated, they correspond to findings in some mouse models of *TOR1A*-related dystonia[49]. Similarly, patchy Purkinje cell loss and axonal swellings (known as torpedo bodies) have been reported in the cerebellum in post-mortem brains of patients with cervical dystonia[50], supporting the emerging role of the cerebellum in dystonia, although this finding requires confirmation[51].

Early studies suggested that dystonia is caused by disruption of the basal ganglia because of the identification of patients with discrete focal lesions (often in the putamen[52]) who had dystonia. However, later studies suggest that dystonia is a network disorder, with involvement of a basal ganglia–cerebello-thalamo-cortical circuit[53]. For example, lesions in other structures, particularly the thalamus, brainstem and cerebellum, have been demonstrated in patients with dystonia[52], and pharmacological and genetic rodent models of dystonia are often associated with pathology in basal ganglia or cerebellar structures[53].

Data from anatomical and functional imaging studies are also consistent with the notion of dystonia as a

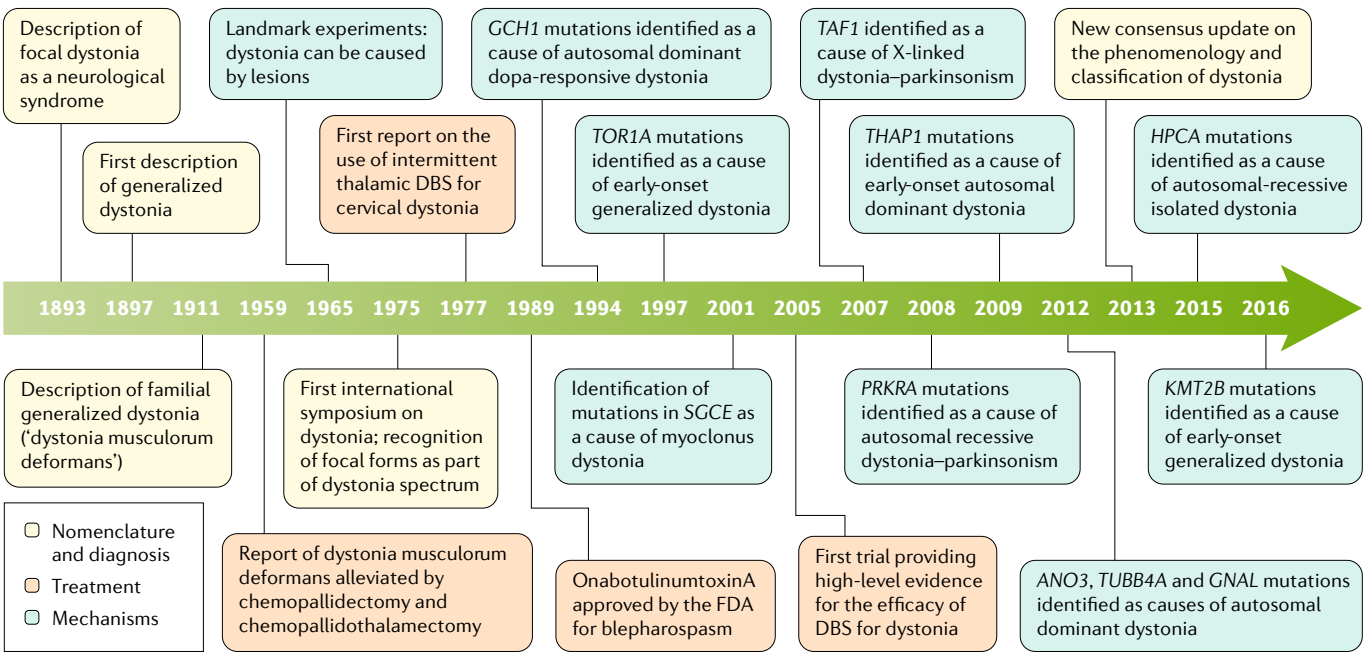

Fig. 1 | **History of dystonia.** Patients with dystonia were initially considered hysterical or suffering from psychiatric disorders[249]. The view of dystonia as a psychiatric disease was attributed partly to the worsening of symptoms with social and mental stress, the relief of symptoms by alleviating manoeuvres (so called sensory tricks) and the strong influence of a school of psychopathology at that time, for which some dystonic movements offered seemingly self-evident psychopathological explanations; for example, dystonic movements causing eye closure or neck turning could be thought of as the patient not wanting to face reality. Furthermore, the failure to find any clear anatomical, physiological or biochemical abnormality in patients with isolated dystonia hindered discovering the organic nature of this disease[250]. In 1975, the first international symposium on dystonia facilitated a paradigm change and, for the first time, the recognition of the full clinical spectrum of dystonia (including idiopathic and hereditary forms) and allowed concerted action on treatment approaches. Since then, the understanding of the underlying pathophysiology of dystonia has improved, a process that has been fuelled by insights from electrophysiological studies and the identification of mutations in several genes linked to monogenic forms of isolated and combined dystonia. The advents of botulinum toxin injection and deep brain stimulation (DBS) have been paradigm shifts for the symptomatic treatment of dystonia. There has also been recognition that non-motor features are common in dystonia, with inherent challenges for management.

Table 1 | **Aetiologies of dystonia**

Type of disorder	Cause	Main phenotype
Idiopathic dystonia		
Disorders without identifiable cause and with dystonia as the sole feature	Sporadic isolated dystonia	Isolated dystonia with a particular pattern regarding age of onset and body distribution, for example early-onset generalized dystonia starting in legs or late-onset cervical dystonia
Genetically defined disorders		
Disorders of abnormal regulation of gene transcription and neuronal circuit development	Dystonia due to mutations in *TOR1A*, *THAP1*, *GNAL* or *ANO3*	Isolated dystonia
	Dystonia due to mutations in *TAF1*, *SGCE*, *KMT2B*, *PRKRA* or *ADCY5*	Combined dystonia
Disorders of the dopamine pathway	Early-onset Parkinson disease (particularly caused by *PRKN* mutations)	Dystonia–parkinsonism that can sometimes present as isolated exercise-induced foot dystonia in early adulthood
	GCH1 mutations	Dopa-responsive dystonia with diurnal fluctuation that is sometimes combined with parkinsonism and pyramidal signs; onset in childhood
	TH mutations	Dystonia–parkinsonism, oculogyric crisis (paroxysmal, conjugate, tonic upward deviation of the eyes), autonomic disturbance, tremor and myoclonus, and onset in infancy
	Other disorders of dopamine synthesis pathway, such as those caused by mutations in *SPR*, *DDC*, *PTS* and *DNAJC12*	Combined dystonia with axial hypotonia and oculogyric crises that has an onset in infancy
	SLC6A3 mutations	Combined dystonia–parkinsonism with axial hypotonia, irritability, delayed motor milestones and onset in infancy
Disorders with metal accumulation in the basal ganglia	Wilson disease (hepatolenticular degeneration with copper accumulation due to *ATP7B* mutations)	Combined dystonia with tremor, parkinsonism, cerebellar, neuropsychiatric or cognitive features and onset in adolescence or early adulthood
	Neuronal iron accumulation syndromes (due to mutations in, for example, *PANK2*, *PLA2G6*, *WDR45* and *IPPK*)	Combined dystonia with parkinsonism, neuropathy, cerebellar, cognitive and/or neuropsychiatric features and onset in childhood or early adulthood
	Manganese transportopathies (caused by mutations in *SLC30A10* or *SLC39A14*)	Combined dystonia–parkinsonism with childhood onset
Metabolic disorders	Amino acidaemias (for example, glutaric acidaemia type 1 owing to *GCDH* mutations)	Combined dystonia with infancy onset and episodes of intermittent metabolic decompensation with encephalopathy
	GM1 (caused by mutations in *GLB1*) and GM2 gangliosidoses (caused by mutations in *HEXA*, *HEXB* or *GM2A*)	Combined dystonia with parkinsonism, ataxia, pyramidal signs, neuropathy, cognitive decline and infantile onset
	Niemann–Pick type C (caused by mutations in *NPC1* or *NPC2*)	Combined dystonia with vertical gaze palsy, deafness, ataxia, parkinsonism and cognitive decline
	Biotin-thiamine-responsive basal ganglia disease (caused by mutations in *SLC19A3*)	Combined dystonia–parkinsonism with encephalopathic episodes
Synaptopathies and transportopathies	Paroxysmal kinesigenic dyskinesias owing to *PRRT2* mutations	Paroxysmal episodes of brief dystonic posturing triggered by sudden movement
	Exercise-induced dystonia owing to *SLC2A1* mutations	Gradual onset of dystonia in a limb after prolonged exercise of that limb; other manifestations include cerebellar ataxia, epilepsy, spasticity, microcephaly and intellectual disability
	ATP1A3 spectrum disorders	Rapid-onset dystonia–parkinsonism and alternating hemiplegia of childhood with dystonic episodes and oculogyric crises
Other disorders	Mitochondrial disorders (owing to nuclear or mitochondrial mutations that affect mitochondrial function)	Dystonia combined with, for example, ataxia, parkinsonism and/or epilepsy
	DNA repair disorders, such as ataxia telangiectasia (caused by mutations in *ATM*) or ataxia with oculomotor apraxia (caused by mutations in *APTX*, *SETX* or *PNKP*)	Combined dystonia–ataxia syndromes with or without other neurological or systemic features
	Spinocerebellar ataxias (various gene mutations resulting in, for example, channelopathies, polyglutamine disease and/or region-specific cell death)	Combined dystonia–ataxia or dystonia with parkinsonism, pyramidal signs or neuropathy

Table 1 (cont.) | **Aetiologies of dystonia**

Type of disorder	Cause	Main phenotype
Genetically defined disorders (cont.)		
Sporadic neurodegeneration disorders	Idiopathic Parkinson disease	Dystonia (for example, of the foot or neck) preceding or accompanying idiopathic Parkinson disease
	Atypical parkinsonism syndromes	Focal dystonia as a feature in late-onset parkinsonism (for example, blepharospasm in progressive supranuclear palsy, antecollis in multisystem atrophy or hand dystonia in corticobasal syndrome)
Drug-induced disorders	Dopamine receptor blockers	Acute dystonic reaction or tardive dystonia'
Toxic disorders	Excess manganese (caused by, for example, ephedrone abuse, chronic liver disease or total parenteral nutrition)	Combined dystonia–parkinsonism with hypermanganesaemia
	Carbon monoxide, methanol, disulfiram or cyanide poisoning	Delayed onset of combined dystonia–parkinsonism
	Wasp sting encephalopathy	Acute dystonic syndrome with pallidostriatal necrosis after wasp sting
Lesions	Basal ganglia lesions, in particular, those in the putamen, caused by, for example, stroke	Contralateral dystonia
	Perinatal hypoxia	Generalized dystonia as part of cerebral palsy
Infectious diseases	Infections causing basal ganglia lesions, for example, toxoplasmosis, cryptococcosis and abscesses	Symptomatic dystonia contralateral to the lesion
	Japanese B encephalitis	Dystonia or other movement disorders as manifestations of a viral encephalitis with prominent basal ganglia affection
Autoimmune diseases	Autoimmune encephalitis (caused by, for example, LGI1-antibodies, NMDAR-antibodies or Ma2-antibodies)	Dystonic posturing, often combined with other signs of encephalopathy

Dystonia with or without other neurological or systemic features can be the presentation of a wide variety of hereditary, acquired or idiopathic disorders. These disorders can be grouped to highlight important mechanistic pathways (for example, dopaminergic signalling) and structures (for example, the basal ganglia or the cerebellum). Of note, this list is not exhaustive, and some aetiological categories have pathophysiological overlap; for example, Wilson disease can be considered as both a disorder of brain metal accumulation and a metabolic disorder. Similarly, toxic or infectious causes might converge in basal ganglia lesions, causing dystonia. LGI1, leucine-rich glioma-inactivated protein 1; NMDAR, *N*-methyl-D-aspartate receptor.

network disorder. Indeed, differences in the volume of the basal ganglia, cerebellum and cortex have been observed in patients with idiopathic and genetic dystonias using voxel-based morphometry (VBM)[54,55]. However, conflicting data have been reported regarding whether these regions are increased or decreased in volume in patients with dystonia compared with healthy controls, even in the same areas of brain[54,55]. One possible explanation for these differences is that the data might be confounded by the presence of dystonia, as volume changes detected using VBM can be observed by reducing or increasing movement (such as by using restraints or by practising movement, respectively), even in healthy individuals[53,56]. Although the majority of functional imaging studies do not show any abnormalities in discrete anatomical regions in individuals with dystonia compared with healthy individuals, it is possible to distinguish particular spatial patterns of activity that differ in patients with dystonia and healthy controls. Thus, ^{18}F-fluorodeoxyglucose PET (FDG–PET) studies of resting metabolic activity identify a pattern in areas including the posterior putamen, globus pallidus, cerebellum and supplementary motor area that accounts for the variation in brain activity between patients but not healthy volunteers[57]. The speculation is that these regions are anatomically linked together in a network that functions differently in patients with dystonia than in healthy individuals. This notion is also consistent with findings from diffusion tensor imaging studies that demonstrated a reduced integrity of projections in the cerebello-thalamo-cortical pathway in patients with *TOR1A* dystonia compared with healthy controls[34]. In general, network dysfunction may help explain why it is so difficult to identify a single pathological locus in dystonia.

The basal ganglia

As previously mentioned, dystonia was initially viewed as a basal ganglia deficit. This view was based on a classical model of basal ganglia circuitry, in which cortical input to the striatum is relayed to two main output nuclei, the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNpr), through indirect and direct pathways (FIG. 3). In this model, activity in the direct pathway facilitates movement by reducing inhibitory output from the GPi, whereas activation of the indirect pathway increases inhibitory outputs and reduces movement. Dystonia was predicted to result from an imbalance in the direct and indirect pathways, which leads to an abnormally low rate of discharge of inhibitory GPi and SNpr inputs to the thalamus, thereby reducing inhibition of the thalamus and increasing the excitability of the motor cortex (FIG. 3). Conversely, in Parkinson disease, overactivity of GPi and SNpr output is speculated to cause increased inhibition of the thalamus and reduced motor cortex excitability. Supporting this hypothesis, intraoperative recordings during deep

brain surgery demonstrated reduced firing rates of GPi neurons in patients with dystonia[58]; however, pallidotomy and pallidal deep brain stimulation (DBS) are effective treatments for both dystonia and Parkinson disease, which has led to a reassessment of this simple model. Current theories regarding the involvement of the basal ganglia in dystonia suggest that rather than imagining that low and high levels of inhibitory output from the GPi or the SNpr switch all movements on or off, respectively, what is more important is the spatial and temporal patterns of activity within these nuclei. These patterns set up the appropriate patterns of excitation and inhibition that are typical of normal movement and become disordered in both dystonia and Parkinson disease[59]. Supporting this theory, the frequency of local field potentials (that is, the summed electrical potential produced by synchronized synaptic activity in the region surrounding the recording electrode) recorded from DBS electrodes inserted into the GPi is abnormal in patients with dystonia. Indeed, in non-human primates, local field potentials oscillate at ~20 Hz during the resting state and increase to ~80 Hz during movement[60]; however, patients with dystonia have more low-frequency activity (3–12 Hz) at rest[58,61]. The implication is that the neurons in the region surrounding the electrode are linked together by this low-frequency activity and that this prevents them from setting up the flexible spatial and temporal patterns of activity within the nucleus that are characteristic of normal movement.

Box 1 | **Glossary of dystonia phenotypes**

Dystonia described by body distribution

- Generalized dystonia: dystonia affecting trunk and at least two other body sites
- Cervical dystonia: dystonia affecting the neck, leading to abnormal postures of the head; subtypes are torticollis (head turning to one side), laterocollis (tilt to the side), retrocollis (neck extension) and anterocollis (neck flexion)
- Cranial dystonia: dystonia affecting the face or voice; may present as → laryngeal dystonia (also called spasmodic dysphonia), → blepharospasm, → oromandibular dystonia or a combination of the latter two (called Meige syndrome)
- Laryngeal dystonia: also called spasmodic dysphonia; dystonia affecting the vocal cords, leading to a strangled, coarse voice with frequent variations in pitch (adductor type) or, less frequently, to a whispering, breathy voice (abductor type)
- Blepharospasm: dystonia characterized by eye closing spasms
- Oromandibular dystonia: dystonia affecting the mouth and/or jaw, leading to involuntary perioral movements, mouth opening or mouth closing
- Hemidystonia: dystonia affecting only one side of the body

Dystonia manifestations characterized by their relation to voluntary actions or triggers

- Writer's cramp: focal, task-specific dystonia affecting the hand and/or the forearm; it manifests as abnormal posturing when patients attempt to write, which increases as writing continues
- Musician's dystonia: task-specific dystonia that manifests in the body part involved when individuals play a musical instrument
- Paroxysmal dystonia: a dystonia that occurs only intermittently with certain triggers, for example, → exercise-induced dystonia and → paroxysmal kinesigenic dyskinesia
- Exercise-induced dystonia: a dystonia that manifests after prolonged exercise as self-limiting episodes of dystonia in the exercised limb; the most typical manifestation is exercise-induced foot dystonia, which results in in-turning of feet after prolonged walking
- Paroxysmal kinesigenic dyskinesia: a dystonia that manifests as brief self-limiting episodes of dystonic posturing, which are triggered by sudden movements

Neuroplasticity

Given the excess muscle activity and co-contraction that is characteristic of dystonia, initial pathophysiological studies in patients concentrated on measuring the excitability of inhibitory connections within the motor system[62]. Most of these studies were performed on patients with limb, cervical or cranial dystonia and demonstrated that these patients have reduced excitability of inhibitory circuits in the spinal cord, brainstem and cortex[62]. Overall, these abnormalities were greatest in neural circuits nearest to the regions of dystonic movements; for example, the neural circuitry that allows one muscle to relax and another to contract in a set of antagonistic muscles (spinal reciprocal inhibition) is less effective in dystonia, particularly in limb dystonias, and blink reflex suppression is abnormal in patients with blepharospasm[62]. In addition, γ-aminobutyric acid (GABA) receptor A ($GABA_A$)-mediated and $GABA_B$-mediated inhibition of corticospinal neurons in the motor cortex leads them to become less excitable in all forms of dystonia[63]. Collectively, these data are compatible with the idea that reduced excitability of inhibitory connections might lead to excess muscle contraction and contribute to the clinical symptoms of dystonia. However, these changes are often observed in unaffected muscles in patients with focal dystonias[64], and accordingly, they are unlikely to be causative factors but might predispose individuals to dystonia in the presence of other triggering factors.

Alterations in synaptic plasticity might also have a role in the pathophysiology of dystonia. Indeed, animal models of dystonia have demonstrated increased long-term potentiation (LTP) and reduced long-term depression (LTD) in corticostriatal projections[65]. In principle, this could lead to the incorporation of unnecessary patterns of muscle activity into learned actions and thus contribute to dystonia. An increase in LTP at corticostriatal synapses has been demonstrated in striatal slices from transgenic mice overexpressing mutant torsin 1A, together with a loss of LTD and synaptic depotentiation (that is, these neuroplastic changes could not be reversed)[66,67]. Overall, these findings support the idea that a loss of inhibition at the circuit level is a central phenomenon in the pathophysiology of dystonia[68]. No equivalent intraoperative studies have been carried out in patients; however, studies in patients have evaluated plasticity of the motor cortex using new methods of transcranial brain stimulation, such as paired associative stimulation protocols (a means to modulate the excitability of the motor system by changing stimulation parameters). Initial work in patients with limb dystonia found a pronounced increase in the responsiveness to tests of both LTP-like and LTD-like plasticity in the human motor cortex[69]. Although this finding has been replicated in several studies, conflicting data have been reported, probably because of the individual variation in the effect sizes[70]. An interesting finding is that it is easier to demonstrate increased cortical synaptic plasticity in patients with organic dystonia than in patients with psychogenic (functional) dystonia, suggesting that it is an important contributor to clinical signs[71]. Finally, within individuals with limb dystonia, homeostatic control of plasticity is reduced in the motor

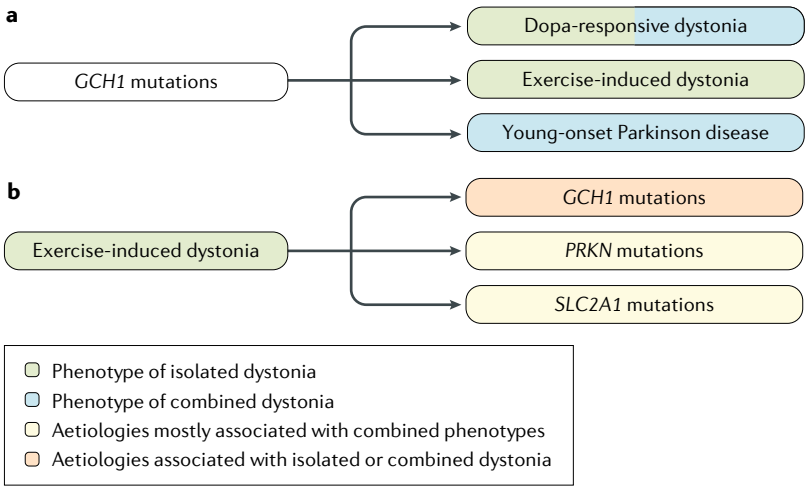

Fig. 2 | **Phenotype–genotype correlations. a** | One gene can lead to many different phenotypes of dystonia. For example, *GCH1* mutations can manifest as isolated dystonia (such as exercise-induced dystonia or dopa-responsive dystonia) and can manifest as dystonia combined with parkinsonism (dystonia–parkinsonism). **b** | Conversely, one dystonia phenotype can be caused by mutations in several genes; for example, exercise-induced dystonia can be caused by *GCH1* mutations (in patients with dopa-responsive dystonia), *SLC2A1* mutations (in patients with glucose transporter type 1 (GLUT1) deficiency) or *PRKN* mutations (in patients with early-onset Parkinson disease).

cortex[72]. These data are all consistent with the idea that excessive muscle contractions in dystonia arise because of unwanted associations between activity in remote muscles and muscles directly involved in the task.

Interestingly, both the excitability of inhibitory connections and the synaptic plasticity in motor cortex change after DBS treatment. Unlike Parkinson disease or essential tremor, in which the response to DBS can be very rapid, the response in dystonia can take days or weeks to reach maximum clinical benefit[73]. Three to six months after starting DBS of the GPi, intracortical $GABA_A$-mediated inhibition improved towards normal levels, following the same time course as the clinical benefit in patients[74]. Interestingly, at 1 month after starting DBS, LTP in the motor cortex, which had been increased before DBS, was absent and returned towards normal levels only over the next 3–6 months as patients achieved maximum clinical benefit[75]. It was postulated that although DBS had an early effect on LTP, the delayed clinical response was due to the presence of a strong motor memory of the abnormal movement patterns. Reduced LTP led to the gradual loss of this motor memory and facilitated the learning of new, more normal patterns of activity.

Sensory involvement

Abnormalities in the sensory system might also contribute to dystonia. Abnormalities in temporal discrimination (that is, the ability to determine whether two sensory stimuli are separated in time) and spatial discrimination (the ability to determine whether two sensory stimuli are separated in location) have been demonstrated in patients with focal dystonia[76], in addition to subtle changes in the somatotopy of the sensory cortex as assessed by functional MRI (fMRI)[77]. Indeed, a recent study suggests that the primary deficit in patients with dystonia is in spatial rather than temporal processing[78]. In addition, deficits in spatial processing might explain why sensory tricks (see the Diagnosis, screening and prevention section below) might be useful in some patients.

Such sensory deficits might be accompanied by disordered sensorimotor integration (the interaction of sensory inputs and motor output). For example, expected sensory inputs are reduced (or 'gated') during movement so that the motor system can respond to unexpected inputs that might otherwise disrupt the action. For example, if we lift a weight that is heavier than expected, the unexpected input is quickly detected and leads to an automatic increase in motor output. Physiologically, this gating can be observed by noting that sensory evoked electroencephalography (EEG) potentials that are produced by the electrical stimulation of a peripheral nerve are smaller at the onset of movement than during rest, implying that the transmission of sensory input to cortex has become less effective[79]. This gating is absent in dystonia and could cause the motor system to assume that movement is not progressing as expected and lead to additional (compensatory) motor output that contributes to dystonia[80]. Similarly, EEG coherence studies demonstrated a reduced interaction between parietal and motor regions during performance of learned movement sequences that was compatible with abnormal interaction between sensory and motor areas[81]. Further evidence for a role of sensorimotor integration in dystonia is based on the role of the 'geste antagoniste' (see the Diagnosis, screening and prevention section). Several physiological studies into this manoeuvre have led to speculation about the mechanism of action. For example, one PET study demonstrated increased activity in the superior parietal cortex ipsilateral to the head turn after the geste antagoniste had been performed and suggested that this finding changed the perceptual balance to favour a more natural head position[82]. Another study demonstrated reduced excitability of the blink reflex after the geste antagoniste, speculating that facial nerve activity associated with this manoeuvre reduced (or gated) the effectiveness of trigeminal sensory afferent signalling, thereby reducing the blink reflex[83]. However, separating cause and effect in such experiments is difficult; although the geste antagoniste can be controlled by asking healthy individuals to mimic the gesture, the change in head posture and muscle contraction that comes with the manoeuvre cannot be controlled for, which could influence results.

Cerebellar involvement

In recognition of dystonia as a network disorder involving the cerebellum as well as basal ganglia, several physiological studies have examined the role of the cerebellum in dystonia using transcranial magnetic stimulation (TMS) and eyeblink classical conditioning (EBCC). TMS over the cerebellum produces a transient reduction in excitability of the hand area of the motor cortex, an effect that is reduced or abolished in patients with focal hand dystonias[84]. These findings are consistent with disruption of the cerebello-thalamo-cortical pathway, which has been demonstrated in studies using PET. EBCC is a form of learning in which an eyeblink response produced by an electrical stimulus to the supraorbital nerve

Table 2 | **Typical clinical presentations of the most common monogenic dystonias**

Gene (previous DYT symbol[a])	Inheritance	Age at onset	Prevalent site at onset	Distribution	Body parts involved	Additional signs
Isolated dystonia						
TOR1A (*DYT1*)	Autosomal dominant	First to third decade	Lower limbs much more likely than upper limbs	Mostly generalized	• Lower limbs[b] • Upper limbs • Trunk	None
THAP1 (*DYT6*)	Autosomal dominant (autosomal recessive in rare cases)	Second to third decade (ranging from first to seventh decade)	Neck and upper limbs	Focal, segmental and generalized	• Neck[b] • Upper limbs[b] • Orofacial areas • Larynx • Lower limbs	None
GNAL (*DYT25*)	Autosomal dominant (autosomal recessive in rare cases)	Fourth decade (ranging from first to seventh decade)	Neck	Mostly focal or segmental and occasionally generalized	• Neck[b] • Orofacial areas • Larynx • Upper limbs • Lower limbs	None
ANO3 (*DYT24*)	Autosomal dominant	Fourth to fifth decade (ranging from first to fifth decade)	Neck and larynx	Segmental	• Neck[b] • Upper limbs • Orofacial areas • Larynx	None
Combined dystonia						
GCH1 (*DYT5a*)	Autosomal dominant (autosomal recessive in rare cases)	First to sixth decade	Lower limbs	Mostly generalized	• Lower limbs[b] • Trunk • Upper limbs	• Diurnal variation with worsening over the day • Parkinsonism • Spasticity
TH (*DYT5b*)	Autosomal recessive	<1 year	Lower limbs	Mostly generalized	• Lower limbs • Trunk • Upper limbs • Orofacial areas	• Parkinsonism • Ptosis • Oculogyric crisis • Developmental delay • Encephalopathy • Myoclonus
SPR	Autosomal recessive	<1 year	Lower limbs	Mostly generalized	• Lower limbs • Trunk • Upper limbs • Orofacial areas	• Parkinsonism • Axial hypotonia • Development delay • Oculogyric crises • Muscle weakness • Intellectual disability
SGCE (*DYT11*)	Autosomal dominant	First to second decade	Neck and upper limbs	Focal and segmental	• Neck[b] • Upper limbs[b] • Orofacial areas	• Prominent lightning-like myoclonic jerks affecting predominantly the neck • Amelioration of motor symptoms (mainly myoclonus) following alcohol ingestion • Prominent psychiatric features (including depression, anxiety and obsessive–compulsive disorders)
KMT2B (*DYT28*)	Autosomal dominant and/or de novo	First decade (ranging from first to second decade)	Upper limbs and lower limbs	Usually generalized and rarely focal	• Orofacial[b] • Larynx[b] • Neck • Upper limbs • Lower limbs[b] • Trunk[b]	• Microcephaly • Short stature • Intellectual disability • Abnormal eye movements • Myoclonus • Dysmorphisms • Psychiatric symptoms • Systemic features
PRKRA (*DYT16*)	Autosomal recessive	First to second decade	Lower limbs, upper limbs and larynx	Generalized	• Orofacial areas • Larynx • Neck • Upper limbs • Lower limbs • Trunk	• Parkinsonism • Hyperreflexia
TAF1 (*DYT3*)	X-linked	Third to fourth decade	Neck and oromandibular areas	Generalized	• Orofacial areas • Neck • Upper limbs • Lower limbs • Trunk	• Parkinsonism • Striatal atrophy on MRI

Table 2 (cont.) | **Typical clinical presentations of the most common monogenic dystonias**

Gene (previous DYT symbol[a])	Inheritance	Age at onset	Prevalent site at onset	Distribution	Body parts involved	Additional signs
Combined dystonia (cont.)						
ATP1A3 (*DYT12*)	Autosomal dominant and/or de novo	First to fourth decade	Oromandibular areas and upper limbs	Generalized or segmental dystonia	• Orofacial areas[b] • Larynx[b] • Upper limbs[b] • Cervical areas • Lower limbs	• Abrupt onset • Fluctuating course • Parkinsonism • Postural instability • Psychiatric features
ADCY5	Autosomal dominant and/or de novo (autosomal recessive in rare cases)	First decade	Lower limbs	Generalized	• Orofacial • Cervical areas • Upper limbs • Lower limbs • Trunk	• Axial hypotonia • Delayed milestones • Facial twitches • Chorea • Myoclonus • Oculomotor apraxia • Episodic exacerbations often triggered by transitions to and from sleep

The table lists the most common and relevant forms of monogenic isolated or combined dystonia. Many genetic conditions in which dystonia is part of the clinical syndrome have been recognized, and they are beyond the scope of this Primer but are reviewed elsewhere[44,252]. [a]The use of the classification system of genetic dystonias that is based on the DYT loci numbering has been recently discouraged and progressively abandoned[253]. [b]Sites most commonly affected.

(the unconditioned stimulus) is repeatedly paired with a preceding auditory cue (the conditioned stimulus); after several pairings, the conditioned stimulus alone initiates the blink response. The association between these stimuli involves the cerebellar cortex and is less effective in patients with cervical dystonia[84], although it is normal in secondary dystonia as well as in *TOR1A*-associated and *THAP1*-associated dystonia, suggesting that the cerebellum has a different role in different forms of dystonia[85,86]. A role for the cerebellum has also been implicated in dystonia owing to the presence of abnormalities in motor learning of tasks that involve cerebellar function. For example, in *TOR1A*-associated dystonia, both individuals with clinical manifestations and those without manifestations are impaired in sequence learning, and fMRI studies demonstrated overactivity of the left cerebellar cortex while the right arm was moved in individuals with *TOR1A*-associated dystonia compared with healthy individuals. However, a recent study failed to replicate a sequence learning effect in cervical dystonia[87–89]. Learning to adapt arm reaching movements to a novel force field or to altered visual feedback in a visuomotor rotation task was also found to be normal in patients with cervical dystonia[90]. Thus the behavioural consequences of the physiological changes in the cerebellum are somewhat unclear.

Dopaminergic involvement

An involvement of the dopaminergic system has been consistently reported in patients with dystonia[91,92]. One typical example of this involvement is the dopa-responsive dystonia syndromes, which are associated with mutations in genes encoding enzymes involved in dopamine synthesis, such as *GCH1*, *TH* and *SPR*, and result in reduced levels of dopamine and related metabolites[93–96]. In addition, dopamine receptor blockers commonly cause dystonia, further supporting a role for this network in dystonia pathophysiology[97]. Neuroimaging studies have demonstrated a reduced availability of D2 dopamine receptors in the striatum of patients with different forms of dystonia (mostly *TOR1A*-related and *THAP1*-related dystonia but also focal dystonia such as writer's cramp or cervical dystonia)[88,98–100], and increased availability of striatal D1 dopamine receptors has been reported in individuals with focal dystonia[101]. These findings corroborate the involvement of striatal dopaminergic dysfunction in the imbalance between the direct and the indirect basal ganglia pathways[102] (FIG. 3).

More-recent evidence from genetic studies further supports a central involvement of striatal dopamine in dystonia pathogenesis; for example, several isolated and combined dystonia-associated genes (such as *GNAL* and *ADCY5*) are expressed mostly in striatal neurons and modulate responses to dopaminergic stimulation[103]. In addition, mutations in *PDE10A* (which encodes cAMP and cAMP-inhibited cGMP 3′,5′-cyclic phosphodiesterase 10A, the main enzyme regulating striatal degradation of cyclic nucleotides) have also been linked to hyperkinetic movement disorders[104,105]. *GNAL* encodes guanine nucleotide-binding protein G(olf) subunit α ($G\alpha_{olf}$), a subunit of the triheteromeric G protein G_{olf}, which is robustly expressed in the striatum and has a role in signal transduction of dopamine and adenosine signalling[106]. $G\alpha_{olf}$ has been observed in striatal spiny projection neurons (SPNs), including SPNs forming both the direct (D1 receptors) and the indirect (D2 and adenosine A2A receptors) pathways, in addition to in cholinergic interneurons[106,107]. D2 and adenosine A2A receptors are co-expressed in SPNs, and A2A receptors have an antagonistic effect on D2 receptors. Both D1 and A2A receptors are coupled to G_{olf} to activate adenylate cyclase type 5 (which is encoded by *ADCY5*, the enzyme responsible for the regulation of cAMP synthesis in the striatum[108]) and cAMP production[106,109,110], whereas D2 receptors are negatively coupled to adenylyl cyclase and restrict cAMP production[109,110]. Accordingly, *GNAL* mutations are expected to lead to uncoupling between the activation of D1 and A2A receptors and cAMP production,

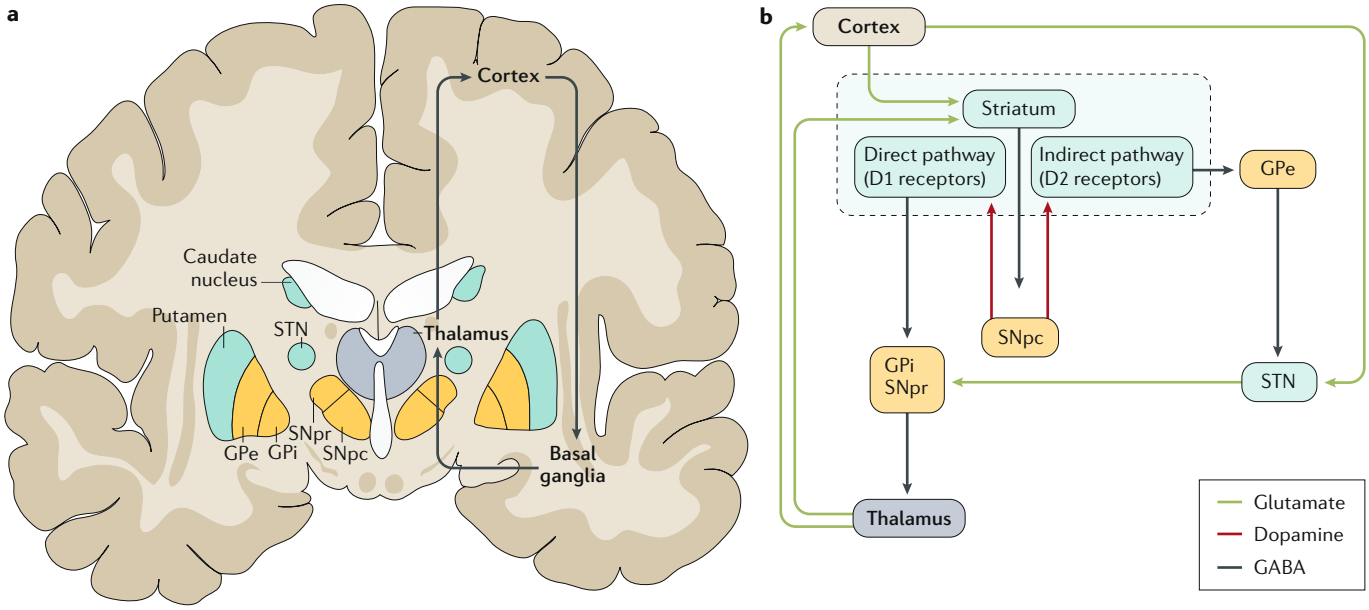

Fig. 3 | **Highly simplified representation of the basal ganglia circuit.** **a** | An overview of the anatomy of the cortico-striato-thalamo circuit is shown. **b** | Cortico-striatal input to the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNpr) travels via two main pathways: the direct pathway and the indirect pathway. The indirect pathway involves relay through the globus pallidus externus (GPe) and the subthalamic nucleus (STN). Stimulation of the direct pathway inhibits neurons of the GPi and the SNpr, which consequently removes inhibition of thalamic neurons and facilitates motor activity. Conversely, stimulation of the indirect pathway leads to excitation of GPi and SNpr neurons, which inhibit thalamic neurons, thereby reducing motor activity. In parallel with this is the 'hyperdirect' pathway, which includes a direct excitatory projection from cortex to STN, but its role in dystonia is at present unclear. The dopaminergic neurons of the substantia nigra pars compacta (SNpc) project to the striatum, where they synapse with excitatory postsynaptic dopamine D1 receptors of the direct pathway and with inhibitory postsynaptic dopamine D2 receptors on striatal neurons of the indirect pathway. GABA, γ-aminobutyric acid. Adapted from REF.[251], Springer Nature Limited.

ultimately leading to an imbalance between direct and indirect pathways, with inhibitory D2 receptors prevailing. Indeed, mouse models of *GNAL*-related dystonia have shown alterations in striatal dopamine function; specifically, the locomotor effects of amphetamine and caffeine (which positively affect dopamine and adenosine signalling, respectively) were markedly reduced in mice with heterozygous *GNAL*-null mutations[109–111], indicating that alterations in $G\alpha_{olf}$ expression might modify the responses to drugs of abuse and impair other behavioural responses linked to dopamine function[109,111,112].

Other dystonia-causing genes, including *KCTD17* (which encodes a protein adaptor for ubiquitin ligation for targeting proteins for proteasomal degradation and was recently implicated in postsynaptic function modulation)[113] and *HPCA* (which encodes neuron-specific calcium-binding protein hippocalcin, a neuronal calcium sensor)[114], have been shown to modulate postsynaptic dopaminergic responses in *Drosophila melanogaster*, although the exact mechanisms are not known[115–117]. Moreover, altered dopaminergic signalling underlies the most frequent genetic dystonias (including those associated with mutations in *TOR1A*, *THAP1*, *KMT2B* and *SGCE*). Reduced expression of D2 receptors has been observed in the striata of patients with *TOR1A* and *THAP1* mutations[88], as well as in the cerebrospinal fluid (CSF) of patients with *KMT2B* mutations[118]. Altered striatal dopaminergic neurotransmission has also been reported in animal models of *TOR1A*-related and *SGCE*-related dystonia[119–122]. Indeed, abnormal striatal D2 receptor function has been demonstrated in a number of *TOR1A* rodent models, whereby D2 receptor activation led to aberrant excitation, rather than inhibition, of cholinergic neurotransmission in the striatum[123]. Modulation of striatal SPNs by acetylcholine released from striatal cholinergic interneurons is central for appropriate motor control, and loss of the reciprocal modulation between striatal dopamine and acetylcholine, leading to increased cholinergic activity, represents a primary pathophysiological event in both Parkinson disease and dystonia. Accordingly, features of impaired striatal plasticity are reverted by anticholinergic agents[124,125], which are one of the few pharmacological options available for the treatment of dystonia (see the Management section).

Molecular mechanisms

The molecular mechanisms underlying the abnormal neuronal activity responsible for dystonic movements are not entirely understood. Yet, as for other complex neurological disorders, the identification of monogenic causes of dystonia has been pivotal for the initial recognition of shared molecular pathways that are likely to be central dystonia mechanisms. As mentioned above, some genetic causes of dystonia influence presynaptic (for example, mutations in *GCH1*, *TH*, *SPR*) and postsynaptic (for example, mutations in *GNAL*, *ADCY5*) dopaminergic signalling in striatal neurons; this section reviews the other convergent pathways that are central for dystonia (FIG. 4). The mechanisms responsible for the pathogenesis of some of the most recently identified dystonia-associated genes (such as, *ANO3*, *HPCA* and *VPS16*) have not been

elucidated yet, although preliminary data suggests that *ANO3* and *HPCA* have a role in regulating calcium signalling in striatal neurons[26,35,126]. In this section, we focus on the convergent molecular pathways that are central to the pathogenesis of the more established genetic forms of dystonias (that is, *TOR1A*-related, *THAP1*-related and *KMT2B*-related dystonias).

Abnormal endoplasmic reticulum homeostasis and stress response. Torsin 1A, the product of *TOR1A*, is mainly localized to the endoplasmic reticulum (ER)[127,128], and the common *TOR1A*-related dystonia-causing mutation results in mislocalization of the protein product from the ER to the nuclear envelope[129]. Several studies in animal models have confirmed a link between the expression of aberrant torsin 1A and defects in ER function, including reduced ER volume, increased ER stress and abnormalities in folding, assembly and trafficking of ER proteins targeted for secretion (for example, synaptic vesicles) or to enter membranes (for example, D2 receptors; see below)[130–134].

Importantly, how *TOR1A*-induced ER dysfunction translates into abnormal neuronal activity is poorly understood, although reduced activation of the eukaryotic translation initiation factor 2 subunit α (eIF2α; also known as EIF2S1) pathway, a critical mediator of ER integrated stress response signalling (that is, the unfolded protein response), might have a central role[135]. In addition, the eIF2α pathway has been linked to the regulation of neuronal LTP, possibly through translational regulation of metabotropic glutamatergic receptors[136,137], and therefore, these results might represent a direct link between torsin 1A, ER stress and abnormal synaptic plasticity. In addition, the dystonia gene *PRKRA* encodes a kinase responsible for activation of the eIF2α pathway response, further supporting a link between the eIF2α pathway and dystonia cellular pathogenesis[138].

Abnormal regulation of gene transcription. The identification of dystonia-causing mutations in *THAP1* and *KMT2B* has implicated aberrant gene transcription as a molecular mechanism of dystonia. *THAP1* encodes THAP domain-containing protein 1, an atypical zinc-finger protein that has a DNA-binding domain that regulates gene transcription[139]. *KMT2B* encodes histone-lysine *N*-methyltransferase 2B, which is involved in chromatin plasticity and the epigenetic regulation of gene expression[140]. Indeed, several loss-of-function mutations have been identified in both genes, suggesting that a loss of their pro-transcriptional activity is the pathogenetic mechanism underlying dystonia. Intriguingly, a direct interaction between *KMT2B*, *THAP1* and *TOR1A* has been suggested. THAP1 binding to the *TOR1A* promoter to repress *TOR1A* expression has been demonstrated in vitro, and *THAP1*-related dystonia-causing mutations were found to impair this interaction[141]. However, whether this association has

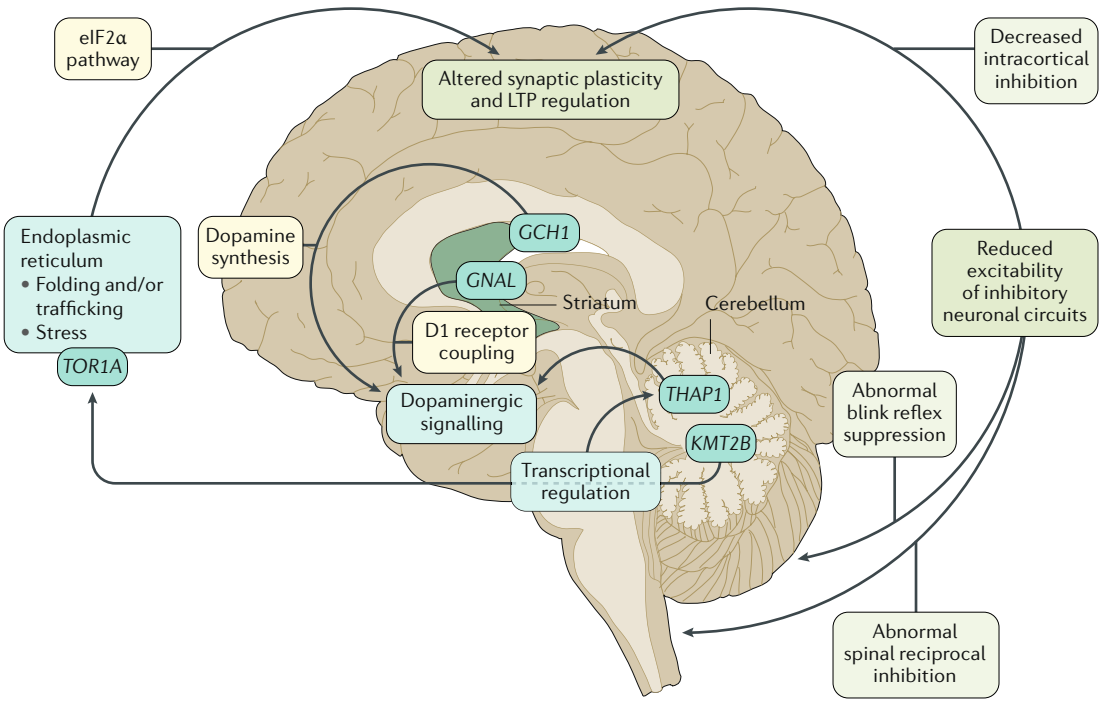

Fig. 4 | **Pathophysiology of dystonia.** A simplified and preliminary model of the pathophysiology of dystonia based on genetic and neurophysiology findings is shown. Most dystonia-associated genes are mainly expressed in the striatum (such as *GNAL*, *ANO3*, *ADCY5*, *HPCA* and *KCTD17*), whereas others have the highest expression in the cerebellum (such as *THAP1* and *KMT2B*), and these two brain structures have a critical role in the pathophysiology of dystonia. Molecular dysfunction related to dystonia genes indicates alterations of transcriptional regulation and dopaminergic signalling, as well as malfunctioning of the endoplasmic reticulum (ER). The eukaryotic translation initiation factor 2 subunit α (eIF2α) pathway links ER function to alternated synaptic plasticity and long-term potentiation (LTP). In a sum, there is a lack of inhibition and increased excitability in the cortical, brainstem and spinal cord circuits, leading to the facilitation of movement. D1 receptor, dopamine D1 receptor.

relevance in vivo has not been established, and no abnormal regulation of *TOR1A* could be detected in a mouse model of *THAP1*-related dystonia[142]. Reduced levels of *TOR1A* and *THAP1* mRNA and protein were detected in fibroblasts from *KMT2B* mutation carriers[118], suggesting that KMT2B is an upstream regulator of other, isolated dystonia-related genes.

The cellular function of THAP1 and KMT2B suggests that these proteins have an essential role for abnormal development and maturation of the neuronal circuits involved in movement production and control. Of note, both *THAP1* and *KMT2B* have the highest brain expression in the cerebellum[118,143], possibly indicating a critical role for these genes in the correct development of cerebellar neurons and pathways. This hypothesis is supported by the observation of subtle but definite structural abnormalities of deep cerebellar nuclei in knock-in and knockout *THAP1* mouse models[142]. Furthermore, THAP1 regulates survival and proliferation of mouse embryonic stem cells, and dystonia-causing mutations result in failure of differentiation towards the neuroectodermal fate[144].

Diagnosis, screening and prevention

General features

According to a consensus statement from the International Movement Disorders Society, dystonia is defined as "sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both"[2]. Dystonic movements are most evident on action and are often patterned. The consensus statement also recognizes and includes tremor as part of the motor phenomenology of dystonia[2]. Dystonic tremor is a rhythmical, albeit often inconstant, patterned movement that can precede the onset of overt dystonic posturing[26]. In some patients, dystonic tremor can decrease in severity and amplitude or can completely stop when the dystonic posture is allowed to fully develop without resistance (that is, the null point), although this might not always occur.

Dystonic movement can spread to adjacent or other body regions during movement of the body part primarily affected by dystonia (known as overflow); for example, patients with writer's cramp might not only have dystonic posturing of the hand while writing but may also have contractions of more proximal muscles[145]. Mirror dystonia is one form of overflow, which refers to unintentional dystonic movement in the contralateral limb when a voluntary movement is performed on one side. Dystonia can be task-specific and occur when patients perform certain actions, such as in writer's cramp or musician's dystonia (two examples of task-specific dystonia) (BOX 1). Similarly, dystonic posturing or tremor can be evident only when patients adopt certain postures. The signs of dystonia can be variable and can worsen with stress and anxiety; in turn, susceptibility for anxiety and depression is considered part of the non-motor syndrome of dystonia[146].

An important feature of dystonia is the geste antagoniste or sensory trick, which comprises a voluntary movement such as, for example, touching the affected or nearby body part to alleviate the dystonic posturing[147]. Typically, patients with cervical dystonia may touch the side of the face to correct the head position (Supplementary Video 2). Often, improvement of the dystonic posture can be discerned even before the touch. This is a fairly specific sign in dystonia and thus a useful clinical clue to the diagnosis.

As indicated in the Epidemiology section, isolated idiopathic or genetic dystonia follows a particular pattern with regard to age of onset, body distribution and sex preponderance.

Early-onset generalized isolated dystonia. Early-onset (that is, symptom presentation in the first three decades of life) manifestations usually have onset in the legs with subsequent generalization (affecting the trunk and at least two other body regions). In most patients, the initial signs consist of inversion of the feet and pigeon-toed walking, before spreading to other regions. Generalization occurs in 70% of patients, but typically, the cranial region is spared[15].

Adult-onset focal or segmental isolated dystonia. Adult-onset focal or segmental dystonia includes task-specific dystonias, cervical dystonia and/or cranial dystonia. Isolated idiopathic dystonia manifesting during middle adulthood (typically during the fourth decade of life) typically affects the arms; the classic example of this form of dystonia is writer's cramp. Writer's cramp manifests initially as excessive tightness of the hand or forearm muscles and subsequently with abnormal hand posturing when attempting to write. Other task-specific dystonias have been described in piano players, typists and hairdressers and after other activities involving prolonged repetitive and stereotyped movements. Later in life, typical manifestations include cervical and/ or cranial dystonia. The most frequent form of cervical dystonia is torticollis (head turning to one side), but other variations exist, such as laterocollis (neck tilting to the side), retrocollis (neck extension) and anterocollis (neck flexion), as well as mixed or tremulous forms. Cranial dystonia includes blepharospasm with involuntary eyelid closure and oromandibular dystonia. Craniocervical dystonias rarely have a known genetic cause, although familial forms do exist, such as those associated with mutations in *ANO3* and *GNAL*[8,148].

Manifestation patterns of isolated genetic dystonia. *TOR1A*-related dystonia typically manifests in childhood with lower-limb dystonia, which tends to generalize within a few years but typically spares the cranial region[15,149]. This characteristic presentation was described by Oppenheim in 1911 as 'dystonia musculorum deformans' and subsequently called primary torsion dystonia.

THAP1-associated, *GNAL*-associated and *ANO3*-associated dystonias have ages of onset that range from the first to the sixth decade of life[23,24,150]. The oromandibular, cervical and laryngeal regions are commonly affected in patients, and the neck is usually the main site of onset (in addition to the arm in individuals with *THAP1* mutations). Head and/or arm tremor (which is often the first manifestation) is a feature of *ANO3*-associated dystonia, which tends to remain focal or segmental and can be associated with myoclonic jerks[150]. Spreading of dystonia can occur in *THAP1* or

GNAL mutation carriers, with subsequent generalization in a subset of patients and reported intra-familial variability[23,24].

Most patients that have *HPCA*-associated, *COL6A3*-associated or *VPS16*-associated dystonia present with early-onset segmental or generalized dystonia. However, larger cohorts are needed to better define genotype–phenotype correlations in recessive isolated dystonia.

Manifestation patterns of combined genetic dystonia. Combined dystonias might be caused by monogenic disorders, such as dystonia–parkinsonism owing to *GCH1*, *PRKRA*, *TAF1* or *ATP1A3* mutations[43] (TABLES 1,2).

GCH1 mutations are usually inherited in a dominant manner and cause early-onset dopa-responsive dystonia (BOX 1; TABLES 1,2). Patients typically have predominantly lower-limb dystonia, which worsens throughout the day (diurnal fluctuation), and an excellent response to treatment with small doses of levodopa[7]. Some patients may have associated parkinsonism, and some may present purely with parkinsonism when onset is at a later age.

Mutations in other genes that are functionally related to *GCH1* (such as *TH*, *SPR* and others) (TABLE 1) have been associated with recessive and more severe forms of dopa-responsive dystonia[151]. The earlier treatment is initiated, the better the prognosis, and a high index of suspicion is therefore justified. Moreover, many patients with dopa-responsive dystonia have been erroneously diagnosed with cerebral palsy, and therefore, anyone with such a diagnosis should be trialled with levodopa.

Individuals with recessive *PRKRA* mutations are characterized by early symptom onset with severe generalized dystonia–parkinsonism with prominent cranial involvement[152–154].

An atypical intronic mutation (a SINE-VNTR-Alu (SVA)-type retrotransposon insertion) in *TAF1* (located on the X chromosome) results in a late-onset neurodegenerative form of X-linked recessive dystonia–parkinsonism, which has exclusively been reported in males from Panay in the Philippines[155].

ATP1A3 mutations were initially identified as the cause of rapid-onset dystonia–parkinsonism, which is a very rare autosomal dominant syndrome that is characterized by abrupt onset of dystonia, typically involving the orobulbar region and the upper limbs, and axial parkinsonism, triggered by either physical or psychological stress[156,157]. De novo *ATP1A3* mutations cause alternating hemiplegia of childhood[158,159], a more common disorder of childhood that is characterized by recurrent hemiplegic (weakness of one side of the body) or hemidystonic (BOX 1) episodes followed in most patients by the development of progressive motor and cognitive dysfunction[160].

Other causes of combined dystonias include dominant point mutations and genomic deletions in *KMT2B* (often occurring de novo). Indeed, mutations in *KMT2B* are a somewhat frequent cause of early-onset generalized dystonia, which often has prominent bulbar involvement and additional features such as small stature, dysmorphia, intellectual disability, epilepsy or spasticity[118,161]. However, although the main phenotype of *KMT2B* mutations is combined dystonia, forms that have only subtle additional features have been reported[118,161,162]. Myoclonus–dystonia, another example of a combined dystonia syndrome, is frequently caused by dominant mutations in *SGCE*[163] and is also rarely associated with dominant mutations in *KCTD17* (REF.[116]); de novo and dominant mutations in *ADCY5* have also been recognized as an important cause of a range of hyperkinetic movement disorders, including myoclonus, dystonia and chorea, and these usually present together in a variable combination[164–166].

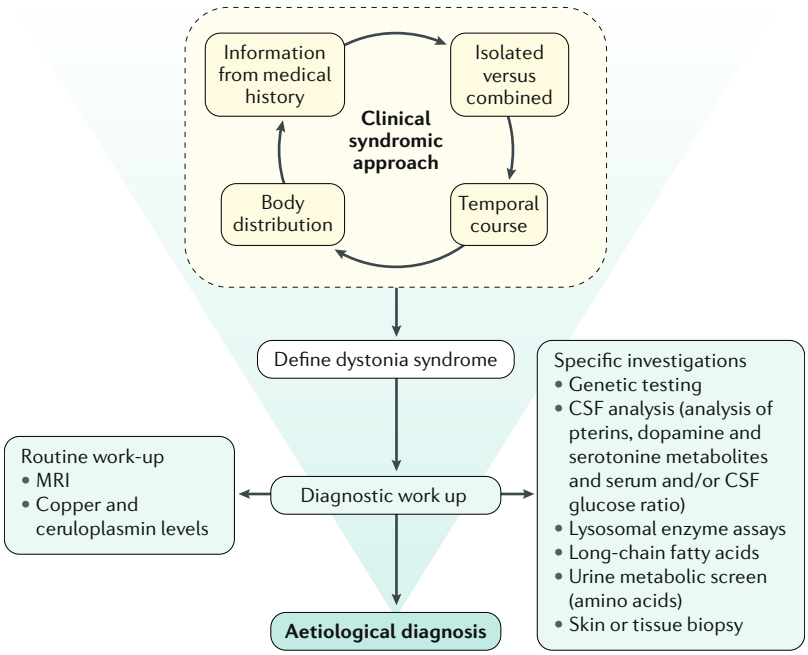

Fig. 5 | **Diagnostic approach.** A clinical syndromic approach, taking into account history and findings from clinical examination (including the distribution of dystonia, the age at onset, temporary evolution and the presence or absence of additional neurological or systemic signs), leads to the diagnosis of a dystonia syndrome, which in turn guides the further diagnostic work-up that aims to identify the aetiology. Generally, if the clinical features are in keeping with isolated idiopathic dystonia, further routine investigations aim to exclude other aetiologies that rarely can manifest with isolated dystonia, such as MRI to exclude structural abnormalities or copper and ceruloplasmin levels to screen for Wilson disease. If clinical features suggest other aetiologies, the diagnostic work-up will be tailored to that patient, and more-specific investigations will be required, including genetic testing and analysis of cerebrospinal fluid (CSF) or tissue biopsy samples, among others.

Diagnostic work-up

Because of the lack of a defining or unifying biomarker for dystonia, its diagnosis remains a clinical one based on the above outlined features. Similarly, because dystonia is not just a single disease but the manifesting sign in many disorders with different aetiologies, the further diagnostic approach is primarily based on the clinical characteristics. These define the syndromic diagnosis that then guides the further investigations aimed at unravelling the underlying aetiology (FIG. 5). Above, we have described the typical pattern of isolated idiopathic dystonia, which represents the majority of individuals with dystonia in outpatient clinics, and highlighted the red flags cautioning against such a diagnosis (BOX 2).

A genetic aetiology of isolated dystonia is suspected if the patient has a positive family history of dystonia or presents early in life. Subsequent genetic testing is

Box 2 | **Red flags against a diagnosis of idiopathic dystonia**

- Unusual pattern of clinical manifestations with regard to the age at onset and distribution
- Sudden onset of symptoms with rapid progression
- History of perinatal birth injury or developmental delay
- Exposure to drugs (such as dopamine receptor blockers)
- Presence of other neurological or systemic signs (which would indicate combined dystonia)
- Prominent bulbar involvement with tongue protrusion and dysphagia
- Hemidystonia (which is indicative of structural lesions causing dystonia)
- Fixed dystonia (which is indicative of psychogenic dystonia)

guided by the clinical characteristics of patients, as described above and in TABLE 2. Identifying a genetic cause of dystonia is important, as some forms can inform prognosis and predict treatment response; for example, *TOR1A*-associated dystonia responds strongly to DBS, whereas the results are less encouraging for dystonia owing to *THAP1* mutations[167].

In general, brain MRI and blood tests in patients with isolated idiopathic dystonia do not reveal any abnormality and are carried out to rule out mimickers of isolated idiopathic dystonia. This is because, rarely, diseases typically presenting as combined dystonia may not manifest the full spectrum of symptoms and therefore mimic isolated dystonia and its causes.

Another consideration during the diagnostic work-up for dystonia is that treatable conditions should not be missed. An example for the above would be Wilson disease, which can be diagnosed using blood tests to assess copper and ceruloplasmin levels, and accordingly, these blood tests should be part of any dystonia work-up. Another treatable cause of combined dystonia is Niemann–Pick type C, a lysosomal storage disorder that can be screened for using lysosomal enzyme assays[168]. It can be diagnosed using skin biopsy (filipin staining demonstrating excessive storage of unesterified cholesterol) or by molecular genetic testing to identify disease-causing mutations in *NPC1* or *NPC2*.

Further examples of disorders that cause combined dystonia are aminoacidaemias (diagnosed on the basis of urine metabolic screen), adrenoleukodystrophy (screening of long-chain fatty acid levels in blood) and mitochondrial disorders (diagnosis is based on muscle biopsy or molecular genetic testing to identify disease-causing mutations)[169]. Other, rare examples of conditions causing combined dystonia with specific treatment implications are reviewed elsewhere[168].

The syndromic diagnosis of dystonia also takes into account that some forms of dystonia have a particular temporal pattern, which might suggest the underlying aetiology.

For example, paroxysmal dystonia occurs after certain triggers, such as prolonged exercise in exercise-induced dystonia (BOX 1). This can be a manifestation of dopa-responsive dystonia owing to *GCH1* mutations (see above and TABLE 2), due to a genetic defect in *SLC2A1* (which encodes glucose transporter type 1, erythrocyte/brain (GLUT1)) or a feature of young-onset Parkinson disease[170]. In this syndrome, the diagnostic work-up can comprise CSF analysis to detect dopamine synthesis pathway defects, as seen with *GCH1*-related dystonia, or measurement of the CSF–serum glucose ratio (which is typically <0.4 in patients with GLUT1 deficiency)[171]. Alternatively, genetic testing for mutations in the respective genes can be undertaken.

Young-onset Parkinson disease, if suspected when presenting as dystonia, can be confirmed by means of an abnormal dopamine transporter (DAT)–single-photon emission CT (SPECT) scan.

Screening and prevention

A predictive biomarker that can identify individuals at risk of developing isolated idiopathic dystonia or a measure to prevent isolated idiopathic or genetic dystonia from manifesting is not available. However, some symptomatic forms of dystonia can be prevented, such as drug-induced dystonia caused by exposure to drugs that block dopamine receptors (also referred to as neuroleptic drugs, such as certain antipsychotics and anti-emetics). Drug-induced dystonia can occur as acute dystonic reaction or as tardive dystonia[172]. Acute dystonic reaction typically occurs immediately after taking the neuroleptic drug and can manifest as oculogyric crises (paroxysmal, conjugate, tonic upward deviation of the eyes), jaw opening dystonia, cervical dystonia or other forms of focal or segmental transient dystonias. Tardive dystonia usually occurs after treatment with neuroleptics for several weeks or months and manifests as retrocollis, opisthotonic posturing (back arching), arm extension and pronation, and other forms of dystonia. Tardive dystonia usually occurs in young individuals, as opposed to typical tardive dyskinesia (orofacial-lingual stereotypy), which occurs most frequently in older women. Acute dystonic reactions can be very distressing but subside when the pharmaceutical agent is withdrawn; however, tardive dystonia often persists and can be severely disabling[173]. To prevent both forms of drug-induced dystonia, careful consideration of the indication of any dopamine receptor blocking agent and limitation of their use to a minimum are recommended.

Management

Although pathogenesis-targeted therapy is desirable, the treatment of dystonia is largely symptomatic owing to a lack of understanding of the exact mechanisms of most dystonias[174]. When appropriate therapy is selected, on the basis of distribution, severity and other factors, dystonic symptoms are generally well managed. In patients with isolated dystonia, the treatment is largely determined by the distribution and severity of symptoms. In general, botulinum toxin (BoNT) is the initial treatment of choice for patients with focal or segmental dystonia, whereas generalized dystonia is typically treated pharmacologically with levodopa, anticholinergics or oral baclofen and surgically with intrathecal baclofen infusion in patients with axial and leg dystonia and by DBS in patients with medically refractory, disabling generalized dystonia. ln patients

with rare dystonias, such as dystonia caused by metabolic abnormalities, structural lesions or autoimmune disorders, the treatment can be directed against the specific aetiology[168].

Assessing the efficacy of therapeutic interventions for dystonia is challenging, as this disorder has a heterogeneous manifestation and the severity of symptoms is difficult to quantify. Thus, most trials use clinical rating scales, such as the Burke–Fahn–Marsden Dystonia Scale (BFMDS), the Unified Dystonia Rating Scale (UDRS), the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the Cervical Dystonia Impact Profile (CDIP-58), in addition to health-related QOL instruments, such as the Craniocervical Dystonia Questionnaire (CDQ-24), among other tools[175]. More-accurate quantitative instruments to assess dystonia are required. In general, the symptomatic therapy for dystonia can be subdivided into physical therapies (including physiotherapy and other ancillary therapies), pharmacological therapies, chemodenervation (BoNT) and surgery (FIG. 6).

Botulinum toxin

The introduction of BoNT in the 1980s represents the most important advance in the treatment of dystonia[176]. In a study of 2,026 patients with isolated dystonia, 61% had been treated with BoNT, making it the most commonly used treatment[177]. BoNT is produced by *Clostridium botulinum* and has seven immunologically distinct serotypes (named A to G), each of which is composed of a 100 kDa heavy chain and a 50 kDa light chain[178]. The heavy chain binds to peripheral cholinergic nerve terminals and facilitates endocytosis of BoNT, following which the light chain is released into the cytoplasm and cleaves the soluble *N*-ethylmaleimide-sensitive factor activating protein receptor (SNARE) proteins that are required for synaptic transmission, specifically, for the fusion of the acetylcholine-containing

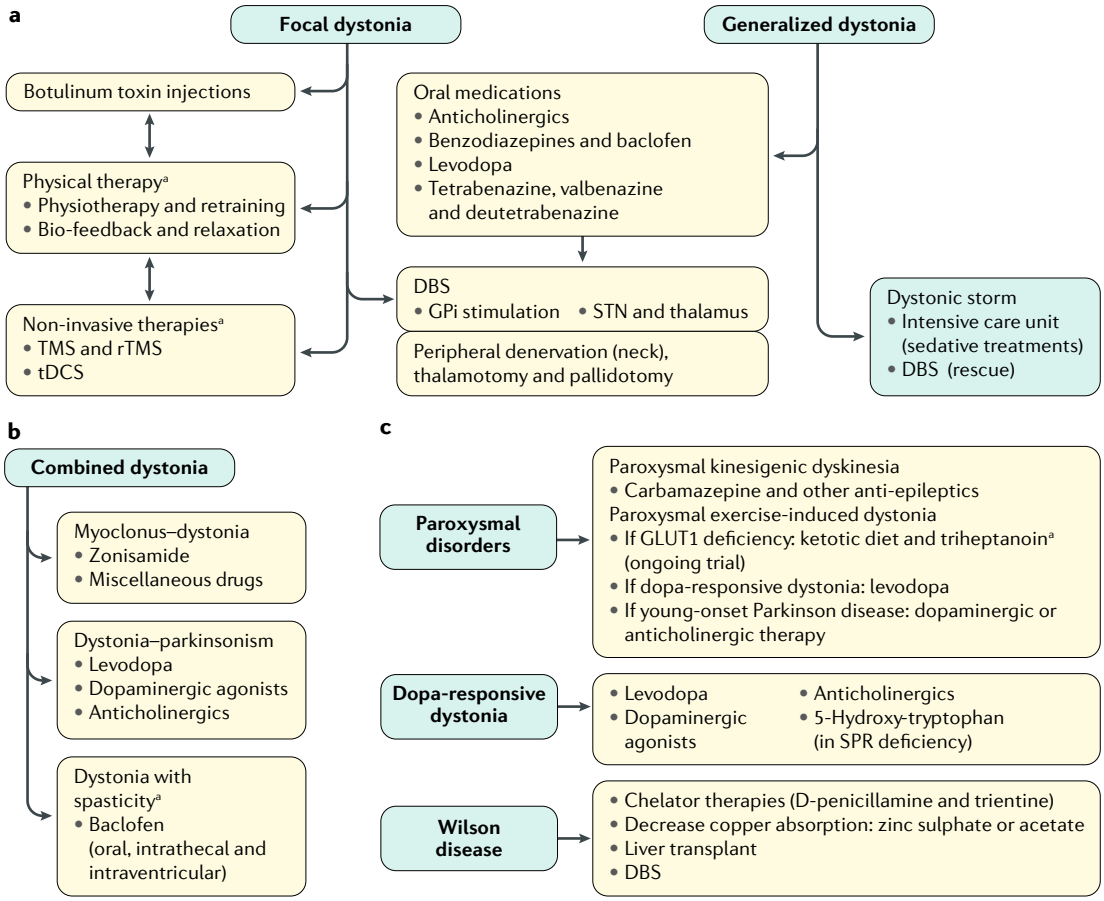

Fig. 6 | **Treatment algorithm for dystonia.** The treatment of dystonia remains symptomatic, and the therapeutic approach is largely orientated at the distribution of dystonic symptoms (for example, whether dystonia is focal or generalized (part **a**)). Therapy comprises botulinum toxin injections (for focal or segmental dystonia), oral medications (mainly for generalized dystonia) and deep brain stimulation (DBS) (for generalized, focal or segmental dystonia), which can be complemented by physical therapies and non-invasive stimulation techniques, although the efficacy of the latter therapy is still to be validated. Treatment of combined dystonia takes into account the other presenting signs (part **b**). Specific dystonia syndromes have specific treatment approaches, such as paroxysmal disorders, dopa-responsive dystonia and Wilson disease (part **c**). A comprehensive discussion of specific treatment approaches in hereditary (mostly combined) dystonias can be found elsewhere[168]. GLUT1, glucose transporter type 1, erythrocyte/brain; GPi, globus pallidus internus; rTMS, repetitive transcranial magnetic stimulation; SPR, sepiapterin reductase; STN, subthalamic nucleus; tDCS, transcranial direct-current stimulation; TMS, transcranial magnetic stimulation. [a]The efficacy of these treatments is still to be validated.

synaptic vesicle with the presynaptic membrane[178]. Only two BoNT serotypes that are approved by the US FDA and the European Medicines Agency (EMA) are commercially available in the United States and Europe: serotypes A and B.

BoNT has been used for the treatment of nearly all forms of focal and segmental dystonia and for many other conditions[176]. BoNT is directly administered into the muscle involved in the dystonic contraction or movement[176], and the clinical beneficial can be observed within a few days and usually persists for 3–4 months, after which the injection is repeated. The most common adverse effects of BoNT are transient and are associated with focal muscle weakness, and they can include ptosis (drooping of the upper eyelid) in patients with blepharospasm or neck weakness and dysphagia in patients with cervical dystonia.

Different formulations of BoNT have different levels of evidence in the American Academy of Neurology practice guidelines for blepharospasm[179] and cervical dystonia. Other practice guidelines for the use of BoNT have variable recommendations based on reported level of evidence, but all guidelines agree that BoNT is the treatment of choice for most patients with focal or segmental dystonia[180,181]. Novel BoNT products that might have some advantages over the currently available formulations are in development. One example is daxibotulinumtoxinA, which has been suggested to have a longer duration of action than the existing types[182].

Physiotherapy and other ancillary therapies

Physical therapies are designed primarily to improve posture and range of motion and to prevent contractures. To date, few trials in patients with cervical dystonia have investigated the effects of multimodal physical therapy plus BoNT treatment compared with BoNT alone[183,184]. In the reported trials, physical therapy plus BoNT groups demonstrated a marked improvement in cervical dystonia symptoms assessed using the TWSTRS[185], improvements in pain, disability and QOL[186] and a prolonged effect of BoNT as compared with BoNT alone[187]. Retraining therapy is most effective in patients who have synergistic dystonic patterns involving the wrist and the forearm compared with those with flexion of fingers[188]. Braces may also be used in some patients as a substitute for an alleviating manoeuvre or a sensory trick, particularly in patients with cervical dystonia[147]. Various hand devices have been developed to help patients with dystonic writer's cramp; however, although immobilization of the affected limb by splints has been advocated by some[189], there are too little data on its benefit or possible side effects to generally recommend this approach, and its benefits and potential risks have not been established as yet[190].

Other, ancillary, treatments for dystonia include non-invasive stimulation techniques, such as repetitive TMS (rTMS) or transcranial direct-current stimulation (tDCS)[191,192]. Despite some encouraging results from open-label pilot studies, whether TMS, tDCS, transcutaneous electrical stimulation and other techniques will be routinely utilized in the treatment of dystonia remains to be seen.

Pharmacological therapies

Anticholinergic drugs. Anticholinergic drugs are most effective for the treatment of generalized and segmental dystonia rather than focal dystonia[3]. Among the oral anticholinergics, trihexyphenidyl is one of few drugs for dystonia that has been evaluated by a prospective double-blind, placebo-controlled trial[193]. In this trial, 71% of participants who received trihexyphenidyl for generalized dystonia had clinical improvement, with sustained improvement in 42% of participants after 2.4 years of follow-up[193]. Trihexyphenidyl and other anticholinergic agents are most useful in patients with isolated generalized dystonia rather than patients with adult-onset focal or combined dystonia. These drugs might also be helpful in patients with acute dystonic reaction and tardive dystonia[173].

Anticholinergic drugs have a somewhat high frequency of adverse effects, such as blurry vision, dry mouth, urinary retention, constipation and cognitive impairment. These adverse effects are particularly common in elderly individuals, although most patients with generalized dystonia are somewhat young. However, although these drugs are better tolerated by children, in one study of childhood dystonia, trihexyphenidyl was discontinued in 52.3% of patients, largely because of anticholinergic side effects such as dry mouth, blurring of vision and cognitive impairment[194]. Starting patients with a low dose of anticholinergic drugs and titrating slowly over several weeks often minimizes the adverse effects and improves tolerability[195].

Levodopa. Levodopa is the treatment of choice for dopa-responsive dystonias[151]. Although some patients can develop nausea, drowsiness, lightheadedness and other acute adverse effects associated with levodopa treatment, patients with dopa-responsive dystonia usually do not experience levodopa-related motor fluctuations or dyskinesias, which are typically associated with levodopa therapy in patients with Parkinson disease[196]. Overall, patients with dopa-responsive dystonias are much more sensitive to the drug than patients with Parkinson disease, such that they need lower doses for beneficial effects. Except for dopa-responsive dystonias, levodopa therapy has little benefit in other types of dystonia, probably because the pathophysiological mechanisms in other dystonias are not based on pathways of dopamine biosynthesis. In addition to levodopa, dopamine receptor agonists and anticholinergic drugs might also be beneficial in patients with various forms of dopa-responsive dystonia.

Antidopaminergic drugs. Dopamine-depleting drugs that act by inhibiting vesicular amine transporter 2 (VMAT2; also known as SLC18A2, and which has a role in the transport of monoamine neurotransmitters into synaptic vesicles), such as tetrabenazine, deutetrabenazine and valbenazine, which are primarily used in the treatment of chorea, tics and tardive dyskinesia, might also have clinical efficacy in patients with dystonia, particularly those with tardive dystonia[197]. Nevertheless, these drugs might cause drowsiness, parkinsonism, depression and akathisia. These side effects may limit the utility of these drugs; their use in patients

with depression should be avoided, and patients should be carefully monitored[198]. Dopamine receptor blocking drugs, such as haloperidol and pimozide, in contrast to the VMAT2 inhibitors, can cause tardive dyskinesia and are not recommended for the treatment of dystonia.

Baclofen. Baclofen, a $GABA_B$ agonist, reduces dystonic movements in some patients with dystonia, particularly in patients with oromandibular dystonia, and dystonic-choreoathetoid cerebral palsy with hypertonia or spasticity[199]. Although little objective evidence supports the efficacy of oral baclofen, more data are available supporting the use of intrathecal and intraventricular baclofen infusions in patients with dystonia. Indeed, several series have provided evidence demonstrating the beneficial effect of baclofen in patients with combined generalized dystonia, mainly in those with cerebral palsy[200], in whom this may be the first-line treatment. An intraventricular baclofen pump was beneficial in two small series of children with refractory generalized dystonia, but further, longitudinal, data are needed before this can be recommended as a standard treatment in these patients[201]. In this study, the most common adverse effects were infection, followed by catheter migration or misplacement.

Other drugs. Benzodiazepines (such as diazepam, clonazepam, lorazepam and midazolam), were the most commonly used oral treatment in an international cross-sectional study of all types of isolated dystonia[177]. These drugs act as muscles relaxants and have an important ancillary role in the off-label treatment of dystonia, although their usefulness is limited by potential adverse effects such as drowsiness and addiction. Other muscle relaxants have been reported to have a clinical benefit in patients, particularly individuals with segmental or generalized dystonia, including cyclobenzaprine, metaxalone, carisoprodol, methocarbamol, orphenadrine and chlorzoxazone[174].

Zonisamide, an anticonvulsant that blocks voltage-dependent sodium and calcium channels and a monoamine oxidase inhibitor, was effective for the treatment of myoclonus–dystonia in a double-blind crossover trial[202]. Zolpidem, an imidazopyridine agonist that binds to and positively modulates $GABA_A$, thereby increasing GABA potency, is effective in patients with different types of generalized dystonia, and sodium oxybate, a salt of γ-hydroxybutyrate, also has reported benefits in myoclonus–dystonia, although these drugs are not routinely given to patients[195,203]. Other drugs used for the treatment of dystonia include gabapentin, an analogue of GABA that acts as a calcium channel α2δ ligand[204]. In addition, topical application (eye drops) of apraclonidine, an α2 adrenergic receptor agonist, has been reported to be beneficial in patients with blepharospasm, an effect that is probably caused by a contraction of the superior tarsal muscle[205].

Surgical therapies

Deep brain stimulation. DBS has emerged as the most effective therapy for patients with medically refractory disabling dystonia in both generalized and severe segmental and focal dystonia. The GPi and, more recently, the subthalamic nucleus (STN) are the two main targets of stimulation as treatment of dystonia owing to their involvement in the control of motor function[206]. In one study, 22 patients with isolated dystonias with GPi DBS had a 51% reduction in BFMDS score 12 months after DBD was commenced compared with the preoperative condition, and this benefit was sustained at 3-year follow-up[207]. In another trial, a robust improvement in dystonia symptoms was reported in 40 patients with isolated segmental and generalized dystonias, and a 27.9-point reduction in the BFMDS motor score was reported at the 5-year follow-up period[208]. Similar improvement was observed in medication-refractory focal (cervical) dystonia, which improved during the initial 6 months following implantation and then stabilized[209]. Moreover, a sustained clinical benefit of up to 78 months was demonstrated in patients with cranial dystonia[210]. Dysarthria is the most frequent complication associated with GPi DBS, but parkinsonism, including freezing of gait, micrographia (small hand writing) and bradykinesia have been observed in some patients[211]. These adverse effects are partly why some surgeons have changed from GPi to STN as targets for DBS treatment of dystonia. In one study, STN DBD improved the BFMDS score by 70.4% in 20 patients with isolated dystonia, and this improvement was sustained for 36 months[212]. The most common related adverse effect with STN DBS is chorea, but numbness, worsened handwriting, weight gain, dysarthria, shoulder pain and depression have been reported[213]. Other stimulation-related adverse events related to GPi or STN DBS include incoordination, paresthesias and perioral tingling, whereas the most frequently reported hardware-related complications were infection, haematoma and wire displacement[214].

Other forms of dystonia might also be suitable for treatment with DBS. For example, a marked benefit was observed with bilateral GPi DBS in patients with tardive dystonia with long-term follow-up[215]. Indeed, some genetic forms of dystonia seem to have a particularly favourable outcome with GPi DBS, for example, dystonias associated with *TOR1A*, *KMT2B* or *SGCE* mutations[118,216,217]. GPi DBS was also effective in *THAP1-associated* and *GNAL*-associated dystonia, although effects were variable[218–221]. DBS is approved by the FDA and the EMA for the treatment of severe dystonia.

Ablative procedures. Pallidotomy and thalamotomy, which were commonly used for the treatment of dystonia in the past, have been essentially completely replaced by DBS. In a long-term follow-up of 15 patients with musician's dystonia, 93% of patients who underwent ventro-oral thalamotomy had a dramatic improvement of dystonic symptoms immediately after the procedure, which was sustained for the mean follow-up period of 30.8 months (range 4–108 months)[222]. Whether focused ultrasound of the thalamus, which has been reported to be effective in the treatment of essential tremor and Parkinson disease, will have utility in the treatment of dystonia is unknown[223].

Dystonic storm

Dystonic storm, also referred to as status dystonicus, is a movement disorder emergency that is a very rare complication of generalized dystonia. Dystonic storm is more common in the paediatric population[224] than in adults[225]. Triggering factors may be intercurrent infection and fever, discontinuation or rapid change in treatments, surgery or trauma. Patients present with increasingly frequent and severe episodes of painful sustained posturing or irregular jerky dystonic movements, which can be associated with fever, respiratory distress and autonomic instability, including tachycardia and diaphoresis (excessive sweating), rhabdomyolysis (skeletal muscle breakdown) and renal failure. Dystonic storm is a medical emergency, and patients suspected of developing dystonic storm should be admitted into an intensive care unit. The initial management includes the treatment of possible triggers, such as infection (with antibiotics), and the adjustment of medication regimens that were recently withdrawn or changed. Additionally, monotherapy or polytherapy using oral agents, such as anticholinergics, tetrabenazine, clonidine and baclofen, can be used. Intravenous medications such as midazolam, propofol and non-depolarizing neuromuscular blockers should be considered as supportive options. The use of DBS targeting the GPi as an effective rescue therapy and an intrathecal baclofen pump should also be considered. If not diagnosed and treated early, dystonic storm can be fatal (which occurs in 10% of patients) or associated with disabling sequelae.

Quality of life

Several studies have investigated the health-related QOL in patients with dystonia and demonstrated a poorer QOL in patients with dystonia. Several factors affect QOL in patients, including impaired physical functioning owing to the presence of motor symptoms[226–231]. The most severe, generalized forms of dystonia can affect all activities of daily living such as walking or hand function[227]. Focal forms of dystonia can also be disabling; for example, laryngeal dystonia can affect communication, and blepharospasm can impede safe driving or walking[228,229,232]. Task-specific dystonia can impede professional occupations, for example, in patients with writer's cramp or musician's dystonia[230,231]. Rehabilitative measures may provide some help, as can treatment with BoNT injections, although this is challenging because of the complexity of anatomy and the narrow therapeutic window for the smaller muscles.

Similarly, patients with dystonia often feel that the abnormal postures or associated dystonic tremors are socially disabling and disfiguring. However, QOL does not necessarily correlate with dystonia severity[233,234]. By contrast, psychiatric comorbidities such as depression and anxiety are independent of dystonia severity and are the most important determinants of QOL and also of perceived treatment response in patients[226,233–236]. Increased levels of anxiety and depression are observed in patients with isolated, idiopathic or genetic dystonias and have been reported in non-manifesting carriers of dystonia-associated genetic mutations[146,237,238]. These insights have important implications for therapy and expectation management, and the current lack of randomized controlled trials and guidelines with regard to treatment of depression and anxiety in dystonia highlights an urgent unmet need.

Pain is the second most important predictor of QOL in patients with dystonia[233] and is present in ~75% of patients with cervical dystonia but occurs less frequently in patients with other focal dystonias[146]. Dystonia-related pain responds to treatment with BoNT injections[234,239]. Patients also report a poor quality of sleep, which correlates with depression but not with dystonia severity or muscle activity during sleep[146,240,241]. Additionally, polysomnography detected a disturbed sleep architecture (decreased sleep efficiency and increased sleep latency), which is likely to contribute to the perceived poor sleep quality[240]. Excessive daytime sleepiness is not an inherent feature of dystonia and might be attributed to anticholinergic medication in some patients[146].

Collectively, these issues in patients with dystonia might affect work life and capacity. Indeed, several studies demonstrated that, in particular, cervical dystonia and dystonia-associated pain negatively affected employment status and productivity[242–245]. The influence of neuropsychiatric comorbidities of dystonia on work life has not yet been systematically assessed. In line with the beneficial effect of BoNT on pain in cervical dystonia, this treatment is also effective in improving work capacity and employment status[242,243].

Outlook

Understanding pathophysiology

Hopefully, insights from genetic studies regarding the molecular mechanisms of dystonia will lead to a better understanding of pathophysiology. The pathophysiological interactions of the basal ganglia, cortex, sensory system and cerebellum require further understanding. Unlike Parkinson disease, in which a β-band frequency as measured by specialized electroencephalography has been linked to bradykinesia, the signature tune of dystonia has to be elucidated and the actions of GPi DBS modelling better understood to improve outcomes.

Diagnosis

One of the greatest challenges in clinical practice and research is the lack of a biomarker for dystonia, which would allow unequivocal diagnosis and identification of homogeneous patient cohorts for studies. Currently, the overall yield of an aetiological diagnosis in patients with dystonia despite advancement in genetics is <30% (K.P.B., unpublished observations). Undoubtedly, next-generation sequencing-based techniques have greatly revolutionized our approach to molecular genetic diagnosis of isolated dystonia, as given the wide clinical and genetic heterogeneity of this condition, a strategy based on gene panels or exome sequencing provides advantages over more focused 'gene by gene' testing. However, conversely, the intrinsic limitations of next-generation sequencing strategies should be considered, which mainly concern our ability to correctly assess and interpret the large number of heterozygous variants emerging from these studies, especially in sporadic cases. For instance, several rare missense variants in *ANO3* were identified not only in patients

with dystonia, but also in healthy individuals, and their pathogenetic role still remains to be established[246]. Similarly, besides the well-characterized GAG deletion in the *TOR1A* gene, a number of rare missense variants of unknown importance have been reported in a subset of patients with variable phenotypes of dystonia[247]. This issue will therefore probably require the expansion of in silico analysis approaches, further international collaborative efforts, with the formation of databases, and, in some cases, further investigations, for example, using functional studies with induced stem cells.

Treatment

Apart from BoNT, which is an intramuscular injection procedure, most of the oral drugs used for dystonia are very old, and there has been no new drug discovery specifically for isolated dystonia. Improved understanding of the pathophysiological mechanisms of dystonia should hopefully enhance new endeavours to develop new treatment approaches and new drugs based on pathophysiology . With the advent of next-generation sequencing and the discovery of new dystonia-causing genes, new drugs related to disease mechanisms in specific genetic forms of dystonia, or indeed, the future possibility of gene therapies, could be developed.

To date, the most efficient, evidence-based treatments for dystonia are BoNT injections and DBS. Despite the beneficial effect of DBS, this technique can be improved, for example, by identifying newer or combined targets for stimulation and feedback loop systems, such as those already developed for tremor and Parkinson disease[248]. In addition, DBS programmes will explore and compare new targets (such as the thalamus (ventralis oralis posterior nucleus)) or new stimulation settings and focus on dystonia in children or rare focal (laryngeal and upper limb) and secondary dystonia (TABLE 3).

The therapeutic use of non-invasive brain stimulation techniques (such as TMS, tDCS and TACs) is an emerging concept for the treatment of dystonia with hopes and pitfalls: although based on robust

Table 3 | **Selected planned or ongoing trials in patients with dystonia**

Treatment	Stage	ClinicalTrials.gov identifier
Pharmacological		
Perampanel in cervical dystonia	Phase I and II	NCT02131467
Incobotulinumtoxin A in musician's dystonia	Phase II crossover	NCT02107261
Safety and preliminary efficacy of daxibotulinumtoxinA in cervical dystonia	Phase II open label	NCT02706795
Clinical and kinematic assessment for determination of onabotulinumtoxinA injection parameters in cervical dystonia	Phase II	NCT02662530
Sodium oxybate in spasmodic dysphonia and voice tremor	Phase II and III	NCT03292458
Comparison of electrophysiologic and ultrasound guidance for onabotulinum-toxin-A injections in focal upper extremity dystonia and spasticity	Phase III	NCT02326818
Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of BoNT type A in cervical dystonia	Phase III	NCT03232320
Neurostimulation (DBS)		
Thalamic (VOP) DBS for secondary dystonia in children and young adults	Open label	NCT03078816
STN DBS for primary cranial cervical dystonia	Stimulation versus sham	NCT02583074
Thalamic (VIM) stimulation in laryngeal dystonia	On versus off stimulation	NCT02558634
STN DBS versus GPi DBS in dystonia	Phase I randomized controlled trial (estimated 40 patients)	NCT02263417
DBS for focal hand dystonia	Phase I and II	NCT02911103
Multi-target pallidal and thalamic DBS for hemidystonia	Phase II nonrandomized	NCT 00773604
Comparison of the efficacy of double monopolar versus interleaving stimulation modes for GPi DBS	Phase IV	NCT01497639
Non-invasive stimulation (pilot and exploratory studies)		
Effect of increasing motor cortex inhibition on task-specific dystonia (rTMS of 0.1–0.5 Hz at a subthreshold intensity)	Pilot study	NCT01823237
TMS for focal hand dystonia (subthreshold rTMS at one of eight frequencies)	Pilot study	NCT01792336
Combined rTMS and BoNT in cervical dystonia	Exploratory study	NCT02542839
tDCS in childhood dystonia	Exploratory study	NCT01460771
Physical therapy and/or exercise		
Exercise training in cervical dystonia (either progressive resistance training or control treatment (fitness protocol))	Prospective, parallel-group and controlled study	NCT03318120
Effect of osteopathic manipulative medicine on motor function and quality of life in cervical dystonia	Open label	NCT02420106

BoNT, botulinum toxin; DBS, deep brain stimulation; GPi, globus pallidus internus; rTMS, repetitive transcranial magnetic stimulation; STN, subthalamic nucleus; tDCS, transcranial direct-current stimulation; TMS, transcranial magnetic stimulation; VIM, ventralis intermedius nucleus; VOP, ventralis oralis posterior nucleus.

pathophysiology (modulation of networks), the current studies are inconclusive and have been carried out only in varied methods. In addition, non-invasive brain stimulation techniques have limitations related to the variability of stimulation protocols and clinical effects (TABLE 3). Despite these limitations, non-invasive rTMS either as an adjuvant to conventional treatments or on its own might have a future role in dystonia treatment, and techniques that might change cerebellar or sensory input such as repetitive sensory stimulation are being researched[192].

Although physical therapy is useful for some forms of dystonia, no standard physiotherapy programme applicable to all forms of cervical or upper-limb dystonia is available. In addition, despite clinical benefits in open studies, a significant effect of physical therapy is still difficult to demonstrate in clinical trials. Studies aimed at the improvement of techniques for better targeting (by ultrasound or electrophysiology) of BoNT are being undertaken, as are trials evaluating the benefit or tolerance of other types of BoNT (TABLE 3). Aside from the motor symptoms of dystonia, recognizing and treating the non-motor symptoms, which do influence the outcomes of conventional therapies, must be addressed.

In other diseases such as Parkinson disease, the recognition of a prodromal, pre-motor phase has spurred attempts of disease prevention. However, these considerations are still in their infancy in dystonia. One study has suggested that perinatal adversities are a triggering factor for symptoms manifesting in *TOR1A* mutation carriers, and future studies exploring factors that can modify the penetrance of dystonia-causing mutations or the manifestations of dystonia in non-genetic forms might pave the way for disease-preventing or disease-modifying strategies[30].

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