



## Review

## Second hit hypothesis in dystonia: Dysfunctional cross talk between neuroplasticity and environment?

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## ABSTRACT

One of the great mysteries in dystonia pathophysiology is the role of environmental factors in disease onset and development. Progress has been made in defining the genetic components of dystonic syndromes, still the mechanisms behind the discrepant relationship between dystonic genotype and phenotype remain largely unclear. Within this review, the preclinical and clinical evidence for environmental stressors as disease modifiers in dystonia pathogenesis are summarized and critically evaluated. The potential role of extragenetic factors is discussed in monogenic as well as adult-onset isolated dystonia. The available clinical evidence for a “second hit” is analyzed in light of the reduced penetrance of monogenic dystonic syndromes and put into context with evidence from animal and cellular models. The contradictory studies on adult-onset dystonia are discussed in detail and backed up by evidence from animal models. Taken together, there is clear evidence of a gene-environment interaction in dystonia, which should be considered in the continued quest to unravel dystonia pathophysiology.

### 1. Background

The possible role of disease modifiers to dystonia pathophysiology has been the foundation of a multitude of clinical and basic research studies. While strides have been made in defining the genetic causes of dystonic syndromes, no conclusive explanation has been found for the markedly reduced penetrance in case of monogenic dystonia, the heterogeneous phenotypes and the triggers behind adult-onset, focal dystonia. Indeed, dystonic syndromes are the third most common movement disorder. The term dystonia encompasses a heterogeneous group of hyperkinetic movement disorders characterized by involuntary, sustained or repetitive movements and postures (Albanese et al., 2013). Dystonia can be of early onset, in which case there is a higher likelihood for an underlying genetic mutation and a higher likelihood for the symptoms to progress from focal to generalized. Dystonia can also be of adult onset, in which case the cause often remains unknown, and dystonia tends to manifest in focal forms or more rarely as segmental/multifocal. Dystonia can also be acquired due to, for example, a (perinatal) brain injury, drug abuse, infections or be of

psychogenic etiology. Despite the differing etiologies and heterogeneous clinical presentations, common pathomechanisms are believed to underlie the syndromes. The main pathomechanisms in dystonia are thought to be maladaptive plasticity, a loss of inhibition, and a sensorimotor disintegration (Quartarone et al., 2006; Quartarone and Pisani, 2011; Martella et al., 2009; Hallett, 2011; Calabresi et al., 2016). However, these pathomechanisms have not been able to explain disease development in its entirety. For monogenic as well as adult-onset, isolated forms of dystonia, the involvement of environmental stressors as disease modifiers has been discussed from the early days. Already in 1888, Gowers discussed the case of a naval officer developing writer's cramp after injuring his thumb (Gowers, 1888). Indeed, in case of adult-onset dystonia, there is a bouquet of studies on the role of non-genetic factors in disease development. However, contradictory results of clinical studies provided evidence for and against the involvement of extragenetic factors in adult-onset dystonia. Especially the relationship between peripheral trauma and dystonia are still a matter for debate (Kumar and Jog, 2011; Jankovic, 2001a; Ganos et al., 2016; Sheehy and Marsden, 1980).

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There are by far fewer studies on the involvement of extragenetic factors for the monogenic group of dystonia syndromes; however, there are several key observations that indicate an involvement of environmental factors. The first being a reduced penetrance, which has been reported for most monogenic dystonic syndromes (Breakefield et al., 2008). For the most common form, DYT-TOR1A dystonia, a penetrance as low as 29% has been described (Opal et al., 2002; Gambarin et al., 2006; Kostić et al., 2006; Bressman et al., 1989; Lange et al., 2021; Hjerminnd et al., 2002; Risch et al., 1990; Lohmann and Klein, 2013). For DYT-THAP1 dystonia a penetrance of 48.4% has been published (Lange et al., 2021). For most other forms of dystonia, the penetrance has been reported to be incomplete; however, the small number of affected families has made it difficult to give an estimate on the penetrance. For DYT-GNAL (Vemula et al., 2013; Fuchs et al., 2013; Putzel et al., 2016), DYT-KMT2B (Meyer et al., 2017), DYT/PARK-GCH1 (Furukawa et al., 1998; Steinberger et al., 1998; Segawa et al., 2003) and DYT/PARK-ATP1A3 (de Carvalho Aguiar et al., 2004; Brashear et al., 2007; Haq et al., 2019) asymptomatic mutation carriers have been reported. For DYT-TOR1A, the penetrance of dystonia patients does not differ between ethnicities, geographical regions or between sex (Martino et al., 2013). Indeed, for monogenic forms of dystonia sex differences have only been reported for DYT-GCH1, which is more frequent among women than men with reported female-to-male ratios between 1.3:1 to 8.3:1 (Furukawa et al., 1998; Segawa et al., 2003; Wijemanne and Jankovic, 2015; Trender-Gerhard et al., 2009; Dobričić et al., 2017).

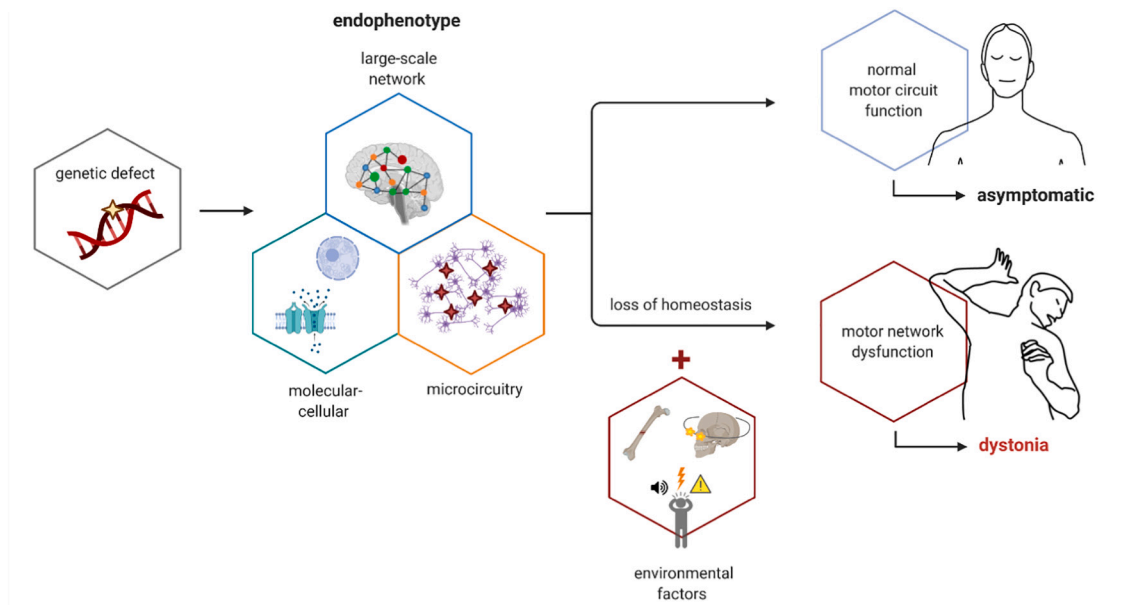
The presence of an endophenotype in asymptomatic DYT-TOR1A mutation carriers indicates that the torsinA defect alone causes functional abnormalities. However, the genetic defect does not seem to be sufficient in inducing dystonic symptoms in patients (Carbon et al., 2011; Eidelberg et al., 1998; Ghilardi et al., 2003). Taken together, it is unclear why the mutation leads to symptoms in some patients, while others remain free of dystonia. Furthermore, the presence of phenotypic variability within dystonic syndromes and even within single families remains unexplained (Opal et al., 2002; Edwards and Bhatia, 2003). A strong intrafamilial variability was described in one family with a TOR1A mutation, where some individuals were asymptomatic carriers, another presented with dystonic tremor with 64 years of age and again another died from the consequences of a dystonic storm (Opal et al., 2002). Phenotypic variability indicates that disease modifiers play an important role in symptom onset. Aside from environmental factors, second genetic mutations or other polymorphisms in the mutated gene have been discussed to be possible modifiers and to contribute to disease manifestation. While a single-nucleotide polymorphism of the *Tor1a* gene, D216H, has been described as a possible genetic modifier, others have found no evidence of these variants having an impact on the development of dystonic symptoms (Risch et al., 2007; Kamm et al., 2006; Brüggemann et al., 2009). Furthermore, the low frequency of this polymorphism at population level indicates that its contribution to penetrance is small and other factors must be involved.

To date, it is unclear how genetic and environmental modifiers impact symptom development in dystonia. The question whether shared modulators affect genetic as well as idiopathic, generalized and focal forms of dystonia in a similar way remains unanswered. In this review we provide an overview of the evidence of the role of environmental factors in dystonia pathogenesis. The literature search was performed in PubMed; English literature between the years of 1888 and 2021 was considered. Search terms employed were: dystonia, second hit, animal models, basal ganglia, synaptic plasticity, endophenotype, motor phenotype. We were unable to consider all articles published within this time period and performed a selection representing the most important aspects to the best of our knowledge. We discuss evidence from human, animal, and cellular studies in monogenic as well as adult-onset, focal forms of dystonia.

## 2. The second hit hypothesis

The second hit hypothesis, also known as the two-hit or double-hit hypothesis, is a concept first introduced by Alfred G. Knudson in 1971 in the field of tumor biology (Knudson Jr., 1971). Knudson hypothesized that two hits to DNA are necessary for the development of cancer. For dystonia, it has been proposed that an endophenotype represents the “first hit” in mutation carriers of monogenic dystonia as well as patients with adult-onset, isolated dystonia. The “second hit” in dystonia pathogenesis has been hypothesized to be an extragenetic, environmental trigger. Thus, the second hit hypothesis proposes that environmental factors disturb a sensorimotor system, where maladaptive plasticity or an otherwise structural and neurochemical endophenotype is barely compensated (Fig. 1).

Indeed, abnormal synaptic plasticity has been reported in monogenic dystonia patients independent of clinical penetrance (Carbon et al., 2011; Ghilardi et al., 2003; Edwards et al., 2006). In patients with focal dystonia, aberrant synaptic plasticity has been reported in brain regions representing affected as well as non-affected body parts (Quartarone et al., 2008). Alterations of plasticity have also been demonstrated in unaffected relatives of patients with adult-onset, idiopathic dystonia (Ghilardi et al., 2003; Bradley et al., 2009). Previous reviews have extensively discussed abnormal synaptic plasticity as a potential endophenotype in mutation carriers of monogenic dystonia as well as in patients with adult-onset, focal dystonia (Quartarone et al., 2006; Quartarone and Pisani, 2011; Calabresi et al., 2016). Concerning the effect of a second hit, it has been suggested that the interplay between an abnormal endophenotypic synaptic plasticity and the neuromodulatory, sensorimotor influences of extragenetic factors lead to a loss of homeostasis (Quartarone et al., 2006; Breakefield et al., 2008; Quartarone et al., 2008; Peterson et al., 2010; Torres-Russotto and Perlmutter, 2008). Physiologically, synaptic plasticity is necessary for motor learning and the adaptation to environmental events. In case of dystonia, excessive plasticity or reduced control of plasticity is believed to lead to a loss of specificity of motor networks and thus to abnormal movement patterns. This excessive plasticity has been shown in animal models as well as in clinical studies using transcranial magnetic stimulation (Martella et al., 2009; Quartarone et al., 2009; Kang et al., 2011; Quartarone et al., 2005). The dopaminergic as well as the cholinergic system, which are both known to be affected in dystonia, seem to be major contributors to the abnormal synaptic plasticity of the basal ganglia. Specifically, the role of altered dopaminergic neurotransmission in the manifestation of dystonia has been extensively studied. Inherited defects of dopaminergic biosynthesis (i.e., caused by mutations in genes involved in dopa-responsive dystonia) or secondary alterations of dopaminergic neurotransmission (e.g., Parkinson's disease, chronic exposure to dopamine-receptor-blocking agents) are well known causes of dystonia. The role of dopamine and acetylcholine has been further discussed in excellent reviews (Calabresi et al., 2016; Peterson et al., 2010; Calabresi et al., 2000). Indeed, a link between the sensorimotor cortex and the basal ganglia in dystonia pathophysiology has been described such as in patients with writer's cramp (Berndt et al., 2018). Anatomically, the nigrostriatal dopaminergic fibers terminate on the shafts of the dendritic spines of striatal medium spiny neurons, while the cortical afferents terminate on the heads of those spines, thereby enabling dopamine modulation of the corticostriatal input. A putative disease mechanism of dystonia could be the inability of the striatum to filter neuronal signals once the activities of direct and indirect basal ganglia pathways become unbalanced due to abnormal dopamine-dependent medium spiny neurons function (Calabresi et al., 2014; Ribot et al., 2019). Peterson et al. hypothesized that the contributions of the two factors might have different weight in early-onset, monogenic forms of dystonia and adult-onset idiopathic dystonia (Peterson et al., 2010). The influence of extragenetic factors might be of more importance in adult onset, task-specific dystonia than in early-onset, monogenic forms of dystonia, where abnormal synaptic plasticity might be



**Fig. 1.** Gene-environment interaction in dystonia. The second hit hypothesis predicts that different environmental triggers can disturb the fragile compensatory mechanisms in gene-mutation carriers and lead to the development of dystonia. Created with [BioRender.com](https://www.biorender.com).

more predominant.

Another factor to consider in the second hit hypothesis is that monogenic forms of dystonia are predominantly of early onset (Table 1). For most forms of monogenic dystonia, mutation carriers develop symptoms before the age of 30, indicating a critical period of vulnerability (Houlden et al., 2010). Mutation carriers outside of this critical period rarely develop dystonic symptoms, a phenomenon that has remained unexplained so far. Interestingly, Maltese et al. identified a similar susceptibility period in young DYT1 knock-in mice (Maltese et al., 2018). Indeed, the authors identified electrophysiological, neurochemical and structural abnormalities in the basal ganglia of DYT1 knock-in mice compared to wildtype animals that were limited to a specific time-window. This window matches the critical period for the development of symptoms in patients with early-onset, monogenic forms of dystonia. Similarly, the *dtz* hamster, which is an animal model for paroxysmal dystonia, shows severe dystonic attacks at 30–40 days of age (Richter and Löscher, 1993; Richter and Löscher, 1998). A spontaneous remission occurs at around 70 days of age. This age-dependency of the dystonic symptoms has been related to an age-dependent deficit of striatal interneurons (Gernert et al., 2000; Hamann et al., 2005). Moreover, a recent report using a new DYT-TOR1A mouse line enabling spatiotemporal control of endogenous torsinA expression (*Dlx5/6-Cre Tor1a<sup>flx/-</sup>*) described a critical time-window of torsinA expression between P21 and P70 that influences brain development and provides a therapeutic window (Li et al., 2021). Whether such age-dependent alterations are also of importance in the sensorimotor network of human dystonia patients is unclear.

The so-called “second hit hypothesis” has been studied in relation to monogenic dystonia as well as adult-onset, focal dystonia in clinical and animal studies and will be discussed in detail within the next paragraphs.

### 3. Gene-environment interaction in monogenic dystonia

#### 3.1. Evidence from clinical studies

The published evidence linking environmental factors to genetic forms of dystonia in clinical studies is sparse (Table 2). For one of the monogenic forms, rapid-onset dystonia-parkinsonism (DYT/PARK-ATP1A3, DYT12), the link between stress and development of symptoms

is well established. Patients are known to develop generalized dystonia and/or parkinsonism within hours to days after exposure to a stressful trigger. Indeed, an array of stress factors capable of leading to the permanent and generalized development of dystonia in DYT/PARK-ATP1A3 have been published (Barbano et al., 2012; Brashear et al., 2007). A recent study by Haq et al. reported that in 77% of DYT/PARK-ATP1A3 mutation carriers, a trigger precedes symptom onset (Haq et al., 2019). Only triggers within one day of dystonia onset were considered for this study, and stress factors ranged from physical activity, infections, heat exposure or fever, psychological stress to alcohol consumption. The question, whether asymptomatic carriers are simply successful in avoiding these triggers or somehow differ from the symptomatic carriers in gene expression or protein processing, remains unanswered.

For DYT-TOR1A dystonia, environmental factors such as perinatal adversities, childhood infections, general anesthesia or physical trauma prior to symptom onset were investigated in a retrospective review of 28 families (Martino et al., 2013). 39 manifesting mutation carriers, 23 non-manifesting mutation carriers, and 48 DYT-TOR1A negative relatives were asked to fill out a questionnaire. The survey revealed a significant association with complications of vaginal delivery and dystonic symptoms in DYT-TOR1A mutation carriers; however, no association was found for a history of trauma, general anesthesia, and childhood infections. Saunders Pullmann et al. reported a higher frequency of childhood infections such as mumps and measles occurring till the age of 6 in 55 symptomatic DYT-TOR1A patients compared to 47 asymptomatic DYT-TOR1A mutation carriers (Saunders Pullmann et al., 2004). The infections occurred more than one year before the onset of dystonia. The study was performed by mailing a semi-structured interview to patients. The authors postulated that a greater rate of childhood illnesses might be associated with symptom development in DYT-TOR1A mutation carriers. Aside from these two retrospective studies, only single case reports are available for DYT-TOR1A dystonia and the role of triggers. One reported on the bite of a moray as a trigger for dystonic movements in a 10-year-old DYT-TOR1A mutation carrier (Gioltzoglou et al., 2006). According to the authors, the trauma was relatively mild, pain however was severe. An initial limping of the leg having suffered the bite turned into a dystonic gait over a few months after the initial event, with spreading to the upper extremities six months later. Edwards et al. reported on the case of 38-year-old DYT-TOR1A mutation carrier

**Table 1**

Median age of onset of the monogenic forms of dystonia. Some of the monogenic dystonic syndromes show an early onset, disease development is rare after the age of 30. This points towards a period of vulnerability for dystonia development.

form of dystonia	median age of onset	references
DYT-TOR1A	9 [68.1% childhood onset, 11.7% adolescence onset, 5.2% > 30 years of age]	(Lange et al., 2021)
DYT-THAP1	15 [34.9% childhood onset, 17.8% adolescence onset, 16.6% early adulthood, 14.5% late adulthood]	(Lange et al., 2021)
DYT-GNAL	38 [15.8% < 20 years of age, 35.5% early adulthood, 39.5% late adulthood]	(Lange et al., 2021)
DYT-ANO3	23 [32.1% childhood onset, 17.0% adolescence onset, 24.5% early adulthood, 24.5% late adulthood]	(Lange et al., 2021)
DYT-KMT2B	6 [86.7% childhood onset, 4.0% adolescence onset, 4.0% early adulthood]	(Lange et al., 2021)
DYT-HPCA	5	(Lange et al., 2021)
DYT-SGCE	childhood to adolescence; adult onset is rare	(Peall et al., 2014; Tezenas du Montcel et al., 2006)
DYT-GCHI/ DYT-TH	6 childhood to adolescence; adult onset is rare	(Segawa et al., 2003)
DYT/PARK-ATP1A3	adolescence [47.0% < 20 years of age, 39.0% early adulthood, 14.0% late adulthood]	(Brashear et al., 2007)
DYT/PARK-PRKRA	8 [69.9% childhood onset, 21.7% adolescence onset, 4.3% early adulthood, 4.3% late adulthood]	(Lange et al., 2021)
DYT/PARK-TAF1	men: 39 years of age; women: 52 years of age	(Evidente et al., 2004)
PxMD-PNKD	infancy to childhood; adult onset is rare	(Gardiner et al., 2015; Erro et al., 2014)
PxMD-PRRT2	10 childhood to adolescence	(Gardiner et al., 2015; Erro et al., 2014; Ebrahimi-Fakhari et al., 2015)
PxMD-SLC2A1	infancy to childhood; adult onset is rare	(Gardiner et al., 2015; Erro et al., 2014)

developing a dystonic posture of the foot within a few days after twisting the ankle (Edwards and Bhatia, 2003). Dystonia later spread to the larynx developing into a dystonic speech. In conclusion, so far, clinical studies have not been able to establish a clear link between environmental factors and disease manifestation. However, they documented the immense variability in disease severity among manifesting dystonic subjects.

A possible role of disease modifiers has not yet been studied in other monogenic forms such as DYT-THAP1 dystonia, which also has a markedly reduced penetrance of about 50%. For paroxysmal dyskinesias (PxMD), a term referring to a group of movement disorders of strong clinical and genetic heterogeneity, attacks involving dystonic posturing with choreic and ballistic movements can be induced by certain triggers. Typical triggers described for PxMD-PKND are coffee, alcohol, stress/excitement or fatigue (Gardiner et al., 2015; Erro et al., 2014). PRRT2-associated paroxysmal movement disorders (PxMD-PRRT2) are often triggered by voluntary movements or the intent to perform a movement, stress, and sleep deprivation (Gardiner et al., 2015; Erro et al., 2014). When considering a role of the second hit hypothesis in PxMD, it has to be remarked that the triggers induce attacks of dyskinesia, but do not induce a permanent change to the sensorimotor system, as is assumed to be the case in monogenic forms of dystonia such as DYT-TOR1A and

DYT/PARK-ATP1A3 or adult-onset idiopathic dystonia.

### 3.2. Evidence from animal and cellular models

One of the first symptomatic rodent models described in dystonia research is the *dtz* hamster, which presents dystonia-like movements spontaneously and in response to environmental stimuli (Löscher et al., 1989). However, aside from the *dtz* hamster that harbors a still unknown causative genetic defect, rodent models for dystonia for the greater part do not recapitulate the clinical features. This could be due to differential developmental compensation between rodents and humans. Another factor at play might be the need for environmental stimuli. Particular environmental stressors might be able to force the endophenotype of transgenic rodent models out of a fragile equilibrium, leading to the development of a dystonic phenotype. The value of symptomatic animal models of dystonia lies in the ability to dissociate the endophenotype resulting from the mutation and the structural as well as neurochemical changes associated with the manifestation of dystonia after the “second hit”. This opens up new possibilities of analyzing the mechanisms of dystonia from molecular to system network level and the exploration of new therapeutic strategies. Animal models with dystonia-like movements induced by an environmental stressor will be discussed within the next paragraphs.

Mouse models for DYT/PARK-ATP1A3 dystonia, which is well-known to be stress-induced, are either asymptomatic or present symptoms not recapitulating the human disease such as seizures. Interestingly, most attempts to induce dystonia-like movements in transgenic DYT/PARK-ATP1A3 mouse models have failed so far (DeAndrade et al., 2011; Sugimoto et al., 2014). An argument could be made that the use of chronic restraint stress was insufficient and too mild for the induction of dystonia-like movements in these rodent models. Isaksen and colleagues published a genetic mouse model for DYT/PARK-ATP1A3 dystonia with convulsion- and dystonia-like movements induced by exposure to cold temperatures (Isaksen et al., 2017). Other stress paradigms such as chronic restraint and exposure to heat, did not induce abnormal movements in these animals. A pharmacological DYT/PARK-ATP1A3 mouse model first introduced by Calderon et al. in 2011, presented for the first time a dystonic and parkinsonian phenotype after stress exposure (Calderon et al., 2011). Ouabain, which selectively blocks the  $\alpha 3$  subunit of the  $\text{Na}^+/\text{K}^+$ -ATPase and as such reproduces the underlying mutation of DYT/PARK-ATP1A3 dystonia, was perfused continuously into the basal ganglia and cerebellum of wild-type mice. The ouabain-perfusion caused mild gait abnormalities; dystonia-like movements had to be induced by additional exposure to electric foot shocks in a warm environment. The authors found aberrant cerebellar activity to correlate with dystonia in their model. However, this pharmacological mouse model has been replicated by others, using a lower ouabain concentration and a mild motor stress paradigm (Rauschenberger et al., 2020a; Rauschenberger et al., 2020b). The authors showed microstructural changes in the basal ganglia independent of stress exposure as an indication for an endophenotype, as well as alterations of the dopaminergic pathway in the basal ganglia dependent of stress exposure as an indication for phenotype-dependent changes.

For DYT-TOR1A dystonia, the underlying gene mutation affects *Tor1a*, which encodes for torsinA. Strides have been made in learning about the function of torsinA, as well as the implications of the mutation. TorsinA is an ATP-binding protein expressed in neuronal as well as non-neuronal tissue and the only member of the AAA+ family to be expressed primarily in the lumen of the endoplasmic reticulum (ER). It has been implicated in a variety of cellular activities, including protein folding, protein quality control of the ER, and synaptic vesicle recycling (Neuwald et al., 1999; Ogura and Wilkinson, 2001). However, it is still unclear whether the DYT-TOR1A mutation acts via a gain- or loss-of-function mechanism and the direct consequences of a malfunction of the protein are unknown. Many of the mouse models with genetically altered torsinA show subtle impairments. The widely used DYT1 knock-

**Table 2**

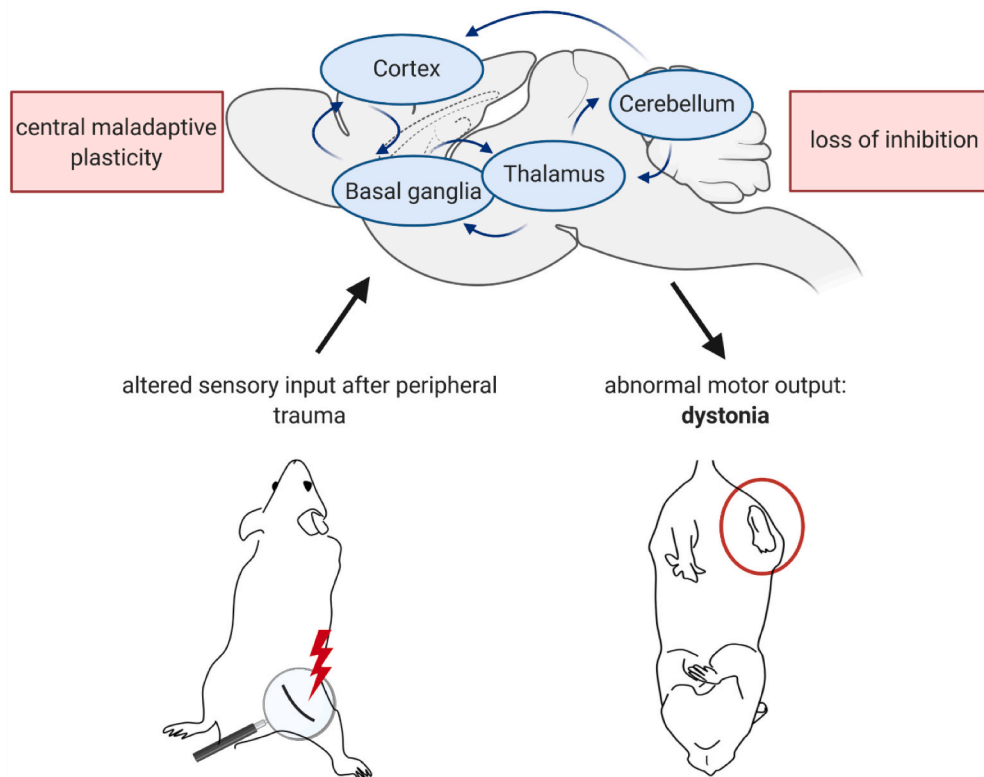
Summary of triggers for development of dystonia reported in literature. A selection of clinical reports and animal studies is displayed.

second hit	clinical reports	animal models	references
peripheral trauma	DYT-TOR1A, adult-onset isolated dystonia	DYT-TOR1A ( <i>Tor1a</i> knockout mice; $\Delta$ ETorA rats); blepharospasm (wildtype rats)	clinical reports (Edwards and Bhatia, 2003; Gioltzoglou et al., 2006; Sankhla et al., 1998; Schrag et al., 1999; Defazio et al., 1998; Jankovic, 2001b; Macerollo et al., 2019); animal studies (Knorr et al., 2021; Ip et al., 2016; Schicatano et al., 1997)
cranial/central trauma	DYT/PARK-ATP1A3, adult-onset isolated dystonia		clinical reports (Sheehy and Marsden, 1980; de Carvalho Aguiar et al., 2004; Zaremba et al., 2004; Frei et al., 2004; Newman et al., 2014; Defazio et al., 1999)
perinatal adversities (childhood) infections	DYT-TOR1A	DYT-TOR1A (TOR1A +/ $\Delta$ gag)	clinical reports (Martino et al., 2013); animal studies (Cascalho et al., 2020)
childbirth	DYT/PARK-ATP1A3		clinical reports (Haq et al., 2019; Saunders Pullmann et al., 2004)
psychological stress	DYT/PARK-ATP1A3 PxMD-PRRT2 PxMD-PNKD PxMD-SLC2A1	DYT/PARK-ATP1A3 (pharmacological mouse model); <i>dtsz</i> hamster	clinical reports (Haq et al., 2019; Erro et al., 2014; Barbano et al., 2012; Pittock et al., 2000); animal studies (Calderon et al., 2011; Richter, 2005)
physical exercise	DYT/PARK-ATP1A3 PxMD-SLC2A1	DYT/PARK-ATP1A3 (pharmacological mouse model)	clinical reports (de Carvalho Aguiar et al., 2004; Haq et al., 2019; Erro et al., 2014); animal studies (Rauschenberger et al., 2020a)
alcohol (abuse)	DYT/PARK-ATP1A3 PxMD-PRRT2 PxMD-PNKD		clinical reports (Haq et al., 2019; Erro et al., 2014; Barbano et al., 2012)
caffeine	PxMD-PRRT2 PxMD-PNKD		clinical reports (Erro et al., 2014)
heat/fever or cold temperatures	DYT/PARK-ATP1A3 PxMD-PNKD	DYT/PARK-ATP1A3 (D801Y ( $\alpha_3^{+/D801Y}$ ) mice)	clinical reports (de Carvalho Aguiar et al., 2004; Haq et al., 2019; Erro et al., 2014); animal studies (Isaksen et al., 2017)
sleep deprivation / fatigue (sudden) movements	PxMD-PRRT2 PxMD-PNKD PxMD-PRRT2		clinical reports (Erro et al., 2014)
overuse	DYT-TOR1A, adult-onset isolated dystonia	wildtype monkeys and rats	clinical reports (van den Bos et al., 2004; Ritz et al., 2009; Gasser et al., 1998; Wu and Jankovic, 2006; Roze et al., 2009; Rozanski et al., 2015; Schmidt et al., 2013); animal studies (Byl et al., 1996; Byl et al., 1997; Barbe et al., 2003; Coq et al., 2009)
dry eye syndrome	adult-onset isolated dystonia (blepharospasm)		clinical reports (Defazio et al., 1998; Martino et al., 2005; Elston et al., 1988)

in mouse model, which carries the same trinucleotide deletion in the *Tor1a* gene observed in humans, shows slight deficits in sensorimotor tasks, a subtle increase in baseline locomotor activity and significant differences in the beam-walking task with increased slipping of the mutant mice (Richter et al., 2017). h $\Delta$ GAG3 mice showed hyperactivity and a reduced learning curve, the latter of which is similar to the impaired learning found in non-manifesting and manifesting DYT-TOR1A patients (Ghilardi et al., 2003; Grundmann et al., 2007). These and other DYT-TOR1A mouse models do not, however, present any abnormal movements resembling a dystonia-like phenotype (Grundmann et al., 2007; Grundmann et al., 2012; Dang et al., 2005; Shashidharan et al., 2005; Sharma et al., 2005; Richter and Richter, 2014). Thus, even though most of these genetic models exhibit some motor dysfunction and are construct-valid, only few of these models have face validity. Mice with conditional deletion of torsinA in the central nervous system presented abnormal twisting movements, however, this mouse model also revealed neurodegeneration in the sensorimotor circuit (Liang et al., 2014). Contrasting this finding, no evidence for neurodegeneration in DYT-TOR1A patients was found to date (Paudel et al., 2014). The induction of a dystonia-like phenotype in DYT-TOR1A rodent models was however achieved via the application of a peripheral nerve crush (Knorr et al., 2021; Ip et al., 2016). The crush injury of the sciatic nerve, which propagates both motor and sensory information, leads to changed sensory input, which was hypothesized to result in maladaptive plasticity in mice with a torsinA mutation (Fig. 2). Following this “second hit” hypothesis, *Tor1a* knockout mice developed focal dystonia-like hindlimb movements after a peripheral nerve injury over an observational period of eight weeks (Ip et al., 2016). Evidence for disturbed dopamine metabolism was found, with naïve *Tor1a* mutants presenting a hypodopaminergic environment compared to the wildtype control group. Moreover, *Tor1a* knockout mice failed to show a

reduction in dopamine metabolism after nerve crush as seen in their wildtype, nerve-crushed counterpart (Ip et al., 2016).

In line with these findings, Knorr et al. published a similar phenomenon in  $\Delta$ ETorA rats carrying a human mutated *Tor1a* (Knorr et al., 2021).  $\Delta$ ETorA rats developed long-lasting dystonia-like movements over an observational period of 12 weeks. The transgenic rats with dystonia-like movements presented a significantly higher striatal dopaminergic turnover compared to control animals, similar to the findings in human DYT-TOR1A patients. Measurements of local-field potentials in the entopeduncular nucleus, the rat equivalent of the human internal globus pallidus, revealed higher theta power in transgenic, nerve-crushed rats compared to wildtype animals. Deep brain stimulation of the entopeduncular nucleus over a 3-week-period led to a significant improvement of dystonia-like movements in  $\Delta$ ETorA rats, thereby supporting the hypothesis of a pathologically altered brain motor network in these rats after peripheral nerve injury. Bhagat and colleagues did not apply a “second hit” per se to their DYT-TOR1A knock-in mouse model, but found *Tor1a* mutants to perform worse than their wildtype counterpart in novel and/or challenging behavioral tests (Bhagat et al., 2016). While DYT-TOR1A knock-in mice performed equally well in locomotor measures in their home cage compared to control mice, they performed worse in a novel open field or on the first day on the accelerating rod. The authors concluded that stress, in form of novel situations, is necessary for motor deficits in their DYT-TOR1A model. In contrast to the nerve-injury-induced dystonia-like movements, an attempt to trigger dystonia by in a DYT-TOR1A knock-in model by mitochondrial complex-II inhibition using 3-nitropropionic acid was unsuccessful, although the dosage was high enough to increase mortality in both wild type and mutant mice (Bode et al., 2012). One possible explanation for this discrepancy is the additional disturbed sensorimotor integration with need for central adaptation that occurs



**Fig. 2.** Peripheral trauma causing dystonia in genetically predisposed rodent models. Central maladaptive plasticity, loss of inhibition and disturbed sensorimotor integration are believed to be main pathogenic drivers behind dystonia development. Created with [BioRender.com](https://www.biorender.com).

after nerve injury.

Again, another study looked at the lipid metabolism in a mouse model of DYT-TOR1A dystonia. The authors found that embryonic lipid metabolism is disturbed in a portion of female TOR1A  $+/Δgag$  mice and that environmental factors such as the maternal diet contribute to this abnormal lipid metabolism (Cascalho et al., 2020). The authors found lipid metabolism to return to normal during post-natal development but proposed that the abnormal metabolism in utero sets the brain up for dystonia development in later life. It was concluded that the interplay of a disturbed lipid metabolism and environmental stimuli during the development phase in utero could explain the reduced penetrance of DYT-TOR1A dystonia. Interestingly, the authors found sex-dependent changes with predominantly female mice showing dystonia-like movements; however, this has thus far not been described for humans (Martino et al., 2013).

On a cellular level, a number of publications in recent years have linked the torsinA mutation and a growing list of other dystonia mutations to a dysregulation of eukaryotic translation initiation factor 2 subunit  $\alpha$  (eIF2 $\alpha$ ), a protein playing a key role in the cellular response to ER stress (Beauvais et al., 2018). Rittiner et al. found a disturbed eIF2 $\alpha$  pathway response to stress in DYT-TOR1A fibroblasts compared to normal controls (Rittiner et al., 2016). Furthermore, Rittiner et al. demonstrated that enhancing eIF2 $\alpha$  signaling rescues corticostriatal long-term depression at cortical synapses onto projection neurons in brain slices of DYT1 knock-in mice (Rittiner et al., 2016). The authors draw a link between the failure of DYT-TOR1A mouse models to reproduce the clinical symptoms and the implication of a stress response pathway. They hypothesize that a second hit is needed to activate this stress response pathway in DYT-TOR1A patients and that its impairment might then lead to dystonic symptoms. The exploration of neuronal ER stress as “second hit” in a DYT1 knock-in mouse model has, however, so far been unsuccessful. Beauvais and colleagues crossbred DYT1 knock-in

mice with p58 knock-out mice, with p58 being a co-chaperone in modulating ER stress (Beauvais et al., 2016). *Tor1a<sup>+ΔE</sup>p58<sup>-/-</sup>* animals did not develop significant motor abnormalities. Aside from DYT-TOR1A, the mutations underlying DYT-THAP1 and DYT-PRKRA dystonia, have been implicated to be responsive to ER stress (Nayak et al., 2014; Vaughn et al., 2015).

Gill et al. reported an impaired mechanotype of human and murine DYT-TOR1A fibroblasts, which leads to a reduced viability following mechanical stretch (Gill et al., 2019). The authors concluded that this finding might translate to neurons, which would entail a reduced ability of cells to adapt to their environment. Mechanical sensitivity is especially important during brain development for neuronal differentiation, proliferation and survival (Barnes et al., 2017). Whether the reduced mechanosensitivity (ability to sense the mechanical properties of the environment) and mechanotransduction (ability to translate mechanical stimuli of the environment to biochemical signals) of cells becomes detrimental when the brain is in addition confronted with a stress factor requiring plasticity, remains speculative.

#### 4. Gene-environment interaction in adult-onset isolated dystonia

Adult-onset focal and segmental isolated dystonia are the most common forms of dystonia and the role of environmental factors in their development will be addressed within this section. The clinical presentation of adult-onset dystonia varies dramatically from blepharospasm and oromandibular dystonia to cervical dystonia and writer’s cramp. Adult-onset, focal or segmental dystonia has long been suspected to be multifactorial. Gender differences have been reported for all forms of craniocervical dystonia (blepharospasm, oromandibular dystonia, cervical dystonia and spasmodic dystonia), which seem to be more frequent in women than in men with female-to-male ratios ranging from 1.6:1 to

3.8:1 (Defazio, 2010a; Defazio et al., 2004; Williams et al., 2017; Hintze et al., 2017; Soland et al., 1996; Defazio et al., 2017; Meoni et al., 2020). However, a male predominance seems to exist in task-specific focal hand dystonia (FHD) such as writer's cramp, golfer's cramp and musician's dystonia (Torres-Russotto and Perlmutter, 2008; Dhungana and Jankovic, 2013; Adler et al., 2011; Defazio et al., 2007; Group, E. S. o. D. i. E. E. C, 2000). Furthermore, the increased occurrence of focal dystonia in certain families has been reported, indicative for a common dystonia-related genetic background (Defazio et al., 2003). This was supported by the observation that the temporal discrimination test (that determines the temporal discrimination threshold, which represents the minimum interval at which paired sequential stimuli are perceived as asynchronous) was abnormal in patients with focal dystonia and in at least one first-degree relative in 22 out of 24 families of index cases who had focal dystonia (Kimmich et al., 2011). Overall, it has been hypothesized that several genes along with environmental factors are needed to reach the threshold for dystonia in adult-onset forms (Phukan et al., 2011).

#### 4.1. Evidence from clinical studies

A plethora of studies on environmental risk factors have been performed in patients with adult-onset, isolated dystonia. Some of these studies grouped patients with focal as well as segmental, multifocal and generalized dystonia under a single phenotype. The portion of patients with focal dystonia largely outweighed patients with generalized dystonia in all of these studies.

Especially for the role of peripheral trauma in dystonia, opinions and study results differ profoundly (Kumar and Jog, 2011; Jankovic, 2001a; Defazio, 2010b). One of the first case-control studies on the interplay of environment and dystonia were performed in an Italian cohort analyzed by the Italian Movement Disorder Study Group (Defazio et al., 1998). For this study, the authors differentiated between central trauma with loss of consciousness and peripheral/extracranial injury. A family history of dystonia or tremor as well as head or face trauma with loss of consciousness, were found to be an independent risk factor for adult-onset dystonia. The authors also found a positive association between focal body injury and dystonia, especially for neck or trunk trauma and cervical dystonia. This study was later criticized by G. Defazio himself for having been liable to false positive results due to being an exploratory study assessing a large number of possible risk factors with some of the observed statistical associations having possibly been confounders (Defazio, 2010b). Within the study, an average of 4.2 years was found to lie between trauma and the development of dystonia, which G. Defazio criticized as being too long of a time interval to be considered causal. Indeed, two later studies using the Italian Dystonia Registry concluded that peripheral trauma could not be considered a risk factor for dystonia (Defazio et al., 2017; Defazio et al., 2020). They solely investigated extracranial injuries and their association to symptom onset. It has to be pointed out that these studies are not case-controlled and aside from a recall bias, also underly a referral bias with patients being recruited only from movement disorder centers. Extracranial injuries that were severe enough to require medical attention, hospitalization or even surgery were considered for the study; no further classification of trauma was performed. The authors reported that only a minority of patients with peripheral injury developed dystonia in the same body part as affected by the injury and that the time between trauma and onset of dystonia varied strongly with a mean of  $8.1 \pm 9.2$  years. Only 0.36% of patients developed dystonia one year or less after trauma. Macerollo and colleagues took advantage of the medical insurance database in Taiwan to study peripheral trauma as a risk factor in dystonia (Macerollo et al., 2019). As such the authors successfully avoided relying on patients' recall for their data and were able to access a large sample size. 65,704 people with peripheral traumatic injury were matched to 65,704 people without peripheral trauma of the database and followed up over a time period of 11 years. Patients with cranial or spinal injuries were excluded from the study; patients developing dystonia within one-year of the

index date of trauma were also excluded from the analysis. The authors' aim was to exclude patients with rapid onset of dystonia after trauma as this could suggest a functional etiology or secondary dystonia due to brain injury. Indeed, the authors found peripheral injuries to be an independent risk factor for the development of dystonia. A clear drawback of the study is, however, that authors were unable to confirm the diagnosis of dystonia in patients and were unable to determine the form of dystonia from the available data. As such no clear link between the type of trauma and the type of dystonia could be drawn. Frei and colleagues reported on a case series of 9 patients developing cervical dystonia within 7 days after neck injury (Frei et al., 2004). Another publication stated that a neck injury preceded cervical dystonia in 9% out of 414 patients (Sheehy and Marsden, 1980). Bohlhalter et al. described a case of a 59-year old woman developing dystonia in the left leg after having injured her left ankle one year before (Bohlhalter et al., 2007). While the injury was initially associated with marked pain and walking difficulties, no pain was reported at the time the dystonic symptoms developed. Intriguingly, the brother of the described patient was described to be suffering from craniocervical dystonia. Furthermore, both the patient, the symptomatic brother as well as one asymptomatic sister of the patient were found to have abnormal motor excitability as analyzed by paired pulse transcranial magnetic stimulation suggesting a familial predisposition. In conclusion, while there are encouraging reports, the association between peripheral trauma and dystonia remains an open question. As previously pointed out in a comprehensive review of clinical studies on dystonia and peripheral trauma, the severity and kind of trauma assessed in studies varies dramatically from mild bruises to bumping the head into a car door (Kumar and Jog, 2011). Moreover, the time interval between trauma and onset of dystonia varies heavily, making the link between trauma and onset of dystonia often questionable. Indeed, a retrospectively matched, case-sibling analysis reported that car accidents with required hospital attendance as well as surgical procedures of any kind were a significant risk factor for the development of cervical dystonia (Molloy et al., 2015). Both of these risk factors encompass a very large variability in severity of trauma. Despite the problem of defining trauma and interval between injury and dystonia onset, it still remains a challenging task to distinguish organic from functional dystonia (Ganos et al., 2016; Baizabal-Carvallo et al., 2019). It is well known that movement disorders to a large degree have a psychiatric component. The term 'causalgia-dystonia' has been used for fixed, "dystonia-like" postures together with pain, which are often documented in association with preceding minor peripheral trauma (Bhatia et al., 1993). Causalgia-dystonia is characterized by an absence of task-specificity and geste antagoniste, a poor response to botulinum toxin as well as a common involvement of limbs (Schrug et al., 2004). Complex regional pain syndrome is often associated with causalgia-dystonia. The pathomechanisms behind causalgia-dystonia remain unclear, however, many authors have suggested a functional origin (Schrug et al., 2004; Hawley and Weiner, 2011). Others have, however, proposed that complex regional pain syndrome may be a variant of organic, posttraumatic dystonia (Frei et al., 2004). Indeed, acute as well as chronic pain have been reported to lead to secondary changes in the excitability of the motor cortex similar to the abnormalities found in patients with focal dystonia (Jodoin et al., 2020; Schabrun et al., 2015; Brighina et al., 2005). This suggests that rather than the peripheral injury itself, the resulting pain might be a trigger for the development of dystonia. Inversely, it was proposed that professional musicians are not only at risk to develop focal dystonia, but also chronic pain due to the somatosensory cortical reorganization taking place as a consequence of extensive sensorimotor training (Zamorano et al., 2014). The study found increased pain sensitivity and decreased tactile acuity in professional musicians with chronic pain as well as pain-free musicians compared to pain-free, non-musicians.

Head injuries with loss of consciousness and their association to dystonia development have also been a matter of debate. Aside from the positive association found by Defazio and colleagues, an Australian

epidemiological study showed a strong association of adult-onset isolated dystonia to head injuries associated with a loss of consciousness (Newman et al., 2014). This study included patients with focal, segmental, multifocal, and generalized dystonia with an age of onset greater than 30 years and with previous exclusion of patients positive for the *Tor1a* or *Thap1* mutations. Other risk factors associated with dystonia were anxiety disorders, tremor, and cigarette smoking. Some factors might have to be considered secondary to dystonia, such as anxiety disorders, while others such as head injuries could represent an environmental risk factor. A multi-center study found head trauma with loss of consciousness prior to onset of dystonia to be a risk factor for spreading of blepharospasm (Defazio et al., 1999). Other case-control studies, however, found no association between head trauma and the development of cervical dystonia (Martino et al., 2007).

Diseases of the anterior segment of the eye, especially dry eye syndrome, have been found to be strongly associated with the development of blepharospasm (Defazio et al., 1998; Martino et al., 2005; Elston et al., 1988). Eye diseases within one year of dystonia onset were found to be stronger associated with blepharospasm than eye disease having occurred at an earlier time point (Martino et al., 2005). The fact that dry, irritated eyes often precede the onset of blepharospasm suggests that this results in abnormal sensory feedback in predisposed subjects, which leads to the development of malfunctioning central motor signaling. For laryngeal dystonia, Tanner et al. found a history of occupational voice use, certain recurring viral infections of the upper respiratory tract, and a family history of neurological conditions to be associated with increased risk of spasmodic dysphonia compared to patients with other voice disorders (Tanner et al., 2012).

FHD is believed to arise from an interplay between subtle abnormalities in neuroplasticity and environmental factors in the form of repeated, highly skilled movements. FHD, of which writer's cramp is the most common form, has been described in almost all professional fields involving prolonged and stereotyped movements (Chen and Hallett, 1998). This includes musicians, athletes, typists, hairdressers, physicians, and surgeons. Synchronous and convergent afferent input from repetitive, highly skilled motor tasks has been proposed to result in the consolidation of abnormal motor patterns. A case-control study of 104 patients suffering from writer's cramp and 104 controls matched for age, sex and socio-professional category found an association between writer's cramp and an unusual increase in the amount of writing in the year prior to onset as well as the time spent writing each day (Roze et al., 2009). The authors hypothesized that the association between the time spent writing and writer's cramp reflects a dose-effect relationship, but that acute triggers such as an abrupt increase in writing time are necessary for the development of this form of task-specific dystonia. They postulated that the homeostatic regulation of cortical plasticity might be overwhelmed, resulting in dystonia. The findings of this study are in keeping with studies on musician's dystonia, where an increase in the time spent practicing musical instruments was also discovered to be a risk factor (Rozanski et al., 2015). Furthermore, Roze et al. reported a non-significant trend for head trauma with loss of consciousness as well as myopia as risk factors for writer's cramp, however, no association was found for peripheral trauma, writing under stress or constrained writing (Roze et al., 2009). Another category of task-specific, focal dystonia is the so called musician's dystonia (Altenmüller and Jabusch, 2010). Similar to reports on writer's cramp, patients with musicians' dystonia spend significantly more time on fine motor tasks than healthy first-degree family members with similar genetic background (Schmidt et al., 2013). Moreover, a later age at first practice and a positive family history are correlated with an increased risk for developing dystonia in musicians. Anecdotally, piano player's dystonia seems often precipitated by changing to a piano that requires more force to play. Another issue, which has been found to be involved in predisposing for musicians' dystonia, but may very well also be relevant to other forms of FHD, are biomechanical abnormalities of the hand, which might entail stressful motor patterns to play as required (Leijnse et al., 2015). Environmental

triggers such as peripheral trauma or pain six months prior to dystonia onset were not found to be a risk factor in one retrospective study comparing 28 professional musicians and 97 relatives (Schmidt et al., 2009). Acute stress was found to have no impact on the motor performance of dystonic musicians compared to non-dystonic musicians, but psycho-diagnostics showed that psychological traits related to stressful and perfectionistic personalities were associated with an earlier manifestation of focal dystonia in professional musicians (Ioannou et al., 2016). The authors hypothesized that these elevated psychological traits might lead to maladaptive neurobiological changes as elevated levels of stress-induced glucocorticoids have been found to lead to maladaptive changes in the brains of animal models. Prolonged repetitive lower limb exercise, such as marathon running, has also been repetitively described as a cause for task-specific dystonia (Wu and Jankovic, 2006; Ahmad et al., 2018; Cutsforth-Gregory et al., 2016). So far, the specific risk factors for developing the so-called runner's dystonia have not been studied. However, Wu and Jankovic pointed out that 2 out of the 5 patients described in their case report had suffered an injury to the dystonic leg within the year prior to developing symptoms (Wu and Jankovic, 2006).

Environmental factors might also be involved in tardive dyskinesia, which can present with dystonia and results from a chronic exposure to dopamine-receptor-blocking agents. The exact mechanisms behind the development of tardive dyskinesia remain unknown. The most popular hypothesis describes that the dopamine receptor blockade results in a dopamine hypersensitivity due to receptor upregulation (Calabresi et al., 2016; Klawans and Rubovits, 1972). However, not all patients treated with long-term antipsychotics develop tardive dyskinesia and the phenotype of patients treated with the same drug varies strongly (Wain and Jankovic, 2013). This suggests that additionally to a disturbance of the dopamine metabolism, a second factor is necessary for the development of tardive dyskinesia. Genetic factors associated with a higher risk for or protection against tardive dyskinesia, have been reported (Müller et al., 2001; Fedorenko et al., 2014). However, other risk factors such as older age, female sex, preceding brain injury, cognitive impairment or extrapyramidal symptoms have also been found to be associated with development of tardive dyskinesia (Kane and Smith, 1982; Wu et al., 2013; Carbon et al., 2017).

#### 4.2. Evidence from animal models

Only very few studies on animal models have been performed to deepen our understanding on adult-onset dystonia and the role of the environment (Evinger, 2005). This is surely due to the limited feasibility of establishing animal models for adult-onset, isolated dystonia as we still have such an incomplete perception of the disease in humans.

For blepharospasm, Schicatano and colleagues were able to show that the combination of a slight pharmacological reduction of striatal dopamine accompanied by a weakening of the orbicularis oculi muscle produces the symptoms of excessive blinking in rats (Schicatano et al., 1997). For this, rats received a unilateral 6-hydroxydopamine (6-OHDA) lesion in the substantia pars compacta and a branch of the facial nerve with partial input to orbicularis oculi muscle was crush-injured. Blinking with the weakened orbicularis oculi muscle was presumed to lead to eye irritation due to inadequate reformation of the tear film. The combination of this predisposing condition and the environmental trigger led to excessive blinking in rats, persisting even after reinnervation of the orbicularis oculi muscle. The authors moreover reported that only the combination, but not the 6-OHDA lesion nor the nerve crush by themselves led to the development of a blepharospasm-like phenotype. Indeed, a human equivalent for this phenomenon has been described in patients with Bell's palsy followed by the development of blepharospasm (Abou Dagher et al., 2013; Baker et al., 1997; Chuke et al., 1996; Cattaneo et al., 2005). Intriguingly, one case report even described apomorphine to alleviate symptoms in one patient with Bell's palsy-induced blepharospasm (Cattaneo et al., 2005).



For task-specific FHD, primate studies have shown that intensive training of repetitive movements lead to changes in the cortical representation of the hand and to the development of focal dystonia (Byl et al., 1996; Byl et al., 1997; Blake et al., 2002). Byl and colleagues reported on monkeys performing repetitive squeezing of a hand piece for a reward over 24 weeks (Byl et al., 1996). Two out of three monkeys developed focal hand dystonia, the third monkey used a variable arm pulling procedure and thus did not develop dystonia within 24 weeks. Inflammation in the hand as an origin of the dystonic movements was excluded. The hand representation area of the somatosensory cortex in the two monkeys with hand dystonia was found to be changed dramatically with a receptive field 10–20 times larger than normal. Similar to findings in writer's cramp, cortical receptive fields were also enlarged for the contralateral, non-dystonic hand (Meunier et al., 2001). Other researchers have established rat models imitating task-specific FHD (Barbe et al., 2003; Coq et al., 2009). In the study of Coq and colleagues, rats performed a repetitive reaching and grasping task for a period of eight weeks. The reaching performance, grip strength and agility declined with cumulative task exposure. The authors furthermore reported an increase in peripheral inflammation and cortical neuroplasticity in animals and concluded that these factors jointly contribute to the development of movement disorders induced by repetitive tasks.

## 5. Future directions of research

The studies on the role of the environment in monogenic and adult-onset forms of dystonia largely present contradictory results, making it difficult to pinpoint the exact role as well as the kind of triggers necessary for dystonia development. While repetitive fine motor tasks and eye diseases of the anterior segment have been shown to be robust triggers for adult-onset, focal dystonia, the same cannot be said for cranial and extracranial trauma. While the role of stress factors is well-established in DYT-PARK/ATP1A3 dystonia, the low numbers of studies in other monogenic forms of dystonia make it impossible to conclude on the role of triggers in their pathogenesis. Contributing factors might be the high amount of retrospective assessments as well as a low number of patients resulting in studies with insufficient power. All retrospective studies relied on subjects filling out questionnaires on their past history of trauma or other events – a method highly vulnerable to recall bias. Environmental stress is difficult to define and perception of stress might be highly variable between individuals. Furthermore, low statistical power can be detrimental, especially when it comes to detecting small effects of relatively rare events such as peripheral trauma. Studies vary strongly in the time spans considered between the stress factor and symptom onset. Some studies included only triggers with a greater time interval than one year before dystonia onset, others considered only triggers within six months of dystonia onset. Many studies on the role of environmental factors in adult-onset, isolated dystonia have grouped patients with focal, segmental, and generalized dystonia into a single phenotype for the identification of risk factors. This is done under the assumption that all adult-onset dystonic syndromes are similar and that environmental triggers have the same amount of significance in focal and generalized dystonia. It has been suggested that environmental factors play a smaller role in generalized dystonia compared to focal dystonia. Large collaborative, prospective studies will be indispensable in identifying risk factors for the development of dystonia. To properly assess the role of peripheral injury in focal dystonia, controlled studies examining the relationship between the severity of trauma and risk of developing dystonia, the time elapsing from injury to dystonia onset need to be performed.

In summary, basic science has made important strides in dystonia research, however, it has not been able to fully explain dystonia pathophysiology and the fact that genotype does not predict phenotype. Clinical data concerning the role of environmental factors in dystonia pathophysiology remain controversial. However, preclinical data analyzing the role of a “second hit” are highly promising. Animal models

of dystonia that follow the “second hit” concept have enabled the differentiation between symptomatic and asymptomatic mutation carriers. These animal models present the possibility to systematically investigate the role of a “second hit” in dystonia pathophysiology and to explore disease development on multiple levels.

## Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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